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Short Communication

Dietary lignans and postmenopausal breast cancer risk by oestrogen receptor status: a prospective cohort study of Swedish women

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Among the 51 823 postmenopausal women in the Swedish Mammography Cohort, we investigated breast cancer risk in relation to the FFQ-based estimated lignan intake by oestrogen receptor (ER) and progesterone receptor (PR) subtypes. A significant 17% risk reduction for breast cancer overall in the high lignan quartile was observed, especially among PMH user ($P_{interaction} < 0.010$), but no heterogeneity across ER/PR subtypes.
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Plant lignans, a major type of phytoestrogens in Nordic countries, are mainly present in cereals, fruit, and vegetables (Adlercreutz, 1998a, b) and are metabolised to mammalian lignans (e.g. enterolactone (ENL)) by the intestinal microflora (Adlercreutz, 2002). Since a preventive action of lignans against breast cancer was suggested (Adlercreutz *et al*, 1982), this has been evaluated *in vitro* (Welshons *et al*, 1987; Hirano *et al*, 1990; Mousavi and Adlercreutz, 1992), *in vivo* (Serraino and Thompson, 1991, 1992) and in clinical studies (Adlercreutz *et al*, 1988, 1991; Phipps *et al*, 1993; Thompson *et al*, 2005). Biological plausibility was discussed in a recent review (Adlercreutz, 2007). Hormone-dependent (Adlercreutz *et al*, 1992, 1993) and other mechanisms (Hirano *et al*, 1990; Kitts *et al*, 1999; Mäkelä *et al*, 1999; Prasad, 2000; Rickard *et al*, 2000) have been suggested. Six prospective (den Tonkelaar *et al*, 2001; Keinan-Boker *et al*, 2004; Kilkkinen *et al*, 2004; Olsen *et al*, 2004; Touillaud *et al*, 2007; Verheus *et al*, 2007) and six case – control studies (Pietinen *et al*, 2001; Dai *et al*, 2002; McCann *et al*, 2002, 2004, 2006; Fink *et al*, 2007) have evaluated the issue among postmenopausal women. Of these, only four considered oestrogen and progesterone receptor status of tumours (ER/PR) (den Tonkelaar *et al*, 2001; Olsen *et al*, 2004; McCann *et al*, 2006; Touillaud *et al*, 2007). We therefore examined the issue in a large population-based cohort study with stratification by family history of breast cancer, level of alcohol intake, body mass index, and use of postmenopausal hormone (PMH).

MATERIALS AND METHODS

The Swedish Mammography Cohort (SMC) was described previously (Wolk *et al*, 1998; Suzuki *et al*, 2006). It was established in 1987 – 90 that all women in Västmanland who were born in 1917 – 48, and in Uppsala born in 1914 – 48, were invited. A total of 66 651 women completed a questionnaire including diet. In 1997, a second questionnaire was sent to all cohort members. We excluded those with missing or incorrect data, with previous cancer (except non-melanoma skin cancer), who were not post-menopausal and who were 70+ years old at baseline leaving a cohort of 51 823 women. The information on diet was collected through self-administrated food-frequency questionnaires in 1987 and 1997. Total lignan intake were estimated using published values of following four lignans; secoisolariciresinol, matairesinol, lariciresinol, and pinoresinol (Mazur *et al*, 1996, 1998a,b, 2000; Adlercreutz and Mazur, 1997; Mazur and Adlercreutz, 1998; Valsta *et al*, 2003; Milder *et al*, 2005; Penalvo *et al*, 2005; Schwartz and Sontag, 2006; Thompson *et al*, 2006). Other nutrients were calculated based on the Swedish National Food Administration database (Bergström *et al*, 1991). Cereals (60%), vegetables (27%), and fruits (10%) are the main sources of our lignans. Among a random sample of 137 women from the cohort, the correlation between the FFQ-based estimates of lignan intake and serum ENL levels measured by time-resolved fluoroimmunoassay (Adlercreutz *et al*, 1998) was $r = 0.2$ (Spearman's rank). Date of breast cancer diagnosis, death, or migration from the study area were identified by linkage of the cohort through the Swedish

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Registration System. Information about receptor status of breast tumours, measured by an Abbott immunoassay (Pousette *et al*, 1986) and an immunohistochemical method, was obtained from Uppsala University Hospital and the Regional Oncology Centre. The study was approved by the Regional Ethics Committee at the Uppsala University Hospital and Karolinska Institute. We used time-dependent multivariate Cox proportional hazards regression model to estimate hazard rate ratios and 95% confidence intervals with age as the time scale (Korn *et al*, 1997). We subdivided lignan intakes into four categories based on approximate quartiles. Trend tests were conducted by using the median value for each category of lignans as a continuous variable. Heterogeneity in the results between the ER + PR + and other subtypes was evaluated using the Wald statistic (Liao, 2004). *P*-value for interaction was evaluated by a likelihood ratio test. Analyses were performed by SAS system, version 9.1 (SAS Institute, Cary, NC, USA). Statistical tests were two-sided, and significance levels defined as $P<0.05$.

