Relationship between Silent Brain Infarction and Amount of Daily Coffee Consumption in Middle Age

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Background: In aging societies such as that of Japan, it is important to characterize lifestyle-related factors that minimize the occurrence of silent brain infarction (SBI) among the middle aged population for preventing vascular dementia in older age. Little is known about the relationship between amount of coffee consumption and SBI. *Methods:* To assess the association between the amount of coffee consumption and SBI in middle age, we statistically analyzed magnetic resonance imaging findings and data from questionnaires of consecutive 242 healthy Japanese individuals whose ages were less than 65 years and who participated in a medical brain-screening program at Teikyo University Chiba Medical Center from June 2008 to June 2009. *Results:* In comparison with noncoffee drinkers (reference group), coffee drinkers who took 3-4 cups/day and 5 or more cups/day had a statistically lower incidence of SBI (.22, .07-.64, .004 and .43, .19-.99, .043, respectively). Upward logistic regression analysis indicated that SBI was influenced by 3 factors: coffee intake of 3 or more cups/day (.43, .22~.84, .014), history of hypertension (4.2, 2.0~8.8, .0001), and unemployment (2.1, 1.0~4.4, .037). As for consecutive 62 participants whose ages were 65 years or older in the same period, logistic regression analysis did not indicate that drinking coffee affected SBI incidence. *Conclusions:* Our report demonstrated that SBI was observed less frequently in middle aged Japanese who consumed 3 cups or more of coffee per day. To avoid senile dementia and/or symptomatic infarction in older age, the middle aged individuals might have to drink more than 3 cups of coffee every day.
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Introduction

In aging societies such as that of Japan, medical prevention of silent brain infarction (SBI) on magnetic resonance imaging (MRI) and identification of lifestyle-related factors that minimize the occurrence of SBI among middle-aged individuals appear to be important for preventing vascular dementia in older age.[1-3] It is well known that individuals who are heavy smokers and have chronic alcoholism, hypertension (HPT), diabetes mellitus (DM), and/or metabolic syndrome often develop SBI.[4-10] Although several reports demonstrated that coffee intake might prevent symptomatic brain infarction,[11-14] for the prevention of SBI, little is known about the effect of coffee drinking.

To investigate the association between daily coffee consumption and SBI in middle age, we conducted a case–control study using data obtained from brain checkups in healthy Japanese whose ages were less than 65 years.

Subjects and Methods

Two hundred forty-two consecutive individuals less than 65 years of age undergoing a brain checkup at Teikyo University Chiba Medical Center from June 2008 to June 2009 participated in this report. Subjects of a brain checkup in Teikyo University Chiba Medical Center are limited to those without history of serious diseases, such as strokes, brain tumors, brain injuries, or malignant tumors in other organs.

All brain checkup attendees are required to complete a detailed questionnaire regarding medical history, occupation, amount of alcohol consumption (gram per day), number of cigarettes smoked per day, amount of coffee intake (number of cups per day), and amount of tea consumption (number of cups per day).

Brain MRI examinations, including T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery imaging, and cervical and brain magnetic resonance angiography, were performed using a General Electric 1.5T Signa HDx machine (GE Healthcare, Fairfield, CT). We obtained permission from all subjects to use the data acquired in this report at the reception of brain checkup examination and the present study has been approved by the ethics committee of the Teikyo University Chiba Medical Center on March 1, 2011.

SBIs were defined as focal lesions greater than 3 mm that were hyperintense on T2-weighted imaging and fluid-attenuated inversion recovery imaging and, if subcortical, hypointense on T1 images.[15] MRI results were evaluated separately by A.M. (a neurosurgeon) and T.O. (a neuroradiologist) with regard to the presence or absence of SBI. The presence of SBI was established only when both A.M. and T.O. agreed on the diagnosis.

