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**Association of urinary phytoestrogen concentrations with serum
concentrations of prostate-specific antigen in the National Health and
Nutrition Examination Survey**

Walser-Domjan, Esther ; Richard, Aline ; Eichholzer, Monika ; Platz, Elizabeth A ; Linseisen, Jakob ;
Rohrmann, Sabine

Abstract: Some clinical trials have shown that high phytoestrogen intake may decrease serum concentrations of prostate-specific antigen (PSA), and phytoestrogens may also lower prostate cancer risk. It was the aim of this study to examine the relationship between the serum PSA level and urine phytoestrogen concentration in generally healthy U.S. men. Eight hundred twenty-four men, 40+ yr old without prostate cancer, who participated in the 2001-2004 NHANES surveys, were included in the analysis. The association of total PSA, free PSA, and PSA ratio [free PSA/total PSA * 100] with concentrations of isoflavones and lignans (standardized for urinary creatinine concentration) was examined using multivariable-adjusted linear and logistic regression models. The linear regression analyses showed no clear association between creatinine-standardized urinary phytoestrogen concentrations and serum total or free PSA levels or PSA ratio. However, the odds of having a PSA ratio <15% rose from Quartile 1 to Quartile 4 of isoflavone excretion (odds ratio = 2.82, 95% confidence interval 1.28-6.22 for top vs. bottom quartile), but there were no associations with having a PSA ratio <25%. In generally healthy U.S. men, 40+ yr old without a diagnosis of prostate cancer, urinary isoflavone, and lignan concentrations were not associated with serum PSA level.

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1 Title

2 Association of urinary phytoestrogen concentrations with serum concentrations of prostate-specific
3 antigen (PSA) in the National Health and Nutrition Examination Survey (NHANES)

4

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28

29 Association Phytoestrogens and PSA in NHANES

30

31 Key words: Phytoestrogens, Prostate-specific antigen, Prostate cancer, NHANES

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33

34

35 Some clinical trials have shown that high phytoestrogen intake may decrease serum concentrations
36 of prostate-specific antigen (PSA), and phytoestrogens may also lower prostate cancer risk. It was
37 the aim of this study to examine the relationship between the serum PSA level and urine
38 phytoestrogen concentration in generally healthy US men. 824 men, 40+ year old without prostate
39 cancer, who participated in the 2001-2004 NHANES surveys, were included in the analysis. The
40 association of total PSA, free PSA, and PSA ratio [free PSA/total PSA * 100] with concentrations
41 of isoflavones and lignans (standardized for urinary creatinine concentration) was examined using
42 multivariable-adjusted linear and logistic regression models. The linear regression analyses showed
43 no clear association between creatinine-standardized urinary phytoestrogen concentrations and
44 serum total or free PSA levels or PSA ratio. However, the odds of having a PSA ratio < 15% rose
45 from quartile 1 to quartile 4 of isoflavone excretion (odds ratio = 2.82, 95 % confidence interval
46 1.28-6.22 for top versus bottom quartile), but there were no associations with having a PSA ratio <
47 25%. In generally healthy US men, 40+ years old without a diagnosis of prostate cancer, urinary
48 isoflavone and lignan concentrations were not associated with serum PSA level.
49

50 Compared to the United States and Europe, the incidence of prostate cancer is lower in China and
51 Japan. The lower incidence in Asian countries is hypothesized to be at least in part be due to the
52 higher consumption of soy products rich in phytoestrogens in Asian countries (1). Isoflavones and
53 lignans are the most common classes of phytoestrogens in the human diet. The most important
54 sources of isoflavones are soybeans and other soy products, but the major sources of phytoestrogens
55 in the US diet are doughnuts, pancakes, waffles and bread, all of which contain added soy (2). The
56 major isoflavones are genistein, daidzein, formononetin, glycitein and biochanin-A. In 30-50% of
57 the human population the gut microflora can metabolize daidzein to equol; o-desmethylangolensin
58 is another intestinal metabolite formed from daidzein (90% of the human population) (3). Lignan
59 concentrations are very high in flaxseed and pumpkin seed. Smaller amounts are found in a variety
60 of foods including nuts and seeds, legumes, whole grain cereals, vegetables and fruits (2).
61 Lariciresinol and pinoresinol contribute most to total lignan intake, followed by secoisolariciresinol
62 and matairesinol (4). In the human body, these plant lignans are not bioavailable but they can be
63 absorbed in the intestine once they are transformed into enterodiols and enterolactone (2).
64 Phytoestrogens are excreted in the urine (2) and an estimate of alimentary intake of isoflavones can
65 be derived from urinary concentration of isoflavones. Several studies have shown that soy
66 consumption correlates with urinary isoflavone excretion (5), even in spot urine (6). In a Finnish
67 study, nutritional intake of lignans was associated with the urinary excretion of enterolignans (7).
68 Prostate-specific antigen (PSA) is a biochemical marker secreted by the prostate that is used for the
69 diagnosis and surveillance of prostate cancer. Generally, healthy men have a low serum level and
70 higher serum levels of PSA are associated with both localized and advanced prostate cancer.
71 However, PSA is organ-specific but not cancer-specific (8), such that PSA levels can be elevated
72 either because of an enlargement or an inflammation of the prostate (9). Also, serum PSA levels are
73 affected by age (10), body mass index (BMI) (11), ethnicity, (12) circulating levels of C-reactive
74 protein (CRP) (13) and possibly by common drugs including statin drugs (14), thiazide diuretics

