Eur J Med Res (2005) 10: 389-394

Dietary Phytoestrogen Intake and Mammographic Density – Results of a Pilot Study

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Abstract: The influence of dietary phytoestrogens provided by Western diets on mammographic density is not well established. Soy and soy products as source of isoflavones were found to be inversely associated with high mammographic density, a marker for breast cancer risk. Another class of phytoestrogens, the lignans, which are more frequent in Western diets, are rarely investigated. Within the European Prospective Investigation into Cancer and Nutrition cohort in Heidelberg (EPIC-Heidelberg) we explored the feasibility of mammogram collection and measurement of mammographic density in order to investigate the association between dietary phytoestrogen intake and breast density patterns. Wolfe classification was used to summarize mammographic density. Dietary habits were assessed by means of a validated food frequency questionnaire.

Out of the 505 randomly selected women, 317 (63%) returned the questionnaire and 310 (61.4%) women provided informed consent to collect mammograms. Dietary intake of seven women with dense patterns (DY) was compared with 47 women without dense patterns. A high dietary intake of fibre (p-value = 0.008) and secoisolariciresinol (p-value = 0.043) is inversely associated with non-dense breast patterns. This is also observed for a high dietary intake of soy-products (p-value = 0.004) and, in tendency, genistein (p-value = 0.069). After adjustment for energy intake and age the groups of dense and non-dense mammographic patterns were different regarding the intake of carbohydrate (p = 0.032), soy-products (p = 0.020), fibre (p = 0.046), and secoisolariciresinol (p = 0.027).

Our results suggest an inverse association between dietary lignan intake and breast density, similar to the findings for isoflavones. To our knowledge this is the first report on this association, but due to the risk of chance finding, this has to be confirmed in a study with sufficient statistical power.

Key words: Diet, phytoestrogens, mammographic density, pilot study, EPIC-Heidelberg

Introduction

In Asian countries, the incidence and mortality of breast cancer is lower than in Western countries [1]. It was suggested that this could be due to the higher consumption of soy products in these countries [2]. This hypothesis was confirmed in several retrospective case-control studies in Asian populations, while studies in Western populations largely failed to find an effect [3, 4]. Phytoestrogens are plant compounds with estrogen-like activity and various other biological activities [5]. The main classes of phytoestrogens are isoflavones, which occur in legumes and beans (mainly soy and soy products) and lignans that occur in the food groups cereals, vegetables, fruit, and nuts and seeds (flaxseed). Furthermore, coumestans occur predominantly with germination, e.g. of bean sprouts, but are also found in fodder crops [5].

In Western countries such as Germany, the average dietary intake of soy and soy products is very low. With a high intake of bread, cereals, vegetables and fruits, lignan intake rises and probably may reveal similar effects as found for isoflavone or soy intake. Recently, a case-control study among premenopausal women in German population revealed decreased breast cancer risk by high intake of the phytoestrogens daizein, genistein, matairesinol, enterodiol and enterolactone [6].

High mammographic density is a well-established marker for breast cancer risk. Harvey and Bovjberg reviewed twelve studies on mammographic density and breast cancer risk and reported that breast cancer risk for dense versus the least dense areas ranges around four [7]. Mammographic breast density may serve as intermediate biomarker for breast cancer risk and thus be an important outcome in regard to prevention strategies.

High soy intake was found to be associated with favourable breast density patterns [8, 9]. Thus, it would be of interest to explore the influence of dietary phytoestrogens typical in Western diets on mammographic density.

Material and Methods

The European Prospective Investigation into Cancer and Nutrition (EPIC)-Project in Heidelberg is in progress since 1994 [10, 11]. In Heidelberg, the recruitment and basic assessment of dietary and lifestyle factors, anthropometric measures and the collection of

blood samples was completed in autumn 1998 [12]. This initial collection of data involved about 25,500 participants from the Heidelberg area, 53% of them are women. The participants were asked to provide detailed information about their smoking habits, physical activity, subjective well-being, medical history and use of medications. Besides completing the questionnaire and a personal interview, the participants also gave blood samples, anthropometric measures and underwent standardized measurement of blood pressure.

Subjects

In a pilot study based on the EPIC-Heidelberg cohort it was explored whether it would be possible to identify women, who received mammography during follow-up and to collect the relevant mammograms. After a median follow-up time of 3.0 years, about 4,500 women in the 1st follow-up reported that they had a mammogram after baseline assessment. To a random sub-sample of these women (N = 505), a short questionnaire was mailed in order to obtain information on all previous mammograms, including where the radiograph was made. Data on former surgery, diagnostic tests (biopsy, puncture), and their indications were also collected. For the collection of the mammograms the radiologists were contacted. The mammograms, which were performed between baseline and first follow-up assessment, were obtained from the radiologists or gynaecologists. The cranio-caudal films of the examination before diagnose of breast cancer were retrieved from the medical records, randomly blinded and scanned by Lumisys scanner 85.