A case–control study for investigating the influence of the amount of daily coffee intake on SBI was conducted with these brain checkup participants. The participants were classified by self-administered questionnaires into 4 groups according to the number of cups of coffee consumed per day: noncoffee drinkers, small-amount drinkers (1-2 cups/day), medium-amount drinkers (3-4 cups/day), and large-amount drinkers (5 cups or more/day).[11] For the cross-sectional analysis, the standardized odds ratios (ORs) were calculated as approximate values of the relative risks of SBI for each parameter with 95% confidence interval (CI) in comparison with noncoffee drinkers (reference group) using the Pearson's chi-square test to analyze the relationship between SBI and independent variables, including 4 groups classified by the number of cups of coffee per day (as defined above); sex; age; occupation (classified into 4 categories including office workers, manual laborers, managers, and unemployed); history of HPT, hyperlipidemia, or DM; heavy smoking (≥20 cigarettes/day); and excessive alcohol consumption (≥30 g/day).

The unpaired *t*-test was used to analyze the difference between SBI and no SBI in continuous variables, including age, systolic blood pressure (SBP), and diastolic blood pressure (DBP) on the day of examination. The multivariate logistic regression analysis (upward analysis) was used to adjust for other risk factors and to generate OR as an estimate of relative risk, taking into account the prevalence of SBI as the dependent variable and factors with a *P* value less than .05 (as assessed using the chi-square test) as the independent variables. All *P* values were 2-sided. The PASW Statistics software version 17.0 (PASW, San Diego, CA) was used for statistical analyses of these data.

Results

The Case (SBI)–Control (No SBI) Study of 242 Brain Checkup Participants Whose Ages Were Less Than 65 Years

The average age ± standard deviation (SD) was 52.6 ± 8.0 years. The age distribution was 30-64 years. The average SBP ± SD was 120.1 ± 13.8 mmHg and the average DBP ± SD was 77.2 ± 10.3 mmHg. In 49 individuals who had SBI (20% of all), 34 had multiple SBIs (14% of all). All but 1 attendant with SBI had single or multiple lacunar infarcts and one had a small infarct in the right occipital lobe. Seventy participants were official workers (29%), 76 were manual laborers (31%), 35 were managers (14%), and 61 were unemployed (25%). Thirty-five participants were not married (14%).

The standardized ORs and 95% CIs calculated using the chi-square test revealed that in coffee drinkers who had 3 or more cups/day had a statistically significantly lower SBI prevalence rate (OR = .41, 95% CI = .22-.79, *P* = .007). Cross-sectional analyses separately for the 4 groups including no coffee drink, 1-2 cups/day, 3-4 cups/day, and 5 cups or more/day revealed that noncoffee drinkers had a statistically significantly higher SBI prevalence rate than the others (OR = 2.31, 95% CI = 1.16-4.63, *P* = .02) and 3-4 cups/day drinkers had a statistically significantly lower SBI prevalence rate than the others (OR = .33, 95% CI = .13-.89, *P* = .03). For other factors than coffee consumption, there were statistically significantly higher SBI prevalence rates in those with a history of HPT (OR = 3.89,95% CI = 1.93-7.87, *P* = .0001), those with a history of hyperlipidemia (OR = 2.32, 95% CI = 1.09-4.94, *P* = .03), and those who were unemployed (OR = 2.03, 95% CI = 1.03-3.97, *P* = .04).

The standardized ORs and 95% CIs calculated using the chi-square test in comparison with noncoffee drinkers (reference group) are displayed in Tables 1 and 2. Multivariate logistic regression analysis revealed that SBI (the dependent variable) was statistically significantly associated only with 3 independent variables including coffee intake of 3 or more cups/day, history of HPT, and unemployment (Table 3). After these results, the expected prevalence of SBI could be calculated using the following equation:

Table 1. *Standardized ORs and 95% CIs between the prevalence of SBI and each 4 types classified by the amount of daily coffee intake, calculated by the chi-square test (noncoffee drinker is set as the reference for ORs)*

Classification by amount of daily coffee consumption	Number	SBI (%)	OR	95% CI, *P* value
Noncoffee drinker (as a reference for ORs)	53	32.1	1	—
Coffee intake 3 or more cups/day	131	13.7	.41	.22-.79, .007*
Coffee intake 1-2 cups/day	58	24.1	.67	.29-1.55, .40
Coffee intake 3-4 cups/day	54	9.3	.22	.07-.64, .004*
Coffee intake 5 or more cups/day	77	16.9	.43	.19-.99, .043**

Abbreviations: CI, confidence interval; OR, odds ratio; SBI, silent brain infarction.
*$P < .01$; **$P < .05$.

