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Lignans and breast cancer risk in pre- and post-menopausal women: meta-analyses of observational studies

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Phyto-oestrogens are plant compounds structurally similar to oestradiol, which have been proposed to have protective effects against breast cancer. The main class of phyto-oestrogens in the Western diet is lignans. Literature reports on the effect of lignans in breast cancer risk have been conflicting. We performed three separate meta-analyses to examine the relationships between (i) plant lignan intake, (ii) enterolignan exposure and (iii) blood enterolactone levels and breast cancer risk. Medline, BIOSIS and EMBASE databases were searched for publications up to 30 September 2008, and 23 studies were included in the random effects meta-analyses. Overall, there was little association between high plant lignan intake and breast cancer risk (11 studies, combined odds ratio (OR): 0.93, 95% confidence interval (95% CI): 0.83–1.03, P = 0.15), but this association was subjected to marked heterogeneity ($I^2 = 44\%$). Restricting the analysis to post-menopausal women, high levels of plant lignan intake were associated with reduced breast cancer risk (7 studies, combined OR: 0.85, 95% CI: 0.78, 0.93, P < 0.001) and heterogeneity was markedly reduced ($I^2 = 0\%$). High enterolignan exposure was also associated with breast cancer (5 studies, combined OR: 0.73, 95% CI: 0.57, 0.92, P = 0.009) but, again, there was marked heterogeneity ($I^2 = 63\%$). No association was found with blood enterolactone levels (combined OR: 0.82, 95% CI: 0.59–1.14, P = 0.24). In conclusion, plant lignans may be associated with a small reduction in post-menopausal breast cancer risk, but further studies are required to confirm these results.

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MATERIALS AND METHODS

A systematic search of Ovid Medline (US National Library of Medicine, Bethesda, MD, USA), BIOSIS (Thompson Reuters, NY, USA) and EMBASE (Reed Elsevier PLC, Amsterdam, The Netherlands) databases for relevant studies published up to and including the date, 30 September 2008 was carried out. Relevant studies included at least one keyword or Medical Subject Heading from each of the following: (i) plant lignans (matuariesinol, secoisolaricresinol, pinoresinol and lарицирсінон), (ii) enterolignans (enterolactone and enterodiol) and (iii) breast cancer. The search strategy excluded reviews, animal and cell culture studies but did not impose any language restrictions.

Abstracts and full texts, where required, were independently screened by two investigators to establish the suitability for inclusion. Studies had to be of case–control or cohort design, evaluating the risk of invasive breast cancer in relation to lignan exposure and reporting odds ratios (ORs) or relative risks, as well as 95% confidence intervals (95% CIs). Cited references were also

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random effects model were calculated and scaled to percentages. The I²-statistic was used to test for heterogeneity (Higgins et al., 2003). Publication or selection bias was investigated by checking for asymmetry in funnel plots (Egger et al., 1997).

Analysis was repeated and sub-divided by menopausal status (pre- and post-menopausal). Statistical analyses were performed using the STATA version 9.2 software (Stata Corporation 2005, College Station, TX, USA).

**RESULTS**

Following screening of abstracts and full texts and grouping into categories, 27 of the 33 articles identified were selected for data extraction. Multiple publications were identified for a number of studies. Four articles (Grace et al., 2004; McCann et al., 2006; Thanos et al., 2006; Piller et al., 2006b) were excluded, as they were based on smaller subgroup analysis of their respective larger studies. The format of certain results prevented their use, but were provided by the authors in a suitable form and therefore included in this study. Overall, 23 publications were used, providing data for 6 cohort, 6 nested case–control and 10 case–control studies. Each article contributed data to one or more meta-analyses resulting in 12 articles on plant lignan intake (see Table 1), 5 on enterolignan exposure (see Table 2) and 9 on blood enterolactone levels.

