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Tea Intake, *COMT* Genotype, and Breast Cancer in Asian-American Women[1]

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ABSTRACT

There is substantial *in vitro* and *in vivo* evidence implicating tea polyphenols as chemopreventive agents against various cancers. In a case-control study conducted among Asian-American women in Los Angeles County, we reported a significant inverse relationship between intake of green tea and risk of breast cancer (A. H. Wu *et al.*, Int. J. Cancer, *106:* 574–579, 2003). Because catechol-containing tea polyphenols are very rapidly *O*-methylated by human catechol-*O*-methyltransferase (*COMT*), we are interested in determining whether the association between tea intake and breast cancer differed in women according to *COMT* genotype. We examined the interrelationships between tea intake, *COMT* genotype, and breast cancer risk in 589 incident cases and 563 population-based controls from a population-based case-control study of breast cancer in Chinese-, Japanese-, and Filipino-American women in Los Angeles County. Risk of breast cancer was influenced significantly by intake of tea, particularly green tea intake. However, the inverse association between tea intake and breast cancer risk was observed only among individuals who possessed at least one low-activity *COMT* allele. Among women who carried at least one low activity *COMT* allele, tea drinkers showed a significantly reduced risk of breast cancer (adjusted odds ratio, 0.48; 95% confidence interval, 0.29–0.77) compared with nontea drinkers after adjustment for relevant demographic, menstrual, reproductive, and dietary factors. This risk reduction was observed in relation to both green tea and black tea intake. In contrast, risk of breast cancer did not differ between tea drinkers and nontea drinkers among those who were homozygous for the high activity *COMT* allele (adjusted odds ratio, 1.02; 95% confidence interval, 0.66–1.60). In conclusion, tea catechins appeared to reduce breast cancer risk in this study of Asian-American women. Reduction in risk was strongest among persons who had the low activity *COMT* alleles, suggesting these individuals were less efficient in eliminating tea catechins and may derive the most benefit from these compounds.

INTRODUCTION

Tea preparations have inhibitory activities against tumorigenesis in many experimental studies (1). However, the bioavailability and biotransformation of tea polyphenols are key factors limiting these activities *in vivo* and may, explain in part, the inconsistent associations reported in epidemiological studies. Methylation is one of the major biotransformation reactions for tea catechins. Zhu *et al.* (2) reported that several catechol-containing tea polyphenols (particularly the epicatechins, epigallocatechins) are very rapidly *O*-methylated by human *COMT*,[3] an enzyme ubiquitously present in humans. *COMT*-mediated *O* methylation of catechins is faster than that of catechol estrogens and endogenous catecholamines (3).

It is known that the *COMT* gene is polymorphic. A G to A transition in the *COMT* gene results in valine to methionine amino acid change in codon 108/158 in the cytosolic/membrane-bound form of the protein. This amino acid change is believed to result in a 3–4-fold decrease in enzymatic activity (4, 5), although a recent study suggests that the difference in catalytic activity may be less (6). It has been hypothesized that individuals who inherit the low activity *COMT* gene may be at increased risk for breast cancer because of an increased accumulation of the catechol estrogen intermediates (7). The relationship between this *COMT* polymorphism and breast cancer risk has been investigated in several epidemiological studies and the results are mixed (8–18).

In a case-control study of breast cancer in Asian-American women, we have reported previously that tea intake, in particular, green tea intake, was inversely associated with risk of breast cancer (19). Because *O*-methylation of tea polyphenols is a main biotransformation reaction for tea catechins, we are interested in determining whether the association between tea intake and breast cancer differed in women according to *COMT* genotype. We hypothesize that the tea catechins would be less rapidly *O*-methylated in persons who have the low activity *COMT* genotype and, thus, the benefit of tea polyphenols may be more apparent in these individuals. In contrast, the tea polyphenols would be more rapidly eliminated among subjects with the high activity *COMT* genotype, and the benefit of tea intake would be less apparent. This hypothesis assumes that methylated polyphenols are "less protective," and this is currently not known. In this article, we present results on the interrelationships among tea intake, *COMT* genotype, and breast cancer risk in Asian-American women in Los Angeles County.

