Green Tea Consumption, Abdominal Obesity as Related Factors of Lacunar Infarction in Korean Women
PAMOS Study

연세대학교 보건대학원

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고 성 규

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지도 오 희 철 교수

이 논문을 보건학석사학위 논문으로 제출함

2004년 2월

연세대학교 보건대학원

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고 성규의 보건학 석사학위논문을 인준함

심사위원 오 희 철 인

심사위원 박 종 구 인

심사위원 손 태 용 인

연세대학교 보건대학원

2004년 2월

Abstract

Background and Purpose : Green tea is well recognized as a protective factor, and abdominal obesity as a risk factor, for cardiovascular disease. The relationship of green tea consumption, abdominal obesity, and interactive effects of both factors with lacunar infarction still remain unclear. Our purpose was to evaluate interaction of green tea consumption and abdominal obesity as related factors for lacunar infarction in Korean women.

Methods : A hospital-based, incident case-control study, restricted to women, was conducted from April 1, 2001 to August 31, 2003 in Korea. Cases (n=233) of first incident lacunar infarction were enrolled and matched by age to stroke-free hospital controls (n=204). All subjects were interviewed, examined and had anthropometric measurements. Odds ratios (ORs) of lacunar infarction were driven in multivariate analysis after adjustment for demographic factors, diet factors, conventional vascular risk factors and atheogenic index.

Results : Compared with the non green tea consumer and obese women group, only the green tea consumption and non obese women group had a protective effect of lacunar infarction when adjusted for age, and age plus diet factors (OR, 0.23; 95% CI, 0.09, 0.59; OR, 0.21; 95% CI, 0.08, 0.56 respectively), but lost their significance after adjustment for age, diet factors, vascular risk factors and full model included atherogenic index factors (OR, 0.32; 95% CI, 0.09 to 1.01; OR, 0.49; 95% CI, 0.12, 1.89 respectively).

Conclusions : The interaction of green tea consumption and non obesity have reduced risk of lacunar infarction, but not after adjustment for age, diet factors, vascular risk factors and atherogenic index. Also individually green tea consumption and abdominal obesity have failed to find an independent relationship with lacunar infarction after adjustment by all risk factors. Green tea consumption and green tea consumption with non obese group seemed to have a protective effect for lacunar infarction. In the results of our study, these results still remain controversial, and then we need further and larger study to get at the root of real causal effect of both relationships.

Key Word : case-control study, ischemic stroke, lacunar infarction, green tea consumption, abdominal obesity

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Introduction

Cerebrovascular disease was found to be the second largest leading cause of death, and a leading cause of chronic disability and morbidity in Korean women. As for the trend of the recent decade, even if the death rate by cerebrovascular disease decreased by 4.8 to 81.7 in 2002 from 86.5 (per 100 thousand population) in 1992, but still have kept up the second largest leading cause of death. In cerebrovascular disease subtypes, cerebral infarction is the most common subtypes and the incidence and prevalence have been increasing in Korea women (1). Cerebral infarction is categorized generally into three pathogenic mechanisms, atherosclerotic disease in extracranial and large intracranial arteries, embolism from the heart and intracranial small-vessel disease (lacunar infarcts) on the basis of the size and location of the affected cerebral arteries and on their pathogenesis (2). Because of differences in pathogenesis, prognosis, and treatments among cerebral infarction subtypes, risk factor assessment for each cerebral infarction subtype should be performed separately. Identification of the underlying cause helps researchers to group patients into specific subtypes for the study of prognosis, and, hopefully, may lead to improved treatments. Small-vessel disease, lacunar infarction, accounts for up to 25% of all ischemic strokes (3, 4).

In South Korea, recently people who concerned about their health promotion and prevention of disease consumed green tea, and It is well known that green tea extracts had a potent antioxidant property and could reduce free radical-induced lipid peroxidation. Systemic administration of green tea extracts immediately after ischemia had been shown to inhibit the hippocampal neuronal damage in the gerbil model of global ischemia (5). Also green tea might modulate serum cholesterol concentration, and enhance

human health because it could reduce the incidence of cardiovascular disease, cancer, and abdominal obesity in various experimental models (6). Early case-control studies of tea consumption found no association with CHD, MI or Stroke, but the lack of an effect might reflect the low prevalence of heavy tea consumption (7, 8). Some (9, 10), but not all (11-13), recent cohort studies reported an inverse association between tea and cardiovascular disease (14). But there were no studies on the relationship between just green tea consumption and lacunar infarction. The prevalence of Korean adult women who had abdominal obesity was rapidly increased and reached to 42% in 2003, in the same manner the prevalence of Americans women who were overweight or obese rapidly increased from 47% to 61% between 1980 and 1999 (15, 16). The impact of obesity on public health is a growing concern because obesity is well recognized to be related to many diseases such as type 2 diabetes mellitus, hypertension, dyslipidemia, gall bladder disease, respiratory disease, sleep apnea, cancer and cardiovascular disease (17, 18). The information about abdominal obesity as a risk factor for ischemic stroke is very limited (19-24), and few or no for lacunar infarction and to date, the relationship between abdominal obesity and lacunar infarction remains less clear.

The purpose of this study was to determine whether green tea consumptions and abdominal obesity, which have been on the increase in South Korea, were independently associated with increased or decreased risk of lacunar infarction, a large proportion of ischemic stroke, among Korean women. We also examined about the effect to the lacunar infarction of interaction between green tea consumptions and abdominal obesity.

