Post-diagnosis 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[3], Shelley A Harris[1,4], Michelle Cotterchio[1,4]

[1] Prevention and Cancer Control, Cancer Care Ontario, 620 University Ave, Toronto, Ontario M5G 2L7 Canada

[2] Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, 150 College St, Toronto, Ontario M5S 3E2 Canada

[3] Centre for Urban Health Solutions, St Michael's Hospital, 30 Bond St, Toronto, Ontario M5B 1W8 Canada

[4] Dalla Lana School of Public Health, University of Toronto, 155 College St, Toronto, Ontario M5T 3M7 Canada

**Address correspondence to*: Beatrice A Boucher, Prevention and Cancer Control, Cancer Care Ontario, 620 University Ave, Toronto, Ontario M5G 2L7 Canada; Tel: 416-971-9800 ext 3238 Email beatrice.boucher@cancercare.on.ca

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Abbreviations used: FFQ, food frequency questionnaire; CI, confidence interval; IQR, interquartile range; OCR, Ontario Cancer Registry.

***Running Title*:** Isoflavones and lignans after breast cancer

Abstract

Background: Isoflavones and lignans (phytoestrogens) are dietary components with potential anti-carcinogenic effects. Although the intake of isoflavones and lignans may affect breast cancer treatment and prognosis – and associations may differ by menopausal status - post-diagnosis intake data are limited.

Objective: We aimed to describe post-diagnosis 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 years, diagnosed with pathologically confirmed breast cancer in April-May 2010 and identified using the Ontario Cancer Registry. Intake in previous 2 months was assessed using questionnaires listing 17 soy and 3 high lignan foods (flaxseed, flaxseed bread, sesame seeds), completed 71 days 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/day). Consumers (n=219) had higher intakes (median isoflavones 1808 µg/day); 7% of isoflavone and 21% of lignan consumers had intakes ≥10 mg/day. Intakes were higher in premenopausal than postmenopausal consumers, particularly for lignans, but were not significantly different (median lignans 4375 vs 1863 µg/day; p=0.07). Lignans were significantly higher than isoflavones among most consumers (postmenopausal means 746 vs 100 µg/day; p<0.0001).

Conclusions: Post-diagnosis lignan intakes from 3 high-content foods may be considerable among newly diagnosed breast cancer patients – yet 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.

Keywords: isoflavones; lignans; phytoestrogens; flaxseed; sesame; breast neoplasms; prognosis; dietary assessment; surveys and questionnaires; breast cancer patients

Introduction

Breast cancer is the leading cancer diagnosis among Canadian women and a major cause of cancer death, particularly in those under 40 years of age (1) where breast cancer is typically more aggressive than in older women (2,3). Thus, identifying factors which 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 anti-carcinogenic 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 post-diagnosis diet, when dietary interactions with treatment may influence cancer prognosis (11). Both isoflavones and lignans may alter the effectiveness of hormonal breast cancer treatment, where beneficial as well as antagonistic effects have been reported experimentally (12-14). However of three population-based breast cancer survival studies examining both isoflavones and lignans, none assessed post-diagnosis 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 five 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 five 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 report intake by menopausal status (22). Given possible treatment and prognostic effects and the limited data on post-diagnosis 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 post-diagnosis 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 years of age at 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 one month, patients who did not opt out (n=417; 90%) were mailed a study questionnaire, which 278 patients completed 71 days 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 months, as well as socio-demographic and health related characteristics. Twenty foods were listed, including 17 soy or soy-containing foods as isoflavone sources (e.g., tofu, protein bar) and three foods containing high levels of lignans (flaxseed, flaxseed bread, sesame seeds). Intake of each food was queried using assigned serving sizes and five frequency response options (never, less than once a week, 1-2 times a week, 3-6 times a week, 1 or more times a day). Derivation of isoflavone and lignan intake (µg per day) involved three steps. First, the frequency responses and assigned servings were used to estimate servings per day based primarily on frequency mid-points. As an example, consuming one serving less than once a week was estimated as 0.5 servings in 7 days, or 0.07 servings per day. Serving frequencies thus ranged from 0.07 to 1 serving per day. Second, for each respondent, the daily serving frequency of each reported food was multiplied by the phytoestrogen content per serving (µg) 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 non-consumers removed).

Statistical analysis

Descriptive statistics were used to estimate consumption prevalence and associated 95% confidence intervals (95% CI) of individual and groups of soy and high lignan foods among pre- and postmenopausal patients. The Pearson χ^2 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. non-consumers removed) using median values and inter-quartile ranges (IQR), 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 total lignan intakes among consumers, paired tests were conducted (Wilcoxon-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).

