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Dietary Intakes of Total and Specific Lignans Are Associated with Clinical Breast Tumor Characteristics[1–3]

Susan E. McCann,[4]* Katie C. Hootman,[7] Anne M. Weaver,[8] Lilian U. Thompson,[10] Carl Morrison,[5] Helena Hwang,[5] Stephen B. Edge,[6] Christine B. Ambrosone,[4] Peter J. Horvath,[9] and Swati A. Kulkarni[6]

[4]Department of Cancer Prevention and Control, [5]Department of Pathology, and [6]Department of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY; [7]Division of Nutritional Sciences, Cornell University, Ithaca, NY; [8]Department of Social and Preventive Medicine, and [9]Department of Exercise and Nutrition Sciences, University at Buffalo, Buffalo, NY; and [10]Department of Nutritional Sciences, University of Toronto, Canada

Abstract

Dietary lignans may affect breast cancer by modifying tumor characteristics likely to affect prognosis. We investigated usual dietary intakes of total and specific lignans with tumor characteristics in 683 women with breast cancer and 611 healthy women without breast cancer enrolled in the Data Bank and BioRepository at Roswell Park Cancer Institute (RPCI). Clinicopathologic data were abstracted from the RPCI breast cancer database. Dietary lignan intakes were calculated from FFQ. OR and 95% CI were estimated with logistic regression adjusting for potential confounders and stratified by menopausal status. Women in the highest compared to the lowest tertile of total lignan intakes had a 40–50% lower odds of breast cancer regardless of menopausal status and substantially reduced odds of an invasive tumor, especially among premenopausal women [OR 0.48 (95% CI 0.26–0.86)]. Lignan intakes were inversely associated with odds of grade 3 tumors among premenopausal women. Lignan intakes were inversely associated with risk of estrogen receptor (ER) negative (ER^-) breast cancer among premenopausal women [OR 0.16 (95% CI 0.03–0.44)] and particularly triple negative tumors [ER^-, progesterone receptor negative, HER2 negative; OR 0.16 (95% CI 0.04–0.62)]. There were significant differences in the contribution to these effects by specific lignans, especially matairesinol and lariciresinol. In summary, in this case-control study of dietary lignan intakes and breast cancer, we found that higher lignan intakes were associated with lower risks of breast cancer with more favorable prognostic characteristics. Future investigations are warranted to explore the strong associations observed with ER^- cancer in premenopausal women. J. Nutr. 142: 91–98, 2012.

Introduction

The phytoestrogen lignans are naturally occurring diphenolic compounds with structural similarity to endogenous estrogens (1). Lignans are widely available in whole grains, seeds, nuts, legumes, fruit, and vegetables, with the highest concentration in flaxseed and bakery products containing flaxseed (2). Although several foods and beverages such as coffee and orange juice have smaller relative amounts of lignans, they are significant contributors to total dietary intake of lignans due to the large amounts of those foods consumed each day (3). Among non-Asian populations, lignans provide the largest contribution to total phytoestrogen intake; however, typical Western dietary lignan intakes from non-flaxseed sources average <1 mg/d (3–5).

In human and experimental studies, high lignan intakes (from flaxseed) affect endocrine and growth factor pathways through a number of mechanisms, including modification of steroid hormone metabolism (6–8), modification of insulin-like growth factor and epidermal growth factor (9,10), and inhibition of aromatase and 17β-hydroxysteroid dehydrogenase (11,12). Lignans inhibit cell proliferation in both ER^+[11] and ER^- cell lines (13,14), reduce tumor growth and metastasis in a number of animal models (15–18), and work synergistically with Tamoxifen to reduce tumor growth (10,13). Several, but not all, epidemiologic studies report reduced risks of breast cancer associated with higher exposure to dietary lignans, expressed as

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[3] Supplemental Table 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
* To whom correspondence should be addressed. E-mail: susan.mccann@roswellpark.org.

[11] Abbreviations used: DBBR, Databank and Biorepository; ER, estrogen receptor; ER^+, ER positive, ER^-, ER negative; HER2, human epidermal growth factor receptor 2; $HER2^+$, HER2 positive; $HER2^-$, HER2 negative; PR, progesterone receptor; PR^+, PR positive; PR^-, PR negative; RPCI, Roswell Park Cancer Institute.

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either dietary intakes or as plasma, serum, or urinary lignan concentrations (19,20). The protective effect of lignans may also be stronger in specific subgroups of women with breast cancer; lower risks have been reported to be limited to premenopausal women (21,23), women with specific *CYP17* genotypes (21,23), and recently for ER^- breast cancer (24,25). This evidence, in addition to the experimental evidence, suggests that lignans may act selectively upon tumors with certain pathologic and/or biologic characteristics. Furthermore, it is becoming increasingly recognized that breast tumors are heterogeneous. Understanding the action of dietary components on individual tumor characteristics may help identify potential agents for primary as well as secondary breast cancer chemoprevention.

Breast cancer treatment success and disease prognosis depends upon a number of histopathologic factors, including tumor size and lymph node status, which are part of breast cancer stage at diagnosis and the individual characteristics of the tumor itself (26). Lack of expression of certain receptors is associated with poorer prognosis, such as negative ER and PR status. Hence, ER status is considered an important predictive factor in breast cancer treatment (27). HER2/*neu* (c-erbB-2) is a proto-oncogene with tyrosine kinase activity similar to epidermal growth factor receptor and is overexpressed in ~18–20% of breast cancers (28,29). As a prognostic factor, HER2 has been associated with increased recurrence and increased mortality (28); however, overexpression is reduced by high dietary lignan intake from flaxseed consumption (30).

