Research Article

Dietary Patterns and Plasma Sex Hormones, Prolactin, and Sex Hormone–Binding Globulin in Premenopausal Women

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Abstract

Background: Sex hormones are important for breast cancer, but it is unclear whether dietary patterns influence hormone concentrations.

Methods: Dietary pattern adherence scores for the alternate Mediterranean diet (aMED), Dietary Approaches to Stop Hypertension (DASH), and Alternative Healthy Eating Index (AHEI) were calculated from semiquantitative food frequency questionnaires administered in 1995 and 1999. Premenopausal plasma concentrations of sex hormones were measured in samples collected in 1996 to 1999. We used generalized linear models to calculate geometric mean hormone concentrations across quartiles of dietary pattern scores among 1,990 women in the Nurses' Health Study II.

Results: We did not observe significant associations between sex hormone concentrations and the DASH pattern and only one suggestive association between follicular estrone concentrations and the aMED pattern [top vs. bottom quartile -4.4%, 95% confidence interval (CI), -10.6% to

2.1%; $P_{trend} = 0.06$]. However, women in the top versus bottom quartile of AHEI score had lower concentrations of follicular (-9.1%; 95% CI, -16.1% to -1.4%; $P_{trend} = 0.04$) and luteal (-7.5%; 95% CI, -13.6% to -0.9%; $P_{trend} = 0.01$) estrone, luteal-free (-9.3%; 95% CI, -16.8% to -1.1%; $P_{trend} = 0.01$) and total (-6.7%; 95% CI, -14.3% to 1.5%; $P_{trend} = 0.04$) estradiol, follicular estradiol (-14.2%; 95% CI, -24.6% to -2.4%; $P_{trend} = 0.05$), and androstenedione (-7.8%; 95% CI, -15.4% to 0.4%; $P_{trend} = 0.03$).

Conclusion: Diet quality measured by the AHEI is inversely associated with premenopausal estrogen concentrations. Given that we did not observe similar associations with the aMED or DASH patterns, our findings should be interpreted with caution.

Impact: Given the role of estrogens in breast cancer etiology, our findings add to the substantial evidence on the benefits of adhering to a healthy diet. *Cancer Epidemiol Biomarkers Prev; 25(5); 791–8. ©2016 AACR.*

Introduction

Sex hormone concentrations have been consistently associated with risk of postmenopausal breast cancer (1, 2), and evidence

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suggests that they are also important in risk of premenopausal breast cancer (3, 4). Although alcohol consumption has been associated with premenopausal sex hormone concentrations (5–7), the potential influence of other dietary factors on premenopausal sex hormone concentrations is unclear. A meta-analysis of 10 intervention studies suggested reductions in estrogen levels with a low-fat and high-fiber dietary intervention (8); however, many of the component studies suffered from serious methodologic flaws, including lack of a control group and the inability to distinguish influences of the diet from the subsequent weight loss that occurred with the dietary modification (9). In several large cross-sectional studies ($n = 595, 393, 90$), including our previous smaller study within the Nurses' Health Study II (NHSII; ref.10), fiber intake was unrelated to premenopausal sex hormone concentrations (10–12). However, wheat bran supplementation reduced serum estrogen concentrations in a randomized study of 58 premenopausal women (13). Although positive associations of saturated fat (11) and total fat (14) with estrogen concentrations have been observed in cross-sectional studies of premenopausal Japanese women, no associations were observed for total fat in other cross-sectional studies, including our own (10, 15).

Considering overall dietary quality instead of individual food components may be advantageous when evaluating health impacts of diet due to the potential synergistic effects of nutrients, which may be more easily detected than benefits of single

nutrients in isolation (16, 17). Several healthy dietary patterns, including the Alternative Healthy Eating Index (AHEI; ref.18), the Dietary Approaches to Stop Hypertension (DASH; ref.19), and the alternate Mediterranean diet (aMED; ref.20) indices for diet quality have been linked with the risk of cancer (21–24), cardiovascular disease (22, 23, 25), type II diabetes mellitus (22, 23), and mortality (23, 26, 27). Further, the AHEI, aMED, and DASH dietary scores were inversely associated with estrogen receptor–negative breast tumors in large prospective studies (28, 29). In addition, inverse associations were observed between AHEI score and concentrations of several estrogens among 578 postmenopausal women, although the associations were largely accounted for by body mass index (BMI; ref.30). To our knowledge, no studies have examined associations between overall dietary patterns and premenopausal sex hormone levels, which are complicated by the variation in sex hormone concentrations across the menstrual cycle. The NHSII provides a unique opportunity to investigate the associations between the AHEI, aMED, and DASH dietary patterns and premenopausal sex hormone concentrations timed within the menstrual cycle. Understanding whether dietary patterns influence premenopausal sex hormone levels may further our understanding of associations between dietary patterns and breast cancer in prior studies.

