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Phytoestrogen and Fiber Intakes in Relation to Incident Vasomotor Symptoms: Results From the Study of Women's Health Across the Nation

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Abstract

OBJECTIVE—While reduction of vasomotor symptoms (VMS, hot flashes/night sweats) has been reported in postmenopausal women who used isoflavones, a clear dose-response has not been shown, has largely not been reported for perimenopausal women and has largely only been for reducing prevalent VMS, not preventing newly developing VMS. We analyzed longitudinal data from the Study of Women's Health Across the Nation (SWAN) for the relation of dietary phytoestrogens and fiber intake to incident VMS in this multi-racial/ethnic cohort.

METHODS—SWAN included 3302 pre- and early perimenopausal women, 1651 of whom reported no VMS at baseline, who were followed with annual visits for 10 years. Dietary intakes of isoflavones, coumestrol, lignans and fiber were assessed by a food frequency questionnaire at baseline and annual visits 5 and 9 and interpolated for intervening years. Number of days of having VMS in the past two weeks was self-reported annually. Using generalized estimating equations multinomial logistic regressions, we modeled incident VMS in relation to isoflavones, lignans, fiber, coumestrol, or total phytoestrogens intake and covariates.

RESULTS—No consistent monotonic relations were observed for any dietary phytoestrogens or fiber to incident VMS, although adjusted odds ratios for some individual quartiles were statistically significant.

CONCLUSIONS—To be certain of any effect of dietary phytoestrogens or fiber in preventing incident VMS, a randomized, placebo-controlled, double-masked trial with sufficient numbers of women in different racial/ethnic, menopausal status and metabolic groups with years of follow-up is required, but our results suggest that a clinically significant or large effect is unlikely.

Keywords

diet; phytoestrogens; vasomotor symptoms; menopause; race/ethnicity

INTRODUCTION

The North American Menopause Society recently issued a position statement on isoflavones for menopausal health (1) in which they summarized the results of 14 randomized placebo-

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controlled trials of soy isoflavone supplements for vasomotor symptoms (VMS). Lower rates of VMS were reported in most studies of postmenopausal women, including in randomized trials, who used soy isoflavone supplements (2–10). However, the effect has not shown a clear dose-response, has largely not been reported for perimenopausal women (as noted in the position statement) even though perimenopausal women have rates of VMS at least as high as those of postmenopausal women (11), has only involved supplements and not dietary isoflavones, and has largely only been related to reducing VMS in women who have them, rather than preventing newly developing incident VMS.

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). Isoflavones, lignans and coumestrol bind to α and β estrogen receptors and are predominantly agonists (12–14). However, the ultimate effects of phytoestrogens on the estrogen pathway are likely to be determined by a variety of factors, including: their relative affinity for α and β estrogen receptors and effects on the conformation of these receptors; their agonist or antagonist properties related to their concentrations and to circulating levels of estradiol; and the different phytoestrogens (isoflavones, lignans and coumestrol) each modifying the metabolism and bioavailability of endogenous estrogen by mechanisms that either increase or decrease such bioavailability (11–18).

In one early trial, postmenopausal women who received soy supplements (containing isoflavones) or wheat flour (contains enterolactones) had a statistically significant reduction in VMS (40% in the soy and 25% in the wheat group), although the rates of decline did not differ significantly (partly due to the small sample size) (2). Most (3–6), but not all (19) subsequent randomized, double blind, controlled clinical trials of soy or soy isoflavones for VMS have observed similar reductions in VMS. In contrast, trials that have included perimenopausal women have not observed lower rates of VMS in relation to higher phytoestrogen administration (20–23). The apparent menopause-stage specific results suggest that the effects of dietary phytoestrogens vary according to menopausal transition (MT) stage, perhaps reflecting differences in circulating endogenous estrogen levels. However, many other aspects of the design and methods of the above-cited trials may also have produced inconsistent results. Several types, doses, and formulations of phytoestrogens have been used. In addition, sample sizes in trials have been small to moderate, ranging from 39 (4) to 177 (5, 20); thus, limited statistical power to detect effects may also have led to inconsistent outcomes. Most importantly, however, these trials have focused on women who already have VMS, and relatively few studies have examined the relation of phytoestrogen intake to developing incident VMS. Further, studies have not examined whether the effects of phytoestrogens on VMS differ by race/ethnicity, perhaps reflecting underlying differences in metabolism, another possible source of differing results.

Additionally, urinary excretion of phytoestrogens and the concentration of plasma sex hormone binding globulin (SHBG) have been positively associated with dietary intake of fiber, which has been inversely related to circulating levels of estradiol (24–34). Few studies have been conducted of the relation of dietary fiber to VMS reporting, but one cross-sectional study of women with prior early stage breast cancer showed a protective effect (35). Further, fiber may be a proxy for lignan intake. If the measurement of fiber is more accurate than the measurement of lignans, the protective association between fiber and VMS reporting may be stronger than that for lignans.