Subjects and Methods

The PAMOS Study

The Prevention and Management of Stroke (PAMOS) Study, which ultimate object is to construct cohort for the study of 2nd attack incidence of ischemic stroke and to examine genetic risk factors in the area of epidemiology, is a hospital-based case-control study that examines risk factors for ischemic stroke in Korean women. This case-control study was conducted at the department of neurology, distributed nationwide five University Hospital, South Korea. The period of investigation was from April 1, 2001 to August 31, 2003.

Selection of Cases

This hospital-based case-control study was undertaken in 5 university teaching hospitals in South Korea (Seoul, Incheon, Wonju, Jeonju, Iksan). Consecutive 233 female hospitalized incident cases were prospectively enrolled between April 1, 2001 and August 31, 2003 with a first-ever lacunar infarction. This study was approved by the Institutional Review Board at main hospital, Sangji University Hospital and all participants provided written informed consents.

Research assistants majoring neurology of each hospital were trained to guarantee intra reliability of diagnosis, face to face interview, and anthropometric assessment among individuals. All hospitalized cerebral infarction patients were divided into subtypes and confirmed lacunar infarction on the basis of the Classification of Cerebrovascular disease III proposed by the National Institute of Neurological Disorders and Stroke. The definition of lacunar infarction of our study was cerebral infarction cases lack evidence of cerebral cortical impairment, cerebellar dysfunction and disturbance of

consciousness. Classification into this lacunar infarction also requires the presence of a relevant brain stem or subcortical hemispheric lesions with a diameter of <1.5 cm as demonstrated on CT or MRI brain scan (25). The diagnosis of stroke was made if reported on computed tomography (CT), magnetic resonance imaging (MRI), or cerebral angiography carried out within 3 weeks of the clinical event. Green tea consumption were obtained almost subjects, 231 cases, only two missing, but waist and hip circumferences were not obtained 56 subjects; therefore 177 cases were included in this analysis.

Selection of Controls

AS Control group, 203 consecutive subjects were identified from among those patients hospitalizing in the same hospitals for Orthopedic, ear, nose, throat, skin and Ophthalmic disorders unrelated to lacunar infaction and recruited during same period with case subjects. For the enrollment for control subject, we recruited female controls matched to 1 control by 5-year age band, hospital, and time of admission. Control subjects were eligible if they had never been diagnosed with a stroke. When a subject was recruited, the research objectives were explained and interviewed briefly to record age, and social economic status, life styles, green tea consumption, anthropometric measurements, conventional vascular disease risk factors. Green tea consumption were obtained all participants, 204 controls, and waist and hip circumferences were not obtained 80 controls; therefore 124 controls were included in this final analysis.

Ascertainments of Exposure to Related Factors of Cases and Controls

The study parameters were obtained from the both case patients and control participants, and the data were collected through face-to-face interviews by well trained research assistants to assess demographic, medical,

lifestyle, marital status, religions status, green tea consumptions, family history of stroke, smoking status, alcohol consumption, meat and vegetable intake frequency, and past history of hypertension. Past history of hypertension was confirmed by history of use of antihypertensive drug, and through biochemical analysis, fasting blood specimens for lipid, glucose, and cholesterol level were acquired. Total cholesterol and HDL cholesterol were measured according to standard practices (26, 27). Total cholesterol, LDL cholesterol, and HDL cholesterol was analyzed with classification criteria of Adult Treatment Panal III (ATP III) of National Cholesterol Education Program (NCEP), NHLBI (28). Fasting glucose was measured with a Hitachi 747 automated spectrometer (Boehringer) and lipid panels (including total cholesterol, LDL, HDL, and triglyceride) were measured with a Hitachi 705 automated spectrometer (Boehringer). Green tea consumption and other data were also assessed through structured interviews using questions according to questionnaire adapted and revised by PAMOS study group. Inquiries were made about consumptions of green tea both during the past year and on average during the participant's drinking lifetime. The defined responses regarding frequency allowed 6 possibilities ranging from never to 2 or more drinks per day. The responses for green tea consumption were then summed to obtain a total overall quantity. Inter and intra reliability were raised by training of researchers. Stroke-free controls were interviewed in person and evaluated in the same manner as cases. Standardized questions were developed and revised several times by PAMOS study meeting regarding the variables.

Anthropometric Assessment

Case and controls had waist and hip circumference measurements performed by trained research assistants. Participants were measured with standing and relaxed without heavy outer garments and among those cases

who were unable to stand, measurements were done supine. Waist circumference was measured with the participant standing with abdomen relaxed, arms at sides, and feet together without footwear. The research assistant faced the participant and measured with a tape to the nearest 0.5 cm in the horizontal plane on the bare skin at the level of the natural waist, the narrowest part of the torso at the end of a normal expiration. Hip circumference was measured with the participant standing in the same position around the buttocks in the horizontal plane at the largest circumference between the waist and thigh. The measurement was usually over the greater trochanters. Weight was measured to the nearest 0.5 kg, and height, to the nearest 0.5 cm. Participants did not wear shoes during height measurements. WHR was defined as waist divided by hip circumference.

Statistical Analyses

As an initial comparison of case patients and controls, status of green tea consumption, and status of abdominal obesity, univariate testing was done continuous variables using the Student t-test for comparisons between means and on categorical variables using chi-square tests for comparisons between values for categorical variables. The relationship between green tea consumption or WHR quartiles classified by control distributions and lacunar infarction was analyzed by simple and multiple conditional logistic regression models for matched case-control data and were used to calculate the odds ratio (OR) and 95% confidence interval (CI). Adjusted ORs were calculated after adjustment for potential confounding factors. For the logistic regression analyses, four models were estimated; model 1 adjusted only age factor; model 2, age and diet factors, model 3 included all of the variables in model 2 as well as conventional vascular risk factors, and model 4, included all factors,

age, diet factors, conventional vascular risk factors and atherogenic index, LDL/HDL ratio.