Measurement of Mammographic Density

The Wolfe classification was used to summarize the mammographic density according to the duct patterns in relation to breast cancer risk. Four categories were defined: N1 (lowest risk), P1 (low risk), P2 (high risk) and DY (highest risk). Therefore, the blinded craniocaudal films were consulted for classification [13]. For the analysis, DY was considered as dense breast pattern and compared to the remaining classes (N1, P1, P2).

Dietary Intake Data

Dietary habits were assessed by means of a detailed validated food frequency questionnaire (FFQ) [14]. The nutrient intake was calculated on the basis of the national food composition table BLS, Version II.3 [15].

Dietary intake of the isoflavones (daidzein, genistein, formononetin, biochanin A), lignans (secoiolariciresinol, matairesinol, enterodiol, enterolacton) and coumestans (coumestrol) was calculated as aglycons based on available analytical data in the literature.[6] Additionally, in-vitro data from Thompson et al. [16] were used to calculate the amount of mammalian lignans (enterolactone, enterodiol) per 100 g of ingested food. The phytoestrogen content of single foods contributing to a FFQ item was used to calculate the amount of phytoestrogens provided by that item. The individual phytoestrogen intake data were based on the phytoestrogen content of the FFQ items and the amount and frequency of item consumption as indicated by the study participants.

Statistical Analysis

Selected sample characteristics of women with high mammogramphic density (N = 7) were compared to women with less dense mammograms (N = 47). Medians of food group and compound consumption were calculated using the SAS procedure UNIVARIATE. Associations between mammographic density and intake of nutrients and dietary phytoestrogens were evaluated by the Wilcoxon test (SAS procedure NPAR1WAY) and the corresponding 95% confidence intervals (CI) of the p-value were calculated [17]. Analysis of variance of continuous dietary exposure factors and breast density adjusted for age and total energy intake was performed (SAS procedure GLM). The data were logarithmically transformed to obtain normal frequency distribution. Statistical significance of differences between subjects with dense and non-dense mammographic patterns was evaluated by F-statistics. Two sided p-values are presented. The statistical software package SAS release 9.1 (SAS Institute, Cary, N.C.; USA) was used for the calculations.

Results

Out of 505 randomly selected women, 317 (63%) returned the questionnaire. Enclosed to the short questionnaire an informed consent to collect mammograms was mailed which was finally provided by 310 (61.4%) women. Out of these, 54 mammograms were randomly collected and scanned.

Seven (13%) women had mammographic dense (DY) and 47 (87%) women non-dense breast patterns. Six (85.7%) women with mammographically dense breast patterns were aged over 55 years, whereas non-dense mammographic patterns were observed in 21 (44.7%) women aged over 55 years. No substantial differences were found after stratification for parity, age at first full term pregnancy, smoking status and educational level (Table 1).

The mean intake of carbohydrates (p-value = 0.015), fibre (p-value = 0.008), nuts and seeds (p-value = 0.012) and soy-products (p-value = 0.004) was higher in women with non-dense than with dense breast patterns. Among phytoestrogens, high secoisolariciresinol intake was associated inversely with breast density (p-value = 0.043). In tendency, this was also found for genistein intake (p-value = 0.069) (Table 2).

Table 3 shows the results of the analysis of variance of continuous dietary exposure factors by groups of breast density adjusted for age and total energy intake. After adjustment for energy intake and age the groups of dense and non-dense mammographic patterns were different regarding the intake of carbohydrate (p = 0.032), soy-products (p = 0.020), fibre (p = 0.046), and secoisolariciresinol (p = 0.027). Further adjustment for body mass index and current use of hormone replacement therapy attenuated these results (data not shown).

Table 1. Sample characteristics of women with dense and non-dense mammographic patterns.

