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Dietary fat subgroups, zinc and vegetable components are related to urine F_{2a}-isoprostane concentration, a measure of oxidative stress, in midlife women[1]

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Abstract

Smoking, diet and physical activity may impact chronic diseases, in part, by promoting or attenuating oxidative stress. We evaluated associations between lifestyle factors and urine F_{2a}-isoprostanes, a marker of oxidative stress among 1610 participants of Study of Women's Health Across the Nation (SWAN). Dietary intake and physical activity were assessed at baseline and year 05 (Y05). These data were related to Y05 urinary F_{2a}-isoprostane concentration with regression analyses. Median urine F_{2a}-isoprostane concentration was 433 ng/L overall, 917 ng/L in smokers (inter-quartile range: 467, 1832 ng/L) and 403 ng/L in non-smokers (inter-quartile range: 228, 709 ng/L; $P<0.0001$ for difference). Higher *trans* fat intake was associated with higher urine F_{2a}-isoprostane concentration; partial Spearman correlations ($\rho_{x|y}$) between Y05 urine F_{2a}-isoprostane concentration and *trans* fatty acids were 0.19 ($P=0.03$) and 0.13 ($P<0.0001$) in smokers and non-smokers, respectively. Increased log *trans* fat intake from baseline to Y05 was associated with higher concentration of logurine F_{2a}-isoprostanes in non-smokers ($\beta=0.131$, SE=0.04, $P=0.0003$). In non-smokers, the partial correlation ($\rho_{x|y}$) between lutein and urine F_{2a}-isoprostane concentration was −0.13 ($P<0.0001$). Increased intake of log lutein from baseline to Y05 was also associated with lower log urine F_{2a}-isoprostane concentration ($\beta=-0.096$, SE=0.03, $P=0.0005$) in non-smokers. Increased zinc intake from baseline to Y05 was associated with lower log urine F_{2a}-isoprostane concentration in smokers and non-smokers ($\beta=-0.346$, SE=0.14, $P=0.01$), and −0.117, 0.04 ($P=0.001$), respectively]. In conclusion, diet (fat subtypes, zinc, vegetable components) and smoking were associated with urine F_{2a}-isoprostanes, a marker of oxidative stress.

Keywords

diet; physical activity; cigarette smoking; isoprostanes; oxidative stress

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INTRODUCTION

Oxidative stress, an unfavorable balance between free radical generation and level of antioxidants, has been implicated in the pathogenesis of cancers, atherosclerosis, and diabetes (1,2). Stable biomarkers of this oxidative stress include F_{2a}-isoprostanes, the prostaglandin-like compounds formed in vivo from the free radical catalyzed peroxidation of arachidonic acid. (3–5). F_{2a}-isoprostanes have been shown to be reliable biomarkers of lipid peroxidation. They are continuously formed under normal physiological conditions, and increased production has been observed with co-occurrence of smoking, alcohol intake, exercise, drug treatment. There is decreased production with dietary antioxidant supplementation, and fruit and vegetable intake (6).

Lifestyle factors, including dietary intake and physical activity, are thought to influence free radical proliferation. Antioxidants mediate oxidative damage by mitigating the progression of unpaired electron transfer associated with free radical formation (7), and they are identified as constituents responsible for the protective effects of fruits and vegetables (8–13).

Polyphenols may be effective in preventing oxidative-stress associated diseases (14,15) but long-term investigations of their efficacy are sparse. Studies have focused on β-carotene, ascorbic acid and vitamin E, and while some evidence supports a protective effect against oxidative damage (16,17), results from randomized, controlled trials in healthy populations are less convincing (18–20). Lutein, from sources including spinach and greens, has been associated with favorable levels of oxidative stress markers (21). While human studies are scarce, intake of saturated (22) and *trans* fats have been implicated in higher oxidative stress levels (23).

Cigarette smoking and environmental tobacco smoke in non-smokers has been associated with higher levels of oxidative stress (24–26). Cigarette smoke has been shown to increase requirements for several antioxidants (27,28); however, smokers generally consume lower levels of antioxidants and higher amounts of saturated and *trans* fats than non-smokers (29, 30). Thus, it is clear that associations between dietary intake and oxidative stress are not comparable in smokers vs. non-smokers.

Physical activity has also been associated with oxidative stress, with indications that this association is apparently related to the intensity and duration of the activity. Physical activity of moderate intensity and duration has been associated with a favorable effect or no increase in F_{2a}-isoprostanes (31,32). The higher oxygen required for muscle activity in higher intensity or endurance exercise may lead to an accumulation of excess reactive oxygen species in anaerobic respiration and increased oxidative stress (33).

We evaluated the association between oxidative stress and lifestyle factors in women being studied longitudinally through the menopausal transition. We postulated that antioxidant intake would be inversely correlated with urine F_{2a}-isoprostanes, a measure of oxidative stress, and that these relationships would differ by cigarette smoking status. We also hypothesized that low or moderate physical activity would be inversely associated with urine F_{2a}-isoprostanes, while more vigorous activity would be linked to higher levels of oxidative stress. Although rates of certain cancers and cardiovascular disease differ by race (34,35), no research on lifestyle factors and oxidative stress has focused on ethnically-diverse, midlife women. Inclusion of diverse women in our analysis adds a key strength, providing a wide range in nutrient intake and physical activity and differing rates of smoking.

MATERIALS AND METHODS

Sampling and Study Population

This report includes data from the baseline and fifth annual follow-up examination (Y05)[2] of the Study of Women's Health Across the Nation (SWAN), a community-based, longitudinal study of the menopausal transition (36). The analysis includes 1610 participants with baseline and Y05 dietary intake and physical activity data who were located in Boston MA, Chicago IL, the Detroit MI area, Los Angeles CA, Oakland CA, or Pittsburgh PA. Observations from the New Jersey SWAN site were excluded because of incomplete data at Y05. Study eligibility criteria at baseline for the SWAN longitudinal cohort were: age 42 to 52 years; intact uterus and at least one ovary; no current use of estrogens or other medications known to affect ovarian function; at least one menstrual period in the 3 mo before enrollment; and, self-identification as a member of a site-eligible racial/ethnic group. Caucasians were recruited at all study sites. African-American women were recruited in Boston, Chicago, Pittsburgh and the Detroit area, while Japanese and Chinese women were recruited at the Los Angeles and Oakland sites, respectively. The Chicago site only provided urine samples for 44 women for a SWAN substudy; these samples were analyzed for $F2_a$-isoprostanes and represent the Chicago site contribution. Institutional Review Board approval was secured for the study protocol and informed consent obtained at each study site.

Assays

$F2_a$-isoprostanes were assayed in urine specimens collected prior to 0900 during the Y05 visit and made available through the SWAN Repository (n=1606). Assays were completed in the CLASS laboratory at the University of Michigan.