MATERIALS AND METHODS

This population-based case-control study has been described in detail previously (19, 20). Breast cancer cases included women who were identified as Chinese, Japanese, or Filipino, between the ages of 25 and 74 years at the time of diagnosis of an incident breast cancer on or after January 1, 1995. Cases were identified through the Los Angeles County CSP, the population-based cancer registry that is a member of the National Cancer Institute Surveillance, Epidemiology, and End Results program, and the statewide California Cancer Registry. Controls were selected from the neighborhoods where cases resided at the time of diagnosis using a well-established, standard algorithm (21). Controls were frequency-matched to cases on specific Asian ethnicity and 5-year age group. Subjects in this analysis included all of the participants who were interviewed by December 2001 and donated a blood specimen. Of the 952 breast cancer case patients and 822 control subjects who were interviewed, blood lymphocytes were obtained on 589 cases and 563 controls.

In-person interviews were conducted using a standardized, structured questionnaire that covered demographic characteristics and migration history, menstrual and reproductive history, body size, physical activity, and diet history (19, 20). The diet questionnaire was modeled after the validated diet instrument used in the Multiethnic Cohort Study being conducted in Hawaii and Los Angeles (22). Dietary intake during the year before cancer diagnosis (for cases) or during the past year (for controls) was determined. In our food frequency questionnaire, separate questions were asked regarding intake of black tea, green tea, herbal tea, regular coffee, and decaffeinated coffee. The frequency of intake (never, 1–2 times/month, 3 times/month, 1–3 times/week, 4–6

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[3] The abbreviations used are: *COMT*, catechol-*O*-methyl transferase; CSP, Cancer Surveillance Program; H/L, high activity/low activity; OR, odds ratio; CI, confidence interval.

times/week, once/day, 2 times/day, and 3 or more times/day) for each beverage and the usual amounts (in units of ½ or 1 measuring cup) drunk each time were asked (½ measuring cup is equivalent to 1 tea cup, which contains 4 fluid ounces or 120 ml). Measuring cups were displayed during the interview to facilitate the estimation of amount of intakes. We estimated consumption (in ml/day) of green and black tea separately and for the two teas combined. Unlike green and black teas, herbal teas are generally not brewed from leaves of the plant, Camellia sinensis, and their constituents can be quite different from those of traditional teas (23). Therefore, we did not include herbal tea in our composite index of tea.

***COMT* H/L Genotyping Methods.** DNA was purified from buffy coats of peripheral blood samples using a PureGene Blood kit (Gentra Systems, Minneapolis, MN) or a QIAamp 96 DNA Blood kit (Qiagen, Valencia, CA). The COMT polymorphism was described previously (8), and a genotyping assay was developed for the H/L polymorphism using the fluorogenic 5′-nuclease assay (TaqMan Assay; Ref. 24). The TaqMan assays were performed using a TaqMan PCR Core Reagent kit (Applied Biosystems, Foster City, CA) according to the manufacturer's instructions. The oligonucleotide primers for amplification of the polymorphic region of COMT were GC009for (5′-GCCATCACCCAGCGGAT-3′) and GC009rev (5′-AACGGGTCAGGCATGCAC-3′). In addition, the fluorogenic oligonucleotide probes used to detect each of the alleles were GC009F (5′-GATTTCGCTGGCATGAAGGACAAG-3′) labeled with 6-FAM to detect the L allele and GC009C (5′-GATTTCGCTGGCGTGAAGGACAAG-3′) labeled with CY3 to detect the H allele (BioSearch Technologies, Novato, CA). PCR amplification using ~10 ng of genomic DNA was performed in a thermal cycler (MWG Biotech, High Point, NC) with an initial step of 95°C for 10 min followed by 50 cycles of 95°C for 25 s and 62°C for 1 min. The fluorescence profile of each well was measured in an ABI 7900HT Sequence Detection System and the results analyzed with Sequence Detection Software (Applied Biosystems). Experimental samples were compared with 12 controls to identify the three genotypes at each locus (H/H, H/L, and L/L). Any samples that were outside the parameters defined by the controls were identified as noninformative and were retested.

