A BRIEF ORIGINAL CONTRIBUTION

Coffee and Serum Gamma-glutamyltransferase: A Study of Self-Defense Officials in Japan

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The relation of coffee drinking and other behavioral factors to serum gamma-glutamyltransferase (GGT) was examined in 2,494 male self-defense officials aged 48–56 years, who received a retirement health examination at the Self-Defense Forces Fukuoka Hospital between October 1986 and December 1990. Coffee, but not green tea, consumption was inversely related to serum GGT independently of body mass index, alcohol use, and smoking. All of the latter variables were also independently and positively associated with serum GGT. Lower levels of serum GGT associated with coffee drinking were more evident among heavier alcohol drinkers and also among heavier smokers. The findings suggest that coffee may inhibit the inducing effects of alcohol and possibly of smoking upon GGT in the liver. *Am J Epidemiol* 1994;139:723–7.

alcohol drinking; coffee; gamma-glutamyltransferase; obesity; smoking

The measurement of serum gamma-glutamyltransferase (GGT) is widely used as a laboratory test for hepatobiliary diseases, especially of alcoholic liver disease (1). Except for alcohol use (2–8) and obesity (5–8), however, little is known concerning behavioral correlates of serum GGT. An inverse relation between coffee consumption and serum GGT has been observed in successive population studies in Norway (7, 8); to our knowledge, no other study has investigated the relation between coffee and serum GGT. Interestingly, a recent prospective study in the United States has reported

a decreased risk of alcoholic, but not nonalcoholic, cirrhosis in relation to coffee consumption, suggesting that coffee drinking may protect the liver from the adverse effects of alcohol (9). We examined the relation of coffee drinking as well as of green tea consumption to serum GGT allowing for obesity, alcohol use, and smoking in cross-sectional data of middle-aged Japanese men.

MATERIALS AND METHODS

Study subjects comprised male self-defense officials who received, between October 1986 and December 1990, a retirement health examination at the Self-Defense Forces Fukuoka Hospital, which is part of the nationwide program for those retiring from the Self-Defense Forces. Details of the health examination and an accompanied lifestyle survey have been described elsewhere (10–12). Comprehensive medical examinations were performed during a 5-day admission, and a self-administered ques-

tionnaire ascertained smoking habit, alcohol use, dietary habits, and other lifestyle characteristics.

Venous blood was taken after an overnight fast for the determination of serum GGT activity and other biochemical measurements with an autoanalyzer (Olympus, Tokyo, Japan) using commercial reagents (Katayama Chemistry, Osaka, Japan) (10). Serum GGT activity was assayed by a calorimetric method (13). Body mass index (kg/m²) was used as a measure of obesity. The reported numbers of cups of brewed and instant coffee consumed per day, on average, in the past year were added to the estimated total coffee consumption. Past smokers were separated from never smokers and, likewise, past drinkers from lifelong abstainers. Alcohol intake was calculated from the reported consumption frequency and quantity for each of five different alcoholic beverages (12).

Of the 2,756 men in the series, we excluded 115 past drinkers because they had significantly higher values of serum GGT as compared with never drinkers; there was no material difference in GGT levels between never and past smokers, and these two groups were combined. Also excluded were 147 men having a level of more than 40 units/liter of serum aspartate aminotransferase and/or alanine aminotransferase to avoid a possible bias, suggested by Klatsky and Armstrong (9), that men with liver dysfunction may have reduced coffee consumption because of impaired caffeine clearance (14, 15).

The age range of the 2,494 men was 48–56 years, and 76 percent were at the age of 52 years. Age was thus omitted in the analysis. Multiple linear regression analysis and analysis of covariance were used to control for confounding variables and to examine possible interactions. Since the distribution of serum GGT values was skewed to the right side, natural logarithms of GGT values were always used in statistical analysis. Two-sided p values less than 0.05 were regarded as statistically significant. All computations were performed by the Statistical Analysis System (16).