Samples were applied to the F_{2a}-isoprostane affinity column, washed with buffer and eluted with 95% ethanol. Following evaporation of the solvent, the dried samples were diluted 1:10 with 0.1 mol/L phosphate buffer and assayed using the F_{2a}-isoprostane enzyme immunoassay (EIA) kit (Cayman Chemical, Ann Arbor, MI). The range of the standard curve was 3.9–500 ng/L. Samples in a 96-well microplate were read at 405 nm. The post-extraction intra- and inter-assay coefficients of variation were 14.4% (51.2 ng/L, n=83 pairs) and 17.5% (51.2 ng/L, n=85) respectively. The intra-assay coefficient of variation for the concentration of F_{2a}-isoprostanes was 5.8% (n=1707 pairs).

Diet and lifestyle data

Dietary and supplement data were obtained at baseline and Y05 from a modified food frequency interviewer-assisted questionnaire (FFQ). Originally developed by Block (37), the questionnaire was designed to obtain "usual" dietary patterns for the previous year and was administered in three languages (English, Chinese or Japanese). All FFQ contained a 103-item core food list; the Chinese and Japanese language versions included additional culturally-specific foods.

Number of daily servings of *Brassica* vegetables, including cabbage, broccoli, cauliflower, brussels sprouts and kale, were specifically assessed due to their association with lower F_{2a}-isoprostane concentration, independent of micronutrient intake (8). For most fruit, a daily serving was quantified as one medium piece, except watermelon (one slice), cantaloupe (1/4 medium) and mangoes or papayas (½ medium). The serving size for prunes and strawberries was ½ cup. While most daily vegetable servings consisted of ½ cup, the exceptions were green salad (one medium bowl), French fries (3/4 cup) and white potatoes (½ cup). Polyphenol values

[2]Abbreviations used: IQR, interquartile range; SWAN, Study of Women's Health Across the Nation; Y05, fifth annual follow-up examination

from Manach (38) were assigned to foods and beverages by using the midpoint of the published range (in mg of the particular polyphenol per serving) for a mean daily serving estimated via FFQ. The contribution of coffee and caffeine were evaluated independently and not included in the total polyphenol value or in hydroxycinnamic acids. Genistein and daidzein intakes, based on database information from Reinli (39), were evaluated separately.

Baseline and Y05 dietary data were excluded from this report under the following conditions: too few or too many solid foods (or food groups) consumed per day (less than 4 or more than 17, respectively; n=104), missing data for more than 10 foods (n=4), and daily energy intake considered too low or too high for usual intake [less than 500 or greater than 20920 kJ/d[3] (5000 kcal/d), respectively; n=14].

Physical activity was assessed usingan adaptation of the Kaiser Physical Activity Survey (40). This 38-questionsurvey is a self-administered questionnaire with establishedtest-retest reliability and validity (40,41). Total possible physical activity scores ranged from 3 to 14 with higher numbers indicating greater activity.

Other lifestyle variables—Weight (kg) was measured using balance beam scales and height (m) was measured using stadiometers. Data on cigarette smoking and environmental tobacco smoke exposure were obtained from a self-administered questionnaire incorporating American Thoracic Society questions (42) and validated questions on environmental tobacco smoke exposure (43).

Statistical approach

SAS Version 9.1 statistical software was used for data management and analyses. The univariate distributions of continuous measures were examined and natural log transformations were employed, as appropriate, to meet the assumptions of normality and to reduce skewness.

Created variables—Due to almost negligible intakes of daidzein and genistein by Caucasian and African-American participants, only Chinese and Japanese participants were included in analyses of these variables. Daily intakes of daidzein and genistein in Chinese and Japanese women were categorized into tertiles. Thirty-third and 66th percentile cutoff values for daidzein intake were 906 μg and 3071 μg, respectively, in Chinese, and 2845 μg and 8992 μg, respectively in Japanese women. Thirty-third and 66th percentile cutoff values for genistein were 1757 μg and 6118 μg, respectively for Chinese and 4039 μg and 13286 μg, respectively in Japanese participants.

Most analyses were stratified based on a smoking status variable that classified participants as active smokers or not. A four-level variable that considered environmental tobacco smoke was used to compare the least squared means of urine F_{2a}-isoprostane concentration. The levels were: 1) non-smokers with no active or environmental tobacco smoke exposure; 2) non-smokers with more than 1 h/wk of environmental tobacco smoke exposure; 3) smokers without environmental tobacco smoke exposure; or 4) smokers with more than 1 h/wk of environmental tobacco smoke exposure.

Physical activity variables were categorized to test the hypothesis that more intense physical activity would have a positive association with urine F_{2a}-isoprostanes while moderate physical activity would have an inverse association. The categories were generated from the total physical activity questionnaire scores at Y05 (cutoffs: 40th and 80th percentiles, 7.25 and 9.4 points, respectively) Additionally, Y05 scores for the questionnaire's "sport" sub-section that

[3] 1 kcal = 4.184 kJ

measures the frequency, intensity, and duration of two sports or exercise activities in the year prior to assessment had cutoffs at the 33rd and 66th percentiles, 2.25 and 3.5 points, and range from 1–5 points.

Statistical analyses—Medians and quartile values (Q1 and Q3), were calculated for continuous measures according to smoking status stratum. The Wilcoxon rank-sum, Kruskal-Wallis and chi-square tests were used to test differences in medians between race/ethnic groups and between smokers and non-smokers.

Partial Spearman correlations ($\rho_{x|y}$) were estimated to describe the statistical associations between Y05 urine F_{2a}-isoprostanes and dietary/supplement intakes after controlling for age, BMI, physical activity, clinical site and race/ethnicity. Additionally, given that antioxidants attenuate oxidative damage caused by high dietary fat intake and because the beneficial effect of antioxidants is dependent on the amount of dietary fat a person consumes, partial Spearman correlations between urine F_{2a}-isoprostanes and antioxidants were also adjusted for Y05 total fat intake.

Multiple variable regression analyses, with log transformed urine F_{2a}-isoprostane concentration as the dependent variable, were used to estimate prospective associations with changes in dietary consumption over time. Significant p-values were two-sided at $\alpha<0.05$. Dietary variables were evaluated singly rather than simultaneously to avoid collinearity.

Associations between individual dietary variables and urine F_{2a}-isoprostane concentration are stratified by smoking status for three reasons. First, there is a strong relationship in our data between smoking status and urine F_{2a}-isoprostane concentration, and this is supported by others (24,44); second, the dietary intake of smokers differed from that of non-smokers in our data and in nationally representative data (30); finally, associations between dietary intake variables and F_{2a}-isoprostanes differed in smokers versus non-smokers in our results and in other investigations (45,46). Because smoking was a behavior rarely reported by Chinese or Japanese women, those few Asian women who reported smoking were excluded from selected analyses, as appropriate.

