Urinary Phytoestrogens and Postmenopausal Breast Cancer Risk


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Abstract

Phytoestrogens are defined as plant substances that are structurally or functionally similar to estradiol. We report the associations of two major phytoestrogens, genistein and enterolactone, with breast cancer risk, using urinary specimens collected 1–9 years before breast cancer was diagnosed. The subjects were 88 breast cancer cases and 268 controls, selected from a cohort of postmenopausal women (n = 14,697) who participated in a breast cancer screening program. Mean levels of urinary genistein and enterolactone were determined by time resolved fluorimmunoassay, using an average of two overnight urinary samples obtained from each participant on the first and the second screening rounds with a time interval of approximately 1 year. Odds ratios (ORs) of the highest to the lowest tertile of urinary phytoestrogen/creatinine concentrations and 95% confidence intervals (CIs) were computed. Higher urinary genistein excretion was weakly and nonsignificantly associated with a reduced breast cancer risk. OR for the highest tertile compared with lowest tertile was 0.83; 95% CI, 0.46–1.51. Higher urinary enterolactone excretion was weakly and nonsignificantly associated with an increased breast cancer risk. OR for the highest tertile compared with lowest tertile was 1.43; 95% CI, 0.79–2.59. Tests for trends for both phytoestrogens were nonsignificant. We were not able to detect the previously reported protective effects of genistein and enterolactone on breast cancer risk in our postmenopausal population of Dutch women. Such an effect may be smaller than expected and/or limited to specific subgroups of the population.

Introduction

Phytoestrogens are naturally occurring compounds in many foods, defined as plant substances that are structurally or functionally similar to estradiol. They consist of a number of classes, mainly isoflavones, lignans, and coumestans (1–3). Soy products and legumes are the main source of isoflavonoid phytoestrogens, such as genistein and daidzein (1–6). Genistein and daidzein have estrogenic, antiestrogenic, and antitumorogenic activity (2, 3, 5). Lignans, such as enterolactone and enterodiol, are mostly found in linseed, whole cereals, legumes, and berries and, to a lesser extent, in other fruit and vegetables (1–3). Limited quantitative data are available for the concentrations of isoflavones and lignans in plant foods (7–9).

Studies on geographical differences in breast cancer incidence suggest a possible preventive role for soy products (5, 10, 11). In several case-control studies conducted in Singapore (12) and Japan (13) and with women of Chinese, Japanese, and Filipino origin in the United States (14), premenopausal women consuming large quantities of soy products had a considerably lower risk of breast cancer compared to women with low consumption [crude OR for the highest tertile compared with the lowest tertile of soy foods consumption was 0.44; 95% CI, 0.24–0.81 (Ref. 12); crude OR for >3 servings/week compared with 1–3 servings/week of tofu (bean curd) was 0.81; 95% CI, 0.67–0.99 (Ref. 13); and crude OR for >1 category increase of tofu consumption was 0.86; 95% CI, 0.76–0.96 (Ref. 14)]. In the American study (14), a lower breast cancer risk was also noted for postmenopausal women consuming higher levels of soy products (crude OR for >1 category increase of tofu consumption was 0.83; 95% CI, 0.69–1.00; Ref. 14). However, no evidence for a protective effect of higher phytoestrogen consumption was found among a mixed pre- and postmenopausal Chinese population (15). Results of a recent prospective study of pre- and postmenopausal Japanese women showed no significant associations between soy foods consumption and breast cancer risk (relative risk for >5 tofu servings/week compared with ≤1/week was 1.07; 95% CI, 0.78–1.47; and relative risk for >5 miso soup servings/week compared with ≤1/week was 0.87; 95% CI, 0.68–1.12; Ref. 16).

Dietary recall or questionnaires usually assess the intake of soy or soy protein as a proxy measurement of the intake of isoflavones (17). Urinary levels of defined phytoestrogens have been used as more accurate markers, because urinary excretion of phytoestrogens is dose-dependent at low to moderate levels of soy protein intake (18) and changes in response to alterations in the intake of vegetables, fruit, and legumes (19). However, Arai et al. (20) have concluded in a recent publication, in which they compared dietary data with plasma concentration or urinary excretion of isoflavones, that measurements of plasma...
concentrations or urinary excretion of daidzein and genistein are satisfactory and useful markers for dietary intake.

