Dietary Intake of Phytoestrogens Is Associated with a Favorable Metabolic Cardiovascular Risk Profile in Postmenopausal U.S. Women: The Framingham Study[1]

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ABSTRACT Hypertension, central obesity and dyslipidemia are associated with high cardiovascular risk. Estrogen therapy in women has beneficial effects on some of these metabolic cardiovascular risk factors. It is not known whether dietary estrogens have similar effects, especially in Western populations. We studied the association between dietary phytoestrogen intake and metabolic cardiovascular risk factors in postmenopausal women. For this purpose, 939 postmenopausal women participating in the Framingham Offspring Study were included in this cross-sectional study. Mean blood pressure, waist-hip ratio (WHR) and lipoprotein levels were determined in quartile categories of dietary phytoestrogen (isoflavones and lignans) intake, determined by a food-frequency questionnaire. In addition, a metabolic syndrome score was defined according to WHO criteria (range 0–6). The WHR was lower in women in the highest quartile of intake of lignans compared with the lowest [−0.017; 95% confidence interval (CI) −0.030 to −0.0016]. In the highest quartile of intake of isoflavones, plasma triglyceride levels were 0.16 mmol/L lower (95% CI, −0.30 to −0.02) compared with the lowest quartile of isoflavones; for lignan intake, this difference was 0.23 mmol/L (95% CI, −0.37 to −0.09). In the highest quartile of isoflavone intake, the mean cardiovascular risk factor metabolic score was 0.43 points lower (95% CI, −0.70 to −0.16) than the lowest quartile. The difference in this score between the extreme quartiles of intake of lignans was −0.55 points (95% CI, −0.82 to −0.28). In conclusion, high intake of phytoestrogens in postmenopausal women appears to be associated with a favorable metabolic cardiovascular risk profile. J. Nutr. 132: 276–282, 2002.

KEY WORDS: • *phytoestrogens* • *postmenopausal women* • *diet* • *cardiovascular disease* • *metabolic*

Women with hypertension, central obesity and dyslipidemia with or without hyperglycemia, which together define the metabolic syndrome, are at high risk of cardiovascular disease (1,2). Menopause is associated with adverse changes in plasma lipoprotein levels (3), body fat distribution (4) and glucose metabolism (5). Hormone replacement therapy (HRT)[3] can partially reverse these changes, depending on the type and dosage of estrogen and the added progestogen (6–12). Adverse effects such as vaginal bleeding and the associated risk of breast cancer in users of combined HRT prompted the search for alternative estrogen-based preventive treatments. Other forms of exogenous estrogens include those produced by plants, the so-called phytoestrogens. They are defined as plant substances that are structurally and functionally similar to 17β-estradiol and that are capable of producing estrogenic effects (**Fig. 1**). Dietary phytoestrogens can be classified in two main groups, i.e., isoflavones and lignans. The major dietary isoflavones are genistein, daidzein, formononetin, biochanin A and coumestrol. The major dietary lignans are matairesinol and secoisolariciresinol. Both isoflavones and lignans undergo substantial metabolism by bacteria in the gastrointestinal tract. For example, colonic bacteria produce the active metabolites enterolactone and enterodiol from dietary lignans. Circulatory phytoestrogens bind to the estrogen receptor at low levels compared with endogenous estrogen (13).

Studies on dietary phytoestrogen intake and menopausal symptoms showed a reduction in the number of hot flashes in women using phytoestrogens, although the clinical relevance of this reduction is debated (14–16). In contrast to conventional HRT, studies exist that indicate an association between a high intake of phytoestrogens and a low risk of breast and endometrial cancer (17–18).

Animal studies showed that phytoestrogens in soy improve

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[3] Abbreviations used: CI, confidence interval; ER, estrogen receptor; FFQ, food-frequency questionnaire; HRT, hormone replacement therapy; WHR, waist-hip ratio.