RESULTS

Among 51 823 women with an average 8.3-year follow-up, 1284 invasive breast cancer cases were diagnosed, with details of ER/PR status available for 1188 cases. Of these, 716 were ER + PR +, 279 ER + PR−, 50 ER−PR +, and 143 ER−PR− tumours. Women with high lignan intake tended to be older, have more education and have greater use of PMH (Table 1).

Overall, we observed a statistically significant inverse association between lignan intake and breast cancer risk (Table 2). Compared to women in the lowest quartile ($<712\ \mu g\ day^{-1}$), the multivariable adjusted relative risks (RR) for the highest quartile ($\geqslant 1036\ \mu g\ day^{-1}$) were 0.83 (95% confidence interval = 0.70–0.97; $P_{trend}=0.042$) for overall, 0.86 (0.69–1.08) for ER + PR +, 0.77 (0.54–1.09) for ER + PR−, 0.92(0.56–1.52) for ER−PR−. There was no evidence for heterogeneity in the results between the ER + PR + and other subtypes (all $P_{heterogeneities}\geqslant 0.65$).

In the full adjusted analysis stratified by family history of breast cancer, by levels of alcohol intake and by body mass index (<25 or $\geqslant 25\ kg/m^2$), there was no evidence for interaction with lignans in relation to overall risk or of any subtype; all $P_{values\ for\ trends}$ were >0.60 and all $P_{values\ for\ interaction}>0.35$. We also observed a significant inverse association of lignans with overall risk among PMH ever-users; the multivariable adjusted RR for the highest quartile of intake compared to the lowest was 46% lower ($P_{trend}=<0.0001$; Table 3). In contrast, among PMH never-users, no association was observed ($P_{interaction}=0.01$). The observed interaction for PMH use seemed to be confined to ER + PR + tumors ($P_{interaction}=0.016$). There was no heterogeneity in the results between ER + PR + and other tumors (all $P_{heterogeneity}\geqslant 0.21$). Lignans were positively correlated with intake of fruits and vegetables ($r=0.4$) and of cereal, fruit and vegetable fibre ($r=0.7$, 0.2 and 0.4, respectively). After adjusting for these factors, the result for lignans was slightly attenuated but still significant among PMH user (Table 3).

DISCUSSION

In this large population-based prospective cohort of postmenopausal women, we observed a significant inverse association between lignan intake and overall breast cancer risk, especially among PMH user. There was no evidence of heterogeneity across ER/PR tumours. These results are similar to our previous study with a significant inverse association between cereal fibre and breast cancer risk among PMH users (Suzuki *et al*, 2008). The estimated lignan intake was correlated with cereal fibre ($r=0.7$) but after adjusting for specific fibres, the association among PMH users was still significant. This inverse association agrees with two previous studies among postmenopausal women (Fink *et al*, 2007; Touillaud *et al*, 2007). Non-significant inverse associations (Pietinen *et al*, 2001; Dai *et al*, 2002; McCann *et al*, 2002, 2004; Keinan-Boker *et al*, 2004; Olsen *et al*, 2004; Verheus *et al*, 2007) and no association (den Tonkelaar *et al*, 2001; Kilkkinen *et al*, 2004; McCann *et al*, 2006) have also been reported.

An inverse association of lignans with risk has been reported among premenopausal women (Dai *et al*, 2002; McCann *et al*, 2002, 2004, 2006; Linseisen *et al*, 2004; Piller *et al*, 2006a), among women with palpable cysts (Boccardo *et al*, 2004), and high epidermal growth factor concentrations (Boccardo *et al*, 2003), and among those carrying the A2 allele of *CYP17* (McCann *et al*, 2002; Piller *et al*, 2006b) possibly associated with increased levels of endogenous hormone (Haiman *et al*, 1999). Given these findings, an inverse relation of risk with lignans is probable in subgroups of women with high circulating oestrogen level just as discussed with

Table 1 Age-standardised[a] characteristics of risk factors for breast cancer according to the levels of lignan intake among 51 823 postmenopausal women in the Swedish Mammography Cohort[b]

