Postdiagnosis Isoflavone and Lignan Intake in Newly Diagnosed Breast Cancer Patients: Cross-Sectional Survey Shows Considerable Intake from Previously Unassessed High-Lignan Foods

Beatrice A Boucher,1,2 Susitha Wanigaratne,4 Shelley A Harris,1,3 and Michelle Cotterchio1,3

1Prevention and Cancer Control, Cancer Care Ontario, Toronto, ON, Canada; 2Department of Nutritional Sciences, Faculty of Medicine, and 3 Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada; and 4 Centre for Urban Health Solutions, St Michael’s Hospital, Toronto, ON, Canada

Abstract

Background: Isoflavones and lignans (phytoestrogens) are dietary components with potential anticarcinogenic effects. Although the intake of isoflavones and lignans may affect breast cancer treatment and prognosis—and associations may differ by menopausal status—postdiagnosis intake data are limited.

Objective: We aimed to describe postdiagnosis isoflavone and lignan intake in newly diagnosed breast cancer patients, examine differences by menopausal status and phytoestrogen type, and inform the assessment of diet and survival in future prognostic studies.

Methods: Our cross-sectional study included 278 women aged 25–74 y, diagnosed with pathologically confirmed breast cancer in April–May 2010 and identified using the Ontario Cancer Registry. Intake in the previous 2 mo was assessed using questionnaires listing 17 soy and 3 high-lignan foods (flaxseed, flaxseed bread, sesame seeds), completed 71 d after breast cancer diagnosis, on average. Food consumption by menopausal status was examined. Geometric mean and median phytoestrogen intakes were estimated among all patients and in consumers only; differences by menopausal status and phytoestrogen type were assessed.

Results: Among all patients, foods were similarly consumed by menopausal status and isoflavone intakes were low (median: 56 µg/d). Consumers (n = 219) had higher intakes (median isoflavones: 1808 µg/d; 7% of isoflavone and 21% of lignan consumers had intakes ≥10 mg/d. Intakes were higher in premenopausal than in postmenopausal consumers, particularly for lignans, but were not significantly different (median lignans: 4375 compared with 1863 µg/d; P = 0.07). Lignans were significantly higher than isoflavones among most consumers (postmenopausal means: 746 compared with 100 µg/d; P < 0.0001).

Conclusions: Postdiagnosis lignan intakes from 3 high-content foods may be considerable among newly diagnosed breast cancer patients, yet they have been unassessed in previous prognostic studies. The inclusion of these foods in dietary assessment methods may improve future intake estimates and the distributions on which breast cancer survival analyses are based. Curr Dev Nutr 2018;2:nzx009.

Introduction

Breast cancer is the leading cancer diagnosis among Canadian women and a major cause of cancer death, particularly in those <40 y of age (1) in whom breast cancer is typically more aggressive than in older women (2, 3). Thus, identifying factors that reduce recurrence and increase survival in both pre- and postmenopausal breast cancer patients is an important public health goal.
There has been increasing interest in the role of diet in breast cancer recurrence and mortality, including for phytoestrogens (4)—dietary components with estrogen-like structures that exert potential anticarcinogenic effects through estrogen-receptor mediated and other activities (5, 6). Phytoestrogens are found in plant-based foods, notably as isoflavones in soy foods, and as lignans in diverse foods, but especially flax and sesame seeds (7). Soy foods and isoflavones are consumed in Western populations but usually at much lower levels than in Asia where soy foods have long been staples (8). Lignans are important phytoestrogens in Western diets, especially when isoflavone intakes are low (8, 9), and flaxseed in particular has been identified as a key contributor in some groups (9, 10).

There are limited data on isoflavone and lignan intake among breast cancer patients, especially regarding postdiagnosis diet, when dietary interactions with treatment may influence cancer prognosis (11). Both isoflavones and lignans may alter the effectiveness of hormonal breast cancer treatment, in which beneficial as well as antagonistic effects have been reported experimentally (12–14). However, of 3 population-based breast cancer survival studies examining both isoflavones and lignans, none assessed postdiagnosis intake (15–17). Additionally, few studies have evaluated intake among breast cancer patients by menopausal status, although differences in intake within the context of menopausal status and its hormonal milieu may ultimately relate to prognosis (15, 18, 19). In this light, a meta-analysis of 5 prospective studies examining isoflavone intake found an association with reduced mortality for both pre- and postmenopausal breast cancer patients and reduced recurrence only among those who were postmenopausal (20). For lignans, a meta-analysis of 5 observational studies reported reduced mortality among postmenopausal patients only (21).

