Short Communication

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

R Suzuki1, T Rylander-Rudqvist1, S Saji2, L Bergkvist3, H Adlercreutz4 and A Wolk*,1

1Division of Nutritional Epidemiology, The Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden; 2Division of Clinical Trials and Research, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan; 3The Department of Surgery and the Center for Clinical Research, Uppsala University, Central Hospital, Västerås, Sweden; 4Institute for Preventive Medicine, Nutrition, and Cancer, Folkhalsan Research Center, and Division of Clinical Chemistry, Biomedicum, University of Helsinki, Helsinki, Finland

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 (Pinteraction < 0.010), but no heterogeneity across ER/PR subtypes.

British Journal of Cancer (2008) 98, 636 – 640. doi:10.1038/sj.bjc.6604175 www.bjcancer.com
Published online 22 January 2008
© 2008 Cancer Research UK

Keywords: breast cancer; oestrogen receptor; progesterone receptor; dietary lignans; risk

Plant lignans, a major type of phytooestrogens 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; Touilaud 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; Touilaud 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-administered food-frequency questionnaires in 1987 and 1997. Total lignan intake were estimated using published values of following four lignans; secoisolariciresinol, matairesinol, laricisoin, and pinosylvin (Mazur et al, 1992, 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 Sonntag, 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
Dietary lignans and postmenopausal breast cancer
R Suzuki et al

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+ and 279 ER/PR−, 50 ER/PR+, and 143 ER−PR−. 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 µg day−1), the multivariable adjusted relative risks (RR) for the highest quartile (>1036 µg day−1) were 0.83 (95% confidence interval = 0.70–0.97; \( P_{\text{trend}} = 0.042 \)) 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 \( P_{\text{heterogeneity}} \geq 0.21 \)).

The results for PMH ever-users (Suzuki et al., 2008). The mean lignan intake was correlated with high circulating oestrogen level just as discussed with those carrying the A2 allele of \( \text{CYP17} \), growth factor concentrations (Boccardo et al., 2004), and high epidermal growth factor concentrations (Boccardo et al., 2003), and among those carrying the A2 allele of \( \text{CYP17} \) (McCann et al., 2002, 2004; 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 PMH ever-users; the multivariable adjusted RR for the highest quartile of intake compared to the lowest was 46% lower (\( P_{\text{trend}} = <0.0001 \); Table 3). In contrast, among PMH never-users, no association was observed (\( P_{\text{interaction}} = 0.01 \)). The observed interaction for PMH use seemed to be confined to ER+PR+ tumours (\( P_{\text{interaction}} = 0.016 \)). There was no heterogeneity in the results between ER+PR+ and other tumours (all \( P_{\text{heterogeneity}} \geq 0.21 \)). 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 (Pietenen 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, Killikainen 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 \( \text{CYP17} \) (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 I

| Characteristics | Q1: <712 | Q2: 712–866 | Q3: 867–1035 | Q4: >1036 |
|----------------|---------|-------------|-------------|-----------|
| Intake of lignans, µg 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.) | 239 (4.5) | 242 (4.6) | 242 (4.5) | 241 (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) | 2.1 (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, % | 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) | 50.9 (7.6) | 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. *Age-standardised to the distribution of person–time of follow-up among all study participants. †Based on the information at 1987 and 1997. ‡Breast cancer in mother, sister, or daughter.
Dietary lignans and postmenopausal breast cancer
R. Suzuki et al

The use of PMH may have a stronger effect than the endogenous oestrogens formed in the liver, which is consistent with the relatively high circulating oestrogen levels from PMH use (Adlercreutz et al., 1992). The biological mechanism is not clear, but may be due to isoflavone (Glazier and Bowman, 2001). The possible biological mechanism is not clear, but may be due to isoflavone (Glazier and Bowman, 2001).

Among 41,795 postmenopausal women with complete information for PMH use in the Swedish Mammography Cohort, a significant association was observed between the estimated intake of lignans and the risk of postmenopausal breast cancer.