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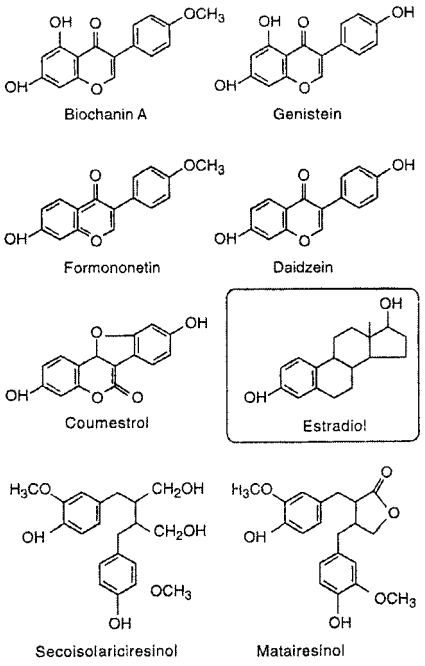

FIGURE 1 Chemical structures of phytoestrogens and estradiol.

plasma lipoproteins and decrease aortic cholesteryl ester content (19–21). Published trials of dietary phytoestrogens and cardiovascular disease risk in humans have concentrated largely on isoflavones, in high supplemental doses, and focused merely on lipids (22). No data exist on the effects of regular dietary intake of phytoestrogens (isoflavones and lignans) on cardiovascular risk factors. The aim of the present study was to investigate the association between dietary phytoestrogen intake and metabolic cardiovascular risk factors, in particular blood pressure, waist-hip ratio (WHR) and plasma lipoprotein levels. We analyzed cross-sectional data obtained in postmenopausal women who participated in the Framingham Offspring Study.

SUBJECTS AND METHODS

Subjects. The Framingham Heart Study, an epidemiologic study of heart disease, was established in Framingham, Massachusetts between 1948 and 1950 with a cohort of 5209 men and women age 30 to 59 y (23). By 1971, the original cohort included 1644 husband-wife pairs and 378 individuals who had developed cardiovascular disease. This study was approved by the Human Investigations Review Committee at New England Medical Center and by the Institutional Review Board for Human Research at Boston University Medical Center. The offspring of these subjects and their spouses were invited to participate, and 5135 of the 6838 eligible individuals participated in the first Framingham Offspring Study examination (24). The offspring cohort has undergone repeated examinations at ~3- to 4-y cycles. Between January 1991 and December 1994, 3799 members of the offspring cohort, of whom 1061 (27.9%) were postmenopausal women (at least 1 y after last menses), participated in the fifth examination cycle. For this analysis, we excluded women who did not fill in a food-frequency questionnaire (FFQ), who left 12 or more items blank on this questionnaire and those with implausibly high ($\geq$ = 16.7 kJ) or low (<2.5 kJ) total energy intake (n = 97). Furthermore, we excluded women with a history of cardiovascular disease or with missing values for lipoprotein concentrations or blood pressure (n = 25). After these exclusions, 939 postmenopausal women remained for analysis.

Design. The study had a cross-sectional design in which dietary intake of phytoestrogens (isoflavones and lignans) was studied in association with systolic and diastolic blood pressure, WHR and lipoprotein levels (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides). In addition, we defined a metabolic syndrome score based on the components of the WHO working definition (2). For each of the following we added one point to the metabolic syndrome score: a systolic blood pressure $\geq$160 mm Hg or use of an antihypertensive treatment; a diastolic blood pressure $\geq$ 90; plasma triglycerides $\geq$1.7 mmol/L or use of cholesterol-lowering medication; HDL cholesterol <1.0 mmol/L; a WHR > 0.85 and a body mass index > 30 kg/m^2 (range of score is 0–6 points).

Identifying food sources of phytoestrogens. To locate published laboratory analysis data for the phytoestrogen content of food items, we conducted a search of the medical (Medline) and agricultural (Agricola) scientific literature and contacted several experts in the field of phytoestrogens. We searched for data on measurements of the phytoestrogens daidzein, genistein, formononetin, biochanin A, coumestrol, matairesinol and secoisolariciresinol in foods. We also searched the literature with the terms phytoestrogens, plant estrogens, isoflavones, coumestans, isoflavones, lignans, enterolactone and enterodiol (25).