Molecular profiling has helped further stratify breast cancer into 4 main subtypes with different prognosis and response to treatment (31). Luminal A and luminal B subtypes are characterized by expression of the ER, with higher ER expression and lower expression of proliferation-related genes associated with luminal A compared to luminal B tumors. Luminal tumors tend to be associated with good prognosis. Luminal A tends to respond better to endocrine therapy and thus has been associated with improved prognosis and outcomes. Luminal B tumors respond less well to endocrine therapy and have been hypothesized to be hormone refractory. HER2-overexpressing subtype, characterized by hormone receptor-negative tumors overexpressing HER2, respond to chemotherapy and trastuzumab therapy, but relapse tends to be high. Basal tumors are negative for ER, PR, and HER2 and overexpress cytokeratins 5 and 6. A major subset of basal-like breast cancers are those that are triple negative (ER, PR, and HER2). This subtype tends to be aggressive, not responsive to hormonal treatment, and is associated with poor prognosis. Associations with known breast cancer risk factors tend to vary with breast cancer subtype, suggesting that tumor subtype may be important in determining the effect of exposures in breast cancer etiology.

Dietary lignan exposure has been associated with a number of physiologic actions that could be important in reducing breast cancer morbidity and mortality, although the current evidence is inconsistent. This inconsistency may be partly due to heterogeneity of tumors in a particular study, and the effect of lignans may be specific to histologic characteristic rather than general. Therefore, we investigated the associations between usual dietary lignan intakes and breast cancer, with particular attention to breast tumor characteristics, in a case-control study conducted at RPCI.

Materials and Methods

Archived clinical, pathologic, and questionnaire data from women with breast cancer diagnosed between December 31, 2003 and December 31, 2008 were obtained from the DBBR at the RPCI (Buffalo, NY). The DBBR is a Cancer Center Support Grant core shared research resource that provides biospecimens and linked data for studies of cancer etiology and prognosis. The protocol for the DBBR was approved by the RPCI Institutional Review Board and all participants provided signed informed consent. Participants were asked to complete a detailed epidemiologic questionnaire and return the completed questionnaire to RPCI in the provided postage-paid envelope. The majority (65%) of participants returned the questionnaire within 2 mo. Initially, 790 women with breast cancer (aged 26–89 y) were available for inclusion in this analysis. We excluded women who completed <90% of the FFQ items or had energy intake <1674 or >16736 kJ/d (n = 56), women with excessive missing clinical data (n = 4), and non-whites (n = 47; excluded because the sample size for non-whites was insufficient for stratified analyses), resulting in a final analytic sample of 683 cases. DBBR control participants were putatively healthy friends or family members of RPCI patients. At the time of recruitment of each patient to the DBBR, participation was also offered to any friends or relatives in the room with the patient. Additionally, controls have been recruited during Buffalo area health fairs, cancer fund raising events, and other local events. When controls were selected for a specific study, only those not related to the cases were chosen, i.e. a control recruited from a prostate cancer case might be chosen for a breast cancer study. Caucasian women with no history of cancer who were enrolled in the DBBR between December 2003 and May 2010 and had energy intakes between 1674 and 16,736 kJ/d were selected as controls and were frequency matched to cases by 10-y age strata. After exclusions for missing data (n = 5), 611 controls were included in the present analyses.

Data regarding clinicopathologic factors from the RPCI breast cancer clinical database were linked with epidemiologic data by the DBBR and included tumor stage and grade, ER and PR status, and HER2 protein expression. The Allred score (32) was used to semiquantitatively evaluate ER and PR expression. ER and PR were considered positive given an Allred score of >2 and negative given an Allred score of ≤2. HER2 expression was measured with an automated cellular image analysis system (ACIS system, ChromaVision Medical Systems). The intensity of membrane staining for the protein indicated the level of gene function and was designated as a continuous variable on a scale of 0–4. A value of <1.5 was considered negative and values >2.5 were considered positive. Cases with borderline HER2 scores (1.5–2.5) were reflex tested by fluorescence in-situ hybridization, which delivers a dichotomous result. A positive fluorescence in-situ hybridization test indicates the amplification of the HER2 gene and a negative test indicates a lack of gene amplification. ER, PR, and HER2 were analyzed herein as positive or negative.

Tumor stage was categorized as in situ (stage 0), stage I, stage II (IIA and IIB), and stage III/IV (IIIA, IIIB, IIIC, IV), respectively, for analysis. Tumor grade was characterized using the Nottingham grading system (33) and classified as grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated).

Because it is not practical to perform gene expression arrays on all breast cancers in the clinic, Nielsen demonstrated that standard immunohistochemical markers could be used to closely approximate the 4 main molecular subtypes in invasive tumors (stage I or higher) (34). We used this classification to examine lignan intakes by breast tumor subgroup. Luminal A tumors were defined as ER^+ and/or PR^+ and $HER2^-$. Luminal B tumors were defined as ER^+ and/or PR^+ and $HER2^+$. Triple negative tumors were defined as ER^-, PR^-, or $HER2^-$. In these analyses, cytokeratin 5/6 staining was not available and therefore precluded us from classifying tumors as basal-like. HER2 array type tumors were classified as $HER2^+$ and ER^-. Finally, any remaining invasive tumors were grouped into an unclassified category.

The DBBR questionnaire included an extensive FFQ querying the usual frequency of use in the year prior to diagnosis of 110 foods and beverages. Although the FFQ used in the DBBR has not been validated in our population, it is similar in design to standard FFQ used in nutritional epidemiology and as such should have comparable validity. Nutrient intake was calculated from the FFQ using USDA food composition data and standard nutrient calculation algorithms. For each nutrient, daily intakes were calculated as the product of the food-specific frequency of use, portion size in grams, and nutrient content summed across all contributing foods. Daily intakes of total lignans and four individual lignans (matairesinol, lariciresinol, pinoresinol, and secoisolariciresinol)

were calculated using the method described for nutrients and published phytoestrogen food composition data (35). Values for the phytoestrogens included in the database were derived through GC-MS analysis of foods and presented on an as-is (wet) basis for all foods. All nutrients and lignan intakes were expressed as average daily intakes.

Daily mean intake of nutrients, total lignans, and the individual lignans, matairesinol, lariciresinol, pinoresinol, and secoisolariciresinol were expressed as continuous variables. To correct the non-normal distribution of lignan intake, we used a natural log transformation. Log-transformed lignan intakes were categorized into tertiles based on the distribution of the controls for analyses of associations with tumor characteristics. Values were back-transformed for presentation.