**Table 2** Relative risks (RRs) and 95% confidence intervals (CI) 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.

| Categories for quartile | Q1 | Q2 | Q3 | Q4 | P<sup>a</sup> | P<sup>b</sup> |
|-------------------------|----|----|----|----|-------------|-------------|
| Lignan intake, µg day<sup>-1</sup> | No. of cases | No. of person-year | No. of cases | No. of person-year | No. of cases | No. of person-year | No. of cases | No. of person-year | No. of cases | No. of person-year | No. of cases | No. of person-year |
| 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<sup>c</sup> | 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<sup>c</sup> | 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<sup>c</sup> | 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<sup>c</sup> | 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 |

**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<sup>a</sup> in the Swedish Mammography Cohort with stratified by use of PMH.

| Use of PMH<sup>b</sup> | No. of cases | No. of person-year | RR (95%CI) | P<sub>trend</sub><sup>b</sup> | P<sub>inc</sub><sup>c</sup> |
|----------------------|-------------|-------------------|-------------|----------------|----------------|
| Ever | 446 | 117 | 1.00 | 0.85 (0.66–1.01) | 0.54 (0.39–0.73) | <0.0001 | <0.01 |
| Never | 528 | 139 | 1.00 | 0.72 (0.55–0.92) | 0.97 (0.76–1.25) | 0.69 |
| Ever | 446 | 117 | 1.00 | 0.90 (0.68–1.19) | 0.64 (0.42–0.99) | 0.042 | 0.010 |
| Never | 528 | 139 | 1.00 | 0.80 (0.61–1.06) | 1.26 (0.88–1.80) | 0.07 |

<sup>a</sup>Among 41,795 postmenopausal women with complete information for PMH use in the Swedish Mammography Cohort. <sup>b</sup>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. <sup>c</sup>Values (two-sided) for heterogeneity from the Wald test compared with four pairs of β-coefficients of ER+PR+ tumours. Multivariable Cox proportional hazard models with age as the time-scale were adjusted for height (continuous), body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30 kg m<sup>-2</sup>), 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, 12, ≥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, ≥18.0 ethanol g day<sup>-1</sup>).
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 non-differential which may attenuate the observed association toward null. Further studies need to elucidate this issue with taking the circulating level of oestrogens into consideration.

ACKNOWLEDGEMENTS

This study was funded by research grants from the Swedish Cancer Foundation and the Swedish Research Council/Longitudinal studies.