RESULTS

Serum GGT values ranged from 5 to 642 units/liter with a median of 24 units/liter; the

TABLE 1. Geometric means of serum gamma-glutamyltransferase activity by selected factors in 2,494 male self-defense officials in Japan, 1986–1990

Factor	No.	Geo-metric mean	95% confidence interval
Body mass index (kg/m²)†			
15.92–21.95	621	21	20–22
21.96–23.51	628	25	24–27
23.52–25.00	627	28	27–30
25.01–33.71	618	34	33–36
			$p = 0.0001$*
Alcohol (ml/day)			
0‡	430	18	17–19
1–29	865	24	23–25
30–59	713	30	29–32
≥60	486	37	35–40
			$p = 0.0001$
Cigarettes (no./day)			
0§	1,271	26	25–27
1–14	107	24	22–28
15–24	721	27	26–29
≥25	395	31	29–33
			$p = 0.0001$
Coffee (cups/day)‖			
0	899	31	30–33
1–2	708	26	24–27
3–4	637	25	23–26
≥5	250	22	20–23
			$p = 0.0001$
Green tea (cups/day)			
0–2	585	26	25–27
3–4	922	26	25–27
5–6	692	28	27–30
≥7	295	27	25–29
			$p = 0.18$

* p values were based on one-way analysis of variance.
† Quartile classification.
‡ Past drinkers were excluded.
§ Never and past smokers were combined.
‖ One cup equals 237 ml.

coefficient of variation was 21 percent in the scale of natural logarithm. Table 1 shows the geometric means of serum GGT according to coffee consumption and other factors. There was a progressive inverse relation between coffee drinking and serum GGT. Both the body mass index and alcohol use were strongly associated with raised serum GGT activities, and cigarette smoking was moderately so. Serum GGT levels varied little according to green tea consumption.

Coffee drinking (cups/day) was significantly correlated with smoking (cigarettes/day) (Spearman's $r = 0.22$) and inversely correlated with green tea consumption (cups/day) ($r = -0.16$). Lower correlations were observed for body mass index ($r = -0.04$) and alcohol consumption ($r = -0.09$). However, an inverse relation between coffee and serum GGT was independent of these factors (table 2). All of the other factors except green tea were also independently and positively associated with serum GGT.

The interactions of coffee and each of the three significant covariates (body mass index, alcohol, and cigarettes) were examined simultaneously in a multiple regression model that included coffee and the three covariates. A highly significant negative interaction was observed for alcohol use ($p = 0.005$) and cigarette smoking ($p = 0.001$); the interaction between coffee and body mass index was not evident ($p = 0.58$) nor was the effect of coffee itself ($p = 0.41$).

TABLE 2. Adjusted average percentage of difference in serum gamma-glutamyltransferase (GGT) activity according to selected factors in 2,494 male self-defense officials in Japan, 1986–1990*

Factor (unit)	% of difference in serum GGT	95% confidence interval
Body mass index (kg/m²)	7.4	6.3 to 8.5
Alcohol (10 ml/day)	6.8	5.9 to 7.6
Cigarettes (no./day)	0.6	0.4 to 0.8
Coffee (cups/day)†	-5.7	-6.9 to -4.4
Green tea (cups/day)	0.0	-0.9 to 0.9

* Based on a multiple linear regression model including all the listed variables as independent variables.
† One cup equals 237 ml.

Figure 1 illustrates the interactions of coffee drinking with alcohol use and smoking. Lower levels of serum GGT associated with coffee consumption were more evident at the higher levels of alcohol consumption and of cigarette smoking.

DISCUSSION

In agreement with results from previous studies in Norway (7, 8), those from this study denoted a strong inverse relation between coffee consumption and serum GGT. This inverse relation was largely due to differentially lower levels of serum GGT not only among heavier alcohol drinkers but also among heavier smokers. These findings are compatible with a prospective observation on coffee and alcoholic cirrhosis (9). In that study, cigarette smoking was also associated with an increased risk of alcoholic cirrhosis, and the smoking-related risk tended to be weakened by coffee drinking.