A descriptive study by Adlercreutz et al. (21), published in 1982, was the first to detect lower urinary excretion of enterolactone, enterodiol, and equol in postmenopausal breast cancer patients \( (n = 7) \) compared with healthy postmenopausal omnivorous \( (n = 10) \) and vegetarian \( (n = 10) \) American women (21). In two recent case-control studies (22, 23), urinary levels of isoflavones (genistein, daidzein, equol, and glycitein) and lignans (enterolactone, enterodiol, and matairesinol) were used as an exposure index instead of dietary questionnaires. Both studies used a mixed pre- and postmenopausal population, and both observed an inverse association between higher urinary excretion of certain isoflavones and lignans and breast cancer risk; i.e., crude OR for the highest quintile compared with the lowest quintile of enterolactone was 0.36; 95% CI, 0.17–0.75 (21); crude OR for the highest tertile compared with the lowest tertile of genistein was 0.59; 95% CI, 0.25–1.43 (22). However, in these retrospective case-control studies, urinary phytoestrogen values were measured in breast cancer patients after diagnosis and, therefore, might have been influenced by metabolic consequences of the disease rather than be its possible causes.

We chose to study two phytoestrogens: genistein (an isoflavone) and enterolactone (a lignan), which represent the main two classes of phytoestrogens and have been studied previously. We determined associations of their urinary excretion with breast cancer risk in a cohort-nested case-control study, using urinary specimens collected 1–9 years before breast cancer was diagnosed.

Materials and Methods

Population. Subjects were 100 postmenopausal breast cancer cases and 300 postmenopausal controls, selected from a cohort of women who participated in a population-based breast cancer-screening program, the Diagnostisch Onderzoek Mammacarcinoom-project in Utrecht, the Netherlands (24). All of the women born between 1911 and 1925, being between 50–64 years of age at start of the project and living in Utrecht and vicinity, were invited. Of them, 72% \( (n = 14,697) \) agreed to participate. The cohort design of the project ensured that only those women who had taken part in the first screening examination were invited for the following screening rounds. Five screening rounds were performed between 1974 and 1984 with changing intervals: 12 months between screen round 1 and 2; 18 months between screen round 2 and 3; 24 months between screen round 3 and 4; and 24 months between screen round 4 and 5 (24, 25). Eligible participants for our study were those who were postmenopausal at first screening examination (natural menopause, defined as a complete cessation of menses for at least 1 year) and provided overnight urinary specimens at the first and second screening visits. The urinary specimens were stored at \(-20^\circ C\). Cases were diagnosed at least 1 year after a negative second screening examination, and diagnosis was confirmed histologically. The first 100 cases fulfilling these criteria were used sequentially, covering a follow-up period of 9 years (1977–1985). Three controls were matched to each case by position and date of cold storage of their urinary specimens for practical reasons (simplifying the retrieval procedure). The controls had to fulfill the same selection criteria as the cases and had to be still in follow-up at the date of diagnosis of the case. Data on age, height, weight, parity, age at menopause, history of benign breast disease, family history, and use of hormone replacement treatment were obtained by means of a self-administered questionnaire filled out at the first screening visit.

Handling of Urinary Samples. Overnight urinary samples were obtained from participants in all of the screening rounds, but for our nested case-control study we have only used specimens collected on the first and the second rounds with a mean interval of 1.04 years (0.92–1.75) between them. Of each sample, 100 ml were stored. For eight cases and 26 controls only one urinary specimen could be retrieved from the cold storage, and for two controls neither of the two urinary specimens were retrievable. They were excluded from the analyses. In addition, complete laboratory data were not obtainable for four cases and for four controls. Consequently, we were left with 88 (88%) cases and 268 (89%) controls for analyses. Phytoestrogen excretion was expressed in relation to creatinine (phytoestrogen:creatinine ratio) on a \( \mu \)mol/mole basis. The mean value of the phytoestrogen:creatinine ratio of the two screening samples was used in the analyses.