Statistical analyses. All statistical analyses were conducted using SAS 9.1 for Windows. All statistical tests were 2-sided and considered significant at $P < 0.05$. We decided a priori to stratify by menopausal status, because the literature supports that this factor may modify the odds of developing certain breast cancer tumor subtypes and other clinicopathologic characteristics. Furthermore, lignan intakes differed by menopausal status. Menopause was defined as self-reported cessation of menses either as natural menopause or hysterectomy with bilateral oophorectomy. Women younger than the median age category of natural menopause (50–54 y) in the study sample reporting hysterectomy with one or more intact ovaries were classified as premenopausal.

Differences in characteristics between cases and controls were assessed with standard descriptive statistics. OR and 95% CI for risk of each tumor characteristic compared to women without breast cancer were estimated with binary logistic regression for dichotomous outcomes or polytomous logistic regression for polychotomous outcomes adjusting for education, age at menarche, BMI, age, cigarette smoking status, alcohol intake, family history of breast cancer, parity and age at first birth (combined variable), history of diabetes, and total energy intake (included as a continuous covariate in the models). Models for postmenopausal women were further adjusted for age at menopause. Heterogeneity of OR was assessed with Wald chi-square. Several potential covariates were assessed for inclusion in the final adjusted models. The included covariates were those variables that changed the OR by at least 10%, had significant parameter estimates, or otherwise improved the fit and interpretation of the final estimates. The unadjusted OR were similar to the adjusted estimates; however, adjustment for these variables slightly strengthened the observed estimates as well as improved the fit of the models. In the interest of clarity and efficiency, we present only the adjusted models.

Results

Compared to controls, premenopausal women with breast cancer were less educated ($P < 0.05$), had lower age at menarche ($P < 0.05$), were more likely to report a history of diabetes ($P < 0.01$), less likely to report drinking alcohol ($P < 0.05$), and had lower intakes of total lignans ($P < 0.05$), lariciresinol ($P < 0.05$), and pinoresinol ($P < 0.01$) (**Table 1**). Premenopausal cases and controls did not differ in age, BMI, parity and age at first birth, family history of breast cancer, cigarette smoking, or mean intakes of secoisolariciresinol and matairesinol.

Among postmenopausal women, compared to controls, women with breast cancer were older ($P < 0.05$), less educated ($P < 0.01$), more likely to report a family history of breast cancer ($P < 0.05$), drink less alcohol ($P < 0.05$), more likely to report a history of diabetes ($P < 0.05$), and have lower intakes of total lignans ($P < 0.05$) and lariciresinol ($P < 0.05$). No differences were observed between postmenopausal cases and controls for age at menarche, parity and age at first birth, cigarette smoking, or intakes of secoisolariciresinol, matairesinol, and pinoresinol.

OR and 95% CI for associations between daily intakes of total and specific lignans with clinicopathologic characteristics compared to women without breast cancer were estimated (**Tables 2–4**). Women in the highest compared to lowest tertile of total lignan intakes had an ~40–50% lower odds of having breast cancer (Table 2). Similarly, higher total lignan intakes were associated with substantially reduced odds of having an invasive tumor, especially among premenopausal women [OR 0.48 (95% CI 0.26–0.86) and OR 0.70 (95% CI 0.47–1.06), pre- and postmenopausal women, respectively). Total lignan intakes were not associated with in situ breast cancer. The reductions in risk of breast cancer and invasive cancer were explained primarily by higher intakes of lariciresinol and pinoresinol in premenopausal women and of lariciresinol and matairesinol in postmenopausal women (Table 2).

For premenopausal women, we observed a borderline significant 50% reduction in the odds of having either a stage I or stage II breast cancer but no association with higher stages (Table 2). These associations were stronger for the specific

TABLE 1 Descriptive characteristics of selected women with breast cancer enrolled in the RPCI DBBR[1,2]

	Premenopausal		Postmenopausal	
Characteristics	Cases (n = 214)	Controls (n = 202)	Cases (n = 469)	Controls (n = 409)
Age, *y*	44.6 ± 5.9	44.4 ± 6.7	63.7 ± 9.7*	62.1 ± 9.4
BMI, *kg/m²*	26.7 ± 6.3	26.5 ± 5.4	28.5 ± 6.0	28.2 ± 6.2
Education, *n (%)*				
High school or less	43 (20)*	24 (12)	182 (39)†	109 (27)
Some college	80 (37)	64 (2)	158 (34)	150 (37)
College graduate	51 (234)	72 (36)	62 (13)	85 (21)
Advanced degree	40 (19)	42 (21)	67 (14)	65 (16)
Age at menarche, *n (%)*				
≤11 y	37 (17)*	35 (17)	97 (21)	84 (21)
12 y	76 (36)	49 (24)	150 (32)	120 (29)
13 y	60 (28)	61 (30)	129 (27)	127 (31)
≥14 y	41 (19)	57 (28)	93 (20)	78 (19)
Parity, age at first birth, *n (%)*				
>2, <30 y	44 (21)	42 (21)	202 (43)	143 (35)
1–2, <30 y or >2, ≥30 y	81 (38)	76 (38)	158 (34)	156 (38)
1–2, ≥30 y	39 (18)	36 (18)	35 (7)	34 (8)
Nulliparous	50 (23)	48 (24)	74 (16)	76 (19)
Family history of breast cancer, *n (%)*				
Yes	42 (20)	35 (17)	107 (23)*	69 (17)
No	172 (80)	167 (83)	362 (77)	340 (83)
Cigarette smoking status, *n (%)*				
Never	134 (63)	111 (55)	230 (49)	206 (50)
Former	55 (26)	65 (32)	193 (41)	170 (42)
Current	25 (12)	26 (13)	46 (10)	33 (8)
Alcohol intake, *n (%)*				
None	55 (26)*	39 (19)	136 (29)*	85 (21)
<1 drink/mo	38 (18)	24 (12)	88 (19)	67 (16)
1–3 drinks/mo	23 (11)	40 (20)	55 (12)	52 (13)
1–6 drinks/wk	75 (35)	68 (34)	118 (25)	139 (34)
≥1 drink/d	23 (11)	31 (15)	72 (15)	66 (16)
History of diabetes, *n (%)*				
Yes	13 (6)†	2 (1)	55 (12)*	28 (7)
No or unknown	201 (94)	200 (1)	414 (88)	381 (93)
Total lignans, *μg/d*	136 ± 78*	156 ± 84	157 ± 100*	173 ± 109
Lariciresinol	46 ± 34*	54 ± 33	52 ± 33*	58 ± 43
Secoisolariciresinol	57 ± 30	62 ± 33	67 ± 45	72 ± 48
Matairesinol	3 ± 2	4 ± 2	3 ± 2	4 ± 2
Pinoresinol	26 ± 21†	32 ± 24	32 ± 31	35 ± 31

