Meta-analyses of lignans and enterolignans in relation to breast cancer risk[1–3]

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ABSTRACT

Background: Epidemiologic studies that examined whether lignans, the most important class of phytoestrogens in the Western diet, protect against breast cancer have yielded inconsistent results.

Objective: In this study, we conducted meta-analyses on the association between lignans and breast cancer risk.

Design: We performed a systematic MEDLINE search to identify epidemiologic studies published between 1997 and August 2009. We calculated pooled risk estimates (REs) for total lignan exposure, dietary lignan intake, enterolignan exposure, and blood or urine concentrations of enterolactone and according to menopausal and estrogen receptor (ER) status of tumors.

Results: We included 21 studies (11 prospective cohort studies and 10 case-control studies) in the meta-analyses. Lignan exposure was not associated with an overall breast cancer risk (RE: 0.92; 95% CI: 0.81, 1.02; *P* for heterogeneity = 0.004). However, in postmenopausal women, high lignan intake was associated with a significant reduced risk of breast cancer (13 studies; RE: 0.86; 95% CI: 0.78, 0.94; *P* for heterogeneity = 0.32). Breast cancer risk was also inversely associated with enterolignan exposure (4 studies; RE: 0.84; 95% CI: 0.71, 0.97) but not with blood or urine enterolactone concentrations. The associations were not significantly different between ER-status subgroups (6 studies).

Conclusions: High lignan exposure may be associated with a reduced breast cancer risk in postmenopausal women. Additional work is warranted to clarify the association between lignan exposure and breast cancer risk. *Am J Clin Nutr* 2010;92:141–53.

INTRODUCTION

Breast cancer is the most common type of cancer worldwide and the most common cause of cancer death among women (1). Higher circulating estrogen concentrations have been associated with an increased risk of breast cancer (2), and many of the established breast cancer risk factors are associated with exposure to endogenous or exogenous sex-steroid hormones. Phytoestrogens are plant-derived estrogen-like compounds that are able to bind to mammalian estrogen receptors (ERs) and have been postulated to have beneficial health effects (3, 4). Phytoestrogens may modulate estrogen metabolism by exerting an inhibitory effect on aromatase and, thereby, lower the amount of circulating estrogen in the body (5, 6). Further proposed protective mechanisms include stimulation of apoptosis, antioxidant activity and competitive binding to ER (3, 6–8).

There are 3 main classes of phytoestrogens: isoflavones, lignans, and coumestans. According to 2 recent meta-analyses (9, 10), consumption of soy products rich in isoflavones may be associated with a small reduction in breast cancer risk in pre- and postmenopausal women, especially in Asian populations. Plant lignans are in high concentrations in flaxseeds and sesame (11) and in appreciable concentrations in sprouts, fruits, berries, vegetables, whole grains, and green tea (12). In Western populations with a low intake of isoflavones, phytoestrogen intake is predominantly derived from intake of plant lignans (13, 14). Therefore, dietary intake of lignans may be more important for prevention purposes than isoflavone consumption. Lignans possess a weaker ER-binding affinity than isoflavones, but lignans also have anticarcinogenic properties (7, 15).

There are several ways to assess lignan exposure. Long-term dietary lignan intake can be measured by dietary questionnaires. However, before being able to enter the blood circulation to exert biologic effects, plant lignans need to be metabolized by the gut microflora into the intestinal lignan metabolites (enterolignans) enterolactone and enterodiol (16). These bioavailable metabolites can be estimated from dietary intake data by using in vitro data from incubation of foods with human feces (17), but this assessment does not take into account interindividual variations in microbial synthesis (18). Measurement of enterolignans in blood and urine (7, 19, 20) is considered to be more objective and precise but only reflects short-time exposure. Lignans could have a protective effect on the development of breast cancer (5, 21), but there is no clear evidence for an inverse association between lignans and breast cancer risk (22, 23).

Therefore, we carried out meta-analyses on epidemiologic studies addressing lignans and breast cancer risk. Lignan exposure has been addressed according to 3 different exposure measurements, including *1*) dietary intake of plant lignans, *2*) estimates of exposure to enterolignans (enterolactone and enterodiol), and *3*)

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enterolactone concentrations in blood or urine. Moreover, we assessed the effect of lignan exposure on breast cancer risk according to menopausal status and the ER status of tumors.

METHODS

Literature review for meta-analyses

A systematic MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed) search was performed to identify epidemiologic studies published between 1997 and August 2009 that reported the association between lignans and breast cancer risk. We used a combination of several Medical Subject Headings (ie, breast neoplasms, phytoestrogens, lignans, diet, nutritional sciences, blood, urine, and epidemiologic studies) and also searched for related key words in all fields. In addition, cited references in retrieved articles were reviewed to identify possible additional articles that may have been missed in the search.

Eligible publications were assessed independently by 3 reviewers (KB, AKZ, and AV). Any disagreement was resolved by consensus. We documented study design, study size, characteristics of the study population, lignan-type assessed, potential confounding factors that were adjusted for, and the dietary assessment method. Relative risks or odds ratios from regression models were extracted and used for the subsequent analyses. The most fully adjusted risk estimates (REs) and CIs for the highest quantile compared with the reference quantile (the lowest quantile) from each study were used for the meta-analyses. If only continuous REs were provided or no overall REs were reported, authors of the respective publications were addressed to obtain the REs for the highest quantile compared with the lowest quantile (18, 24). From the REs, the SE of the estimate (SEE) was directly derived as SEE = [log (95% CI, upper limit) − log (95% CI, lower limit)]/3.92 and was used in the calculation of the pooled estimates.

If REs for the whole study population (including pre- and postmenopausal women) that assessed the association between lignans and breast cancer risk were available, the estimates were used for the calculation of the pooled REs. Otherwise, when only estimates stratified by menopausal status were reported, the estimates were firstly pooled by using a fixed-effects model and included afterwards in the calculation of the pooled estimates (25–29).

We initially calculated a pooled estimate for all studies. Biomarker measurements, rather than dietary intake estimates, were included when both estimates were available from one study population. Subsequently, separate analyses were performed for dietary intake and biomarker studies. Studies using either blood or urine for biomarker measurements were analyzed together because blood and urine concentrations of enterodiol and enterolactone were previously shown to correlate very well (18). Analyses of the biomarker studies were also conducted for all women and subgroups of women according to menopausal status (overall, premenopausal, and postmenopausal) because menopausal status might modify the effects of lignans on breast cancer risk. Finally, we pooled all studies reporting separate REs by receptor status according to ER status.

Statistical methods

All analyses were carried out with the meta and rmeta packages of the statistical software environment R (version 2.7.1) (30). The statistical analyses included a test of heterogeneity to determine whether the study results (of groups) were significantly heterogeneous. Thereby, the correct model for the combination of single-study results to a common pooled estimate could be determined. Several statistical and quantifying measurements were used to assess the heterogeneity of a set of point estimates together with the respective SEs [eg, the Q statistics (31) that yielded a (2-sided) P value and the τ^2 heterogeneity estimator (32)].

Weighting was performed by the inverse-variance method (33) on the basis of 2 commonly used models: the fixed-effects model (34) and the random-effects model (32). In the prior model, one assumes that the effects are all in the same direction and, thus, are results of a common pooled effect, whereas in the latter model, there is no assumption that the effects are similar. Thus in the random-effects model, the study results are combined in a more independent way by allowing variability within and heterogeneity between studies, respectively. Fixed-effects models were used when heterogeneity was low ($P > 0.1$). Otherwise, random-effects models were used. The individual study results and combined pooled estimates were illustrated in forest plots. Analyses were conducted for all women combined, all women stratified by menopausal status, and all women stratified by ER status of their tumors. For subgroup analyses, differences between the pooled REs were determined by the Q statistic.

In addition, a sensitivity analysis was conducted to investigate publication bias of the included studies. This was visualized by using a funnel plot (35, 36) and quantified by using weighted linear regression of the effect estimate on its SEE (37).