Food-frequency questionnaire. The self-administered FFQ on dietary intake developed by Willett and colleagues (26) was used for extraction of the dietary data (25). This questionnaire lists 130 individual food items with specified portion sizes; study participants were asked how often, on average, they had consumed these food items during the previous year. Nine responses were possible, ranging from "never or less than once per month" to "more then six times per day." The questionnaire also requested information about the use of specified vitamin and mineral supplements, the brand of breakfast cereal and included open-ended sections for information on foods and supplements not specified on the questionnaire. The Willett FFQ has not been validated for dietary phytoestrogens, but it has been validated for a number of micronutrients including zinc, magnesium, calcium, vitamin E, vitamin C, folate, vitamin A and dietary fiber.

Scoring phytoestrogen intake. Using the information from our review of the literature, we calculated and assigned for each food item in the FFQ values for the isoflavones daidzein, genistein, formononetin, biochanin A and coumestrol, and for the lignans matairesinol and secoisolariciresinol. Each phytoestrogen content of a food item was then scored in seven categories (**Table 1**) according to the following guidelines. All values found in the literature were converted to mg/100 g food. Values expressed on a dry weight basis were converted to a wet weight basis either by using moisture content provided by the author, by assuming commonly expected moisture content for that particular food (27) or by using adjustments for the method of preparation (28). When the specific phytoestrogen content was reported as "a trace" or "traceable," the value of 10 ng/100 g was assigned; this value is based on the sensitivity of the method used (29). When more values were reported from the same or different original sources in the literature, we used the highest value to score the phytoestrogen content of a food. If wet and dry weights were reported from different original sources in the literature, we used the reported wet weight value to score. If the questionnaire listed similar food items on the same line, we used the phytoestrogen data for the food most commonly eaten. If values for the most common food were

TABLE 1

Scoring of phytoestrogen concentrations of food items

Phytoestrogen	Score
mg/100 g wet weight	*mg/100 g*
Nondetectable, 0	0
0 < * < 0.001	0.0005
0.001 $\leq$ * < 0.01	0.005
0.01 $\leq$ * < 0.1	0.05
0.1 $\leq$ * < 1	0.5
1 $\leq$ * < 10	5
$\geq$10	50

unavailable, any value found on one of the other food items in line was used. When there was no information available on the lignan precursors matairesinol and secoisolaraisinol, we estimated these values by using data on the biologically active products enterolactone and enterodiol (30). If we did not have any information about the phytoestrogen content of a food item, we assigned a value using data of a similar food item if available; if not, we imputed the value zero. We estimated the amount of the phytoestrogens in breakfast cereal by using the fiber content of the cereal as a proxy for the phytoestrogen content, using the Nutrition Data system of the University of Minnesota (31). The average phytoestrogen content of wheat, triticale and rye was used to estimate the amount of phytoestrogen per gram fiber. Finally we multiplied the score of each food item by the serving size of the food. This final phytoestrogen amount of each food item was multiplied by the frequency of the consumption of that food and then summed across foods to obtain the total individual intake of each phytoestrogen.

Measurement of cardiovascular risk factors. All individuals were examined at the Framingham Heart Study clinic, where a history was elicited and a physical examination was performed. Height and weight were measured and body mass index was calculated (weight in kilograms divided by the square of height in meters). Waist girth was measured at the level of the umbilicus with an anthropometric tape to the nearest 0.63 cm. The hip girth was measured at the level of the maximal protrusion of the gluteal muscles with a tape measure to the nearest 0.63 cm. The WHR was calculated from these measurements. Blood pressure was determined after the participant sat for at least 5 min with a mercury column sphygmomanometer. Blood samples were obtained from fasting subjects. Cholesterol and triglycerides were measured by enzymatic methods (32), and HDL cholesterol values were determined after precipatation of LDL and VLDL with dextran sulfate-magnesium (33). For this study the LDL cholesterol was estimated indirectly for persons with plasma triglyceride values < 4.52 mmol/L (according the Friedewald formula) (34); women with higher plasma triglycerides were excluded from analyses.