[1] Values are mean ± SD for continuous variables and n (%) for categorical variables. Symbols indicate different from corresponding controls: *$P < 0.05$; †$P < 0.01$. DBBR, Databank and BioRepository; RPCI, Roswell Park Cancer Institute.
[2] Means were compared by Student's t test, proportions by Pearson's χ^2.

TABLE 2 OR (95% CI) for the associations between daily intakes of total and specific lignans with breast tumor characteristics in the RPCI DBBR[1,2]

		Tumor status		Stage			Grade		
Lignan intake, μg/d	Case status	In situ	Invasive	I	II	III/IV	1	2	3
Premenopausal women (n = 416)									
Total lignans									
<119	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
119–187	0.80 (0.49–1.31)	1.14 (0.50–2.62)	0.74 (0.44–1.25)	0.52 (0.26–1.02)	0.84 (0.42–1.69)	1.05 (0.37–2.99)	0.86 (0.14–5.27)	1.24 (0.53–2.87)	0.66 (0.37–1.18)
>187	0.51 (0.29–0.90)	0.71 (0.26–1.97)	0.48 (0.26–0.86)	0.51 (0.25–1.06)	0.46 (0.20–1.09)	0.43 (0.11–1.73)	0.97 (0.12–7.91)	0.60 (0.22–1.66)	0.43 (0.22–0.85)
Lariciresinol									
<38.6	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
38.6–61.5	0.63 (0.38–1.05)	0.65 (0.26–1.61)	0.63 (0.37–1.07)	0.45 (0.22–0.89)	0.66 (0.32–1.35)	1.49 (0.51–4.33)	0.39 (0.05–3.00)	0.72 (0.30–1.68)	0.67 (0.37–1.21)
>61.5	0.50 (0.29–0.87)	0.84 (0.34–2.07)	0.44 (0.25–0.80)	0.46 (0.23–0.94)	0.40 (0.17–0.92)	0.51 (0.13–2.08)	4.13 (0.45–38.23)	0.38 (0.14–1.04)	0.42 (0.22–0.83)
Secoisolariciresinol									
<47.5	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
47.5–74.8	0.83 (0.51–1.37)	1.36 (0.57–3.25)	0.74 (0.44–1.25)	0.65 (0.34–1.27)	0.47 (0.22–1.02)	1.61 (0.56–4.58)	0.90 (0.16–5.06)	0.97 (0.41–2.31)	0.69 (0.38–1.24)
>74.8	0.78 (0.44–1.38)	1.54 (0.56–4.23)	0.68 (0.37–1.23)	0.68 (0.32–1.44)	0.81 (0.36–1.81)	0.45 (0.10–2.07)	0.67 (0.09–5.22)	0.98 (0.37–2.60)	0.62 (0.31–1.23)
Matairesinol									
<2.6	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.6–4.4	0.95 (0.57–1.57)	1.93 (0.81–4.60)	0.81 (0.48–1.38)	0.79 (0.40–1.53)	0.74 (0.35–1.56)	1.43 (0.49–4.24)	0.79 (0.16–3.98)	0.85 (0.34–2.12)	0.76 (0.42–1.38)
>4.4	0.64 (0.36–1.14)	0.96 (0.33–2.78)	0.60 (0.33–1.09)	0.52 (0.24–1.13)	0.75 (0.33–1.73)	0.57 (0.16–2.06)	0.07 (0.01–1.08)	1.13 (0.42–3.03)	0.46 (0.23–0.92)
Pinoresinol									
<18.9	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
18.9–37.4	0.71 (0.43–1.17)	0.84 (0.37–1.93)	0.68 (0.40–1.15)	0.45 (0.23–0.91)	0.86 (0.42–1.76)	1.18 (0.41–3.40)	1.03 (0.18–5.87)	0.75 (0.32–1.77)	0.65 (0.36–1.18)
>37.4	0.47 (0.27–0.81)	0.46 (0.17–1.22)	0.47 (0.27–0.83)	0.48 (0.24–0.98)	0.42 (0.18–0.99)	0.51 (0.14–1.84)	1.24 (0.18–8.74)	0.53 (0.21–1.38)	0.48 (0.25–0.91)
Postmenopausal women (n = 878)									
Total lignans									
<119	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
119–187	0.77 (0.54–1.10)	0.80 (0.42–1.53)	0.77 (0.53–1.12)	0.84 (0.55–1.28)	0.79 (0.45–1.39)	0.22 (0.06–0.85)	0.86 (0.39–1.93)	0.94 (0.54–1.66)	0.72 (0.46–1.13)
>187	0.69 (0.47–1.02)	0.65 (0.32–1.32)	0.70 (0.47–1.06)	0.82 (0.52–1.30)	0.55 (0.29–1.05)	0.71 (0.23–2.16)	0.58 (0.22–1.51)	0.64 (0.34–1.22)	0.85 (0.53–1.36)
Lariciresinol									
<38.6	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
38.6–61.5	0.76 (0.54–1.08)	0.72 (0.38–1.36)	0.77 (0.54–1.12)	0.70 (0.46–1.07)	1.02 (0.59–1.76)	0.62 (0.21–1.82)	0.60 (0.27–1.34)	0.83 (0.48–1.44)	0.83 (0.54–1.28)
>61.5	0.72 (0.50–1.04)	0.67 (0.34–1.32)	0.73 (0.50–1.08)	0.79 (0.52–1.21)	0.64 (0.34–1.18)	0.83 (0.29–2.39)	0.42 (0.17–1.07)	0.75 (0.41–1.36)	0.86 (0.55–1.34)
Secoisolariciresinol									
<47.5	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
47.5–74.8	0.86 (0.60–1.23)	0.96 (0.49–1.87)	0.85 (0.58–1.23)	0.83 (0.54–1.26)	1.04 (0.59–1.83)	0.35 (0.11–1.19)	0.91 (0.40–2.05)	0.72 (0.41–1.26)	0.91 (0.58–1.40)
>74.8	0.91 (0.61–1.36)	1.08 (0.52–2.25)	0.88 (0.58–1.34)	0.89 (0.56–1.43)	0.86 (0.44–1.66)	1.52 (0.45–5.17)	0.81 (0.31–2.13)	0.67 (0.35–1.27)	1.05 (0.64–1.71)
Matairesinol									
<2.6	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2.6–4.4	0.70 (0.49–0.99)	0.94 (0.51–1.73)	0.65 (0.45–0.94)	0.54 (0.36–0.81)	0.98 (0.56–1.72)	0.85 (0.33–2.21)	0.73 (0.33–1.59)	0.73 (0.42–1.25)	0.61 (0.39–0.94)
>4.4	0.57 (0.38–0.84)	0.54 (0.25–1.15)	0.57 (0.38–0.87)	0.55 (0.35–0.86)	0.79 (0.41–1.49)	0.35 (0.09–1.33)	0.42 (0.16–1.09)	0.48 (0.25–0.92)	0.73 (0.45–1.17)
Pinoresinol									
<18.9	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
18.9–37.4	0.88 (0.62–1.25)	1.08 (0.58–1.99)	0.84 (0.58–1.22)	0.87 (0.58–1.31)	0.83 (0.47–1.47)	0.66 (0.24–1.79)	0.87 (0.40–1.89)	0.98 (0.57–1.70)	0.79 (0.51–1.22)
>37.4	0.77 (0.53–1.11)	0.62 (0.30–1.25)	0.80 (0.55–1.17)	0.83 (0.54–1.27)	0.89 (0.50–1.60)	0.48 (0.16–1.47)	0.51 (0.20–1.29)	0.69 (0.38–1.25)	1.03 (0.66–1.60)