RESULTS

Thirty-two articles (18, 22, 24–29, 38–61) that assessed the association between lignans and breast cancer risk were identified. All studies were conducted in women from Western populations, the only exception being one study (50) on the association between urinary enterolignans and breast cancer risk in postmenopausal women from Shanghai. After excluding 4 articles (45, 59–61) on the basis of smaller subgroup analyses of their respective larger studies, one article (58) that assessed intake of phytoestrogens in adolescents, one article (53) that included women having a palpable cyst, and 2 articles (24, 46) that did not report overall plant lignan or enterolignan intake, 24 articles were included in the meta-analyses. Twenty-one of these articles were independent studies: 9 studies (25, 26, 28, 29, 38, 39, 41–44) reported only on dietary intake of lignans and enterolignans, 10 studies (18, 25, 47–52, 54, 57) reported solely on biomarker measurement, and 2 studies reporting on both dietary intake and biomarker measurement assessments (22, 40, 55, 56).

Epidemiologic studies that investigated the association of dietary lignans and calculated enterolignans with breast cancer risk in premenopausal and/or postmenopausal women are summarized in **Table 1**. Of the 11 studies published, 4 studies were prospective cohort studies, and 7 studies were case-control studies. Five of these studies (26, 28, 29, 40–42) stratified their analyses by ER status of the tumor. The association between enterolignan concentrations in plasma, serum, or urine and breast cancer risk was investigated in 12 studies: 8 nested case-control studies within a cohort study and 4 case-control studies (**Table 2**). Nine studies (18, 45, 49, 51, 52, 54–57) investigated

TABLE 1
Studies on dietary lignans and calculated enterolignans and breast cancer risk included in the meta-analyses[1]

Study	Design (study name), location	Population (no. of cases/total cohort or no. of control subjects)	Phytoestrogens studied (exposure differences)	OR or RR (95% CI)	Adjustment factors/comments and dietary-assessment method
Horn-Ross et al, 2001 (38)	Population-based, case-control (Bay Area Breast Cancer Study), United States	All women (1272/1610)	Plant lignans (Q5 compared with Q1; ≥224 compared with <104 μg/d, respectively)	1.30 (1.00, 1.60)	Age, race, age at menarche, parity, lactation, total-energy intake, family history of BC, education, BMI, HRT, history of BBD 113-item FFQ
McCann et al, 2002 (25)	Population-based, case-control (WEB Study), United States	Premenopausal (301/316)	Enterolignans (Q3 compared with Q1; ≥670 compared with ≤460 μg/d, respectively)	0.49 (0.32, 0.75)	Age, education, parity, BMI, history of BBD, family history of BC, age at menarche, total-energy intake FFQ
		Postmenopausal (439/494)	Enterolignans (Q3 compared with Q1; ≥670 compared with ≤460 μg/d, respectively)	0.72 (0.51, 1.02)	
dos Santos Silva et al, 2004 (39)	Population-based, case-control, United Kingdom	All women (240/477)	Plant lignans (Q4 compared with Q1; ≥236 compared with <85 μg/d, respectively)	0.75 (0.44, 1.07)	Age at menarche, age at first birth, parous, parity, breast feeding, family history of BC, menopausal status, time since menopause, education, nonstarch polysaccharides 207-item FFQ
Keinan-Boker et al, 2004 (22)	Prospective cohort (Prospect-EPIC), Netherlands	All women (280/80,215)	Enterolignans (Q4 compared with Q1; median: 770 compared with 590 μg/d, respectively)	0.70 (0.46, 1.09)	Age at enrollment, age at first birth, height, weight, parity, physical activity, OC, HRT, marital status, education, total-energy intake 178-item FFQ
Linseisen et al, 2004 (40)	Population-based, case-control, Germany	Premenopausal (278/666)	Plant lignans (Q4 compared with Q1; ≥1428.2 compared with <302.5 μg/d, respectively)	1.10 (0.72, 1.70)	Family history of BC, parity, breast feeding, total-energy intake, BMI, alcohol, education Effect modification by ER status investigated 176-item FFQ
			Enterolignans (Q4 compared with Q1; ≥1109.8 compared with <470.4 μg/d, respectively)	0.61 (0.39, 0.98)	

(Continued)

TABLE 1 (*Continued*)

Study	Design (study name), location	Population (no. of cases/total cohort or no. of control subjects)	Phytoestrogens studied (exposure differences)	OR or RR (95% CI)	Adjustment factors/comments and dietary-assessment method
McCann et al, 2004 (26)	Population-based, case-control (WEB Study), United States	Premenopausal (315/593)	Plant lignans (Q4 compared with Q1; >673 compared with <329 μg/d, respectively)	0.66 (0.44, 0.98)	Age, education, race, BMI, age at menarche, parity, age at first birth, history of BBD, family history of BC, smoking, total-energy intake Effect modification by ER status investigated 98-item FFQ
		Postmenopausal (807/1443)	Plant lignans (Q4 compared with Q1; >713 compared with <337 μg/d, respectively)	0.93 (0.71, 1.22)	
Touillaud et al, 2006 (29) and 2007 (28)	Prospective cohort (E3N Study), France	Premenopausal (402/26,868)	Plant lignans (Q4 compared with Q1; ≥1357 compared with <843 μg/d, respectively)[2]	1.07 (0.81, 1.41)	Age, cohort, age at menarche, height, BMI, history of BBD or lobular carcinoma in situ, family history of BC, OC, HRT, age at first full-term pregnancy, parity, age at menopause, geographic area, alcohol, smoking, total-energy intake, education (only for premenopausal women) Effect modification by ER/PR status investigated for postmenopausal women 208-item FFQ
			Enterolignans (Q4 compared with Q1; ≥1289 compared with <902 μg/d, respectively)	0.94 (0.71, 1.24)	
		Postmenopausal (1469/58,049)	Plant lignans (Q4 compared with Q1; ≥1395 compared with <878 μg/d, respectively)[2]	0.83 (0.71, 0.96)	
			Enterolignans (Q4 compared with Q1; ≥896 compared with <653 μg/d, respectively)	0.89 (0.77, 1.03)	
Fink et al, 2007 (41)	Population-based case-control (LIBCSP), United States	All (1434/1404)	Plant lignans (Q5 compared with Q1; ≥9900 compared with <2100 μg/d, respectively)	0.82 (0.64, 1.04)	Age, total-energy intake Effect modification by ER/PR status investigated 94-item FFQ
		Premenopausal (457/487)	Plant lignans (Q5 compared with Q1; ≥9400 compared with <2400 μg/d, respectively)	1.24 (0.81, 1.92)	

(Continued)

TABLE 1 (*Continued*)

Study	Design (study name), location	Population (no. of cases/total cohort or no. of control subjects)	Phytoestrogens studied (exposure differences)	OR or RR (95% CI)	Adjustment factors/comments and dietary-assessment method
		Postmenopausal (977/953)	Plant lignans (Q5 compared with Q1; ≥10300 compared with <2500 μg/d, respectively)	0.69 (0.51, 0.94)	
Cotterchio et al, 2008 (42)	Population-based, case-control (Ontario Women's Diet and Health Study), Canada	All (3063/3370)	Plant lignans (Q5 compared with Q1; ≥5355 compared with <256 μg/d, respectively)[2]	0.81 (0.65, 0.99)	Age, family history of BC, history of BBD, dietary fiber intake, age at first live birth, duration HRT (only for postmenopausal women) 178-item FFQ
		Premenopausal (930/1211)	Plant lignans (Q5 compared with Q1; ≥5355 compared with <256 μg/d, respectively)	0.81 (0.58, 1.12)	
		Postmenopausal (2067/2154)	Plant lignans (Q5 compared with Q1; ≥5355 compared with <256 μg/d, respectively)	0.82 (0.63, 1.07)	
Hedelin et al, 2008 (43)	Prospective cohort (SWLH Cohort), Sweden	All (1014/1014)	Plant lignans (Q4 compared with Q1; median 1639 and 1632 μg/d for case and control subjects, respectively)[3]	1.09 (0.91, 1.31)	Age, BMI, OC, age at first pregnancy, age at menarche, parity, cancer in sisters or mothers, total-energy intake, alcohol, saturated fat 80-item FFQ
		Premenopausal		1.11 (0.86, 1.45)	
		Postmenopausal		1.07 (0.83, 1.38)	
Suzuki et al, 2008 (44)	Prospective cohort (SMC Study), Sweden	Postmenopausal (1284/51,823)	Plant lignans (Q4 compared with Q1; ≥1036 compared with ≤712 μg/d, respectively)[2]	0.83 (0.70, 0.97)	Age, height, BMI, parity, age at first birth, age at menarche, age at menopause, type of menopause, OC, HRT, family history of BC (first degree), history of BBD, total-energy intake, energy adjusted total fat intake, alcohol Effect modification by ER/PR status investigated 670-item FFQ (1987), 93-item FFQ (1997)

