Published in final edited form as:
Menopause. 2013 April ; 20(4): 428–436. doi:10.1097/gme.0b013e3182703c9c.

The Relationship Between Dietary Phytoestrogens and Development of Urinary Incontinence in Midlife Women

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Abstract

Objective—Because exogenous estrogen treatment has been associated with a higher risk of urinary incontinence, our objective was to evaluate the longitudinal relationships of dietary phytoestrogen intakes (isoflavones, coumestans and lignans) and the development of incontinence in midlife women transitioning through menopause.

Methods—The Study of Women's health Across the Nation (SWAN) Phytoestrogen Study was developed within SWAN, a community-based, multisite, multi-racial/ethnic, prospective cohort study. SWAN interviewers administered a food consumption assessment at baseline and at follow-up visits 5 and 9. The SWAN Phytoestrogen study created a phytonutrient data base that allowed estimation of usual daily intakes of four isoflavones, four lignans and coumestrol. On an annual self-administered questionnaire, participants reported on frequency and type of incontinence. We used discrete proportional hazards models to evaluate whether estimated daily intake of each phytoestrogen class at the visit previous to the first report of incontinence was associated with the development of monthly or more incontinence compared to remaining continent.

Results—We found no association or patterns of association between developing any, stress or urge incontinence and the reported daily dietary intake of isoflavones, coumestrol, and lignans in the visit previous to the onset of incontinence.

Conclusions—The results of this longitudinal study provide important information to better understand estrogen-like substances on the continence mechanism in midlife women. Our study shows that neither high nor low dietary intakes of isoflavones, coumestrol and lignans prevent stress or urge incontinence. Future studies should evaluate whether serum levels of phytoestrogens or their metabolites impact incontinence symptoms.

Keywords

Phytoestrogen; isoflavone; coumestrol; lignan; urinary incontinence

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The authors have no conflict of interest to disclose.

Introduction

Exogenous estrogen has been used variably to treat urinary incontinence. While systemic, conjugated equine estrogens are associated with the development and worsening of both stress and urge incontinence in post-menopausal women[1–3], other types and routes of estrogens have not been as well studied with mixed results[4]. Selective estrogen receptor modulators (SERMS) have variable effects on incontinence. For example, testing of levormeloxifene, a SERM with high estrogenic activity on urogenital tissues[5–7], was halted in part due to an associated four-fold increased incidence of incontinence, from 4% to 17%[8]. Additionally, the development of incontinence appeared to be dose related with a higher rate of incontinence among women taking higher levormeloxifine doses[9]. Meanwhile, raloxifene, a SERM with low estrogenic activity on the urogenital tissues, had no effect on incontinence[10]. The clinical effect of pharmaceutical estrogens and SERMs on incontinence raises interest in the effects of dietary sources of estrogen receptor modulating compounds[11, 12].

Phytoestrogens ("plant estrogens") are heterocyclic phenols found in many plant foods. Three major categories occur within the general class of phytoestrogens: isoflavones (e.g. daidzein and genistein), coumestans (e.g., coumestrol), and lignans (e.g. secoisolariciresinol and matairesinol). Based on the primary action of these classes on estrogen receptors *and the highest level of evidence that the action of systemic estrogens increase the risk of developing incontinence,* we hypothesized that isoflavones and coumestrol's more agonist action would be associated with an increased risk of developing both stress and urge incontinence while lignan's more antagonist action would reduce the occurrence of both incontinence types[13]. There is scant data evaluating the effects of individual phytoestrogen classes on incontinence. In one small pilot trial, twelve weeks of a "phytoestrogen deficient diet" was associated with an increased frequency of urge incontinence only while a soy (isoflavone) rich diet did not have an effect on incontinence[11]. These results encourage further investigation of phytoestrogens on incontinence, but large epidemiological studies are first needed to explore associations between different classes of dietary phytoestrogens and incontinence.

Our objective was to evaluate the longitudinal relationships of dietary intakes of isoflavones, coumestans or lignans, and the development of incontinence in midlife women transitioning through menopause.

Methods

Study sample

The Study of Women's Health Across the Nation (SWAN) Phytoestrogen Study sample is derived from participants in SWAN, a community-based, multisite, multi-racial/ethnic, prospective cohort study of the menopausal transition (MT) and midlife[14]. Briefly, entry criteria for the SWAN cohort were: age 42 to 52 years; having at least one ovary and an intact uterus; no current use of estrogens or other medications known to affect ovarian function; having had least one menstrual period in the 3 months prior to screening; and self-identification as white, African American, Hispanic, Chinese, or Japanese. Women in SWAN have been followed for over 10 years at 7 sites. Usual dietary intake data were collected using a food frequency questionnaire (FFQ) administered at baseline and during follow-up visits 5 and 9. In the Phytoestrogen Study, participants from 6 SWAN sites (Boston, Chicago, Detroit, Pittsburgh, Oakland, and Los Angeles [N=2870] were eligible for inclusion. We omitted data from one SWAN site (Newark) because of high attrition (up to 45%) and because that site did not collect any dietary data at follow-up 9. We also excluded participants based on availability of diet data and dietary quality control standards as

follows: did not have diet assessment (N = 11); reported intake of less than 4 or greater than 17 solid foods per day (N = 130); skipped more than 10 food items when responding to the FFQ (N = 1); had a calculated daily energy intake of <500 kcal or >5,000 kcal (N = 7). If participants met any of these diet-based exclusionary criteria at later visits, we set their dietary variables to missing for those visits. Thus, the SWAN Phytoestrogen Study sample consists of 2721 women at baseline, 1905 at follow-up visit 5, and 1677 at follow-up visit 9. Inclusion in the current study of phytoestrogens and incontinence required that participants reported no incontinence at baseline so that they could be followed for new reports of incontinence (N=1459 women at baseline, 981 at follow-up visit 5, and 883 at follow-up visit 9).