75 (15), nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (16). With respect to the
76 effect of phytoestrogens, a small prospective Austrian intervention study observed a significant
77 decrease in total PSA levels with daily administration of an isoflavone extract for one year in
78 healthy men with elevated PSA levels (17). In another small double-blind placebo-controlled trial,
79 the level of total PSA was lowered and the PSA ratio was increased in men diagnosed with prostate
80 cancer **who** consumed bread with different phytoestrogen concentrations (18). Another randomized
81 trial that administered isoflavone supplements showed no change in PSA concentrations (1).
82 As reviewed above, to date there are only few studies in humans about the possible association of
83 urine concentration or dietary intake of phytoestrogens with serum level of PSA, which yielded
84 partly contradictory results (1, 17-19). It is currently also unclear whether the intake of
85 phytoestrogens with a regular diet in the general population has an effect on PSA concentrations of
86 generally healthy men. Thus, our study offered the opportunity to examine whether phytoestrogen
87 concentration as observed in men with a normal diet were associated with PSA concentration in a
88 large representative sample of US men. We hypothesized that men with higher concentrations of
89 phytoestrogens in the urine have lower serum total PSA level and higher ratio of total to free PSA.

90

91 Materials and methods

92 The National Health and Nutrition Examination Survey (NHANES) is conducted by the US
93 National Center for Health Statistics of the Centers for Disease Control and Prevention. Since 1999
94 each year data are collected from a representative sample that covers all age groups of the civilian
95 non-institutionalized US population over 2 month of age. The survey is unique because it includes
96 interviews (questionnaires), physical and laboratory examinations.

97 In the NHANES surveys of the years 2001-2002 and 2003-2004, PSA serum and phytoestrogen
98 urine levels were measured (20). To address our study questions, our study sample included men
99 meeting the following criteria: age 40 years or older, measured blood concentration of PSA,

100 measured urine concentration of phytoestrogens, never diagnosed with prostate cancer, no recent
101 prostate biopsy, prostate examination or infection prior to venipuncture. The 2001-2002 and 2003-
102 2004 NHANES surveys included 10301 males, of which 3326 were age 40 years or older. PSA has
103 been measured in 2701 men. 155 of them did not meet the prostate exclusion criteria. So, after
104 subtracting those who had no phytoestrogen measurement (N=2546 as phytoestrogens were
105 measured only in a random subsample of the NHANES populations) 824 men were eligible for our
106 study.

107

108 PSA, phytoestrogen and creatinine measurement

109 The Access Hybritech Assay was used to measure concentrations of total and free PSA (Beckman
110 Access, Fullerton CA). The PSA ratio was calculated by dividing the concentration of free PSA by
111 the concentration of total PSA and multiplying by 100 (20, 21).

112 Spot urine samples were collected in a standardized manner as described previously (22). The
113 analysis of phytoestrogens (daidzein, o-desmethylangolensin equol, genistein, enterodiol, and
114 enterolactone) was carried out with high performance liquid chromatography (HPLC) and tandem
115 mass spectrometric (MS/MS) detection (20, 21). Creatinine concentration, which was used to
116 standardize urinary phytoestrogen, was analyzed using a Jaffe rate reaction measured with a CX3
117 analyzer (Beckman Instruments, Brea, CA) (22). For the statistical analysis, we evaluated the
118 associations for the sum of isoflavones (daidzein, o-desmethylangolensin equol, genistein), the sum
119 of enterolignans (enterodiol and enterolactone) and the sum of all isoflavones and enterolignans.