[1] Values are OR and 95% CI for risk of each tumor characteristic compared to women without breast cancer estimated with logistic regression adjusting for education, age at menarche, BMI, age, cigarette smoking status, alcohol intake, family history of breast cancer, parity and age at first birth (combined variable), history of diabetes, and total energy intake. Models for postmenopausal women further adjusted for age at menopause. DBBR, Databank and BioRepository; RPCI, Roswell Park Cancer Institute.

[2] All analyses except in situ vs. invasive cancer were limited to those women with invasive cancer. In analyses for each tumor characteristic, cases were limited to women with known values for that characteristic.

lignans lariciresinol and pinoresinol. Lignan intakes were not clearly associated with stage among postmenopausal women, except for a significant 50% reduction in risk of Stage I cancers for postmenopausal women with high intakes of matairesinol. Higher total lignan intakes and matairesinol intakes were associated with lower risk of grade 3 tumors, primarily among premenopausal women.

We further investigated associations between lignan intakes and individual receptor status (Table 3). Higher total lignan intakes were strongly inversely associated with risk of ER^- breast cancer among premenopausal women [OR 0.16 (95% CI 0.03–0.44)] independent of the specific lignan, but were inversely related to ER^+ breast cancer among postmenopausal women [OR 0.64 (95% CI 0.42–1.00)] predominantly related to lariciresinol and matairesinol. We observed similar associations for PR status (Table 3). Higher intakes of total lignans were associated with both negative and positive HER2 status in premenopausal women, although the estimates were much stronger for $HER2^+$

TABLE 3 OR (95% CI) for the associations between daily intake of total and specific lignans and breast tumor receptor status in the RPCI DBBR[1,2]