	Dense N = 7		Non-dense N = 47		P-value*
	N	%	*N*	%	
Age /years					0.053
<=55 years	1	14.3	26	55.3	
>55 years	6	85.7	21	44.7	
Menopausal –status					0.479
premenopausal	0	-	4	8.5	
postmeopausal	6	85.7	26	55.3	
perimenopausal	1	14.3	15	31.9	
not known	0	-	2	4.3	
Parity					0.966
0	1	14.3	7	14.9	
>= 1	6	85.7	47	85.1	
Age first full-term pregnancy					0.747
<=30 years	5	85.3	31	77.5	
> 30 years	1	16.7	9	22.5	
BMI (kg/m^2)					0.652
<25	2	25.6	22	46.8	
25– 30	3	42.9	16	34.0	
>= 30	2	28.6	9	19.2	
Smoking Status					0.723
Never	5	74.4	26	55.3	
Former	1	14.3	11	23.4	
Current	1	14.3	10	21.3	
Current hormone use					0.105
No	6	85.7	25	53.2	
Yes	1	14.3	22	46.8	
Educational level					0.769
High (University)	1	14.2	5	10.6	
Medium (Professional training)	3	42.9	27	57.5	
Low (no professional training)	3	42.9	15	31.9	

* chi^2-Test , Fisher's Exact Test respectively

Table 2. Crude dietary intake of selected food groups, nutrients, and phytoestrogens of women with dense (N = 7) and non-dense mammographic patterns (N = 47).

	Dense (N = 7)		Non-dense (N = 47)		p-value*
Nutrient	Median	95% CI	Median	95% CI	
Total energy intake (kcal/d)	1232.6	1194.4-1641.3	1573.2	1445.2- 1784.0	0.168
Protein (g/d)	61.0	40.2-63.0	58.4	50.7-60.8	0.728
Carbohydrate (g/d)	136.0	95.4-142.4	171.7	160.7- 191.0	0.015
Fat (g/d)	59.4	52.0 -78.7	64.3	59.9 – 71.6	0.671
Alcohol (g/d)	10.0	1.3-17.5	4.7	1.5-9.3	0.479
Cereal products (g/d)	110.7	104.9-124.5	135.9	119.9-164.6	0.139
Soy-products (g/d)	0.03	0.01 -0.04	0.13	0.08 -0.21	0.004
Nuts und seeds (g/d)	0.34	0 – 1.68	1.68	0.94 – 2.27	0.012
Fibre (g/d)	12.0	10.9-14.0	17.0	15.6-18.0	0.008
Secoisolariciresinol (µg/d)	167.4	102.5-516.4	548.8	241.2-1879.9	0.043
Matairesinol (µg/d)	15.2	10.6-16.3	21.4	18.0-25.2	0.153
Enterodiol (µg/d)	154.5	92.4-183.3	180.3	138.1-249.5	0.241
Enterolactone (µg/d)	130.1	117.9-204.6	181.2	146.8-203.6	0.202
Enterodiol + -lactone (µg/d)	284.6	210.2-387.9	391.3	311.1-440.2	0.176
Daidzein (µg/d)	65.0	28.0-165.4	90.4	53.1-133.1	0.528
Genistein (µg/d)	18.1	16.0-56.4	35.9	28.9-45.3	0.069
Daidzein+ Gensitein (µg/d)	99.4	47.4-181.4	125.9	99.4-192.4	0.212

* Wilcoxon Test

Table 3. Comparison of age and energy –adjusted mean intake of selected food groups and nutrients of women with dense and non-dense mammographic patterns.

	Dense N = 7		Non-dense N = 47		
Nutrient	Adjusted mean	SEM*	Adjusted mean	SEM*	P-value
Protein (g/d)	59.4	4.0	59.1	1.5	0.971
Carbohydrate (g/d)	145.5	14.0	173.8	5.2	0.032
Fat (g/d)	70.6	38.5	64.4	14.3	0.115
Alcohol (g/d)	20.4	7.3	12.6	2.7	0.270
Cereal products (g/d)	117.5	20.1	143.0	7.5	0.441
Soy-products (g/d)	0.01	0.21	0.36	0.08	0.020
Nuts und seeds (g/d)	0.97	1.7	3.0	0.63	0.101
Fibre (g/d)	13.1	1.8	17.2	0.65	0.046
Secoisolariciresinol (µg/d)	213.2	515.8	1263.6	191.6	0.027
Matairesinol (µg /d)	18.3	5.1	23.4	1.9	0.282
Enterodiol (µg/d)	133.0	92.4	291.2	34.3	0.120
Enterolactone (µg/d)	138.1	34.1	193.7	12.7	0.222
Enterodiol + -lactone (µg/d)	271.2	121.5	484.9	45.1	0.130
Daidzein (µg/d)	61.2	51.8	127.8	19.2	0.356
Genistein (µg/d)	23.4	20.0	58.2	7.4	0.114
Daidzein+ Gensitein (µg/d)	84.6	60.5	186.0	22.5	0.264

*SEM standard error of the mean

Discussion

Within the EPIC-cohort about 60% of the approached women provided written informed consent to collect mammograms. It was feasible to select the relevant mammograms from the medical records, to scan the films, and to appraise the mammographic density according to the Wolfe classification [13].