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Table 1  Characteristics of studies included in the review of plant lignans and breast cancer risk

| First author/ year) country | Parent study | Study design (follow-up) | Controls/ cohort size | Menopausal status | Lignans measured | Dietary assessment | Adjusted confounders |
|-----------------------------|--------------|--------------------------|-----------------------|------------------|------------------|-------------------|---------------------|
| Hom-Ross et al (2002) United States | California Teachers Study | Prospective cohort (222 249 person-years; 2 years)** | 711 | 111 526 | Pre-M and Post-M | M, S | Self-reported 11-item FFQ | Age at 1st birth and menarche, BMI, daily caloric intake, ethnicity, family history, menopausal status, nulliparity, physical activity |
| Touillaud et al (2006) France | E3N Study | Prospective cohort (117 652 person-years; 4.2 years)** | 402 | 26 868 | Pre-M | M, S, P, L | Self-reported 201-item FFQ | Age at 1st birth and at menarche, alcohol, BBD, BMI, education, family history, energy, geographic area, height, OC, parity |
| Touillaud et al (2007) France | E3N Study | Prospective cohort (383 425 person-years; 7.7 years)** | 1469 | 58 049 | Post-M | M, S, P, L | Self-reported 208-item FFQ | Age at 1st birth, menopause, alcohol, BBD, BMI, energy, family history, height, HRT, OC, parity, smoking |
| Hedelin et al (2008) Sweden | SWLH cohort | Prospective cohort (13 years)** | 1014 | 1014 | Pre-M and Post-M | M, S, P, L, Sy, Med | Self-reported 80-item FFQ | Age at menarche and 1st pregnancy, alcohol, BMI, energy, family history, OC, parity, saturated fat |
| Suzuki et al (2008) Sweden | SMC Study | Prospective cohort (430 339 person-years; 8.3 years)** | 1284 | 51 823 | Post-M | M, S, P, L | Self-reported 67-item FFQ (1987), 93-item FFQ (1997) | Age at 1st birth, menarche and menopause, alcohol, BBD, BMI, education, energy, family history, height, HRT, OC, parity |
| Hom-Ross et al (2001) United States | Bay Area Breast Cancer Study | Population-based case–control | 1272 | 1610 | Pre-M and Post-M | M, S | Self-reported 94-item FFQ | Age, age at menarche, BBD, BMI, daily caloric intake, education, family history, HRT, lactation, menopausal status, parity, race |
| dos Santos Silva et al (2004) United Kingdom | Case–control (GP’s patient lists) | | 240 | 477 | Pre-M and Post-M | M, S | Interviewed 207-item FFQ | Age at 1st birth and at menarche, education, family history, lactation, menopausal status, parity |
| Lieseisen et al (2004) Germany | Population-based case–control | | 278 | 666 | Pre-M | M, S | Self-reported 176-item FFQ | Alcohol, BMI, education, energy, family history, lactation, parity |
| McCann et al (2004) United States | WEB Study | Population-based case–control | 1122 | 2036 | Pre-M and Post-M | M, S | Self-reported 98-item FFQ | Age, age at 1st birth, menarche and menopause, BBD, BMI, education, energy, age at menopause, parity, race, smoking |
| Fink et al (2007) United States | LIBCSP Study | Population-based case–control | 1434 | 1404 | Pre-M and Post-M | M, S | Self-reported 94-item FFQ | Age and energy |
| Cotterslak et al (2008) Canada | Ontario Women’s Diet and Health Study | Population-based case–control | 3063 | 3370 | Post-M | M, S, P, L | Self-reported 178-item FFQ | Age, age at 1st live birth, BBD, dietary fibre intake, family history, HRT |
| Torres-Sanchez et al (2008) Mexico | Hospital based case–control | | 141 | 141 | Pre-M and Post-M | M, S, P, L | Interviewed 100-item FFQ | Age, energy, lifetime lactation, menopausal status |