[1] OR, odds ratio; RR, relative risk; Q, quantile; BC, breast cancer; HRT, use of hormone replacement therapy; BBD, benign breast disease; FFQ, food-frequency questionnaire; WEB Study, Western New York Exposure and Breast Cancer Study; EPIC, European Prospective Investigation into Cancer and Nutrition; OC, use of oral contraceptives; ER, estrogen receptor; E3N Study, Etude Epidémiologique Nationale auprès de femmes de la Mutuelle Générale de l'Éducation Nationale; PR, progesterone receptor; LIBSCP, Long Island Breast Cancer Study Project; SWLH Cohort, Scandinavian Women's Lifestyle and Health Cohort; SMC, Swedish Mammography Cohort.

[2] Sum of secoisolariciresinol, matairesinol, pinoresinol, and lariciresinol.

[3] Sum of secoisolariciresinol, matairesinol, pinoresinol, lariciresinol, syringaresinol, medioresinol, enterolactone, and enterodiol.

TABLE 2
Studies on serum, urine, and plasma enterolignans and breast cancer risk included in the meta-analyses[1]

Study	Design (study name), location	Population (no. of cases/total cohort or no. of control subjects)	Phytoestrogens studied (exposure differences)	OR or RR (95% CI)	Adjustment factors and comments
Ingram et al, 1997 (47)	Hospital-based, case-control study, Australia	All women (144/144)	Urinary enterolactone (Q4 compared with Q1; ≥5250 compared with ≤1450 nmol/24 h, respectively)	0.36 (0.15, 0.86)	Age at menarche, total fat intake, alcohol
den Tonkelaar et al, 2001 (48)	Prospective cohort, nested case-control (DOM-project), Netherlands	Postmenopausal (88/268)	Urinary enterolactone (Q3 compared with Q1; mean: 969.9 compared with 235.6 μmol/mol creatinine, respectively)	1.43 (0.79, 2.59)	BMI, age at menarche, age at first birth, age at menopause, batch Effect modification by ER status investigated
Pietinen et al, 2001 (49)	Population-based, case-control (Kuopio Breast Cancer Study), Finland	All women (194/208)	Serum enterolactone (Q5 compared with Q1; >34.8 compared with <6.19 nmol/L, respectively)	0.38 (0.18, 0.77)	Age, area, age at menarche, age at first full-term pregnancy, OC, HRT, first-degree family history of BC, history of BBD, education, alcohol intake, smoking, physical activity, WHR, BMI
		Premenopausal (68/no information)	Serum enterolactone (Q5 compared with Q1; >30.0 compared with <5.5 nmol/L, respectively)	0.42 (0.10, 1.77)	
		Postmenopausal (126/no information)	Serum enterolactone (Q5 compared with Q1; >37.7 compared with <6.3 nmol/L, respectively)	0.50 (0.19, 1.28)	
Dai et al, 2002 (50)	Population-based, case-control (Shanghai Breast Cancer Study), China	All women (250/250)	Urinary enterolactone (Q3 compared with Q1; interquartile range: 0.23–4.25 and 0.50–7.56 nmoL/mg creatinine for case and control subjects, respectively)	0.42 (0.25, 0.69)	Age at first live birth, meat intake, physical activity, fibroadenoma
		Premenopausal (132/132)	Urinary enterolignans (Q3 compared with Q1; interquartile range: 0.34–5.22 and 0.82–8.56 nmoL/mg creatinine for case and control subjects, respectively)	0.24 (0.12, 0.50)	
		Postmenopausal (118/118)		0.62 (0.31, 1.26)	
Hultén et al, 2002 (51)	Prospective cohort, nested case-control (VIP, MONICA, and MSP), Sweden	All women (248/492)	Plasma enterolactone (Q4 compared with Q1; median 39.8 compared with 5.3 nmol/L, respectively)	1.10 (0.70, 1.70)	Smoking, BMI, menopausal status
Kilkkinen et al, 2004 (52)	Cross-sectional population surveys, nested case-control, Finland	All women (206/215)	Serum enterolactone (Q4 compared with Q1; median 45.4 compared with 5.3 nmol/L, respectively)	1.30 (0.73, 2.31)	Alcohol, smoking, education, BMI, physical activity
		Premenopausal (69/no information)	Serum enterolactone (Q3 compared with Q1; median 39.8 compared with 7.4 nmol/L, respectively)	0.73 (0.34, 1.59)	
		Postmenopausal (137/no information)	Serum enterolactone (Q3 compared with Q1; 38.5 compared with 6.9 nmol/L)	1.22 (0.69, 2.16)	
Olsen et al, 2004 (54)	Prospective cohort, nested case-control (Diet, Cancer and Health study), Denmark	Postmenopausal (381/381)	Plasma enterolactone (Q4 compared with Q1; >48 compared with <14.4 nmol/L, respectively)	0.55 (0.36, 0.85)	Age, HRT Effect modification by ER status investigated

(Continued)

TABLE 2 (*Continued*)

Study	Design (study name), location	Population (no. of cases/total cohort or no. of control subjects)	Phytoestrogens studied (exposure differences)	OR or RR (95% CI)	Adjustment factors and comments
Zeleniuch-Jacquotte et al, 2004 (27)	Prospective cohort, nested case-control (NYU Women's Health Study), United States	Premenopausal (198/198)	Serum enterolactone (Q5 compared with Q1; ≥24.1 compared with ≤4.98 nmol/L, respectively)	1.60 (0.70, 3.40)	Matching factors, age at menarche, family history of BC, nulliparity, age at first birth, height, BMI
		Postmenopausal (228/228)	Serum enterolactone (Q5 compared with Q1; ≥29.08 compared with ≤5.4 nmol/L, respectively)	1.00 (0.50, 2.10)	
Piller et al, 2006 (55)	Population-based, case-control, Germany	Premenopausal (192/231)	Plasma enterolactone (Q4 compared with Q1; median 24.96 compared with 1.38 nmol/L, respectively)	0.38 (0.17, 0.85)	Family history of BC, number of births, duration of breast feeding, age at menarche, OC use, alcohol, BMI, education, day of TR-FIA, time between surgery, day of blood sampling
Verheus et al, 2007 (56)	Prospective cohort, nested case-control (Prospect-EPIC), Netherlands	All women (383/383)	Plasma enterolactone (Q3 compared with Q1)	1.10 (0.76, 1.57)	Crude REs for all women Adjusted for age at menarche and having a family history of BC for pre- and postmenopausal women
		Premenopausal (87/87)	Plasma enterolactone (Q3 compared with Q1; interquartile range: 1.66–6.24 and 1.66–5.01 ng/mL for case and control subjects, respectively)	1.72 (0.80, 3.71)	
		Postmenopausal (296/296)	Plasma enterolactone (Q3 compared with Q1; interquartile range: 1.58–5.12 and 1.48–5.49 ng/mL for case and control subjects, respectively)	0.97 (0.63, 1.48)	
Sonestedt et al, 2008 (57)	Prospective cohort, nested case-control, (MDC Study), Sweden	Postmenopausal (366/733)	Plasma enterolactone (Q4 compared with Q1; median 36.8 compared with 4.9 nmol/L, respectively)	0.73 (0.45, 1.19)	Weight, height, education, smoking, household activity, alcohol consumption, age at menopause, parity, age at first birth, current HRT Effect modification by ER status investigated
Ward et al, 2008 (18)	Prospective cohort, nested case-control (EPIC-Norfolk), United Kingdom	All women (219/891)	Serum enterolactone (Q4 compared with Q1; mean: 8.34 ng/mL)	1.12 (0.70, 1.79)	Age, weight, family history of BC, social class, use of oral contraceptives, menopausal status, HRT, parity, breastfeeding, age at menarche, fat, energy intake, batch Effect modification by ER status investigated