Evidence from these small-to-moderate sized studies suggests that soy or soy isoflavones suppress VMS in postmenopausal but not perimenopausal women. Effects of other classes of phytoestrogens remain uncertain, and their effects on development of new, rather than

reduction of existing, VMS have not been well-studied. We undertook several analyses to build upon prior work by testing the relation between dietary phytoestrogens and development of incident VMS longitudinally, considering the relations in each stage of the MT. As outlined above, the effects of phytoestrogens on VMS would be expected to differ according to the specific phytoestrogen and MT stage—a theory we tested in the multi-racial/ethnic longitudinal cohort Study of Women's Health Across the Nation (SWAN). We improved the phytonutrient database used to determine dietary intake in SWAN (36) to investigate whether other classes of phytoestrogens, in addition to isoflavones, particularly lignans as well as dietary fiber, were related to incident reporting of VMS in SWAN. These analyses examined the longitudinal relations between each of the three main classes of phytoestrogens and dietary fiber (exposures) and incident VMS (outcome).

Specifically, we undertook analyses of SWAN's annual data and dietary assessment to test the following hypotheses: 1) higher dietary intake of total isoflavones, total lignans, coumestrol and/or dietary fiber would be associated with lower rates of reporting newly occurring VMS longitudinally; and 2) the relation to incident VMS of each class of phytoestrogens and dietary would vary by MT stage, with stronger benefit observed in the postmenopause.

METHODS

Study Participants

Eligibility for the *cohort at baseline* included: age 42–52 years, intact uterus and at least one ovary, not currently using exogenous hormones affecting ovarian function, a menstrual period in the previous three months, and self-identification with each site's designated racial/ethnic groups. Each site screened one minority population (African Americans in Pittsburgh, Boston, Detroit area and Chicago; Japanese in Los Angeles; Chinese in the Oakland, California area; and Hispanics in New Jersey) and a white population, using community-based sampling (37). Each site recruited approximately 450 eligible participants (total = 3302). The Institutional Review Boards at all sites approved the protocol, and all participants provided signed, written informed consent.

The following exclusions were applied to create the Sub-study cohort. The New Jersey SWAN site was omitted (n=432) because of high attrition (at SWAN follow-up visit 5, retention was 18% for white and 45% for Hispanic women) and because that site did not collect any dietary data at follow-up visit 9. The following diet-based exclusions were applied to the 6 participating SWAN sites at baseline: participant did not have dietary 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 (N = 1), or had a calculated daily energy intake of <500 kcal or >5,000 kcal (N = 7). If any of these diet-based exclusionary criteria were met at later visits, dietary variables were set to missing for those visits. Thus, the SWAN Sub-study cohort included 2721 women at baseline, 1905 (70.0%) at follow-up visit 5, and 1673 (61.5%) at follow-up visit 9, based on the availability of acceptable dietary data.

Additionally, the following exclusions applied for the current analysis of phytoestrogens and vasomotor symptoms: women who had VMS at baseline (to enable evaluation of dietary intake with incident VMS, n=1070, leaving 1651 women without VMS at baseline); self-reported hormone use or unknown current menopause status because of hormone use (n=3749 observations out of 29,931 observations); and observations concurrent with pregnancy (n=6). Of the 1651 women without VMS at baseline, 1081 (65.5%) completed annual visit 5, and 1184 (71.7%) completed visit 9; baseline and visits 5 and 9 were the only visits when dietary data were collected. Of the 1081, 942 (87%) provided dietary data at visit 5 and 954 of the 1184 (80.6%) provided dietary data at visit 9. Women who did not

complete the food frequency questionnaire were more likely (differed significantly and by more than 10%) than those who did to report premenstrual symptoms and to be: white or black (non-Asian), early perimenopausal at baseline, less educated, previously married, in a lower income household, current smokers, and more exposed passively to smoke (data not shown). We adjusted for these characteristics in multivariate analyses, to reduce possible nonresponse bias (38).

Data Collection

The baseline and annual clinic visits included an in-person interview, self-administered questionnaires and measurement of weight, height (using calibrated scales and a stadiometer), and waist and hip circumferences. Dietary data were obtained using a modified 1995 Block Food Frequency Questionnaire (39, 40), with 103 core food items, based on responses of African Americans and whites in the Second National Health and Nutrition Examination Survey (NHANES) (39, 41). Foods for the Hispanic, Chinese and Japanese versions were also added, identified from the Hispanic HANES (42) and focus groups. Frequently consumed sources of dietary phytoestrogens were also included (43) (tofu, soymilk, soy sauce and meat substitutes made from soy). Common protocols, manual of operations, training and staff certification for administering the protocols were used at all sites. All data collection instruments were translated into Cantonese, Japanese and Spanish and back-translated; discrepancies in translation were resolved by two translators.

