**Supplementary Materials**

**Table S1.** Comparison of three laboratory methods for testing urinary phytoestrogens in NHANES 1999-2010

**Table S2.** Baseline characteristics of 8,844 participants in quartiles of total urinary phytoestrogens from NHANES 1999-2010

**Table S3.** The association between urinary phytoestrogens and HRCs stratified by menopausal status among females from NHANES 1999-2010

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**Figure S1.** Flowchart of the screening process of eligible participants from NHANES 1999–2010

**Figure S2.** Restricted cubic splines for dose-response relationships between urinary phytoestrogens and HRCs from NHANES 1999-2010

**Figure S3.** Forest plot for the association between urinary phytoestrogens and breast cancer among females from NHANES 1999-2010

**Figure S4.** Forest plot for the association between urinary phytoestrogens and prostate cancer among males from NHANES 1999-2010

**Table S1. Comparison of three** **laboratory methods for testing urinary phytoestrogens in NHANES 1999-2010**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **NHANES 1999-2002** | **NHANES 2003-2004** | **NHANES 2005-2010** |
| **Method** | HPLC-APCI-MS/MS | HPLC-ESI-MS/MS | HPLC-APPI-MS/MS |
| **Chromatographic column** | C18 A Keystone Prism reverse phase column (3 mm \* 50 mm, 5 μm) | ThermoElectron Betasil C18 analytical column (3 mm \* 50 mm, 5 μm) | Kinetex C18 analytical column (2.1 mm \* 50 mm, 2.6 μm) |
| **Mobile Phase A** | 10mM ammonium acetate buffer pH 6.5 | 10mM ammonium acetate buffer pH 6.5 | 100% H2O |
| **Mobile Phase B** | Methanol : Acetonitrile (1:1) | Methanol : Acetonitrile (1:1) | 100% methanol |
| **Mass Spectrometer** | Sciex API III tandem mass spectrometer | Sciex API 4000 triple quadrupole mass spectrometer | Sciex API 4000 triple quadrupole mass spectrometer |
| **Iron source** | Negative | Negative | Negative |
| **Detection mode** | MRM | MRM | MRM |
| **Nebulizing gas** | Nitrogen (80 psi) | Nitrogen (60 psi) | Nitrogen (60 psi) |
| **Interface temperatures** | 500 °C | 550 °C | 450 °C |
| **Needle voltages** | –3 V | –3500 V | –875 V |

Abbreviations: HN-APCI, heated nebulizer-atmospheric pressure chemical ionization; HPLC-APCI-MS/MS, high performance liquid chromatography-atmospheric pressure chemical ionization-tandem mass spectrometry; HPLC-ESI-MS/MS, high performance liquid chromatography-electrospry ionization-tandem mass spectrometry; HPLC-APPI-MS/MS, high performance liquid chromatography-atmospheric pressure photoionization-tandem mass spectrometry; MRM, multiple reaction monitoring.