When total environmental smoke exposure was evaluated, there was a graded increase in the least squared means of urine F_{2a}-isoprostane concentration according to cigarette smoke exposure. However, after adjustment for age, clinical site, BMI, physical activity and race, a significant difference in least squared means of urine F_{2a}-isoprostane concentration was only observed between active smokers and non-smokers, regardless of environmental tobacco smoke exposure status. Thus, the analyses is stratified based on active smoking.

RESULTS

The overall median concentration of urine F_{2a}-isoprostanes was 433 ng/L. Because cigarette smoking status differed by race, dietary intake and urine F_{2a}-isoprostane concentration, results are reported by smoking status. Median urine F_{2a}-isoprostane concentration was more than twice as high in women who smoked [917 ng/L, inter-quartile range (IQR): 467, 1832 ng/L] as in non-smokers (403 ng/L, IQR: 228, 709 ng/L; P <0.0001 for difference). Smoking was reported by 21% and 10% of African-American and Caucasian women, respectively, and by 1% and 8% of the Chinese and Japanese women, respectively (Table 1). Among non-smokers, Chinese and Japanese women had significantly lower median urine F_{2a}-isoprostane concentration compared to the other two racial/ethnic groups (P<0.0001; Table 1).

Dietary intake and physical activity score at Y05 by smoking status

In general, women who smoked had dietary intakes lower in micronutrients, polyphenols, fruits and vegetables and higher in fat than non-smokers (Table 2). Women who smoked reported somewhat lower levels of physical activity than non-smokers [median physical activity questionnaire scores: 7.0 (IQR: 5.9, 8.5) vs. 7.9 (IQR: 6.5, 9.2), respectively; P <0.0001 for difference].

Overall, 52~61% women reported use of one of the following supplements: β-carotene, vitamins A, C, D, E or zinc; women who smoked were less likely to report dietary supplement (46~55%) use than non-smokers (56~67%; comparison of smokers vs. non-smokers taking at least one supplement vs. none P =0.001).

Concurrent associations between nutrients, foods, and urinary F_{2a}-isoprostane concentration

Among both smokers and non-smokers, there were significant positive partial Spearman correlations between the urine F_{2a}-isoprostane concentration and *trans* fatty acid intake [$\rho_{x|y}$ = 0.19 (P =0.03) and 0.13 (P <0.0001), respectively]. These partial correlations reflect the direction and strength of the association of interest, after accounting for the variation from age, race, BMI, physical activity and clinical site. We observed a significant partial correlation among non-smokers between saturated fat and the urine F_{2a}-isoprostane concentration ($\rho_{x|y}$ = 0.07; P =0.007). Although the partial correlation between saturated fat and the urine F_{2a}-isoprostane concentration among smokers was the same direction and similar magnitude as that for *trans* fats ($\rho_{x|y}$ = 0.14), this value was not statistically significant (P = 0.1). Higher vitamin E combined diet and supplement intake was associated with lower concentration of urine F_{2a}-isoprostane concentration in both smokers and non-smokers [$\rho_{x|y}$ =−0.2 (P =0.02) and −0.12 (P <0.0001), respectively].

In non-smokers, higher intakes of lutein ($\rho_{x|y}$ = −0.13; P <0.0001), β-carotene ($\rho_{x|y}$ =−0.13; P <0.0001), along with more daily vegetable servings ($\rho_{x|y}$ =−0.12; P <0.0001) and *Brassica* vegetable servings ($\rho_{x|y}$ =−0.11; P =0.0001) were associated with lower concentration of urine F_{2a}-isoprostanes.

Among smokers, we found inverse partial correlations between concentration of urine F_{2a}-isoprostanes and vitamin D ($\rho_{x|y}$ =−0.18; P =0.04), total polyphenols ($\rho_{x|y}$ =−0.18; P =0.04), and isoflavones ($\rho_{x|y}$ =−0.2; P =0.02), indicating lower oxidative stress with higher intakes. There was a borderline concurrent association with zinc ($\rho_{x|y}$ = −0.17, P =0.05) in smokers.

Further, in the Japanese women, there were inverse partial correlations with urine F_{2a}-isoprostane concentration for daidzein [$\rho_{x|y}$ =−0.15 (P =0.03)] and genistein [$\rho_{x|y}$ = −0.15 (P=0.04)], while in Chinese women, there was a borderline association with genistein [$\rho_{x|y}$ = −0.15 (P =0.05)].

No relationships were found between coffee or caffeine and urine F_{2a}-isoprostane concentrations.

Nutrient intake change (baseline to Y05) and concentration of urinary F_{2a}-isoprostanes at Y05

Increased *trans* fat intake between baseline and Y05 follow-up was associated with significantly higher concentration of urine F_{2a}-isoprostanes (Table 3) among non-smokers. Increased lutein and vitamin C consumption between baseline and Y05 follow-up was associated with significantly lower concentration of urine F_{2a}-isoprostanes in non-smokers.

Increased zinc consumption was associated with significantly lower concentration of urine F_{2a}-isoprostanes among smokers and non-smokers.

Among African-American and Caucasian women who smoked, an increase in total isoflavone intake (not including genistein or daidzein) from baseline to Y05 was associated with significantly lower concentration of urine F_{2a}-isoprostanes (Table 4). High baseline intake of daidzein was significantly associated with lower urine F_{2a}-isoprostane concentration in non-smoking Chinese and Japanese women, respectively, compared to their respective counterparts with the lowest intake. Higher baseline intake of genistein was also significantly associated with lower urine F_{2a}-isoprostane concentrations in non-smoking Chinese women compared to Chinese women with the lowest intake.

Among non-smokers, higher *Brassica* vegetable consumption at baseline and increased consumption of *Brassica* vegetables from baseline to Y05 was associated with significantly lower urine F_{2a}-isoprostane concentration. Also among non-smokers, women in the highest category of baseline broccoli consumption (greater than 1.5 servings/wk) had significantly lower urine F_{2a}-isoprostane concentration than women from the lowest category ($\leq$ 0.625 servings/wk).

Physical activity

We examined physical activity as a continuous variable, dichotomized as a categorical variable (vigorous vs. not vigorous), and as an ordinal variable in regression analyses. There were no statistically significant associations with urine F_{2a}-isoprostane concentration.

DISCUSSION

We evaluated whether nutritional factors, physical activity, and smoking behaviors were associated with increased oxidative stress as assessed by urine F_{2a}-isoprostane concentrations in a large multi-race/ethnic sample of midlife women. This has important public health implications because oxidative stress is believed to contribute to risk for cardiovascular disease, diabetes and cancers (1–2), and lifestyle behaviors are potentially modifiable.