In the present study, subjects with non-dense mammographic breasts study had higher mean intake levels of carbohydrates, fibre, nuts and seeds, and soy-products than women with dense mammographic patterns. Secoisolariciresinol intake and, in tendeny, genistein intake was inversely associated with mammographic density. Energy adjustment slightly attenuated the observed associations.

In case-control studies in Asian populations, high soy intake was found to be associated with favourable breast density patterns [18, 19]. This is consistent with our observations of inverse associations between mammographic density and soy-products and genistein. However, due to the low intake levels of isoflavones in Western countries, this result was unexpected. On the contrary, recent intervention studies with isoflavones from red clover soy products (biochanin A, formononetin, genistein, daidzein) or soy products failed to see an effect on breast density [20, 21].

A high intake of dietary fibre is associated with a high plant lignan (secoisolariciresinol, matairesinol) intake. Both are inversely related to breast density in our study. Plant lignans have to be converted to mammalian lignans (enterodiol, enterolacton) by the gut microflora before absorption [22]. The estimated amount of enterolignans in our study is based on in vitro data of Thomson et al. [23] which can not reflect the variability in gut flora activity between subjects. Frankenfeld et al. observed that the daidzein-metabolising phenotypes showed lower mammographic density compared to the non-metabolising phenotypes, suggesting that intestinal bacterial profiles influence the mammographic density in postmenopausal women [24].

Breast density is influenced by hormone environment, as it relates to the menstrual cycle and its altered by hormonal interventions such as hormone replacement therapy or tamoxifen [25]. Several potential mechanisms of phytoestrogen action on breast tissue are being discussed. Soy supplementation revealed a weak estrogenic effect on breast tissue [26]. Soy-derived phytoestrogens displayed a higher binding affinity to estrogen receptor (ER) β compared to ERα [27]. For the lignans, however, both estrogenic and antiestrogenic effects were reported, which may be dose-dependent [28, 29]. In vitro and in vivo studies have described also other mechanisms such as the inhibition of tyrosine kinase, alteration of growth factor activity (e.g. insulin like growth factor (IGF)-I), the inhibition of several enzymes (e.g. 3β-hydroxysteroid dehydrogenase, 17β-hydroxysteroid dehydrogenase type1, 5α-reductase), and antioxidant activity [5, 30]. In a randomized trial for dietary supplementation of isoflavones no effect on estradiol, follicle stimulating hormone (FSH) or luteinizing hormone (LH) serums levels in postmenopausal women was found [20]. In addition, no association with the tyrosine kinase activity in leucocytes was observed. However, in a nested case-control study dietary isoflavone intake was inversely correlated with plasma estradiol [31]. There is evidence that dietary supplementation of soy isoflavonoides or lignans increased sex hormone binding globuline (SHBG) levels, which may result in lower levels of free estradiol [32, 33, 34]. Furthermore, high consumption of isoflavones or lignans increased the

urinary ratio of 2:16α-hydroxyl estrogens (OHE) and decreased the ratio of 2:4-OHE, which is known to be genotoxic [35, 36]. However, rather higher then lower 2:16α OHE ratios were associated with unfavourable mammographic density [37].

For IGFBP-3 an inverse and for the IGF-I/IGF-BP3 ratio a positive relationship with mammographic density was found [38]. Since diets rich in phytoestrogen are associated with low IGF- and high IGFPB levels, this may be a potential mechanism through which phytoestrogens can influence mammographic density.

The main limitation of your analyses is the small number; however, this pilot study is to the best of our knowledge the first report on intake of phytoestrogens typical for Western diets in relation to mammographic density. We could not control for the bioconversion of precursors (e.g. matairesinol and secoisilariciresionol) to enterolactone and enterodiol which depends on the microflora of the gut. Mammographic density is related to age; especially with menopause the breast tissue becomes more radiolucent. The results have to be interpreted with caution. Due to the large number of statistical tests performed, associations by chance can not be ruled out.

The present study, however, contributes to the discussion regarding the effect of dietary phytoestrogens particular in Western diets on breast density. Further studies are needed, including larger numbers of subjects and biomarker of internal dose, in order to confirm the observed associations.

Acknowledgement: The authors give thanks to the volunteers for participation, the physicians for cooperation and Dr. Christiane Marx, who supported the scanning of the mammograms. Supported by grants from the European Community (SI2.326938) and Deutsche Krebshilfe e.V. (70-2488).

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Received: May 19, 2005 / Accepted: August 4, 2005

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