**Table S2.** **Baseline characteristics of 8,844 participants in quartiles of total urinary phytoestrogens from NHANES 1999-2010**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Total urinary phytoestrogens (****μg/g creatinine)** | | | |  |
|  | **Quartile 1**  **(1.03-314.58)** | **Quartile 2**  **(314.59-711.17)** | **Quartile 3**  **(711.18-1520.08)** | **Quartile 4**  **(1520.09-142862.61)** | ***P*-value** |
| **No. of participants** | 2269 | 2310 | 2263 | 2002 |  |
| **Age, years (mean±SD)** | 41.6±0.4 | 44.8±0.5 | 47.7±0.5 | 49.7±0.6 | <0.001 |
| **Gender, %** |  |  |  |  | <0.001 |
| Male | 59.6 | 52.6 | 45.9 | 38.7 |  |
| Female | 40.4 | 47.4 | 54.1 | 61.3 |  |
| **Race/Ethnicity, %** |  |  |  |  | <0.001 |
| NH white | 64.5 | 67.4 | 70.4 | 75.4 |  |
| NH black | 14.9 | 13.5 | 12.0 | 6.5 |  |
| Mexican American | 9.0 | 9.6 | 8.6 | 6.2 |  |
| Other | 11.6 | 9.4 | 8.9 | 12.0 |  |
| **Education, %** |  |  |  |  | <0.001 |
| Below high school | 21.9 | 20.4 | 17.1 | 15.6 |  |
| High school | 29.5 | 27.1 | 26.6 | 18.3 |  |
| College or above | 48.5 | 52.4 | 56.3 | 66.1 |  |
| **Marital status, %** |  |  |  |  | <0.001 |
| Married/living with partner | 60.2 | 62.2 | 66.0 | 68.7 |  |
| Divorced/separated/widowed | 17.3 | 19.4 | 18.6 | 18.5 |  |
| Never married | 22.5 | 18.4 | 15.3 | 12.8 |  |
| **PIR, %** |  |  |  |  | <0.001 |
| 0~1.30 | 26.5 | 20.6 | 18.4 | 16.0 |  |
| 1.31~3.50 | 36.2 | 37.0 | 38.9 | 33.3 |  |
| 3.51~ | 37.3 | 42.4 | 42.6 | 50.7 |  |
| **BMI, %** |  |  |  |  | <0.001 |
| <25 | 25.3 | 29.2 | 35.1 | 43.0 |  |
| 25-30 | 31.4 | 33.8 | 32.4 | 31.5 |  |
| >30 | 43.3 | 36.9 | 32.4 | 25.5 |  |
| **Physical activity, %** |  |  |  |  | 0.106 |
| Vigorous | 30.5 | 30.8 | 29.1 | 30.1 |  |
| Moderate | 28.7 | 25.9 | 29.9 | 25.0 |  |
| Inactive | 40.8 | 43.3 | 41.0 | 44.9 |  |
| **Smoking status, %** |  |  |  |  | <0.001 |
| Non-smoker | 48.2 | 49.7 | 53.5 | 57.5 |  |
| Current smoking | 31.9 | 28.4 | 20.4 | 16.1 |  |
| Former smokers | 19.9 | 21.8 | 26.1 | 26.4 |  |
| **Alcohol intake, %** |  |  |  |  | 0.103 |
| No drinking | 72.8 | 69.7 | 70.4 | 67.2 |  |
| Moderate drinking | 9.4 | 10.2 | 11.0 | 12.7 |  |
| Heavy drinking | 17.8 | 20.1 | 18.7 | 20.1 |  |
| **Hypertension, %** | 43.4 | 45.2 | 45.1 | 44.1 | 0.799 |
| DBP, mm Hg | 72.3±0.4 | 71.2±0.4 | 70.4±0.4 | 70.2±0.3 | <0.001 |
| SBP, mm Hg | 122.0±0.5 | 122.6±0.5 | 122.1±0.5 | 122.2±0.6 | 0.719 |
| **Diabetes, %** | 11.5 | 11.4 | 11.8 | 11.8 | 0.978 |
| HbA1c, % | 5.5±0.0 | 5.5±0.0 | 5.5±0.0 | 5.5±0.0 | 0.541 |
| Fasting glucose, mg/dL | 104.1±1.3 | 103.7±1.1 | 103.2±0.9 | 103.4±1.0 | 0.742 |
| OGTT, mg/dL | 121.7±4.3 | 122.2±2.8 | 110.6±2.1 | 111.6±3.2 | <0.001 |
| **Dyslipidemia, %** | 56.3 | 55.1 | 52.1 | 50.6 | 0.049 |
| HDL-c, mg/dL | 49.0±0.6 | 51.5±0.5 | 53.9±0.5 | 57.1±0.5 | <0.001 |
| LDL-c, mg/dL | 114.8±1.7 | 116.0±1.7 | 115.3±1.3 | 116.3±1.6 | 0.460 |
| TG, mg/dL | 177.2±7.9 | 140.6±4.4 | 125.5±2.6 | 122.0±3.9 | <0.001 |
| **TEI, kcal/d (mean±SD)** | 2,324.7±32.6 | 2,274.8±30.8 | 2,134.6±28.5 | 2,086.4±26.7 | <0.001 |
| **Fat intake, g/d (mean±SD)** | 86.8±1.6 | 85.8±1.3 | 81.4±1.4 | 78.4±1.5 | <0.001 |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test; PIR, poverty income ratio; SBP, systolic blood pressure; SD, standard deviation; TEI, total energy intake; TG, triglyceride.

Data were expressed as the weighted mean±SD or weighted proportion. Sampling-weighted Rao-Scott chi-square tests were performed for categorical variables and sampling-weighted analysis of variance (ANOVA) methods were performed for continuous variables. A level of <0.05 for two-sided *P* values was considered statistically significant.