Measurement of potential dietary confounders. Nutrient intakes were computed by multiplying the frequency of consumption of each food item by the nutrient content of the specified portions, using composition values from USDA sources supplemented with other data, including the components of specific multivitamins and breakfast cereals.

TABLE 2

General characteristics of the 939 postmenopausal women participating in the Framingham Offspring Study[1]

Characteristic	
Age, *y*	59.0 ± 7.5
Age at menopause, *y*	46.4 ± 6.7
Body mass index, *kg/m²*	27.0 ± 5.4
Waist-hip ratio	0.85 ± 0.087
Total cholesterol, *mmol/L*	5.59 ± 0.93
HDL cholesterol, *mmol/L*	1.48 ± 0.41
LDL cholesterol, *mmol/L*	3.39 ± 0.90
Triglycerides, *mmol/L*	1.57 ± 0.73
Systolic blood pressure, *mmHg*	128.5 ± 20.2
Diastolic blood pressure, *mmHg*	73.8 ± 10.1
Energy intake, *kJ/d*	7.2 ± 2.4
Dietary fiber intake, *mg/d*	19.3 ± 8.6
Potassium intake, *mg/d*	3021 ± 1054
Cholesterol intake, *mg/d*	205 ± 88.8
Alcohol intake, *g/d*	7.1 ± 11.9
Use of antihypertensives, *n* (%)	190 (20.3)
Use of cholesterol lowering medication, *n* (%)	53 (5.6)
Diabetes mellitus, *n* (%)	26 (2.8)
Use of hormone replacement therapy, *n* (%)	219 (23.4)
Smoking cigarettes regularly in last year, *n* (%)	169 (18.0)

[1] Values are means ± SD or *n* (%).

TABLE 3

Phytoestrogen intake in the diet of 939 postmenopausal women participating in the Framingham Offspring Study

	Mean ± SD	Median (interquartile range)
	mg/d	
Daidzein	0.292 ± 2.129	0.039 (0.024–0.057)
Genistein	0.341 ± 2.144	0.070 (0.028–0.120)
Formononetin	0.125 ± 0.491	0.031 (0.013–0.044)
Biochanin A	0.010 ± 0.048	0.006 (0.002–0.011)
Coumestrol	0.011 ± 0.049	0.001 (0.000–0.002)
Matairesinol	0.029 ± 0.020	0.025 (0.016–0.036)
Secoisolariciresinol	0.606 ± 0.356	0.534 (0.383–0.761)
Total isoflavones	0.779 ± 4.413	0.155 (0.100–0.236)
Total lignans	0.645 ± 0.364	0.579 (0.416–0.798)

Data analysis. To analyze the association between phytoestrogen intake and cardiovascular risk factors, we added the individual intake of daidzein, genistein, formononetin, biochanin A and coumestrol to calculate total individual intakes of isoflavones and we added the intake of matairesinol and secoisolaraisinol to calculate the total intake of lignans. Women were categorized according to quartile categories with respect to their phytoestrogen intake (isoflavone and lignan intakes separately). Results are presented as means of blood pressure, WHR, lipoproteins and metabolic syndrome score with 95% confidence intervals (95% CI) in the quartiles of intake. When applicable, we excluded women using antihypertensive drugs (blood pressure analysis) or cholesterol-lowering medication (lipoprotein analysis). Analyses were adjusted for age, body mass index, HRT use (current use/no current use), smoking (yes/no), fiber intake, and when necessary, for dietary potassium intake (blood pressure analysis) or alcohol and cholesterol intake (lipoprotein analysis). Mean differences are presented between the lowest and highest quartile categories of intake with 95% CI. Trend analyses were done using a linear regression model employing the median values of the quartile categories of intake. All analyses were performed with the SAS statistical package, version 6.11 (SAS Institute, Cary, NC).

RESULTS

Participants characteristics. The mean age of the participants was 59 ± 7.5 y (**Table 2**). Of the participating women, a minority smoked regularly during the last year, 20% used antihypertensive medication, 6% used cholesterol-lowering medication and 23% used HRT. The median total daily intake of isoflavones was low (0.155 mg), whereas the median total daily intake of lignans was somewhat higher (0.579 mg) (**Table 3**).