Results

The basic characteristics of the 233 stroke patients and the 204 controls were shown Table 1. There was no significant difference in age distribution between the controls and the cases, mean ages of controls and cases were 65.15±11.76 and 66.49 (10.72 years, respectively. Table 1, also showed the unadjusted odds ratios for the development of lacunar infarction for the two groups characteristics of particular interest, green tea consumption and waist hip ratio. Green tea consumptions were analyzed into three categorization methods, yes or no, above or below of one cup per day, and none, <1 cup a week, <1 cup a day, >=1 cup a day, and all classifications of green tea consumption had protective effects of lacunar infarction, the odds ratio were 0.58, 0.49 and 0.43~0.67 (95% CI, 0.37~0.93, 0.26~0.94, and 0.19~1.43) respectively. In waist hip ratio, cases were more common than controls significantly, as a risk factor, the odds ratio of waist hip ratio was 1.97 (95% CI, 1.23~3.17), but in our study population, BMI was not significantly associated with lacunar infartion, in fact, BMI had a slight inverse association with ischemic stroke. These patterns of findings had been noted by others (24). Coffee consumption, meat intake frequency, vegetable intake frequency were not different their frequencies between two groups, but current smoking, current drinking, family history of stroke, marital status of separated by death, past history of hypertension, high total cholesterol, high low density lipoprotein were more common, and atherogenic index was higher among the case subjects, while religious status were more prevalent among the controls.

To assess for other confounding factors that may have affected green tea consumptions and the level of waist hip ratio in our study subjects, we simply performed analyses of association of green tea consumption and other risk factors and between abdominal obesity and other risk factors. The

associations of green tea consumptions classified by yes or no with other risk factors were shown in Table 2. A significant association of green tea consumption with meat intake frequency, vegetable intake frequency, smoking status, drinking status, marital status, and high HDL cholesterol were observed. But WHR, BMI, and other factors were also not different significantly. In Table 3, we analyzed our data according to abdominal obesity important risk factors of lacunar infarction. Participants were divided into two groups, abdominal obesity group and non obesity group by median based on the waist-hip ratio of the distribution of control group, none obese was defined below of 0.9157, obese was above 0.9158. Among the 170 abdominal obese group, vegetable intake frequency, drinking, past history of hypertension, high total cholesterol, high LDL cholesterol levels and LDL-C/HDL-C ratio were higher than controls significantly, and green tea consumptions, coffee consumptions, meat intake frequency, smoking, marital status, family history of stroke, religion status were similar between two groups.

We also analyzed of the associations between the green tea consumptions and risks of lacunar infarction in Table 4. The methods of adjustment were analyzed separately with four models for analysis, for age (Model 1), age plus diet factors, such as coffee consumptions, meat and vegetable intake frequencies (Model 2), and Model 3 was added conventional vascular risk factors, such as, smoking status, drinking status, family history of stroke, religion status, marital status, past history of hypertension to Model 2, and Model 4, also adjusted for age, diet factors, vascular risk factors and atherogenic index (low density lipoprotein cholesterol/high density lipoprotein cholesterol. Engaging in any green tea consumptions were independently related to a reduced risk of lacunar infarction after adjustment for age, diet factors, cardiovascular factors, and athrogenic index (LDL-C/HDL-C) even though, not significant, but the trends of ORs for green tea consumptions were in the protective direction. Especially, when we used the no-consumption

group as a reference, heavy green tea consumption groups, above one cup a day, seen protective effects in unadjusted model and model 1 and 2 (ORs=0.47, 0.48, and 0.43; CIs=0.24~0.90, 0.25~0.93, and 0.22~0.84 respectively). In all models, except for model 3, heavy green tea consumption group appeared significant protective than light-moderate green tea consumption groups, below one cup a day, suggesting a dose-response relationship between the intensity of green tea consumptions and lacunar infarction.

In Table 5, the variable of one of two primary interests, WHR, quartiles based on the distributions among control participants, was also adjusted and analyzed separately with four models. Unadjusted for other risk factors, a risk effect was seen for lacunar infarction in obese women patient (OR, 1.97; 95% CI, 1.22~3.17). In multivariable analysis, adjusted for age only (Model 1), age and diet factors (Model 2) were similar to unadjusted analysis (ORs, 2.00, 1.74; 95% CIs, 1.22~3.26, 1.05~2.89), but adjusted age, diet factors, conventional vascular factors (Model 3), and age, diet factors, vascular risk factors, LDL/HDL ratio (Model 4) were not significant, but it shown the risk trends.

With the results of Table 1 to 5, we knew that waist hip ratio was a potential risk factor of lacunar infarction, and green tea consumption was a potential protective factor of lacunar infarction. So, we supposed that green tea consumption and waist hip ratio would have interaction, because the results of table 2 and 3 showed that they didn't have correlations and in table 4 and 5 they appeared to be a potential protective and risk factor of lacunar infarction. In table 6, we simply combined abdominal obesity status based on the waist-hip ratio of the distribution of control group and green tea intake status based on current consumer or non consumer, and simply analyzed the difference of frequencies by using cross tabs. Abdominal obesity was divided by two

methods, one was by abdominal obese and non obese woman, the other was by quartiles of WHR based on the distribution of control group. The distribution of green tea intake status and abdominal obesity status combinations were significantly different. In control groups, current green tea consumer and non obese woman was more common, and in case groups, green tea non consumer and obese women combination was more frequent.