**Table S3.** **The association between urinary phytoestrogens and HRCs stratified by menopausal status among females from NHANES 1999-2010**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Urinary phytoestrogens** | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** | ***P* for trend** |
| **Premenopausal (n=1,743)** |  |  |  |  |  |
| Total phytoestrogen |  |  |  |  |  |
| Range, μg/g creatinine | 3.67-327.97 | 327.98-742.69 | 742.70-1591.46 | 1591.47-142862.61 |  |
| N (HRCs/non-HRCs) | 8/614 | 12/587 | 11/550 | 14/491 |  |
| OR (95% CI) | 1.00 (Ref) | 3.53 (0.85-14.69) | 2.31 (0.44-12.12) | 6.30 (1.38-28.75) | 0.030 |
| Isoflavone |  |  |  |  |  |
| Range, μg/g creatinine | 2.34-44.19 | 44.20-104.64 | 104.65-325.51 | 325.52-111751.63 |  |
| N (HRCs/non-HRCs) | 6/605 | 12/545 | 12/556 | 15/536 |  |
| OR (95% CI) | 1.00 (Ref) | 5.80 (1.37-24.47) | 2.78 (0.71-10.87) | 4.06 (1.13-14.66) | 0.197 |
| Daidzein |  |  |  |  |  |
| Range, μg/g creatinine | 0.23-18.13 | 18.14-49.68 | 49.69-169.79 | 169.80-67500.00 |  |
| N (HRCs/non-HRCs) | 4/596 | 11/538 | 16/551 | 14/557 |  |
| OR (95% CI) | 1.00 (Ref) | 6.15 (1.34-28.22) | 8.84 (1.92-40.84) | 6.83 (1.60-29.17) | 0.014 |
| Genistein |  |  |  |  |  |
| Range, μg/g creatinine | 0.07-8.45 | 8.46-21.90 | 21.91-72.91 | 72.92-37687.50 |  |
| N (HRCs/non-HRCs) | 8/548 | 10/557 | 10/575 | 17/562 |  |
| OR (95% CI) | 1.00 (Ref) | 2.95 (1.09-8.00) | 1.05 (0.23-4.68) | 1.80 (0.62-5.21) | 0.832 |
| O-DMA |  |  |  |  |  |
| Range, μg/g creatinine | 0.04-0.79 | 0.80-3.43 | 3.44-22.52 | 22.53-10267.86 |  |
| N (HRCs/non-HRCs) | 7/653 | 8/556 | 13/534 | 17/499 |  |
| OR (95% CI) | 1.00 (Ref) | 1.52 (0.24-9.55) | 3.19 (0.62-16.36) | 4.19 (0.81-21.60) | 0.036 |
| Equol |  |  |  |  |  |
| Range, μg/g creatinine | 0.01-3.70 | 3.71-7.93 | 7.94-16.08 | 16.09-12000.00 |  |
| N (HRCs/non-HRCs) | 8/678 | 12/608 | 15/474 | 10/482 |  |
| OR (95% CI) | 1.00 (Ref) | 3.35 (0.51-22.26) | 11.35 (1.60-80.44) | 3.71 (0.66-20.85) | 0.008 |
| Lignan |  |  |  |  |  |
| Range, μg/g creatinine | 1.18-180.30 | 180.31-465.97 | 465.98-1035.66 | 1035.67-142797.70 |  |
| N (HRCs/non-HRCs) | 9/637 | 11/572 | 13/536 | 12/497 |  |
| OR (95% CI) | 1.00 (Ref) | 5.83 (1.41-24.06) | 4.32 (1.02-18.20) | 11.38 (1.89-68.44) | 0.012 |
| Enterodiol |  |  |  |  |  |
| Range, μg/g creatinine | 0.01-18.58 | 18.59-49.37 | 49.38-114.35 | 114.36-17400.00 |  |
| N (HRCs/non-HRCs) | 12/641 | 8/619 | 15/508 | 10/474 |  |
| OR (95% CI) | 1.00 (Ref) | 1.00 (0.26-3.79) | 4.40 (1.23-15.69) | 5.93 (1.55-22.62) | 0.003 |
| Enterolactone |  |  |  |  |  |
| Range, μg/g creatinine | 0.18-111.99 | 112.00-378.77 | 378.78-900.75 | 900.76-130888.95 |  |