Blood pressure and body fat distribution. The difference in systolic blood pressure between the highest and the lowest quartile categories of isoflavone intake was −2.0 mm Hg (95% CI, −5.9 to 1.9); the difference in diastolic blood pressure between these quartile categories was −0.7 (95% CI, −2.7 to 1.4) (**Table 4**). The difference in mean systolic blood pressure between the highest and the lowest quartile categories of lignan intake was −2.0 mm Hg (95% CI, −5.8 to 1.9); the difference in diastolic blood pressure between these quartile categories was −1.1 (95% CI, −3.2 to 1.0). Adjusted mean WHR in the highest quartile category of intake of isoflavones was 0.005 lower (95% CI, −0.021 to 0.016) compared with the lowest quartile category of intake. The difference in WHR between the extreme quartile categories of intake of lignans was −0.017 (95% CI, −0.030 to −0.0016; test for trend, $P < 0.05$).

TABLE 4

Dietary intake of isoflavones, lignans and blood pressure and body fat distribution in the daily diet of 939 postmenopausal women participating in the Framingham Offspring Study[1]

	Systolic blood pressure[3]	Diastolic blood pressure[3]	Waist-hip ratio[2]
		mmHg	
Isoflavones			
≤0.100 *mg*	127.1 (124.4; 129.8)	73.8 (72.4; 75.3)	0.853 (0.842; 0.863)
0.101–0.155 *mg*	125.2 (122.7; 127.6)	71.9 (70.7–73.2)	0.855 (0.845; 0.865)
0.156–0.236 *mg*	124.0 (121.6; 126.4)	73.1 (71.8; 74.4)	0.853 (0.843; 0.863)
>0.236 *mg*	125.1 (122.5; 127.7)	73.2 (71.8; 74.6)	0.847 (0.836; 0.858)
Difference between extreme quartiles	−2.0 (−5.9; 1.9)	−0.7 (−2.7; 1.4)	−0.005 (−0.021; 0.016)
P-value test for trend	0.67	0.89	0.35
Lignans			
≤0.407 *mg*	126.8 (124.1; 129.5)	73.7 (72.3; 75.2)	0.858 (0.848; 0.869)
0.408–0.565 *mg*	123.6 (121.2; 126.0)	73.4 (72.1; 74.7)	0.854 (0.844; 0.864)
0.566–0.788 *mg*	126.1 (123.7; 128.5)	72.2 (70.9; 73.5)	0.855 (0.845; 0.865)
>0.788 *mg*	124.8 (122.3; 127.4)	72.6 (71.3; 74.0)	0.841 (0.830; 0.851)
Difference between extreme quartiles	−2.0 (−5.8; 1.9)	−1.1 (−3.2; 1.0)	−0.017 (−0.030; −0.0016)*
P-value test for trend	0.59	0.24	0.03

[1] Values other then *P*-values are means with 95% confidence intervals in parentheses.
[2] Adjusted for age, body mass index, use of hormone replacement therapy, smoking and dietary fiber intake.
[3] Excluding users of antihypertensives; adjusted for age, body mass index, use of hormone replacement therapy, smoking, dietary fiber intake and potassium intake.
* $P < 0.05$.

Serum lipids. There were no differences in mean total cholesterol and LDL cholesterol between the extreme quartile categories of intake of isoflavones nor for lignans (**Table 5**). In the highest quartile category of intake of isoflavones, HDL cholesterol was 0.06 mmol/L (95% CI, −0.02 to 0.14) higher than the lowest quartile category. The difference in triglyceride levels between the highest and lowest quartile category of intake for isoflavones was −0.16 mmol/L (95% CI, −0.30 to −0.02). The difference in HDL cholesterol between the highest and lowest quartile categories of intake for lignans was 0.06 mmol/L. (95% CI, −0.01 to 0.13) and the difference in triglycerides was −0.23 mmol/L (95% CI, −0.37 to −0.09; test for trend, $P < 0.05$).