[1] OR, odds ratio; RR, relative risk; Q, quantile; DOM-project, Diagnostisch Onderzoek Mammacarcinoom-project; ER, estrogen receptor; OC, oral contraceptives; HRT, use of hormone replacement therapy; BC, breast cancer; BBD, benign breast disease; WHR, waist-to-hip ratio; VIP, The Västerbotten Intervention Project; MONICA, Monitoring of Trends and Cardiovascular Disease study; EPIC, European Prospective Investigation into Cancer and Nutrition; MSP, Mammary Screening Project; NYU, New York University; TR-FIA, time-resolved fluoroimmunoassay; REs, risk estimates; MDC, Malmö Diet and Cancer Study.

the effect of enterolactone in plasma or serum, and 3 studies (47, 48, 50) assessed the effect of urinary enterolactone. Four studies (18, 48, 54, 57) examined the association of blood or urine enterolactone concentrations for ER-positive and ER-negative breast tumors, separately. Quantiles used for the calculation of the REs and adjustment variables are also shown in Tables 1 and 2.

Dietary intake of lignans or calculated enterolignans was inversely associated with breast cancer risk in 9 (22, 25, 26, 28, 39–42, 44) of the 11 studies (3 prospective cohort and 6 case-control studies). In the other studies (29, 43), nonsignificant increased breast cancer risks with higher plant lignan intake were observed. For the separate calculation of enterolignans, 4 studies (22, 25, 28, 29, 40) showed inverse associations with breast cancer risk. Six (47, 49, 50, 54, 55, 57) of the 12 studies on enterolignan concentrations in plasma, serum, or urine showed decreased breast cancer REs, and 4 of the mentioned studies were significant (47, 49, 54, 55). Overall, there was no significant decreased risk of breast cancer associated with the highest compared with the lowest quantiles of lignan exposure (intake or biomarker-based), with a pooled RE of 0.92 (95% CI: 0.81, 1.02) (**Figure 1**, **Table 3**). There was significant heterogeneity across studies ($P_{\text{heterogeneity}} = 0.005$). When subgrouping the studies by menopausal status, no association for premenopausal women was shown, but a significant inverse association for postmenopausal women was observed (pooled RE: 0.86; 95% CI: 0.78, 0.94).

Nine studies (18, 26, 28, 40, 41, 44, 48, 54, 57) also evaluated the association of lignans and enterolignans with breast cancer risk by ER status, and 7 (26, 28, 41, 44, 48, 54, 57) of these studies were in postmenopausal women. One study (22) only reported REs for ER-positive but not ER-negative tumors. Another study (48) did not report REs and only mentioned a slight change in risk when considering ER-positive tumors compared with the whole study population. High lignan exposure was not significantly associated with either ER-positive or ER-negative tumors (data not shown). In postmenopausal women, there was no indication that high lignan intakes were differently associated with ER-positive tumors (pooled RE: 0.82; 95% CI: 0.69, 0.94) and ER-negative tumors (pooled RE: 0.87; 95% CI: 0.67, 1.08) ($P_{\text{interaction}} = 0.70$).

The association with breast cancer risk separately for calculated dietary plant lignans and dietary enterolignans is shown in **Figure 2**. There was an inverse association between dietary plant lignans and breast cancer risk, which was not significant (pooled RE: 0.94; 95% CI: 0.82, 1.05) (Figure 2A), and studies were significantly heterogeneous ($P_{\text{heterogeneity}} = 0.02$, $\tau^2 = 0.0159$) (Table 3). When subgrouping the studies by menopausal status, no association for premenopausal women was shown, but a significant inverse association for postmenopausal women was observed (pooled RE: 0.86; 95% CI: 0.77, 0.94). High exposure to dietary enterolignans reduced breast cancer risk by 16% (pooled RE: 0.84; 95% CI: 0.71, 0.97 (Figure 2B), and there was no significant heterogeneity across studies ($P_{\text{heterogeneity}} = 0.42$, $\tau^2 = 0$) (Table 3).

The combined breast cancer REs of studies that assessed plasma, serum, and urinary enterolactone concentrations are shown in **Figure 3**. Overall, no significant association was observed; the pooled RE was 0.90 (95% CI: 0.69, 1.10), and there was significant heterogeneity between studies ($P_{\text{heterogeneity}} = 0.03$, $\tau^2 = 0.0597$) (Table 3). Assessment by menopausal status revealed nonsignificant reduced REs in premenopausal (pooled RE: 0.70; 95% CI: 0.32, 1.07; $\tau^2 = 0.1540$) and postmenopausal women (pooled RE: 0.85; 95% CI: 0.63, 1.07; $\tau^2 = 0.0380$)

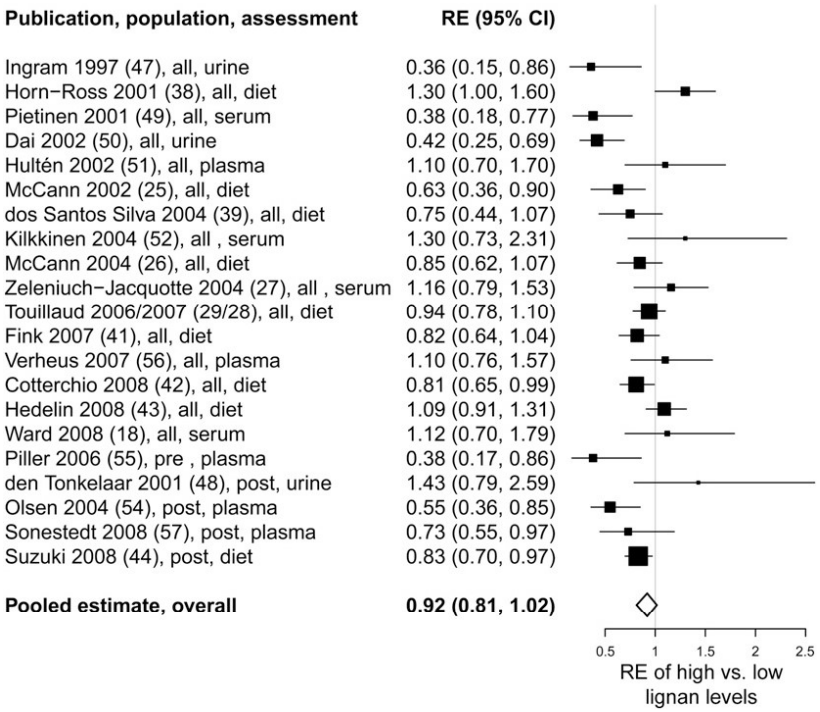

FIGURE 1. Association between enterolignans/lignans and breast cancer risk. Risk estimates (RE) from individual studies are represented by black filled boxes. Pooled estimates with 95% CIs from random-effects models are represented by unfilled diamonds. Relative sample sizes are represented by the sizes of symbols. Horizontal lines indicate 95% CIs for the respective RE. Premenopausal women (pre), postmenopausal women (post), and a combination of pre- and postmenopausal women (all) are shown.

