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Association of Coffee, Green Tea, and Caffeine Intakes With Serum Concentrations of Estradiol and Sex Hormone-Binding Globulin in Premenopausal Japanese Women

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Abstract: Caffeine intake has been proposed to influence breast cancer risk. Its effect may be mediated by hormonal changes. The relationships between caffeine-containing beverages (coffee, green tea, black tea, oolong tea, and cola) and serum concentrations of estradiol and sex hormone-binding globulin were evaluated in 50 premenopausal Japanese women. Intakes of caffeine and caffeine-containing beverages were assessed by a semiquantitative food-frequency questionnaire. Blood samples were obtained from each woman on Days 11 and 22 of her menstrual cycle. High intakes of caffeinated coffee, green tea, and total caffeine were commonly correlated with increasing sex hormone-binding globulin on Days 11 and 22 of the cycle after controlling for potential confounders [Spearman correlation coefficients (r) ranged from 0.23 to 0.31]. Green tea but not caffeinated coffee intake was inversely correlated with estradiol on Day 11 of the cycle ($r = -0.32$, $p = 0.04$). Although the effect of caffeine cannot be distinguished from effects of coffee and green tea, consumption of caffeine-containing beverages appeared to favorably alter hormone levels associated with the risk of developing breast cancer.

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Introduction

Studies of coffee or caffeine intake as a potential risk factor for breast cancer have yielded contradictory results. A cohort study of Norwegian women (1) showed that high consumption of coffee was significantly associated with decreased risk (50%) of breast cancer in lean women. Most previous case-control studies, however, have failed to identify an inverse association between coffee or caffeine intake and breast cancer risk (2–7).

There is convincing evidence that endogenous hormones, especially estrogens, have an important role in the etiology of breast cancer (8). Sex hormone-binding globulin (SHBG), which is a major determinant of bioavailable estradiol (E_2), has also been suggested to be related to breast cancer (9). If caffeine intake modulates circulating estrogens, it would affect breast cancer risk. Few studies addressed the relationship between caffeine or coffee intake and endogenous hormones. Positive associations of caffeine intake with plasma estrone and SHBG were reported in a cross-sectional study of postmenopausal women in the United States (10). Caffeine intake was inversely associated with percent free E_2 and positively associated with SHBG in a study of perimenopausal women in the United States (11). In another study, however, neither E_2 nor estrone was associated with coffee intake in pre- and postmenopausal women in the United States (12).

In the present study we examined the relationships between intakes of caffeine-containing beverages (coffee, green tea, black tea, oolong tea, and cola) and serum concentrations of E_2 and SHBG in premenopausal Japanese women.

Materials and Methods

Fifty healthy college women aged 21–42 years participated in the present study in 1994 in Gifu, Japan. Participants provided information on basic demographic characteristics, diet, physical activity, and menstrual and reproductive histories by means of a self-administered questionnaire. Dietary intake was assessed using a semiquantitative food-frequency questionnaire. The questionnaire included 169 food items. For each food item, participants were asked to indicate the average frequency of consumption during the year before the study and the usual portion size of each food item. For coffee (caffeinated and decaffeinated), green tea, black tea, oolong tea, and cola, participants chose one of nine possible response categories for the frequency questions, ranging from never to four or more times per day. Portion sizes for these items were not requested to be specified, and the standard units were specified using natural units usually used. Individual nutrient intake was estimated from the consumption frequency and portion size data using the standard tables of food composition in Japan. We also estimated caffeine intake on the assumption that caffeinated coffee contained

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40 mg of caffeine per 100 ml, green tea 20 mg/100 ml, black tea 50 mg/100 ml, oolong tea 20 mg/100 ml, and cola 30 mg/100 ml. The dietary collection methods have been described in detail elsewhere (13). The dietary questionnaire was validated against 12 daily diet records at about one-month intervals over one year. The Spearman correlation coefficients between the questionnaire and the 12 daily diet records were 0.58 for caffeinated coffee, 0.40 for green tea, 0.44 for black tea, 0.72 for oolong tea, and 0.37 for cola. The correlation coefficients for nutrient intakes such as fat (total fat and saturated, polyunsaturated, and monounsaturated fat), protein (animal and vegetable protein), carbohydrate, crude fiber, salt, calcium, carotene, retinol, and vitamins A, C, and E varied from 0.39 for vitamin C to 0.72 for calcium.