Independent variables—For dietary phytoestrogen exposure variables, we used a new database developed as described by Huang (36). In brief, the original phytoestrogen database for use in SWAN was constructed in 1994 and contained information about two isoflavones (daidzein and genistein) and coumestrol. Huang et al (36) expanded this original database, covering the period between 1994 and 2008, which allowed computation of nutrient values for: four isoflavones ($\mu\text{g/day}$) as the sum of Formononetin, Daidzein, Genistein, and Glycitein; coumestrol ($\mu\text{g/day}$); four lignans ($\mu\text{g/day}$) as the sum of Matairesinol, Lariciresinol, Pinoresinol and Secoisolariciresinol; and dietary fiber (mg/day) and total phytoestrogens ($\mu\text{g/day}$). These were assessed from the food frequency questionnaires completed by participants at baseline and annual visits 5 and 9. We interpolated values for visits 1–4, 6–8 and 10 and for women who were missing dietary data at visits 5 or 9 (44). We also re-ran analyses using only visits at which the FFQ was conducted (baseline and follow-ups 5 and 9) as well as using last observation carried forward rather than model-based interpolation (results from all three methods were similar, so only the models using interpolation are presented). Dietary variables were linearly regressed over follow-up time (number of years since SWAN baseline visit). This longitudinal linear regression model was used to output each participant's random intercept and slope as well as the fixed slope and intercept for each of the dietary variables. We produced loess curves to assess linearity as the first step in interpolation. For each dietary variable, the fixed and random intercepts were summed, and the fixed and random slopes were summed. Time was multiplied by each summed slope and added to the summed intercept. Finally, to assess the quality of the interpolation, each original dietary variable value was linearly regressed with its interpolated value; a slope close to 1.0 and an intercept close to 0 would signal that the interpolation was robust. The correlation between the original and interpolated values was also computed, with higher correlations indicating better interpolation.

Outcome variable—The frequency of vasomotor symptoms (VMS, hot flashes/flushes and/or night sweats), 0, occurring 1–5 days, or 6+ days in the prior two weeks were asked at each annual visit. We excluded women who reported any VMS at baseline, leaving 1651 without baseline VMS, so as to examine relations of phytoestrogen intake to newly

developing VMS during follow-up; this allowed for a better assessment of temporal ordering of VMS and phytoestrogen intake. For these analyses, the annual reports of VMS were categorized as a three-category ordinal outcome variable for the multinomial logistic regressions described below: none in the past 2 weeks, 1–5 days in the past 2 weeks, or VMS on six or more days in the past 2 weeks.

Covariates—*Time-invariant covariates*, measured at baseline included variables previously shown to be related to VMS (11): educational level (less than high school, high school, some college, college or post baccalaureate degree); race/ethnicity (self-designated white, African American, Japanese, or Chinese); anxiety score (as a binary variable, using a cutoff value of >4 or ≤ 4 for a summed score of numbers of days in the past two weeks (ranging from 0=no days to 4=every day) of reporting irritability or grouchiness, feeling tense or nervous, heart pounding or racing, and feeling fearful for no reason); depressive symptom score (score ≤ 16 on a 20-item scale of the extent to which each item was experienced in the previous week) (45); history of premenstrual symptoms; symptom sensitivity at visit 1 (using quartiles of a summed score of degree of awareness of loud noise, hot or cold, hunger, pain and things happening in one's body, with responses ranging from 1=not at all true to 5=extremely true) (46); SWAN study site; marital status; overall health score; passive smoke exposure (person hours/week) (47); and quartiles of physical activity score (48–49). In our final model only site, physical activity, education, marital status, number of pre-menstrual symptoms, depressive symptom score, and symptom sensitivity were retained.

Annually-measured *time varying covariates* included: age (years); MT stage (premenopausal, indicating a menstrual period in the prior three months and no change in menstrual regularity in the prior year; early peri-menopausal, indicating menses in the prior three months and changes in regularity in the prior year; late peri-menopausal, indicating no menses in the prior three months but menses in the prior 11 months; and postmenopausal, indicating ≥ 12 months of amenorrhea); BMI (weight in kilograms/(height in meters)²) categories (<25 , 25–29.9 and ≥ 30); total kilocalories of energy intake and fiber from the food frequency questionnaires at baseline and annual visits 5 and 9 and interpolated for the intervening years; perceived stress (a summed scale asking how often over the prior two weeks four aspects of stress were experienced, ranging from 1=never to 5=very often) (50); annual serum estradiol level; annual sex hormone binding globulin (SHBG); day of menstrual cycle of the blood draw; current smoking (51); alcohol use in the past 24 hours; number of life events; and social support (52) with visit 9 interpolated from the previous visit. The final model only retained annual serum estradiol level, day of cycle, age, menopause status, BMI categories, and perceived stress.

Data Analyses

Analyses were restricted to women who did not report VMS at baseline ($n=1651$) so that the relation of dietary phytoestrogen to incident VMS over follow-up could be assessed. Dietary variables were natural log transformed to handle skewness. To allow for non-linear associations with VMS frequency and to facilitate assessment of interaction of dietary intakes with menopause status, each of the three main classes of phytoestrogens and dietary fiber were categorized according to sample quartiles, using the top quartile as the reference category in analyses. In addition, we tested for linear associations (trend) by treating the quartiles as a continuous variable (1 through 4).

The distributions of the phytoestrogen classes and of dietary fiber differed across the four racial/ethnic groups. The distribution of the isoflavones was strongly bimodal with two almost non-overlapping peaks; the Chinese and Japanese (hereafter called Asian) women

had vastly higher isoflavone intakes compared to the African American and white (hereafter called non-Asian) women. Thus, we created separate Asian and non-Asian quartiles for all three classes of phytoestrogens and fiber and stratified all analyses by Asian/non-Asian ethnicity.

