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Dietary Phytoestrogens Are Not Associated with Risk of Overall Breast Cancer But Diets Rich in Coumestrol Are Inversely Associated with Risk of Estrogen Receptor and Progesterone Receptor Negative Breast Tumors in Swedish Women[1,2]

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Abstract

Results from epidemiological and experimental studies indicate that phytoestrogens may protect against breast cancer. Because one of the biological effects of phytoestrogens is probably estrogenic, it's possible that the preventive effect on breast cancer differs by estrogen receptor (ER) or progesterone receptor (PR) status of the tumor. We evaluated the associations between dietary phytoestrogen (isoflavonoids, lignans, and coumestrol) intake and risk of breast cancer and whether the ER/PR statuses of the tumor influence this relationship. In 1991–2 a prospective population-based cohort study among Swedish pre- and postmenopausal women was performed, making questionnaire data available for 45,448 women. A total of 1014 invasive breast cancers were diagnosed until December 2004. Cox proportional hazards models were performed to estimate multivariate risk ratios, 95% CI for associations with risk of breast cancer. Intakes of lignan, isoflavonoid, or coumestrol were not associated with breast cancer risk overall or before or after 50 y of age. The effects of lignans or isoflavonoids were independent of receptor status. However, intake of coumestrol was associated with decreased risk of receptor negative tumors (ER−PR−) but not positive tumors. The risk of ER−PR− tumors was significantly lower (50%) in women with intermediate coumestrol intake compared with those who did not consume any. In conclusion, we found no association between intake of isoflavonoids or lignans and breast cancer risk. Our results of a decreased risk of ER−PR− tumors in women with intermediate intake of coumestrol could be due to chance because of the low intake. The results should be confirmed in other studies. J. Nutr. 138: 938–945, 2008.

Introduction

Phytoestrogens are compounds naturally found in plant foods. Results from experimental studies indicate that these compounds, structurally related to endogenous estrogens, protect against breast cancer. Ecological studies have supported this protective role of phytoestrogens, with lower breast cancer prevalence in Asian countries where the soy food consumption is high (rich in the phytoestrogens isoflavones) and higher breast cancer prevalence in Western countries where the intake of soy foods is much lower (1). Results from several case-control and cohort studies also indicate an inverse association between breast cancer risk and intake of soybean phytoestrogens, mainly isoflavonoids (2–5). Lignans, the other class of phytoestrogens, have also been found to be inversely related to breast cancer risk (5). The majority of the prospective studies reported nonsignificant associations; however, nearly all of these studies investigated serum or urinary levels of lignans and few investigated dietary lignan intake. The most investigated lignan compounds are matairesinol (MAT)[7] and secoisolariciresinol (SECO) and so

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[7] Abbreviations used: ER, estrogen receptor; ER+/ER−, estrogen receptor α positive/negative tumor; MAT, matairesinol; PR, progesterone receptor; RR, risk ratio; SECO, secoisolariciresinol.

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far, only 1 study has investigated the newly identified lignan precursors lariciresinol and pinoresinol in relation to breast cancer risk. In this study, Touilland et al. (6) found an inverse relationship for total lignans, and of lariciresinol in particular, and postmenopausal breast cancer risk. So far no study to our knowledge has investigated the effect of the newly identified lignan precursors syringaresinol and medioresinol in relation to breast cancer risk.

High levels of endogenous hormones are associated with increased risk of breast cancer (7,8) and play a major role in the promotion and progression of breast tumors (9). Sixty to 80% of breast cancer tumors express estrogen receptor (ER) α, often at high levels [ERα positive tumors (ER+)] and high levels of progesterone receptor (PR+) are correlated to the occurrence of ERα (10). Some of the known nondietary breast cancer risk factors have been found to differ for ER+ and ER− tumors (11) and this may also be the case for the dietary risk factors. Because phytoestrogens bind to the ER, they may influence mechanisms that determinate the levels of ER or PR in breast tumors. However, epidemiological studies of the relationship between intake of phytoestrogens and ER status do not show any clear pattern (12–17) and only 3 studies have investigated the relationship with PR status (6,13,16).

Lignan compounds especially are found in the fiber-rich outer layer of cereal grains (18). Urinary levels of the lignan metabolite enterolactone are correlated with intake of grain fiber and breast cancer patients have been found to have lower levels of urinary and plasma enterolactone than healthy controls (19–21). It has been hypothesized that fiber and lignan intake may be associated with a decreased risk of breast cancer (22), because fiber may reduce breast cancer risk itself by interfering with the enterohepatic metabolism of estrogens, reducing their levels in the body (23).

The aim of this prospective population-based study in Swedish women was to examine the association between dietary intake of phytoestrogens and risk of pre- and postmenopausal breast cancer and to evaluate if the associations differ by ER or PR status. We also evaluated the association between dietary intake of cereal and vegetable fiber and risk of breast cancer.