120

121 **Data collection**

122 Age, race/ethnicity, socioeconomic status, smoking status, intake of NSAID and physical activity
123 were determined in a household interview prior to the examination. During a face-to-face interview
124 in the mobile examination center (MEC), questions about alcohol consumption were asked. The

125 intake of prescribed medication such as statin drugs and thiazide diuretics was assessed by a
126 personal interview by trained NHANES staff during a 1-month period prior to the survey date (23).
127 Trained personnel measured body weight and height in the MEC. Standing height was measured in
128 meters with a stadiometer. The participants were weighted in kilograms using a digital weight scale.
129 Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the
130 height in meters (24). CRP was measured by the latex-enhanced nephelometry method (21).

131

132 Statistical analysis

133 All statistical analyses accounted for the complex sample design by using the appropriate weights
134 and sampling factors (25). For the characterization of the subpopulation, we computed arithmetic
135 means of all continuous parameters and percentages of all categorical parameters. These
136 calculations were also made by quartiles of genistein urine concentration. **Creatinine is a very good**
137 **parameter for the excretion performance of the kidneys and is used to determine the so called**
138 **creatinine clearance as measure for the glomerular filtration (26), and both creatinine and**
139 **phytoestrogen concentrations rise with the excretion performance of the kidneys.** Therefore, all
140 analyses were performed by standardizing the phytoestrogen concentration in $\mu\text{g/g}$ creatinine in
141 urine. Linear regression was used to examine the associations of total PSA and PSA ratio serum
142 levels with phytoestrogen urine concentrations. Because both phytoestrogen concentrations in urine
143 and PSA variables were not normally distributed in the study population, these values were
144 transformed using the natural logarithm (14). In the linear regression we controlled for age
145 (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other),
146 C-reactive protein (continuous), pain relievers (taken nearly every day for a month or longer
147 yes/no), statin drugs (used in the past month yes/no), thiazide diuretics (used in the past month
148 yes/no), smoking (ever smokers, never smokers), alcohol consumption (missing, abstinent, <1 drink
149 per day, 1-2 drinks per day, e 3 drinks per day), poverty-income ratio (0-0.99 = below poverty, e 1 =

150 at or above poverty) (27), physical activity (any vigorous activities over past 30 days for at least 10
151 minutes that caused heavy sweating or large increases in breathing or heart rate, 1 = yes, 0 = no)
152 (28), BMI (continuous), educational level (<high school, High School Diploma (including GED
153 [General Education Development]), >high school, refused/don't know/missing). In linear models,
154 where both the dependent and the independent variables have been ln-transformed, the dependent
155 variable can be interpreted as percent changes for a one-percent increase in the independent variable
156 while all other variables in the model are held constant. In addition to linear models, logistic
157 regression models were used to test if there is an association between urine concentrations of
158 phytoestrogens and abnormal levels of total PSA and PSA ratio. For the logistic regression, the
159 outcome variable *total PSA* was converted into a categorical variable using 2.5 and 4.0 ng/ml as
160 threshold values, which have been used for prostate cancer detection in different publications (29-
161 31). A lower PSA ratio is suggestive of prostate cancer. In our study, *PSA ratio* was converted into
162 a categorical variable using, as proposed in some studies, 15% as threshold value (32, 33) and 25%
163 as an alternative threshold, which was proposed in other publications (32, 33). Phytoestrogen urine
164 concentrations were categorized into quartiles. We controlled for the above-mentioned confounders
165 in the logistic regression models.

166 Stata IC/ 11.2 software (College Station, Texas) was used to perform the analyses.

167 The Institutional Review Board of the National Center for Health Statistics, Centers for Disease
168 Control and Prevention, approved all protocols for the implementation of NHANES 2001-2004.

169 Informed consent was obtained for all participants (14).

170

171 Results

172 Table 1 shows the baseline characteristics of the study population. Mean age of the participants was
173 54.6 years; mean BMI was in the overweight range (28.8 kg/m²). Most men were non-Hispanic
174 White (58%), were married (68.6%), and 47.6% of men had an education level higher than high

175 school or GED. Fourteen percent of the study population lived below poverty level. The majority of
176 men were ever smokers (71.6%) and 43.5% of the men drank more than one alcoholic drink per day
177 in the past 12 months prior to the survey date.

178 Mean total and free PSA serum concentration were in the normal range (1.5 (standard error [SE] \pm
179 0.1) and 0.4 (\pm 0.1) ng/ml, respectively); mean PSA ratio was 30.2% (\pm 0.6%). Mean genistein,
180 enterodiol and enterolactone concentrations were 190.4 (\pm 27.1), 146.9 (\pm 41.8) and 910.7 (\pm 104.7)
181 ng/ml, respectively.