Metabolic syndrome. The mean difference between the highest and lowest quartile categories of intake of isoflavones was −0.43 (95% CI, −0.70 to −0.16; test for trend $P < 0.05$) (**Table 6**). The mean difference between the highest and lowest quartile categories of intake of lignans was −0.55 (95% CI, −0.82 to −0.28; test for trend, $P < 0.05$).

DISCUSSION

We found significant inverse associations between dietary intake of lignans and WHR, and between intake of isoflavones and lignans and plasma triglyceride levels. The metabolic syndrome score, based on the cardiovascular risk factor com-

TABLE 5

Phytoestrogen intake and serum lipids of 939 postmenopausal women participating in the Framingham Offspring Study[1,2]

	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides
		mmol/L		
Isoflavones				
≤0.100 *mg*	5.57 (5.44; 5.70)	3.36 (3.24; 3.48)	1.46 (1.41; 1.51)	1.62 (1.53; 1.71)
0.101–0.155 *mg*	5.54 (5.42; 5.66)	3.35 (3.24; 3.47)	1.51 (1.46; 1.56)	1.48 (1.39; 1.56)
0.156–0.236 *mg*	5.65 (5.53; 5.77)	3.43 (3.31; 3.54)	1.50 (1.45; 1.55)	1.58 (1.50; 1.67)
>0.236 *mg*	5.58 (5.45; 5.71)	3.38 (3.26; 3.51)	1.52 (1.47; 1.58)	1.46 (1.37; 1.55)
Difference between extreme quartiles	−0.01 (−0.19; 0.21)	0.02 (−0.16; 0.20)	0.06 (−0.02; 0.14)	−0.16 (−0.30; −0.02)*
P-value test for trend	0.99	0.90	0.20	0.07
Lignans				
≤0.407 *mg*	5.59 (5.46; 5.72)	3.37 (3.25; 3.50)	1.46 (1.41; 1.52)	1.64 (1.55; 1.73)
0.408–0.565 *mg*	5.62 (5.50; 5.75)	3.40 (3.28; 3.52)	1.51 (1.46; 1.56)	1.56 (1.47; 1.64)
0.566–0.788 *mg*	5.59 (5.47; 5.71)	3.39 (3.27; 3.50)	1.50 (1.45; 1.54)	1.54 (1.45; 1.63)
>0.788 *mg*	5.53 (5.41; 5.66)	3.36 (3.24; 3.49)	1.53 (1.48; 1.58)	1.40 (1.31; 1.49)
Difference between extreme quartiles	−0.06 (−0.25; 0.13)	−0.01 (−0.19; 0.17)	0.06 (−0.01; 0.13)	−0.23 (−0.37; −0.09)*
P-value test for trend	0.47	0.84	0.15	0.001

[1] Values other then *P*-values are means with 95% confidence intervals in parentheses.
[2] Excluding cholesterol-lowering medication users; adjusted for age, body mass index, use of hormone therapy replacement, smoking, cholesterol, alcohol and fiber intake.
* $P < 0.05$

TABLE 6

Dietary intake of isoflavones and lignans and the metabolic syndrome score of 939 postmenopausal women participating in the Framingham Offspring Study[1,2]

Quartile categories of intake	Metabolic syndrome score[3]
Isoflavones	
≤0.100 *mg*	1.74 (1.55; 1.92)
0.101–0.155 *mg*	1.45 (1.27; 1.63)
0.156–0.236 *mg*	1.46 (1.29; 1.64)
>0.236 *mg*	1.30 (1.11; 1.49)
Difference between extreme quartiles	−0.43 (−0.70; −0.16)*
P-value test for trend	0.014
Lignans	
≤0.407 *mg*	1.76 (1.58; 1.94)
0.408–0.565 *mg*	1.56 (1.39; 1.74)
0.566–0.788 *mg*	1.41 (1.24; 1.59)
>0.788 *mg*	1.21 (1.03; 1.39)
Difference between extreme quartiles	−0.55 (−0.82; −0.28)*
P-value test for trend	0.0001

[1] Values other than *P*-values are means with 95% confidence intervals in parentheses.