Our results show associations between higher intake of *trans* fats and higher concentration of urine F_{2a}-isoprostanes in smokers and non-smokers concurrently and in non-smokers prospectively. In animal studies, *trans* fat intake is associated with increased oxidative stress (23). In human studies, higher intakes of *trans* fatty acids have been associated with elevated coronary heart disease risk (47);

Trans fats, found in some margarines, crackers, salad dressings and other foods, are a result of food processing when hydrogen is added to unsaturated fats in vegetable oils to increase shelf-life. Thus, the link between higher *trans* fat intake and higher F_{2a}-isoprostanes, a measure of arachidonic acid peroxidation, is logical because *trans* fats are partially hydrogenated polyunsaturated fats. After ingestion, *trans* fats can be incorporated into cellular membrane phospholipids, often displacing cis-polyunsaturated fatty acids, leading to decreased cell membrane fluidity (48). This reduced fluidity allows for increased activity of free radicals in the phospholipid bilayer, precipitating oxidative damage. F_{2a}-isoprostanes and several prostaglandins arise from the peroxidation of arachidonic acid (48), a metabolic process believed to contribute to heart disease through altered platelet aggregation and the promotion of insulin resistance (49–51).

We also found an association between urine F_{2a}-isoprostanes and saturated fats among non-smokers. We were unable to resolve whether the association with urine F_{2a}-isoprostanes was only with *trans* fat, with saturated fats, or both. In our analyses, the types of fat intake were

highly correlated, precluding their simultaneous inclusion in a regression model. Further, the two types of fats are not readily distinguished, biologically. Relatively greater proportions of both saturated and *trans* fatty acids are stored in the phospholipid bilayer leading to increased cell membrane rigidity compared to less saturated fats. Finally, both fat subtypes are found in many of the same foods.

Fairly consistent inverse associations were found with lutein intake; however, less consistent inverse associations were found for β-carotene and lycopene. Block (16) reported that lutein, α and β-carotene and lycopene were inversely related to F_{2a}-isoprostanes. However, in multiple variable analyses adjusting for sex, age, race, smoking status and BMI, only β-carotene remained statistically significant in their analysis.

While lutein, β-carotene and lycopene are found in many of the same foods, there is more commonality in good dietary sources of lutein and β-carotene. Structurally, all three molecules contain long polyene chains; however, β-carotene and lutein have ring structures at either end of the chains, while the lycopene chain contains uncyclized ends. The double bonds on the polyene chains of all three molecules can contribute to oxidation/reduction reactions, thus limiting peroxidation of membrane phospholipids. It is noteworthy that the hydroxyl functional group on lutein's ε-ring provides an additional target for oxidation/reduction that the others do not possess.

We observed inverse associations between both daidzein and genistein intakes and urine concentration of F_{2a}-isoprostanes in Chinese and Japanese women. The association between soy intake and coronary heart disease has been reported (52–53); however, intervention studies with intermediate, oxidative stress marker endpoints have provided mixed results (54–56). Due to the relative absence of smoking in Chinese and Japanese women, it was not possible to ascertain whether high genistein and daidzein intake would minimize the impact of smoking on the isoprostanes. The inclusion of other broad classes of polyphenols and their evaluation in all women indicated that polyphenols, apart from genistein and daidzein, could be important contributors to the amelioration of oxidative stress.

Several associations between dietary intake and urine F_{2a}-isoprostanes were different among smokers versus non-smokers, supporting the idea that smoking modifies these associations. Because smokers have higher concentration of isoprostanes and consume lower amounts of antioxidants and more *trans* and saturated fats than non-smokers, they may be more responsive to the beneficial effect of antioxidants (57). Among the strongest inverse concurrent associations observed were among smokers for vitamins C and E. Research indicates that vitamin C has the capacity for regeneration by other antioxidants and subsequent re-enlistment for oxidation/reduction actions (58,59). Although vitamin E has been reported to disappear in response to oxidative stressors such as cigarette smoke (59), evidence is mixed and a protective effect for cardiovascular disease has not been established (18,60).

Concurrent relationships between lower zinc and higher urine F_{2a}-isoprostane concentration were noteworthy in both smokers and non-smokers, and increases in zinc intake over time were also related to lower urine F_{2a}-isoprostane concentration in both groups. The mechanisms of action for zinc's antioxidant effects are an area of active research. Zinc's antioxidant effects are thought to occur through displacement of pro-oxidant metals, such as iron and copper upon binding with cell membranes, thus decreasing free radical production at the ligand-binding site (61). The zinc-containing enzyme Cu-Zn superoxide dismutase is thought to be a critical enzyme for oxygen free radical defense (62).

Environmental tobacco smoke exposure has been proposed as a risk factor for cardiovascular disease (63). Some evidence shows that it is associated with oxidative stress markers similar to that of active smokers (26). In our investigation, although we observed a graded increase in

least squared means of urine F_{2a}-isoprostanes according to increasing levels of total smoke exposure, statistically significant differences based on environmental tobacco smoke exposure disappeared in analyses adjusted for other relevant variables.

In models adjusted for covariates, physical activity was not associated with urine F_{2a}-isoprostanes. Our inability to detect an association could have been due to the small observed range of physical activity scores in our sample and lack of a sizable sub-group of women with regular intense physical activity. The absence of a statistically significant association has also been reported in older persons (32) in whom intense physical activity is less common.

Our investigation had strengths and limitations. Our diverse sample provided a wide range in lifestyle exposures, including intake of soy products and other food sources of polyphenols. A major advantage of this investigation was the availability of exposure data at two points in time. The use of F_{2a}-isoprostanes as a marker of oxidative stress was a strength due to their specificity for lipid peroxidation and chemical stability (64,65). Little diurnal variation is observed, and therefore, measurement of urine F_{2a}-isoprostanes in a single early morning sample has been described as adequate to represent the daily isoprostane excretion in humans (66). Nonetheless, nutrient values obtained from FFQ inevitably involve some misclassification error due to the difficulty in recalling and quantifying items consumed during the past year and recall of physical activity is susceptible to misclassification error for similar reasons. While the level of Type I error was set at 0.05 for each nutrient or food component, the numerous statistical tests may increase the likelihood of delineating false positive findings; thus, it is important to evaluate the findings also on the basis of the existing literature and biological plausibility. Further, analyses of Chinese and Japanese women who smoked were not possible due to the small numbers of such smokers.

This investigation consistently showed that dietary *trans* fatty acid intakes were associated with oxidative stress, as measured by urine F_{2a}-isoprostanes, while we observed a protective association for lutein and zinc intakes. Our results suggest that oxidative stress levels may be modifiable by changes in intake of these nutrients over time. Furthermore, the magnitude of concurrent and prospective associations in women who smoke suggest that those with elevated oxidative stress or cancer and cardiac disease risk, may particularly benefit from decreasing *trans* fat intake and increasing intakes of lutein and other antioxidants (47,57). Finally, this study provided no evidence to consider physical activity as a primary mediator of oxidative stress.