182 In the linear regression models, the associations of phytoestrogen concentrations with total or free
183 PSA serum levels and PSA ratio were not statistically significant (Table 2).

184 There was no clear pattern of the association between urinary phytoestrogen concentrations and
185 odds of having elevated total PSA concentration, and none of the associations were statistically
186 significant (Table 3). However, the sum of isoflavones and the sum of all phytoestrogens were
187 associated with an increased odds of having a PSA ratio < 15%, when comparing top versus bottom
188 quartiles. For example, men in the top quartile of the sum of isoflavones had an OR = 2.82 (95% CI
189 1.28-6.22) of having a PSA ratio < 15% compared with men in the bottom quartile. In contrast,
190 there were no statistically significant associations between urine isoflavone levels and odds of
191 having PSA ratio < 25%.

192 In sub-analyses, we computed linear regressions for the subgroup of the men without limited renal
193 function (which was defined as not having a chronic kidney disease: glomerular filtration rate
194 \geq 60ml/min/1.73m²; unweighted n=320; data not shown) (34). The results of the linear regressions
195 of the subgroup were similar to the results of the linear regression of the main sample and not
196 statistically significant.

197

198 Discussion

199 A PSA-decreasing effect of phytoestrogens has been observed in cell cultures and mice (35-39). In
200 LNCaP cells, genistein abrogated the stimulation of PSA by 17^β-estradiol, and equol administration
201 reduced PSA levels (35, 39). Some human feeding studies, which examined participants with
202 pathological changes in the tissue of the prostate, have shown declines in PSA levels with
203 phytoestrogen intake (17, 18, 40) or administration of soy milk (19), whereas another human
204 feeding study found no significant effect of soy consumption on serum total or free PSA levels in
205 healthy men (41). Also, in a double-blind, placebo-controlled randomized trial among men with
206 prostate cancer, the administration of isoflavone supplements did not change PSA concentrations
207 (42), but another soy intervention study observed a decrease of PSA concentrations (43). However,
208 to the best of our knowledge, our study is the first effort to investigate the cross-sectional
209 association between urinary phytoestrogen concentration and serum PSA level in a group of men of
210 the general US population. We observed no clear association between urinary phytoestrogen
211 concentration and having elevated total or free PSA concentration in the examined population.
212 However, men in the top quartiles of isoflavones and the sum of all phytoestrogens, i.e., isoflavones
213 and lignans, had an elevated odds of having a PSA ratio below 15%. However, there was no
214 statistically significant odds ratio when using a cut point of 25%.

215 The anticancer potential of the isoflavone tectorigenin was demonstrated on the molecular level
216 (44) and the chemopreventive potential of genistein against prostate cancer was shown in two
217 animal models (45). The anti prostate cancer effect of the phytoestrogen group of isoflavones could
218 be hypothesized in the possible action of isoflavones on the androgen receptor (AR) in prostate
219 tumor cells (19). Additionally the isoflavone genistein is able to inhibit several cancer promoting
220 factors on the molecular level (1). A meta-analysis of 8 studies (US, Canada, Japan, China and
221 Taiwan) reported an inverse association of soy food consumption with the risk for prostate cancer.
222 (46) Moreover, a nested case-control study among Japanese men observed that serum daidzein,
223 genistein and equol seemed to dose-dependently reduce prostate cancer risk (47). However, in our

224 study, the outcome was circulating level of PSA, which in the US has been used as a screening
225 instrument for prostate cancer. PSA, however, is not cancer-specific; higher levels of serum PSA
226 are also observed in benign prostate conditions such as benign prostatic hyperplasia and prostatitis.
227 In evaluating whether phytoestrogens influence the likelihood of an abnormal PSA result, we used a
228 PSA cut point of 4 ng/ml, which is often used as threshold value for prostate biopsy (48), and of 2.5
229 ng/ml, which is sometimes used clinically for prostate cancer screening (29, 49), but we observed
230 no statistically significant associations for either cut-point. In contrast, we observed an increased
231 odds of having a PSA ratio < 15% with increasing isoflavone excretion. However, there were no
232 associations when using a PSA ratio of 25% as a cut-off and we cannot exclude that the first
233 observation is merely a chance finding.