Biochemical Analyses. TR-FIA for enterolactone and genistein was performed as described previously (26, 27). The original method for plasma enterolactone was slightly modified as follows: 1 ml of 0.1 M acetate buffer (pH 5) containing \( \beta \)-glucuronidase and sulfatase (hydrolyzing reagent) plus 50 \( \mu \)l of urine were mixed and incubated overnight at 37°C. Twenty \( \mu \)l of standard or diluted hydrolyzed urine, 100 \( \mu \)l of antiserum for enterolactone or genistein, respectively, and 100 \( \mu \)l of Eu-labeled enterolactone or genistein were incubated on DELFIA plate shaker at room temperature for 90 min and washed using DELFIA plate washer. Enhancement solution (200 \( \mu \)l) was added, and the strips were shaken for 5 min. After an additional 5 min, fluorescence was measured in a VICTOR 1420 multilabel counter. Interassay variation for both enterolactone and genistein were 2.4–6.4% and 4.4–9.7%, respectively, depending on concentration. Storage procedures did not affect urinary levels of genistein and enterolactone, according to stability tests we used previously \( ^{5} \) (\(<5\%\) change expected after a storage period of 100 years in \(-20^\circ C\)). For 10 controls and five cases, values for genistein were below the detection limit, \(<73.5 \)nmol/liter. These values were set at 50 nmol/liter.

TR-FIA results were proved to correlate significantly to results obtained by the GC-MS method. Uehara et al. (27) measured urinary enterolactone and genistein in 215 samples obtained from healthy Finnish women and found that more than 50% of the values ranged between 1–7 \( \mu \)mol/24 h and \(<0.1–0.6 \)\( \mu \)mol/24 h, respectively. The correlation coefficients between the TR-FIA method and the GC-MS methods were \( r = 0.87 \) (\( P < 0.001 \)) for enterolactone and \( r = 0.88 \) (\( P < 0.001 \)) for genistein. However, mean values for enterolactone were approximately 30% higher, whereas mean values of genistein were about 115% higher in the TR-FIA method compared with the GC-MS results (27).

Creatinine was analyzed using an enzymatic colorimetric method (28).

Statistical Analyses. Tertiles of enterolactone/creatinine and genistein/creatinine were defined on the basis of cases and controls distribution, as shown in Table 2. Because the matching of cases and controls (for position and date of cold storage) was done for practical reasons only, we did not use a conditional logistic regression model. Instead, multiple logistic regression was used to obtain ORs adjusted for batch in the

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Unpublished data.
biochemical analyses and for known risk factors for breast cancer.

Tests for trend were performed by logistic regression assigning the tertile median value to each individual in that tertile. Subgroup analyses were performed for estrogen receptor positive breast cancer cases and according to years of follow-up. Statistical analyses were performed using SPSS 8.0 statistical package (29). All of the statistical tests were two-sided.

**Within-person Variability.** Within-person variability was evaluated using data from 89 controls (a subset of the total 300 controls) who participated in the baseline screening round as well as from in one of the three subsequent screening examinations: 31 subjects from the second, 29 subjects from the third, or 29 subjects from the fourth, on average 1, 2.5, and 4.5 years after the first screening round, respectively. This way we could cover a time period of around 4.5 years (average interval between first and fourth screening examinations), whereas by using the first and second urinary samples only, we would have covered a period of 1 year. Covering a longer period of time seemed more relevant for assessing within-person variability when regarding food-intake changes that are time-dependent by nature. Pearson correlation coefficients were calculated for log-transformed concentrations in controls between the first and the second, third, and fourth consecutive screening visits. The coefficients were 0.28, 0.58, and 0.27 for enterolactone and 0.26, 0.18, and −0.17 for genistein, respectively. On the basis of the four moments of urine collection covering a 4.5-year period, CVs of within and between persons were calculated. Because we used the mean concentration of two subsequent screening samples in our study, the within-person CV for our exposure marker was divided by the square root of two. For genistein, the CVs of within and between persons were 49% (74%: √2) and 33%; whereas for enterolactone, the CVs amounted to 40% (60%: √2) and 48%, respectively.