[2] Adjusted for age; use of hormone replacement therapy, smoking and dietary fiber intake.

[3] Metabolic syndrome score: one point for each of the following: systolic blood pressure ≥160 mmHg or use of antihypertensives; diastolic blood pressure ≥90 mmHg; plasma triglycerides ≥1.7 mmol/L or use of cholesterol-lowering medication; plasma HDL cholesterol <1.0 mmol/L; waist hip ratio >0.85; body mass index >30 kg/m^2 (range 0–6).

* $P < 0.05$

ponents, was markedly lower in women with a high intake of isoflavones and lignans.

Using a FFQ, we were able to quantify the average exposure to dietary phytoestrogens in the previous year. This is particularly important for a study of dietary phytoestrogen intake because food containing large amounts of phytoestrogen are most likely to be consumed weekly or monthly, not on a daily bases. One of the major disadvantages of studies using biochemical indicators such as urinary excretion to measure the phytoestrogen exposure is the short period of intake (24 h) that this excretion reflects (29).

To avoid the suggestion of a degree of precision for which the reported data in the literature are too limited and too preliminary, we scored the highest value reported in the literature into seven categories (Table 1) instead of using the exact measurements of phytoestrogen content reported in the literature. Moreover, differences in phytoestrogen content of food items among types, brands or different countries are not known because most measurements were performed in one country using only a few types or brands. By using categories instead of exact amounts of phytoestrogen, these differences do not influence our results as long as they are within a 10-fold range of the data we used for our classification. Finally, we divided the cohort into quartile categories of intake and did not use continuous data on phytoestrogen intake. This further reduces the influence of error in the measured data, but also reduces the power to detect an association.

Two main concerns remain; the first is error in exposure measurement due to missing data on some of the food items consumed in the Western diet. We had data on almost all vegetable and fruit items in the FFQ, which are the food groups most likely to contain phytoestrogens. The industrial use of soybean meal could cause the presence of phytoestrogens in food items such as donuts and white bread, although the processing of the meal possibly reduces these amounts. Until now, only one research group has quantified the dietary intake of phytoestrogens to study the association between dietary intake of phytoestrogens and prostate cancer in a case-control design (35,36). This group used a modified Block FFQ to measure the intake of several phytoestrogens and used the original values as reported in the literature with adjustments for cooking and preparation. The median dietary intakes of different phytoestrogens (36) were similar to the intakes in our study.

The second remaining concern is residual confounding due to unmeasured or unknown factors. In particular, confounding due to other nutrient intakes is potentially important. However, the availability of extensive FFQ data on other nutrients enabled adjustment in the multivariate analyses. We adjusted for dietary fiber intake because dietary phytoestrogens are also present in foods that contain fiber and dietary fiber intake is inversely associated with coronary heart disease (37). A high dietary lignan intake was associated with a low metabolic risk score. A possible explanation for this result could be that high lignan consumers consume more plant foods, of lower energy, causing a lower body mass index and therefore a lower metabolic risk score. Additional analyses with adjustment for total energy or saturated fat intake did not materially influence the results.

We also adjusted for age, smoking and HRT use. We included HRT use as a confounder because it was associated with phytoestrogen intake, probably via dietary and life style habits, and with the metabolic cardiovascular risk factors. In our data, HRT was not an effect-modifier in the association between phytoestrogens and cardiovascular risk factors (P of interaction variable > 0.10). Even after proper adjustment for confounders, a causal interpretation of our findings is inherently restricted by the cross-sectional nature of the design.

Estrogens act by binding to the estrogen receptor (ER), an intranuclear binding protein; two types have now been identified, ERα and ERβ. These receptors, like all steroid hormone receptors, are transcription factors that alter gene expression when they are activated (38). Phytoestrogens bind to ER with low affinity compared with endogenous estrogens and, depending on the tissue, may exert either estrogenic or antiestrogenic effects. In postmenopausal women, endogenous estrogen levels are very low and phytoestrogens are more likely to bind to ER, leading to biological effects.