REFERENCES

Adlercreutz H (1998a) Epidemiology of Phytooestrogens. London: Bailliere Tindall
Adlercreutz H (1998b) Epidemiology of phytoestrogens. Baillieres Clin Endocrinol Metab 12: 605–623
Adlercreutz H (2002) Phyto-oestrogens and cancer. Lancet Oncol 3: 364–373
Adlercreutz H (2007) Lignans and human health. Crit Rev Clin Lab Sci 44: 483–525
Adlercreutz H, Bannwart C, Wåhålå K, Mäkelä T, Brunow G, Hase T, Arosenmaa PJ, Kellis Jr JT, Vicker LE (1993) Inhibition of human aromatase by mammalian lignans and isoflavonoid phytoestrogens. J Steroid Biochem Mol Biol 44: 147–153
Adlercreutz H, Fotsis T, Heikkilä R, Dwyer JT, Woods M, Goldin BR, Gorbach SL (1982) Excretion of the lignans enterolactone and enterodiol and of equal in omnivorous and vegetarian postmenopausal women and in women with breast cancer. Lancet 2: 1295–1299
Adlercreutz H, Höckerstedt K, Bannwart C, Hämäläinen E, Fotsis T, Bloigu S (1988) Association between dietary fiber, urinary excretion of lignans and isoflavonoid phytoestrogens, and plasma non-protein bound sex hormones in relation to breast cancer. In Progress in Cancer Research and Therapy: Hormones and Cancer, Bresciani F, King RB, Lippman ME, Raynaud J-P (eds) Vol. 35, 409 – 412. New York: Raven Press, Ltd
Adlercreutz H, Honjo H, Higashl A, Fotsis T, Hämäläinen E, Hasegawa T, Okada H (1991) Urinary excretion of lignans and isoflavonoid phytoestrogens in Japanese men and women consuming a traditional Japanese diet. Am J Clin Nutr 54: 1093–1100
Adlercreutz H, Mazur W (1997) Phyto-oestrogens and Western diseases. Ann Med 29: 95–120
Adlercreutz H, Mousavi Y, Clark J, Höckerstedt K, Wåhålå K, Mäkelä T, Hase T (1992) Dietary phytoestrogens and cancer: in vitro and in vivo studies. J Steroid Biochem Mol Biol 41: 331–337
Adlercreutz H, Wang GJ, Lapcik O, Hampl R, Wåhålå K, Mäkelä T, Luisa K, Talme M, Mikola H (1998) Time-resolved fluoroenmunoassay for plasma enterolactone. Anal Biochem 265: 208–215
Bergström LKE, Hagman U, Eriksson HB, Bruce Å (1991) The food composition database KOST: the National Food Administration’s information system for nutritive value of foods. Vår Föda 43: 439–447
Boccardo F, Lunardi G, Guglielmini P, Parodi M, Muraldo R, Schettini G, Rubagotti A (2002) Dietary phytoestrogens and breast cancer risk. Breast Cancer Res Treat 79: 17–23
Cleland WH, Mendelson CR, Simpson ER (1985) Effects of aging and obesity on aromatase activity of human adipose cells. J Clin Endocrinol Metab 60: 174–177
Dai Q, Franke AA, Jin F, Shu XO, Heberd JR, Custer LJ, Cheng J, Gao YT, Zheng W (2002) Urinary excretion of phytoestrogens and risk of breast cancer among Chinese women in Shanghai. Cancer Epidemiol Biomarkers Prev 11: 815–821
den Tonkelaar I, Keinan-Boker L, Veer PV, Arts CJ, Adlercreutz H, Thijsen JH, Peeters PH (2001) Urinary phytoestrogens and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 10: 223–228
Fink BNS, Steck SE, Wolff MS, Britton JA, Kabat GC, Schroeder JC, Teitelbaum SL, Neugut AI, Gammon MD (2007) Dietary flavonoid intake and breast cancer risk among women on Long Island. Am J Epidemiol 165: 514–523
Glazer MG, Bowman MA (2001) A review of the evidence for the use of phytoestrogens as a replacement for traditional estrogen replacement therapy. Arch Intern Med 161: 1161–1172
Haiman CA, Hankinson SE, Spiegelman D, Colditz GA, Willett WC, Speizer FE, Kelsey KT, Hunter DJ (1999) The relationship between a polymorphism in CYP17 with plasma hormone levels and breast cancer. Cancer Res 59: 1015–1020
Hankinson SE, Willett WC, Manson JE, Colditz GA, Hunter DJ, Spiegelman D, Barbieri RL, Speizer FE (1998) Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. J Natl Cancer Inst 90: 1292–1299
Hedelin M, Klint A, Chang ET, Bellocco R, Johansson JE, Andersson SO, Heinonen SM, Adlercreutz H, Adami HO, Gronberg H, Balter KA (2006) Dietary phytoestrogens, serum enterolactone and risk of prostate cancer: the cancer prostate Sweden study (Sweden). Cancer Causes Control 17: 169–180
Hirano T, Fukunoka K, Oka N, Naito T, Hosaka K, Mitsuhashi H, Matsumoto Y (1990) Antiproliferative activity of mammalian lignan derivatives against the human breast carcinoma cell line, ZR-75-1. Cancer Invest 8: 595–599
Johnsen NF, Hausner H, Olsen A, Tetens I, Christensen J, Knudsen KE, Overvad K, Tjonneland A (2004) Intake of whole grains and vegetables determines the plasma enterolactone concentration of Danish women. J Nutr 134: 2691–2697
Jurgens FR DW, Downey LJ, Abernethy WD, Cutler NR, Conrad J (1992) A comparison of circulating hormone levels in postmenopausal women receiving hormone replacement therapy. Am J Obstet Gynecol 167: 459–460
Keinan-Boker L, van der Schouw YT, Grobbee DE, Peeters PH (2004) Dietary phytoestrogens and breast cancer risk. Am J Clin Nutr 79: 282–288
Kilkkinen A, Stumpf K, Pietinen P, Valsta LM, Tapaniainen H, Adlercreutz H (2001) Determinants of serum enterolactone concentration. Am J Clin Nutr 73: 1094–1100
Kilkkinen A, Valsta LM, Virtamo J, Stumpf K, Adlercreutz H, Pietinen P (2003) Intake of lignans is associated with serum enterolactone concentration in Finnish men and women. J Nutr 133: 1830–1833
Kilkkinen A, Virtamo J, Vartiainen E, Sankila R, Virtanen MJ, Adlercreutz H, Pietinen P (2004) Serum enterolactone concentration is not associated with breast cancer risk in a nested case-control study. Int J Cancer 108: 277–280
Kitts DD, Yuan YW, Wijewickreme AN, Thompson LU (1999) Antioxidant activity of the flavessed lignan secoisolariciresinol diglycoside and its mammalian lignan metabolites enterodiol and enterolactone. Mol Cell Biochem 202: 91–100
Korn EL, Graubard BI, Midthune D (1997) Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol 145: 72–80
Liao TF (2004) Comparing social groups: Wald Statistics for testing equality among multiple Logit Models. Int J Comparative Sociology 45: 3–16
Linsey KR, Flinner R, Hermann S, Chang-Clark J (2004) Dietary phytoestrogen intake and premenopausal breast cancer risk in a German case–control study. Int J Cancer 110: 284–290
Mäkelä S, Strauss L, Sarainen N, Salmi S, Streng T, Joshi S, Santti R (1999) Dietary phytoestrogens—mechanisms of action and possible role in the development of hormonally dependent diseases. In Natural Antioxidants and Anticarcinogens in Nutrition, Health and Disease, Kumpulainen JT, Salonen JT (eds) pp 349–355. London: Royal Society of Chemistry
Mazur W, Adlercreutz H (1998) Naturally occurring oestrogens in food. Pure & Appl Chem 70: 1759–1776
Mazur W, Fotsis T, Wåhålå K, Ojala S, Salakka A, Adlercreutz H (1996) Isotope dilution gas chromatographic-mass spectrometric method for dietary lignans and postmenopausal breast cancer