Results

As previously described, most breast cancer patients in this study were Caucasian (7% were East-Asian), 77% were postmenopausal, and the average age was 56 years; about 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) vs postmenopausal: 52% (95% CI: 45- 59); p=0.18) or high lignan foods (premenopausal: 65% (95% CI: 52-76) vs. postmenopausal: 69% (95% CI: 62-75); p=0.55) in the previous 2 months (reported intake frequencies ranged from < 1 time per week to 1+ times per day) (**Table 1**). However, a significantly higher proportion of premenopausal patients consumed soy nuts (18% vs. 9% postmenopausal, p=0.04).

Among all patients (n=278), median and mean total phytoestrogen intakes were 2012 µg/day (IQR: 190-8568) and 561 µg/day (95% CI: 366-860), respectively (**Table 2**). Patients consumed a median of 56 µg/day (IQR: 0-2049) and mean of 44 µg/day (95% CI: 28-68) of isoflavones (genistein was the largest contributor) and a median of 394 µg/day (IQR: 0-3463) and mean of 170 µg/day (95% CI: 108-267) 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/day (IQR: 517-5288) among consumers versus 56 µg/day (IQR: 0-2049) already reported for all patients. High intakes (≥10,000 µg/day) 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 postmenopausal consumers, and noticeably so for lignans, differences were not statistically significant. As an example, median lignan intake in premenopausal consumers was 4375 µg/day (IQR: 611-10990) compared to postmenopausal consumers at 1863 µg/day (IQR: 394-3654) (p=0.07). All consumers and

postmenopausal consumers had significantly higher lignan than isoflavone intakes (e.g. postmenopausal means 746 vs 100 µg/day, respectively; $p<0.0001$), although differences were not significant for premenopausal consumers (**Table 4**).

Discussion

This study uniquely examined the post-diagnosis 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/day in a number of consumers. While intakes 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 isoflavones.

Post-diagnosis isoflavone intake among breast cancer patients

One small cross-sectional (23), two large prospective (18,24) and one pooled analysis (25) among North American breast cancer patients reported higher post-diagnosis isoflavone intake than our study. Guha et al. (18) reported a mean intake of 4100 µg/day which contrasts dramatically with our mean of 44 µg/day, although this difference was tempered when only consumers were assessed (6385 vs 1043 µg/day, respectively). Mean intake in the study by Caan et al. (24) was also higher (2600 µg/day; as reported in ref 25) than our study, although medians were less discrepant at <300 vs 56 µg/day, respectively.

Various factors may account for our lower isoflavone intakes, including a higher prevalence of non-consumers (46% in our study vs 23% in Guha et al. (18)). However, even after removing non-consumers, 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 at least once per week (22). Discrepancies may have also arisen from study-specific isoflavone values assigned to foods, since there is large variation due 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. for the three soy foods named in their food frequency questionnaire (FFQ) - tofu, soy milk, veggie burgers (24) were generally higher than ours (7). Although isoflavone contents for tofu were similar, their values for soy milk and veggie burgers were 2 to 5 times higher than ours (7120 vs 2994 µg/100g; 8760 vs 1656 µg/100g, 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, where lower 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% vs 5-7%) on reducing isoflavone intake would have been opposed by our lower prevalence of obesity (22% vs 26-27%) and higher prevalence of Asians (7% vs 1-4%) (18, 23-25).

Alternatively, since our patients were diagnosed with breast cancer approximately 2 months prior to study entry, and other studies included women diagnosed 2 years before, on average (18,24), our findings suggest the possibility that newly diagnosed breast cancer patients in North

America consume fewer isoflavones than longer-term survivors, which may have important treatment and prognosis implications (11). Recent epidemiological 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 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/day (i.e. 47,000 µg/day) (28) and 89% of patients consumed ≥10 mg/day (i.e. 10,000 µg/day; as reported in ref 25) versus 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 post-diagnosis 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 pre-diagnosis 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 two pre-diagnosis studies (16,19) and our post-diagnosis study were roughly similar (245-317 vs 170 µg/day, respectively). However, two other studies (15,17) reported medians that were 4 to 10 times larger than ours (1400-3900 vs 394 µg/day, respectively), as well as considerable between-country variation (e.g. 900 and 3300 µg/day 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 post-diagnosis intakes may be comparable at best, issues of dietary assessment challenge this interpretation. Our questionnaire included three 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. included 39 lignan foods (tea had highest content at 3 mg/100g) but omitted the three foods we identified as high lignan sources (7-379 mg/100g) (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 underrepresent total post-diagnosis 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 three 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/day - a level not usually documented in breast cancer prognosis 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/day 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 post-diagnosis 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 epidemiological studies to date (12).

Isoflavone and lignan intake by menopausal status

Studies of post-diagnosis isoflavone intake are equivocal regarding differences by menopausal status among breast cancer cases diagnosed 2 years 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. However, 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 report post-diagnosis lignan intake by menopausal status and 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 years (16). However, as described earlier, both studies assessed pre-diagnosis intake based on foods other than our three 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 has reported the post-diagnosis 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 three 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).