Materials and Methods

Study population

The NHSII is a prospective cohort established in 1989 among 116,430 female registered nurses, ages 25 to 42 years. Women in this cohort completed a baseline questionnaire and are followed biennially to update exposure information and ascertain disease diagnoses. Between 1996 and 1999, a total of 29,611 women in the NHSII (ages 32–54 years) provided blood samples. A description of the blood collection procedure has been detailed in a prior publication (31). Briefly, early follicular (3–5 days) and midluteal (7–9 days before expected start of the next cycle) blood samples were obtained from 18,521 premenopausal women who had neither taken oral contraceptives nor been pregnant or breastfed within 6 months from blood draw. Women aliquoted and froze follicular samples 8 to 24 hours after collection. A single untimed blood sample was collected from the remaining 11,090 women. All samples were shipped overnight on ice and processed by our laboratory into plasma, red blood cell, and white blood cell components; samples have been stored in continuously monitored liquid nitrogen freezers since collection. The stability of sex hormone concentrations over time using these methods has been demonstrated (32).

Women in this cross-sectional study have served as controls in nested case–control studies of breast cancer ($n = 1,252$; ref. 3), ovarian cancer ($n = 43$; ref.33), endometriosis ($n = 569$), and rheumatoid arthritis ($n = 18$; ref.34) or as participants in a hormone reproducibility study ($n = 108$; ref.32). A total of 1,990 premenopausal women with measures of diet and sex hormone concentrations were included in this analysis. This study was approved by the Committee on the Use of Human Subjects in Research at the Brigham and Women's Hospital (Boston, MA).

Laboratory assays

The details of laboratory assay methods used to quantify plasma concentrations of estrogens, androgens, progesterone, prolactin, and sex hormone–binding globulin (SHBG) have been described previously (35, 36). Luteal and follicular samples were assayed for estrone, estradiol, and estrone sulfate. Testosterone, androstenedione, and prolactin concentrations were assayed in luteal and/or follicular samples, as well as untimed samples. DHEA, dehydroepiandrosterone sulfate (DHEAS), and SHBG were measured in luteal and untimed samples, and progesterone was measured in luteal samples. Assays were performed in different batches at different laboratories. Some batches of estrogens ($n = 3$), testosterone ($n = 5$), androstenedione ($n = 2$), and progesterone ($n = 1$) were assayed at Quest Diagnostics. Organic extraction and celite column chromatography followed by RIA were used to quantify estrogens and testosterone. Estrone sulfate was assessed by RIA of estrone, after the extraction of estrone, enzyme hydrolysis, and column chromatography. Organic extraction and RIA was used to assay progesterone. Four batches of estrogens and testosterone were assayed at Mayo Medical Laboratories using LC/MS-MS. Two batches of DHEA and androstenedione and four batches of DHEAS, SHBG, and progesterone were assayed at the Royal Marsden Hospital (London, United Kingdom). Androstenedione was assayed by RIA and DHEAS; SHBG and progesterone were assayed by chemiluminescent enzyme immunoassay. One batch of progesterone (RIA) and three batches of SHBG (chemiluminescent enzyme immunoassay) were assayed at Massachusetts General Hospital (Boston, MA), and one batch of SHBG and progesterone were assayed at Boston Children's Hospital (Boston, MA). Prolactin was measured using microparticle enzyme immunoassay at the Massachusetts General Hospital using the AxSYM Immunoassay System. We included 10% blinded replicates in each batch to assess laboratory precision. Except for a single batch of progesterone (17%), within-batch coefficients of variation were between 2% and 15% for all analytes.

Dietary assessment

Starting in 1991, women completed a validated semiquantitative food frequency questionnaire (FFQ) every four years, assessing usual intake of the most commonly eaten foods during the past year (37, 38). For this study, average aMED, AHEI, and DASH dietary pattern adherence scores were calculated from the 1995 and 1999 FFQs.

Scoring methods for dietary pattern indices have been described in detail elsewhere (18, 19, 39). Briefly, for the aMED score, women were assigned 1 point for being above the median number of servings per day for the following components: fruit, vegetables, legumes and soy, nuts, fish and seafood, whole grains, and the ratio of monounsaturated to saturated fatty acids. Women were assigned 1 point for red and processed meat below the median intake and 1 point for moderate alcohol intake (5–15 g/day; ref. 28). The DASH score was derived by assigning 1 to 5 points based on quintile of intake in servings per day of fruit, vegetables, nuts, legumes and soy, red and processed meats, whole grains, low-fat dairy, and sodium in milligrams (40). Sweetened beverages were derived from quartiles of usual intake due to less variability in this measure. Scoring was inverse for red and processed meat, sugar-sweetened beverages, and sodium, with more points for less consumption. The AHEI score was modified from the Healthy Eating Index developed by the United States Department of Agriculture and is based on the consumption of 11 components: fruits, vegetables, red and processed meat, trans fat, polyunsaturated fat, long-chain (n-3) fats, whole grains, nuts and legumes, sugar-sweetened beverages and fruit juice,

Table 1. Characteristics at blood draw of 1,990 premenopausal women in the NHSII by dietary pattern score