Subjects and Methods

Study population. The study design and exposure assessment have been described in detail elsewhere (24). In brief, women aged 30–49 y, residing in the Uppsala Health Care Region in Sweden between 1991 and 1992, formed the source population for this study. Of this source population, 96,000 women were randomly selected from 4 age strata (30–34, 35–39, 40–44, and 45–49 y) and invited to participate in the Swedish component of the Scandinavian Women's Lifestyle and Health Cohort. The women were asked to fill in a questionnaire, and of those invited, over one-half participated, and 49,261 returned the questionnaires and were enrolled in the study. The Swedish Data Inspection Board and the regional Ethical Committee approved the study.

Classification of phytoestrogens. Phytoestrogens are naturally occurring hormone-like compounds found in plant food and can be subdivided into coumestans, isoflavonoids, and lignans. Coumestrol (a coumestan) and the isoflavonoids genistein, daidzein, and their plant precursors biochanin A and formononetin, are mainly found in soybeans and clover. Plant lignans, such as MAT and SECO, are converted by the mammalian gastrointestinal microflora to mammalian lignans, enterolactone and enterodiol, respectively (18). Until recently, only 2 plant lignan precursors for mammalian lignans were known: SECO and MAT. Lariciresinol, pinoresinol, syringaresinol, and medioresinol are newly identified enterolactone precursors, found mainly in cereals and seeds (25).

Exposure assessment. The self-administered questionnaire assessed known and potential risk factors for breast cancer, including average intake of foods and beverages (24). Dietary habits during the 6 mo preceding enrolment in the study were ascertained through a validated FFQ that covered the frequency of consumption and quantity of ~80 food items and beverages, including 50 items containing phytoestrogens (26). For example, participants were asked how often, on average, they ate beans, soy, or lentils; green peas; pea soup; broccoli; cauliflower; white or red cabbage; spinach; onion or leek; carrot; swede or beetroot; porridge or gruel; wheat or oat bran; cereals or müsli, nuts or almonds; apples or pears: never/seldom, 1–3 times/mo, 1 time/wk, 2 times/wk, 3–4 times/wk, 5–6 times/wk, 1 time/d, 2 times/d, or 3 times/d. The participants were also asked how many slices of bread they ate per day or week: wheat bread, whole-meal bread (bread baked of coarse and whole-meal flour), or crisp bread (mostly baked of rye meal). To estimate individual intake of energy and nutrients, we linked the dietary information from the questionnaire to the nutrient database created by the Swedish National Food Administration (food table of 1989) (27). To estimate the intake of specific phytoestrogens, we created a database (28) with information from recently published analytical data for the content of isoflavonoids (genistein, daidzein, biochanin A, formononetin, and equol), coumestans (coumestrol), and lignans (MAT and SECO) in food products. The content of the newly discovered plant lignans lariciresinol, pinoresinol, syringaresinol, and medioresinol in different grain flours was used to estimate lignan content of bread and cereal products and was added to the database. Based on the levels of genistein, daidzein, equol, MAT, enterodiol, and enterolactone in raw cow's milk, we estimated the content of these compounds in different kinds of milk products and the information was added to the database (28). The analyses of all phytoestrogen compounds in food products were conducted using isotope dilution GC-MS performed in a laboratory in Finland (18,25). In addition to the FFQ part of the questionnaire, participants were asked how often, on average, they ate berries: times per week, times per month, or seldom/never. The reported frequency together with an estimated portion size (115 g berries per portion for all women) was used to calculate intake of berries (g/d).

Follow-up. Follow-up of the cohort was achieved through linkages with existing nationwide health registers in Sweden. Because each resident in Sweden has a personal national registration number, one can link the data from the cohort with these registers for virtually complete follow-up with respect to death and emigration. From the total population registers, we received information on the dates of death for women who died during the follow-up period and dates of emigration until December 31, 2004. The national cancer registry provided data on prevalent cancer cases at cohort enrolment and on incident of invasive breast cancers as well as other cancers diagnosed in the cohort during follow-up. The start of follow-up was defined as the date of return of the questionnaire. Observation time was calculated from date of entry into the cohort until the occurrence of incident breast cancer, emigration, death, or the end of the observation period (December 31, 2004). ER status (ER− or ER+) and PR status (PR− and PR+) was obtained by linkage with the regional cancer registry in Uppsala (29), which is based on the patient's original medical records. ER and PR status was determined by means of an Abbott immunoassay (30). We defined receptor positive tumors as ≥0.05 fmol receptor/μg DNA, or ≥10 fmol receptor/mg protein.