Using multinomial logistic regression with generalized estimating equations (GEE) [53, 54] to account for within-woman correlation, we modeled odds ratios (ORs) and 95% confidence intervals (CI) for incident VMS at each follow-up visit as a function of the primary predictors (isoflavones, lignans, fiber and coumestrol) and time-varying and time invariant covariates, and modeling with and without time-varying estradiol to determine if this was a potential mechanism of action. We used a p value <0.2 to enter covariates into the regression models and retained those with $p<0.05$. We used multinomial rather than ordinal logistic regression, despite the inherent ordering of the VMS outcome, because preliminary analyses suggested that the former model is more flexible and fit the data better than the latter model, which assumes proportional odds for the cumulative logits.

To ensure that our primary exposures were measured prior to the VMS outcome, the time-varying dietary variables were lagged, ie, taken from dietary data for the visit prior to the VMS outcomes -- eg, Visit 5 VMS was modeled as a function of baseline dietary variables and visit 4 dietary variables (or equivalently, change between baseline and visit 4). Each dietary variable had its own model to avoid multicollinearity. We also tested the interaction between menopausal status and phytoestrogen and dietary fiber intake exposures. We also conducted exploratory analyses using structural equation modeling to ensure that reverse causation was not occurring, ie, that women with more frequent VMS were increasing their intake of isoflavones to treat their symptoms.

RESULTS

Because we restricted our analyses to women who did not report VMS at baseline so that we could see the relation of isoflavones and other phytoestrogens to development of VMS over follow-up, we first compared baseline characteristics of women who did ($n=1070$) and did not ($n=1651$) report VMS at baseline (Table 1). Women with the following characteristics were significantly more likely to report VMS at baseline: white or black race, early peri-menopausal, less educated, unemployed, lower annual household income, blood not collected on days 2–5 (related to being peri-menopausal), elevated depressive symptom score, poorer self-assessed health, more premenstrual symptoms, smokers, passive exposure to cigarette smoke, elevated anxiety score, older, higher parity, higher BMI, higher symptom sensitivity score, higher stress score, higher life events score, lower phytoestrogen intake and higher calorie intake.

Findings for African Americans and whites (Non-Asians)

Isoflavones—In *adjusted* models (Table 2a), no baseline or lagged isoflavone quartiles were significantly related to incident VMS of any frequency, except that the lowest quartile of *lagged isoflavone* intake had a significantly reduced OR for 1–5 days of VMS in the prior two weeks (OR=0.76, 95% CI 0.61, 0.95, $p=0.016$), and the p -value for trend over the quartiles was statistically significant ($p=0.018$) for 1–5 days of VMS. When we interpolated the isoflavone values using the approach of last time point followed forward, the magnitude and direction of odds ratios were largely similar, but the relation of lagged isoflavone intake to 1–5 days of VMS and the overall comparison of groups were no longer significant (data not shown).

Coumestrol—In *adjusted* models (Table 2b), *lagged coumestrol* intake among non-Asians was not significantly related to incident VMS of any frequency. However, the three lowest

quartiles of *baseline coumestrol* had significantly reduced adjusted ORs compared to the highest quartile for 1–5 days of VMS in the prior two weeks (ORs ranging from 0.72 for the lowest quartile to 0.80 for the third quartile) with the p-value for trend=0.010, reflecting decreasing odds ratios with decreasing quartiles of baseline intake. Only the second quartile of *baseline coumestrol* had a significantly reduced OR compared to the highest quartile for 6+ days of VMS in the prior two weeks (OR=0.69, 95% CI 0.50, 0.95, p=0.021), and no significant trends were observed over the quartiles.

Lignans—In *adjusted* models (Table 2c), both *lagged* and *baseline lignan* intakes were not significantly related to any incident VMS in non-Asian women. However, the p-value for trend was statistically significant for lagged lignan intake related to 6+ days of VMS in the prior two weeks, reflecting increasing odds ratios with decreasing quartiles of intake.

Fiber—In *adjusted* models, lagged fiber intake was not significantly associated to incident VMS of any frequency in non-Asian women (Table 2d). The second and third quartiles of baseline fiber had significantly higher ORs compared to the highest quartile for 6+ days of VMS in the prior 2 weeks (for the second quartile OR=1.56, 95% CI 1.12, 2.17, p=0.009, and for the third quartile OR=1.40, 95% CI 1.02, 1.91, p=0.034), although the p-values for trend were not statistically significant.

Findings for Chinese and Japanese women (Asians)

Isoflavones—In *adjusted* models for Asian women (Table 3a), neither *lagged* nor *baseline isoflavone* intakes were significantly related to incident VMS of any frequency.