We previously published cross-sectional findings on the consumption of phytoestrogen foods among newly diagnosed breast cancer patients but did not quantify phytoestrogen intake per se, nor did we report intake by menopausal status (22). Given possible treatment and prognostic effects and the limited data on postdiagnosis intake, the current study aimed to describe isoflavone and lignan intake in these patients and examine consumption differences by menopausal status and phytoestrogen type. Findings will contribute to an understanding of postdiagnosis intake in newly diagnosed breast cancer patients and inform the development of dietary assessment methods and analyses in future prognostic studies.

Methods

Details related to patient recruitment and data collection are described elsewhere (22). In brief, the study was conducted using the Ontario Cancer Registry (OCR) to identify women diagnosed with pathologically confirmed invasive breast cancer in April and May of 2010 and who were 25–74 y of age at the time of diagnosis. Cancer Care Ontario (where OCR is housed) mailed letters to 462 eligible breast cancer patients and requested notification if they wanted to opt out and not be contacted by study staff. After 1 mo, patients who did not opt out (n = 417; 90%) were mailed a study questionnaire, which 278 patients completed 71 d after diagnosis on average (67% response rate). Ethics approval was obtained from the Health Sciences Research Ethics Board at the University of Toronto. All participants who completed questionnaires were considered to have implied consent.

Deriving Daily Phytoestrogen Intakes from Foods

The mailed self-administered questionnaire collected information on the consumption of specific isoflavone and lignan foods in the last 2 mo, as well as sociodemographic and health-related characteristics. Twenty foods were listed, including 17 soy or soy-containing foods as isoflavone sources (e.g., tofu, protein bar) and 3 foods containing high amounts of lignans (flaxseed, flaxseed bread, sesame seeds). Intake of each food was queried using assigned serving sizes and 5 frequency response options (never, <1 time/wk, 1–2 times/wk, 3–6 times/wk, ≥1 time/d). Derivation of isoflavone and lignan intake (micrograms per day) involved 3 steps. First, the frequency responses and assigned servings were used to estimate servings per day based primarily on frequency midpoints. As an example, consuming 1 serving ≤1 time/wk was estimated as 0.5 servings in 7 d, or 0.07 servings/d. Serving frequencies thus ranged from 0.07 to 1 serving/d. Second, for each respondent, the daily serving frequency of each reported food was multiplied by the phytoestrogen content per serving (micrograms) to estimate daily phytoestrogen intake per food. Phytoestrogen contents were primarily based on those reported for isoflavones (genistein, daidzein, formononetin, glycitein) and lignans (secoisolariciresinol, pinoresinol, lariciresinol, matairesinol) by Thompson et al. (7). Finally, phytoestrogen intakes per day (isoflavones and lignans, individually and total) were estimated by summing daily intakes per food across all foods per respondent, and combined for group estimates. Intake estimates were reported for all patients and among consumers only (i.e., with nonconsumers removed).

Statistical Analysis

Descriptive statistics were used to estimate consumption prevalence and associated 95% CIs of individual and groups of soy and high-lignan foods among pre- and postmenopausal patients. The Pearson χ² test was used to identify significant food consumption differences between pre- and postmenopausal patients.

Daily phytoestrogen intakes (isoflavones, lignans, total phytoestrogens) were estimated among patients and consumers (i.e., nonconsumers removed) using median values and IQRs, as well as geometric means and 95% CIs. Intake distributions were natural log-transformed to approximate normal, from which the means and 95% CIs were estimated and then transformed back to the original scale to report geometric means and accompanying 95% CIs throughout.

To determine whether there was a significant difference between total isoflavone and lignan intakes among consumers, paired tests were conducted (Wilcoxon’s Signed Rank test for median difference and paired t test for mean difference using natural log-transformed data). Testing for significant differences between pre- and postmenopausal consumers for median and mean intakes was conducted using the Wilcoxon–Mann–Whitney test and independent t test (using natural log-transformed data), respectively. Significant differences were defined as those with P values < 0.05. All data were analyzed using SAS version 9.2 (SAS Institute, Cary, NC).
TABLE 1 Prevalence (%) and 95% CIs of soy and high-lignan foods ever consumed in previous 2 mo among newly diagnosed breast cancer patients by menopausal status (n = 278) 1