	Quartiles of estimated total lignan intake, $\mu g\ day^{-1}$			
Characteristics	**Q1 <712 n = 12 730 (24.6%)**	**Q2 712–866 n = 13 030 (25.1%)**	**Q3 867–1035 n = 13 011 (25.1%)**	**Q4 ⩾1036 n = 13 052 (25.2%)**
Intake of lignans, $\mu g\ day^{-1}$, median	613.6	791.8	942.7	1175.1
Age at entry, years, mean (s.d.)	59.1 (8.1)	59.1 (7.9)	59.6 (7.8)	60.6 (7.7)
Age at menarche, years, mean (s.d.)	13.2 (1.3)	13.2 (1.2)	13.2 (1.2)	13.2 (1.3)
Age at first birth, years, mean (s.d.)	23.9 (4.5)	24.2 (4.6)	24.2 (4.5)	24.1 (4.4)
Body mass index, $kg\ m^{-2}$, mean (s.d.)	25.2 (4.1)	25.2 (3.9)	25.1 (3.9)	25.1 (4.0)
Number of children, *n*, mean (s.d.)	2.1 (1.3)	2.2 (1.2)	2.1 (1.2)	2.1 (1.3)
Age at menopause, years, mean (s.d.)	50.6 (4.9)	50.8 (4.8)	50.9 (4.6)	50.8 (4.8)
⩾12 years of education, %	8.1	10.1	11.1	12.4
Ever use of oral contraceptives, %	53.5	54.3	54.8	54.2
Ever use of postmenopausal hormones, %	42.1	44.7	46.6	44.8
Family history of breast cancer, %[c]	7.8	8.5	8.2	8.0
Total energy intake, $kcal\ day^{-1}$, mean (s.d.)	1532 (447)	1604 (428)	1616 (421)	1628 (465)
Total fat intake, $g\ day^{-1}$, mean (s.d.)	56.0 (8.3)	53.1 (7.5)	50.9 (7.6)	47.7 (8.3)
Alcohol intake, ethanol $g\ day^{-1}$, mean (s.d.)	3.2 (5.1)	3.6 (5.4)	3.5 (4.5)	3.1 (6.1)

s.d. = standard deviation. [a]Age-standardised to the distribution of person–time of follow-up among all study participants. [b]Based on the information at 1987 and 1997. [c]Breast cancer in mother, sister, or daughter.

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Table 2 Relative risks (RRs) and 95% confidence intervals for the association between FFQ-based estimated intake of lignans and postmenopausal breast cancer risk by receptor-defined subtype among 51 823 postmenopausal women in the Swedish Mammography Cohort

		Quartiles of estimated total lignan intake, $\mu g\,day^{-1}$					
Categories for quartile Lignan intake, $\mu g\,day^{-1}$	**No. of cases**	**Q1 <712**	**Q2 712–866**	**Q3 867–1035**	**Q4 ⩾1036**	P^a	P^b
No of person-year		101 994	105 399	107 791	115 147		
All invasive tumours							
Age-adjusted RR	1284	1.00	0.86 (0.74–1.00)	0.87 (0.74–1.01)	0.86 (0.74–1.00)	0.09	
Multivariable-adjusted RR[c]	1284	1.00	0.83 (0.71-0.97)	0.83 (0.70-0.97)	0.83 (0.70-0.97)	0.042	
ER+PR+tumours							
Age-adjusted RR	716	1.00	0.82 (0.66-1.01)	0.90 (0.73-1.10)	0.89 (0.72-1.09)	0.44	
Multivariable-adjusted RR[c]	716	1.00	0.79 (0.63–0.97)	0.86 (0.69–1.06)	0.86 (0.69–1.08)	0.35	
ER+PR−tumours							
Age-adjusted RR	279	1.00	0.81 (0.59-1.12)	0.67 (0.48-0.94)	0.77 (0.56-1.07)	0.09	
Multivariable-adjusted RR[c]	279	1.00	0.77 (0.56–1.07)	0.64 (0.45–0.90)	0.77 (0.54–1.09)	0.12	0.65
ER−PR−tumours							
Age-adjusted RR	143	1.00	0.85 (0.53-1.36)	0.93 (0.59-1.46)	0.87 (0.55-1.38)	0.66	
Multivariable-adjusted RR[c]	143	1.00	0.87 (0.54–1.40)	0.96 (0.60–1.54)	0.92 (0.56–1.52)	0.86	0.99

ER, oestrogen receptor; PR, progesterone receptor. [a]Two sided *P*-values for trend were calculated using the Wald statistics using the median values for each category of intake of lignan as continuous variable. [b]*P*-values (two-sided) for heterogeneity from the Wald test compared with four pairs of β-coefficients of ER+PR+tumours. [c]Multivariable Cox proportional harzard models with age as the time-scales were adjusted for height (continuous), body mass index (<18.5, 18.5–24.9, 25–29.9, ⩾30 $kg\,m^{-2}$), education (<12 years of education, ⩾12 years of education), parity (nulliparous, 1–2, ⩾3), age at first birth (nulliparous, <26, 26–30, ⩾31 years), age at menarche (⩽12, 13, ⩾14 years, missing), age at menopause (<51, ⩾51 years), type of menopause (natural, surgery), use of oral contraceptives (ever, never, missing), use of postmenopausal hormones (ever, never, missing), family history of breast cancer among first-degree relatives (yes/no), history of benign breast disease (yes/no), quintiles of total energy intake, quintiles of energy-adjusted total fat intake, and alcohol intake (nondrinkers, <3.4, 3.4–9.9, ⩾10.0 ethanol $g\,day^{-1}$).