234 PSA screening is not optimal for detecting prostate cancer, with the consequence of possible
235 overtreatment of men who have a pathological PSA but who have no prostate cancer or, on the
236 other hand a prostate cancer that remains clinical unapparent (50, 51). Several factors also influence
237 the PSA level. Besides inflammation of the prostate, urinary retention, ejaculation and ambulation
238 have an influence on the PSA value (52).

239 Compared to the data of the study of Valentín-Blasini et al. (53), phytoestrogen concentrations in
240 this subpopulation of US men 40+ years old were in almost the same range. However, urinary
241 levels of isoflavones of our sample were lower than measured in Vietnamese and Japanese samples
242 (54). Thus, our results may indicate that the range of isoflavone intake in a general group of US
243 men might be too narrow and too low to significantly affect PSA concentration in healthy men. An
244 analysis of the Asian subgroup in our sample was not possible due to a small sample size (1.7% of
245 the study population). On the other hand, levels of lignans of our sample were higher compared to
246 the samples of the Asian study (54), supporting the importance of looking at lignan levels in
247 addition to isoflavones in European and North-American societies.

248 The cross-sectional study design is one of the limitations of our study. To test whether
249 phytoestrogen consumption affects PSA concentration, multiple measurements would better reflect
250 actual PSA and phytoestrogen levels. Indeed, a decrease in the rate of rise of serum PSA levels in
251 men with PSA recurrent disease was shown in two trials (19, 55), but a third trial did not report any
252 association (1). However, the number of participants in these trials was limited and larger
253 prospective studies are warranted.

254 A further limitation is the use of spot urine samples for the determination of phytoestrogen levels.
255 Measurements in spot urines may not be representative for the habitual nutritional intake of
256 phytoestrogens. The half-lives of phytoestrogens are in the range of 3-10 hours (53). However, in a
257 previous analysis of NHANES III data, urinary and serum levels of phytoestrogens showed a good
258 correlation (daidzein $r=0.72$) (53). In addition, the problematic accuracy of PSA such that changes
259 in PSA concentration over time can either be physiological or pathological has been discussed in
260 different publications (1, 19, 56).

261 In conclusion, the results of this study based on the 2001-2004 NHANES surveys, a population with
262 a generally low intake of phytoestrogens compared with, e.g. Asian populations, showed no clear
263 relationship between serum PSA level and urinary phytoestrogen concentration. We observed an
264 increased odds of having a PSA ratio $< 15\%$ with high phytoestrogen levels, but there was no
265 association when using a different cut-point for categorizing PSA ratio. Longitudinal studies among
266 healthy men, preferably with multiple measurements of phytoestrogens and PSA, may be better
267 suited to address the question whether habitual phytoestrogen intake has an effect on PSA
268 concentration than cross-sectional studies.

269

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272

273 Acknowledgements

274 We thank all individuals at the National Center for Health Statistics (NCHS) of the Centers for

275 Disease Control and Prevention who were responsible for the planning and administering of

276 NHANES.

277

Table 1. Baseline characteristics by quartiles of urine genistein concentration, men 40+ years old in NHANES 2001-2004

Characteristic	Mean / percentage *†	SE of mean
	N=824	
Age (years)	54.6	0.4
BMI (kg/m ²)	28.8	0.3
Race (%)		
Non-Hispanic white	58.0	
Non-Hispanic black	18.5	
Hispanic	21.8	
Other	1.7	
Education level (%)**		
<High school	29.4	
High school/GED	22.9	
>High School	47.6	
Living below poverty (PIR < 1) (%)	14.0	
Smoking history – ever smoker (%)	71.6	
Average number of alcoholic drinks/day –past 12 months (%)**		
0	32.2	
d1	21.5	
>1	43.5	
Any vigorous activity over past 30 days (%)	27.2	
Use of pain relievers (NSAIDs) nearly every day for a month or longer (%)	30.6	
Statin use, past month (%)	12.0	
Thiazide diuretic use, past month (%)	9.0	
Creatinine, urine (mg/dl)	143.6	3.1
C-reactive protein (mg/dl)	0.4	0.1
Total PSA (ng/ml)	1.5	0.1
Free PSA (ng/ml)	0.4	0.1
PSA ratio (%)	30.2	0.6
Isoflavones		
Daidzein (ng/ml)	318.0	46.1
Genistein (ng/ml)	190.4	27.1
o-Desmethylangolensin (ng/ml)	45.1	7.7
Equol (ng/ml)	21.1	5.3
Lignans		
Enterodiol (ng/ml)	146.9	41.8
Enterolactone (ng/ml)	910.7	104.7

279 BMI, body mass index; GED, General Education Development; PIR, Poverty Income Ratio; SE, standard error.

280 * Values are means or percentages unless otherwise noted.