TABLE 3
Results of the meta-analyses for calculated dietary plant lignans, calculated dietary enterolignans, and measured enterolactone (blood or urine) overall and by subgroups[1]

Group	No. of studies	τ^{2}[2]	$P_{\text{heterogeneity}}$[3]	Model used	Pooled estimate (95% CI)
All lignan-exposure measurements combined					
All studies	21	0.0246	0.0050	REM	0.92 (0.81, 1.02)
Premenopausal	10	0.0476	0.0450	REM	0.87 (0.66, 1.08)
Postmenopausal	13	0.0027	0.3472	FEM	0.86 (0.78, 0.94)
ER-positive	6	0	0.6929	FEM	0.82 (0.69, 0.94)
ER-negative	6	0	0.6028	FEM	0.87 (0.67, 1.08)
Calculated dietary plant lignans					
All studies	9	0.0159	0.0214	REM	0.94 (0.82, 1.05)
Premenopausal	6	0.0081	0.2729	FEM	1.01 (0.87, 1.15)
Postmenopausal	6	0	0.4900	FEM	0.86 (0.77, 0.94)
ER-positive	4	0	0.5468	FEM	0.85 (0.71, 0.99)
ER-negative	4	0	0.5080	FEM	0.90 (0.68, 1.12)
Calculated dietary enterolignans					
All studies	4	0	0.4197	FEM	0.84 (0.71, 0.97)
Measured enterolactone					
All studies	12	0.0597	0.0301	REM	0.90 (0.69, 1.10)
Premenopausal	5	0.1540	0.1195	FEM	0.70 (0.32, 1.07)
Postmenopausal	7	0.0380	0.2046	FEM	0.85 (0.63, 1.07)
ER-positive	2	0	0.8340	FEM	0.71 (0.47, 0.96)
ER-negative	2	0	0.3356	FEM	0.72 (0.21, 1.24)

[1] ER, estrogen receptor; FEM, fixed-effects model; REM, random-effects model.
[2] Estimator for heterogeneity.
[3] Values based on the Q statistic of heterogeneity (2-sided).

when the highest to the lowest quantiles of enterolactone were compared. Two biomarker measurement studies (18, 57) also showed no differential association for postmenopausal ER-positive and ER-negative tumors ($P_{\text{interaction}} = 0.98$).

DISCUSSION

We conducted several meta-analyses to assess the strength of the current evidence for an effect of high lignan intake compared with low lignan intake on breast cancer risk and included 11 cohort (or nested case-control) and 10 case-control studies. Overall, no clear association between lignan exposure (dietary or biomarker assessment) and breast cancer risk was observed, and there was significant heterogeneity across studies. However, in postmenopausal women we showed a significant decreased breast cancer risk on the basis of 13 studies that showed limited heterogeneity. The inverse association did not appear to be different for ER-positive and ER-negative tumors. When differentiating by lignan-exposure measurements, this risk reduction in postmenopausal women remained significant for high dietary plant-lignan intake. Although based on only 4 studies, an overall significant protective effect of high dietary enterolignan exposure was also shown. Enterolactone concentrations were not associated with a risk overall or by menopausal status.

Significant findings according to lignan-exposure measurements were recently reported (62). Pooled REs in those meta-analyses were in the same direction but slightly different because of differences in inclusion criteria (eg, no overall effect estimation and exclusion of studies of urine measurements), and stratification by ER status was not performed (62). These observations suggest that plant lignans confer a protective effect for breast cancer in postmenopausal women but not in premenopausal women. It is possible that the mechanism by which lignans act may be effective only at low endogenous estradiol concentrations as shown in postmenopausal women. Higher lignan concentrations were shown to be associated with higher sex hormone–binding globulin (SHBG) concentrations and higher binding of free estradiol (63, 64). Enterolactone may reduce estrogen concentrations through the inhibition of enzymes involved in estrogen synthesis and metabolism, such as aromatase and 17 β-hydroxsteroid dehydrogenase (65, 66).

We did not observe any difference in lignan effects according to ER status of tumors, which corroborates additional proposed mechanisms of action including the reduction of angiogenesis and stimulation of apoptosis (7, 67). Flaxseed, the main source of dietary lignans, was shown to be able to inhibit the proliferation of ER-positive and ER-negative tumor cells (68, 69). Thus, it is also possible that other food constituents in lignan-rich diets, for example α-linoleic acid (70), cause a protective effect (62). Unfortunately, potential differential effects of lignan exposure on the risk of ER-positive and ER-negative breast cancer could not be fully elucidated because only a small number of studies stratified their results by ER status. More studies assessing the effect modification by ER status are needed to clarify this issue.

There are strengths and limitations to the different measures of lignan exposure. Food-frequency questionnaires assess dietary habits generally over the entire previous 6 months or longer and, thus, are able to capture the long-term situation of lignan intake. However, there are limitations leading to measurement errors that are not only due to recall bias but also to the estimation by using food-composition databases, which may not be complete for the whole range of foods consumed (39). Measured enterolactone concentrations are expected to reflect short-term intake and were previously shown to weakly correlate with dietary intake of plant

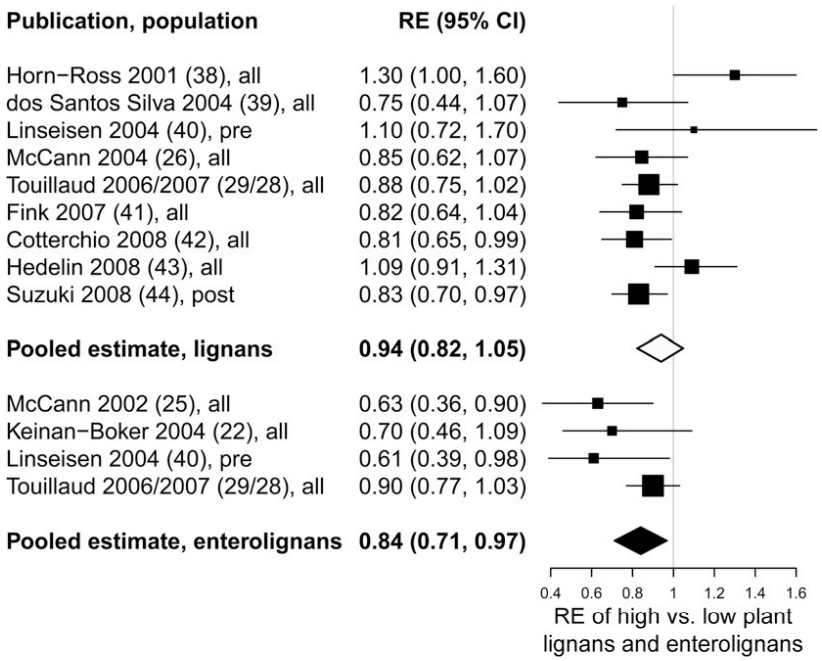

FIGURE 2. Association between calculated dietary plant lignans and enterolignans with breast cancer in studies. Risk estimates (RE) from individual studies are represented by black filled boxes. Pooled estimates with 95% CIs from random-effects models are represented by unfilled diamonds. Pooled estimates with 95% CIs from fixed-effects models are represented by filled black diamonds. Relative sample sizes are represented by the sizes of symbols. Horizontal lines indicate 95% CIs for the respective RE. Premenopausal women (pre), postmenopausal women (post), and a combination of pre- and postmenopausal women (all) are shown.

lignans (55). However, we did not find a significant risk reduction in studies measuring enterolactone concentrations in body fluids, although 2 studies (28, 57) observed a significant reduced risk in postmenopausal women with ER-positive tumors. Biomarker measurements, which account for activity of the intestinal microflora, are considered to be more accurate and not prone to recall bias; however, measurement in a single blood or urine sample may only reflect recent dietary intake. As the gut microflora may differ by its concentration and composition from one person to the other (71), antimicrobials (ie, antibiotics) may lead to intra- and interindividual variations in amounts of intestinal lignan metabolites that are converted from consumed lignans by the gut bacteria (72). Further, intraindividual variation within and between days (73) and interindividual variation in age, bowel movement, body mass index, and other lifestyle factors, such as smoking, may affect serum-enterolactone concentrations (15, 74, 75). It has also been suggested that gut transit time and a diet rich in fat modulate the production of enterolignans and, thus, may contribute to interindividual variation (15, 75, 76). However, antibiotics are regarded to have the strongest effect (15). Enterolactone measurements may also be affected by cancer therapy after diagnosis; for example, isoflavones and lignans were both shown to affect tamoxifen action (77, 78).

Heterogeneity was shown to be significant when all studies and in some subgroups of the meta-analyses were considered. Although random-effects models were used to account for heterogeneity, this may have had an effect on the estimation of pooled effects. There are multiple possible sources of heterogeneity. Study heterogeneity in the overall estimate may have been attributable to the fact that different measurement types (dietary intakes and biomarker measurements) were combined and that the intakes between the studies varied strongly. The observation that the pooled estimates separately for the different measurement types were also significantly heterogeneous suggests that combining different measurement types may not fully explain the heterogeneity observed. Stratification by menopausal status reduced heterogeneity, particularly for the pooled estimates for postmenopausal women. If the effect of lignan exposure is truly differential by menopausal status, combining studies in pre- and postmenopausal women may have led to considerable heterogeneity in the overall effect. Generally, there was greater study heterogeneity for premenopausal women than for postmenopausal women, which, in part, might also be due to the smaller size of studies in premenopausal women.