	Dietary pattern					
	aMED score		DASH score		AHEI (no alcohol)	
	Q1	Q4	Q1	Q4	Q1	Q4
	(*n* = 565)	(*n* = 481)	(*n* = 477)	(*n* = 494)	(*n* = 496)	(*n* = 497)
aMED score (mean, SD)	2.2 (0.8)	6.7 (0.7)	2.5 (1.2)	6.2 (1.1)	3.0 (1.4)	5.8 (1.4)
DASH score (mean, SD)	19.7 (3.3)	29.2 (3.1)	18.0 (2.0)	30.4 (2.0)	20.7 (3.7)	28.2 (3.8)
AHEI score (mean, SD)	40.1 (7.0)	55.6 (9.1)	39.7 (6.9)	55.8 (8.9)	35.5 (3.8)	60.2 (5.7)
Age in years (mean, SD)	42.2 (4.1)	43.2 (3.9)	42.1 (4.0)	43.5 (3.9)	41.7 (4.1)	43.6 (3.9)
BMI, kg/m^2 (mean, SD)	26.3 (6.8)	25.4 (6.5)	26.6 (7.1)	25.4 (6.6)	26.3 (6.8)	25.8 (7.0)
BMI at age 18, kg/m^2 (mean, SD)	21.0 (3.1)	21.2 (3.2)	21.0 (3.1)	21.2 (3.0)	20.8 (2.8)	21.5 (3.3)
Height in inches (mean, SD)	64.6 (2.6)	65.2 (2.6)	64.8 (2.6)	65.3 (2.6)	64.8 (2.6)	65.0 (2.5)
Physical activity in MET-h/week (mean, SD)	14.2 (15.4)	23.6 (20.5)	14.5 (16.5)	23.7 (20.7)	12.6 (12.8)	22.5 (20.6)
Energy intake, g/day (mean, SD)	1,622 (441)	2,109 (474)	1,635 (472)	2,069 (467)	1,962 (502)	1,784 (493)
Carbohydrates, g/day (mean, SD)	202 (65.8)	288 (70.1)	200 (69.2)	290 (65.9)	252 (72.7)	242 (76.4)
Protein, g/day (mean, SD)	73.7 (19.8)	93.9 (24.6)	72.5 (20.2)	93.5 (25.1)	85.2 (22.6)	82.6 (25.0)
Total fat, g/day (mean, SD)	58.4 (19.0)	65.8 (20.8)	60.6 (20.4)	62.1 (20.7)	69.1 (21.0)	55.6 (20.2)
Animal fat, g/day (mean, SD)	34.5 (12.3)	30.5 (13.5)	35.1 (12.7)	29.1 (12.7)	40.1 (12.5)	25.0 (11.0)
Vegetable fat, g/day (mean, SD)	23.9 (9.6)	35.3 (12.3)	25.5 (10.3)	33.1 (13.0)	29.0 (11.4)	30.6 (13.6)
Trans fat, g/day (mean, SD)	2.9 (1.3)	2.6 (1.4)	3.2 (1.5)	2.4 (1.2)	3.7 (1.5)	2.0 (1.0)
Fiber, g/day (mean, SD)	14.0 (4.3)	28.0 (7.8)	13.7 (4.1)	28.4 (8.1)	16.7 (5.6)	25.3 (9.5)
Alcohol consumption in g/day (mean, SD)	2.6 (5.9)	5.8 (7.0)	3.2 (5.8)	4.5 (6.6)	2.9 (6.1)	4.6 (6.5)
Parous (%)	85.0%	73.4%	82.2%	73.5%	88.1%	70.0%
Parity[a] (mean, SD)	2.1 (1.2)	1.7 (1.3)	2.0 (1.3)	1.7 (1.3)	2.2 (1.3)	1.5 (1.2)
Age at first birth[a] (mean, SD)	26.0 (4.3)	27.1 (4.9)	26.1 (4.3)	27.4 (4.9)	26.2 (4.1)	27.4 (4.8)
Past oral contraceptive use (%)	86.4%	84.6%	88.1%	82.8%	86.5%	82.9%
Past breastfeeding history (%)	67.8%	64.7%	63.7%	65.4%	70.8%	60.0%
Current smoker (%)	9.4%	6.0%	12.8%	5.1%	10.1%	5.2%
Family history of breast cancer (%)	7.8%	11.2%	9.4%	9.7%	7.3%	10.9%
Benign breast disease history (%)	42.5%	47.8%	43.0%	49.4%	38.5%	49.3%
Caucasian (%)	95.8%	93.6%	95.6%	93.3%	94.4%	93.0%
Age at menarche between 12–13 years (%)	59.1%	63.4%	58.7%	61.1%	61.5%	58.4%
Usual menstrual cycle pattern regular (%)	90.6%	93.5%	89.1%	93.7%	89.2%	95.4%

[a]Among parous women.

moderate alcohol consumption, and sodium (22). Given the association we observed between alcohol and premenopausal sex hormone concentrations (5), we omitted the alcohol component of the AHEI score for this analysis. For the AHEI score, points were assigned on a scale from 0 to 10, with 10 indicating greater adherence to the recommended levels of serving per day; intermediate scores were categorized proportionately. Total scores consisted of the sum of points across all dietary components, with a higher score indicating a higher adherence, ranging from 0 to 8 for aMED, 8 to 39 for the DASH, and 2.5 to 87.5 for the AHEI; dietary pattern scores were categorized into quartiles for analyses.