Statistical Methods. In this analysis, which included 589 breast cancer case patients and 564 control subjects, we calculated ORs (relative risk estimates), their corresponding 95% CIs, and *P*s by conditional logistic regression methods, with matched sets defined jointly by age (<39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and 70+), specific Asian ethnicity (Chinese, Japanese, and Filipino) and birthplace (United States born, non-United States born). The relationship between *COMT* genotype and breast cancer risk was first investigated separately in the three Asian ethnic group. After establishing that the *COMT* genotype and breast cancer association did not differ significantly by Asian ethnicity (Table 2), we investigated the interrelationship between tea intake and *COMT* genotype in all three of the Asian groups combined using conditional logistic regression models described above. Because <10% of women in this study were homozygous for the low activity *COMT* L allele, we investigated the tea-breast cancer association separately for women who possessed at least one *COMT*-L allele and those with two high activity alleles (*COMT*-HH). Nondrinkers of black and green tea served as the baseline group and they were compared with women who drank black tea only, green tea only, or both green and black tea combined. Education (less than high school, high school, some college, college graduate, and postgraduate), age at menarche (<12, 12–13, 14–15, and 16+), parity (never pregnant, ever pregnant but no live births, and 1+ live birth; categorical), current body mass index (in quartiles), total caloric intake (continuous), menopausal status (premenopausal and postmenopausal), use of menopausal hormones (never, former, and current), physical activity, smoking status (no and yes) and intake of alcohol (no and yes), coffee (no, < = 120, >120 to 240, and >240 ml), soy (< = 1.74, >1.74 to 6.24, >6.24 to 12.68, and > = 12.68 mg of isoflavones/1000 kcal), and dark leafy greens (<4 times/week *versus* >4 times/week) were included as covariates in our analyses. All of the *P*s quoted are two-sided.

Table 1 *Demographic characteristics of the breast cancer case patients and control subjects who were interviewed and donated blood specimens (in percents)*

	Cases		Controls	
	Interviewed (*n* = 952)	Donated blood (*n* = 589)	Interviewed (*n* = 822)	Donated blood (*n* = 563)
Age				
<40	8.3	8.8	11.8	10.5
40–49	33.4	31.6	36.0	35.0
50–59	29.5	28.9	26.2	27.2
60–69	19.5	20.9	16.9	17.8
70+	9.2	9.8	9.1	9.6
Mean age	53.1	53.3	51.8	52.3
Birthplace				
US born	23.2	27.2	27.9	32.9
Non-US born	76.8	72.8	72.1	67.1
Education				
<High school	21.2	20.2	18.5	17.1
High school	20.8	22.6	26.2	26.1
Some college	41.0	39.7	38.6	40.0
College graduate	16.9	17.5	16.8	16.9

Table 2 *Association between COMT genotype and breast cancer in Asian-American women*

COMT	Cases	Controls	Adjusted OR[a]	95% CI
All subjects				
HH	328	282	1.00	
HL	213	229	0.82	0.64–1.06
LL	48	51	0.84	0.54–1.30
P (2 df)			0.28	
HL or LL	261	280	0.82	0.65–1.05
Chinese				
HH	97	106	1.00	
HL	67	78	1.00	0.64–1.54
LL	14	15	0.89	0.40–2.00
HL or LL	81	93	0.98	0.64–1.48
Japanese				
HH	88	86	1.00	
HL	89	87	0.96	0.63–1.46
LL	16	24	0.74	0.36–1.53
HL or LL	105	111	0.92	0.61–1.38
Filipino				
HH	143	90	1.00	
HL	57	64	0.56	0.36–0.88
LL	18	12	0.94	0.43–2.05
HL or LL	75	76	0.62	0.41–0.94

[a] Conditional logistic regression models with matched sets defined jointly by age (≤39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70+), Asian ethnicity (Chinese, Japanese, Filipino), and birthplace (US born, non-US born) were employed. In ethnic-specific analysis, the model included age and birthplace.

RESULTS

This analysis on tea and *COMT* genotype included 589 breast cancer patients (178 Chinese, 193 Japanese, and 218 Filipinos) and 564 control women (199 Chinese, 197 Japanese, and 168 Filipinos) who were interviewed and donated blood specimens. Demographic characteristics of the participants who donated blood specimens were similar to the cases and controls we have interviewed in the parent case-control study. There was a small excess of subjects who were United States born among those who donated blood specimens (Table 1).

Compared with women with two high activity *COMT* alleles (*COMT* HH), risk of breast cancer was reduced in women who possessed one low activity allele (*COMT* HL; adjusted OR, 0.82; 95% CI, 0.64–1.06) or two low activity alleles (*COMT*-LL; adjusted OR, 0.84; 95% CI, 0.54–1.30). This risk pattern was observed in all three of the Asian ethnic groups, although a statistically significant association was found only in Filipino women (Table 2).

The univariate associations between tea intake and breast cancer in this expanded data set were comparable with our earlier published results (19). In the present study, compared with non-tea drinkers, women who drank black tea only showed little risk reduction (adjusted OR, 0.93; 95% CI, 0.65–1.33), but those who drank green tea only (adjusted OR, 0.63; 95% CI, 0.41–0.98) or who drank both green and black tea (adjusted OR, 0.66; 95% CI, 0.46–0.96) showed significantly reduced risks (data not shown).