| Foods consumed in previous 2 mo 2 | Premenopausal patients (n = 65) | Postmenopausal patients (n = 213) | P value 3 |
|----------------------------------|---------------------------------|-----------------------------------|-----------|
|                                  | n                  | % (95% CI) | n                  | % (95% CI) |          |
| Soy foods                        |                    |           |                    |           |          |
| Any soy food                     | 40                 | 62 (49, 73) | 111                | 52 (45, 59) | 0.18     |
| Any tofu, soybeans, soy milk, soy nuts | 30                 | 46 (34, 59) | 75                 | 35 (29, 42) | 0.11     |
| Tofu or bean curd                | 14                 | 23 (13, 35) | 45                 | 22 (16, 28) | 0.87     |
| Soy or tamari sauce              | 9                  | 15 (7, 26) | 47                 | 23 (17, 29) | 0.17     |
| Soybeans                         | 17                 | 27 (17, 40) | 37                 | 18 (13, 24) | 0.10     |
| Soy milk                         | 16                 | 26 (16, 39) | 35                 | 17 (12, 23) | 0.11     |
| Black bean sauce                | 15                 | 24 (14, 37) | 34                 | 16 (12, 22) | 0.16     |
| Soy burger, soy meat-substitutes | 9                  | 15 (7, 26) | 25                 | 12 (8, 17) | 0.60     |
| Miso soup                        | 10                 | 16 (8, 28) | 21                 | 10 (6, 15) | 0.19     |
| Soy nuts, roasted soybeans       | 11                 | 18 (9, 30) | 18                 | 9 (5, 13) | 0.04     |
| Soy bean sprouts                 | 9                  | 15 (7, 26) | 20                 | 10 (6, 14) | 0.27     |
| Energy or protein bars           | 10                 | 16 (8, 28) | 17                 | 8 (5, 13) | 0.07     |
| High-lignan foods                |                    |           |                    |           |          |
| Any high-lignan food             | 42                 | 65 (52, 76) | 146               | 69 (62, 75) | 0.55     |
| Bread (flaxseed, multigrain with flaxseed) | 32                 | 52 (39, 65) | 109                | 52 (45, 59) | 0.91     |
| Sesame seeds, sesame butter, or tahini | 20                 | 32 (21, 45) | 74                 | 36 (29, 42) | 0.63     |
| Flaxseed                         | 25                 | 40 (28, 54) | 63                 | 30 (24, 37) | 0.14     |

1 Patients reported consuming various foods from <1 time/wk to ≥1 time/d.
2 Includes foods consumed by ≥10% of pre- or postmenopausal patients; other soy foods on questionnaire (soy yogurt, frozen soy yogurt, soy ice cream; bacon bits from soy or textured vegetable protein; miso paste (not as soup); soy protein powder; tempeh; soy cheese) were consumed by <10% of both pre- and postmenopausal patients.
3 P value based on Pearson χ 2 test.

Results

As previously described, most breast cancer patients in this study were Caucasian (7% were East-Asian), 77% were postmenopausal, and the mean age was 56 y; approximately half of the participants were overweight or obese, never smoked, or had completed postsecondary education (22).

There was no significant difference by menopausal status in the overall proportion of patients ever consuming soy foods [premenopausal: 62% (95% CI: 49, 73%) compared with postmenopausal: 52% (95% CI: 45, 59%); P = 0.18] or high-lignan foods [premenopausal: 65% (95% CI: 52, 76%) compared with postmenopausal: 69% (95% CI: 62, 75%); P = 0.55] in the previous 2 mo (reported intake frequencies ranged from <1 time/wk to ≥1 time/d) (Table 1). However, a significantly higher proportion of premenopausal patients consumed soy nuts (18% compared with 9% postmenopausal, P = 0.04).

Among all patients (n = 278), median and mean total phytoestrogen intakes were 2011.7 µg/d (IQR: 190–8568 µg/d) and 561.3 µg/d (95% CI: 366, 860 µg/d), respectively (Table 2). Patients consumed a median of 56 µg/d (IQR: 0–2049 µg/d) and mean of 44 µg/d (95% CI: 28, 68 µg/d) of isoflavones (genistein was the largest contributor) and a median of 394 µg/d (IQR: 0–3463 µg/d) and mean of 170 µg/d (95% CI: 108, 267 µg/d) of lignans (secoisolariciresinol was the largest contributor).

Intakes were much higher among phytoestrogen consumers (n = 219) (Table 3) than among all patients reported in Table 2. For example, median isoflavone intake was 1808 µg/d (IQR: 517–5288 µg/d) among consumers with 56 µg/d (IQR: 0–2049 µg/d) already reported for all patients. High intakes (≥10,000 µg/d) were observed in 7% (11/151) of isoflavone consumers, 21% (39/188) of lignan consumers, and 26% (56/219) of total phytoestrogen consumers. Although all phytoestrogen intakes were higher in premenopausal than in postmenopausal consumers, and noticeably so for lignans, differences were not statistically significant. As an example, median lignin intake in premenopausal consumers was 4375 µg/d (IQR: 611–10,990 µg/d) compared with postmenopausal consumers at 1863 µg/d (IQR: 394–3654 µg/d) (P = 0.07). All consumers and postmenopausal consumers had significantly higher lignin than isoflavone intakes (e.g., postmenopausal means 746 compared with 100 µg/d, respectively; P < 0.0001), although differences were not significant for premenopausal consumers (Table 4).