The interactive effects of current green tea intake and non obese women were analyzed simultaneously using a binary logistic regression analysis adjusted for age, diet factors, conventional vascular risk factors, and atherogenic index with each model 1 to 4. Especially our results showed statistical significance in case of current green tea consumer and non obese combination group compared to green tea non consumer and obese women combination group in unadjusted, adjusted model 1 and 2. Supposing that green tea consumer and obese women combination group showed decreased ORs, but not significant, in all models compared to non consumer, obese group. For model 3 and model 4, even if the trend of protective effect was seen, the protective effects were lost their statistical significance. A dose-response relationship was observed in current green tea consumer and obese combination group, but in the green tea consumer and non obese group lost their significance as well as increased the ORs.

Table 1. Distribution of Basic Characteristics of Cases and Controls in PAMOS Study.

Variable		Controls (n=233)	Cases (n=204)	ORs $ (95% CI)	P value
Age at screening, mean(SD), y		65.15 (11.76)	66.49 (10.72)	1.01(0.00~1.03)	0.118
Green tea consumption (n, %)	No	169(73.1)	168(82.4)	0.58(0.37~0.93)	0.023
	Yes	62(26.1)	36(17.6)		
Green tea consumption/day (n, %)	< 1	199(86.1)	189(92.6)	0.49(0.26~0.94)	0.032
	>= 1	32(13.9)	15(7.4)		
Green tea consumption (n, %)	None	169(73.2)	168(82.4)		0.051
	<1 cup a day	30(13.0)	21(10.3)	0.70(0.38~1.27)	0.250
	>=1 cup a day	32(14.8)	15(7.3)	0.47(0.24~0.90))	0.023
WHR # (n, %)	Non obese women	89(50.3)	42(31.6)	1.97(1.23~3.17)	0.005
	Obese women	88(49.7)	82(69.4)		
BMI £ (n, %)	Non obese women	94(52.5)	60(47.6)	1.22(0.77~1.92)	0.400
	Obese women	85(47.5)	66(52.4)		
Coffee consumption (n, %)	No	109(47.2)	99(48.7)	0.97(0.66~1.44)	0.888
	Yes	122(52.8)	104(51.3)		
Meat intake frequency, day (n, %)	< 1	124(54.6)	106(52.2)	1.10(0.75~1.61)	0.617
	>= 1	103(45.4)	97(47.7)		
Vegetables intake frequency, day(n, %)					
	< 1	32(14.0)	36(17.6)	0.76(0.45~1.27)	0.295
	>= 1	197(86.0)	68(82.4)		
Smoking (n, %)	Never	202(87.5)	170(84.2)		0.617
	Past	13(5.6)	14(6.9)	1.28(0.59~2.80)	0.535
	Current	16(6.9)	18(8.9)	1.34(0.66~2.70)	0.419
Drinking (n, %)	Never	182(78.8)	135(66.2)		0.007
	Past	21(9.0)	22(10.8)	1.41(0.75~2.67)	0.289
	Current	28(12.2)	47(23.0)	2.26(1.35~3.80)	0.002
Family history of Stroke (n, %)	No	195(85.2)	127(62.6)	3.43(2.16~5.44)	<0.001
	Yes	34(14.8)	76(37.4)		
Marital status	Current marriage	141(63.2)	100(49.8)	1.74(1.18~2.56)	0.005
	Separated by death	82(36.8)	101(50.1)		
Religion (n, %)	No	56(24.5)	69(35.4)	0.59(0.38~0.90)	0.014
	Yes	173(75.5)	126(64.6)		
Past history of Hypertension (n, %)	No	107(74.8)	55(27.0)	8.01(4.57~13.09)	<0.001
	Yes	36(25.2)	137(73.0)		
TC, mean±SD, mg/dL	~ <200	78(62.4)	94(47.0)		0.002
	200~<240	38(30.4)	63(31.5)	1.38(0.83~2.27)	0.213
	240 ~	9(7.2)	43(21.5)	3.96(1.82~8.64)	0.001
LDLC, mean±SD, mg/dL	~ <100	47(38.5)	32(16.1)		<0.001
	100~<130	39(32.0)	73(36.7)	2.75(1.52~4.98)	0.001
	130~<160	25(20.5)	54(27.1)	3.17(1.65~6.10)	0.001
	160~<190	8(6.6)	29(14.6)	5.32(2.16~13.13)	0.015
	190 ~	3(2.5)	11(5.5)	5.39(1.39~20.84)	<0.001
HDLC, mean±SD, mg/dL	~ <40	53(42.7)	78(39.2)		0.799
	40~<60	62(50.0)	107(53.8)	1.17(0.73~1.87)	0.505
	60 ~	9(7.3)	14(7.0)	1.06(0.43~2.62)	0.905
LDL-C/HDL-C €, mean(SD)		2.71(0.87)	3.13(1.06)	1.57(1.22~2.02)	<0.001

WHR, Waist-Hip Ratio = circumference of waist over hip, based on the distributions of controls. Non obese < 0.9157, obese > 0.9158. £ BMI, Body Mass Index, Non obese < 25kg/m^2, obese >=25kg/m^2.

$ ORs = Odds Ratios, & p-value of Chi-square test, student t-test, linear trend, € LDL-C/HDL-C, Atherogenic index = Low density lipoprotein cholesterol/High density lipoprotein cholesterol. TC=Total cholesterol, LDL-C=Low density lipoprotein cholesterol, HDLC=High density lipoprotein cholesterol.

Table 2. General Characteristics and Conventional Vascular Risk Factors by Green Tea Consumption.