Statistical methods. Among the 49,261 Swedish women included in the study, 1372 invasive breast cancer cases were diagnosed by the end of follow-up in December 2004. The following were sequentially excluded: those with prevalent breast cancer (diagnosed before entering the cohort, $n = 281$), those with energy intakes outside the first (1846 kJ/d) and 99th (12,473 kJ/d) percentiles ($n = 983$), and those with missing values in any of the adjustment covariates ($n = 2549$). Thus, a total of 45,448 women (1014 breast cancer cases) were available for the analysis. We do not have information about menopausal status after the start of follow-up. Based on the mean age at menopause in Sweden being 50 y, the effect of menopausal status and other risk factors in different periods of life were evaluated by fitting separate models for breast cancer occurring before and after 50 y of age (31). Of the total 1014 breast cancer cases, 494 occurred before 50 y of age. When analyzing the time course starting at 50 y of age, 28,476 women were available for analysis (when censoring

women with breast cancer before 50 y of age, women who died or emigrated, or who were too young to reach 50 y at the end of follow up). Among these 28,476 women, 520 breast cancer cases occurred.

We had information on joint ER/PR status for 737 (73%) of all cases. Of the tumors with known receptor status, 130 were ER−PR−, 118 were ER+PR−, 40 were ER−PR+, and 449 were ER+PR+.

The association between phytoestrogens and risk of breast cancer was evaluated by Cox proportional hazard models utilizing attained age as time scale (32). We interpreted relative hazards as estimates of risk ratios (RR), given with 95% CI. This corresponds to a 2-sided 5% level of significance.

Nutrient density was obtained through dividing the estimated intake of phytoestrogens (μg/d) and other nutrients by the total energy intake (MJ/d) (multivariate nutrient density model) (33).

A combined food item variable consisting of foods rich in all phytoestrogens (isoflavonoids and coumestrol as well as lignans) was created by adding the daily intakes in grams of the following foods: berries, nuts, beans/soy, crisp bread, and wine. A corresponding variable was created from a group of food items rich in lignans by adding the daily intakes in grams of berries, nuts, crisp bread, whole-grain bread, and wine. These foods were chosen after we ranked food items evaluated in the questionnaire according to the lignan or isoflavonoid content per edible portion. The food items containing the highest phytoestrogen levels were those included in the summary variables. All exposures except coumestrol were categorized into quartiles and for each comparison of dietary intake, the lowest quartile was used as the reference category. Coumestrol was split into 3 categories, because 67% of the women had 0 intakes and they form the reference group. The remaining women were split into 2 groups of equal size using a cut-off at the median of 0.014 μg/(d·MJ).

For the fiber analyses, we divided the individual dietary intake of fiber by the individual body weight to adjust for the volume of the gastrointestinal tract, which should affect the volume of its content, because a small person is expected to have a smaller intestinal volume than a large person (34).

Age- and energy-adjusted models were fitted, as well as models adjusted for additional potential confounders, including BMI, oral contraceptives, age at first pregnancy, age at menarche, parity, breast cancer among sisters or mothers, smoking status, education, and selected food groups and nutrient densities categorized into quartiles. Variables in the models were continued or categorized as defined in **Table 1**. The selection of covariates included in the final multivariate models was based on significance and previous subject matter knowledge and those included in the final models were known risk factors or considered to be important confounding factors for the relation between the main exposure and breast cancer (Table 3 and Fig. 1, footnotes). BMI was not included in the model for the analysis of fiber divided by the body weight. The age-and energy-adjusted models did not differ from the multivariate-adjusted models and therefore only the full models are presented in Table 3. In analyses of the different phytoestrogen compounds, we adjusted mutually for other classes of phytoestrogens (isoflavonoids, lignans, and coumestrol); however, none of the adjustments changed the estimates and they were removed from the final model. Analyses were performed using SAS version 9.1.

Results

Characteristics of study participants. Baseline characteristics and intake of nutrients in the study participants are presented in Table 1. In general, women who developed breast cancer tended to be older, have lower parity, and reported having a first-degree relative with a history of breast cancer more often than women who did not develop breast cancer. Intake of main groups of macronutrients and dietary mean intake of fiber, meat, dairy products, fatty fish, vegetables, fruit, cereals, or beans were very similar between the 2 groups. The entire cohort was ethnically homogeneous and most of the women grew up in Sweden (92%) or other Nordic countries (5%) (data not shown).