BBD = benign breast disease; BMI = body mass index; E3N = French Component of the European Prospective Investigation into Diet and Cancer (EPIC) Study; FFQ = food frequency questionnaire; GP = general practitioner; HRT = hormone replacement therapy; L = larcisinosil; LIBCSP = Long Island Breast Cancer Study Project; M = matairesinol; Med = medioresinol; OC = oral contraceptive; P = pinosil; Pren-M = perimenopausal; Pre-M = pre-menopausal; Post-M = post-menopausal; S = secoisolariciresinol; SMC = Swedish Mammography Cohort; SWLH = Scandinavian Women’s Lifestyle and Health Cohort; Sy = syringaresinol; WEB = Western New York Exposure and Breast Cancer Study. *Median follow-up; **Mean follow-up.
(see Table 3). Details of the adjustments made in each study (the most fully adjusted model was used in the meta-analysis) are shown in Tables 1–3.

There was no association between plant lignan intake and risk when 11 studies were combined, although there was a slight protective effect. The risk in the highest intake group was 0.93 times (95% CI: 0.83–1.03, \( P = 0.15 \)) that of the lowest intake group (see Figure 1). When studies were analysed by menopausal status, a statistically significant reduction in risk was seen with the highest intake category of plant lignans vs the lowest intake in post-menopausal women (7 studies, combined OR: 0.85, 95% CI: 0.78, 0.93, \( P < 0.001 \)), with little sign of between-study heterogeneity.

### Table 2

| First author/ (year)/ country | Parent study | Study design (median follow-up) | Cases | Controls/ cohort size | Menopausal status | Diet assessment | Adjusted confounders |
|-------------------------------|--------------|---------------------------------|-------|-----------------------|------------------|-----------------|---------------------|
| Keinan-Boker et al (2004) The Netherlands | Prospective- EPIC | Prospective Cohort (5.2 years) | 280 | 80,215 | Pre-M, Peri-M and Post-M combined | Self-reported | Age at 1st birth and study entry, education, energy, height, HRT, marital status, OC, parity, physical activity, weight |
| Touillaud et al (2006) France | E3N Study | Prospective Cohort (4.2 years) | 402 | 117,652 | Pre-M | Self-reported | Age at 1st birth and menarche, alcohol, BBD, BMI, education, energy, family history, geographic area, height, OC, parity |
| Touillaud et al (2007) France | E3N Study | Prospective cohort (7.7 years) | 1469 | 383,425 | Post-M | Self-reported | Age at 1st birth, at menarche and menopause, alcohol, BBD, BMI, energy, family history, geographic area, height, HRT, OC, parity, smoking |
| Cann et al (2002) United States | WEB Study | Population-based case–control | 301,439 | 316,494 | Post-M | FFQ | Age at menarche, BBD, BMI, education, energy, family history, parity; further adjusted for age at menopause |
| Lineisen et al (2004) Germany | Population-based case–control | 278 | 666 | Pre-M | Self-reported | Age at menarche, BBD, BMI, breast-feeding, education, energy, family history, parity; controls matched by exact age to cases |

BBD = benign breast disease; BMI = body mass index; E3N = French Component of the European Prospective Investigation into Diet and Cancer (EPIC) Study; FFQ = food frequency questionnaire; HRT = hormone replacement therapy; OC = oral contraceptive; Peri-M = Peri-menopausal; Pre-M = pre-menopausal; Post-M = post-menopausal; Prospect-EPIC = Dutch Cohort of EPIC Study; WEB = Western New York Exposure and Breast Cancer Study.