Coumestrol—In *adjusted* models (Table 3b), both *lagged* and *baseline coumestrol* intakes were not significantly related to incident VMS of any frequency in Asian women, except the lowest quartile of *lagged coumestrol* intake had an increased adjusted OR, compared to the highest quartile, for 6+ days of VMS in the prior two weeks (OR=2.59, 95% CI 1.19, 5.63), and the p-value for trend was 0.052, reflecting increasing odds ratios for 6+ days of VMS with decreasing intake of lagged coumestrol.

Lignans and fiber—*Lagged lignan* intake was not significantly related to any incident VMS in *adjusted* models for Asian women (Table 3c), except the third quartile compared to the highest quartile for the VMS 6+ days (OR=1.80, 95% CI 1.01, 3.22, p=0.046). However, *baseline lignan* intake had a significantly reduced *adjusted* ORs for the third quartile compared to the highest quartile for 1–5 days of VMS in the prior two weeks (OR=0.61, 95% CI 0.39, 0.94, p=0.027) and showed a significant trend (p=0.039) with increased ORs with increasing intake for 6+ days of VMS in the prior two weeks (Table 3c). When we interpolated values using the approach of last time point followed forward, the odds ratios for lignan intake related to 1–5 days of VMS all became greater than 1.0 and were significant for the second and third quartiles, and the overall comparison of groups became significant (data not shown). No significant *adjusted* associations were observed for *lagged* or *baseline fiber* intake among Asian women (Table 3d), except that the second quartile of *baseline fiber* intake had a significantly increased adjusted OR compared to the highest quartile for 6+ days of VMS in the prior two weeks (OR=3.23, 95% CI 1.46, 7.16, p=0.004) (Table 3d).

Supplemental analyses—Because some of the few statistically significant findings were in directions opposite to what we expected, we estimated structural equation models to determine if the results were due to reverse causation, and we observed no such indication (data not shown). We also examined interactions of each type of phytoestrogen and fiber with menopause status in relation to incident VMS in Asians and non-Asians separately.

Due to small cell counts among Asians, we categorized time-varying phytoestrogens and fiber as above or below the median, rather than into quartiles. Only one statistically significant interaction ($p<0.05$) was identified, for high versus low isoflavones in Asians ($p=0.020$ for interaction). The pattern of effect modification by menopause status differed for 1–5 days of VMS versus none and 6+ days of VMS versus none, however, with the strongest benefit of high isoflavone consumption being during late perimenopause and postmenopause for 1–5 days of VMS but during premenopause for 6+ days (data not shown). Given this discrepancy, as well as the lack of a main effect for isoflavones and the multiple statistical comparisons undertaken, these results may be attributable to chance. Similarly, the couple of changes in findings noted above when interpolating dietary intakes using the last time followed forward method were probably due to chance, resulting from the large number of statistical comparisons made.

DISCUSSION

In our longitudinal analyses of a large, multi-racial/ethnic cohort of midlife women followed for 10 years, no consistent significant patterns emerged of the relation of individual phytoestrogen categories (total isoflavones, coumestrol or lignans) or fiber to incident VMS. Although some adjusted odds ratios were statistically significant, patterns were largely not monotonic for amount of intake of each phytoestrogen or fiber in relation to frequency of VMS. Thus, the few significant individual point estimates may well have been due to chance, given the many statistical comparisons that were made.

It is reasonable to compare our findings to trials aimed at reducing VMS in women who already have them that have included perimenopausal women because for at least half of the duration of follow-up in this study most of our participants were not postmenopausal. Consistent with our findings, most such trials have not observed reductions in VMS in relation to higher phytoestrogen dose administrations (20–23). Most, but not all (19), trials to reduce VMS in postmenopausal women using phytoestrogen supplementation have found significant but relatively modest reductions, findings which are largely inconsistent with our findings. However, because these trials have focused on reducing VMS in women who already have them and thus have already undergone or are experiencing the physiologic changes that result in VMS, the effects of phytoestrogens may not be comparable to our study of incident VMS in women who did not have them at baseline.

Our study had several important strengths. First, it included some of the largest numbers of midlife women from four racial/ethnic groups that have been included in any studies of the relation of phytoestrogen intakes to VMS to date. Second, it included ten years of longitudinal data points for VMS as our study participants underwent the menopausal transition, a time when the occurrence of such symptoms increases (11). Third, it included an enhanced database of dietary intake of phytoestrogens with updated estimates of such intake based on currently available food products (36). Fourth, the estimated dietary intakes of phytoestrogen and fiber were made independently of any assessment of VMS reporting in study participants. Finally, the study was unique in its potentially important preventive implications because we only analyzed dietary phytoestrogen and fiber intakes in relation to incident VMS in women who did not report VMS at baseline.

However, the study also had a number of limitations which must be considered when interpreting the findings. First, the study was observational, not a randomized trial, so that other uncontrolled characteristics of women may have determined their phytoestrogen and fiber intake and also been related to their VMS reporting. Second, both dietary intake and VMS were self-reported, without validation, so that misclassification could have occurred in both the exposures and the outcome. Third, the proportion of women in our analytic baseline

sample who completed the dietary and other questionnaires at visit 5 was 70% and at visit 9 was 61.6%, which could have introduced participation bias. Finally, despite the relatively large numbers of women studied in this cohort, the sample size became too small to evaluate effect modification by both race/ethnicity and menopausal status so that meaningful modifications may have not been detected as statistically significant.