TABLE 1 Selected baseline characteristics of participants with questionnaire data in the Women's Lifestyle and Health Study[1]

Characteristics	Cohort without breast cancer	Cohort with breast cancer
n	45,448	1014
Age at entry to cohort, *y*	40 ± 6	42 ± 5
BMI, *kg/m²*	23 ± 4	23 ± 4
Education, *n (%)*		
0–10 y	12,851 (30)	308 (31)
11–13 y	17,146 (39)	359 (36)
>13 y	13,633 (31)	330 (33)
Smoking status, *n (%)*		
Never	17,948 (40)	416 (41)
Ever	26,381 (60)	595 (59)
Use of oral contraceptives, *n (%)*		
Never	7183 (16)	168 (16)
Former	31,495 (71)	727 (72)
Current	5756 (13)	119 (12)
Age at first childbirth, *y*	21 ± 9	21 ± 10
Parity, *n (%)*		
Nulliparous	6105 (14)	163 (16)
1 child	6855 (15)	161 (16)
2 children	19,236 (43)	447 (44)
3 children	9251 (21)	197 (19)
≥4 children	2987 (7)	46 (5)
Age at menarche, *y*	13 ± 1	13 ± 1
Breast cancer in sisters or mothers, *n (%)*	1997 (4)	88 (9)
Total energy intake, *kJ/d*	6522 ± 1882	6395 ± 1850
Fat	32	32
Protein	16	16
Carbohydrate	52	52
Alcohol	0.6	0.8
Dietary intake,[2] *g/d*		
Meat	80 (22–147)	75 (23–137)
Dairy products	368 (14–846)	345 (17–846)
Fatty fish	8 (0–21)	8 (0–21)
Vegetables	87 (20–182)	86 (19–166)
Fruit	124 (11–308)	127 (15–329)
Cereals	139 (45–284)	137 (45–286)
Beans	3 (0–10)	3 (0–10)
Cereal fiber	8 (3–14)	8 (4–15)
Vegetable fiber	5.5 (2–15)	5.5 (2–11)

[1] Values are means ± SD or *n* (%) unless otherwise noted.
[2] Mean (5th–95th percentiles).

The mean daily intake of lignans was higher than that of isoflavonoids (**Table 2**). The intake of phytoestrogens in women who developed breast cancer did not differ substantially from the intake in women who did not develop breast cancer. In both groups, the highest median intakes of lignans were for syringaresinol and medioresinol.

Rye bread, wheat bread, cereals, and berries contributed the most to the intake of lignans, whereas beans (soy beans, other beans, and lentils) were the most important dietary source of isoflavonoids and coumestrol. Intake of berries and wine contributed 42 and 7%, respectively, to the intake of SECO (data not shown).

Dietary phytoestrogen and breast cancer risk. Dietary intakes of total lignan, total isoflavonoid compounds, or coumestrol were not associated with risk of overall breast cancer (**Table 3**). Similarly, there were no apparent associations with risk of breast

TABLE 2 Daily intake of phytoestrogen estimated from FFQ in Swedish women

	Estimated daily phytoestrogen intake					
	Cohort without breast cancer, $n = 45{,}448$			Cohort with breast cancer, $n = 1014$		
Compound	Mean ± SD	Median	Range	Mean ± SD	Median	Range
			μg/d			
Genistein	41 ± 99	1.6	0–2976	44 ± 107	1.5	0.07–1171
Daidzein	30 ± 68	4	0–2036	32 ± 74	4	0.06–803
Coumestrol	0.05 ± 0.1	0	0–3.9	0.06 ± 0.1	0	0–1.5
Formononetin	0.7 ± 0.5	0.6	0–10	0.7 ± 0.5	0.6	0–4
Biochanin A	0.2 ± 0.2	0.2	0–5	0.2 ± 0.2	0.2	0–1
Secoisolarici-resinol[1]	116 ± 43	115	0–834	120 ± 45	118	0–344
MAT	26 ± 13	24	0.4–171	27 ± 13	25	0.4–91
Lariciresinol[2]	194 ± 101	179	0–1668	196 ± 102	178	0–846
Pinoresinol[2]	162 ± 89	149	0–1363	164 ± 88	149	0–708
Syringaresinol[2]	903 ± 475	831	0–8023	911 ± 478	833	0–4000
Medioresinol[2]	352 ± 192	322	0–3036	355 ± 190	320	0–1580
Enterolactone[3]	11 ± 9	9	0–110	10 ± 8	8	0–67
Enterodiol[3]	0.04 ± 0.03	0.03	0–0.4	0.04 ± 0.03	0.03	0–0.3
Equol[3]	0.8 ± 0.7	0.7	0–8	0.7 ± 0.6	0.6	0–5
Total isoflavonoids[4]	73 ± 166	7	0–5023	78 ± 181	7	0.2–1979
Total lignans[5]	1763 ± 886	1632	15–14,473	1784 ± 887	1639	31–7435

[1] Total SECO (sum of anhydrosecoisolariciresinol and SECO).
[2] Lignan content is available only for bread and cereal products.
[3] Mammalian lignans and equol content are available only for milk products.
[4] Including genistein, daidzein, formononetin, biochanin A, and equol.
[5] SECO, MAT, lariciresinol, pinoresinol, syringaresinol, medioresinol, enterolactone, and enterodiol.

cancer when individual phytoestrogens were examined separately. Women > 50 y of age had significantly decreased risk for intermediate dietary intake of total isoflavonoids (RR = 0.74; CI%, 0.58–0.96); however, the inverse relationship was no longer significant after multivariate adjustment (RR = 0.78; CI%, 0.61–1.01). For all other compounds the risk estimates were similar for women < or >50 y of age. Multivariate adjustment for age, BMI, oral contraceptives, age at first pregnancy, age at menarche, parity, family history of breast cancer, total energy intake, intake of alcohol, and saturated fat did not change any of the estimates substantially.