**Results**

Cases were nonsignificantly older, taller, and heavier than controls. They had a somewhat earlier age at menarche and later age at first birth than controls and were more often nulliparous.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 88) Mean (SE)</th>
<th>Controls (n = 268) Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at second examination (yrs)</td>
<td>59.2 (0.37)</td>
<td>58.6 (0.24)</td>
</tr>
<tr>
<td>Age at menarche (yrs)a</td>
<td>13.1 (0.37)</td>
<td>13.5 (0.11)</td>
</tr>
<tr>
<td>Age at first birth (yrs)b</td>
<td>27.7 (0.56)</td>
<td>26.5 (0.31)</td>
</tr>
<tr>
<td>Age at menopause (yrs)</td>
<td>49.5 (0.50)</td>
<td>49.5 (0.27)</td>
</tr>
<tr>
<td>Quetlet index (kg/m²), second round</td>
<td>26.1 (0.42)</td>
<td>25.9 (0.24)</td>
</tr>
<tr>
<td>Height (cm), second round</td>
<td>162.2 (0.63)</td>
<td>161.7 (0.37)</td>
</tr>
<tr>
<td>Weight (kg), second round</td>
<td>69.9 (1.07)</td>
<td>69.3 (0.66)</td>
</tr>
</tbody>
</table>

Parity

<table>
<thead>
<tr>
<th>Parity</th>
<th>Cases (n = 88)</th>
<th>Controls (n = 268)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>17</td>
<td>46</td>
</tr>
<tr>
<td>1–2</td>
<td>25</td>
<td>102</td>
</tr>
<tr>
<td>3–4</td>
<td>31</td>
<td>79</td>
</tr>
<tr>
<td>5 and over</td>
<td>15</td>
<td>41</td>
</tr>
<tr>
<td>Benign breast disease</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Family history of breast cancer</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Estrogen supplementation</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Smoking</td>
<td>13</td>
<td>62</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of cases (n = 88) and controls (n = 268)

They had benign breast disease (P = 0.044) or a family history of breast cancer (P = 0.038) more often than controls. Cases were less often smokers than controls were (P = 0.100). Characteristics of cases and controls are shown in Table 1.

Table 2 shows that crude OR for highest versus lowest tertile of genistein is 0.83 (95% CI, 0.46–1.51), whereas crude OR for highest versus lowest tertile of enterolactone is 1.43 (95% CI, 0.79–2.59). Adjustment for age, height, weight, parity, age at menopause, history of benign breast disease, family history estrogen supplements, smoking, and laboratory run did not affect the results substantially (<10% change in ORs; data not shown). Tests for trends for both phytoestrogens were nonsignificant.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>Test for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterolactone/creatinine</td>
<td>7.16–379.0 (235.6)</td>
<td>26</td>
<td>91</td>
<td>1</td>
</tr>
<tr>
<td>Genistein/creatinine</td>
<td>10.2–67.1 (48.4)</td>
<td>31</td>
<td>86</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. OR and 95% CI for breast cancer in tertiles of enterolactone/creatinine and genistein/creatinine

a Data available only for 22 cases and 145 controls who attended the fifth screening examination.

b Data apply to 71 cases and 222 controls who gave birth.

c Crude OR.

d For multivariate analyses, based on the median values of the tertiles.

Range, μmol/mol; numbers in parentheses, mean.
and a positive association for higher enterolactone excretion, was only observed for the first 3 years of follow-up and still nonsignificant (P for trend for genistein, 0.20; for enterolactone, 0.15). For longer periods of follow-up, the results were diluted.

Table 4 represents a summary of main results for enterolactone and genistein.