TABLE 2 Median [IQR] and geometric mean (95% CI) intakes of total and individual phytoestrogens among newly diagnosed breast cancer patients (n = 278)

| Total phytoestrogens | Median [IQR] 1 | Geometric mean (95% CI) µg/d |
|----------------------|---------------|----------------------------|
| Total isoflavones    | 2011.7 [190.3–8568.3] | 561.3 (366.4, 859.8) |
| Genistein            | 55.7 [0–2049.1] | 43.6 (27.9, 68.2) |
| Daidzein             | 32.0 [0–1248.6] | 32.3 (21.3, 48.8) |
| Formononetin         | 13.6 [0–683.7] | 25.2 (16.8, 37.6) |
| Glycitein            | 0 [0–0.4] | 0.8 (0.7, 0.9) |
| Total lignans        | 394.1 [0–3463.3] | 170.0 (108.2, 267.2) |
| Secoisolariciresinol | 203.1 [0–3027.4] | 95.6 (58.9, 155.0) |
| Pinoresinol          | 5.7 [0–162.3] | 9.1 (6.5, 12.7) |
| Laricresinol         | 22.5 [0–52.3] | 9.4 (7.3, 12.1) |
| Matairesinol         | 1.2 [0–4.1] | 1.9 (1.7, 2.3) |

1 IQRs include zeros for isoflavones and lignans since lower 25th percentile overlapped with 46% of patients consuming no isoflavones and 32% of patients consuming no lignans.
TABLE 3  Median [IQR] and geometric mean (95% CI) total isoflavone, lignan, and phytoestrogen intakes among consumers of each type, and differences by menopausal status (n = 219)

|                      | Total isoflavones |          | Total lignans |          | Total phytoestrogens |          |
|----------------------|------------------|----------|---------------|----------|----------------------|----------|
|                      | n                | Median [IQR] | Geometric mean (95% CI) | n         | Median [IQR]         | Geometric mean (95% CI) | n         | Median [IQR] | Geometric mean (95% CI) |
| Premenopausal        | 151              | 1807.6   | (517.3–5287.9) | 1043.2   | 1998.5   | (394.1–8556.2)      | 188       | 1987.9   | (1545.5, 2557.1)       |
| Postmenopausal       | 40               | 2696.8   | (435.9–5549.2) | 1395.4   | 4374.6   | (611.2–10,989.9)    | 42        | 3013.9   | (1720.5, 5279.7)       |
| All consumers        | 188              | 1807.6   | (517.3–5287.9) | 1043.2   | 1998.5   | (394.1–8556.2)      | 188       | 1987.9   | (1545.5, 2557.1)       |
| Mean difference      |                  | 0.39     | 0.32          |          | 0.35     | 0.31               |          | 0.39     | 0.32               |

1 Among patients who consumed isoflavones; 11 consumers had intakes ≥10,000 µg/d.
2 Among patients who consumed lignans; 39 consumers had intakes ≥10,000 µg/d.
3 Among patients who consumed one or both of isoflavones and/or lignans; 56 consumers had intakes ≥10,000 µg/d.
4 Test for difference in intake between pre- and postmenopausal consumers; P value for median difference based on Wilcoxon-Mann-Whitney test; P value for mean difference based on t test of natural log-transformed values.

Discussion

This study uniquely examined the postdiagnosis dietary intake of isoflavones and lignans among newly diagnosed breast cancer patients, and differences by menopausal status. Soy and high-lignan foods were similarly consumed by pre- and postmenopausal patients overall. Average isoflavone intakes were particularly low among all patients combined. Isoflavone, lignan, and total phytoestrogen intakes were higher among consumers than in all patients combined, and reached ≥10 mg/d in a number of consumers. Although intake were higher among premenopausal than postmenopausal consumers, especially for lignans, differences were not statistically significant. All consumers and postmenopausal consumers had significantly higher intakes of lignans than of isoflavones.

Postdiagnosis Isoflavone Intake among Breast Cancer Patients

One small cross-sectional (23), 2 large prospective (18, 24), and 1 pooled analysis (25) among North American breast cancer patients reported higher postdiagnosis isoflavone intake than our study. Guha et al. (18) reported a mean intake of 4100 µg/d which contrasts dramatically with our mean of 44 µg/d, although this difference was tempered when only consumers were assessed (6385 compared with 1043 µg/d, respectively).

Mean intake in the study by Caan et al. (24) was also higher [2600 µg/d; as reported in (25)] than in our study, although means were lower at <300 compared with 56 µg/d, respectively.