None of the participants had a history of diabetes or endocrine diseases or used oral contraceptives. One woman had used another type of hormonal medication for less than one year but not during the year preceding that in which the study was carried out.

The blood samples were collected from each subject in the morning on Days 11 and 22 of her menstrual cycle. The first day of menstrual bleeding was considered to be Day 1 of the cycle. All blood samples were taken over 26 days during the winter of 1994. The blood was centrifuged, and the serum was separated and stored at −80°C until assayed. One of us carried out all the assays in one batch. Serum concentrations of total E_2 and SHBG were measured by radioimmunoassay using kits purchased from Diagnostic Products. The intra-assay coefficients of variation based on control pools were 9.8% for E_2 and 5.3% for SHBG.

Serum concentrations of E_2 and SHBG were logarithmically transformed for statistical analyses. The nutrient intakes were adjusted for total energy using the method proposed by Willett (14) after logarithmic transformation. We used the Spearman rank correlation coefficients to assess the associations between hormone concentrations and intakes of caffeine-containing beverages. Potential confounders of these associations were included in regression models as covariates to calculate partial correlation coefficients. Although the blood samples were obtained from each subject on the same day of the menstrual cycle, E_2 was still shown to vary with cycle length. Therefore, cycle length was categorized into five groups: <28, 28–29, 30, and ≥31 days and irregular cycle. These were used as covariates in the models. All statistical analyses were performed using SAS programs (15).

Results

Table 1 shows demographic characteristics, intakes of caffeine-containing beverages, and serum concentrations of E_2 and SHBG among the subjects. Green tea was most frequently taken, and the mean consumption level was high.

Caffeinated coffee intake was significantly positively correlated with SHBG on Day 11 of the cycle after controlling for age, body mass index (BMI), and cycle length ($r = 0.30$, $p = 0.04$). Caffeinated coffee intake was also positively correlated with SHBG on Day 22 of the cycle, but the correlation was not statistically significant ($r = 0.23$, $p = 0.13$) (Table 2). We previously found that fat and crude fiber intakes were associated with E_2 on Day 11 of the cycle in the study subjects (16). Additional adjustments for fat and crude fiber intakes did not alter the correlations between caffeinated coffee intake and E_2 or SHBG.

Table 1. Descriptive Characteristics and Serum Concentrations of E_2 and SHBG in Study Subjects[a,b]

Variables	Values
Age, yrs	27.4 ± 7.3
BMI, kg/m^2	20.6 ± 2.0
Intake of caffeine-containing beverages, ml/day	
Caffeinated coffee	145.1 ± 165.5
Green tea	397.7 ± 331.5
Black tea	21.8 ± 30.1
Oolong tea	142.5 ± 234.2
Cola	35.8 ± 66.0
Total caffeine, mg/day	181.9 ± 109.8
E_2, pg/ml	
Day 11	73.2 ± 47.5
Day 22	98.1 ± 47.5
SHBG, nmol/l	
Day 11	78.4 ± 31.6
Day 22	85.5 ± 32.1

a: Values are means ± SD.

b: Abbreviations are as follows: E_2, estradiol; SHBG, sex hormone-binding globulin; BMI, body mass index; Day 11, Day 11 of menstrual cycle; Day 22, Day 22 of menstrual cycle.