Phytoestrogen Intake

At baseline and at follow-up visits 5 and 9, SWAN used an interviewer-administered dietary assessment to determine usual food consumption during the past year. The SWAN diet instrument had 3 components: 1) a full food frequency questionnaire (FFQ); 2) an "Ethnic Foods Page", and 3) open-ended questions. The SWAN FFQs were based on the Block FFQ[15] and 4 SWAN versions tailored to language/ethnicity. The English-language version contained a 103-item core food list, based on Second National Health and Nutrition Examination Survey (NHANES II). The Chinese and Japanese ethnic group versions included the same 103-item core food list plus 12 to 16 additional foods appropriate for the each group, called the "Ethnic Foods Pages". Finally, all women were asked an open-ended question about any other foods eaten at least weekly. The SWAN Phytoestrogen Study created a new phytonutrient data base using all available data through 2008 and computed usual daily intakes of 4 isoflavones, 4 lignans and coumestrol[16, 17].

Urinary Incontinence

SWAN obtained baseline and annual information on incontinence symptoms, incontinence frequency and type though a self-administered questionnaire. Based on response to the question: "In the past year (or since your last study visit), have you ever leaked even a small amount of urine involuntarily?", we classified frequency of incontinence as "almost daily/ daily" (daily), "several days per week" (weekly), "less than one day per week" (monthly), "less than once a month" or "none." We defined any incontinence as incontinence occurring at least monthly. We considered incontinence occurring less than once a month as clinically insignificant and subject to a higher misclassification rate and therefore combined this category with "no incontinence." We categorized type of incontinence as "stress" if participants reported leakage with "coughing, laughing, sneezing, jogging, jumping, with physical activity or picking up an object from the floor" or as "urge" if participants reported leakage "when you have the urge to void and can't reach the toilet fast enough."

Women who were continent at baseline but then reported incontinence at any of the annual follow-up visits were considered to have incident incontinence and were compared to women who did not develop incontinence over the same time frame.

When a woman was missing data on frequency and type of incontinence from one or two visits, we imputed values as follows[18, 19]. If the missing value occurred at year 10, we imputed the value at the previous visit. If women reported no incontinence in the years previous and subsequent to a missing incontinence report, we assumed no incontinence in those missng years. If a woman was missing incontinence data in the one to two years previous to a first report of incontinence we randomly assigned her missing values to either no incontinence or the frequency and/or type of incontinence in that subsequent year. We imputed incontinence frequency for 1959 observations (6.5% of all observations), and incontinence type for 3207 observations (10.7% of all observations)

Other Co-Variates

Our baseline covariates included baseline age, BMI, diabetes, parity, socioeconomic status, education, number of premenstrual symptoms, as well as symptom sensitivity from the first annual follow up visit. Time dependent co-variates were menopause stage, hormone use, perceived stress, SHBG and E2 level. We also evaluated time-varying covariates from the visit previous (lagged) because we would anticipate incontinence to develop or not develop after the emergence or change in the variable: incident diabetes, hypertension, depressive symptoms and anxiety symptoms, smoking status, weight change (current year value subtracted from previous year value in pounds), number of stressful life events, overall health and caloric intake.

Co-variates were ascertained by the following methods. SWAN classified menopause transition stage annually from menstrual bleeding patterns. Pre-menopause was less than three months of amenorrhea and no menstrual irregularities in the previous year; early peri-menopause was less than three months of amenorrhea and some menstrual irregularities in previous year; late peri-menopause was three to 11 months of amenorrhea; and postmenopause as 12 consecutive months of amenorrhea. We calculated body mass index (BMI) as weight in kilograms/(height in meters)^2 based on measurements taken annually by certified staff who used calibrated scales and a stadiometer. Screening socioeconomic status was approximated by level of difficulty paying for basics (food, heat and shelter). Interviewers obtained self-reported medical histories, smoking history and medication use. We considered a woman diabetic if she reported the diagnosis of diabetes or reported the use of diabetic medications. Each year SWAN used the same questions from the Center for Epidemiological Studies-Depression scale[20] (we defined depressive symptoms as a score of 16 or above), the Medical Outcomes Study Social Support Survey[21], the Life Stressors and Social Resources Inventory[22], and the Psychiatric Epidemiology Research Interview[23]. SWAN measured anxiety symptoms by a summed score of days in the past two weeks in which certain symptoms were experienced (grouchiness or irritability, feeling tense or nervous, pounding or racing heart, feeling fear for no reason); we defined anxiety symptoms by a score of 4 or more[24]. At year one only, SWAN combined responses to questions assessing sensitivity to physical sensations into a Symptom Sensitivity Scale[25]. For estradiol (E2), SWAN used a rabbit anti-E2-6 ACS-180 immunoassay with a lower limit of detection of 1.0 pg/mL and conducted duplicate E2 assays with results reported as the arithmetic mean for each participant (coefficient of variation of 3–12%). We adjusted these levels by day of menstrual cycle for women still having periods and sex hormone binding globulin (SHBG).

Phytoestrogen interpolation

SWAN measured study outcomes annually, but dietary exposure variables were measured only at visits 00, 05, and 09. To handle the differences in measurement schedules, dietary variables were interpolated one at a time using random effects modeling as a function of time on study[26], after applying a log transformation due to right-skewness. These models were stratified on race, due to large racial/ethnic differences in phytoestrogen consumption. Loess curves indicated linear time trends, thus each model included a random (woman-specific) intercept and slope for time on study. The woman-specific regression coefficients are weighted averages of the coefficients from the full sample and the coefficients from each participant's data only[27]. Adding predictors other than time on study did little to improve prediction, and missing predictor data reduced the available sample size.