Various factors may account for our lower isoflavone intakes, including a higher prevalence of nonconsumers [46% in our study compared with 23% in Guha et al. (18)]. However, even after removing nonconsumers, our intakes are low, and warrant consideration of other factors. Soy items may have been eaten less frequently in our study, and we previously noted that soy milk was the only food consumed to soybean variety and growing or processing factors, particularly in the international literature (7, 26). As an example, mean USDA values (27) used by Caan et al. (24) for the 3 soy foods named in their FFQ—touf, soy milk, and veggie burgers—were generally higher than ours (7). Although isoflavone contents for tofu were similar, their values for soy milk and veggie burgers were 2–5 times higher than ours (7120 g/100 g; 8760 compared with 1656 µg/100 g, respectively). The USDA database incorporated international data, whereas our values were based on specific foods consumed and analyzed in Canada.

Isoflavone consumption after breast cancer diagnosis has been reported to vary with demographic and lifestyle factors, and lower

TABLE 4  Median [IQR] and geometric mean (95% CI) total isoflavone and lignan intakes among all consumers and consumers by menopausal status, and differences by phytoestrogen type (n = 219)

|                      | Premenopausal consumers (n = 54) |          | Postmenopausal consumers (n = 165) |          | All consumers (n = 219) |          |
|----------------------|----------------------------------|----------|-----------------------------------|----------|-------------------------|----------|
|                      | µg/d                            | Median [IQR] | Geometric mean (95% CI) | n         | Median [IQR] | Geometric mean (95% CI) | n         | Median [IQR] | Geometric mean (95% CI) |
| Total isoflavones    | 761.5                           | [0-5082.9] | 213.5                             | (82.6, 552.1) | 517.3 | [0-3300.0] | 100.0 | (56.8, 175.9) | 548.5 | [0-3801.6] | 120.5 |
|                      | 788.1                           | [190.3–9167.4] | 508.1                             | (187.6, 1376.5) | 611.2 | [203.7–3626.8] | 745.7 | (479.8, 1158.9) | 774.7 | [203.7–4796.0] | 678.4 |
| P value¹             | 0.06                            | 0.04     | <0.0001                           |          | 0.0007                 | <0.0001               |

1 Paired test for difference between isoflavone and lignan intakes among consumers; P value for median difference based on Wilcoxon’s Signed Rank test; P value for mean difference based on paired t test of natural log-transformed values.
intake is more likely among North American patients who are less educated, older, current smokers, obese, or non-Asian (24, 25). However, none of these factors satisfactorily explain our lower intakes, since education and mean age in our study were intermediate to others, and any effect of our higher prevalence of smokers (10% compared with 5–7%) on reducing isoflavone intake would have been opposed by our lower prevalence of obesity (22% compared with 26–27%) and higher prevalence of Asians (7% compared with 1–4%) (18, 23–25).

Alternatively, since our patients were diagnosed with breast cancer ~2 mo prior to study entry, and other studies included women diagnosed 2 y before, on average (18, 24), our findings suggest the possibility that newly diagnosed breast cancer patients in North America consume fewer isoflavones than do longer-term survivors, which may have important treatment and prognosis implications (11). Recent epidemiologic studies have consistently reported that high post-diagnosis isoflavone intake combined with hormonal therapy (e.g., tamoxifen) appears to have synergistic beneficial effects on breast cancer prognosis through possible mechanisms such as competing with estrogen for estrogen receptor binding and increasing synthesis of sex hormone binding globulin (18, 24, 28). We previously reported that >10% of these newly diagnosed breast cancer patients stopped eating soy foods after their cancer diagnosis (22). However, it is not known if patients continue to avoid, resume, or initiate consumption over time, since the trajectory of isoflavone intake after breast cancer diagnosis has not been explored and therefore it merits investigation in prospective studies designed to repeat dietary assessment at critical time points relative to diagnosis (11).

Despite the study differences just described, ours and other North American studies report dietary isoflavone intakes that are distinct from those in Asia, as illustrated by a study from Shanghai where mean intake after breast cancer diagnosis was much higher at 47 mg/d (i.e., 47,000 µg/d) (28) and 89% of patients consumed ≥10 mg/d [i.e., 10,000 µg/d; as reported in (25)] compared with 4% of all patients in our study. Although this high level of dietary isoflavone intake is common in Asia (29) but unusual in North America, it has been associated with reduced breast cancer recurrence and improved survival in both settings (25).