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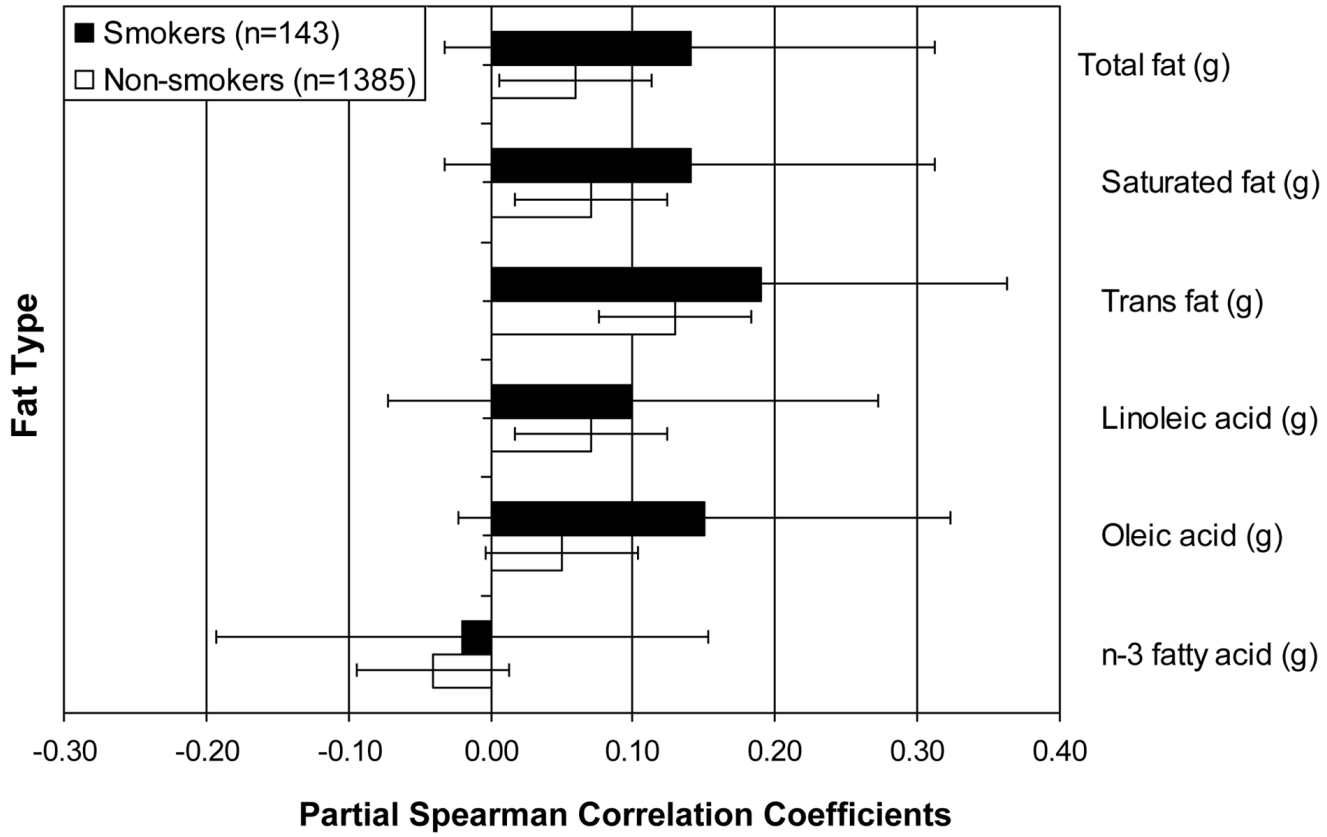

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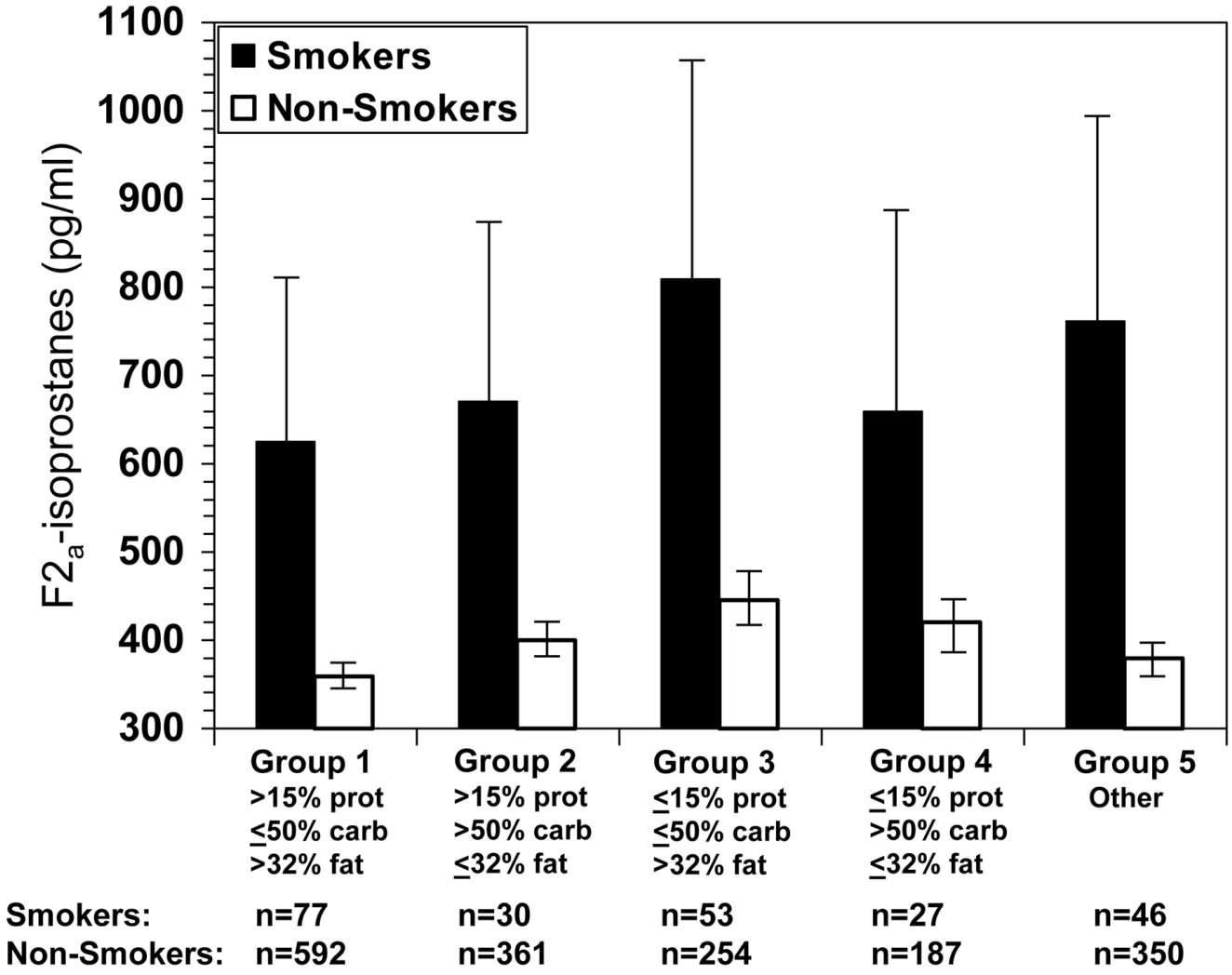