To assess the performance of these models, we compared fitted values with observed values from visits 00, 05, and 09. Pearson correlations between fitted and observed, accounting for within-woman correlation[28] ranged from 0.978 to 0.996, indicating excellent agreement. Additionally, linear regressions of observed values on fitted values indicated no systematic

bias, as intercepts were close to 0 and slopes were close to 1. Finally, loess curves for observed values versus time on study overlapped considerably with corresponding curves for fitted values.

We interpolated (i.e., imputed) logged dietary variables for visits at which the FFQ was not administered, using the participant-specific intercept and slope coefficients and the relevant value of time on study for each non-FFQ study visit. Given the high agreement between observed and fitted values, we did not employ multiple imputation. Additionally, we ran two sets of sensitivity analyses: first, including only predictor and outcome data observed at FFQ visits (00, 05, and 09); and second, including all visits in analyses but carrying the last measured dietary variable value forward, which implicitly imputes based on only a single previous observation, in contrast to the model-based imputation based on all of a woman's observed FFQ data. Results from these sensitivity analyses were similar to those using the interpolated dietary values, except on two occasions. Specifically, there was a statistically significant association in the same positive direction between the second tertile of ligand intake and stress incontinence where there had been none in the non-Asian group and no association between the second tertile of isoflavone intake and stress incontinence in the Asian group where there had been one (data not shown). While these results suggest that some differences in interpolation may affect the significance of our results, the lack of a monotonic association and similar ORs suggest no important effect. Thus we present the interpolated results which we feel to be more representative of phytoestrogen intakes[29].

Data analysis

First, we plotted distributions of the logged values of each class of phytoestrogen (total isoflavones, coumestrol, and total lignans) in each racial/ethnic group. We found a mostly bimodal distribution of isoflavones and coumestrol, with different means and distributions between the Chinese and Japanese intakes and the African American and white phytoestrogen intakes. *Because these intake distributions had little overlap, we categorized women into Asian (Chinese and Japanese) and non-Asian (white and African American) racial groups for our analyses (*Figure 1). For consistency between isoflavones, coumestrol and lignans, and to allow for possible non-linear associations, we categorized each phytoestrogen class based on tertiles in the Asian and non-Asian subgroups and ran relational analyses in stratified samples of Asian and non-Asian women.

We compared proportions and means of each variable at baseline for women who did and did not develop incontinence using the chi-squared and Wilcoxon Sign Rank test for categorical and continuous variables respectively. For baseline phytoestrogen class comparisons, we used the Wilcoxon Sign Rank test due to skewness. We used discrete proportional hazards models[30] to evaluate whether phytoestrogen intake at the previous visit was associated with the development of monthly or more incontinence compared with no development of any incontinence at the current visit. For all our analyses, we evaluated phytoestrogen consumption from the previous visit to ensure that the dietary exposures preceded new onset incontinence. We created similar separate models for stress and urge incontinence. For stress incontinence, our comparison group was those women who had no development of stress incontinence and for urge incontinence it was those women who had no development of urge incontinence.

The candidate covariates described above were chosen based on the literature, a priori hypotheses and/or association with the outcome in univariable analysis at $p < 0.10$. *We also adjusted for correlates of the missing FFQ data that reduced our sample size over the study, including ethnicity (stratifying factor), education level, weight, and anxiety, in order to reduce possible nonresponse bias*[31]. We used SAS 9.2, SAS Institute Inc., Cary, NC, USA.

Results

Women who developed incontinence (incident incontinence) differed in several ways from women who remained continent. Those with new onset incontinence had a higher level of education, reported less economic hardship (that is, had an easier time paying for basic necessities), were more likely to have diabetes, a higher BMI and a higher calorie intake, and were more likely to report anxiety symptoms, pre-menstrual symptoms, and life stressors compared to women who never reported incontinence (Table 1).

The mean intakes of isoflavones were about 10-fold lower in the non-Asian compared with the Asian group. Coumestrol intake in non-Asians was about half that of the Asian group, while lignan was only slightly lower (Table 2).

Over the 10 years of observation, the number of women reporting new onset monthly or more incontinence of any type declined (Table 3). The cumulative incidence rate of the entire sample over 10 years for any incontinence was 135 per 1000 person-years. Asian women had a lower cumulative incidence of incontinence (105 per 1000 person-years) compared with non-Asian women (146 per 1000 person-years) with urge incontinence being more common in the non-Asian group (92 per 1000 person-years) compared with the Asian group (53 per 1000 person-years), but stress incontinence being more similar (95 per 1000 person-years in non-Asians versus 92 per 1000 person-years in Asians).

In both unadjusted and multivariable models, we found no statistically significant ($p<0.05$) or consistent patterns of association between developing any incontinence, or specific subtypes (stress or urge incontinence) and the reported dietary intake of isoflavones, coumestrol, or lignans. The exposure to each class of phytoestrogen was estimated based on the visit previous to the reported onset of incontinence (Table 4). While Asian and non-Asian women have different intake ranges of each phytoestrogen class (Figure 1), our results show that within these ranges, dietary phytoestrogens did not prevent or increase the odds of developing incontinence of any type, regardless of menopausal stage.

Discussion

Alpha and beta estrogen receptors (ERs) have been variably identified in urogenital tissues (bladder, urethra, vaginal mucosa, levator ani muscles, and pubo-cervical fascia[32–34]) and in the central and peripheral nervous systems[35]. Exogenous estrogen appears to reduce collagen concentration, decrease the cross-linking of collagen,[36] and increase the levels of collagen turnover in peri-urethral tissues[37–39], which may lead to weakened urethral support and stress incontinence. In animal studies, estrogen increases the collagen to smooth muscle ratio in the bladder wall, increasing mean resting bladder tension and contractility which may impact urge incontinence.[40–42] Though the effects on the continence mechanism are unknown, estrogen has a neuromodulation function, increasing sympathetic nerve density in the pelvis and regulating neurotrophins[43].