Table 3 shows the tea-breast cancer associations separately by *COMT* genotype (*COMT*-HH *versus* *COMT*-HL and *COMT*-LL combined). Among women who were homozygous for the high activity COMT-H allele, tea consumption had little effect on breast cancer risk. However, among women with at least one low activity *COMT* allele, risk of breast cancer was significantly reduced in association with both green tea and black tea intake. The risks associated with tea drinking among those with *COMT* HH genotype (OR, 1.02; 95% CI, 0.66–1.60) and *COMT* H/L + LL genotype (OR, 0.48; 95% CI, 0.29–0.77) was marginally statistically different from each other ($P = 0.07$). When we investigated the associations by the amount of tea consumed, risk estimates were close to 1.0 for various amounts of green/black tea drank among women with the *COMT* HH genotype. Among women who were *COMT* L allele carriers, breast cancer risk was significantly reduced 40–60% for different amounts of tea drank, but there was not a smooth trend of decreasing risk with increasing amounts of intake (Table 3). The inverse association between tea intake and breast cancer risk among carriers of the *COMT* L allele was found in each of the three Asian ethnic groups; results were statistically significant among Japanese-American women (Table 4). In contrast, tea drinking was not associated with a reduced risk of breast cancer among women who were homozygous for the *COMT* H genotype in each of the three Asian groups.

DISCUSSION

The prevalence of the *L allele* among Chinese (27.1%) and Japanese (34.3%) control women in this study was similar to prevalences reported for Chinese (25.2%; Ref. 13) and Japanese (33.0%; Ref. 15) in Taiwan and Japan, respectively. The prevalence of the *L allele* among Filipino control women (26.5%) was similar to the other Asian groups (we are not aware of published data in Filipino women). Genotype frequencies for the *L allele* were in Hardy-Weinberg equilibrium for all three groups of Asian control women (*P*s were from 0.78 to 0.90) and for Chinese and Japanese women with breast cancer (*P*s were 0.61 and 0.32, respectively) but not for Filipino cases ($P = 0.001$). Approximately 50% of Asian control women (53% of Chinese, 44% of Japanese, 54% of Filipino) in the present study were homozygous for *COMT* HH, 9% were homozygous for the low activity *COMT* genotype (8% Chinese, 12% Japanese, and 7% Filipino) and 41% were heterozygotes (39% Chinese, 44% Japanese, and 39% Filipinos). We investigated the tea-breast cancer association separately for those homozygous for the *COMT* H allele and those with at least one low activity *COMT* allele because of the relatively low prevalence of the *COMT LL* genotype. There are also supportive data that individuals with *COMT HL* genotype displayed reduced *COMT* activity compared with those who were homozygous for *HH genotype* (25).

Earlier, when we examined tea intake in relation to breast cancer without taking *COMT* genotype into consideration, it was not apparent that black tea exerts any putative effect on breast cancer. We primarily noted an inverse relation with risk only for intake of green tea (19). Interestingly, in the present study, when only subjects positive for the low-activity *COMT* allele were considered, both black and green tea exhibited comparable levels of breast cancer protection. Multiple *in vitro* studies have shown that green and black tea extracts, and tea polyphenols all possess the ability to suppress growth of human breast cancer cell lines (26, 27). In experimental animals, 7,12-dimethylbenz(*a*)-anthracene (DMBA)-treated rats given drinking water with 2% black tea extracts had statistically significant, 50% reduction in mammary tumor incidence compared with DMBA-treated rats given water only (35% *versus* 70%; Ref. 28).

Our study suggests that *COMT* genotype may possess opposing effects on breast cancer risk. We observed that the beneficial effect of tea on breast cancer was confined to women positive for the low-activity allele. On the other hand, methylated catechol estrogens, namely, 2-methoxy-estradiol, are considered "good estrogens" on the basis that they have little or no estrogen-binding affinity, lack uterotropic activity, and demonstrate antiproliferative and apoptotic activities in mammary cancer cell lines, at least at very high concentrations (29). In other words, under the catechol estrogen hypothesis, the low-activity allele is associated with increased breast cancer risk. This dual effect of *COMT* genotype on breast cancer risk may explain, in part, the conflicting results on *COMT* genotype and breast cancer in diverse western (8–12, 16–18) and eastern populations (13–15).