**Lignan Intake among Breast Cancer Patients**

Our study uniquely describes the postdiagnosis consumption of lignans among breast cancer patients, whereas previous studies of lignans and breast cancer prognosis (all conducted in North America and Europe) have assessed prediagnosis intake (15–17, 19). It is nonetheless useful to compare findings, since the relative impact of diet before and after breast cancer diagnosis has not been determined, and combined exposures over a long time frame may be important (30, 31). Mean lignan intakes in 2 prediagnosis studies (16, 19) and our post-diagnosis study were roughly similar (245–317 compared with 170 µg/d, respectively). However, 2 other studies (15, 17) reported medians that were 4–10 times larger than ours (1400–3900 compared with 394 µg/d, respectively), as well as considerable between-country variation (e.g., 900 and 3300 µg/d for Netherlands and Italy, respectively), which suggests the need for studies in other populations where lignan-rich foods such as sesame seeds are habitually consumed (e.g., Middle East).

Although this comparison implies that pre- and postdiagnosis intakes may be comparable at best, issues of dietary assessment challenge this interpretation. Our questionnaire included 3 foods with high lignan contents (flaxseed, flaxseed bread, sesame seeds), whereas others only included foods with relatively low contents. As an example, the FFQ used by Fink et al. (32) included 39 lignan foods (tea had the highest content at 3 mg/100 g) but omitted the 3 foods we identified as high-lignan sources (7–379 mg/100 g) (7, 32). Thus, given that pre- and post-diagnosis intakes were estimated from mutually exclusive foods, it is not possible to quantify their relative lignan contributions along the breast cancer trajectory, although it is clear that all studies underestimated total consumption and improved dietary assessment methods are needed (33).

By excluding low-lignan sources, our estimates underestimate total postdiagnosis intake, particularly given expected lignan increases from higher fruit, vegetable, and whole grain consumption after breast cancer diagnosis (34, 35). On the other hand, our estimates among lignan consumers suggest that studies not assessing our 3 high-lignan foods may have severely underestimated total intake and the distributions on which risk of breast cancer recurrence and survival were based. In particular, our finding that 21% of lignan consumers had intakes ≥10 mg/d—a level not usually documented in breast cancer prognostic studies (15–17, 19)—indicates the potential utility of capturing these high-lignan foods and broadening intake distributions to enhance risk assessments. A 10 mg/d cut-point has been used in “isoflavone” studies and found to be associated with improved breast cancer recurrence and mortality (25), although it is unknown if this threshold also applies to lignans. It is useful to note, however, that high pre- or postdiagnosis levels of circulating enterolignans (reflecting total lignan intake) have been consistently associated with reduced breast cancer mortality and recurrence risk (21, 36–38). Additionally, although several experimental studies suggest that lignans may increase the effectiveness of hormonal treatment such as tamoxifen and improve breast cancer prognosis (through actions such as estrogen receptor and growth factor signaling pathways), these treatment effects have been inadequately examined in lignan epidemiologic studies to date (12).

**Isoflavone and Lignan Intake by Menopausal Status**

Studies of postdiagnosis isoflavone intake are equivocal regarding differences by menopausal status among breast cancer cases diagnosed 2 y before, on average. Similar to our findings, Caan et al. (24) reported no differences by menopausal status; however, another US study (18) and pooled US data (25) suggest significantly higher isoflavone intakes among premenopausal women. Yet, in a large study in China where isoflavones are typically consumed and at much higher levels than in North America, no differences were found by menopausal status (28). If our earlier suggestion holds true, that newly diagnosed breast cancer patients in North America consume fewer isoflavones than longer-term survivors, they may be doing so generally, regardless of menopausal status—and it would be beneficial to examine this in prospective studies given the possible treatment and prognostic implications.

Our study is the first, to our knowledge, to report postdiagnosis lignan intake by menopausal status, and we found that premenopausal consumers had higher intakes than postmenopausal consumers, although differences were not statistically significant. In contrast, a prognostic study that assessed lignans by menopausal status reported lower premenopausal intake (19) which was also suggested in another study.
showing low intake in the youngest age tertile of 27–50 y (16). However, as described earlier, both studies assessed prediagnosis intake based on foods other than our 3 rich-lignan sources. Nonetheless, it is possible that our suggestion of higher premenopausal consumption may only apply to our specific high-lignan foods or only among newly diagnosed breast cancer patients, and these issues merit further consideration in studies with adequate numbers of premenopausal women.

Comparison of Lignan and Isoflavone Intakes after Breast Cancer Diagnosis

No other study, to our knowledge, has reported the postdiagnosis intake of lignans and isoflavones, and our finding that lignans were consumed at significantly higher levels contributes to a growing understanding of their importance in Western diets (8, 9, 39), including among newly diagnosed breast cancer patients, as demonstrated here. Additionally, our estimates would have been more positively weighted towards lignans if additional plant foods and not just 3 high-lignan items had been assessed. By comparison, our isoflavone estimates were likely adequate as they were derived from a broad list of soy foods which have been shown to account for most isoflavone intake in Western diets, including in multiethnic groups (8, 9, 39).