CONCLUSION

We did not observe any consistent, monotonic relations between categories of phytoestrogen or dietary fiber intake to incident VMS in our large, multi-racial/ethnic cohort of midlife women followed for 10 years through the menopausal transition. Although this observational cohort study was large, had a diverse study sample and had high quality dietary, outcome and covariate data, to be certain of any effect of phytoestrogens or fiber in preventing VMS in midlife women who do not yet have them, a large, randomized, placebo-controlled, double-masked trial would need to be undertaken that: 1) studied different categories and doses of phytoestrogens and fiber; 2) included sufficient numbers of women in different stages of the menopausal transition; 3) provided sufficiently long follow-up (on the order of several years to a decade); 4) was sufficiently well-powered to be able to determine if select subsets of women (likely based on genetically-determined metabolism capabilities, such as being an equol producer) might benefit from increased intake of phytoestrogens and/or fiber; and 5) provided some validation or objective measures of VMS. Given that a high proportion of (indeed most) women develop VMS during the menopausal transition and that these are frequent (11) and disturbing to many women who are affected by them (55), identifying whether a lifestyle modification, such as increased dietary phytoestrogen and/or fiber, which might reduce the occurrence and/or frequency of VMS would provide important information to midlife women and their health care providers, although the findings of our longitudinal observational study suggest that such a reduction is likely to be small if it exists at all.

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Table 1
Comparison of Baseline Characteristics, Women with and without Vasomotor Symptoms at Baseline, SWAN.

Variable at Baseline	Categories of Variable	No Baseline VMS (n=1651)		Had Baseline VMS (n=1070)		P-value
		N	%	N	%	
Categorical Baseline Variables						
Race/Ethnicity	Chinese/Japanese	341	68.2	159	31.8	<0.001
	White/Black	1310	59.0	911	41.0	
Menopause status	Premenopause	977	68.1	457	31.9	<0.001
	Early Perimenopause	642	51.6	603	48.4	
Educational attainment	<High school	45	45.9	53	54.1	<0.001
	High school	251	56.4	194	43.6	
	>High school	470	52.9	418	47.1	
	College	392	66.4	198	33.6	
	Graduate school	483	70.7	200	29.3	
Interview language	Cantonese	72	67.3	35	32.7	0.129
	English	1513	60.1	1003	39.9	
	Japanese	66	67.3	32	32.7	
Marital status	Currently married/partner	1104	62.0	678	38.0	0.091
	Never married	224	59.4	153	40.6	
	Previously married	304	56.8	231	43.2	
Employed	No	260	56.3	202	43.7	0.038
	Yes	1363	61.5	855	38.5	
Annual household income	< \$20,000	133	46.2	155	53.8	<0.001
	\$20,000 – \$34,999	218	53.6	189	46.4	
	\$35,000 – \$49,999	308	63.1	180	36.9	
	\$50,000 – \$74,999	421	63.6	241	36.4	
	\$75,000 or more	531	66.3	270	33.7	
Day of cycle for blood draw	Day 2–5	1320	62.0	808	38.0	0.013
	Not day 2–5/Unknown	331	56.4	256	43.6	
Depressive Symptom Score	16 or more	254	42.0	351	58.0	<0.001
	<16	1397	66.0	719	34.0	

Variable at Baseline	Categories of Variable	No Baseline VMS (n=1651)		Had Baseline VMS (n=1070)		P-value
		N	%	N	%	
Overall Health	Excellent	122	55.7	97	44.3	<0.001
	Very good	221	60.5	144	39.5	
	Good	1128	64.9	611	35.1	
	Fair	157	45.0	192	55.0	
	Poor	11	37.9	18	62.1	
Number of Pre-menstrual symptoms	0–2 symptoms	669	69.5	294	30.5	<0.001
	3–4 symptoms	943	55.5	756	44.5	
Alcohol use in past 24 hours	No	1387	60.6	903	39.4	0.867
	Yes	241	61.0	154	39.0	
Current smoking	No	1411	62.8	836	37.2	<0.001
	Yes	228	50.4	224	49.6	
Person-hours/week passive smoke exposure	0	780	66.2	398	33.8	<0.001
	1–4	446	59.2	307	40.8	
	5+	413	53.6	357	46.4	<0.001
Anxiety Score Sum	4 or less	1540	64.9	833	35.1	
	>4	104	30.5	237	69.5	
Continuous Baseline Variables						
Age (years), range 42.02–53.03 yrs		Mean	Std Dev	Mean	Std Dev	
Number of children, range 0, 12		46.2	2.6	46.6	2.7	<0.001
BMI (kg/m ²), range 14.99, 64.84		1.9	1.4	2.1	1.4	<0.001
Symptom sensitivity scale score, range 0, 20		27.5	7.2	29.2	7.5	<0.001
Perceived stress scale, range 4, 19		9.9	3.5	10.7	3.6	<0.001
Life Events scale, range 0, 17		8.1	2.8	8.9	2.9	<0.001
Social Support, range 0, 16		3.5	2.4	4.3	2.8	<0.001
Physical Activity total score without work, range 3, 14		12.6	3.0	12.3	3.3	0.002
		7.8	1.8	7.7	1.7	0.060
		Median	IQR ^a	Median	IQR	Wilcoxon p-value
Phytoestrogen intake-µg, range 42.3, 377,672.5		786.3	2008.5	736.2	1347.4	0.047
Isoflavones intake-µg, range 2.9, 376,608.4		478.1	1873.3	411.9	1279.9	0.065