Whereas additional research is needed to establish the biological

Table 3 *Risk of breast cancer in association with intake of tea and COMT genotype among Asian-American women*

			COMT HH			*COMT* H/L + LL
Tea	Case	Control	OR[a] (95% CI)	Case	Control	OR[a] (95% CI)
Black and green tea						
Non-tea drinker	83	68	1.00	74	54	1.00
Black tea only	107	60	1.50 (0.90–2.49)	51	71	0.44 (0.25–0.78)
Green tea only	43	45	0.86 (0.46–1.62)	44	58	0.42 (0.22–0.80)
Black and green tea	95	109	0.65 (0.38–1.10)	92	97	0.56 (0.32–0.98)
Black and green tea						
Nondrinker	83	68	1.00	74	54	1.00
Black and green tea	245	214	1.02 (0.66–1.60)	187	226	0.48 (0.29–0.77)
P			0.85			0.002
Black and green tea						
Nondrinker	83	68	1.00	74	54	1.00
<=85.7 ml/day	106	87	1.07 (0.66–1.74)	70	101	0.41 (0.24–0.70)
>85.7–209.4 ml/day	47	45	0.90 (0.49–1.66)	32	31	0.64 (0.31–1.31)
>209.4 ml/day	92	82	1.02 (0.59–1.75)	85	94	0.52 (0.29–0.90)
P trend			0.93			0.13
Herbal tea						
No	237	203	1.00	197	196	1.00
Yes	91	79	1.19 (0.78–1.81)	64	84	0.86 (0.54–1.36)
Coffee drinking[b]						
Nondrinker	87	69	1.00	69	60	1.00
Regular + decaf	241	213	0.80 (0.52–1.24)	192	220	0.73 (0.45–1.18)
P			0.32			0.20

[a] Conditional logistic regression models with matched sets defined jointly by age (≤39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70+), Asian-ethnicity (Chinese, Japanese, Filipino), and birthplace (US born, non-US born) were employed. Education, age at menarche, pregnancy, current body mass index, menopausal status, use of menopausal hormones, intake of soy (≤1.79, >1.79–6.24, >6.24–12.68, >12.68 mg of isoflavones/1000 kcal), dark green vegetables (≤3× *vs.* 4+/wk), smoking history (no/yes), alcohol intake (no/yes), coffee intake (0, >0–120, >120–240, >240 ml/day), and physical activity (0, 1–19, 20+ years) were included as covariates.

[b] Black and green tea intake was included but coffee was excluded in the multivariate model.

Table 4 *Risk of breast cancer in association with intake of tea and COMT genotype in Chinese, Japanese, and Filipino women*

			COMT HH			*COMT* H/L + LL
	Ca	Co	OR (95% CI)[a]	Ca	Co	OR (95% CI)[a]
Chinese						
Nontea drinker	18	22	1.00	20	18	1.00
Tea drinker	79	84	1.23 (0.6–2.6)	61	75	0.80 (0.4–1.7)
P			0.58			0.54
Japanese						
Nontea drinker	11	8	1.00	18	5	1.00
Tea drinker	77	78	0.63 (0.2–1.7)	87	106	0.16 (0.05–0.5)
P			0.35			0.001
Filipino						
Nontea drinker	54	38	1.00	36	31	1.00
Tea drinker	89	52	1.18 (0.7–2.0)	39	45	0.65 (0.3–1.3)
P			0.54			0.21

[a] Conditional logistic regression models with matched sets defined jointly by age (≤39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70+) and birthplace (US born, non-US born) were employed.

plausibility of our observations, our study represents one of the larger case-control studies on *COMT* and breast cancer. Our study allows comparison of risk estimates in three Asian ethnic groups, and the results are internally consistent in that the *COMT*-breast cancer association was similar in Chinese, Japanese, and Filipino women (Table 2). The protective effect of tea among individuals who possessed at least one low-activity *COMT* allele was also observed in all three of the Asian groups, although these results were only statistically significant among Japanese women (Table 4). Nonetheless, the ethnic-specific sample sizes in the present study are still limited, and our novel observations should be considered preliminary and requiring confirmation by larger studies conducted in genetically homogeneous populations with wide ranges in tea intake profiles (both type and frequency). Blood specimens were obtained on only 62% of our case patients and 68% of our control subjects interviewed. However, the demographic characteristics of those who donated blood specimens were generally similar to all of the subjects interviewed (Table 1).

In summary, the present study extended our earlier finding that green tea protects against breast cancer (19). Polymorphism in *COMT*, which catalyzes a major metabolic pathway of tea polyphenols, was found to modify the tea-breast cancer association. The protective effect of tea was mainly confined to women positive for the low-activity *COMT* allele. Interestingly, in the latter subgroup of women, both black and green tea show comparable levels of protection against breast cancer.

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