The large differences in lignan and enterolignan concentrations between the studies may be another source of heterogeneity. Although some of this variation may be real, the use of various dietary databases may have led to differences in estimated plant-lignan intake between the studies. It is also likely that recent studies used more complete databases, so that more recent studies may have generally estimated higher plant-lignan intake than earlier studies. Some recent studies also estimated intake of the plant lignans pinoresinol, and lariciresinol in addition to secoisolariciresinol and matairesinol. Thus, our pooled estimates may have been affected by comparisons made at different amounts of plant-lignan intake. The studies also used different quantile ranges to categorize their data, which resulted in varying increments of lignan exposures between the studies. This is a drawback of our analyses and meta-analyses in general, in which estimates of different increments of quantitative exposure are used for pooling. From each study we used the estimates of the highest quantile compared with the lowest quantile of exposure because the individual intake values were not available; thus, we recognized that these increments may not be comparable because of variation in lignan exposure levels and increment levels between studies. Moreover, several studies indicated

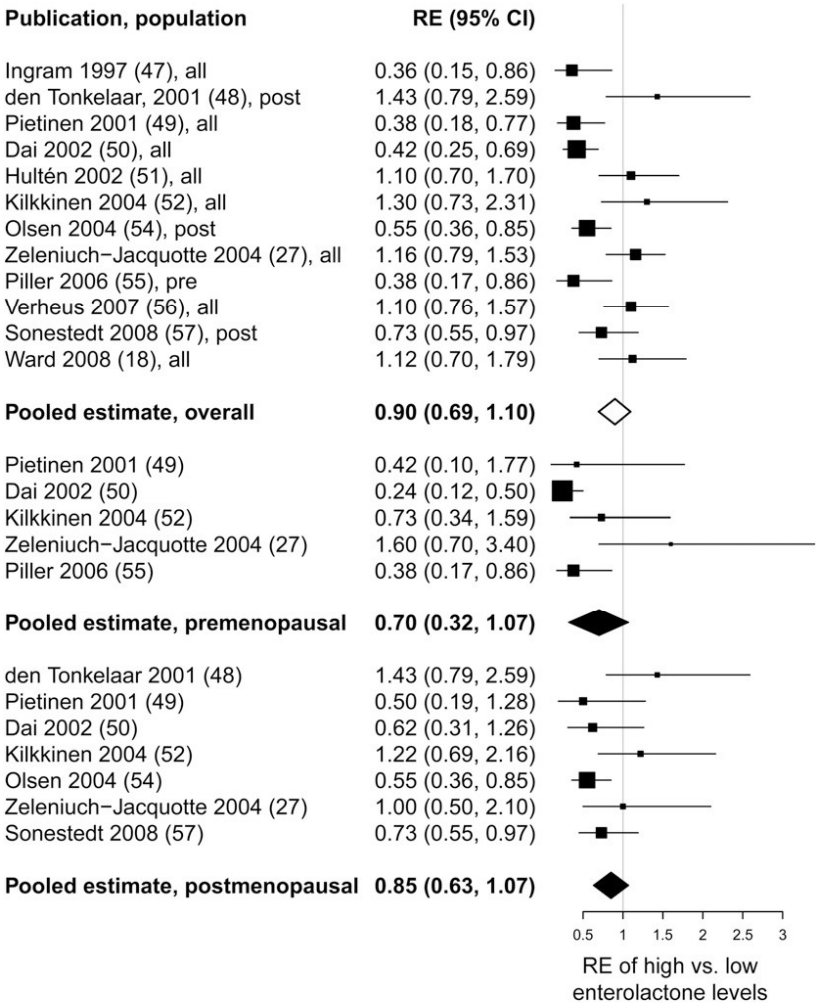

FIGURE 3. Association between serum, plasma, and urine enterolactone biomarkers with breast cancer risk according to menopausal status. Risk estimates (RE) from individual studies are represented by black filled boxes. Pooled estimates with 95% CIs from random-effects models are represented by unfilled diamonds. Pooled estimates from fixed-effects models are represented by filled black diamonds. Relative sample sizes are represented by the sizes of symbols. Horizontal lines indicate 95% CIs for the respective RE. Premenopausal women (pre), postmenopausal women (post), and a combination of pre- and postmenopausal women (all) are shown.

a nonlinear association between lignan exposure (22, 26–29, 38, 42, 51, 52, 54, 56, 57) and breast cancer risk, which we were not able to investigate.

Finally, general study aspects are likely to contribute to heterogeneity between the studies as well. All individual study REs were adjusted for potential but varying confounding factors, and therefore, residual confounding cannot be excluded. Several studies (38, 39, 47, 51) reported an overall number of case and control subjects without specifying the exact number of pre- and postmenopausal participants. Also, several studies (18, 22, 38, 39, 47, 51) did not analyze or report their data by menopausal status; therefore, not all studies could be included in the subgroup analysis according to menopausal status.

Publication bias can be excluded because the funnel plots were relatively symmetrical (the funnel plot for all studies is shown in **Figure 4**), and the linear regression analysis resulted in nonsignificant asymmetry of the funnel plot for all studies (P = 0.56).

Phytoestrogen-gene interactions may explain, in part, the conflicting results with respect to the effects of phytoestrogens on breast cancer risk (65). For example, phytoestrogens may modulate sex hormone–binding globulin and sex-hormone concentrations in postmenopausal women and interact with genetic variants involved in estrogen signaling pathways. Nevertheless, not much is known in the field of lignans and genetic polymorphisms in association with breast cancer risk. Two studies (25, 61) reported that the *CYP17* 5′-untranslated region *Msp*A1 genetic polymorphism modifies the association between lignan exposure and premenopausal breast cancer risk. Another recent study showed suggestive evidence for an interaction between enterolactone concentrations and one of several investigated polymorphisms in the ER α gene (79).

The effect of phytoestrogens on breast cancer prognosis has scarcely been investigated. One study (80) observed no association between high lignan intake compared with low lignan intake in relation to breast cancer–specific mortality (hazard ratio: 0.95; 95% CI: 0.60, 1.51). Additional experimental studies in the estrogenic and nonestrogenic activities of different lignans in breast tissue may help to elucidate the biological mechanisms of phytoestrogens in modulating breast cancer risk.

In conclusion, lignans were not significantly inversely associated with overall breast cancer risk. However, we showed that

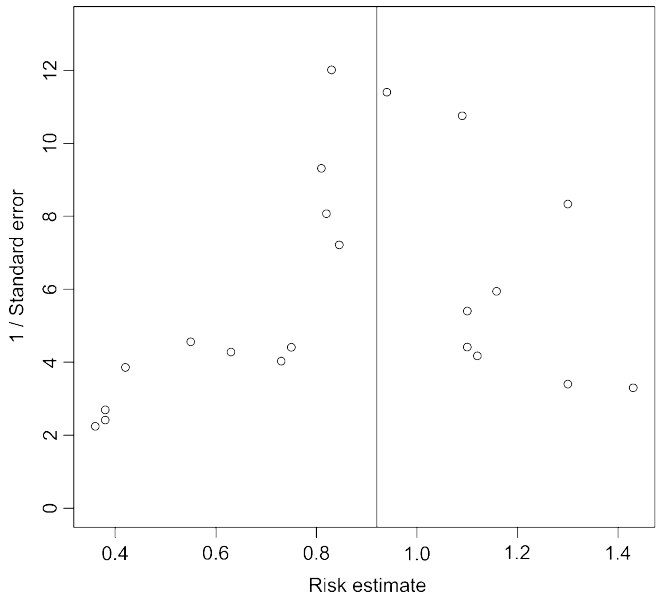

FIGURE 4. Funnel plot of risk estimates of all studies included in the meta-analyses for high lignan exposure compared with low lignan exposure and the inverse SE of the risk estimates.

high lignan exposure, particularly high plant-lignan intake, was associated with a risk reduction especially in postmenopausal women. It remains unclear whether the effect of lignans on breast cancer risk differs by ER status of the tumor. Therefore, further studies are warranted to confirm the observed protective effect of lignan exposure on postmenopausal breast cancer risk, and to assess possible genetic modifying effects that could clarify the association between exposure to lignans and breast cancer risk.