We found no association between the reported dietary intakes of three phytoestrogen classes (isoflavones, coumestrol, or lignans) and developing any type of incontinence in women transitioning through menopause. There are a number of explanations for this null finding. Most likely, while estrogen treatment is associated with developing incontinence, the phytoestrogens we studied may have no discernible effects due to lower binding affinities for the estrogen receptors compared to estradiol[13]. Additionally, phytoestrogens bind alpha and beta receptors with different affinities and with different agonist and antagonistic properties[13], so the balance of this binding variation for isoflavones, coumestrol and lignans in the urogenital tract in midlife women may not produce tissue effects that pre-dispose to stress or urge incontinence.

We chose to evaluate phytoestrogen consumption in the year previous to the first report of monthly or more incontinence to be certain that the dietary isoflavone, coumestrol and lignan intake levels of interest would precede that incident episode. In our interpolation process we found very little with-in woman variation in phytoestrogen intake from year to year, and so those levels were likely similar through the year of the incident incontinence episode. Because the levels of phytoestrogen intake in the SWAN Asian participants had different medians and ranges than the intake in the non-Asian women, we avoided co-linearity between race and phytoestrogen intake by creating stratified models using Asian and non-Asian tertiles. While exposure levels in Asian and non-Asian strata were unequal (ie: the highest isoflavone tertile in non-Asians was roughly equivalent to the lowest in Asians) we did not find any association between phytoestrogen intake and incontinence in either group and so it is unlikely that racial dissimilarities in food sources or other factors are important in our null findings.

Evaluation of phytoestrogen effects on women's health outcomes have had varied results. About 30–50% of individuals have gut bacteria that metabolize some phytoestrogens into more active serum metabolites, and variation in metabolite production may account for differences in clinical effects of phytoestrogen intake seen across studies of, for example, bone density and hot flushes[44]. Since our study evaluated dietary intake of phytoestrogens, we could not determine whether different serum concentrations of more active metabolites may prevent or promote the development of incontinence.

Other limitations in our study include the unavoidable measurement error in underestimating phytonutrient intakes and small-area variation in isoflavone content of soy crops can lead to inaccuracies[45]. Yet the relative rankings of phytonutrient intakes are likely robust and SWAN minimized differential misclassification by designing their FFQs to accommodate mixed dishes and account for ethnic foods. *While attrition in longitudinal analyses may have an impact on the generalizability of our results, we included as predictors important factors correlated with attrition to account for possible nonresponse bias.*

The incidence of incontinence declined over the time frame of our study. Explanations for this finding include lower incidence in the early post-menopause which coincides with the later years of the study for most women, and the significant reduction in the women at risk for incontinence over the course of the study given how common incontinence is in midlife women as well as cohort attrition in longitudinal analysis. Our incontinence outcomes were self-reported and have the advantage of reflecting womens' experience of incontinence but the disadvantage of lower precision in diagnosing type (stress and urge) of incontinence. SWAN used the same incontinence questions on an annual basis. These questions were similar to validated questions and those that have been used widely in other incontinence epidemiological studies of incontinence type[46, 47]. The sensitivity and specificity of self-reported stress and urge incontinence is estimated at 71–85%% and 60–79% respectively in validated questionnaires[48, 49].

Conclusion

While epidemiological studies that show no association are often deemed uninteresting, the results of this longitudinal study provide important information to better understand the role of estrogen-like substances on the continence mechanism in mid-life women. *Our study has important generalizable public health relevance showing* that neither high nor low dietary intakes of isoflavones, coumestrol, or lignans prevent stress or urge incontinence. *Before concluding that phytoestrogens have no effect on incontinence, however,* future studies should evaluate whether *individual variation in phytoestrogen metabolism measured by* serum levels of phytoestrogens and/or their metabolites, impact incontinence symptoms.

Acknowledgments

Financial Support

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants NR004061; AG012505, AG012535, AG012531, AG012539, AG012546, AG012553, AG012554, AG012495). The content of this article manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH. The SWAN Phytoestrogen Ancillary Study was supported by: AG030448

Clinical Centers: *University of Michigan, Ann Arbor – Siobán Harlow, PI 2011 – present, MaryFran Sowers, PI 1994–2011; Massachusetts General Hospital, Boston, MA – Joel Finkelstein, PI 1999 – present; Robert Neer, PI 1994 – 1999; Rush University, Rush University Medical Center, Chicago, IL – Howard Kravitz, PI 2009 – present; Lynda Powell, PI 1994 – 2009; University of California, Davis/Kaiser – Ellen Gold, PI; University of California, Los Angeles – Gail Greendale, PI; Albert Einstein College of Medicine, Bronx, NY – Carol Derby, PI 2011 – present, Rachel Wildman, PI 2010 – 2011; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004;* and the *University of Pittsburgh, Pittsburgh, PA – Karen Matthews, PI.*

NIH Program Office: *National Institute on Aging, Bethesda, MD – Sherry Sherman 1994 – present; Marcia Ory 1994 – 2001; National Institute of Nursing Research, Bethesda, MD – Program Officers.*

Central Laboratory: *University of Michigan, Ann Arbor – Daniel McConnell* (Central Ligand Assay Satellite Services).

Coordinating Center: *University of Pittsburgh, Pittsburgh, PA – Kim Sutton-Tyrrell, PI 2001 – present; New England Research Institutes, Watertown, MA - Sonja McKinlay, PI 1995 – 2001.*

Steering Committee: Susan Johnson, Current Chair; Chris Gallagher, Former Chair

We thank the study staff at each site and all the women who participated in SWAN.