Breast cancer and food items rich in phytoestrogens were not associated. For instance, the RR comparing the highest to the lowest quartile of phytoestrogen-rich food intake was 1.06 (95% CI, 0.88–1.27) (data not shown). The results were similar for food items rich in lignans (berries, nuts, crisp bread, wholegrain bread, and wine).

Dietary fiber and breast cancer risk (data not shown). Dietary intakes of total fiber, cereal fiber, or vegetable fiber were not associated with risk of breast cancer. The results were similar when we adjusted for the volume of gastrointestinal tract. For example, the RR comparing increasing quartiles of cereal fiber intake [g/(d·kg body weight)] to the lowest quartile were, respectively, 0.92 (95% CI, 0.77–1.11), 1.06 (95% CI, 0.88–1.28), and 1.03 (95% CI, 0.83–1.27), and the RR comparing increasing quartiles of vegetable fiber intake [g/(d·kg body weight)] were, respectively, 0.93 (95% CI, 0.77–1.11), 1.05 (95% CI, 0.88–1.26) and 0.98 (95% CI, 0.81–1.19).

Dietary phytoestrogen, fiber, and receptor defined breast cancer risk. Dietary intake of coumestrol was associated with hormone receptor negative tumors (PR−), (**Fig. 1**). Intermediate dietary intake of coumestrol had the strongest inverse association. After multivariate adjustment, the risk of breast cancer was 50% lower in the 2nd category of estimated intake than in the lowest category of estimated intake. There was no significant association between coumestrol categories and ER+PR+ tumors. A similar J-shaped pattern was seen for isoflavonoids and ER−PR−. However, the result was not significant and the RR comparing increasing quartiles of isoflavonoid intake to the lowest quartile among women with ER−PR− tumors were, respectively, 1.4 (95% CI, 0.9–2.2), 0.6 (95% CI, 0.4–1.1), and 0.9 (95% CI, 0.5–1.5). The effects of total lignans, individual lignans, or fiber (data not shown) were independent of hormone receptor status.

We also performed analyses for ER+PR− tumors and found no associations between intake of any of the phytoestrogen compounds or fiber and ER+PR− tumors (data not shown). Due to the low number of cases with ER−PR+ tumors, we did not perform any analysis for this subgroup. Separate analyses for ER+, ER−, PR+, and PR− tumors showed similar results as for the combined receptor groups ER+PR+ and ER−PR−.

We repeated all analyses separately for women before or after 50 y of age and the estimates were similar across age groups (data not shown).

Discussion

In this large population-based prospective cohort study, we found no inverse association between dietary intake of phytoestrogens and risk of breast cancer, either overall or by ER/PR status and the risk estimates were similar for breast cancer occurring before or after 50 y of age. However, we detected an inverse but nonlinear association between intake of coumestrol, the most estrogenic phytoestrogen compound, and ER−/PR− breast tumors.

The isoflavonoid intake in this study was low (<0.1 mg/d) as expected, because the intake of soy and beans is low and soy additives to other foods are uncommon in Sweden (28). A recent

TABLE 3 Risk of breast cancer in Swedish women in relation to estimated dietary intake of specific phytoestrogens, total lignans, and total isoflavonoids, estimated as RR with 95% CI[1,2]