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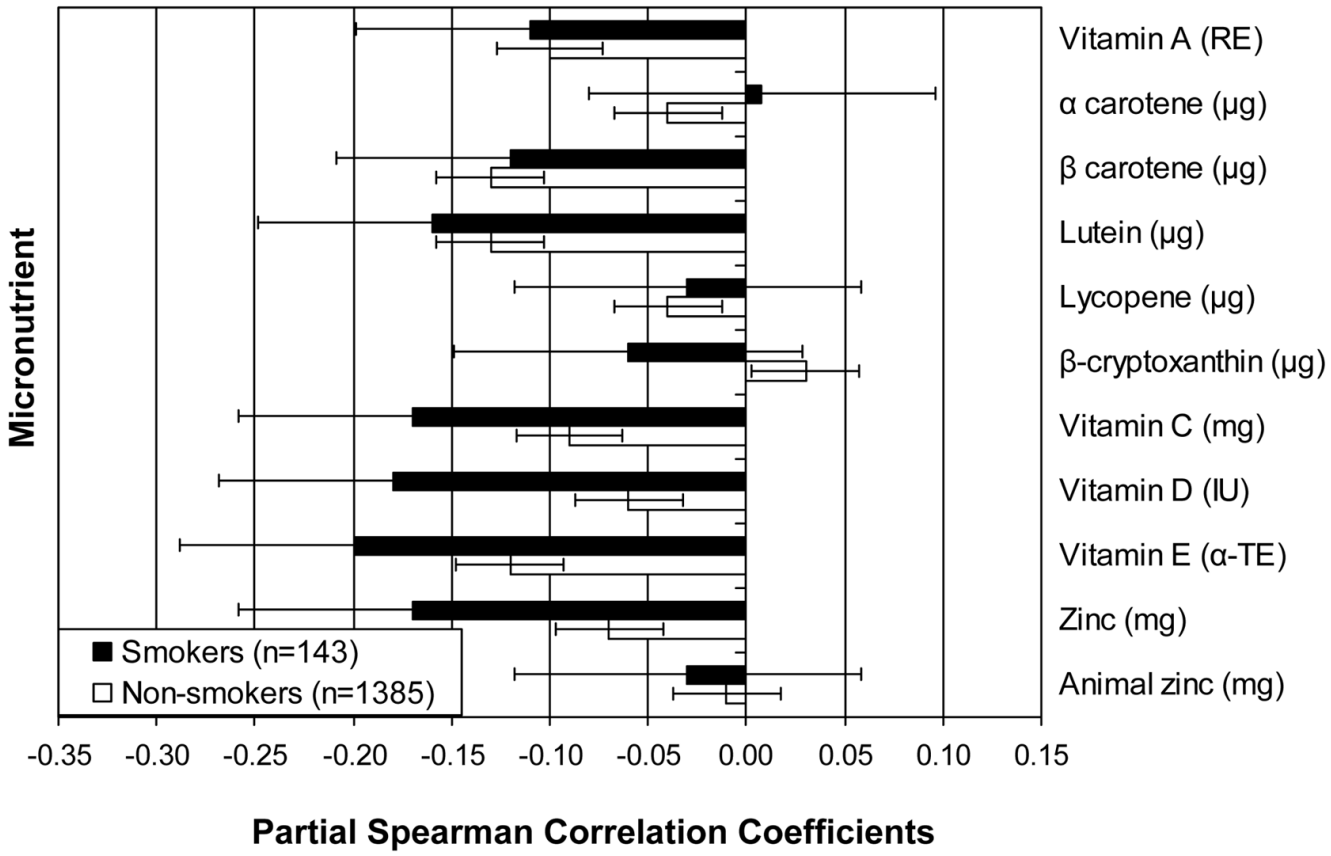

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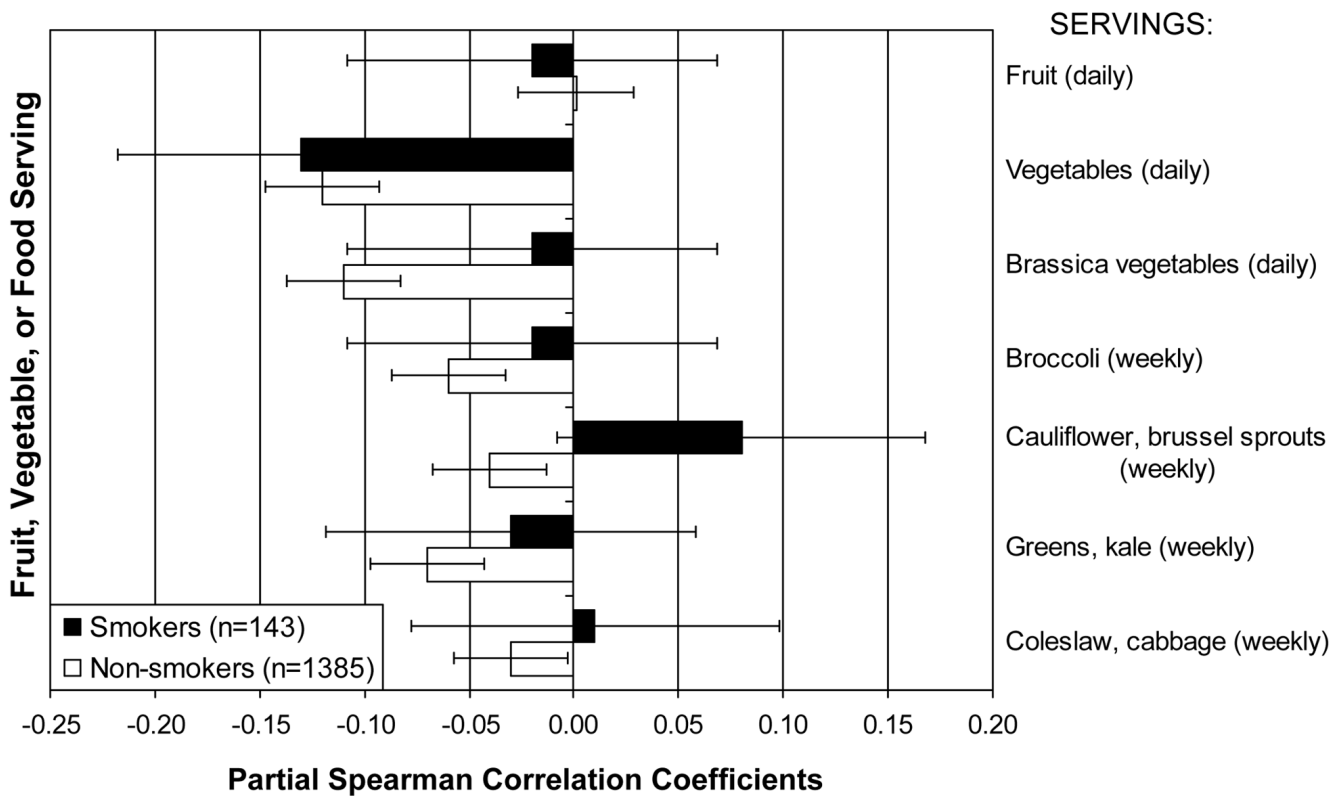