Variable		Green tea No (n=337)	Green tea Yes (n=98)	P value
Age at screening, mean(SD), y		66.70(10.20)	63.59(12.44)	0.025
WHR (n, %)	Non obese women	95(41.7)	36(49.3)	0.279
	Obese women	133(58.3)	37(50.7)	
BMI (n, %)	Non obese women	108(46.8)	46(62.2)	0.023
	Obese women	123(53.2)	28(37.8)	
Coffee consumption (n, %)	No	215(63.8)	55(56.7)	0.204
	Yes	122(36.2)	42(43.3)	
Meat intake frequency, day (n, %)	< 1	190(57.0)	40(41.2)	0.006
	>= 1	143(43.0)	57(58.8)	
Vegetables intake frequency, day(n, %)	< 1	44(13.1)	24(24.7)	0.005
	>= 1	292(86.9)	73(75.3)	
Smoking (n, %)	Never	293(87.5)	79(80.6)	0.004
	Past	14(4.2)	13(13.3)	
	Current	28(8.3)	6(6.1)	
Drinking (n, %)	Never	248(73.6)	69(70.4)	0.037
	Past	27(8.0)	16(16.3)	
	Current	62(18.4)	13(13.3)	
Family history of Stroke (n, %)	No	252(75.2)	70(72.2)	0.543
	Yes	83(24.8)	27(27.8)	
Marital status	Current marriage	179(59.7)	62(66.6)	0.043
	Separated by death	151(40.3)	32(34.0)	
Religion (n, %)	No	103(31.3)	22(23.2)	0.125
	Yes	226(68.7)	73(76.8)	
Past history of Hypertension (n, %)	No	124(48.1)	38(49.4)	0.897
	Yes	134(51.9)	39(50.6)	
TC, mean±SD, mg/dL	~ <200	133(52.4)	39(54.9)	0.870
	200~<240	79(31.1)	22(31.0)	
	240 ~	42(16.5)	10(15.1)	
LDLC, mean±SD, mg/dL	~ <100	60(23.9)	19(27.1)	0.923
	100~<130	86(34.3)	26(37.1)	
	130~<160	64(25.5)	15(21.4)	
	160~<190	30(12.0)	7(10.0)	
	190 ~	11(4.6)	3(5.4)	
HDLC, mean±SD, mg/dL	~ <40	103(40.9)	28(39.4)	0.033
	40~<60	136(54.0)	33(46.5)	
	60 ~	13(5.1)	10(14.1)	
LDL-C/HDL-C, mean(SD)		3.00(1.03)	2.86(0.94)	0.306

Table 3. General Characteristics and Conventional Vascular Risk Factors by Waist Hip Ratio.

Variable		Non obese women(n=131)	Obese women (n=170)	P value
Age at screening, mean(SD), y		62.08(12.18)	67.80(9.68)	<0.001
Green tea consumption (n, %)	No	95(73.1)	133(82.4)	0.279
	Yes	36(26.1)	37(17.6)	
Green tea consumption/day (n, %)	< 1	109(83.2)	151(88.8)	0.177
	>= 1	22(16.8)	19(11.2)	
Green tea consumption (n, %)	None	95(72.5)	133(78.2)	0.362
	<1 cup a day	14(10.7)	18(10.6)	
	>=1 cup a day	22(15.8)	19(11.2)	
Coffee consumption (n, %)	No	73(55.7)	98(58.0)	0.695
	Yes	58(44.3)	71(42.0)	
Meat intake frequency, day (n, %)	< 1	70(54.7)	78(45.9)	0.132
	>= 1	58(45.3)	92(54.1)	
Vegetables intake frequency, day(n, %)	< 1	13(10.1)	37(22.8)	0.007
	>= 1	116(89.9)	133(78.2)	
Smoking (n, %)	Never	118(90.0)	141(83.4)	0.251
	Past	6(4.7)	13(7.7)	
	Current	7(5.3)	15(8.9)	
Drinking (n, %)	Never	96(73.3)	133(78.2)	0.071
	Past	8(6.1)	17(10.0)	
	Current	27(20.6)	20(11.8)	
Family history of Stroke (n, %)	No	103(78.6)	126(75.5)	0.519
	Yes	28(21.4)	41(24.5)	
Marital status	Current marriage	76(62.3)	90(65.2)	0.099
	Separated by death	46(37.7)	48(34.8)	
Religion (n, %)	No	32(25.6)	50(30.0)	0.309
	Yes	98(75.4)	117(70.0)	
Past history of Hypertension (n, %)	No	56(62.2)	50(41.0)	0.003
	Yes	34(37.8)	72(59.0)	
TC, mean±SD, mg/dL	~ <200	56(66.7)	48(41.7)	0.001
	200~<240	21(25.0)	42(36.6)	
	240 ~	7(8.3)	25(21.7)	
LDLC, mean±SD, mg/dL	~ <100	27(32.1)	16(14.2)	0.001
	100~<130	34(40.5)	38(33.6)	
	130~<160	18(21.4)	33(29.2)	
	160~<190	2(2.4)	19(16.8)	
	190 ~	3(3.6)	7(6.2)	
HDLC, mean±SD, mg/dL	~ <40	37(35.7)	50(43.9)	0.749
	40~<60	42(50.0)	54(47.4)	
	60 ~	5(14.3)	10(8.7)	
LDL-C/HDL-C €, mean(SD)		2.75(1.06)	3.23(1.04)	0.002

WHR, Waist-Hip Ratio = circumference of waist over hip, based on the distributions of controls. Non obese < 0.9157, obese > 0.9158.

Table 4. Associations of Green Tea Consumption Status with Other Risk Factors.