	All women			Women <50 y[3]			Women ≥50 y[3]		
Dietary intake, μg/(d·MJ)	Cases/person-years	RR	95 CI%[4]	Cases/person-years	RR	95 CI%[4]	Cases/person-years	RR	95 CI%[4]
SECO	200/140,304	1.0	Reference	110/105,411	1.0	Reference	90/35,552	1.0	Reference
	235/149,058	1.04	0.86–1.26	120/108,583	1.00	0.77–1.30	115/40,904	1.08	0.82–1.43
	281/148,899	1.15	0.95–1.38	127/100,915	1.10	0.85–1.44	154/48,423	1.20	0.92–1.56
	298/146,014	1.13	0.93–1.37	137/89,289	1.28	0.97–1.69	161/57,322	1.02	0.77–1.34
MAT	215/142,564	1.0	Reference	123/109,227	1.0	Reference	92/33,900	1.0	Reference
	255/147,655	1.03	0.86–1.24	118/105,060	0.92	0.71–1.18	137/43,105	1.16	0.89–1.51
	250/148,624	0.95	0.79–1.14	135/99,961	1.07	0.84–1.37	115/49,139	0.84	0.64–1.11
	294/145,431	1.09	0.91–1.31	118/89,949	1.01	0.78–1.32	176/56,057	1.17	0.90–1.51
Lariciresinol	219/143,429	1.0	Reference	113/106,772	1.0	Reference	106/37,253	1.0	Reference
	264/148,694	1.10	0.92–1.32	135/105,023	1.17	0.91–1.50	129/44,185	1.03	0.81–1.36
	258/149,179	1.03	0.86–1.24	128/100,638	1.14	0.88–1.47	130/49,044	0.94	0.74–1.24
	273/145,863	1.10	0.92–1.32	118/93,083	1.12	0.86–1.46	155/53,392	1.08	0.85–1.41
Pinoresinol	224/143,327	1.0	Reference	120/107,173	1.0	Reference	104/36,688	1.0	Reference
	253/148,794	1.02	0.85–1.22	120/105,424	0.97	0.75–1.25	133/43,919	1.07	0.82–1.38
	270/149,086	1.05	0.88–1.26	144/100,648	1.20	0.94–1.54	126/48,978	0.92	0.71–1.20
	267/145,959	1.03	0.86–1.24	110/92,272	0.98	0.75–1.28	157/54,289	1.07	0.83–1.36
Syringaresinol	220/143,400	1.0	Reference	117/106,582	1.0	Reference	103/37,435	1.0	Reference
	261/148,590	1.08	0.90–1.30	125/104,945	1.05	0.81–1.35	136/44,132	1.12	0.88–1.48
	259/149,113	1.03	0.86–1.24	132/100,378	1.14	0.88–1.46	127/49,246	0.94	0.73–1.23
	274/146,063	1.10	0.92–1.32	120/93,611	1.10	0.85–1.43	154/53,059	1.10	0.86–1.42
Medioresinol	227/143,322	1.0	Reference	120/106,881	1.0	Reference	107/37,006	1.0	Reference
	245/148,597	0.98	0.82–1.17	118/105,154	0.96	0.74–1.24	127/43,991	1.00	0.78–1.30
	274/149,338	1.05	0.88–1.25	137/100,611	1.14	0.89–1.46	137/49,232	0.96	0.75–1.24
	268/145,909	1.02	0.86–1.23	119/92,870	1.06	0.82–1.38	149/53,646	1.00	0.78–1.29
Genistein	241/144,788	1.0	Reference	125/106,502	1.0	Reference	116/39,731	1.0	Reference
	266/148,680	1.03	0.87–1.23	131/103,082	1.05	0.82–1.35	135/46,081	1.02	0.79–1.30
	231/145,478	0.90	0.75–1.08	113/98,609	0.93	0.77–1.20	118/47,391	0.87	0.67–1.13
	276/148,219	1.01	0.84–1.20	125/98,225	0.98	0.76–1.26	151/50,671	1.03	0.80–1.31
Daidzein	229/144,153	1.0	Reference	114/105,448	1.0	Reference	115/39,288	1.0	Reference
	279/148,774	1.14	0.96–1.36	143/102,834	1.27	0.99–1.63	136/46,457	1.03	0.80–1.32
	227/145,968	0.93	0.77–1.12	109/99,131	0.99	0.75–1.29	118/47,284	0.89	0.68–1.15
	279/148,270	1.07	0.90–1.28	128/98,103	1.11	0.86–1.44	151/50,845	1.03	0.81–1.32
Coumestrol	630/369,249	1.0	Reference	315/257,943	1.0	Reference	315/11,2618	1.0	Reference
	199/115,433	0.97	0.82–1.15	90/79,956	0.86	0.68–1.10	109/35,871	1.09	0.87–1.37
	185/102,483	0.99	0.83–1.16	89/67,617	1.00	0.79–1.28	96/35,385	0.97	0.77–1.22
Total lignans[5]	216/142,898	1.0	Reference	114/107,278	1.0	Reference	102/36,190	1.0	Reference
	256/147,809	1.074	0.89–1.28	125/104,521	1.08	0.83–1.39	131/43,784	1.06	0.82–1.37
	269/148,305	1.08	0.90–1.29	137/99,958	1.21	0.94–1.56	132/48,813	0.96	0.74–1.24
	273/145,262	1.09	0.91–1.31	118/92,441	1.11	0.86–1.45	155/53,415	1.07	0.83–1.38
Total isoflavonoids[6]	249/145,168	1.0	Reference	120/105,715	1.0	Reference	129/40,020	1.0	Reference
	263/148,631	1.00	0.84–1.19	136/103,010	1.16	0.90–1.48	127/46,114	0.88	0.69–1.12
	226/145,083	0.87	0.72–1.04	112/98,594	0.97	0.75–1.27	114/46,972	0.78	0.61–1.01
	276/148,283	0.98	0.83–1.17	126/98,198	1.04	0.81–1.34	150/50,768	0.93	0.73–1.18