The highest concentrations of isoflavones are found in soybeans and the highest concentrations of lignans in linseeds (39). Consumption of these foods is uncommon in most Western countries. However, small concentrations of isoflavones and lignans have been measured in several fruits and vegetables (29,30,40–44), in bread (45), and also in coffee (46), tea (46), beer (47) and wine (40). These diverse sources of phytoestrogens allowed us to study a range of dietary intakes in spite of the low median intake of phytoestrogens.

Several studies indicate that there is no significant effect of menopause on systolic or diastolic blood pressure apart from the effect of aging (48–52). No significant effect was found in trials studying the effects of HRT on blood pressure (6,53). The results of our study suggest that phytoestrogen intake is not associated with blood pressure.

After menopause, there is an increase in android fat distribution and a reduction in gynoid fat (54). Estrogen replacement therapy appears to decrease the amount of abdominal fat without changing total body fat mass parameters (7). We speculate that that the inverse association we found between lignan intake and WHR could be explained by identical effects of phytoestrogens on body fat distribution.

In postmenopausal women, total cholesterol, LDL cholesterol, lipoprotein (a) and triglyceride levels are increased and HDL cholesterol is decreased compared with premenopausal women of the same age (55). Most HRT-regimens lower total cholesterol, LDL cholesterol and lipoprotein (a), slightly increase HDL cholesterol (6), but also increase triglyceride levels. The effects of phytoestrogens on the lipid profile have been studied in several trials with soy supplements. The average decrease in triglycerides was 0.15 mmol/L in soy users compared with placebo-treated groups (22). This effect is comparable to the difference we found in triglycerides between the extreme quartile categories of intake of isoflavones (Table 5), in spite of the much higher intakes in the trials. A nonsignificant HDL cholesterol increase of 2.4% was found in the soy trials. We found a nonsignificant difference ($P = 0.05$) of ~4% comparing the extreme quartile categories of intake of isoflavones. In the soy trials, total cholesterol and LDL cholesterol also decreased significantly. In contrast, our results showed no association between isoflavone intake and total of LDL cholesterol. Possible explanations for these dissimilar findings are the differences in quantities of intake or other components of soy that may be responsible for differences in lipoproteins. Lignan intake in relation to lipoproteins has not been reported in other studies. The associations we found between lignan intake and the different lipoproteins are comparable to our results on isoflavone intake.

Patients with diabetes mellitus experience a two- to fourfold risk of developing cardiovascular disease compared with nondiabetics. Insulin resistance is found in patients with type 2 diabetes but also in individuals who do not have evidence of frank diabetes. Evidence is accumulating that insulin resistance may be the common etiological factor that underlies components of the metabolic syndrome (56–59). Experimental studies in animals have consistently shown that natural and synthetic estrogens can augment the pancreatic insulin response to glucose and increase peripheral insulin sensitivity (60–62). There are only a few studies of the effects of administration of estradiol alone on carbohydrate metabolism in women, but these generally confirm the potentially beneficial effects of estrogen (8,9). Studies with combined HRT indicate that the addition of a progestogen adversely affects the glucose metabolism and could induce insulin resistance (11,12). The effect of phytoestrogen on insulin metabolism has not been studied directly. Our results on the metabolic syndrome score may indicate that phytoestrogen intake is associated with a lower risk of developing diabetes mellitus and therefore a lower risk of developing cardiovascular disease among postmenopausal women. Alone, each component of the metabolic syndrome cluster conveys increased cardiovascular disease risk; in combination, however, they become much more powerful (63). It would be interesting to study dietary phytoestrogen intake in association with the incidence of diabetes mellitus in a longitudinal study design.

In summary, this study on dietary phytoestrogen intake and metabolic cardiovascular risk factors in postmenopausal women indicates that a high phytoestrogen intake is associated with a favorable metabolic cardiovascular risk profile. A more comprehensive database and studies with cardiovascular endpoints in a longitudinal design are warranted to delineate further the role of phytoestrogen intake in cardiovascular disease risk.

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