The correlations between the different dietary patterns were moderate to strong, with Spearman correlation coefficients of 0.61 between AHEI and DASH, 0.63 between AHEI and aMED, and 0.80 between DASH and aMED.

Statistical analyses

Given the normal fluctuation of sex hormone levels throughout the menstrual cycle, we examined estrogen models separately for the follicular and luteal phases and progesterone in the luteal phase and tested for statistical interaction by menstrual cycle phase using the Wald test. In addition, we created a score for total estrogen exposure by ranking women within distributions of estrone, estradiol, and free estradiol (the estrogens available for the largest population) and summing ranks across the estrogens. As the concentrations of testosterone, free testosterone, androstenedione, and prolactin did not vary substantially by menstrual phase and the average concentration more accurately represents

long-term levels (32, 41), we used the average of the follicular and luteal blood sample values, when available for these hormones. We excluded 0 (estrone sulfate) to 13 (prolactin) extreme values detected with the generalized extreme studentized deviate many-outlier detection approach (42). We observed batch-to-batch variation among quality control samples and adjusted for batch according to methods described by Rosner and colleagues (43) as we have used previously (5, 44).

We assessed potential nonlinearity of continuous predictors in our model nonparametrically, with stepwise restricted cubic splines (45–47). Tests for nonlinearity used the likelihood ratio test to compare models with only the linear term with the model with the linear and the cubic spline terms. We used generalized linear models to estimate geometric mean hormone concentrations across quartiles of dietary pattern scores standardized to the marginal distribution of the covariates. We estimated the percentage difference and 95% confidence intervals (CI) comparing the top and bottom quartiles of dietary pattern score. We modeled each dietary pattern continuously using the median of each quartile and examined linear trends using the Wald test.

Multivariate models were adjusted for age at blood collection, date of blood collection, time of day of blood collection, fasting status, race, smoking status and duration, energy intake, alcohol consumption, physical activity in MET-hours per week, parity and age at first birth, age at menarche, duration of oral contraceptive use, and BMI at blood draw. Covariates were chosen based on prior knowledge of factors associated with sex hormone levels and dietary intake. We additionally included variables for blood draw

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Table 2. Adjusted geometric mean concentration of plasma hormones by DASH dietary pattern score quartiles among up to 1,990 premenopausal women in the NHSII

| Hormone range | N | DASH score | | | | P_{trend}, median of Qs | Percent difference[a] and 95% CI |
		Q1 (11.5–20.5)	Q2 (21.0–24.0)	Q3 (24.5–27.5)	Q4 (28.0–36.5)		
Follicular estradiol (pg/mL)	1,397	69.9	67.2	62.6	64.5	0.13	−7.7% (−19.0% to 5.3%)
Luteal estradiol (pg/mL)	1,524	152	152	154	153	0.84	0.5% (−7.6% to 9.2%)
Follicular-free estradiol	1,361	0.73	0.73	0.67	0.73	0.52	−0.2% (−9.7% to 10.4%)
Luteal-free estradiol	1,508	1.88	1.90	1.86	1.85	0.65	−1.6% (−10.2% to 7.8%)
Follicular estrone (pg/mL)	1,417	48.3	47.5	45.0	45.9	0.11	−4.9% (−11.9% to 2.6%)
Luteal estrone (pg/mL)	1,571	90.8	90.5	91.6	89.2	0.74	−1.7% (−8.7% to 5.7%)
Follicular estrone sulfate (pg/mL)	444	761	881	833	779	*	2.3% (−19.9% to 30.6%)
Luteal estrone sulfate (pg/mL)	449	1,608	1,729	1,454	1,361	0.14	−15.4% (−37.3% to 14.2%)
Luteal progesterone (ng/dL)	1,587	1,180	1,176	1,241	1,241	0.18	5.2% (−4.1% to 15.4%)
DHEA (ng/dL)[b]	386	774	863	757	707	0.08	−8.7% (−19.9% to 4.2%)
DHEAS (μg/dL)[b]	1,083	124	125	124	126	0.84	1.6% (−8.8% to 13.1%)
Testosterone (ng/dL)[c]	1,956	23.9	23.4	24.1	23.7	0.95	−0.9% (−6.3% to 4.8%)
Free testosterone (ng/dL)[c]	1,898	0.19	0.19	0.19	0.19	0.81	0.3% (−6.6% to 7.6%)
Androstenedione (ng/dL)[c]	626	126	132	128	121	0.34	−3.6% (−12.4% to 6.2%)
Prolactin (ng/dL)[c]	1,300	22.5	21.1	20.2	22.4	0.86	−0.3% (−10.9% to 11.6%)
SHBG (nmol/L)[c]	1,675	71.8	69.2	72.3	70.4	0.93	−1.9% (−8.3% to 5.0%)