| N (HRCs/non-HRCs) | 11/592 | 8/598 | 12/546 | 14/506 |  |
| OR (95% CI) | 1.00 (Ref) | 4.07 (1.08-15.32) | 0.90 (0.23-3.52) | 8.13 (1.59-41.57) | 0.041 |
| **Postmenopausal (n=2,125)** |  |  |  |  |  |
| Total phytoestrogen |  |  |  |  |  |
| Range, μg/g creatinine | 2.93-502.64 | 502.65-1041.86 | 1041.87-2094.83 | 2094.84-65885.47 |  |
| N (HRCs/non-HRCs) | 58/1477 | 55/1083 | 51/886 | 57/745 |  |
| OR (95% CI) | 1.00 (Ref) | 0.92 (0.53-1.62) | 1.39 (0.80-2.41) | 1.67 (0.93-2.99) | 0.038 |
| Isoflavone |  |  |  |  |  |
| Range, μg/g creatinine | 2.17-60.06 | 60.07-148.70 | 148.71-506.95 | 506.96-64712.84 |  |
| N (HRCs/non-HRCs) | 43/788 | 52/580 | 53/587 | 46/520 |  |
| OR (95% CI) | 1.00 (Ref) | 1.81 (0.98-3.35) | 2.05 (1.09-3.86) | 1.83 (0.94-3.57) | 0.074 |
| Daidzein |  |  |  |  |  |
| Range, μg/g creatinine | 0.14-24.39 | 24.40-71.26 | 71.27-269.99 | 270.00-58947.37 |  |
| N (HRCs/non-HRCs) | 38/737 | 58/592 | 53/625 | 45/521 |  |
| OR (95% CI) | 1.00 (Ref) | 2.21 (1.15-4.27) | 1.98 (1.17-3.37) | 1.87 (0.92-3.79) | 0.108 |
| Genistein |  |  |  |  |  |
| Range, μg/g creatinine | 0.10-11.49 | 11.50-33.39 | 33.40-124.51 | 124.52-11895.09 |  |
| N (HRCs/non-HRCs) | 42/696 | 53/651 | 48/596 | 51/532 |  |
| OR (95% CI) | 1.00 (Ref) | 1.17 (0.54-2.55) | 1.61 (0.74-3.50) | 1.59 (0.73-3.48) | 0.174 |
| O-DMA |  |  |  |  |  |
| Range, μg/g creatinine | 0.03-1.13 | 1.14-5.76 | 5.77-42.49 | 42.50-34166.67 |  |
| N (HRCs/non-HRCs) | 61/779 | 45/649 | 45/588 | 43/459 |  |
| OR (95% CI) | 1.00 (Ref) | 1.22 (0.64-2.34) | 0.96 (0.51-1.79) | 1.23 (0.67-2.28) | 0.675 |
| Equol |  |  |  |  |  |
| Range, μg/g creatinine | 0.05-4.42 | 4.43-8.72 | 8.73-17.86 | 17.87-11117.65 |  |
| N (HRCs/non-HRCs) | 56/783 | 45/642 | 49/541 | 44/509 |  |
| OR (95% CI) | 1.00 (Ref) | 0.75 (0.40-1.38) | 1.67 (0.94-2.94) | 1.48 (0.74-2.93) | 0.077 |
| Lignan |  |  |  |  |  |
| Range, μg/g creatinine | 0.12-255.63 | 255.64-670.05 | 670.06-1387.96 | 1387.97-47545.45 |  |
| N (HRCs/non-HRCs) | 49/740 | 47/679 | 50/554 | 48/502 |  |
| OR (95% CI) | 1.00 (Ref) | 1.23 (0.63-2.38) | 1.43 (0.69-2.98) | 1.15 (0.55-2.43) | 0.630 |
| Enterodiol |  |  |  |  |  |
| Range, μg/g creatinine | 0.02-24.98 | 24.99-64.08 | 64.09-146.47 | 146.48-40909.09 |  |
| N (HRCs/non-HRCs) | 46/774 | 39/677 | 57/564 | 52/460 |  |
| OR (95% CI) | 1.00 (Ref) | 0.90 (0.41-1.96) | 1.45 (0.74-2.84) | 1.95 (1.05-3.62) | 0.015 |
| Enterolactone |  |  |  |  |  |
| Range, μg/g creatinine | 0.09-148.80 | 148.81-536.35 | 536.36-1201.81 | 1201.82-33754.73 |  |
| N (HRCs/non-HRCs) | 55/682 | 42/691 | 50/583 | 47/519 |  |
| OR (95% CI) | 1.00 (Ref) | 0.85 (0.45-1.60) | 1.06(0.52-2.18) | 0.83 (0.38-1.81) | 0.777 |