	Level of Green tea intake		
Models	none	<1 cup per day ORs (95% CIs)	>= 1 cup per day ORs (95% CIs)
	1.0	0.70 (0.38, 1.27)	0.47 (0.24, 0.90)
Age **a**	1.0	0.72 (0.39, 1.32)	0.48 (0.25, 0.93)
Age+diet factors **b**	1.0	0.66 (0.36, 1.24)	0.43 (0.22, 0.84)
Age+diet factors +vauscular risk factors **c**	1.0	0.30 (0.08, 1.19)	0.66 (0.22, 1.96)
Age+diet factors+vascular risk factors+LDL/HDL ratio **d**	1.0	0.56 (0.10, 3.38)	0.30 (0.16, 1.77)

a Model 1, the odds ratio adjusted for age, the 95% confidence interval is for this odds ratio.

b Model 2, the odds ratio also adjusted for age, and diet factors, such as, coffee consumption, meat and vegetable intake frequencies.

c Mode 3, the odds ratio also adjusted for age, diet factors, and vascular risk factors, such as, smoking status, drinking status, family history of stroke, religion status, marital status, past history of hypertension.

d Model 4, the odds ratio also adjusted for age, diet factors, vascular risk factors and atherogenic index (low density lipoprotein cholesterol/high density lipoprotein cholesterol).

Table 5. Associations of Abdominal Obesity Represented by WHR with Other Risk Factors.

	Abdominal Obesity Status	
Models	Non obese, n=177	Obese, n=124, ORs (95% CIs)
	1.0	1.97 (1.22, 3.17)
Age **a**	1.0	2.00 (1.22, 3.26)
Age + diet factors **b**	1.0	1.74 (1.05, 2.89)
Age + diet factor + vascular risk factor **c**	1.0	0.98 (0.45, 2.11)
Age+diet factor +v ascular risk factor + LDL-C/HDL-C ratio **d**	1.0	0.68 (0.27, 1.66)

a Model 1, the odds ratio adjusted for age, the 95% confidence interval is for this odds ratio.

b Model 2, the odds ratio also adjusted for age, and diet factors, such as, green tea consumption, coffee consumption, meat and vegetable intake frequencies.

c Mode 3, the odds ratio also adjusted for age, diet factors, and vascular risk factors, such as, smoking status, drinking status, family history of stroke, religion status, marital status, past history of hypertension.

d Model 4, the odds ratio also adjusted for age, diet factors, vascular risk factors and atherogenic index (low density lipoprotein cholesterol/high density lipoprotein cholesterol).

Table 6. Distribution Divided by Green Tea Consumption and Abdominal Obesity Status of Cases and Controls Groups.

Variable		Controls (n=233)	Cases (n=204)	P value
Green tea No	+ WHR > 50%	67	66	0.015
Green tea No	+ WHR < 50%	61	34	
Green tea Yes	+ WHR > 50%	21	16	
Green tea Yes	+ WHR < 50%	28	8	
Green tea No	+ WHR 1st Q	29	12	0.049
Green tea No	+ WHR 2nd Q	32	22	
Green tea No	+ WHR 3rd Q	34	38	
Green tea No	+ WHR 4th Q	33	28	
Green tea Yes	+ WHR 1st Q	15	2	
Green tea Yes	+ WHR 2nd Q	13	6	
Green tea Yes	+ WHR 3rd Q	10	9	
Green tea Yes	+ WHR 4th Q	11	7	

Table 7. Association of Lacunar Infarction With Interaction of Green Tea Consumption and Abdominal obesity.

	Level of Green tea intake and abdominal obesity		
Models	Green tea No+ WHR > 50%	Green tea Yes+ WHR > 50% ORs(95% CIs)	Green tea Yes+ WHR < 50% Ors(95% CIs)
		0.77(0.37, 1.61)	0.29(0.12, 0.68)
Age **a**	1.0	0.75(0.35, 1.57)	0.23(0.09, 0.59)
Age+diet factor **b**	1.0	0.57(0.26, 1.27)	0.21(0.08, 0.56)
Age+diet factors+vascular risk factors **c**	1.0	0.42(0.12, 1.45)	0.32(0.09,1.01)
Age+diet factors+vascular risk factors+LDL/HDL ratio **d**	1.0	0.34(0.08, 1.42)	0.49(0.12, 1.89)

a Model 1, the odds ratio adjusted for age, the 95% confidence interval is for this odds ratio.

b Model 2, the odds ratio also adjusted for age, and diet factors, such as, coffee consumption, meat and vegetable intake frequencies.

c Mode 3, the odds ratio also adjusted for age, diet factors, and vascular risk factors, such as, smoking status, drinking status, family history of stroke, religion status, marital status, past history of hypertension.

d Model 4, the odds ratio also adjusted for age, diet factors, vascular risk factors and atherogenic index (low density lipoprotein cholesterol/high density lipoprotein cholesterol).

Discussion

In this hospital-based case-control study among Korean women, we studied the association between lacunar infarction and related factors. We particularly analyzed the association between green tea consumption and lacunar infarction, the relationship of waist-hip ratio and lacunar infarction, and then the interactive effects of green tea consumption and status of abdominal obesity by waist-hip ratio level based on the distribution of control participants to the lacunar infarction using multivariate analysis.