### Table 3

| First author/ (year)/ country | Parent study | Design (follow-up) | Cases | Controls/ cohort size | Method | Menopausal status | Mean ENL cases (nmol/l) | Mean ENL controls/cohort (nmol/l) | Adjusted confounders |
|-------------------------------|--------------|--------------------|-------|-----------------------|--------|------------------|------------------------|--------------------------|---------------------|
| Roccardo et al (2003) Italy | Diabetic cohorts | Prospective cohort (6.5 years after cyst aspiration) | 18 | 383 | TR-FIA | Pre-M and Post-M | 14.7 | 19.6 | Age, cyst type and family history |
| Hultén et al (2002) Sweden | MONICA and MSP studies | Cross-sectional population surveys | 248 | 492 | TR-FIA | Pre-M and Post-M | 26.8 VIP and MONICA 19.3 MSP 25.2 | 22.9 VIP and MONICA 20.4 MSP 24.0 | BMI, menopausal status, smoking None |
| Klikkinen et al (2003) Finland | Diet, Cancer and Health Study | Nesting case–control | 206 | 215 | TR-FIA | Pre-M and Post-M | 18.3 | 18.6 | Age, HRT (through matching of controls) |
| Olsen et al (2004) Denmark | Nesting case–control | Nesting case–control | 381 | 381 | TR-FIA | Pre-M | Not provided | Not provided | Age at 1st live birth and menarche, ln(BMI), family history, ln(height), nulliparity |
| Zeleniuch-Jacquotte et al (2004) United States | Nesting case–control | Nesting case–control | 417 | 417 | TR-FIA | Pre-M | 18.3 | 18.6 | Age at menarche and family history (Pre-M) Crude OR (Post-M) |
| Verhees et al (2007) The Netherlands | EPIC-Norfolk | Nesting case–control | 383 | 383 | LC/MS | Pre-M | 2.98 (ng/ml) 2.71 (ng/ml) | 2.66 (ng/ml) | Age at menarche and breast-feeding, energy, family history, fat, HRT, OC, menopausal status, parity, social class, weight |
| Ward et al (2006) United Kingdom | EPIC-Norfolk | Nesting case–control (9.5 years; 11 261 person-years) | 219 | 891 | LC/MS | All | 5.83 (ng/ml)* | 5.00 (ng/ml)* | Age at menarche, alcohol, BMI, education, family history, OC, physical activity, smoking, waist to hip ratio |
| Pietinen et al (2001) Finland | Kuopio Breast Cancer Study | Population-based case–control | 194 | 208 | TR-FIA | Pre-M | 16.6 | 21.2 | Crude OR (Post-M) |
| Pfifer et al (2006) Germany | Population-based case–control | 192 | 231 | TR-FIA | Pre-M | 11.6 | 12.2 | Age at menarche, alcohol, BMI, breast-feeding, day of analysis, education, family history, OC, parity, time difference between surgery and blood sampling day |

BBD = benign breast disease; BMI = body mass index; ENL = enterolactone; HRT = hormone replacement therapy; LC = liquid chromatography; MONICA = Monitoring of Trends and Cardiovascular Disease Study; MS = mass spectrometry; MSP = Mammary Screening Project; NYU = New York University; OC = oral contraceptive; Peri-M = peri-menopausal; Pre-M = pre-menopausal; Post-M = post-menopausal; Prospect-EPIC = Dutch Cohort of the European Prospective Investigation into Diet and Cancer (EPIC) Study; TR-FIA = time-resolved fluoroimmunoassay; VIP = Västerbotten Intervention Project. *Median values. Means not provided.
(I² = 0%, 95% CI: 0, 71, P = 0.46) (see Figure 2). The same effect was not observed in pre-menopausal women (7 studies, combined OR: 0.97, 95% CI: 0.82, 1.15, P = 0.73). The funnel plot of studies examining plant lignan intake and overall breast cancer risk showed symmetry, suggesting a lack of publication bias.

There was a statistically significant inverse association between enterolignan exposure and overall risk (combined OR: 0.73, 95% CI: 0.57, 0.92, P = 0.009) (Figure 3), although there was marked heterogeneity (I² = 63%, 95% CI: 0.0, 88, P = 0.04), but there was no association between exposure and risk by menopausal status (pre-menopausal breast cancer risk: 3 studies, combined OR: 0.67, 95% CI: 0.44 – 1.02, P = 0.06; post-menopausal: 2 studies, combined OR: 0.85, 95% CI: 0.72 – 1.01, P = 0.06).