Abbreviations: CI, confidence interval; HRCs, hormone-related cancers; NHANES, National Health and Nutrition Examination Survey; O-DMA, O-desmethylangolensin; OR, odds ratio.

Adjusted for age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, or other), education level (below high school, high school, or college or above), marital status (married/living with partner, divorced/separated/widowed, or never married), poverty income ratio (0~1.30, 1.31~3.50, or 3.51~), body mass index (<25, 25-30, or >30 kg/m2), physical activity (vigorous, moderate, or inactive), smoking status (non-smoker, current smoking, or former smokers), alcohol intake (no drinking, moderate drinking, or heavy drinking), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), total energy intake (continuous), fat intake (continuous).

**Table S4.** **The association between urinary phytoestrogens and HRCs diagnosed within/over 5 years from NHANES 1999-2010**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Urinary phytoestrogens** |  | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** | ***P* for trend** |
| Total phytoestrogen |  |  |  |  |  |  |
| Within 5 years | N | 28 | 37 | 44 | 53 |  |
|  | OR (95% CI) | 1.00 (Ref) | 0.58 (0.26-1.29) | 0.72 (0.34-1.51) | 1.29 (0.63-2.63) | 0.247 |
| Over 5 years | N | 27 | 52 | 63 | 68 |  |
|  | OR (95% CI) | 1.00 (Ref) | 1.86 (0.92-3.78) | 1.40 (0.65-3.00) | 1.25 (0.58-2.70) | 0.839 |
| Isoflavone |  |  |  |  |  |  |
| Within 5 years | N | 38 | 32 | 41 | 51 |  |
|  | OR (95% CI) | 1.00 (Ref) | 0.78 (0.33-1.81) | 1.41 (0.65-3.03) | 1.49 (0.76-2.92) | 0.060 |
| Over 5 years | N | 36 | 48 | 70 | 56 |  |
|  | OR (95% CI) | 1.00 (Ref) | 1.69 (0.75-3.84) | 2.22 (1.14-4.33) | 1.39 (0.69-2.83) | 0.392 |
| Daidzein |  |  |  |  |  |  |
| Within 5 years | N | 35 | 38 | 38 | 51 |  |
|  | OR (95% CI) | 1.00 (Ref) | 1.43 (0.63-3.22) | 1.63 (0.75-3.57) | 1.78 (0.93-3.41) | 0.052 |
| Over 5 years | N | 31 | 52 | 71 | 56 |  |
|  | OR (95% CI) | 1.00 (Ref) | 2.10 (1.12-3.92) | 2.76 (1.50-5.10) | 1.86 (0.92-3.78) | 0.095 |
| Genistein |  |  |  |  |  |  |
| Within 5 years | N | 33 | 35 | 40 | 54 |  |
|  | OR (95% CI) | 1.00 (Ref) | 1.63 (0.66-4.05) | 1.22 (0.50-2.96) | 1.68 (0.76-3.72) | 0.307 |
| Over 5 years | N | 34 | 54 | 58 | 64 |  |
|  | OR (95% CI) | 1.00 (Ref) | 1.55 (0.84-2.89) | 1.71 (0.83-3.54) | 1.40 (0.65-3.02) | 0.459 |
| O-DMA |  |  |  |  |  |  |
| Within 5 years | N | 41 | 40 | 34 | 47 |  |
|  | OR (95% CI) | 1.00 (Ref) | 0.84 (0.42-1.68) | 0.56 (0.24-1.34) | 1.07 (0.54-2.12) | 0.961 |
| Over 5 years | N | 35 | 58 | 55 | 62 |  |
|  | OR (95% CI) | 1.00 (Ref) | 1.35 (0.77-2.37) | 1.71 (0.85-3.46) | 1.51 (0.79-2.91) | 0.190 |
| Equol |  |  |  |  |  |  |
| Within 5 years | N | 47 | 33 | 43 | 39 |  |
|  | OR (95% CI) | 1.00 (Ref) | 0.71 (0.35-1.46) | 1.21 (0.60-2.43) | 1.05 (0.49-2.27) | 0.569 |
| Over 5 years | N | 41 | 53 | 67 | 49 |  |
|  | OR (95% CI) | 1.00 (Ref) | 0.85 (0.43-1.66) | 1.59 (0.74-3.40) | 1.02 (0.51-2.05) | 0.551 |
| Lignan |  |  |  |  |  |  |
| Within 5 years | N | 38 | 27 | 43 | 54 |  |
|  | OR (95% CI) | 1.00 (Ref) | 0.36 (0.17-0.79) | 0.60 (0.31-1.16) | 0.91 (0.44-1.92) | 0.729 |
| Over 5 years | N | 30 | 43 | 58 | 79 |  |
|  | OR (95% CI) | 1.00 (Ref) | 2.47 (1.25-4.85) | 1.56 (0.77-3.20) | 1.81 (0.84-3.90) | 0.554 |
| Enterodiol |  |  |  |  |  |  |
| Within 5 years | N | 34 | 36 | 38 | 54 |  |
|  | OR (95% CI) | 1.00 (Ref) | 1.18 (0.45-1.28) | 1.43 (0.57-3.60) | 2.75 (1.21-6.25) | 0.005 |
| Over 5 years | N | 33 | 39 | 67 | 71 |  |
|  | OR (95% CI) | 1.00 (Ref) | 0.62 (0.30-1.28) | 1.43 (0.74-2.76) | 1.58 (0.80-3.12) | 0.039 |
| Enterolactone |  |  |  |  |  |  |
| Within 5 years | N | 35 | 29 | 45 | 53 |  |
|  | OR (95% CI) | 1.00 (Ref) | 0.58 (0.25-1.30) | 0.68 (0.33-1.37) | 1.02 (0.49-2.13) | 0.729 |
| Over 5 years | N | 39 | 40 | 50 | 81 |  |
|  | OR (95% CI) | 1.00 (Ref) | 2.18 (1.15-4.14) | 1.06 (0.51-2.21) | 1.51 (0.73-3.11) | 0.847 |

Abbreviations: CI, confidence interval; HRCs, hormone-related cancers; NHANES, National Health and Nutrition Examination Survey; O-DMA, O-desmethylangolensin; OR, odds ratio.

Adjusted for age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, or other), education level (below high school, high school, or college or above), marital status (married/living with partner, divorced/separated/widowed, or never married), poverty income ratio (0~1.30, 1.31~3.50, or 3.51~), body mass index (<25, 25-30, or >30 kg/m2), physical activity (vigorous, moderate, or inactive), smoking status (non-smoker, current smoking, or former smokers), alcohol intake (no drinking, moderate drinking, or heavy drinking), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), total energy intake (continuous), fat intake (continuous).