281 † The sum of the percentages may not always be 100 due to rounding.

282 ** Does not add up to 100% because of missing information.

283

284 Table 2. Linear regression: outcome variables total PSA, free PSA and PSA ratio levels in the serum, exposure variables creatinine-
 285 adjusted phytoestrogen-levels in the urine controlled for confounders†; NHANES 2001-2004

Phytoestrogen‡	Beta-coefficient	SE	Change in % per 1% change in total or free PSA concentration of PSA ratio		
			change in %	95% CI	
Total PSA concentration§					
Sum of isoflavones	-0.008	0.026	-0.80	-5.73	to 4.39
Sum of lignans	0.013	0.02	1.31	-2.59	to 5.36
Sum of phytoestrogens	-0.012	0.022	-1.19	-5.36	to 3.16
Free PSA concentration					
Sum of isoflavones	-0.007	0.013	-0.7	-3.2	to 1.9
Sum of lignans	0.0001	0.009	0.01	-1.7	to 1.8
Sum of phytoestrogens	-0.003	0.007	-0.3	-1.7	to 1.1
PSA ratio (%)§					
Sum of isoflavones	0.011	0.014	1.11	-1.63	to 3.92
Sum of lignans	0.001	0.014	0.10	-2.61	to 2.88
Sum of phytoestrogens	0.011	0.015	1.11	-1.82	to 4.12

286 CI, confidence interval; SE, standard error

287 * $P < 0.05$

288 † Adjusted for age, race/ethnicity, poverty-income-ratio, educational level, BMI, C-reactive protein, NSAIDs, statins, thiazide
 289 diuretics, smoking, alcohol-consumption, physical activity

290 ‡ Units of creatinine-adjusted phytoestrogen concentration were per 500µg/g creatinine, urine

291 § PSA-level units: The natural logarithm of total PSA in ng/ml, of free PSA in ng/ml and of PSA Ratio in %

292

293 Table 3. Association between quartiles of urine phytoestrogen concentration* and elevated total PSA concentration or PSA ratio,
 294 NHANES 2001-2004†

	Quartiles of phytoestrogen concentration								p-trend
	1 OR	2 OR	95% CI	3 OR	95% CI	4 OR	95% CI		
Total PSA >2.5ng/ml									
Sum of isoflavones	1.00	0.80	0.40,1.60	0.88	0.47,1.67	0.84	0.37,1.87	0.65	
Sum of lignans	1.00	1.70	0.78,3.70	2.18	0.93,5.12	1.69	0.65,4.41	0.26	
Sum of phytoestrogens	1.00	1.06	0.46,2.45	0.96	0.37,2.49	1.11	0.47,2.64	0.88	
Total PSA >4.0ng/ml									
Sum of isoflavones	1.00	1.05	0.60,1.84	1.59	0.85,2.99	1.31	0.44,3.88	0.39	
Sum of lignans	1.00	1.81	0.41,8.05	3.25	0.83,12.7	2.17	0.46,10.3	0.25	
Sum of phytoestrogens	1.00	1.19	0.45,3.12	1.33	0.45,3.97	1.33	0.37,4.85	0.66	
PSA ratio <15%									
Sum of isoflavones	1.00	1.04	0.39,2.82	1.52	0.67,3.44	2.82	1.28,6.22	0.02	
Sum of lignans	1.00	0.45	0.12,1.76	1.02	0.35,2.95	2.30	0.88,5.99	0.06	
Sum of phytoestrogens	1.00	2.40	0.79,7.29	1.65	0.55,4.90	3.77	1.34,10.6	0.03	
PSA ratio <25%									
Sum of isoflavones	1.00	0.85	0.51,1.41	0.91	0.49,1.69	0.99	0.50,1.97	0.99	
Sum of lignans	1.00	0.68	0.43,1.08	0.75	0.42,1.33	1.00	0.60,1.67	0.95	
Sum of phytoestrogens	1.00	0.92	0.54,1.58	0.91	0.54,1.54	1.08	0.64,1.81	0.81	

295 CI, confidence interval.

296 * Phytoestrogen concentration units: µg/g creatinine, urine

297 † Adjusted for age, race/ethnicity, C-reactive protein, NSAIDs, statins, thiazide diuretics, smoking, alcohol-consumption, poverty-
 298 income-ratio, physical activity, BMI, educational level

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302 References

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