It is unclear whether smoking is independently and positively associated with serum GGT. Our reported association between smoking and serum GGT is consistent with a cross-sectional study of British men (5). In Norwegian studies (7, 8), however, cigarette smoking was not related to raised serum GGT activities in males, whereas there was an independent association between the two in females. Some other studies found a positive relation without controlling for alcohol drinking (4, 6) or no clear association (2, 3) between smoking and serum GGT. If an increase in serum GGT activity associated with smoking is suppressed by coffee drinking, a positive association between smoking and serum GGT would not be clear in populations in which coffee drinking is ubiquitous. This possibility, however, needs confirmation by other studies.

Although our data were cross-sectional, it is unlikely that a raised activity in serum GGT caused a reduction in coffee consumption. We excluded men who had increased levels of the aminotransferases, thereby reducing the possibility that men with impaired liver function might reduce coffee
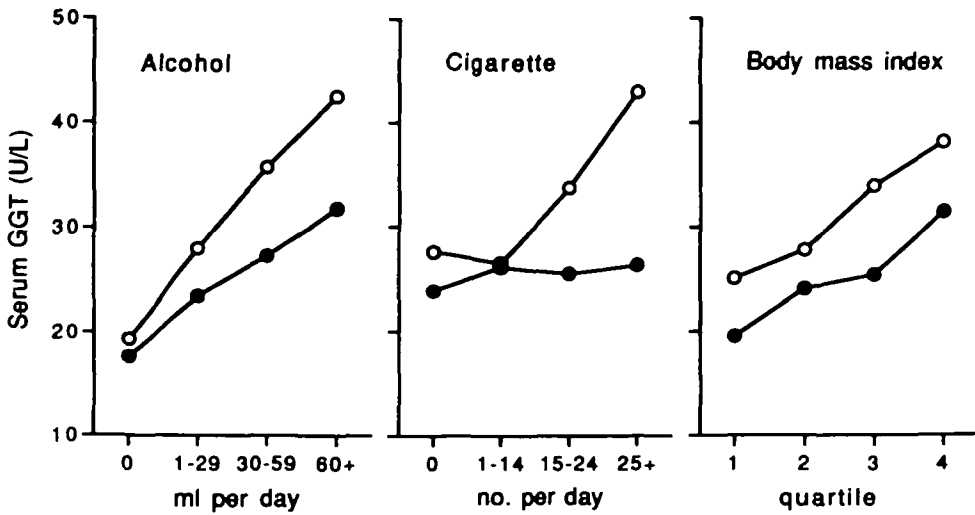
FIGURE 1. Adjusted geometric means of serum gamma-glutamyltransferase (GGT) according to alcohol use, cigarette smoking, and body mass index for men consuming coffee daily (●) and not daily (○), controlling for two of the three variables by analysis of covariance, in 2,494 male self-defense officials in Japan, 1986–1990. U/L, units/liter.

consumption because of reduced caffeine clearance (9). Obesity and alcohol drinking were the most important factors for raised serum GGT activities in our study population as well. Coffee drinking was negatively, but weakly, associated with body mass index and alcohol use, and uncontrolled confounding effects of these factors would not totally explain the observed inverse relation between coffee and serum GGT. Furthermore, such residual confounding effects are unlikely to have produced the more prominent inverse relation between coffee and serum GGT among heavier alcohol drinkers. A confounding effect of smoking only attenuates an inverse relation between coffee and serum GGT.

Our findings strongly suggest that coffee may inhibit the inducing effects of alcohol ingestion (1) and possibly of smoking upon GGT in the liver. We have no plausible explanation as to the underlying biologic mechanisms. Caffeine is unlikely to exert such an effect because the consumption of green tea, another major source of caffeine intake in Japan, was not associated with serum GGT. Alcohol is a well-known determinant of serum high-density lipoprotein

cholesterol, and thus it may be interesting to know whether coffee attenuates the effect of alcohol in raising serum high-density lipoprotein cholesterol; in the present study, however, coffee was not associated with serum high-density lipoprotein cholesterol, and there was no measurable interaction between coffee and alcohol.

It was noted in a Norwegian study that the inverse relation between coffee and serum GGT was much stronger for boiled coffee than for filtered coffee (8). We cannot address this matter, however; brewed coffee in Japan is mainly filtered, but instant coffee was more popular in our study population (11). The possible beneficial effects of coffee upon the liver deserve further investigation.

ACKNOWLEDGMENTS

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