Green tea intake was significantly inversely correlated with E_2 on Day 11 after controlling for age, BMI, and cycle length ($r = -0.35$, $p = 0.02$). Although the correlations were positive between green tea consumption and SHBG on Days 11 and 22 of the cycle, they did not achieve statistical significance after controlling for age, BMI, and cycle length ($r = 0.25$, $p = 0.10$). Additional adjustment for fat and fiber intakes raised the correlation with a statistical significance ($r = 0.31$, $p = 0.05$). Additional adjustment for caffeinated coffee intake did not change the results substantially.

Black tea and oolong tea intakes were not significantly correlated with E_2 or SHBG. Additional adjustment for caffeinated coffee intake decreased the inverse correlations of black tea intake with SHBG ($r = -0.01$ and -0.03 on Days 11 and 22 of the cycle, respectively) and increased the positive correlations of oolong tea intake with SHBG ($r = 0.15$ and 0.02 on Days 11 and 22 of the cycle, respectively). However, none of these correlations was statistically significant.

Cola intake was nonsignificantly positively correlated with SHBG on Days 11 and 22 of the cycle.

Estimated total caffeine intake was inversely correlated with E_2 on Day 11 of the cycle, although this correlation did not attain statistical significance. There were positive correlations between total caffeine intake and SHBG on Days 11 and 22 of the cycle after controlling for age, BMI, and cycle length ($r = 0.29$, $p = 0.05$ and $r = 0.32$, $p = 0.04$,

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Table 2. Spearman Correlation Coefficients Between Intakes of Caffeine-Containing Beverages and Serum Concentration of E_2 and SHBG[a,b]

	E_2		SHBG	
	Day 11	Day 22	Day 11	Day 22
Caffeinated coffee				
Adjusted for				
Age, BMI, and cycle length	0.20	0.12	0.30*	0.23
Green tea				
Adjusted for				
Age, BMI, and cycle length	−0.35*	0.03	0.16	0.25
+ Fat and crude fiber intakes	−0.32*	0.04	0.20	0.31*
Black tea				
Adjusted for				
Age, BMI, and cycle length	−0.11	0.19	−0.10	−0.09
Oolong tea				
Adjusted for				
Age, BMI, and cycle length	0.003	0.20	0.08	−0.03
Cola				
Adjusted for				
Age, BMI, and cycle length	0.18	0.30	0.27	0.22
Total caffeine				
Adjusted for				
Age, BMI, and cycle length	−0.18	0.11	0.29	0.32*
+ Fat and crude fiber intakes	−0.22	0.11	0.28	0.32*

a: See Table 1 footnote for definition of abbreviations.
b: Statistical significance is as follows: *, $p < 0.05$.

respectively). The results for total caffeine intake in relation to SHBG were similar after additionally controlling for fat and crude fiber intakes.

We considered potentially confounding effects of other variables such as age at menarche, age at first birth, parity, physical activity level, smoking, alcohol consumption, and other macro- and micronutrient intakes. Adjustments for these factors did not change the results substantially.

Discussion

We found that increasing caffeinated coffee and green tea intakes was significantly associated with SHBG in premenopausal Japanese women. Positive association of caffeine intake with SHBG was reported in two earlier studies: the Rancho Bernardo Study on postmenopausal women reported by Ferrini and Barrett-Connor ($r = 0.09$, $p = 0.03$) (10) and the study on perimenopausal women reported by London and co-workers ($r = 0.13$, $p < 0.05$) (11). To our knowledge, one study addressed the relationships between caffeine intake and hormone levels in premenopausal women. Cooper and colleagues (12) measured E_2 and estrone (but not SHBG) in premenopausal women and found no associations of these hormones with caffeine intake.