Table 3 Multivariable relative risks (RRs) and 95% confidence intervals (CI) for the association between total lignan intake and all postmenopausal breast cancer risk among 41 795 postmenopausal women[a] in the Swedish Mammography Cohort with stratified by use of PMH

		Quartiles of estimated total lignan intake, $\mu g\,day^{-1}$									
		Q1		**Q2**		**Q3**		**Q4**			
	No of cases	**No**	**Ref.**	**No**	**RR (95%CI)**	**No**	**RR (95%CI)**	**No**	**RR (95%CI)**	P_{trend}^b	P_{int}^c
Use of PMH[d]											
Ever	446	117	1.00	133	0.85 (0.66–1.10)	119	0.75 (0.57–0.98)	77	0.54 (0.39–0.73)	<0.0001	<0.01
Never	528	139	1.00	109	0.72 (0.55–0.92)	127	0.85 (0.66–1.09)	153	0.97 (0.76–1.25)	0.69	
Use of PMH[e]											
Ever	446	117	1.00	133	0.90 (0.68–1.19)	119	0.83 (0.59–1.17)	77	0.64 (0.42–0.99)	0.042	0.010
Never	528	139	1.00	109	0.80 (0.61–1.06)	127	1.06 (0.78–1.44)	153	1.26 (0.88–1.80)	0.07	

[a]Among 41 795 postmenopausal women with complete information for PMH use in the Swedish Mammography Cohort. [b]Two-sided *P*-values for trend were calculated using the median values for each category of dietary lignan intake as continuous variable. [c]Two-sided *P*-values for interaction were calculated based on −2 log likelihood test based on the model. [d]Multivariable-adjusted RR adjusted for age (the time-scale), height (continuous), education (<12 years of education, ⩾12 years of education), parity (nulliparous, 1–2, ⩾3), age at first birth (nulliparous, <26, 26–30, ⩾31 years), age at menarche (⩽12, 13, ⩾14 years, missing), age at menopause (<51, ⩾51 years), type of menopause (natural, surgery), use of oral contraceptives (ever, never, missing), use of postmenopausal hormones (ever, never, missing), total energy intake (quintiles), energy adjusted total fat intake (quintiles), alcohol intake (nondrinkers, <3.4, 3.4–9.9, ⩾10.0). [e]Multivariable-adjusted model as above further adjusted for consumption of fruits and vegetables (quintiles), energy-adjusted dietary fibre intake (quintile; cereal, fruit, and vegetable fibre independently).

regard to isoflavone (Glazier and Bowman, 2001). The possible biological mechanism is not clear, but *in vitro* studies also showed that lignan ENL in the presence of oestrogens suppressed the oestrogen-induced proliferation in MCF-7 breast cancer cell (Mousavi and Adlercreutz, 1992) and stimulated the synthesis of sex hormone-binding globulin in liver cells (Adlercreutz *et al*, 1992).

The lack of association among overweight women may be due to the relatively high circulating oestrogen levels from PMH use having a stronger effect than the endogenous oestrogens formed in peripheral tissues (Cleland *et al*, 1985; Jurgens *et al*, 1992; Hankinson *et al*, 1998). Compared to lean women, obese women tend to have a lower prevalence of PMH use (Suzuki *et al*, 2006) and lower level of plasma ENL (Kilkkinen *et al*, 2001; Johnsen *et al*, 2004). Body fat might attenuate the effect of lignans by suppressing intestinal microflora activity (Nishizawa *et al*, 1988), or trapping ENL (Johnsen *et al*, 2004).

Our finding for ER+PR+ tumours among PMH users partly agrees with a prospective study (Touillaud *et al*, 2007), though these results were not confined to PMH users. No association was

reported in two prospective studies (den Tonkelaar *et al*, 2001; Olsen *et al*, 2004) and a case–control study (McCann *et al*, 2006). Some nutrient misclassification and individual variation in intestinal microflora, as well as the lack of detailed information about PMH use are all relevant. Lignan estimates were not highly correlated with plasma ENL, but the observed correlation was comparable to those reported previously (Kilkkinen *et al*, 2003; Hedelin *et al*, 2006). In prospective cohort design, this misclassification of exposure tends to be nondifferential which may attenuate the observed association toward null. Further studies need to elucidate this issue with taking the circulating level of oestrogens into consideration.

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