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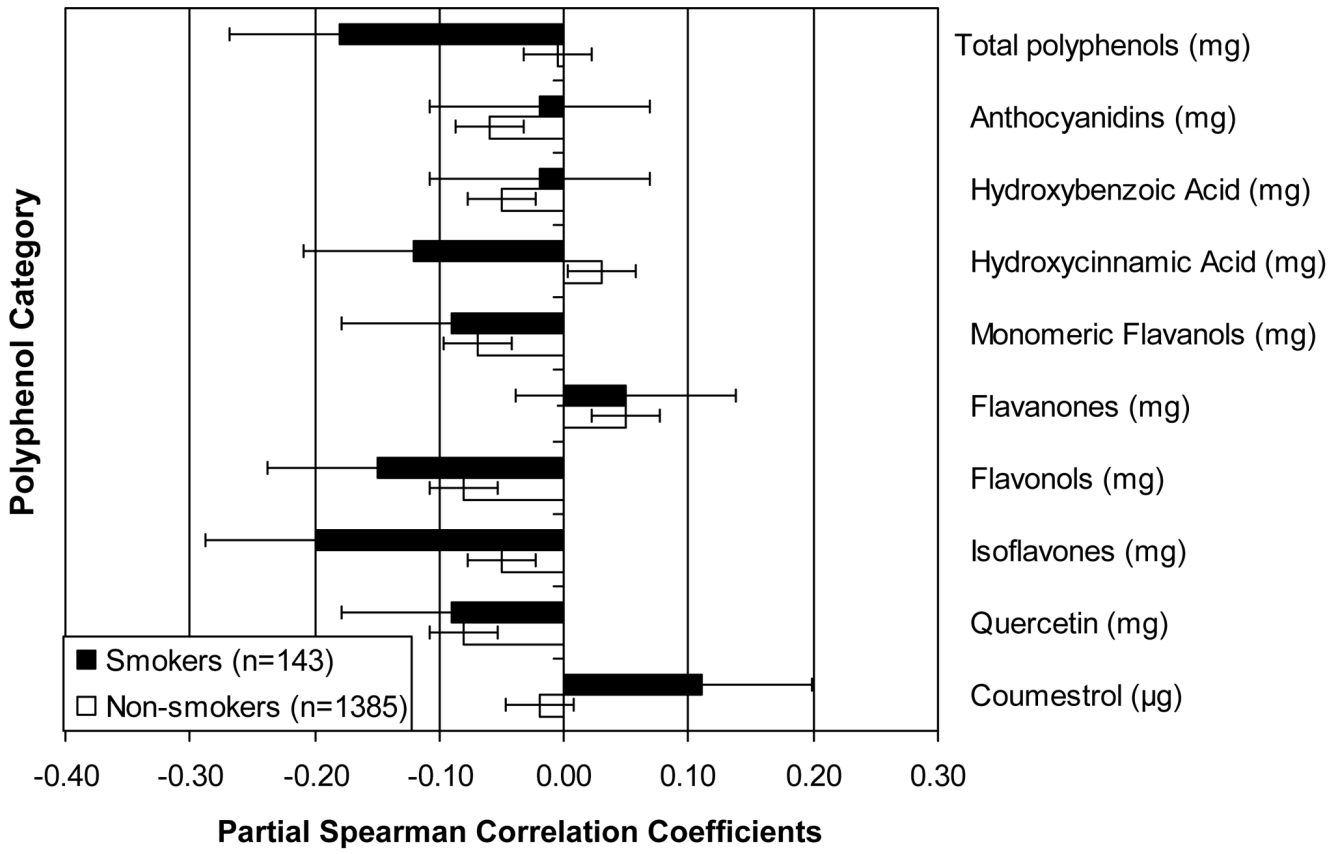

5. .

TABLE 1

Characteristics of SWAN participants according to smoking status and race[1]

	Smokers				Non-Smokers			
	African American	**Caucasian**	**Chinese[2]**	**Japanese[2]**	**African American**	**Caucasian**	**Chinese**	**Japanese**
n	76	81	2	17	283	747	194	206
Age, y	51 [48, 53]	50 [48, 52]	-	-	51 [49, 53]	51 [49, 53]	51 [49, 53]	51 [49, 53]
BMI, kg/m^2	31 [27, 37]*	28 [24, 32]	-	-	33 [27, 39]*	27 [23, 32]	23 [21, 25]	23 [21, 26]
Physical activity score	6.7 [5.4, 8.3]*	7.1 [6.1, 8.7]			7.3 [6.0, 8.7]*	8.3 [6.8,9.5]	7.3 [6.2, 8.4]	7.9 [6.9, 9.0]
Urine F_{2a}-isoprostane level, ng/L	1226 [721, 2074]*	803 [470, 1676]	-	-	599 [361, 1021]*	444 [242, 744]	284 [175, 408]	262 [167, 453]
Economic stress					Frequency (%)			
Very hard to pay for basics	13 (12)*	2 (2)	-	-	39 (9)*	22 (2)	1 (0)	3 (1)
Somewhat hard to pay for basics	41 (37)	32 (31)	-	-	115 (28)	114 (13)	29 (16)	44 (21)
Not hard to pay for basics	57 (51)	68 (67)	-	-	260 (63)	772 (85)	159 (84)	165 (78)

[1] Values are medians and quartiles [Q1, Q3] collected at year 5, except economic stress, for which data collected at year 6 are presented; information is presented for those with urine F_{2a}-isoprostanes data.

* Values different between race/ethnicity among smokers, $P<0.05$ (Wilcoxon rank-sum or chi-square test) or non-smokers, $P<0.05$ (Kruskal-Wallis or chi-square test).