	Estrogen receptor status		PR status		HER2 *neu* status	
Lignan intake, μg/d	Negative	Positive	Negative	Positive	Negative	Positive
Premenopausal women (n = 416)						
Total lignans						
<119	1.00†	1.00	1.00†	1.00	1.00	1.00
119–187	0.32 (0.12–0.84)	0.92 (0.53–1.60)	0.41 (0.18–0.95)	0.92 (0.52–1.62)	0.72 (0.41–1.26)	0.81 (0.32–2.06)
>187	0.12 (0.03–0.44)	0.71 (0.38–1.33)	0.19 (0.07–0.57)	0.70 (0.37–1.32)	0.56 (0.30–1.05)	0.21 (0.05–0.87)
Lariciresinol						
<38.6	1.00†	1.00	1.00†	1.00	1.00	1.00
38.6–61.5	0.24 (0.09–0.68)	0.83 (0.47–1.47)	0.27 (0.11–0.67)	0.88 (0.49–1.57)	0.64 (0.37–1.14)	0.61 (0.22–1.70)
>61.5	0.13 (0.04–0.44)	0.65 (0.35–1.20)	0.16 (0.05–0.47)	0.68 (0.36–1.28)	0.46 (0.25–0.87)	0.45 (0.14–1.42)
Secoisolariciresinol						
<47.5	1.00	1.00	1.00	1.00	1.00	1.00
47.5–74.8	0.41 (0.16–1.03)	0.84 (0.47–1.48)	0.52 (0.23–1.18)	0.82 (0.46–1.47)	0.73 (0.41–1.29)	0.79 (0.31–2.03)
>74.8	0.25 (0.07–0.88)	0.89 (0.47–1.69)	0.34 (0.12–0.98)	0.89 (0.47–1.71)	0.77 (0.41–1.46)	0.39 (0.09–1.61)
Matairesinol						
<2.6	1.00	1.00	1.00	1.00	1.00	1.00
2.6–4.4	0.80 (0.32–1.99)	0.80 (0.45–1.41)	0.87 (0.38–2.00)	0.78 (0.44–1.39)	0.90 (0.51–1.58)	0.53 (0.18–1.54)
>4.4	0.53 (0.18–1.55)	0.57 (0.29–1.09)	0.68 (0.26–1.77)	0.52 (0.27–1.01)	0.57 (0.30–1.10)	0.48 (0.15–1.52)
Pinoresinol						
<18.9	1.00†	1.00	1.00†	1.00	1.00	1.00
18.9–37.4	0.08 (0.02–0.36)	1.01 (0.57–1.76)	0.15 (0.05–0.47)	1.02 (0.58–1.79)	0.69 (0.39–1.21)	0.57 (0.20–1.62)
>37.4	0.24 (0.09–0.67)	0.62 (0.33–1.16)	0.36 (0.15–0.85)	0.58 (0.31–1.10)	0.46 (0.25–0.86)	0.63 (0.22–1.81)
Postmenopausal women (n = 878)						
Total lignans						
<119	1.00	1.00	1.00	1.00	1.00	1.00
119–187	0.89 (0.44–1.82)	0.76 (0.51–1.12)	0.95 (0.55–1.63)	0.71 (0.47–1.08)	0.80 (0.54–1.19)	0.68 (0.31–1.48)
>187	1.28 (0.63–2.60)	0.64 (0.42–1.00)	1.02 (0.57–1.82)	0.63 (0.40–1.00)	0.78 (0.51–1.19)	0.54 (0.23–1.26)
Lariciresinol						
<38.6	1.00	1.00	1.00	1.00	1.00	1.00
38.6–61.5	0.79 (0.39–1.59)	0.81 (0.55–1.19)	1.07 (0.63–1.82)	0.70 (0.46–1.06)	0.79 (0.54–1.16)	0.91 (0.43–1.91)
>61.5	1.24 (0.63–2.43)	0.68 (0.45–1.02)	1.06 (0.61–1.83)	0.66 (0.42–1.01)	0.80 (0.53–1.20)	0.56 (0.24–1.30)
Secoisolariciresinol						
<47.5	1.00	1.00	1.00	1.00	1.00	1.00
47.5–74.8	1.17 (0.58–2.37)	0.80 (0.54–1.19)	1.05 (0.61–1.79)	0.78 (0.51–1.18)	0.83 (0.56–1.24)	0.99 (0.47–2.13)
>74.8	1.60 (0.74–3.45)	0.80 (0.51–1.26)	1.10 (0.60–2.01)	0.84 (0.52–1.35)	0.95 (0.61–1.48)	0.69 (0.28–1.70)
Matairesinol						
<2.6	1.00	1.00	1.00	1.00	1.00	1.00
2.6–4.4	0.69 (0.34–1.38)	0.66 (0.45–0.98)	0.63 (0.37–1.09)	0.69 (0.46–1.03)	0.68 (0.46–1.00)	0.63 (0.30–1.34)
>4.4	0.82 (0.40–1.68)	0.55 (0.35–0.85)	0.85 (0.49–1.50)	0.49 (0.31–0.79)	0.66 (0.43–1.02)	0.36 (0.14–0.89)
Pinoresinol						
<18.9	1.00	1.00	1.00	1.00	1.00	1.00
18.9–37.4	1.05 (0.53–2.11)	0.84 (0.57–1.25)	1.12 (0.65–1.91)	0.79 (0.53–1.19)	0.85 (0.58–1.26)	1.10 (0.52–2.30)
>37.4	1.42 (0.72–2.79)	0.73 (0.48–1.10)	1.26 (0.73–2.17)	0.68 (0.44–1.04)	0.90 (0.60–1.34)	0.60 (0.26–1.39)

[1] Values are OR and 95% CI for risk of each tumor characteristic compared to women without breast cancer estimated with logistic regression adjusting for education, age at menarche, BMI, age, cigarette smoking status, alcohol intake, family history of breast cancer, parity and age at first birth (combined variable), history of diabetes, and total energy intake. Models for postmenopausal women further adjusted for age at menopause. †P-heterogeneity < 0.05. DBBR, Databank and Biorepository; HER2, human epidermal growth factor receptor 2; RPCI, Roswell Park Cancer Institute.

[2] All analyses except in situ vs. invasive cancer were limited to those women with invasive cancer. In analyses for each tumor characteristic, cases were limited to women with known values for that characteristic.

[OR 0.21 (95% CI 0.05–0.87)] than for HER2$^-$ [OR 0.56 (95% CI 0.30–1.05)]. Total lignan intakes and HER2 status in postmenopausal women were not associated, but women with higher intakes of matairesinol had lower risks of HER2$^+$ tumors [OR 0.36 (95% CI 0.14–0.89)].

Finally, we examined associations between dietary lignan intakes and breast tumor subtype (Table 4). Among premenopausal women, we observed no associations between lignan intakes and luminal A, luminal B, or HER2 array tumors. However, women in the highest compared to the lowest tertile of total lignan intake had greatly reduced odds of having triple negative tumors [ER$^-$, PR$-$, HER2$^-$; OR 0.16 (95% CI 0.04–0.62)]. The reduction in risk of premenopausal triple negative breast cancer appeared to be primarily expressed for lariciresinol and pinoresinol. Contrary to the findings observed in premenopausal women, lignan intakes were not associated with triple negative tumors in postmenopausal women. Furthermore, no associations were observed for luminal B or HER2 array tumors, although we

TABLE 4 OR (95% CI) for the associations between daily intake of total and specific lignans and breast tumor subtype in the RPCI DBBR[1,2]