### Discussion
To our knowledge, this is the first prospective study addressing the association between urinary phytoestrogen levels and breast cancer risk. Our findings indicate that if higher urinary genistein and enterolactone excretion levels are indeed associated with a reduced breast cancer risk, it is likely to be a weak association only. These results are in agreement with a recently published prospective study (16) regarding associations between soy food consumption and breast cancer risk in a Japanese population. They are not in accordance with the strong inverse associations of phytoestrogens with breast cancer previously reported (12–14, 22, 23).

Regarding exposure assessment, both random errors and the level of exposure need attention. Within-person variance was large (49% for genistein and 40% for enterolactone) and quite similar to the between-person variance (33% for genistein and 48% for enterolactone) in our study population. The ratio of the within-person:between-person variance relevant to the extent of random misclassification was 1.5 (49%/33%) for genistein and slightly better for enterolactone, i.e., 0.83 (40%/48%), suggesting substantial attenuation both in our results as well as in studies published previously, i.e., the studies done by Ingram et al. (22) and Zheng et al. (23). However, because such information is not included in the two other studies, there are no grounds to conclude that the variance ratios in them would be much more reliable.

Laboratory error (CV, ~5%) contributes only little to within-person variance, so that the within-person CV largely reflects the true variance in daily consumption of phytoestrogens. Regarding the levels and range of exposure to phytoestrogens published thus far, our median enterolactone excretion values are in the same order of magnitude as reported in the Australian study (22), i.e., a median value of 3098 nmol/24 h for enterolactone among the controls. Assuming a daily creatinine excretion of 1 g (equaling 0.00884 mol) and a 30% measurement difference using the TR-IFA compared with the GS-MS methods, our median enterolactone level among controls is similar, i.e., 3290 nmol/24 h. The median value for genistein among controls in the Chinese study population was 2.17 nmol/mg creatinine (23), which is two to three times higher than the median among controls in our study, i.e., 0.81 nmol/mg creatinine. This gap probably reflects the widely different Oriental and Western dietary patterns (4, 17, 21).

Urinary excretion of isoflavones primarily reflects the intake levels of soy foods over the 24–96-h period before urine collection. However, recent consumption is strongly related to past consumption if the study population is habitually consuming the foods of interest. We have measured levels of genistein and enterolactone in two overnight urinary samples (1 year apart) each participant and used the mean of both values for analysis. Assuming a Western-style habitual diet in this Dutch elderly population with low intake of isoflavones (soy beans, soy products, and legumes) and low-to-moderate intake of lignans (whole grains, fruit, and vegetables; Ref. 30), we may expect that the mean value of phytoestrogen measured will be relevant to the habitual intake in this population. In fact, the low relative and the relatively large within-person variation in intake of soy products in Western populations (4, 17, 21) might complicate the detection of weaker associations between isoflavones and breast cancer. Lignans are more widespread in Western diet foods than isoflavones (30), but lack of information concerning levels and range of exposure in studies published thus far. Our median enterolactone excretion values are in the same order of magnitude as reported in the Australian study (22), i.e., 3098 nmol/24 h for enterolactone among the controls. Assuming a daily creatinine excretion of 1 g (equaling 0.00884 mol) and a 30% measurement difference using the TR-IFA compared with the GS-MS methods, our median enterolactone level among controls is similar, i.e., 3290 nmol/24 h. The median value for genistein among controls in the Chinese study population was 2.17 nmol/mg creatinine (23), which is two to three times higher than the median among controls in our study, i.e., 0.81 nmol/mg creatinine. This gap probably reflects the widely different Oriental and Western dietary patterns (4, 17, 21).

Bioavailability of phytoestrogens is multifactorial and depends on individual variability in isoflavone absorption, metabolism by gastrointestinal bacteria, and endogenous hormones (1, 3, 31, 32). Urinary excretion of phytoestrogens in response to daily consumption of soy-containing foods differs according to race/ethnicity (33) and is dose-dependent at low to moderate levels of soy consumption (18). It also differs according to the type of phytoestrogen ingested (1) and is influenced by antibiotics, either as drugs or as residues in food, because of the changes in gut flora (1). We have no reason to believe that cases differed substantially from controls in regard to race/ethnicity (because over 95% of study participants were Dutch Caucasians) or antibiotic treatment.
An average of first and second examination rounds results. Because the controls’ response rate was altered eating habits among cases (22, 23). In addition, selection bias may have occurred, especially in the Australian study, and mechanistic evidence. J. Clin. Endocrinol. Metab., 83: 297–303, 1998.