[2] Values not estimated due to small cell sizes

TABLE 2

Dietary intake of SWAN participants by smoking status[1]

	Smokers[2]	Non-Smokers[3]
n	143	1385
Energy[4], kJ/d	7824 [5908, 10305]*	6849 [5452, 8556]
Total fat, g/d	74.3 [54.4, 98.8]*	61.2 [45.1, 79.8]
Saturated fatty acid, g/d	25.4 [17.3, 34.8]*	18.0 [13.0, 25.0]
Trans fatty acid, g/d	5.9 [3.4, 8.9]*	4.2 [2.6, 7.2]
Linoleic fatty acid, g/d	14.0 [9.6, 18.0]*	11.8 [8.3, 16.6]
Oleic fatty acid, g/d	23.4 [21.0, 37.8]*	24.0 [17.4, 31.4]
(n-3) fatty acid, g/d	1.4 [1.0, 1.7]	1.2 [0.9, 1.7]
Vitamin A, RE/d	6703 [3782, 10573]*	8586 [5684, 11892]
α-carotene, μg/d	116.8 [31.3, 294.8]*	190.4 [96.8, 386.2]
β-carotene, μg/d	2357 [1311, 4647]*	3134 [2050, 5078]
Lutein, μg/d	1633 [872, 3546]	1757 [982, 3338]
Lycopene, μg/d	1011 [439, 1570]*	1325 [738, 2244]
β-cryptoxanthin, μg/d	96.5 [50.4, 157.3]	93.7 [49.9, 151.7]
Vitamin C, mg/d	136.1 [71.0, 226.1]*	166.6 [103.4, 309.1]
Vitamin D, μg/d	4.3 [2.3, 11.9]*	7.6 [2.8, 12.4]
Vitamin E, α-TE/d	15.5 [8.7, 31.6]*	25.5 [10.5, 90.2]
Zinc, mg/d	12.4 [7.8, 23.7]	15.9 [8.8, 23.1]
Animal zinc, mg/d	5.5 [4.2, 7.6]*	4.4 [3.2, 6.1]
Fruit[5], servings/d	1.0 [0.5, 1.4]*	1.1 [0.7, 1.7]
Vegetables[6], servings/d	1.5 [0.8, 2.1]*	1.9 [1.2, 3.0]
Brassica vegetables, servings/d	0.3 [0.2, 0.6]	0.3 [0.2, 0.6]
Broccoli, servings/wk	1.0 [0.25, 2.0]*	1.0 [0.6, 2.0]
Cauliflower, Brussels sprouts, servings/wk	0.25 [0, 0.6]	0.25 [0, 0.6]
Greens, kale, servings/wk	0 [0, 0.6]*	0 [0, 0.3]
Coleslaw, cabbage, servings/wk	0.25 [0, 0.6]	0.25 [0, 0.6]
Total polyphenols, mg/d	580.2 [269.7, 795.9]*	356.3 [202.2, 630.7]
Anthocyanidins, mg/d	22.6 [6.5, 58.2]*	39.6 [17.6, 94.4]
Hydroxybenzoic acid, mg/d	1.2 [0.3, 3.1]*	1.5 [0.9, 5.4]
Hydroxycinnamic acid, mg/d	530.7 [157.6, 559.3]*	161.8 [24.5, 527.3]
Monomeric flavanols, mg/d	23.4 [12.5, 44.6]*	34.9 [16.7, 83.5]
Flavanones, mg/d	10.7 [0, 33.0]	10.7 [0, 33.0]
Flavonols, mg/d	14.8 [8.3, 23.0]	16.3 [10.0, 24.4]
Isoflavones, mg/d	1.5 [1.0, 2.3]*	2.5 [1.0, 12.4]
Quercetin, mg/d	4.2 [2.2, 7.3]*	5.8 [3.4, 10.3]

[1] Values are medians and quartiles [Q1, Q3] collected at Y05.

[*] Different from non-smokers, $P<0.05$ (Wilcoxon rank-sum test)

[2] Includes African Americans and Caucasians, n=143; Japanese and Chinese smokers were excluded due to small cell sizes

[3] Includes all ethnic groups, n=1385

[4] To convert kcal to kJ, multiply by 4.184

[5] A ½ cup serving of fruit is approximately 123 grams

[6] A ½ cup serving of chopped vegetables is approximately 90 grams

TABLE 3

Associations between log urine F_{2a}-isoprostanes and change in nutrient intake from baseline to Y05 in regression analyses according to smoking classification

Independent variable[1]	Smokers[2]			Non-Smokers[3]		
	β (SE)	*p value*	*Partial r^2 (%)*	*β (SE)*	*p value*	*Partial r^2 (%)*
Change in *trans* fat intake	0.186 (0.14)	NS[4]	1.4	0.131 (0.04)	0.0003	1.0
Change in saturated fat intake	0.292 (0.2)	NS	1.7	0.047 (0.06)	NS	0.1
Change in lutein intake	−0.134 (0.09)	NS	1.7	−0.096 (0.03)	0.0005	0.9
Change in lycopene intake	−0.014 (0.1)	NS	0.0	−0.003 (0.03)	NS	0.0
Change in β-carotene intake from diet/ supplements	−0.094 (0.11)	NS	0.6	−0.055 (0.03)	NS	0.2
Change in vitamin C intake	−0.166 (0.09)	NS	2.6	−0.074 (0.03)	0.007	0.6
Change in Zinc intake	−0.346 (0.14)	0.01	5.0	−0.117 (0.04)	0.001	0.8

[1] Independent variables in regression models were constructed as log (Y05 *variable*)- log (baseline *variable*)

[2] Includes African-Americans and Caucasians, n=136; models were adjusted for site, baseline value of independent variable of interest, along with baseline values and change from baseline to Y05 values for fat intake, age, BMI and physical activity score; Japanese and Chinese smokers were excluded due to small cell sizes

[3] Includes all ethnic groups, n=1321; models were adjusted for site, race/ethnicity, baseline value of independent variable of interest, along with baseline values and change from baseline to Y05 values for fat intake, age, BMI and physical activity score

[4] NS=non-significant, $P > 0.05$

TABLE 4

Associations of log urine F_{2a}-isoprostanes with phytoestrogen intakes in regression models according to smoking classification and race/ethnicity[1]

Independent variable	Smokers[2]		Non-Smokers					
	African American & Caucasian		African American & Caucasian[3]		Chinese[4]		Japanese[4]	
	β (SE)	*Partial r^2 (%)*	*β (SE)*	*Partial r^2 (%)*	*β (SE)*	*Partial r^2 (%)*	*β (SE)*	*Partial r^2 (%)*
Change in isoflavones intake[5]	−0.285 (0.11)*	5.3	−0.008 (0.02)	0.01	−0.049 (0.05)	0.6	−0.106 (0.07)	1.2
High baseline daidzein intake[6]					−0.334 (0.14)*	3.2	−0.319 (0.16)*	2.3
High baseline genistein intake[6]					−0.435 (0.14)*	5.3	−0.231 (0.16)	1.1

[1] *$P < 0.05$

[2] n=136. Model adjusted for site, baseline value of independent variable of interest, along with baseline values and change from baseline to Y05 values for fat intake, age, BMI and physical activity score; Japanese and Chinese smokers were excluded due to small cell sizes

[3] n=960. Model adjusted for site, baseline value of independent variable of interest, along with baseline values and change from baseline to Y05 values for fat intake, age, BMI and physical activity score

[4] Chinese n=178, Japanese n=185. Models adjusted for baseline value of independent variable of interest, along with baseline values and change from baseline to Y05 values for fat intake, age, BMI and physical activity score

[5] Independent variables in regression models were: log (Y05 *variable*)- log (baseline *variable*)

[6] "High" intake was highest tertile; the reference group was the lowest tertile of intake