Recent years, green tea consumption have been in an increase in quantity in South Korea due to the increase in number of persons interested in prevention of diseases and health promotion. Green tea partly proved to be inversely associated with the risk of lacunar infarction with a significant reduction among higher green tea consumer, drinking >= 1 cup a day, when unadjusted, adjusted for age (model 1) and adjusted for age plus diet factors, such as coffee consumption, meat, and vegetable consumption (model 2), relative to the reference, non consumer. The odds ratio was 0.47 for univariate analysis (95% CI, 0.24, 0.90), 0.48 for model 1 (95% CI, 0.25, 0.93), 0.43 for model 2 (95% CI, 0.22, 0.84), while when it was adjusted for age, diet factors plus smoking status, drinking status, family history of stroke, marital status, religion status and past history of hypertension as conventional vascular risk factors (model 3) and adjusted for model 3 plus atherogenic index, Low density lipoprotein cholesterol/high density lipoprotein cholesterol ratio, (model 4), the OR were 0.66 (95% CI, 0.22,1.96), and OR=0.30 (95% CI=0.16,1.77. Supposing that significant associations of high green tea consumption and lacunar infarction were shown in unadjusted model and adjusted model 1 and 2, they were lost their significance after adjustment for model 3 and 4, but model 3 and model 4 showed to have the reduction of

28~70%, maintaining the trend of reduction of risk, even if they lost their significance. Among those green tea consumption <1 cup a day groups also appeared to have beneficial protective effects on lacunar infarction, in all models, 1 to 4, even if they didn't show statistically significant reduction of the risks of this disease. Abdominal obesity was appeared not to be associated with lacunar infarction in our data. Abdominal obesity was defined by a high waist hip ratio, well presenting abdominal obesity, based on the distributions among control participants. Our results had mixed outcomes, abdominal obesity showed risk effect significantly on the lacunar infarction in model 1 and 2, with 74~100% rise, but in model 3 and 4, they lost their significance and rather show protective tendencies than show risk tendency.

We found that green tea consumption and low waist hip ratio showed a significant synergistic interaction for the prevention of lacunar infarction, in univariate analysis (OR;0.29, 95% CI;0.12,0.68) and in multivariate analysis, when adjusted for age (model 1, OR;0.23, 95% CI;0.09,0.59), for age plus diet factors (model 2, OR;0.21, 95% CI;0.08-0.56). But after adjustment for age, diet factors plus smoking status, drinking status, family history of stroke, marital status, religion status and systolic and diastolic blood pressure as conventional vascular risk factors (model 3, OR;0.32, 95% CI;0.09,1.01), and full model, LDL/HDL addition to model 3 (model 4, OR;0.49, 95% CI;0.12,1.89), these data didn't show a statistical significance.

These investigations have lots of strengths compared with previous studies. Up to now, there were no studies on the interactive effects of green tea consumption and abdominal obesity as the related factors of the lacunar infarction. Most previous studies on the green tea consumption had an important limitation, which was imprecision of the exposure measurements. These studies referred simply to tea, including all kinds of teas, usually comprising a heterogeneous group of beverage, including fermented black tea,

half fermented oolongs, unfermented green tea, and sweetened ice tea, and it might even be understood to include fruit tea or herbal teas (29). Just only study for association of green tea and stroke from Japan (30) included all subtypes of stroke, not for only lacunar infarction.

The measurement of waist circumference alone is a simple indicator of abdominal obesity but has not been found to be a good predictor of stroke in other studies (24, 31), and these results were same with our results. Another obesity index, BMI have reported that they had a slight inverse association with ischemic stroke (31), but BMI was not significantly associated with ischemic stroke, in our outcomes, table 1 showed that there were no association between lacunar infarction and BMI. A measurement of WHR may be a more useful method to assess abdominal fat accumulation and a better predictor of an increased risk for stroke than BMI or waist circumference. Because WHR is a more difficult measure to standardize in the clinic compared with BMI and to measure in large persons, it has been used less extensively in practice. Despite these limitations, the value of WHR argues for adding this measurement to vascular risk assessments (32).

On the basis of several in vitro and in vivo studies, green tea and compounds of green tea catechins have shown considerable promise in reducing the risk of ischemic stroke by changes in polyamine levels (33), inhibition of ischemic damage (5, 34), or estrogen-like activity (35), inhibiting H_2O_2 or ferrous ion-induced lipid peroxidation (36). By these in vitro, in vivo study results, we could offer two possible explanations for the inverse association between tea and the reduced risk of lacunar infarction of our study. First, flavonoids in green tea may reduce ischemic infarction by inhibiting low density lipoprotein cholesterol oxidation (11), reducing platelet aggregation (37), or reducing ischemic damage (34). Some mechanisms have been proposed for the association between abdominal obesity and cardiovascular

risk factors. Increased peripheral concentrations of insulin (38) and increased triglyceride concentration (39), and associated with abdominal obesity, might be due to the direct deposition of free fatty acids into the portal vein from intra-abdominal adipocytes. Also elevated blood pressure (40) and metabolic syndrome may be associated with abdominal obesity (32). Uncomplicated abdominal obesity is related to endothelial dysfunction, an early marker of atherosclerotic disease (41) as well as platelet activation through enhanced lipid peroxidation and inflammation (42).

In human studies, the effects of green tea for prevention of ischemic stroke were not identical. Hertog et al (9) reported reductions in fatal and nonfatal stroke in 522 older Dutch men initially free of stroke in the highest tertile of flavonoid intake comprising 61% of black tea as the major food source. And another study of 10054 Finnish subjects indicated an association between higher flavonoid intake and a lower risk of cerebrovascular mortality (43). But as different reports, Sesso et al (14) study showed that increasing tea intake was not associated with the risk of CVD which including stroke, with a no significant linear trend (P=0.36), and another study of Sesso et al (44) showed only among highest tea intake consumer, >=4 cups a day, referent to none tea consumer, had protective effects of tea intake on vascular events, including stroke, the relative risks (RRs) was 0.33 (95% CI, 0.14, 0.80). Another population-based cohort form Finland showed no association between quercetin and stroke in women (45) with ORs in increasing quartiles of 1.00 (reference), 1.02, 1.18, and 0.33 for important vascular events, including stroke, in the Women's Health Study (WHS) – which indicate the lack of significant linear trend (P=0.07) (44). These results parallel the shape of reduction association noted for tea and lacunar infarction in our study, 0.56 and 0.30 in full model adjustment. Although our results didn't show significant difference between green tea consumption and lacunar infarction, a true inverse association may have been

masked because of the low prevalence of heavy tea consumption of control 32, case 15, or because of potential recall, information, or selection biases. And another reason, we could guess that higher tea consumption might be a surrogate for a healthier lifestyle.