Expected prevalence of SBI

$$= 1/[1 + e(-1.552 + (\text{unemployed}: .762, \text{the others}: 0)$$
$$+ (\text{HPT}: 1.440, \text{no HPT}: 0)$$
$$- (\text{coffee intake} \geq 3 \text{ cups/day}: -.851,$$
$$\text{coffee intake} < 3 \text{ cups/day}: 0)]$$

The Hosmer and Lemeshow test for goodness of fit demonstrated that the estimated values calculated using this equation fit well with the actually observed values ($P = .595$).

Analysis of Brain Checkup Participants Whose Ages Were 65 Years or Older

For 62 consecutive individuals whose ages were 65 years or older and who underwent brain checkups at Teikyo University Chiba Medical Center in the same study period (from June 2008 to June 2009), the factors in the ques-tionnaires which would have an effect on SBI prevalence were determined. The average age ± SD was 70.1 ± 3.8 years. The age distribution was 65-81 years. The average SBP ± SD was 127.5 ± 14.5 mmHg and the average DBP ± SD was 79.8 ± 8.2 mmHg. Twenty-eight (45%) had SBI and 26 (42%) had multiple SBI. Participants included 12 manual laborers (16.7%), 2 official workers (3%), 1 manager (1.6%), and 51 unemployed (82%). Upward logistic regression analysis revealed that SBI prevalence was statistically significantly associated only with history of HPT (OR = 4.3, $P = .008$, 95% CI = 1.5~12.9) and that there were no statistically significant difference between coffee consumption and SBI prevalence.

Discussion

Using data of brain screening examinations of 242 Japanese healthy adults under 65 years old, the present report

Table 2. *Standardized ORs and 95% CIs between 4 types classified by the amount of daily coffee intake and independent variables extracted from questionnaires of study attendants, calculated by the chi-square test (noncoffee drinker is used as a reference for ORs)*

Classification by amount of daily coffee consumption	HL (OR, 95% CI, *P* value)	HPT (OR, 95% CI, *P* value)	DM (OR, 95% CI, *P* value)	heavy smoker (OR, 95% CI, *P* value)
Noncoffee drinkers (as a reference for ORs)	—	—	—	—
Coffee intake 1-2 cups/day	1.63, .61-4.30, .35	1.96, .76-5.10, .24	2.41, .45-12.96, .44	2.00, .64-6.29, .28
Coffee intake 3-4 cups/day	.57, .18-1.88, .39	.70, .23-2.19, .58	3.80, .75-19.20, .16	2.74, .89-8.43, .11
Coffee intake 5 or more cups/day	1.14, .44-2.98, .81	1.59, .63-4.02, .37	2.96, .60-14.52, .20	4.62, 1.64-13.0, .003*

Classification by amount of daily coffee consumption	Excessive alcohol consumption (OR, 95% CI, *P* value)	Managers (OR, 95% CI, *P* value)	Unemployed (OR, 95% CI, *P* value)
Noncoffee drinkers (as a reference for ODs)	—	—	—
Coffee intake 1-2 cups/day	1.86, .79-4.40, .20	1.32, .39-4.43, .76	.57, .25-1.30, .22
Coffee intake 3-4cups/day	3.55, 1.51-8.31, .04**	3.36, 1.11-10.13, .04**	.51, .22-1.20, .14
Coffee intake 5 or more cups/day	1.95, .86-4.40, .12	1.27, .40-4.03, .78	.47, .21-1.03, .07

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HL, hyperlipidemia; HPT, hypertension; OR, odds ratio.
*$P < .01$; **$P < .05$.

Table 3. *Multivariate logistic regression analysis (with the upward selection technique)**

The independent variables	Coefficients	OR	95% CI, *P* value
Coffee intake 3 or more cups/day	−.85	.43	.22-.84, .01**
Unemployed	.76	2.14	1.05-4.38, .04*
History of HPT	1.44	4.22	2.03-8.80, .0001*
Percentage of correct classifications = 81.0%			

Abbreviations: CI, confidence interval; HPT, hypertension; OR, odds ratio.