Strengths and Limitations

Findings must ultimately be interpreted within the context of study strengths and limitations, some of which have already been discussed. Our study uniquely assessed the postdiagnosis intake of both isoflavones and lignans and differences by menopausal status using a population-specific compositional database and contributions from important lignan foods that have been overlooked in other studies. However, our questionnaire did not assess total diet and therefore phytoestrogen intakes were underestimated. Our sample size of pre- and postmenopausal breast cancer patients likely limited our ability to detect significant differences in stratified analyses. Thus, findings should be confirmed in larger samples, particularly of premenopausal patients. Our questionnaire response rate (67%) potentially contributed to selection bias and to different isoflavone and lignan estimates than if nonrespondents had also been included. Additionally, no study concerned with intake among breast cancer patients and/or prognosis, including ours, has quantified the phytoestrogen contributions from dietary supplements. Although the assessment of supplement use is fraught with challenges (22, 40), its inclusion in pre- and postdiagnosis intake measures in prognostic studies is of utmost importance given potentially high phytoestrogen contributions and reported associations with reduced primary breast cancer risk (41, 42).

Conclusions

Our cross-sectional study among newly diagnosed breast cancer patients found that isoflavone intake from foods was generally low. Lignan intake was higher than isoflavones in most consumers and may be greater in premenopausal than in postmenopausal patients. Although a number of patients consumed phytoestrogens—particularly lignans—at levels previously associated with improved breast cancer prognosis (≥10 mg/d), our suggestion that isoflavone consumption in newly diagnosed breast cancer patients may be lower than in longer-term survivors in North America is of interest given the possible impact on treatment and prognosis. Our findings also highlight the importance of examining high-lignan foods (flaxseed, flaxseed bread, sesame seeds) in future breast cancer prognosis studies since their inclusion has the potential to improve dietary assessment and the intake distributions on which survival analyses are based.

Acknowledgments

The authors’ responsibilities were as follows—BAB and MC: designed and conducted the original research and data collection; SW: analyzed the data; BAB: wrote the manuscript and had primary responsibility for final content; and all authors: contributed to the analytic decisions and interpretation, critically revised the manuscript, and read and approved the final manuscript.

References

1. Canadian Cancer Society’s Advisory Committee on Cancer Statistics. Canadian cancer statistics 2016 [cited 2017 Aug 11]. Available from: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2016-EN.pdf?la=en.
2. Vetto JT, Luoh SW, Naik A. Breast cancer in premenopausal women. Curr Probl Surg 2009;46:944–1004.
3. Brenner DR, Brockton NT, Kotsopoulos J, Cotterchio M, Boucher BA, Courneya KS, Knight JA, Olivetto IA, Quan ML, Friedenreich CM. Breast cancer survival among young women: a review of the role of modifiable lifestyle factors. Cancer Causes Control 2016;27:459–72.
4. World Cancer Research Fund International, American Institute for Cancer Research. Continuous update project report: diet, nutrition, physical activity, and breast cancer survivors. 2014 [cited 2017 Aug 11]. Available from: http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports/breast-cancer-survivors.
5. Setchell KDR. Phytoestrogens: the biochemistry, physiology, and implications for human health of soy isoflavones. Am J Clin Nutr 1998;68:1335–46S.
6. Taylor CK, Levy RM, Elliott JC, Burnett BP. The effect of genistein aglycone on cancer and cancer risk: a review of in vitro, preclinical, and clinical studies. Nutr Rev 2009;67:398–415.
7. Thompson LU, Boucher BA, Liu Z, Cotterchio M, Kreiger N. Phytoestrogen content of foods consumed in Canada, including isoflavones, lignans, and coumestan. Nutr Cancer 2006;54:184–201.
8. Huang MH, Norris J, Han W, Block T, Gold E, Crawford S, Greendale GA. Development of an updated phytoestrogen database for use with the SWAN food frequency questionnaire: intakes and food sources in a community-based, multiethnic cohort study. Nutr Cancer 2012;64:228–44.
9. Cotterchio M, Boucher BA, Kreiger N, Mills CA, Thompson LU. Dietary phytoestrogen intake—lignans and isoflavones—and breast cancer risk (Canada). Cancer Causes Control 2008;19:259–72.
10. Meija L, Söderholm P, Samaletdin A, Ignace G, Silksna I, Joffe R, Lejnieks A, Lietuvietis V, Krams I, Adlercreutz H. Dietary intake and major sources of plant lignans in Latvian men and women. Int J Food Sci Nutr 2013;64:535–43.
11. Kushi LH, Kwan ML, Lee MM, Ambrosone CB. Lifestyle factors and survival in women with breast cancer. J Nutr 2007;137:2365–42S.
12. Mason JK, Thompson LU. Flaxseed and its lignan and oil components: can they play a role in reducing the risk of and improving the treatment of breast cancer? Appl Physiol Nutr Metab 2014;39:663–78.
13. Zhang X, Cook KL, Warri A, Cruz IM, Rosim M, Riskin J, Helferich W, Doerge D, Clarke R, Hilakivi-Clarke L. Lifetime genotype increase the response of mammary tumors to tamoxifen in rats. Clin Cancer Res 2017;23:814–24.
14. Ju YH, Doerge DR, Wooding KA, Hartman JA, Kwak J, Helferich WG. Dietary genotype negates the inhibitory effect of letrozole on the growth of aromatase-expressing estrogen-dependent human breast cancer cells (MCF-7Ca) in vivo. Carcinogenesis 2008;29:2162–8.
15. Kyro C, Zamora-Ros R, Scalbert A, Tjonneland A, Dossus L, Johansen C, Bidstrup PE, Weiderpass E, Christensen J, Ward H, et al. Pre-diagnostic polyphenol intake and breast cancer survival: the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Breast Cancer Res Treat 2015;154:389–401.