282 ***Strengths and limitations***

283 Findings must ultimately be interpreted within the context of study strengths and limitations,
284 some of which have already been discussed. Our study uniquely assessed the post-diagnosis
285 intake of both isoflavones and lignans and differences by menopausal status using a population-
286 specific compositional database and contributions from important lignan foods that have been
287 overlooked in other studies. However, our questionnaire did not assess total diet and therefore
288 phytoestrogen intakes were underestimated. Our sample size of pre- and postmenopausal breast
289 cancer patients likely limited our ability to detect significant differences in stratified analyses.
290 Thus, findings should be confirmed in larger samples, particularly of premenopausal patients.
291 Our questionnaire response rate (67%) potentially contributed to selection bias and to different
292 isoflavone and lignan estimates than if non-respondents had also been included. Additionally, no
293 study concerned with intake among breast cancer patients and/or prognosis, including ours, has
294 quantified the phytoestrogen contributions from dietary supplements. Although the assessment of
295 supplement use is fraught with challenges (22,40), its inclusion in pre- and post-diagnosis intake
296 measures in prognostic studies is of utmost importance given potentially high phytoestrogen
297 contributions and reported associations with reduced primary breast cancer risk (41,42).
298
299 **Conclusions**
300 Our cross-sectional study among newly diagnosed breast cancer patients found that isoflavone
301 intake from foods was generally low. Lignan intake was higher than isoflavones in most
302 consumers and may be greater in premenopausal than postmenopausal patients. Although a
303 number of patients consumed phytoestrogens - particularly lignans - at levels previously
304 associated with improved breast cancer prognosis (≥10mg/day), 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.

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TABLE 1. Prevalence (%) and 95% confidence intervals (CI) of soy and high lignan foods ever consumed in previous 2 months among newly diagnosed breast cancer patients by menopausal status (n=278)[1].

	Premenopausal patients (n=65)		Postmenopausal patients (n=213)		
Foods consumed in previous 2 months[2]	**n**	**% (95% Cl)**	**n**	**% (95% CI)**	***P* value[3]**
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 per week to 1+ times per day.

[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; 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

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

	Median (IQR)[1] µg/day	**Geometric mean (95% CI)** µg/day
Total phytoestrogens	2011.7 (190.3-8568.3)	561.3 (366.4-859.8)
Total isoflavones	55.7 (0-2049.1)	43.6 (27.9-68.2)
Genistein	32.0 (0-1248.6)	32.3 (21.3-48.8)
Daidzein	13.6 (0-683.7)	25.2 (16.8-37.6)
Formononetin	0 (0-0.4)	0.8 (0.7-0.9)
Glycitein	0.4 (0-88.7)	7.1 (5.4-9.5)
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)
Lariciresinol	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[1] µg/day			Total lignans[2] µg/day			Total phytoestrogens[3] µg/day		
	n	Median (IQR)	Geometric mean (95% CI)	n	Median (IQR)	Geometric mean (95% CI)	n	Median (IQR)	Geometric mean (95% CI)
All consumers	151	1807.6 (517.3-5287.9)	1043.2 (742.5-1465.6)	188	1998.5 (394.1-8556.2)	1987.9 (1545.5-2557.1)	219	3805.7 (688.9-10418.9)	3089.2 (2460.0-3879.4)
Premenopausal consumers	40	2696.8 (435.9-5549.2)	1395.4 (794.7-2450.3)	42	4374.6 (611.2-10989.9)	3013.9 (1720.5-5279.7)	54	6417.1 (1155.9-14030.2)	3997.6 (2499.6-6393.2)
Postmenopausal consumers	111	1551.9	939.4	146	1862.7	1763.6	165	3678.4	2839.3

	(517.3-5094.6)	(620.1-1423.0)	(394.1-3653.6)	(1333.9-2331.9)	(611.2-9272.1)	(2189.5-3681.9)
***P* value**[4]	0.39	0.32	0.07	0.08	0.14	0.21

[1] Among patients who consumed isoflavones; 11 consumers had intakes ≥10,000 µg/day.

[2] Among patients who consumed lignans; 39 consumers had intakes ≥10,000 µg/day.

[3] Among patients who consumed one or both isoflavones and/or lignans; 56 consumers had intakes ≥10,000 µg/day.

[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.

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/day	**Median (IQR)**	**Geometric mean (95% CI)**	**Median (IQR)**	**Geometric mean (95% CI)**	**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 (74.1-196.2)
Total lignans	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 (449.1-1024.9)
***P* value**[1]	0.06	0.27	0.005	<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 signed-rank test; *P* value for mean difference based on paired *t*-test of natural-log transformed values.