Variable at Baseline	Categories of Variable	No Baseline VMS (n=1651)		Had Baseline VMS (n=1070)		P-value
		N	%	N	%	
Coumestrol intake-µg, range 0.09, 623.4		14.5	35.5	13.1	28.8	0.208
Lignans intake-µg, range 27.5, 7033.4		239.5	178.5	237.0	185.2	0.407
Dietary Fiber intake-gms, range 1.7, 61.8		11.5	6.7	11.4	6.9	0.574
Total calories, range 544.7, 4877.8		1707.0	815.9	1827.8	921.4	<0.001

^a IQR=Interquartile range

Adjusted^a Odds Ratios for Incident VMS Related to Lagged^b and Baseline Phytoestrogen Intake, African Americans/whites (N=17,004 observations)

Table 2

a. Isoflavones							
Days of VMS in Past 2 Weeks ^c							
Lagged ^b Isoflavone Quartiles (µg)	1–5 Days			6+ Days			p-value for trend
	Adjusted ^a Odds Ratio	95% CI	p-value for trend	Adjusted ^a Odds Ratio ^b	95% CI	p-value for trend	
1 st quartile <5.30	0.76	0.61 0.95	0.018	1.05	0.79 1.38	0.751	
2 nd 5.30 to <5.86	0.98	0.80 1.20		0.85	0.65 1.11		
3 rd 5.86 to <6.60	0.89	0.74 1.07		1.07	0.84 1.35		
Baseline Isoflavone Quartiles (µg)							
1 st quartile <4.94	0.89	0.69 1.14	0.288	1.10	0.80 1.52	0.655	
2 nd 4.94 to <5.70	1.01	0.80 1.29		0.79	0.57 1.10		
3 rd 5.70 to <6.66	0.89	0.70 1.12		0.94	0.69 1.27		
b. Coumestrol							
Lagged ^b Coumestrol Quartiles (µg)	1–5 Days			6+ Days			p-value for trend
	Adjusted ^a Odds Ratio	95% CI	p-value for trend	Adjusted ^a Odds Ratio	95% CI	p-value for trend	
1 st quartile <0.88	1.16	0.90 1.50	0.427	0.91	0.66 1.25	0.767	
2 nd 0.88 to <1.60	1.09	0.88 1.35		0.98	0.75 1.29		
3 rd 1.60 to <2.32	1.16	0.96 1.39		1.06	0.84 1.34		
Baseline Coumestrol Quartiles (µg)							
1 st quartile <0.86	0.72	0.55 0.96	0.010	1.06	0.74 1.50	0.673	
2 nd 0.86 to <2.13	0.79	0.62 1.01		0.69	0.50 0.95		
3 rd 2.13 to <3.23	0.80	0.63 1.01		0.93	0.68 1.26		
c. Lignans							
Lagged ^b Lignan Quartiles (µg)	1–5 Days			6+ Days			p-value for trend
	Adjusted ^a Odds Ratio	95% CI	p-value for trend	Adjusted ^a Odds Ratio	95% CI	p-value for trend	

a. Isoflavones	Days of VMS in Past 2 Weeks ^c						
	1–5 Days			6+ Days			p-value for trend
	Lagged ^b Isoflavone Quartiles (µg)	Adjusted ^a Odds Ratio	95% CI	p-value for trend	Adjusted ^a Odds Ratio ^b	95% CI	
1 st quartile <5.21		1.10	0.83	1.46	0.646	1.28	0.031
		0.95	0.75	1.20		1.15	
		0.97	0.79	1.18		1.03	
Baseline Lignan Quartiles (µg)							
1 st quartile <5.04		1.26	0.92	1.72	0.292	0.95	0.890
		1.10	0.84	1.43		1.06	
		1.28	1.01	1.63		0.95	
d. Fiber							
Lagged ^b Fiber Quartiles (g)	1–5 Days			6+ Days			p-value for trend
	Adjusted ^a Odds Ratio	95% CI	p-value for trend	Adjusted ^a Odds Ratio	95% CI	p-value for trend	
1 st quartile <2.14	1.04	0.80	1.36	0.892	0.98	0.70	0.707
	1.06	0.84	1.33		0.86	0.64	1.14
	1.03	0.84	1.25		0.86	0.66	1.10
Baseline Fiber Quartiles (g)							
1 st quartile <2.11	1.25	0.93	1.69	0.183	1.39	0.95	0.084
	1.10	0.85	1.42		1.56	1.12	2.17
	1.15	0.91	1.46		1.40	1.02	1.91

^a Adjusted for time varying E2, day of cycle on which blood was drawn, age quartiles, menopause status, perceived stress, and BMI, and time invariant site, baseline physical activity, education, baseline marital status, baseline number of premenstrual symptoms, baseline symptom sensitivity quartiles and baseline CESD score

^b The baseline time point is not included (lag phytoestrogen variables at baseline are always missing).