NOTE: All geometric mean concentrations are adjusted for age at blood collection in years (continuous), BMI at blood collection in kg/m² (<22.5, 22.5 to <25, 25 to <27.5, 27.5 to <30, 30+), total energy intake in kcal/day (continuous), smoking (never smoker, past smoker with ≥ 5 years since quitting, past smoker with <5 years since quitting, current smoker of <15 cigarettes per day, current smoker of 15+ cigarettes per day), alcohol use (nondrinker, ≤10 g/day, 10.1–20 g/day, >20 g/day), duration of past oral contraceptive use (never, <4 years, 4+ years), age at first birth/parity (nulliparous, 1–2 children and age at first birth < 25 years, 1–2 children and age at first birth > 25 years, >3 children and age at first birth < 25 years, >3 children and age at first birth > 25 years), age at menarche (<12, 12–13, >13 years), physical activity in MET-hours/week (<3, 3–<9, 9–<18, 18–<27, 27+), date of blood collection (month/year, ≤1/97, 2/97–1/98, 2/98–1/99, ≥2/99), time of day of blood collection (1–8 am, 9 am to noon, 1–4 pm, 5 pm to midnight), and fasting status (<10, ≥10 hours). Models that included luteal or average of timed samples also were adjusted for the difference between luteal blood draw date and date of next menstrual period (3–7, 8–12, 13–17, 18–21 days, unknown/untimed).
[a]Percent difference between Q4 versus Q1.
[b]Luteal/untimed.
[c]Average of follicular and luteal measures, or untimed.
*P value for nonlinearity = 0.03 and P value for the overall significance of the curve = 0.06.

timing and fasting status in the model to reduce extraneous variation. Models that included luteal or average of timed samples also were adjusted for the difference between luteal blood draw date and date of next menstrual period.

We assessed whether associations differed by BMI (<25 vs. ≥25 kg/m²) and age (<45 vs. ≥45 years) using stratified models and calculated P values for interaction terms between BMI, age, and a continuous dietary pattern score weighted by the median of each quartile using the Wald test. We examined multivariate models with and without BMI to assess the influence of BMI on sex hormone concentrations. We conducted *a priori* sensitivity analyses among ovulatory women with timed samples (defined by luteal progesterone ≥ 400 ng/dL). All statistical tests were two sided and considered statistically significant at $P < 0.05$; statistical analyses were conducted using SAS software, version 9.2 (SAS Institute, Inc).

Results

Women in the highest versus lowest quartiles of the aMED, DASH, and AHEI dietary patterns were slightly older, leaner, much more likely to be physically active, less likely to be parous and to be current smokers, had a slightly older age at first birth, and were more likely to have history of benign breast disease, family history of breast cancer, and report regular menstrual cycles (Table 1). Of note, women in the highest versus lowest quartiles of the aMED and DASH dietary patterns consumed more carbohydrates, protein, and total fat and had higher energy intake overall, whereas women in the highest versus lowest quartile of the AHEI pattern consumed less of these macronutrients and had lower energy intake.

The DASH dietary pattern was not significantly associated with any of the sex hormone concentrations examined (Table 2). We observed a suggestive inverse trend in concentrations of follicular estrone with improved aMED diet adherence (P_{trend} = 0.06), but no other significant associations were observed for the other sex hormones and the aMED dietary pattern (Table 3). However, AHEI diet score was inversely associated with several estrogen concentrations (Table 4). Compared with women in the lowest quartile, those in the highest quartile of AHEI quality score had lower concentrations of follicular estrone (−9.1%; 95% CI, −16.1% to −1.4%; P_{trend} = 0.04), luteal estrone (−7.5%; 95% CI, −13.6% to −0.9%; P_{trend} = 0.01), follicular estradiol (−14.2%; 95% CI, −24.6% to −2.4%; P_{trend} = 0.05), and luteal estradiol (−6.7%; 95% CI, −14.3% to 1.5%; P_{trend} = 0.04) concentrations. AHEI was inversely associated with luteal-free estradiol (−9.3%; 95% CI, −16.8% to −1.1%; P_{trend} = 0.01) and suggestively with follicular-free estradiol (−9.2%; 95% CI, −18.2% to 0.8%; P_{trend} = 0.10). AHEI score was inversely associated with the total estrogen score (−5.6%; 95% CI, −11.2% to 0.4%; P_{trend} = 0.03); we did not observe any evidence of interaction by menstrual cycle phase for the associations of AHEI score and estradiol (P = 0.79), free estradiol (P = 0.76), estrone (P = 0.48), or estrone sulfate (P = 0.58). AHEI diet score was also inversely associated with androstenedione concentrations (top vs. bottom quartile: 7.8% (95% CI, −15.4% to 0.4%; P_{trend} = 0.03). We did not observe any other significant associations between the AHEI dietary score and premenopausal concentrations of estrone sulfate, progesterone, prolactin, SHBG, and other androgens, including DHEA, DHEAS, testosterone, or free testosterone. Results for the observed associations with dietary patterns did not differ in analyses stratified by age or BMI or in models