Lignan intake, μg/d	Luminal A	Luminal B	HER2 array	Triple negative
Premenopausal women (n = 416)				
Total lignans				
<119	1.00[†]	1.00	1.00	1.00
119–187	0.95 (0.52–1.71)	0.67 (0.23–1.94)	NA	0.20 (0.06–0.69)
>187	0.75 (0.38–1.48)	0.33 (0.08–1.47)	NA	0.16 (0.04–0.62)
Lariciresinol				
<38.6	1.00[†]	1.00	1.00	1.00
38.6–61.5	0.89 (0.49–1.63)	0.52 (0.16–1.77)	NA	0.09 (0.02–0.45)
>61.5	0.61 (0.31–1.19)	0.67 (0.20–2.27)	NA	0.17 (0.05–0.61)
Secoisolariciresinol				
<47.5	1.00	1.00	1.00	1.00
47.5–74.8	0.86 (0.47–1.58)	0.59 (0.19–1.78)	NA	0.28 (0.09–0.87)
>74.8	0.94 (0.48–1.87)	0.53 (0.12–2.30)	NA	0.32 (0.09–1.16)
Matairesinol				
<2.6	1.00	1.00	1.00	1.00
2.6–4.4	0.95 (0.52–1.74)	0.40 (0.11–1.50)	NA	0.69 (0.24–2.02)
>4.4	0.57 (0.28–1.15)	0.84 (0.23–3.03)	NA	0.69 (0.20–2.33)
Pinoresinol				
<18.9	1.00	1.00	1.00	1.00
18.9–37.4	1.04 (0.57–1.87)	0.77 (0.25–2.39)	NA	NA
>37.4	0.57 (0.29–1.12)	0.75 (0.22–2.54)	0.18 (0.01–6.83)	0.21 (0.06–0.69)
Postmenopausal women (n = 878)				
Total lignans				
<119	1.00	1.00	1.00	1.00
119–187	0.78 (0.52–1.18)	0.64 (0.23–1.76)	0.66 (0.20–2.15)	0.91 (0.38–2.17)
>187	0.66 (0.42–1.04)	0.59 (0.20–1.72)	0.44 (0.11–1.71)	1.68 (0.73–3.87)
Lariciresinol				
<38.6	1.00	1.00	1.00	1.00
38.6–61.5	0.80 (0.54–1.20)	0.91 (0.36–2.32)	0.92 (0.29–2.91)	0.71 (0.30–1.66)
>61.5	0.71 (0.46–1.09)	0.60 (0.20–1.75)	0.51 (0.14–1.94)	1.43 (0.66–3.10)
Secoisolariciresinol				
<47.5	1.00	1.00	1.00	1.00
47.5–74.8	0.75 (0.50–1.14)	1.32 (0.49–3.55)	0.59 (0.18–1.95)	1.49 (0.62–3.57)
>74.8	0.80 (0.50–1.29)	0.84 (0.26–2.68)	0.51 (0.13–1.98)	2.45 (0.96–6.27)
Matairesinol				
<2.6	1.00	1.00	1.00	1.00
2.6–4.4	0.68 (0.46–1.02)	0.63 (0.24–1.61)	0.64 (0.19–2.14)	0.68 (0.29–1.59)
>4.4	0.58 (0.37–0.92)	0.39 (0.12–1.23)	0.36 (0.09–1.46)	1.11 (0.48–2.56)
Pinoresinol				
<18.9	1.00	1.00	1.00	1.00
18.9–37.4	0.81 (0.54–1.21)	1.26 (0.50–3.19)	0.86 (0.26–2.85)	1.19 (0.51–2.78)
>37.4	0.78 (0.51–1.19)	0.49 (0.16–1.46)	0.79 (0.23–2.68)	1.91 (0.86–4.28)

[1] Values are OR and 95% CI for risk of each tumor characteristic compared to women without breast cancer estimated with logistic regression adjusting for education, age at menarche, BMI, age, cigarette smoking status, alcohol intake, family history of breast cancer, parity and age at first birth (combined variable), history of diabetes, and total energy intake. Models for postmenopausal women further adjusted for age at menopause. [†]P-heterogeneity < 0.05. DBBR, Databank and Biorepository; HER2, human epidermal growth factor receptor 2; RPCI, Roswell Park Cancer Institute.

[2] All analyses except in situ vs. invasive cancer were limited to those women with invasive cancer. In analyses for each tumor characteristic, cases were limited to women with known values for that characteristic.

did observe a weak, nonsignificant inverse association with luminal A tumors for total lignans and lariciresinol [OR 0.66 (95% CI 0.42–1.04) and OR 0.71 (95% CI 0.46–1.09), respectively] and an ~40% reduction in risk of luminal A tumors associated with matairesinol intakes [OR 0.58 (95% CI 0.37–0.92)].

Discussion

In this case-control study of lignans and breast cancer, we found that relatively higher lignan intakes were associated with lower odds of having any breast cancer, having an invasive breast cancer, and having a locally advanced breast cancer. These associations did not translate into higher risks of tumor characteristics with less favorable prognosis; rather, we observed no associations between lignan intakes and later stage or grade. As we previously reported in a separate study (26), we observed an inverse association between lignan intakes and likelihood of negative ER status, particularly triple negative tumors. We also observed inverse associations between lignan intakes and odds of HER2$^+$ tumors. Although previous studies have investigated

associations between lignan intakes and ER status, to our knowledge, this is the first study to provide a comprehensive examination of lignan intakes and breast tumor predictive and prognostic characteristics. Overall, our data support that women with breast cancer who had higher lignan intakes were more likely to have tumors with more favorable prognostic factors; therefore, lignans may be an important component of a diet with chemoprevention potential.