^c Referent categories are no VMS in past two weeks and 4th quartile of isoflavones, coumestrol, lignans or fiber

Adjusted^a Odds Ratios for Incident VMS Related to Lagged^b and Baseline Phytoestrogen Intake, Chinese/Japanese (N=5,364 observations)

Table 3

a. Isoflavones		Days of VMS in Past 2 Weeks ^c				
		1-5 Days		6+ Days		
Lagged ^b Isoflavones Quartiles (µg)	Adjusted ^a Odds Ratio	95% CI	p-value for trend	Adjusted ^a Odds Ratio	95% CI	p-value for trend
1 st quartile <8.82	0.98	0.60	1.61	1.44	0.66	3.14
2 nd 8.82 to <9.50	0.88	0.57	1.36	1.52	0.77	3.00
3 rd 9.50 to <10.18	0.90	0.62	1.31	1.07	0.60	1.92
Baseline Isoflavone Quartiles (µg)						
1 st quartile <8.09	0.70	0.40	1.23	0.47	0.19	1.16
2 nd 8.09 to <9.12	1.12	0.69	1.84	0.77	0.35	1.68
3 rd 9.12 to <10.01	0.98	0.60	1.59	0.63	0.29	1.37
b. Coumestrol						
		1-5 Days		6+ Days		
Lagged ^b Coumestrol Quartiles (µg)	Adjusted ^a Odds Ratio	95% CI	p-value for trend	Adjusted ^a Odds Ratio	95% CI	p-value for trend
1 st quartile <3.11	0.87	0.54	1.39	2.59	1.19	5.63
2 nd 3.11 to <3.71	0.94	0.63	1.40	1.83	0.94	3.56
3 rd 3.71 to <4.17	0.93	0.66	1.32	1.32	0.73	2.39
Baseline Coumestrol Quartiles(µg)						
1 st quartile <3.18	0.89	0.52	1.52	0.48	0.21	1.14
2 nd 3.18 to <3.75	0.72	0.45	1.14	0.48	0.22	1.02
3 rd 3.75 to <4.38	0.91	0.60	1.40	0.61	0.30	1.22
c. Lignans						
		1-5 Days		6+ Days		
Lagged ^b Lignan Quartiles (µg)	Adjusted ^a Odds Ratio	95% CI	p-value for trend	Adjusted ^a Odds Ratio	95% CI	p-value for trend

a. Isoflavones		Days of VMS in Past 2 Weeks ^c					
		1–5 Days			6+ Days		
Lagged ^b Isoflavones Quartiles (µg)	Adjusted ^a Odds Ratio	95% CI	p-value for trend	Adjusted ^a Odds Ratio	95% CI	p-value for trend	
1 st quartile <5.52	0.80	0.49 1.30	0.166	2.13	0.97 4.65	0.186	
2 nd 5.52 to <5.81	0.96	0.63 1.46		1.76	0.90 3.44		
3 rd 5.81 to <6.08	1.29	0.91 1.85		1.80	1.01 3.22		
Baseline Lignans Quartiles (µg)							
1 st quartile <5.32	0.92	0.54 1.56	0.975	0.45	0.19 1.05	0.039	
2 nd 5.32 to <5.73	0.90	0.56 1.45		0.50	0.23 1.08		
3 rd 5.73 to <6.11	0.61	0.39 0.94		0.55	0.27 1.11		
d. Fiber							
Days of VMS in Past 2 Weeks ^c							
		1–5 Days			6+ Days		
Lagged ^b Fiber Quartiles (g)	Adjusted Odds Ratio ^a	95% CI	p-value for trend	Adjusted Odds Ratio ^a	95% CI	p-value for trend	
1 st quartile <2.29	1.15	0.70 1.88	0.178	1.23	0.58 2.60	0.974	
2 nd 2.29 to <2.52	1.40	0.91 2.16		0.85	0.43 1.70		
3 rd 2.52 to <2.73	1.03	0.71 1.50		0.95	0.52 1.72		
Baseline Fiber Quartiles (g)							
1 st quartile <2.26	0.79	0.46 1.35	0.284	1.30	0.54 3.13	0.461	
2 nd 2.26 to <2.52	0.78	0.47 1.27		3.23	1.46 7.16		
3 rd 2.52 to <2.78	1.10	0.71 1.72		1.77	0.82 3.80		

^a Adjusted for time varying E2, day of cycle on which blood was drawn, age quartiles, menopause status, perceived stress, and BMI, and time invariant site, baseline physical activity, education, baseline marital status, baseline number of premenstrual symptoms, baseline symptom sensitivity quartiles and baseline CESD score

^b The baseline time point is not included (lag phytoestrogen variables at baseline are always missing).

^c Referent categories are no VMS in past two weeks and 4th quartile of isoflavones, coumestrol, lignans or fiber