R Suzuki et al

British Journal of Cancer (2008) 98(3), 636 – 640

© 2008 Cancer Research UK
Dietary lignans and postmenopausal breast cancer

R. Suzuki et al

the determination of isoflavonoids, coumestrol, and lignans in food samples. *Anal Biochem* 233(2): 169–180

Mazur WM, Duke JA, Wålå K, Rasku S, Adlercreutz H (1998a) Isoflavonoids and lignans in legumes: nutritional and health aspects in humans. *J Nutr Biochem* 9: 193–200

Mazur WM, Uehara M, Wålå K, Adlercreutz H (2000) Phyto-oestrogen content of berries, and plasma concentrations and urinary excretion of enterolactone after a single strawberry-meal in human subjects. *Br J Nutr* 83: 381–387

Mazur WM, Wålå K, Rasku S, Salakka A, Hase T, Adlercreutz H (1998b) Lignan and isoflavonoid concentrations in tea and coffee. *Br J Nutr* 79: 37–45

McCann SE, Kulkarni S, Trevisan M, Vito D, Nie J, Edge SB, Muti P, Freudenberg JL (2006) Dietary lignan intakes and risk of breast cancer by tumor estrogen receptor status. *Breast Cancer Res Treat* 99: 309–311

McCann SE, Moysich KB, Freudenberg JL, Ambroseon CB, Shields PG (2002) The risk of breast cancer associated with dietary lignans differs by CYP17 genotype in women. *J Nutr* 132: 3036–3041

McCann SE, Muti P, Vito D, Edge SB, Trevisan M, Freudenberg JL (2004) Dietary lignan intakes and risk of pre- and postmenopausal breast cancer. *Int J Cancer* 111: 440–443

Milder IE, Arts IC, van de Putte B, Venema DP, Hollman PC (2005) Lignan contents of Dutch plant foods: a database including lariciresinol, pinoresinol, secoisolariciresinol and matairesinol. *Br J Nutr* 93: 393–402

Mousavi Y, Adlercreutz H (1992) Enterolactone and estradiol inhibit each other’s proliferative effect on MCF-7 breast cancer cells in culture. *J Steroid Biochem Mol Biol* 41: 615–619

Nishizawa Y, Imai Z, Tanishita H, Yano I, Kawai Y, Mormii H (1988) Enterolactone and estradiol inhibit each other’s proliferation of breast cancer cells in vitro and premenopausal breast cancer risk in humans. *Br J Nutr* 83: 158–162

Olsen A, Knudsen KE, Thomsen BL, Loft S, Stripp C, Overvad K, Møller S, Tjonneland A (2004) Plasma enterolactone and breast cancer incidence and premenopausal breast cancer risk defined by estrogen and progesterone receptor status. *Cancer Epidemiol Biomarkers Prev* 13: 1984–1989

Penalvo JL, Haajanen KM, Botting N, Adlercreutz H (2005) Quantification of lignans in food using isotope dilution gas chromatography/mass spectrometry. *J Agric Food Chem* 53: 9342–9347

Phipps WR, Martini MC, Lamp EW, Slavin JL, Kurzer MS (1993) Effect of flax seed ingestion on the menstrual cycle. *J Clin Endocrinol Metab* 77: 1215–1219