There was no association between blood enterolactone and breast cancer risk (combined OR: 0.82, 95% CI: 0.59 – 1.14, P = 0.24) (Figure 4). Results of analysis by menopausal status were similar for both pre-menopausal women (5 studies, combined OR: 0.85, 95% CI: 0.43 – 1.58, P = 0.61) and post-menopausal women (6 studies, combined OR: 0.86, 95% CI: 0.66, 1.14, P = 0.28).

**DISCUSSION**

This is the first systematic review and meta-analysis of exposure to lignans and breast cancer risk based on studies using dietary assessments and serum measurements. Although exposure can be assessed by urine analysis, few studies have used this methodology and therefore, these were not included (Ingram et al., 1997; den Tonkelaar et al., 2001; Dai et al., 2002). The results show that there was no association between plant lignan intake and overall risk, and this association was subjected to marked heterogeneity.
However in post-menopausal women, there is a small but significant reduction in risk and a reduction in heterogeneity. A significantly decreased risk with increasing enterolignan exposure was also found. However, there was significant heterogeneity between studies making it difficult to draw clear conclusions, and the effect did not persist when analyses were stratified by menopausal status, although the number of studies included in these stratified analyses was very small. Finally, there was no association between enterolactone concentrations in blood and overall risk, or when analysis was stratified by menopausal status.

The protective action of plant lignans against breast cancer in post-menopausal, but not in pre-menopausal women, would suggest that lignan activity has a physiologic effect only at low oestradiol levels. One of the mechanisms of action may be greater sex hormone-binding globulin production and binding of free oestradiol (Adlercreutz et al, 1989, 1992; Zeleniuch-Jacquotte et al, 2004; Low et al, 2007). Binding of type II nuclear oestrogen receptor (Adlercreutz et al, 1992; Adlercreutz, 2007) and altering oestrogen synthesis within the breast cells and extragonadal sites, such as the adipose tissue, are other possible mechanisms (Adlercreutz et al, 1993; Saarinen et al, 2007). Binding of type II nuclear oestrogen receptor (Adlercreutz et al, 1992; Adlercreutz, 2007) and altering oestrogen synthesis within the breast cells and extragonadal sites, such as the adipose tissue, are other possible mechanisms (Adlercreutz et al, 1993; Saarinen et al, 2007). Binding of type II nuclear oestrogen receptor (Adlercreutz et al, 1992; Adlercreutz, 2007) and altering oestrogen synthesis within the breast cells and extragonadal sites, such as the adipose tissue, are other possible mechanisms (Adlercreutz et al, 1993; Saarinen et al, 2007). Binding of type II nuclear oestrogen receptor (Adlercreutz et al, 1992; Adlercreutz, 2007) and altering oestrogen synthesis within the breast cells and extragonadal sites, such as the adipose tissue, are other possible mechanisms (Adlercreutz et al, 1993; Saarinen et al, 2007). Binding of type II nuclear oestrogen receptor (Adlercreutz et al, 1992; Adlercreutz, 2007) and altering oestrogen synthesis within the breast cells and extragonadal sites, such as the adipose tissue, are other possible mechanisms (Adlercreutz et al, 1993; Saarinen et al, 2007). Binding of type II nuclear oestrogen receptor (Adlercreutz et al, 1992; Adlercreutz, 2007) and altering oestrogen synthesis within the breast cells and extragonadal sites, such as the adipose tissue, are other possible mechanisms (Adlercreutz et al, 1993; Saarinen et al, 2007). Binding of type II nuclear oestrogen receptor (Adlercreutz et al, 1992; Adlercreutz, 2007) and altering oestrogen synthesis within the breast cells and extragonadal sites, such as the adipose tissue, are other possible mechanisms (Adlercreutz et al, 1993; Saarinen et al, 2007). Binding of type II nuclear oestrogen receptor (Adlercreutz et al, 1992; Adlercreutz, 2007) and altering oestrogen synthesis within the breast cells and extragonadal sites, such as the adipose tissue, are other possible mechanisms (Adlercreutz et al, 1993; Saarinen et al, 2007). Binding of type II nuclear oestrogen receptor (Adlercreutz et al, 1992; Adlercreutz, 2007) and altering oestrogen synthesis within the breast cells and extragonadal sites, such as the adipose tissue, are other possible mechanisms (Adlercreutz et al, 1993; Saarinen et al, 2007). Binding of type II nuclear oestrogen receptor (Adlercreutz et al, 1992; Adlercreutz, 2007) and altering oestrogen synthesis within the breast cells and extragonadal sites, such as the adipose tissue, are other possible mechanisms (Adlercreutz et al, 1993; Saarinen et al, 2007).
intake of plant lignans (Hausner et al., 2004). For example, blood levels of enterolactone can be modulated by age, smoking, frequency of defecation, weight–obesity–body mass index and regular alcohol intake (Kilkkinen et al., 2001, 2002; Horner et al., 2002; Milder et al., 2007), and these factors could potentially differ by menopausal status (in particular, age and body mass index). As bacterial enzymes are involved in lignan metabolism, the use of antibiotics has also been shown to affect enterolactone serum concentration (Kilkkinen et al., 2002); antibiotic use was generally not controlled for in these studies.