16. Swann R, Perkins KA, Velentzas LS, Ciria C, Dutton SJ, Mulligan AA, Woodside JV, Cantwell MM, Leatham AJ, Robertson CE, et al. The DietCompLyf study: a prospective cohort study of breast cancer survival and phytoestrogen consumption. Maturitas 2013;75:232–40.

17. Fink BN, Steck SE, Wolff MS, Britton JA, Kabat GC, Gaudet MM, Abrahamson PE, Bell P, Schroeder JC, Teitelbaum SL, et al. Dietary flavonoid intake and breast cancer survival among women on Long Island. Cancer Epidemiol Biomarkers Prev 2007;16:2285–92.

18. Guha N, Quesenberry CP, Weltzien EK, Castillo AL, Caan BJ. Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the Life After Cancer Epidemiology study. Breast Cancer Res Treat 2009;118:395–405.

19. McCann SE, Thompson LU, Nie J, Dorn J, Trevisan M, Shields PG, Ambrosone CB, Edge SB, Li HF, Kasprzak C, et al. Dietary lignan intakes in relation to survival among women with breast cancer: the Western New York Exposures and Breast Cancer (WEB) study. Breast Cancer Res Treat 2010;122:229–35.

20. Chi F, Wu R, Zeng YC, Xing R, Liu Y, Xu ZG. Post-diagnosis soy food intake and breast cancer survival: a meta-analysis of cohort studies. Asian Pac J Cancer Prev 2013;14:2407–12.

21. Seibold P, Vrieling A, Johnson TS, Buck K, Behrens S, Kaaks R, Linseisen J, Obi N, Heinz J, Flesch-Jaynes D, et al. Enterolactone concentrations and prognosis after postmenopausal breast cancer: assessment of effect modification and meta-analysis. Int J Cancer 2014;135:923–33.

22. Boucher BA, Cotterchio M, Curca IA, Kreiger N, Harris SA, Kirsh VA, Goodwin PJ. Intake of phytoestrogen foods and supplements among women recently diagnosed with breast cancer in Ontario, Canada. Nutr Cancer 2012;64:695–703.

23. Lammersfeld CA, King J, Walker S, Vashi PG, Grutsch JF, Cappell HG, Gupta D. Prevalence, sources, and predictors of soy consumption in breast cancer patients. Nutr J 2009;8:2.

24. Caan BJ, Natarajan L, Parker B, Gold EB, Thomson C, Newman V, Rock CL, Pu M, Al-Delaimy W, Pierce JP. Soy food consumption and breast cancer prognosis. Cancer Epidemiol Biomarkers Prev 2011;20:854–8.

25. Nechuta SJ, Caan BJ, Chen WY, Lu W, Chen Z, Kuan ML, Flatt SW, Zheng Y, Zheng W, Pierce JP, et al. Soy food intake after diagnosis of breast cancer and survival: an in-depth analysis of combined evidence from cohort studies of US and Chinese women. Am J Clin Nutr 2012;96:123–32.

26. Peterson JJ, Dwyer JT, Jacques PF, McCullough ML. Improving the estimation of flavonoid intake for study of health outcomes. Nutr Rev 2015;73:535–76.

27. U.S. Department of Agriculture. USDA-Iowa State University database on the isoflavone content of foods (release 1.4). 2007 [cited 2017 Aug 11]. Available from: http://www.ars.usda.gov/SP2UserFiles/Place/80400525/Data/isoav1-4.pdf.