*P < .01; **P < .05.

demonstrated that SBI was observed less frequently in those who consumed coffee 3 or more cups/day than in the other. With regard to stroke, Larsson et al[11] reported that low or no coffee consumption is associated with an increased risk of stroke in women and that high consumption of coffee and tea reduces the risk of cerebral infarction among men, independent of known cardiovascular risk factors, and furthermore, findings from a meta-analysis with 10,003 cases of stroke and 479,689 participants indicate that moderate coffee consumption may be weakly inversely associated with risk of stroke.[13] Liebeskind et al[14] analyzed data of the Third National Health and Nutrition Examination Survey (1988-1994) and concluded that heavier daily coffee consumption is associated with decreased stroke prevalence, despite smoking tendency in heavy coffee drinkers. However, a review of the literature available on MEDLINE revealed that no previous reports had analyzed the relationship between SBI prevalence and amount of daily coffee consumption.

We also found that unemployed middle aged individuals had more SBI than employed individuals. This would be explained by reduced spending for healthcare services under unemployment.[16]

Many dietary reports have demonstrated that nutrition may have a significant role in the prevention of stroke.[17] There is consistent evidence of an inverse association between the intake of fruits and vegetables and the risk of stroke.[18] Consuming at least 2 servings of fish per week may confer a protective effect by beneficial influence of ω3 lipid on atherosclerosis.[19] Several reports have demonstrated that tea consumption reduces the incidence of stroke.[11,12] However, the present report did not reveal that daily tea consumption affects the prevalence of SBI. We speculated that this is mainly because in Japan there are many daily tea drinkers, and that actually in this report 198 of 242 (81.8%) participants daily drank more than a cup of green and/or black tea and the number of nontea drinkers was so small to be statistically ana-

lyzed by contingency table analysis because of its statistically small power.

Although our analysis did not demonstrate the influence of smoking on SBI prevalence, we speculate that the large restraining effect of coffee intake on SBI prevalence may have overcome the aggravating effect of smoking. Smokers preferred to drink coffee (OR = 2.148, 95% CI = 1.259-3.667, *P* = .027).[14]

The percentage of constituents in roasted coffee beans are polysaccharides (37%-55%), lipids (9%-18%), proteins (11%-13%), minerals (3%-4.5%), chlorogenic acids (0%-5.5%), caffeine (.9%-2.4%), and trigonelline (.6%-1.2%).[20] The phenolic compounds of coffee (including chlorogenic acid) exhibit antioxidant activity and increase the resistance of LDL to oxidative modification.[21] Caffeine is a methylxanthine stimulant alkaloid that is widely used in over-the-counter diet pills, painkillers, and stimulants. Coffee consumption has been reported to be inversely associated with metabolic syndrome,[22] and chlorogenic acid and trigonelline reduce glucose and insulin responses in individuals with type 2 DM.[23] Eskelinen et al reported that individuals who drank 3-5 cups of coffee/day had the lowest risk of dementia/Alzheimer's disease (risk decreased by 65% in these individuals).[24,25] Trigonelline has been reported to facilitate the regeneration of dendrites and axons, in addition to improving memory, in Alzheimer's disease mouse models.[25] The preventive effects of coffee intake on SBI reflect the complex synergism of the various beneficial and healthy effects of coffee, as mentioned above.

In contrast, some authors have reported adverse effects of massive coffee intake, including spontaneous abortion,[26] short-term risk of acute myocardial infarction,[27] and increased risk of bladder cancer[28] and postmenopausal ovarian cancer.[29] Several authors have reported disadvantageous effects of coffee consumption in hypertensive patients. Hu et al[30] and Uiterwaal et al[31] separately reported that higher coffee intake significantly increases blood pressure in individuals with a history of HPT. Moreover, Hakim et al[32] revealed that consumption of coffee is associated with an increased risk of thromboembolic stroke in hypertensive men. Other side effects of coffee include insomnia, anxiety, tremor, nervous restlessness, palpitations, and headaches.

Clarification of the benefits and risks associated with daily coffee intake would help reduce the prevalence of SBI. Identification of the components of coffee that are most beneficial for preventing SBI is one of important future research goals.

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