References

1. Hendrix SL, Cochrane BB, Nygaard IE, et al. Effects of estrogen with and without progestin on urinary incontinence. Jama. Feb 23; 2005 293(8):935–948. [PubMed: 15728164]
2. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T. Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study. Obstet Gynecol. Jan; 2001 97(1):116–120. [PubMed: 11152919]
3. Steinauer JE, Waetjen LE, Vittinghoff E, et al. Postmenopausal hormone therapy: does it cause incontinence? Obstet Gynecol. Nov; 2005 106(5):940–945. [PubMed: 16260510]
4. Cody JD, Richardson K, Moehrer B, Hextall A, Glazener CM. Oestrogen therapy for urinary incontinence in post-menopausal women. Cochrane Database Syst Rev. 2009; 4:CD001405. [PubMed: 19821277]
5. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. Jama. Jun 16; 1999 281(23):2189–2197. [PubMed: 10376571]
6. Cohen FJ, Watts S, Shah A, Akers R, Plouffe L Jr. Uterine effects of 3-year raloxifene therapy in postmenopausal women younger than age 60. Obstet Gynecol. Jan; 2000 95(1):104–110. [PubMed: 10636511]
7. Davies GC, Huster WJ, Lu Y, Plouffe L Jr, Lakshmanan M. Adverse events reported by postmenopausal women in controlled trials with raloxifene. Obstet Gynecol. 1999; 93(4):558–565. [PubMed: 10214833]
8. Hendrix SL, McNeeley SG. Effect of selective estrogen receptor modulators on reproductive tissues other than endometrium. Ann N Y Acad Sci. Dec.2001 949:243–250. [PubMed: 11795359]
9. Goldstein SR, Nanavati N. Adverse events that are associated with the selective estrogen receptor modulator levormeloxifene in an aborted phase III osteoporosis treatment study. Am J Obstet Gynecol. Sep; 2002 187(3):521–527. [PubMed: 12237621]

10. Waetjen LE, Brown JS, Modelska K, Blackwell T, Vittinghoff E, Cummings SR. Effect of raloxifene on urinary incontinence: a randomized controlled trial. Obstet Gynecol. Feb; 2004 103(2):261–266. [PubMed: 14754693]
11. Manonai J, Songchitsomboon S, Chanda K, Hong JH, Komindr S. The effect of a soy-rich diet on urogenital atrophy: a randomized, cross-over trial. Maturitas. May 20; 2006 54(2):135–140. [PubMed: 16297576]
12. Tomaszewski J, Adamiak A, Skorupski P, Rzeski W, Rechberger T. Effect of 17 beta-estradiol and phytoestrogen daidzein on the proliferation of pubocervical fascia and skin fibroblasts derived from women suffering from stress urinary incontinence. Ginekol Pol. Oct; 2003 74(10):1410–1414. [PubMed: 14669453]
13. Mueller SO, Simon S, Chae K, Metzler M, Korach KS. Phytoestrogens and their human metabolites show distinct agonistic and antagonistic properties on estrogen receptor alpha (ERalpha) and ERbeta in human cells. Toxicol Sci. Jul; 2004 80(1):14–25. [PubMed: 15084758]
14. Sowers, M.; Crawford, S.; Sternfeld, B., et al. SWAN: A Multicenter, Multiethnic, Community-Based Cohort Study of Women and the Menopausal Transition. In: Lobo, RA.; Kelsey, JL.; Marcus, R., editors. Menopause: Biology and Pathobiology. San Diego: Academic Press; 2000. p. 175-188.
15. Block G, Thompson F, Hartman A, Larkin F, Guire K. Comparison of two dietary questionnaires validated against multiple dietary records collected during a 1-year period. Journal of the American Dietician Association. 1992; 92:686–693.
16. Huang MH, Harrison GG, Mohamed MM, et al. Assessing the accuracy of a food frequency questionnaire for estimating usual intake of phytoestrogens. Nutr Cancer. 2000; 37(2):145–154. [PubMed: 11142086]
17. Huang MH, Norris J, Han W, et al. Development of an updated phytoestrogen database for use with the SWAN food frequency questionnaire: intakes and food sources in a community-based, multiethnic cohort study. Nutr Cancer. 64(2):228–244. [PubMed: 22211850]
18. Waetjen LE, Feng WY, Ye J, et al. Factors associated with worsening and improving urinary incontinence across the menopausal transition. Obstet Gynecol. Mar; 2008 111(3):667–677. [PubMed: 18310370]
19. Waetjen LE, Ye J, Feng WY, et al. Association between menopausal transition stages and developing urinary incontinence. Obstet Gynecol. Nov; 2009 114(5):989–998. [PubMed: 20168098]
20. Radloff L. The CES-D Scale: A self-report depression scale for research in the general population. Appl Psychol Meas. 1977; 1:385–283.
21. Sherbourne CD, Stewart AL. The MOS social support survey. Social Science and Medicine. 1991; 32(6):705–714. [PubMed: 2035047]
22. Moos RH, Fenn CB, Billings AG, Moos BS. Assessing life stressors and social resources: applications to alcoholic patients. J Subst Abuse. 1988; 1(2):135–152. [PubMed: 2980865]
23. Dohrenwend, B.; Dohrenwend, B. Life stress and ilness: Formulation of the issues. New York: Prodist; 1981.
24. Gold EB, Block G, Crawford S, et al. Lifestyle and demographic factors in relation to vasomotor symptoms: baseline results from the Study of Women's Health Across the Nation. Am J Epidemiol. Jun 15; 2004 159(12):1189–1199. [PubMed: 15191936]
25. Barsky AJ, Goodson JD, Lane RS, Cleary PD. The amplification of somatic symptoms. Psychosom Med. Sep-Oct;1988 50(5):510–519. [PubMed: 3186894]
26. Beydoun MA, Lhotsky A, Wang Y, et al. Association of adiposity status and changes in early to mid-adulthood with incidence of Alzheimer's disease. Am J Epidemiol. Nov 15; 2008 168(10): 1179–1189. [PubMed: 18835864]
27. Fitzmaurice, GM.; Laird, NM.; Ware, JH. Applied Longitudinal Analysis. New York: John Wiley; 2004.
28. Lipsitz S, Leong T, Ibraham J, Lipschultz S. A partial correlation coefficient and coefficient of determination for multivariate normal repeated measures data. The Statistician. 2001; 50(Part 1): 87–95.