The increased SHBG concentration associated with caffeinated coffee, green tea, and total caffeine intake, together with findings from previous studies, suggests an effect of caffeine on metabolism of SHBG. Inasmuch as SHBG is mainly synthesized in the liver, Ferrini and Barrett-Connor (10) indicated a caffeine effect on hepatic metabolism. The lack of positive association of black tea intake with SHBG in the present study is probably due to the small number of black tea drinkers and their low intake levels. However, we cannot exclude the possibility that components of coffee and green tea other than caffeine may affect SHBG level. Caffeinated coffee intake was significantly correlated with increased SHBG on Day 11 of the cycle, but the correlation between green tea intake and SHBG was somewhat higher on Day 22 than on Day 11 of the cycle. Although the observed associations between decaffeinated coffee intake and SHBG ($r = 0.04$ and -0.18 on Days 11 and 22, respectively) were different from those observed between caffeinated coffee intake and SHBG ($r = 0.30$ and 0.23, respectively), this discrepancy might be by chance because of the small number of decaffeinated coffee drinkers ($n = 3$).

In addition, the inverse association of E_2 with green tea, but not caffeinated coffee, intake may reflect the effect of components of green tea other than caffeine on estrogen metabolism. It is possible that coffee and green tea may interfere with different mechanisms of metabolism of sex hormones. Tea leaves contain various kinds of polyphenols. The main constituent of the polyphenols, (−)-epigallocatechin gallate, blocks the specific binding of estrogen to the estrogen receptor of the mammary cancer cell line MCF-7 (17). We speculate that green tea polyphenols may interfere with estrogen metabolism, resulting in reduction of estrogen synthesis. Green tea is consumed regularly by the majority of Japanese. High intake of green tea among the Japanese population might contribute to the low incidence rate of breast cancer in Japan.

Green tea, as well as total caffeine, intake was negatively correlated with E_2 but, on the other hand, positively correlated

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with SHBG. The results suggest that the positive correlation between E_2 and SHBG, which was observed in general, is lost as a result of green tea and possibly total caffeine intakes.

We reanalyzed data using the ratio of E_2 to SHBG (E_2/SHBG) instead of E_2, because this ratio may reflect the level of bioavailable estrogen. The correlation coefficients were −0.32 ($p = 0.04$) and −0.07 ($p = 0.67$) between E_2/SHBG and green tea intake and −0.35 (0.02) and −0.05 ($p = 0.75$) between E_2/SHBG and total caffeine intake on Days 11 and 22 of the cycle, respectively. The results suggest a decreased risk of breast cancer among those with high intake of green tea or total caffeine. However, the correlations between caffeinated coffee and E_2/SHBG were weak ($r = -0.06$, $p = 0.69$ and $r = -0.05$, $p = 0.77$ on Days 11 and 22 of the cycle, respectively).

The relations of green tea intake to E_2 and SHBG were not altered after additional adjustment for caffeinated coffee intake. Adjustment for green tea intake also did not change the relations of caffeinated coffee intake to E_2 and SHBG, except the positive correlation coefficient for E_2 on Day 11 was increased from 0.20 to 0.26.

The observed associations may be subject to confounding from variables related to the intakes of caffeine-containing beverages. In particular, green tea intake appeared to be associated with a traditional Japanese diet. Lower E_2 levels among vegetarians have been observed in some previous studies (18,19). It has been suggested that diet is an important modifier of SHBG (20,21). In the present study, adjustments for covariates such as dietary intakes of fat, fiber, carotene, retinol, and vitamins, A, C, and E, as well as smoking and alcohol intake, did not appreciably modify the results. However, we cannot deny the possibility of residual confounding effects related to these factors.

Imprecision in the measurements of caffeine-containing beverages and nutrient intakes used for adjustments may have affected the findings. However, it is unlikely that such measurement errors are dependent on hormone levels.

The observed correlations between SHBG and caffeinated coffee and total caffeine intake were relatively strong compared with those from the previous studies, although precision was not high because of the small sample in the present study. Vatten and associates (1) found a significant inverse association of coffee intake with risk of breast cancer in lean women (BMI < 24). The subjects in the present study represent the standard Japanese women in terms of body size, and only three of them have a BMI >24. The association of coffee or caffeine intake with SHBG level may be stronger in lean, i.e., Japanese, women.

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