[1] RR (95% CI) were obtained by Cox proportional hazards models. Exposures are categorized into quartiles and the lowest quartile was used as the reference category.
[2] Intake of coumestrol was split into 3 categories, women with 0 intake form the reference group. The remaining women were split into 2 groups of equal size with a cut-off at a median of 0.014 μg/(d·MJ).
[3] Mean age of natural menopause in Swedish women is 50 y of age, and women under or above 50 y of age can be considered as pre- or postmenopausal women, respectively.
[4] Adjusted for age, BMI, oral contraceptives, age at first pregnancy, age at menarche, parity, cancer in sisters or mothers, and intake of total energy intake, alcohol, and saturated fat.
[5] Including SECO, MAT, lariciresinol, pinoresinol, syringaresinol, medioresinol, enterolactone, and enterodiol.
[6] Including genistein, daidzein, formononetin, biochanin A, and equol.

meta-analysis reported that >1 g/d soy protein (i.e. > 3 mg/d isoflavones) may reduce premenopausal breast cancer risk (2). Our finding is similar to earlier prospective cohorts in Western populations with correspondingly low soy intakes (35,36).

The lack of association between total lignans and breast cancer risk in this study does not confirm earlier findings from some case-control studies (5). However, our results are in agreement with all earlier prospective cohorts (35–37), except 1 (6) that reported an inverse association between high dietary intakes of total plant lignans as well as lariciresinol and breast cancer risk in postmenopausal French women (6). The inconsistent results may be due to differences in the populations studied. For instance, our women were mainly premenopausal at enrolment and were followed for 13 y, whereas the women in the

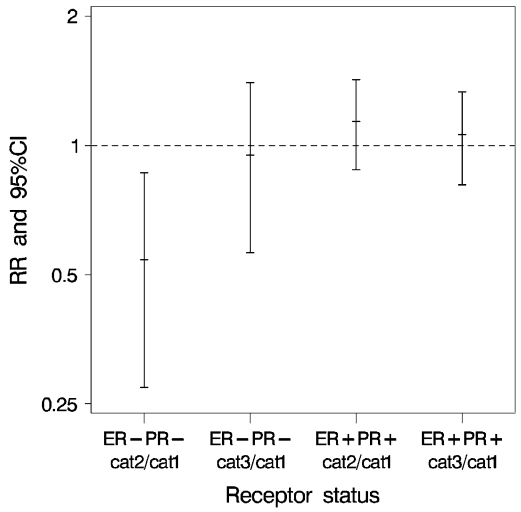

FIGURE 1 Risk of breast cancer in relation to estimated dietary intake of coumestrol, stratified by ER and PR, estimated as RR with 95% CI. RR were obtained by Cox proportional hazards models, adjusted for age, BMI, oral contraceptives, age at first pregnancy, age at menarche, parity, cancer in sisters or mothers, and intake of total energy, alcohol, and saturated fat. Intake of coumestrol was divided into 3 categories; women with 0 intake form the reference group (cat1). The remaining women were split into 2 equally large groups: cat 2 and cat 3 [cutoff at median, 0.014 μg/(d·MJ)].

French study were postmenopausal and followed for 7.7 y (6). Further, the total lignan intakes are not entirely comparable between the 2 studies. Our lignan intake was higher, because we included the new lignans syringaresinol and medioresinol and both these compounds contributed substantially to total lignan intake (51 and 20%, respectively). Another explanation for the inconsistent results may be differences in the food sources for the individual lignans. In our study, SECO and MAT originated mainly from rye bread, cereals, berries, and wine, similar to the sources found in the French study (6) and in other Western populations (38,39). However, we calculated lariciresinol from only bread and cereals, whereas the main sources of lariciresinol in the French study were cruciferous vegetables, green beans, citrus fruits, pears, tea, coffee, and bread (6). Finally, the transformation of plant lignans into mammalian lignans is highly dependent of the individual micro flora in the gut, which can differ between populations (40,41).