Table 3. Adjusted geometric mean concentration of plasma hormones by aMED dietary pattern score quartiles among up to 1,990 premenopausal women in the NHSII

Hormone range	N	aMED score				P_{trend}, median of Qs	Percent difference[a] and 95% CI
		Q1 (0–3)	Q2 (3.5–4)	Q3 (4.5–5.5)	Q4 (6.0–9.0)		
Follicular estradiol (pg/mL)	1,397	70.7	69.1	59.1	67.7	0.23	−4.2% (−17.2% to 10.8%)
Luteal estradiol (pg/mL)	1,524	156	149	154	150	0.38	−4.5% (−12.5% to 4.4%)
Follicular-free estradiol (pg/mL)	1,361	0.75	0.72	0.67	0.75	0.75	0.8% (−8.9% to 11.6%)
Luteal-free estradiol (pg/mL)	1,508	1.95	1.84	1.91	1.79	0.13	−8.3% (−16.8% to 1.0%)
Follicular estrone (pg/mL)	1,417	49.3	47.0	44.6	47.1	0.06	−4.4% (−10.6% to 2.1%)
Luteal estrone (pg/mL)	1,571	92.8	91.0	88.8	89.4	0.26	−3.7% (−10.7% to 3.8%)
Follicular estrone sulfate (pg/mL)	444	853	749	789	880	0.69	3.2% (−16.1% to 26.9%)
Luteal estrone sulfate (pg/mL)	449	1,759	1,401	1,521	1,491	0.26	−15.2% (−34.0% to 8.9%)
Luteal progesterone (ng/dL)	1,587	1,248	1,166	1,193	1,227	0.62	−1.7% (−10.1% to 7.6%)
DHEA (ng/dL)[b]	386	837	909	890	773	0.34	−7.7% (−20.4% to 7.0%)
DHEAS (µg/dL)[b]	1,083	123	126	129	124	0.67	1.1% (−8.9% to 12.3%)
Testosterone (ng/dL)[c]	1,956	23.5	23.9	24.1	23.4	0.94	−0.3% (−5.6% to 5.4%)
Free testosterone (ng/dL)[c]	1,898	0.18	0.19	0.20	0.18	*	−3.0% (−9.5% to 3.9%)
Androstenedione (ng/dL)[c]	626	128	131	129	119	0.19	−7.1% (−16.3% to 3.2%)
Prolactin (ng/dL)[c]	1,300	22.4	19.6	21.5	22.7	0.72	1.5% (−9.1% to 13.4%)
SHBG (nmol/L)[c]	1,675	71.5	70.3	69.3	72.4	0.89	1.3% (−5.5% to 8.5%)

NOTE: All geometric mean concentrations are adjusted for age at blood collection (continuous), BMI at blood collection (<22.5, 22.5 to <25, 25 to <27.5, 27.5 to <30, 30+), total kilocalories (continuous), smoking (never smoker, past smoker with ≥ 5 years since quitting, past smoker with <5 years since quitting, current smoker of <15 cigarettes per day, current smoker of 15+ cigarettes per day), alcohol use (nondrinker, ≤10 g/day, 10.1–20 g/day, >20 g/day), duration of past oral contraceptive use (never, <4 years, 4+ years), age at first birth/parity (nulliparous, 1–2 children and age at first birth < 25 years, 1–2 children and age at first birth > 25 years, >3 children and age at first birth < 25 years, >3 children and age at first birth > 25 years), age at menarche (<12, 12–13, >13 years), physical activity in MET-hours/week (<3, 3–<9, 9–<18, 18–<27, 27+), date of blood collection (month/year, ≤1/97, 2/97–1/98, 2/98–1/99, ≥2/99), time of day of blood collection (1–8 am, 9 am to noon, 1–4 pm, 5 pm to midnight), and fasting status (<10, ≥10 hours). Models that included luteal or average of timed samples also were adjusted for the difference between luteal blood draw date and date of next menstrual period (3–7, 8–12, 13–17, 18–21 days, unknown/untimed).
[a]Percent difference between Q4 versus Q1.
[b]Luteal/untimed.
[c]Average of follicular and luteal measures, or untimed.
*P value for nonlinearity = 0.04 and P value for overall significance of the curve = 0.06.

restricted to blood samples collected during ovulatory cycles (data not shown). Furthermore, results were generally similar in multivariate models unadjusted for BMI, although the associations between AHEI diet score and follicular ($P_{trend} = 0.16$) and luteal ($P_{trend} = 0.06$) estradiol were no longer statistically significant in models unadjusted for BMI. We observed statistically nonlinear associations between aMED and free testosterone ($P = 0.04$) and DASH and follicular estrone sulfate ($P = 0.03$). Thus, we did not estimate a P value for trend for these associations.