Lignans have been most widely studied for their hormonal activities, and early research presumed that the primary mode of action was through competitive inhibition of the ER (36). Therefore, higher lignan intakes might be expected to be more strongly associated with ER^+ breast cancer. On the contrary, similar to our previous study and that of Olsen (24,37), higher lignan intakes were associated with reduced risks of ER^- breast cancer in these data, especially among premenopausal women. Additionally, we observed lower risks of triple negative cancers in premenopausal women with higher lignan intakes. The mechanism for an inverse association with ER^- breast cancer is unclear but may be partly a result of an inhibition of ER^+ tumors losing sensitivity to estrogen and progressing to an ER^- state. Furthermore, because the inverse associations with ER^- and triple negative cancers were observed primarily in premenopausal women, it may be that the phytoestrogen action of lignans is overwhelmed in an estrogen-rich environment.

To our knowledge, our study is the first to examine associations between lignan intakes and HER2 receptor status in breast cancer. Our findings for HER2 are somewhat equivocal, because higher lignan intakes were inversely associated with the likelihood of both $HER2^+$ and $HER2^-$ tumors, although the inverse association was much stronger for $HER2^+$ and the reduced odds for $HER2^-$ were not significant. Finally, although we were able to examine breast tumor subtype, the only notable associations were with triple negative breast tumors.

Beyond their potential as hormone modulators, lignans possess a number of activities that could affect cancer cell growth and differentiation. Experimentally, lignans have been shown to inhibit breast cancer proliferation and metastasis in rodent models (17,18,38) as well as in human studies, as evidenced by decreases in Ki-67 and increases in apoptosis measured by TUNEL (30). Although we observed reduced odds of invasive, lower stage tumors associated with higher lignan intakes, we did not observe associations with more advanced tumors, suggesting that lignans may inhibit promotion of tumors to more aggressive states.

Our study was unique in our inclusion of data for individual lignans. Foods contributing most highly to matairesinol intakes were onions, oranges, salty snacks, peaches, and coffee ($R^2 > 0.90$) and those contributing most highly to lariciresinol were broccoli, winter squash, berries, apricots, and coffee ($R^2 > 0.90$). It is not surprising that secoisolariciresinol intakes were relatively low, because we did not query flaxseed, and this is the predominant lignan in that food. Interestingly, overall lignan intakes were low in our sample compared to previous reports (22,35). Although we used a comprehensive database to calculate lignan intakes, diet was assessed with an FFQ. It is possible that our FFQ did not contain specific foods contributing highly to lignan intakes and, particularly, we did not ask about flaxseed use or tea. On the other hand, in this study, the primary sources ($R^2 > 0.90$) of lignan intakes were apricots, broccoli, berries, coffee, and red wine, similar to our previous investigations (22,25), increasing our confidence that we were capturing sources of lignans important in the western New York region.

Our study has some limitations. In addition to the potential underestimation of lignan intakes by the FFQ, the case-control study design may be susceptible to several types of bias. Lignans are phytochemicals calculated from foods and as such may be over- or underestimated if the major food sources are not commonly known. Given that we did not query flaxseed, a major lignan source, this is a limitation for our study. However, ~99% of the lignans in flaxseed is secoisolariciresinol (35) and the addition of flaxseed to the FFQ would be less likely to affect the relationships with lariciresinol, matairesinol, and pinoresinol and may even further strengthen the associations already observed with secoisolariciresinol. Our FFQ also did not query tea or rye bread. These foods are important sources of lignans in European populations, but less so in western New York. Omission of these two foods is more likely to result in an underestimation of intake rather than to affect the ranking of intake.

Case-control studies may also be susceptible to recall bias if the cases are more likely than controls to "remember" an exposure. This source of bias is less likely with data from the DBBR, because the questionnaire is administered in the same manner to all participants independently of a study question. Another potential limitation is that all cases were patients obtaining treatment at RPCI and controls were recruited from nonrelated friends and family of RPCI patients; therefore, our results may not be generalizable to women with in the general population. Finally, there was a slight difference in recruitment period between cases and controls. The data utilized herein are part of an NIH-funded project that includes an aim involving immunohistochemistry of banked tumor tissue; therefore, we had to define a time period from which we were going to include cases (and obtain tumor tissue). Controls were selected later and from the entire pool of potential controls. There is only a 2-y difference between the end of inclusion for cases compared to controls and it is unlikely that dietary exposures would differ greatly over those 2 y.

On the other hand, our study has several strengths. Although it is true that sample size is limited for some of the analyses, we have extensive dietary and clinical data on a large sample of women with breast cancer and controls and we were able to investigate multiple breast cancer characteristics that are of prognostic value. The small sample sizes for some of the less common tumor characteristics may have reduced our ability to detect associations with lignan intakes; however, we were still able to identify associations with several tumor characteristics previously reported in the literature.

Furthermore, we had information on specific lignans that may be important in determining mechanisms related to lignan intakes. Evidence is accumulating that the effect of an exposure such as diet may depend upon individual characteristics of the outcome in question. Breast cancer is a heterogeneous disease and the tumor characteristics examined herein have been utilized as both prognostic and predictive factors. For example, ER^- status is considered to have poorer prognosis because of fewer treatment options and rates of ER^- breast cancer are higher among younger women (44.1% ages 30–34 y vs. 14.9% ages 80–84 y) (39). Similarly, rates of triple negative cancers are relatively low, yet this subtype has poor prognosis due to the lack of efficacious treatments. Therefore, the identification of modifiable lifestyle factors that could potentially reduce the occurrence of these less favorable tumor types could have considerable impact on the burden of the disease.

In summary, in this case-control study of dietary lignan intakes and breast cancer, we found that higher lignan intakes were associated with lower risks of breast cancer with more favorable prognostic characteristics. Future investigations are warranted to explore the strong associations observed with $ER-$ cancer in premenopausal women.

Acknowledgments

S.E.M. designed and conducted the study, provided direction for statistical analyses, drafted the final manuscript, and had primary responsibility for final content; K.C.H. analyzed data and contributed to manuscript preparation; A.M.W. analyzed data and reviewed final draft; L.U.T. contributed to drafting final manuscript; C.M. and H.H. provided pathologic data and input on interpretation of pathologic data; S.B.E. provided oversight of the RPCI breast cancer clinical database; and C.B.A., P.J.H., and S.A.K. contributed to drafting final manuscript. All authors have read and approved the final manuscript.

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