**Table S5. Baseline characteristics of 678 participants with female cancer biomarkers from NHANES 2001-2002**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | CA125, U/mL  (geometric mean±SD) | CA15.3, mU/mL  (geometric mean±SD) | HE4, pM  (geometric mean±SD) |
|  |  | 12.0±0.3 | 901.7±29.7 | 14.6±0.6 |
| **Age, years (mean±SD)** | 45.8±0.8 | / | / | / |
| pearson’s r |  | -0.110 | 0.007 | 0.480 |
| *P*-value |  | 0.004 | 0.861 | <0.001 |
| **Race/Ethnicity, %** |  |  |  |  |
| NH white | 71.6 | 12.3±0.4 | 911.1±31.6 | 15.2±0.7 |
| NH black | 11.6 | 10.1±0.9 | 960.5±68.8 | 12.9±0.9 |
| Mexican American | 6.5 | 12.2±0.8 | 852.1±108.6 | 11.5±0.7 |
| Other | 10.3 | 12.4±1.9 | 809.6±122.6 | 14.5±2.7 |
| *P*-value |  | 0.178 | 0.808 | 0.026 |
| **Education, %** |  |  |  |  |
| Below high school | 19.0 | 11.4±0.8 | 951.8±71.4 | 16.5±1.8 |
| High school | 24.2 | 12.5±0.9 | 945.1±58.3 | 16.1±1.1 |
| College or above | 56.8 | 12.0±0.4 | 872.0±48.4 | 13.4±0.5 |
| *P*-value |  | 0.729 | 0.595 | 0.013 |
| **Marital status, %** |  |  |  |  |
| Married/living with partner | 64.1 | 12.3±0.5 | 906.0±31.1 | 14.0±0.5 |
| Divorced/separated/widowed | 20.5 | 11.4±0.6 | 961.1±77.2 | 20.5±2.0 |
| Never married | 15.5 | 11.8±0.6 | 813.4±44.3 | 11.2±0.8 |
| *P*-value |  | 0.600 | 0.024 | <0.001 |
| **PIR, %** |  |  |  |  |
| 0~1.30 | 23.9 | 11.8±0.7 | 977.5±77.1 | 16.0±1.8 |
| 1.31~3.50 | 32.6 | 11.4±0.7 | 893.8±56.3 | 15.4±1.0 |
| 3.51~ | 43.5 | 12.8±0.9 | 866.3±50.6 | 13.2±0.7 |
| *P*-value |  | 0.519 | 0.485 | 0.134 |
| **BMI, %** |  |  |  |  |
| <25 | 39.5 | 12.2±0.8 | 876.5±55.4 | 14.1±0.6 |
| 25-30 | 28.7 | 11.8±0.7 | 919.2±63.0 | 14.2±1.1 |
| >30 | 31.8 | 11.7±0.6 | 936.3±51.7 | 15.3±0.7 |
| *P*-value |  | 0.900 | 0.751 | 0.410 |
| **Physical activity, %** |  |  |  |  |
| Vigorous | 36.2 | 12.1±0.5 | 908.0±60.4 | 12.9±0.8 |
| Moderate | 30.9 | 11.7±0.7 | 814.0±38.5 | 16.1±1.0 |
| Inactive | 32.9 | 12.1±0.7 | 996.4±76.9 | 14.6±1.0 |
| *P*-value |  | 0.842 | 0.071 | 0.093 |
| **Smoking status, %** |  |  |  |  |
| Non-smoker | 60.8 | 12.2±0.5 | 922.1±48.7 | 13.1±0.5 |
| Current smoking | 21.6 | 11.2±0.8 | 831.6±45.2 | 18.8±1.6 |
| Former smokers | 17.6 | 12.4±1.1 | 922.7±74.1 | 15.4±1.2 |
| *P*-value |  | 0.648 | 0.506 | 0.003 |
| **Alcohol intake, %** |  |  |  |  |
| No drinking | 78.8 | 12.0±0.4 | 920.4±37.6 | 14.5±0.7 |
| Moderate drinking | 8.4 | 11.8±1.5 | 805.0±101.0 | 16.4±1.7 |
| Heavy drinking | 12.9 | 11.2±1.5 | 901.7±50.6 | 13.5±1.4 |
| *P*-value |  | 0.881 | 0.552 | 0.381 |
| **Hypertension, %** |  |  |  |  |
| No | 60.3 | 12.4±0.4 | 914.6±45.5 | 13.3±0.6 |
| Yes | 39.7 | 11.0±0.5 | 898.8±40.9 | 16.7±0.8 |
| *P*-value |  | 0.040 | 0.797 | <0.001 |
| **Diabetes, %** |  |  |  |  |
| No | 92.1 | 12.0±0.3 | 897.0±30.5 | 14.1±0.5 |
| Yes | 7.9 | 11.7±1.0 | 959.2±113.6 | 21.4±2.4 |
| *P*-value |  | 0.741 | 0.592 | 0.001 |
| **Dyslipidemia, %** |  |  |  |  |
| No | 57.8 | 11.5±0.5 | 888.2±43.4 | 13.4±0.4 |
| Yes | 42.2 | 12.9±0.5 | 926.9±48.4 | 16.3±1.2 |
| *P*-value |  | 0.117 | 0.585 | 0.011 |
| **TEI, kcal/d (mean±SD)** | 1773.0±40.3 | / | / | / |
| pearson’s *r* |  | -0.018 | 0.032 | -0.114 |
| *P*-value |  | 0.647 | 0.421 | 0.004 |
| **Fat intake, g/d (mean±SD)** | 66.6±1.7 | / | / | / |
| pearson’s *r* |  | -0.024 | 0.009 | -0.091 |
| *P*-value |  | 0.536 | 0.828 | 0.020 |
| **HRCs, %** |  |  |  |  |
| No | 96.8 | 12.0±0.3 | 905.5±33.1 | 14.4±0.6 |
| Yes | 3.2 | 12.6±2.3 | 796.2±126.9 | 21.1±1.5 |
| *P*-value |  | 0.761 | 0.486 | <0.001 |

Abbreviations: BMI, body mass index; CA125, cancer antigen 125; CA15.3, cancer antigen 15.3; HE4, human epididymal secretory protein E4; HRCs, hormone-related cancers; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; PIR, poverty income ratio; SD, standard deviation; TEI, total energy intake.