It is also possible that the protective effect is caused directly by the plant lignans or chemicals within the metabolic pathway other than enterolactone, or even by a synergistic effect between plant lignans and enterolignans. However, other food constituents found to be associated with plant lignans may exert the effect. For example, α-linoleic acid, which is also thought to have anti-cancer effects (Thompson, 2003; Bougnoux and Chajes, 2003, p. 232), is found in very high levels in flaxseed, the richest source of plant lignans (Thompson et al., 1991).

Determining plant lignan intake has various limitations, which could lead to an over- or under-estimation of food content. Some food composition databases are incomplete in terms of not containing values for the more recently discovered plant lignans (e.g., medioresinol) or for the whole range of foods consumed by the study population. In addition, there are various analytical methods for determining food values; hence, databases compiled from published values determined by different methodologies may contain inherent errors. It has also been shown that the amount of lignans in food can differ according to crop variety, location, year of harvest and processing (Thompson et al., 1997; Kuijsten et al., 2005). Dietary measurement error associated with FFQs (food frequency questionnaires) is also possible. FFQs that were used varied in length, ranging from 67 to 208 items. Only one study validated its FFQ specifically for plant lignan assessment (Torres-Sanchez et al., 2008), although a UK study used the combination of an FFQ and 24-h recalls to group participants into quartiles of intake (dos Santos Silva et al., 2004). In addition, the possibility of residual confounding cannot be ruled out.

Consumption of soy food, rich in isoflavones, has been shown to reduce breast cancer risk in Asian women but not in Western women (Wu et al., 2008), suggesting that ethnicity may play a role in this effect. It is not known whether there are differential physiologic effects of lignans in people of different races, although there is some evidence of variation in the urinary excretion of lignans between white, African American and Latino women (Horn-Ross et al., 1997). Of the 23 articles used for the meta-analyses, only 3 American studies provided complete data with regard to ethnicity (Horn-Ross et al., 2001, 2002; McCann et al., 2004); hence, it was impossible perform sub-analyses for examining this.

In summary, the meta-analyses presented in this study, indicate that plant lignans and enterolignans are unlikely to significantly protect all women against breast cancer development. However, our results suggest that high plant lignan intake is associated with a 15% decreased risk in post-menopausal women, which is a small reduction that could be due to residual confounding. If real, the reason for the selective effect is not clear. Additional studies of the effect of lignan exposure on post-menopausal breast cancer risk are needed to confirm these findings before reassessing the current dietary guidelines.

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can't be exactly reproduced as it contains references and scientific data that are not in a standard format for natural text. However, I can provide a summary of the key points:

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