29. Greendale GA, Huang MH, Leung K, et al. Dietary phytoestrogen intakes and cognitive function during the menopausal transition: results from the Study of Women's Health Across the Nation Phytoestrogen Study. Menopause. Mar 12.
30. Diggle, P.; Heagerty, P.; Liang, K.; Zeger, S. Analysis of Longitudinal Data. 2. Oxford University Press; USA: 2002.
31. Little, RJA.; Rubin, DB. Statistical analysis with missing data. 2. New York: Wiley; 2002.
32. Gebhart JB, Rickard DJ, Barrett TJ, et al. Expression of estrogen receptor isoforms alpha and beta messenger RNA in vaginal tissue of premenopausal and postmenopausal women. Am J Obstet Gynecol. Dec; 2001 185(6):1325–1330. discussion 1330–1321. [PubMed: 11744904]
33. Copas P, Bukovsky A, Asbury B, Elder RF, Caudle MR. Estrogen, progesterone, and androgen receptor expression in levator ani muscle and fascia. J Womens Health Gend Based Med. Oct; 2001 10(8):785–795. [PubMed: 11703891]
34. Smith P, Heimer G, Norgren A, Ulmsten U. Steroid hormone receptors in pelvic muscles and ligaments in women. Gynecol Obstet Invest. 1990; 30(1):27–30. [PubMed: 2227608]
35. Zoubina EV, Smith PG. Expression of estrogen receptors alpha and beta by sympathetic ganglion neurons projecting to the proximal urethra of female rats. J Urol. Jan; 2003 169(1):382–385. [PubMed: 12478195]
36. Keane DP, Sims TJ, Abrams P, Bailey AJ. Analysis of collagen status in premenopausal nulliparous women with genuine stress incontinence. Br J Obstet Gynaecol. Sep; 1997 104(9): 994–998. [PubMed: 9307523]
37. Falconer C, Ekman-Ordeberg G, Ulmsten U, Westergren-Thorsson G, Barchan K, Malmstrom A. Changes in paraurethral connective tissue at menopause are counteracted by estrogen. Maturitas. Jul; 1996 24(3):197–204. [PubMed: 8844634]
38. Falconer C, Ekman-Ordeberg G, Blomgren B, et al. Paraurethral connective tissue in stress-incontinent women after menopause. Acta Obstet Gynecol Scand. Jan; 1998 77(1):95–100. [PubMed: 9492727]
39. Jackson S, James M, Abrams P. The effect of oestradiol on vaginal collagen metabolism in postmenopausal women with genuine stress incontinence. Bjog. Mar; 2002 109(3):339–344. [PubMed: 11950190]
40. Aikawa K, Sugino T, Matsumoto S, Chichester P, Whitbeck C, Levin RM. The effect of ovariectomy and estradiol on rabbit bladder smooth muscle contraction and morphology. J Urol. Aug; 2003 170(2 Pt 1):634–637. [PubMed: 12853846]
41. Sartori MG, Girao MJ, de Jesus Simoes M, Sartori JP, Baracat EC, Rodrigues de Lima G. Quantitative evaluation of collagen and muscle fibers in the lower urinary tract of castrated and under-hormone replacement female rats. Clin Exp Obstet Gynecol. 2001; 28(2):92–96. [PubMed: 11491384]
42. Fleischmann N, Christ G, Sclafani T, Melman A. The effect of ovariectomy and long-term estrogen replacement on bladder structure and function in the rat. J Urol. Sep; 2002 168(3):1265–1268. [PubMed: 12187279]
43. Zoubina EV, Mize AL, Alper RH, Smith PG. Acute and chronic estrogen supplementation decreases uterine sympathetic innervation in ovariectomized adult virgin rats. Histol Histopathol. Oct; 2001 16(4):989–996. [PubMed: 11642748]
44. Lampe JW. Is equol the key to the efficacy of soy foods? Am J Clin Nutr. May; 2009 89(5): 1664S–1667S. [PubMed: 19357217]
45. Lee SJ, Ahn JK, Kim SH, et al. Variation in isoflavone of soybean cultivars with location and storage duration. J Agric Food Chem. May 21; 2003 51(11):3382–3389. [PubMed: 12744671]
46. Brown JS, Grady D, Ouslander JG, Herzog AR, Varner RE, Posner SF. Prevalence of urinary incontinence and associated risk factors in postmenopausal women. Heart & Estrogen/Progestin Replacement Study (HERS) Research Group. Obstet Gynecol. 1999; 94(1):66–70. [PubMed: 10389720]
47. Jackson RA, Vittinghoff E, Kanaya AM, et al. Urinary incontinence in elderly women: findings from the Health, Aging, and Body Composition Study. Obstet Gynecol. Aug; 2004 104(2):301–307. [PubMed: 15292003]

48. Bradley CS, Rovner ES, Morgan MA, et al. A new questionnaire for urinary incontinence diagnosis in women: development and testing. Am J Obstet Gynecol. Jan; 2005 192(1):66–73. [PubMed: 15672005]

49. Brown JS, Bradley CS, Subak LL, et al. The sensitivity and specificity of a simple test to distinguish between urge and stress urinary incontinence. Ann Intern Med. May 16; 2006 144(10): 715–723. [PubMed: 16702587]