Data were expressed as the weighted mean±SD, weighted geometric mean±SD or weighted proportion. Sampling-weighted analysis of variance (ANOVA) methods were performed for categorical variables and weighted pearson’s correlation analyses were performed for continuous variables. A level of <0.05 for two-sided *P* values was considered statistically significant.

**Table S6. Baseline characteristics of 2,159 participants with male cancer biomarkers from NHANES 2001-2010**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Total PSA, ng/mL  (geometric mean±SD) | | Free PSA, ng/mL  (geometric mean±SD) | | | PSA ratio, % (mean±SD) |
|  |  | 0.96±0.02 | | 0.27±0.00 | | | 30.71±0.39 |
| **Age, years (mean±SD)** | 54.51±0.26 | / | | / | | | / |
| pearson’s r |  | 0.350 | | 0.385 | | | -0.020 |
| *P*-value |  | <0.001 | | <0.001 | | | 0.351 |
| **Race/Ethnicity, %** |  |  | |  | | |  |
| NH white | 75.3 | 0.96±0.02 | | 0.28±0.01 | | | 31.05±0.42 |
| NH black | 9.5 | 0.97±0.04 | | 0.27±0.01 | | | 30.24±0.67 |
| Mexican American | 6.2 | 0.98±0.05 | | 0.26±0.01 | | | 28.61±0.62 |
| Other | 9.0 | 0.96±0.06 | | 0.26±0.01 | | | 29.83±1.22 |
| *P*-value |  | 0.990 | | 0.439 | | | 0.009 |
| **Education, %** |  |  | |  | | |  |
| Below high school | 18.0 | 1.02±0.05 | | 0.29±0.01 | | | 31.07±0.81 |
| High school | 25.6 | 0.94±0.04 | | 0.26±0.01 | | | 29.88±0.69 |
| College or above | 56.4 | 0.96±0.03 | | 0.27±0.01 | | | 30.97±0.56 |
| *P*-value |  | 0.396 | | 0.147 | | | 0.389 |
| **Marital status, %** |  |  | |  | | |  |
| Married/living with partner | 74.9 | 0.96±0.02 | | 0.27±0.01 | | | 31.19±0.48 |
| Divorced/separated/widowed | 18.3 | 1.03±0.05 | | 0.27±0.01 | | | 28.75±0.61 |
| Never married | 6.8 | 0.88±0.08 | | 0.24±0.02 | | | 30.84±1.93 |
| *P*-value |  | 0.262 | | 0.158 | | | 0.011 |
| **PIR, %** |  |  | |  | | |  |
| 0~1.30 | 15.1 | 0.93±0.04 | | 0.25±0.01 | | | 30.04±1.00 |
| 1.31~3.50 | 33.4 | 0.99±0.03 | | 0.28±0.01 | | | 30.88±0.57 |
| 3.51~ | 51.5 | 0.94±0.03 | | 0.27±0.01 | | | 31.00±0.55 |
| *P*-value |  | 0.522 | | 0.142 | | | 0.628 |
| **BMI, %** |  |  | |  | | |  |
| <25 | 22.0 | 1.10±0.05 | | 0.30±0.01 | | | 30.65±0.91 |
| 25-30 | 40.6 | 0.98±0.03 | | 0.28±0.01 | | | 31.27±0.51 |
| >30 | 37.4 | 0.87±0.03 | | 0.24±0.01 | | | 30.31±0.57 |
| *P*-value |  | <0.001 | | <0.001 | | | 0.365 |
| **Physical activity, %** |  |  | |  | | |  |
| Vigorous | 33.0 | 0.92±0.03 | | 0.26±0.01 | | | 30.64±0.56 |
| Moderate | 28.0 | 0.97±0.04 | | 0.27±0.01 | | | 30.82±0.76 |
| Inactive | 39.0 | 1.00±0.03 | | 0.28±0.01 | | | 30.52±0.58 |
| *P*-value |  | 0.223 | | 0.205 | | | 0.950 |
| **Smoking status, %** |  |  | |  | | |  |
| Non-smoker | 41.9 | 0.97±0.03 | | 0.28±0.01 | | | 31.09±0.54 |
| Current smoking | 22.5 | 0.90±0.04 | | 0.24±0.01 | | | 29.09±0.90 |
| Former smokers | 35.6 | 1.00±0.03 | | 0.29±0.01 | | | 31.29±0.58 |
| *P*-value |  | 0.178 | | <0.001 | | | 0.113 |
| **Alcohol intake, %** |  |  | |  | | |  |
| No drinking | 63.2 | 0.96±0.02 | | 0.27±0.01 | | | 31.02±0.38 |
| Moderate drinking | 15.3 | 0.95±0.06 | | 0.26±0.01 | | | 30.27±0.98 |
| Heavy drinking | 21.6 | 0.97±0.05 | | 0.27±0.01 | | | 30.74±1.00 |
| *P*-value |  | 0.967 | | 0.653 | | | 0.761 |
| **Hypertension, %** |  |  | |  | | |  |
| No | 39.0 | 1.02±0.03 | | 0.28±0.01 | | | 30.41±0.52 |
| Yes | 61.0 | 0.88±0.03 | | 0.25±0.01 | | | 31.25±0.56 |
| *P*-value |  | 0.001 | | 0.002 | | | 0.274 |
| **Diabetes, %** |  |  | |  | | |  |
| No | 83.2 | 0.97±0.02 | | 0.27±0.01 | | | 30.47±0.41 |
| Yes | 16.8 | 0.96±0.05 | | 0.28±0.01 | | | 31.90±1.04 |
| *P*-value |  | 0.919 | | 0.624 | | | 0.202 |
| **Dyslipidemia, %** |  |  | |  | | |  |
| No | 31.6 | 0.98±0.03 | | 0.27±0.01 | | | 30.62±0.78 |
| Yes | 68.4 | 0.96±0.03 | | 0.27±0.01 | | | 30.76±0.42 |
| *P*-value |  | 0.672 | | 0.920 | | | 0.876 |
| **TEI, kcal/d (mean±SD)** | 2465.04±28.30 | / | | / | | | / |
| pearson’s r |  | -0.117 | | -0.129 | | | 0.005 |
| *P*-value |  | <0.001 | | <0.001 | | | 0.833 |
| **Fat intake, g/d (mean±SD)** | 94.2±1.4 | | / | | / | / | |
| pearson’s *r* |  | | -0.109 | | -0.114 | 0.008 | |
| *P*-value |  | | <0.001 | | <0.001 | 0.707 | |
| **HRCs, %** |  |  | |  | | |  |
| No | 99.3 | 0.97±0.02 | | 0.27±0.00 | | | 30.74±0.38 |
| Yes | 0.7 | 0.83±0.19 | | 0.20±0.04 | | | 26.42±2.00 |
| *P*-value |  | 0.511 | | 0.110 | | | 0.038 |