The authors' responsibilities were as follows—KB, AKZ, AV, JL, and JC-C: contributed to the conception and design of the manuscript; KB: performed statistical analyses and compiled the final manuscript; KB, AKZ, and AV: contributed to the literature search, interpretation of data, figures, and tables, and writing of the manuscript; KB and AKZ: wrote the first version of the manuscript; AV, JL, and JC-C: read and critically revised the manuscript; and all authors: approved the final manuscript. None of the authors reported a conflict of interest.

REFERENCES

1. Hortobagyi GN, de la Garza SJ, Pritchard K, et al. The global breast cancer burden: variations in epidemiology and survival. Clin Breast Cancer 2005;6:391–401.
2. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. N Engl J Med 2006;354:270–82.
3. Piersen CE. Phytoestrogens in botanical dietary supplements: implications for cancer. Integr Cancer Ther 2003;2:120–38.
4. Adlercreutz H. Phyto-oestrogens and cancer. Lancet Oncol 2002;3: 364–73.
5. Haggans CJ, Hutchins AM, Olson BA, Thomas W, Martini MC, Slavin JL. Effect of flaxseed consumption on urinary estrogen metabolites in postmenopausal women. Nutr Cancer 1999;33:188–95.
6. Adlercreutz H, Bannwart C, Wahala K, et al. Inhibition of human aromatase by mammalian lignans and isoflavonoid phytoestrogens. J Steroid Biochem Mol Biol 1993;44:147–53.
7. Mense SM, Hei TK, Ganju RK, Bhat HK. Phytoestrogens and breast cancer prevention: possible mechanisms of action. Environ Health Perspect 2008;116:426–33.
8. Rice S, Whitehead SA. Phytoestrogens and breast cancer–promoters or protectors? Endocr Relat Cancer 2006;13:995–1015 .
9. Trock BJ, Hilakivi-Clarke L, Clarke R. Meta-analysis of soy intake and breast cancer risk. J Natl Cancer Inst 2006;98:459–71.
10. Wu AH, Yu MC, Tseng CC, Pike MC. Epidemiology of soy exposures and breast cancer risk. Br J Cancer 2008;98:9–14.
11. Coulman KD, Liu Z, Hum WQ, Michaelides J, Thompson LU. Whole sesame seed is as rich a source of mammalian lignan precursors as whole flaxseed. Nutr Cancer 2005;52:156–65.
12. Mazur W. Phytoestrogen content in foods. Baillieres Clin Endocrinol Metab 1998;12:729–42.
13. Yuan JM, Wang QS, Ross RK, Henderson BE, Yu MC. Diet and breast cancer in Shanghai and Tianjin, China. Br J Cancer 1995;71:1353–8.
14. Lee HP, Gourley L, Duffy SW, Esteve J, Lee J, Day NE. Dietary effects on breast-cancer risk in Singapore. Lancet 1991;337:1197–200.
15. Adlercreutz H. Lignans and human health. Crit Rev Clin Lab Sci 2007; 44:483–525.
16. Borriello SP, Setchell KD, Axelson M, Lawson AM. Production and metabolism of lignans by the human faecal flora. J Appl Bacteriol 1985; 58:37–43.
17. Thompson LU, Robb P, Serraino M, Cheung F. Mammalian lignan production from various foods. Nutr Cancer 1991;16:43–52.
18. Ward H, Chapelais G, Kuhnle GG, Luben R, Khaw KT, Bingham S. Breast cancer risk in relation to urinary and serum biomarkers of phytoestrogen exposure in the European Prospective into Cancer-Norfolk cohort study. Breast Cancer Res 2008;10:R32.
19. Niemeyer HB, Honig D, Lange-Bohmer, Jacobs E, Kulling SE, Metzler M. Oxidative metabolites of the mammalian lignans enterodiol and enterolactone in rat bile and urine. J Agric Food Chem 2000;48:2910–9.
20. Lampe JW, Atkinson C, Hullar MA. Assessing exposure to lignans and their metabolites in humans. J AOAC Int 2006;89:1174–81.
21. Haggans CJ, Travelli EJ, Thomas W, Martini MC, Slavin JL. The effect of flaxseed and wheat bran consumption on urinary estrogen metabolites in premenopausal women. Cancer Epidemiol Biomarkers Prev 2000;9: 719–25.
22. Keinan-Boker L, van der Schouw YT, Grobbee DE, Peeters PH. Dietary phytoestrogens and breast cancer risk. Am J Clin Nutr 2004;79:282–8.
23. Boccardo F, Puntoni M, Guglielmini P, Rubagotti A. Enterolactone as a risk factor for breast cancer: a review of the published evidence. Clin Chim Acta 2006;365:58–67.
24. Horn-Ross PL, Hoggatt KJ, West DW, et al. Recent diet and breast cancer risk: the California Teachers Study (USA). Cancer Causes Control 2002;13:407–15.
25. McCann SE, Moysich KB, Freudenheim JL, Ambrosone CB, Shields PG. The risk of breast cancer associated with dietary lignans differs by CYP17 genotype in women. J Nutr 2002;132:3036–41.
26. McCann SE, Muti P, Vito D, Edge SB, Trevisan M, Freudenheim JL. Dietary lignan intakes and risk of pre- and postmenopausal breast cancer. Int J Cancer 2004;111:440–3.
27. Zeleniuch-Jacquotte A, Adlercreutz H, Shore RE, et al. Circulating enterolactone and risk of breast cancer: a prospective study in New York. Br J Cancer 2004;91:99–105.
28. Touillaud MS, Thiebaut AC, Fournier A, Niravong M, Boutron-Ruault MC, Clavel-Chapelon F. Dietary lignan intake and postmenopausal breast cancer risk by estrogen and progesterone receptor status. J Natl Cancer Inst 2007;99:475–86.
29. Touillaud MS, Thiebaut AC, Niravong M, Boutron-Ruault MC, Clavel-Chapelon F. No association between dietary phytoestrogens and risk of premenopausal breast cancer in a French cohort study. Cancer Epidemiol Biomarkers Prev 2006;15:2574–6.
30. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2008.
31. Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10:101–29.
32. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
33. Hedges LV, Olkin I. Statistical methods for meta-analysis. New York, NY: Academic Press, 1985.
34. Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. Stat Med 1991;10:1665–77.
35. Light RJ, Pillemer DB. Summing up. The science of reviewing research. Cambridge, MA: Harvard University Press, 1984.
36. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol 2001;54:1046–55.
37. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–33.