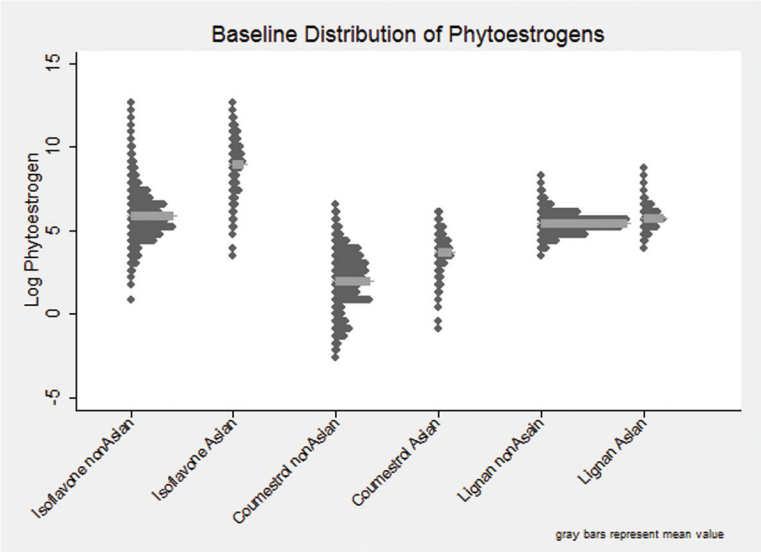

Figure 1.
Baseline Distribution of Isoflavone, Coumestrol, and Lignan Intake by Asian and Non-Asian Groups.
See attached TIF file.

Table 1

Baseline Characteristics of SWAN Phytoestrogen Women Who Developed Incident Incontinence and Remained Continent over 10 years of Follow-Up*

	All Women (N=1459)		Incident Incontinence (N=880)		Remained Continent (N=579)		Chi-Squared p-value†
Category	**N**	**%**	**N**	**%**	**N**	**%**	
Race/ethnicity							
African American	*527*	*36.12*	303	57.50	224	42.50	0.025
Caucasian	*622*	*42.63*	403	64.79	219	35.21	
Chinese	*158*	*10.83*	87	55.06	71	44.94	
Japanese	*152*	*10.42*	87	57.24	65	42.76	
Education							
Less than high school	*66*	*4.56*	30	45.45	36	54.55	0.004
High school equivalent	*255*	*17.61*	137	53.73	118	46.27	
Some college	*472*	*32.60*	284	60.17	188	39.83	
College grad	*308*	*21.27*	192	62.34	116	37.66	
Graduate school	*347*	*23.96*	228	65.71	119	34.29	
Difficulty paying for basics							
Not very hard	*932*	*65.31*	544	58.37	388	41.63	0.026
Somewhat hard	*399*	*27.96*	264	66.17	135	33.83	
Very hard	*96*	*6.73*	56	58.33	40	41.67	
Overall Health							
Excellent	*133*	*9.20*	76	57.14	57	42.86	0.350
Very good	*185*	*12.80*	119	64.32	66	35.68	
Good	*956*	*66.16*	567	59.31	389	40.69	
Fair	*155*	*10.73*	101	65.16	54	34.84	
Poor	*16*	*1.11*	8	50.00	8	50.00	
Menopause status							
Premenopausal	*815*	*57.11*	499	61.23	316	38.77	0.427
Early Per menopause	*612*	*42.89*	362	59.15	250	40.85	
Parity							

Category	All Women (N=1459) N	%	Incident Incontinence (N=880) N	%	Remained Continent (N=579) N	%	Chi-Squared p-value†
Parous	*1160*	*81.01*	711	61.29	449	38.71	0.191
Nulliparous	*272*	*18.99*	155	56.99	117	43.01	
Diabetes							
Yes	*46*	*3.16*	35	76.09	11	23.91	0.027
No	*1412*	*96.84*	845	59.84	567	40.16	
Depressive Symptoms							
Depressed (16 or more)	*278*	*19.05*	177	63.67	101	36.33	0.204
Not Depressed (<16)	*1181*	*80.95*	703	59.53	478	40.47	
Anxiety symptoms							
4 or less	*1333*	*91.74*	794	59.56	539	40.44	0.039
>4	*120*	*8.26*	83	69.17	37	30.83	
Premenstrual symptoms							
0–3 symptoms	*587*	*41.25*	330	56.22	257	43.78	0.013
3–4 symptoms	*836*	*58.75*	525	62.80	311	37.20	
Mean (SD)							*Wilcoxon p-value†*
Age	*45.76*	*2.65*	45.72	2.63	45.81	2.67	0.562
BMI	*27.19*	*6.88*	27.86	7.20	26.19	6.23	<0.001
Perceived stress	*8.18*	*2.86*	8.38	2.83	7.88	2.88	0.001
Social Support	*12.64*	*3.08*	12.52	3.02	12.83	3.16	0.007
Symptom sensitivity	*10.05*	*3.57*	10.00	3.42	10.14	3.84	0.720
Stressful Life Events	*3.48*	*2.30*	3.67	2.33	3.19	2.23	<0.001
Premenstrual symptoms	*0.59*	*0.49*	0.61	0.49	0.55	0.50	0.013
Estradiol	*78.25*	*75.55*	76.58	70.59	80.78	82.51	0.855

Category	All Women (N=1459)		Incident Incontinence (N=880)		Remained Continent (N=579)		Chi-Squared p-value†
	N	%	N	%	N	%	
FSH	*24.40*	*26.15*	23.66	26.05	25.51	26.27	0.063
SHBG	*47.37*	*25.28*	45.48	23.46	50.24	27.60	0.002
Caloric intake	*1833.66*	*691.92*	1862.49	691.57	1789.83	690.74	0.025
Fiber intake	*12.53*	*6.06*	12.49	5.77	12.58	6.47	0.812

*Incident incontinence = reported no incontinence at baseline but developed incontinence in any follow up year, Remained continent = never developed incontinence over the 10 years in SWAN

†p-value compares incident and remained continent groups

SD = standard deviation

Table 2

Baseline Dietary Phytoestrogen Intake by Class in Women Who Developed Incontinence and Who Remained Continent Over 10 Years in SWAN*