Pietinen P, Stumpf K, Männistö S, Kataja V, Uusitupa M, Adlercreutz H (2001) Serum enterolactone and risk of breast cancer: a case-control study in eastern Finland. *Cancer Epidemiol Biomarkers Preven* 10: 339–344

Piller R, Chang-Claude J, Linseisen J (2006a) Plasma enterolactone and genistein and the risk of premenopausal breast cancer. *Eur J Cancer Prev* 15: 225–232

Piller R, Verla-Tebit E, Wang-Gohrke S, Linseisen J, Chang-Claude J (2006b) CYP17 genotype modifies the association between lignan supply and premenopausal breast cancer risk in humans. *J Nutr* 136: 1596–1603

Pousette A, Gustafsson SA, Thorbjörnblad AM, Nordgren A, Sallstrom J, Lindgren A, Sundelin P, Gustafsson JA (1986) Quantitation of estrogen receptor in seventy-five specimens of breast cancer: comparison between an immunoassay (Abbott ER-EIA monoclonal) and a [3H]estradiol binding assay based on isoelectric focusing in polyacrylamide gel. *Cancer Res* 46: 4308s–4309s

Prasad K (2000) Antioxidant activity of secoisolariciresinol diglucoside-derived metabolites, secoisolariciresinol, enterodiol, and enterolactone. *Int Angiol* 20: 220–225

Rickard SE, Yuan YV, Thompson LU (2000) Plasma insulin-like growth factor I levels in rats are reduced by dietary supplementation of flaxseed or its lignan secoisolariciresinol diglucoside. *Cancer Lett* 161: 47–55

Schwartz H, Sontag G (2006) Determination of secoisolariciresinol, lariciresinol and isolariciresinol in plant foods by high performance liquid chromatography coupled with coulometric electrode array detection. *J Chromatogr B Analyt Technol Biomed Life Sci* 838: 78–85

Serraino M, Thompson LU (1991) The effect of flaxseed supplementation on early risk markers for mammary carcinogenesis. *Cancer Lett* 60: 135–142

Serraino M, Thompson LU (1992) The effect of flaxseed supplementation on the initiation and promotional stages of mammary tumorigenesis. *Nature* 17: 153–159

Suzuki R, Rylander-Rudqvist T, Ye W, Saji S, Adlercreutz H, Wolk A (2008) Dietary fiber intake and risk of postmenopausal breast cancer defined by estrogen and progesterone receptor status-A prospective cohort study among Swedish women. *Int J Cancer* 122: 403–412

Suzuki R, Rylander-Rudqvist T, Ye W, Saji S, Wolk A (2006) Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: A Prospective Cohort Study. *Int J Cancer* 119: 1683–1689

Thompson LU, Boucher BA, Liu Z, Cotterchio M, Kreiger N (2006) Phytoestrogen content of foods consumed in Canada, including isoflavones, lignans, and coumestan. *Nature* 54: 184–201

Thompson LU, Chen JM, Li T, Strasser-Weippl K, Goss PE (2005) Dietary flaxseed alters tumor biological markers in postmenopausal breast cancer. *Clin Cancer Res* 11: 3828–3835

Touillaud MS, Thiebaut AG, Fournier A, Niravong M, Boulton-Ruault MC, Clavel-Chapelon F (2007) Dietary lignan intake and postmenopausal breast cancer risk by estrogen and progesterone receptor status. *J Natl Cancer Inst* 99: 475–486

Valsta LM, Kilkkinen A, Mazur W, Nurmi T, Lampi AM, Ovaskainen ML, Korhonen T, Adlercreutz H, Pietinen P (2003) Phyto-oestrogen database of foods and average intake in Finland. *Br J Nutr* 89(Suppl 1): S31–S38

Verheus M, van Gils CH, Keinan-Boker L, Grace PB, Bingham SA, Peeters PH (2007) Plasma phytoestrogens and subsequent breast cancer risk. *J Clin Oncol* 25: 648–655

Welshons WV, Murphy CS, Koch R, Calaf G, Jordan VC (1987) Stimulation of breast cancer cells in vitro by the environmental estrogen enterolactone and the phytoestrogen equol. *Breast Cancer Res Treat* 10: 169–175

Wolk A, Bergstrom R, Hunter D, Willett W, Ljung H, Holmberg L, Bergkvist L, Bruce A, Adami HO (1998) A prospective study of association of monounsaturated fat and other types of fat with risk of breast cancer. *Arch Intern Med* 158: 41–45