38. Horn-Ross PL, John EM, Lee M, et al. Phytoestrogen consumption and breast cancer risk in a multiethnic population: the Bay Area Breast Cancer Study. Am J Epidemiol 2001;154:434–41.
39. dos Santos Silva I, Mangtani P, McCormack V, Bhakta D, McMichael AJ, Sevak L. Phyto-oestrogen intake and breast cancer risk in South Asian women in England: findings from a population-based case-control study. Cancer Causes Control 2004;15:805–18.
40. Linseisen J, Piller R, Hermann S, Chang-Claude J. Dietary phytoestrogen intake and premenopausal breast cancer risk in a German case-control study. Int J Cancer 2004;110:284–90 .
41. Fink BN, Steck SE, Wolff MS, et al. Dietary flavonoid intake and breast cancer risk among women on Long Island. Am J Epidemiol 2007;165: 514–23 .
42. 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.
43. Hedelin M, Lof M, Olsson M, Adlercreutz H, Sandin S, Weiderpass E. 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. J Nutr 2008;138:938–45.
44. Suzuki R, Rylander-Rudqvist T, Saji S, Bergkvist L, Adlercreutz H, Wolk A. Dietary lignans and postmenopausal breast cancer risk by oestrogen receptor status: a prospective cohort study of Swedish women. Br J Cancer 2008;98:636–40.
45. McCann SE, Kulkarni S, Trevisan M, et al. Dietary lignan intakes and risk of breast cancer by tumor estrogen receptor status. Breast Cancer Res Treat 2006;99:309–11.
46. Torres-Sanchez L, Galvan-Portillo M, Wolff MS, Lopez-Carrillo L. Dietary consumption of phytochemicals and breast cancer risk in Mexican women. Public Health Nutr 2009;12:825–31.
47. Ingram D, Sanders K, Kolybaba M, Lopez D. Case-control study of phyto-oestrogens and breast cancer. Lancet 1997;350:990–4.
48. den Tonkelaar I, Keinan-Boker L, Veer PV, et al. Urinary phytoestrogens and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 2001;10:223–8.
49. Pietinen P, Stumpf K, Mannisto S, Kataja V, Uusitupa M, Adlercreutz H. Serum enterolactone and risk of breast cancer: a case-control study in eastern Finland. Cancer Epidemiol Biomarkers Prev 2001;10:339–44.
50. Dai Q, Franke AA, Jin F, et al. Urinary excretion of phytoestrogens and risk of breast cancer among Chinese women in Shanghai. Cancer Epidemiol Biomarkers Prev 2002;11:815–21.
51. Hultén K, Winkvist A, Lenner P, Johansson R, Adlercreutz H, Hallmans G. An incident case-referent study on plasma enterolactone and breast cancer risk. Eur J Nutr 2002;41:168–76.
52. Kilkkinen A, Virtamo J, Vartiainen E, et al. Serum enterolactone concentration is not associated with breast cancer risk in a nested case-control study. Int J Cancer 2004;108:277–80.
53. Boccardo F, Lunardi G, Guglielmini P, et al. Serum enterolactone levels and the risk of breast cancer in women with palpable cysts. Eur J Cancer 2004;40:84–9.
54. Olsen A, Knudsen KE, Thomsen BL, et al. Plasma enterolactone and breast cancer incidence by estrogen receptor status. Cancer Epidemiol Biomarkers Prev 2004;13:2084–9.
55. Piller R, Chang-Claude J, Linseisen J. Plasma enterolactone and genistein and the risk of premenopausal breast cancer. Eur J Cancer Prev 2006;15:225–32.
56. Verheus M, van Gils CH, Keinan-Boker L, Grace PB, Bingham SA, Peeters PH. Plasma phytoestrogens and subsequent breast cancer risk. J Clin Oncol 2007;25:648–55.
57. Sonestedt E, Borgquist S, Ericson U, et al. Enterolactone is differently associated with estrogen receptor beta-negative and -positive breast cancer in a Swedish nested case-control study. Cancer Epidemiol Biomarkers Prev 2008;17:3241–51.
58. Thanos J, Cotterchio M, Boucher BA, Kreiger N, Thompson LU. Adolescent dietary phytoestrogen intake and breast cancer risk (Canada). Cancer Causes Control 2006;17:1253–61.
59. Grace PB, Taylor JI, Low YL, et al. Phytoestrogen concentrations in serum and spot urine as biomarkers for dietary phytoestrogen intake and their relation to breast cancer risk in European prospective investigation of cancer and nutrition-norfolk. Cancer Epidemiol Biomarkers Prev 2004;13:698–708.
60. Piller R, Verla-Tebit E, Wang-Gohrke S, Linseisen J, Chang-Claude J. CYP17 genotype modifies the association between lignan supply and premenopausal breast cancer risk in humans. J Nutr 2006;136: 1596–603.
61. Dai Q, Franke AA, Yu H, et al. Urinary phytoestrogen excretion and breast cancer risk: evaluating potential effect modifiers endogenous estrogens and anthropometrics. Cancer Epidemiol Biomarkers Prev 2003;12:497–502.
62. Velentzis LS, Cantwell MM, Cardwell C, Keshtgar MR, Leathem AJ, Woodside JV. Lignans and breast cancer risk in pre- and post-menopausal women: meta-analyses of observational studies. Br J Cancer 2009;100:1492–8.
63. Adlercreutz H, Hockerstedt K, Bannwart C, et al. Effect of dietary components, including lignans and phytoestrogens, on enterohepatic circulation and liver metabolism of estrogens and on sex hormone binding globulin (SHBG). J Steroid Biochem 1987;27:1135–44.
64. Low YL, Dunning AM, Dowsett M, et al. Phytoestrogen exposure is associated with circulating sex hormone levels in postmenopausal women and interact with ESR1 and NR1I2 gene variants. Cancer Epidemiol Biomarkers Prev 2007;16:1009–16.
65. Wang C, Makela T, Hase T, Adlercreutz H, Kurzer MS. Lignans and flavonoids inhibit aromatase enzyme in human preadipocytes. J Steroid Biochem Mol Biol 1994;50:205–12.
66. Brooks JD, Thompson LU. Mammalian lignans and genistein decrease the activities of aromatase and 17beta-hydroxysteroid dehydrogenase in MCF-7 cells. J Steroid Biochem Mol Biol 2005;94:461–7.
67. Bergman Jungeström M, Thompson LU, Dabrosin C. Flaxseed and its lignans inhibit estradiol-induced growth, angiogenesis, and secretion of vascular endothelial growth factor in human breast cancer xenografts in vivo. Clin Cancer Res 2007;13:1061–7.
68. Chen J, Hui E, Ip T, Thompson LU. Dietary flaxseed enhances the inhibitory effect of tamoxifen on the growth of estrogen-dependent human breast cancer (mcf-7) in nude mice. Clin Cancer Res 2004;10:7703–11.
69. Chen J, Stavro PM, Thompson LU. Dietary flaxseed inhibits human breast cancer growth and metastasis and downregulates expression of insulin-like growth factor and epidermal growth factor receptor. Nutr Cancer 2002;43:187–92.
70. Bozan B, Temelli F. Chemical composition and oxidative stability of flax, safflower and poppy seed and seed oils. Bioresour Technol 2008; 99:6354–9.
71. Blaut M. Relationship of prebiotics and food to intestinal microflora. Eur J Nutr 2002;41(suppl 1):I11–6.
72. Kilkkinen A, Pietinen P, Klaukka T, Virtamo J, Korhonen P, Adlercreutz H. Use of oral antimicrobials decreases serum enterolactone concentration. Am J Epidemiol 2002;155:472–7.
73. Hausner H, Johnsen NF, Hallund J, Tetens I. A single measurement is inadequate to estimate enterolactone levels in Danish postmenopausal women due to large intraindividual variation. J Nutr 2004;134: 1197–200.
74. Kilkkinen A, Stumpf K, Pietinen P, Valsta LM, Tapanainen H, Adlercreutz H. Determinants of serum enterolactone concentration. Am J Clin Nutr 2001;73:1094–100.
75. Johnsen NF, Hausner H, Olsen A, et al. Intake of whole grains and vegetables determines the plasma enterolactone concentration of Danish women. J Nutr 2004;134:2691–7.
76. Wang LQ. Mammalian phytoestrogens: enterodiol and enterolactone. J Chromatogr B Analyt Technol Biomed Life Sci 2002;777:289–309.
77. Schwartz JA, Liu G, Brooks SC. Genistein-mediated attenuation of tamoxifen-induced antagonism from estrogen receptor-regulated genes. Biochem Biophys Res Commun 1998;253:38–43.
78. Chen J, Power KA, Mann J, Cheng A, Thompson LU. Dietary flaxseed interaction with tamoxifen induced tumor regression in athymic mice with MCF-7 xenografts by downregulating the expression of estrogen related gene products and signal transduction pathways. Nutr Cancer 2007;58:162–70.
79. Sonestedt E, Ivarsson MI, Harlid S, et al. The protective association of high plasma enterolactone with breast cancer is reasonably robust in women with polymorphisms in the estrogen receptor alpha and beta genes. J Nutr 2009;139:993–1001.
80. Fink BN, Steck SE, Wolff MS, et al. Dietary flavonoid intake and breast cancer survival among women on Long Island. Cancer Epidemiol Biomarkers Prev 2007;16:2285–92.