Abbreviations: BMI, body mass index; HRCs, hormone-related cancers; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; PIR, poverty income ratio; PSA, prostate specific antigen; SD, standard deviation; TEI, total energy intake.

Data were expressed as the weighted mean±SD, weighted geometric mean±SD or weighted proportion. Sampling-weighted analysis of variance (ANOVA) methods were performed for categorical variables and weighted pearson’s correlation analyses were performed for continuous variables. A level of <0.05 for two-sided *P* values was considered statistically significant.



**Figure S1. Flowchart of the screening process of eligible participants from NHANES 1999–2010.**

Abbreviations: CA125, cancer antigen 125; CA15.3, cancer antigen 15.3; HE4, human epididymal secretory protein E4; HRCs, hormone-related cancers; MEC, mobile examination center; NHANES, National Health and Nutrition Examination Survey; PSA, prostate specific antigen



**Figure S2.** **Restricted cubic splines for dose-response relationships between urinary phytoestrogens and HRCs from NHANES 1999-2010**

The brown line represents the estimated OR and the brown filled areas represent their 95% CI. The dotted line corresponds to the reference point. The restricted cubic spline models were adjusted for age (continuous), gender (female or male), race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, or other), education level (below high school, high school, or college or above), marital status (married/living with partner, divorced/separated/widowed, or never married), poverty income ratio (0~1.30, 1.31~3.50, or 3.51~), body mass index (<25, 25-30, or >30 kg/m2), physical activity (vigorous, moderate, or inactive), smoking status (non-smoker, current smoking, or former smokers), alcohol intake (no drinking, moderate drinking, or heavy drinking), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), total energy intake (continuous), fat intake (continuous). A level of <0.05 for two-sided *P* values was considered statistically significant.

Abbreviations: CI, confidence interval; HRCs, hormone-related cancers; NHANES, National Health and Nutrition Examination Survey; O-DMA, O-desmethylangolensin; OR, odds ratio.



**Figure S3. Forest plot for the association between urinary phytoestrogens and breast cancer among females from NHANES 1999-2010**

Adjusted for age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, or other), education level (below high school, high school, or college or above), marital status (married/living with partner, divorced/separated/widowed, or never married), poverty income ratio (0~1.30, 1.31~3.50, or 3.51~), body mass index (<25, 25-30, or >30 kg/m2), physical activity (vigorous, moderate, or inactive), smoking status (non-smoker, current smoking, or former smokers), alcohol intake (no drinking, moderate drinking, or heavy drinking), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), total energy intake (continuous), fat intake (continuous).

Abbreviations: CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; O-DMA, O-desmethylangolensin; OR, odds ratio.



**Figure S4. Forest plot for the association between urinary phytoestrogens and prostate cancer among males from NHANES 1999-2010**

Adjusted for age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, or other), education level (below high school, high school, or college or above), marital status (married/living with partner, divorced/separated/widowed, or never married), poverty income ratio (0~1.30, 1.31~3.50, or 3.51~), body mass index (<25, 25-30, or >30 kg/m2), physical activity (vigorous, moderate, or inactive), smoking status (non-smoker, current smoking, or former smokers), alcohol intake (no drinking, moderate drinking, or heavy drinking), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), total energy intake (continuous), fat intake (continuous).

Abbreviations: CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; O-DMA, O-desmethylangolensin; OR, odds ratio.