The two former studies that focused on urinary levels of phytoestrogens in Australian and Chinese populations included newly diagnosed breast cancer patients, thus urinary levels of phytoestrogens in their cases might have been influenced by metabolic changes after the presence of breast cancer or by altered eating habits among cases (22, 23). In addition, selection bias may have occurred, especially in the Australian study, because the controls’ response rate was <50%, and the controls may have represented a health-conscious sector in the general population, exposed to “healthier” eating patterns (22). However, even if such a bias was present, it is unlikely to cause the differences of results observed between that study and ours, because the mean values of enterolactone in both control groups are comparable. Bias attributable to the selection of controls is also unlikely in the Chinese study because only 6% of the controls refused to participate (23). We used a case-control study design nested in a prospective cohort, in which urinary specimens were obtained 1–9 years before breast cancer diagnosis. Because cases and controls are selected from the same cohort, selection bias is unlikely to occur. Furthermore, the diagnosis of breast cancer was at least 1 year after collection of urinary samples, and all of the participants had been screened for the disease (and found to be negative) at two subsequent screening examinations, making presence of breast cancer at the time of urinary collection quite unlikely.

The possibility of a differential risk profile in premenopausal compared with postmenopausal women should also be considered. We have used a homogeneous postmenopausal population in contrast to both former case-control studies, which were conducted among a mixed pre- and postmenopausal population (22, 23). Several previous studies addressed the issue of intake of isoflavones in premenopausal women. Their main findings [soy protein daily intake significantly increased follicular phase length, suppressed luteinizing hormone and follicular stimulating hormone mid-cycle surges, and delayed menstruation by 1–5 days (34), as well as reduced circulating ovarian steroids and adrenal androgens (31)] suggested that dietary estrogens may play a role in protecting women against breast cancer in several ways: (a) increased menstrual cycle length and thus reduced lifetime exposure to estrogens; (b) increased follicular phase length which eventually results in a reduced lifetime exposure to luteal phase in which mitotic rate of breast tissue is almost 4-fold greater (compared with the follicular phase) and, therefore, the risk for a carcinogenic transformation is greater; (c) an antiestrogenic effect of reduced proliferation of breast epithelial cells caused by phytoestrogens; and (d) decreased circulating ovarian steroid levels caused by phytoestrogens (31, 34). Postmenopausal women apparently respond differently to a soy-supplemented diet. Measured luteinizing hormone, follicular stimulating hormone, and endogenous estrogen levels were not significantly changed by it (35). So phytoestrogens might have a protective role in premenopausal but not in postmenopausal women. It should also be noted that, despite the previously detected inverse association between soy product exposure and breast cancer risk, phytoestrogens are weak estrogens and might stimulate cell proliferation and estrogen-dependent gene expression (17, 32, 36, 37). This could be of significance in postmenopausal women with low endogenous estrogen values. In conclusion, phytoestrogens may prove to have differential roles in certain subgroups of the population. In fact, it was also suggested that perhaps protective effects of phytoestrogens are applicable only in subjects exposed to high levels of soy intake in the uterus (through the placenta) or in early childhood (soy milk feeding; Refs. 1, 17, 38).

In the present prospective study in postmenopausal women with low urinary levels of genistein and enterolactone, we were not able to confirm clear protective associations for both substances that have been reported previously (22, 23). Clearer associations between urinary phytoestrogens and breast cancer risk may be present among women with higher exposure to phytoestrogens. Prospective studies in large populations, accounting for menopausal status, are needed to determine the relationships between isoflavones, lignans, and subsequent breast cancer risk.

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References
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