Intermediate levels of intake of coumestrol were inversely associated with ER− tumors. To our knowledge, such a finding has not been reported before (16,36). The coumestrol intake was low, 0.05 μg/d, which is similar to earlier reports in Western women with low soy intake (36,42). We do not know the mechanisms behind this finding, but it could be mediated through binding to ERß (43–45). The J-shaped risk function, also found in studies of enterolactone and risk of prostate cancer (28,46,47), testicular cancer (48), and breast cancer (49), is difficult to explain. It could be that high phytoestrogen levels cause alterations in hormone balance or other factors that influence both phytoestrogen metabolism and breast cancer risk or because of toxic effect of high phytoestrogen levels. Because coumestrol particularly derives from beans, including soybeans, which contain an abundance of fiber and also lignans, the possible protective effect of coumestrol could be due to the association of this isoflavone with other compounds in beans. The estrogenic activity of coumestrol is 2.4 times greater than that of genistein and 15 times stronger than that of daidzein (50). However, the low intake of coumestrol-containing food in this population could probably not lead to sufficient estrogenic activity to compete with endogenous estrogens. Our findings of a protective effect of coumestrol may be due to chance.

This is the first study, to our knowledge, which has investigated the association between the newly discovered lignans syringaresinol and medioresinol and breast cancer risk. No association was found. This finding needs to be confirmed in other populations, preferably also including the intake of these new lignans from other food sources than bread and cereal products.

Comparison between studies of dietary phytoestrogen intakes and disease is limited by differences in phytoestrogen databases used in various studies. Databases often differ in calculation methods, chosen references, analytical methods, and origin of analysis of phytoestrogens in food items. A strength of this study is that we used a phytoestrogen database designed for a Swedish population (28) and that the phytoestrogen content in the foods was analyzed by 1 method and carried out in the same laboratory (18).

The somewhat inconsistent results between phytoestrogens and breast cancer risk in different studies may to some extent be explained by diet-gene interactions. For instance, we have previously reported an inverse association between phytoestrogens, coumestrol, and isoflavonoids and prostate cancer risk that was strongly modified by a nucleotide sequence variant in the ERß gene (51). Isoflavonoids were negatively correlated with plasma estradiol levels only in women with a certain type of polymorphism in the estrogen receptor-α *Pvu* II gene (52), whereas lignans were negatively associated to estrone levels in women with specific genotypes of the estrogen receptor-α1–4 gene (53). Further, risk of breast cancer was substantially reduced in premenopausal women with high intake of lignans if they had at least 1 A2 allele for the gene CYP17 (54). Unfortunately, we could not evaluate any diet-gene interactions, because this cohort did not include any biological samples.

A recent review (55) concluded that the origin of lignans in the diet seems to play a role in affecting disease risk, particularly breast cancer risk. This seemed to be especially true for cereal fiber with its high concentrations of lignans, which influence enterohepatic circulation of estrogens (23), lowering estrogen levels and in this way reducing breast cancer risk. The intake of total fiber was low in both groups including cereal fiber intake. Our results indicate that fiber and phytoestrogens do not play any role in the development of breast cancer in this population, existing mainly of premenopausal women.

Strengths of our study include its prospective design, large size, and complete follow-up. The ethnic homogeneity of our study population reduces the risk of confounding by unmeasured factors. Cancer registration in Sweden is obligatory, making the assessment of cases virtually complete. In addition, we adjusted for several known nutritional and nonnutritional risk factors for breast cancer. Our study was limited by the fact that we were unable to adjust for use of antibiotics, because antibiotics can affect the bacterial microflora in the gut (56), which transforms plant lignans into mammalian lignans (40). Further, misclassification of phytoestrogen intake due to measurement error associated with the FFQ is unavoidable but likely nondifferential in this study, thus attenuating any true association. Food consumption was measured only once, entailing misclassification among those women who changed their dietary habits during follow-up, e.g. by increasing their flaxseed intake (rich in phytoestrogens). We can only speculate whether the flaxseed intake has increased since 1991/1992, because national surveys

have not measured trends in flaxseed intake. However, we do not think so, because dietary patterns tend to be reasonably well correlated from year to year (33). Furthermore, even though the intake of flaxseed should have increased slightly since 1991, the intake of flaxseed is probably still too low in this population to detect an association with breast cancer risk (57). Finally, another limitation is that we lacked information on joint ER/PR status for 27% of the cases. A recent study in Sweden reported that missing information on ER and PR status in the registries is more common in women with smaller breast tumors (11). Small tumors are more often receptor positive (11) and in the former study, the associations between risk factors and tumors with missing receptor status were similar to those for the ER+PR+ group (11). Our risk estimates between different phytoestrogens and breast cancer risk only differed by ER/PR status for coumestrol. In additional analyses, our risk estimates for coumestrol and tumors with unknown receptor status were similar to the corresponding results for ER+PR+ tumors.

In conclusion, we found no association between isoflavonoids, total lignans, or fiber and breast cancer risk either overall or by ER/PR status. Furthermore, the risk estimates were similar for breast cancer occurring before or after 50 y of age. Intermediate levels of coumestrol intake were associated with a decreased risk for receptor negative breast tumors, but this finding needs to be confirmed in other studies, preferably also evaluating ERß status.

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