	Incident Incontinence (N=880)		*Remained Continent (N=579)*		**Wilcoxon p-value**
Phytoestrogen intake in mcg	**Median**	**Quartile Range**	**Median**	**Quartile Range**	
For Chinese/Japanese					
Isoflavones	11512.17	24748.64	9717.91	15265.30	0.137
Coumestrol	45.93	71.54	39.00	56.00	0.304
Ligans	339.41	297.70	291.43	226.70	0.076
For Black/White					
Isoflavones	292.01	614.30	315.60	707.26	0.559
Coumestrol	8.17	22.90	8.09	22.19	0.405
Ligans	237.78	172.98	207.65	148.50	0.009

* Incident Incontinence = reported no incontinence at baseline but developed incontinence in any follow up year, Remained continent = never developed incontinence over the 10 years in SWAN

Table 3

Frequency of Incident Any, Stress and Urge Urinary Incontinence in Years 1–10 in SWAN*, **

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Developed UI										
Asians										
Any	59	23	27	20	13	9	7	3	5	7
Stress	53	31	23	17	10	10	7	5	9	7
Urge	34	22	22	20	12	9	6	13	11	13
Non-Asians										
Any	274	142	80	61	47	22	30	22	15	13
Stress	221	130	89	57	42	24	38	32	21	8
Urge	258	146	103	68	44	36	59	33	39	32

*Figures in table are the number of women who developed new-onset of urinary incontinence during each year of follow-up.

**Definitions of incontinence include: any incontinence = first report of stress, or urge or both in women who reported no incontinence in the previous years, stress incontinence = first report of stress incontinence in women who reported no stress incontinence in the previous years, urge incontinence = first report of urge incontinence in women who reported no urge incontinence in the previous years

Table 4

Adjusted Association between Phytoestrogen Tertiles and Developing Any, Stress or Urge Incontinence between Asians and Non-Asians

Asians (Japanese and Chinese)*					Non-Asians (African American and white)†				
Type of Phytoestrogen by tertiles (mcg)	**Type of Incontinence**	**OR**	**95% CI**	**Group p- value**	**Type of Phytoestrogen by tertiles (mcg)**	**Type of Incontinence**	**OR**	**95% CI**	**Group p–value**
Isoflavones					**Isoflavones**				
1st tertile ≤ 9.06	Any			0.306	1st tertile ≤ 5.50	Any			0.140
	Stress	Ref		0.017		Stress	Ref		0.940
	Urge			0.219		Urge			0.773
2nd tertile 9.07–9.94	Any	0.74	0.45, 1.23		2nd tertile 5.51–6.29	Any	1.02	0.80, 1.29	
	Stress	0.54	0.32, 0.91			Stress	0.99	0.78, 1.25	
	Urge	0.68	0.43, 1.05			Urge	0.93	0.75, 1.14	
3rd tertile ≥ 9.95	Any	1.11	0.67, 1.84		3rd tertile ≥ 6.30	Any	0.80	0.62, 1.04	
	Stress	1.14	0.70, 1.84			Stress	0.96	0.75, 1.22	
	Urge	0.80	0.50, 1.29			Urge	0.96	0.77, 1.19	
Coumestrol					**Coumestrol**				
1st tertile ≤ 3.36	Any			0.787	1st tertile ≤ 1.18	Any			0.522
	Stress	Ref		0.865		Stress	Ref		0.625
	Urge			0.986		Urge			0.743
2nd tertile 3.37–3.99	Any	0.89	0.54, 1.47		2nd tertile 1.19–2.07	Any	0.91	0.70, 1.17	
	Stress	0.93	0.58, 1.50			Stress	1.13	0.88, 1.45	
	Urge	0.98	0.63, 1.54			Urge	1.06	0.84, 1.34	
3rd tertile ≥ 4.00	Any	1.06	0.64, 1.75		3rd tertile ≥ 2.08	Any	0.87	0.68, 1.11	
	Stress	0.87	0.53, 1.43			Stress	1.08	0.85, 1.37	
	Urge	1.02	0.65, 1.60			Urge	1.09	0.87, 1.36	
Lignans					**Lignans**				

Asians (Japanese and Chinese)*					Non-Asians (African American and white)†				
Type of Phytoestrogen by tertiles (mcg)	**Type of Incontinence**	**OR**	**95% CI**	**Group p- value**	**Type of Phytoestrogen by tertiles (mcg)**	**Type of Incontinence**	**OR**	**95% CI**	**Group p–value**
1st tertile ≤ 5.63	Any			0.281	1st tertile ≤5.29	Any			0.466
	Stress	Ref		0.870		Stress	Ref		0.259
	Urge			0.185		Urge			0.714
2nd tertile 5.64–5.98	Any	1.26	0.75, 2.21		2nd tertile 5.30–5.62	Any	1.17	0.91, 1.50	
	Stress	0.99	0.61, 1.61			Stress	1.18	0.93, 1.49	
	Urge	1.24	0.78, 1.98			Urge	1.04	0.83, 1.30	
3rd tertile ≥ 5.99	Any	1.53	0.91, 2.59		3rd tertile ≥ 5.63	Any	1.05	0.81, 1.36	
	Stress	1.12	0.68, 1.85			Stress	0.99	0.77, 1.26	
	Urge	1.54	0.97, 2.44			Urge	0.10	0.88, 1.37	

OR = odds ratio, CI = confidence interval, Ref = reference

All models adjusted for: study time, menopausal status, weight changes, life events, anxiety symptoms, total caloric intake, education level, parity, history of premenstrual symptoms, baseline age, baseline body mass index, symptom sensitivity, sex hormone binding globulin (SHBG), estradiol (E2), day of cycle that serum for E2 and SHBG was obtained.

*Asians, number of observations: Any incontinence (N = 1343) Stress incontinence (N = 1524) Urge incontinence (N = 2490)

†Non-Asians, number of observations: Any incontinence (N = 3333) Stress incontinence (N = 4810) Urge incontinence (N = 6423)