To further explore which components of the AHEI dietary pattern may be driving the observed inverse associations with estrogen concentrations, we examined models of the AHEI pattern omitting individual components (Supplementary Table 1). Inverse associations of the AHEI pattern and follicular estradiol, follicular and luteal-free estradiol, and follicular estrone appeared to be largely driven by the sugar-sweetened beverages component. However, several components of the AHEI pattern appear to be contributing to the observed inverse associations of AHEI pattern and luteal estradiol and luteal estrone.

Discussion

In this large cross-sectional study, we observed inverse associations between overall AHEI dietary quality and estrogen concentrations among premenopausal women. However, the aMED and DASH dietary patterns were not significantly associated with plasma concentrations of sex hormones.

To our knowledge, this is the first study to examine overall dietary patterns and sex hormone concentrations among premenopausal women. Although BMI largely accounted for observed inverse associations between the AHEI dietary pattern and postmenopausal plasma estradiol and free estradiol in a prior analysis (30), this was not the case among premenopausal women. Although we observed an inverse trend in concentrations of androstenedione with improving AHEI diet adherence, we did not observe any other significant associations between any of the dietary patterns and concentrations of androgens, suggesting that dietary patterns may not be strongly associated with androgen concentrations. This finding is generally consistent with the few prior studies to examine associations between specific dietary components, including fat, fiber, and energy intake, and premenopausal androgen concentrations (12, 48).

Although we observed several significant associations between the AHEI dietary pattern and estrogen concentrations in this study, it is not entirely clear why the AHEI pattern is associated with estrogen concentrations, whereas the DASH and aMED patterns, which share several common dietary components and are strongly correlated with the AHEI pattern, may not be as important. Each of these dietary patterns incorporates intakes of fruits and vegetables, whole grains, red and processed meats, and nuts and soy. Although trans fats and omega fatty acids are only included in the AHEI dietary pattern, these components were not driving the observed associations of the AHEI pattern with estrogen concentrations. However, our findings suggest that sugar-sweetened beverages may be important. Although sweetened soda was positively associated with premenopausal estradiol concentrations in a prior cross-sectional study of 259 women (49), other cross-sectional studies did not observe associations between soda consumption and premenopausal sex hormones

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Table 4. Adjusted geometric mean concentration of plasma hormones by AHEI (not including alcohol) dietary pattern score quartiles among up to 1,990 premenopausal women in the NHSII

Hormone range	N	AHEI score				P_{trend}, median of Qs	Percent difference[a] and 95% CI
		Q1 (21.5–40.2)	Q2 (40.3–46.2)	Q3 (46.2–53.2)	Q4 (53.2–81.1)		
Follicular estradiol (pg/mL)	1,397	75.3	60.9	66.5	64.6	0.05	−14.2% (−24.6% to −2.4%)
Luteal estradiol (pg/mL)	1,524	156	159	150	146	0.04	−6.7% (−14.3% to 1.5%)
Follicular-free estradiol	1,361	0.78	0.69	0.69	0.71	0.10	−9.2% (−18.2% to 0.8%)
Luteal-free estradiol	1,508	1.92	1.98	1.89	1.75	0.01	−9.3% (−16.8% to −1.1%)
Follicular estrone (pg/mL)	1,417	49.9	45.6	46.4	45.4	0.04	−9.1% (−16.1% to −1.4%)
Luteal estrone (pg/mL)	1,571	91.7	94.5	91.7	84.9	0.01	−7.5% (−13.6% to −0.9%)
Follicular estrone sulfate (pg/mL)	444	814	847	860	765	0.43	−6.0%(−22.2% to 13.6%)
Luteal estrone sulfate (pg/mL)	449	1,577	1,690	1,584	1,468	0.36	−6.9% (−24.3% to 14.5%)
Luteal progesterone (ng/dL)	1,587	1,189	1,197	1,233	1,225	0.45	3.0% (−5.9% to 12.8%)
DHEA (ng/dL)[b]	386	854	848	864	807	0.46	−5.5% (−17.8% to 8.7%)
DHEAS (µg/dL)[b]	1,083	123	127	129	121	0.78	−1.6% (−11.0% to 8.8%)
Testosterone (ng/dL)[c]	1,956	23.7	24.5	24.3	22.8	0.11	−3.7% (−8.5% to 1.3%)
Free testosterone (ng/dL)[c]	1,898	0.19	0.20	0.20	0.18	0.09	−6.0% (−12.4% to 0.9%)
Androstenedione (ng/dL)[c]	626	130	134	129	120	0.03	−7.8% (−15.4% to 0.4%)
Prolactin (ng/dL)[c]	1,300	21.8	20.6	22.0	21.9	0.60	0.5% (−9.9% to 12.1%)
SHBG (nmol/L)[c]	1,675	71.9	68.8	70.6	71.9	0.73	−0.04% (−6.5% to 6.9%)

NOTE: All geometric mean concentrations are adjusted for age at blood collection (continuous), BMI at blood collection (<22.5, 22.5 to <25, 25 to <27.5, 27.5 to <30, 30+), total kilocalories (continuous), smoking (never smoker, past smoker with ≥ 5 years since quitting, past smoker with <5 years since quitting, current smoker of <15 cigarettes per day, current smoker of 15+ cigarettes per day), alcohol use (nondrinker, ≤10 g/day, 10.1–20 g/day, >20 g/day), duration of past oral contraceptive use (never, <4 years, 4+ years), age at first birth/parity (nulliparous, 1–2 children and age at first birth < 25 years, 1–2 children and age at first birth > 25 years, >3 children and age at first birth < 25 years, >3 children and age at first birth > 25 years), age at menarche (<12, 12–13, >13 years), physical activity in MET-hours/week (<3, 3 to <9, 9 to <18, 18 to <27, 27+), date of blood collection (month/year, ≤1/97, 2/97–1/98, 2/98–1/99, ≥2/99), time of day of blood collection (1–8 am, 9 am to noon, 1–4 pm, 5 pm to midnight), and fasting status (<10, ≥10 hours). Models that included luteal or average of timed samples also were adjusted for the difference between luteal blood draw date and date of next menstrual period (3–7, 8–12, 13–17, 18–21 days, unknown/untimed).
[a]Percent difference between Q4 versus Q1.
[b]Luteal/untimed.
[c]Average of follicular and luteal measures, or untimed.

($n = 50$; 498; refs. 50, 51). Furthermore, in a prospective study of over 18,000 women, soda consumption was positively associated with increased risk of ovulatory disorder (52), suggesting that specific components of soda may be important for reproductive function. Although our results may be due in part to chance, the consistency of findings for AHEI with several estrogen concentrations warrants further investigation.

There are several biologic mechanisms that may be responsible for the observed associations between AHEI and premenopausal estrogen concentrations. For example, whole grains, vegetables, and other foods rich in fiber may influence estrogen metabolism (53, 54) and have been associated with a reduction in premenopausal estrogen levels in one study (13), although not in others (7, 10–12). Indeed, sources of fiber bind to estradiol (55, 56) and may reduce plasma estrogen levels by increasing fecal excretion (57, 58), as has been shown in animal studies (59). Potential biologic mechanisms for associations of dietary fat and sex hormone concentrations are less clear, although dietary fat intake can increase free fatty acids, which could displace estradiol from albumin, thereby increasing free estradiol concentrations (60, 61). However, SHBG concentrations may be more important determinants of free estradiol concentrations than the hypothesized displacement of estradiol, and we did not observe any associations between free estradiol levels and dietary fat in this study.

Strengths of the study include the ability to examine associations between overall dietary patterns, allowing for the synergistic effects of nutrients, and that estrogens were measured in both the follicular and luteal phases of the menstrual cycle, accounting for the variation in sex hormone concentrations across the menstrual cycle. In addition, evaluating overall dietary quality can complement the traditional methods by providing a comprehensive representation of dietary influences that can subsequently be investigated through a single-nutrient approach. To our knowledge, this is the first study to date to examine associations of diet quality scores and sex hormone concentrations among premenopausal women. We were able to account for multiple potential confounding lifestyle factors in our analysis. An additional strength of this analysis was the assessment of dietary patterns by validated FFQ. Given the cross-sectional design of this study, we are limited in our ability to attribute causality to the observed associations. Although we only had one- or two-timed hormone measures per participant to capture the association with habitual dietary pattern, one androgen measure is reproducible in our population of premenopausal women over 2 to 3 years [intraclass correlations (ICC), 0.58–0.94]. Although ICCs for estrogens are lower (0.38–0.69; ref.32), we observed several significant associations with estrogens in this study. Finally, due to the large number of associations examined as part of this study, several of which were examined without strong a priori hypotheses, we cannot rule out the possibility of observing several observations by chance.

In conclusion, we observed inverse associations between overall dietary quality measured by the AHEI and estrogen concentrations among premenopausal women, but no associations with dietary quality as assessed by aMED or DASH patterns. The observed associations with AHEI, along with the role of estrogen in breast cancer risk and the reduced risk of other cancers (22–24), cardiovascular disease (22, 23, 25), type II diabetes mellitus (22, 23), and certain breast cancer subtypes (28) associated with AHEI dietary adherence, add to the

substantial evidence of the health benefits of adhering to a healthy dietary pattern.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The authors assume full responsibility for analyses and interpretation of these data.

Authors' Contributions

Conception and design: W.C. Willett, S.E. Hankinson, A.H. Eliassen

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W.C. Willett, S.E. Hankinson, A.H. Eliassen

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.A. Hirko, D. Spiegelman, E. Cho, S.E. Hankinson, A.H. Eliassen

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Dietary Patterns and Plasma Sex Hormones, Prolactin, and Sex Hormone–Binding Globulin in Premenopausal Women

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