Because of the association of obesity with conventional risk factors for cardiovascular disease, many studies have found a positive association between obesity and the risk of fatal and nonfatal stroke, range from 1.5 to 2.0 of RRs and recent studies have also assessed measurements of the distribution of body fat as predictors of stroke, specially the waist-hip ratio (46-49). But in some cohort studies, WHR was no longer an independent risk factor for stroke after adjustment for hypertension and blood lipid levels (50, 51), an association between metropolitan relative weight and atherothrombotic stroke was found in women but not in men (19). These previous study results were corresponding to our study results. But the number of events in these cohort studies and our case-control study were small, so we need to further and large human research to demonstrate our results authentically.

Several important limitations of this study should be considered. First, our study was a case-control study rather than prospective cohort study. The hospital-based approach of this case-control study design matched by age, and restricted to women, help to minimize the potential biases often associated with case-control studies. Some control selection bias could have existed, but the distribution of WHR and green tea consumption were similar to other study distribution in Korea, implying that control selection bias was less likely. Second, WHR as anthropometric measurement was performed after hospitalization, so might not accurately reflect the premorbid status of obesity because weight and waist and hip circumferences could be changed by inadequate nutritional intake after acute stroke. However, we made special efforts to collect anthropometric questionnaire data within 72 hours after stroke,

and it is unlikely that significant changes in waist or hip measurements would have occurred in that time. Measurement error may also have occurred because WHR was measured in the supine position in some cases that were unable to stand. In a pilot study, waist circumferences measured when supine were slightly smaller than when measured standing, whereas hip circumferences did not differ by position measured. Therefore, measurement errors in WHR because some cases could not stand would have led to an underestimation of the OR. Third, misclassification on green tea consumption might have occurred, but in Korea, green tea producing districts were rare, the variance of tea content would not big. Finally, alternatively, higher tea consumption may be a surrogate for a healthy lifestyle. Our data suggest that tea consumers differ from nonconsumers in terms of health behaviors and medical conditions. Nevertheless, adjustment for neither coronary risk factors nor individual lipids changed the risk estimates.

In summary, in our results we got two results, the first was that the interaction of green tea consumer and low WHR group had significant protective effects when adjusted for only age, and age plus diet factors, while for full models, non significant reduction of the risk of lacunar infarction. In adjustment of full model, the insignificant interaction effect of green tea consumption and abdominal obesity was considered that the past history of hypertension and athreogenic index had affected the results because they had a possibility of mediator of lacunar infarction. The second, green tea consumption was seemed more strong protective effects than non obese women in the results of our study, both interaction analysis and individual multivariate analysis. More data from prospective cohort studies will help to distinguish whether the interaction of tea consumption and low WHR has a true biological effect or serve as a surrogate for a risk profile promoting lower lacunar infarction risk.

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Acknowledgement

Incident lacunar infarction cases and age matched controls were collected by PAMOS (Prevention And Management Of Stroke) study, which is conducted by Sangji University Oriental Hospital, Kyungwon University Seoul Oriental Hospital, Kyungwon University Incheon Oriental Hospital. I am grateful to all PAMOS team, especially O.M.D, Ph. D. JH Park, O.M.D, Ph. D. CY Jeon.

국문초록

소공성경색 관련인자로서의 녹차의 섭취와 복부비만

연세대학교 보건대학원

역학 및 건강증진학과

고 성 규

연구배경 및 목적 : 녹차는 심혈관계질환의 보호인자로, 그리고 복부비만은 위험인자로 많이 연구되어지고 있으나, 허혈성뇌졸중 중 특히 소공성경색에 대해서는 아직 연구되어진바 없다. 또 소공성경색에 영향을 미치는 녹차와 복부비만의 상호작용에 대해서 역시 연구된 바가 없어, 이번 연구를 통해 녹차, 복부비만, 그리고 두 인자의 상호작용에 의한 소공성경색과의 인과관계에 대해 규명하고자 하였다.

연구대상 및 방법 : 2001 년 4 월부터 2003 년 8 월까지, 한국인 여성을 대상으로 환자대조군 연구를 수행하였다. 5 곳의 한의과대학 부속병원에서 233 명의 처음 발병한 소공성경색환자와 연령별 짝짓기를 한 204 명의 소공성경색과 관련되지 않은 대조군이 선정되었다. 모든 자료는 검사자간 신뢰도를 제고한 전공의에 의해

설문지, 인터뷰, 신체계측 및 생화학적 검사를 통해 모아졌으며, 로지스틱회귀분석에 의해 다양한 모델의 혼란변수를 통제하여 분석하여졌다.

연구결과 : 녹차를 마시지 않으면서 복부비만을 가진 군에 비해, 녹차를 마시면서 복부비만이 없는 군의 경우, 연령만 보정한 경우와 연령 및 식이요인을 보정한 경우 유의한 수준에서 소공성경색에 대한 보호효과를 가졌으나 (OR, 0.23; 95% CI, 0.09, 0.59; OR, 0.21; 95% CI, 0.08, 0.56), 연령, 식이요인, 심혈관위험요인을 보정한 경우와 거기에 더해 지질인자를 보정한 경우에는 위험비를 떨어뜨리긴 했으나 통계적인 유의성은 없었다 (OR, 0.34; 95% CI, 0.08, 1.42; OR, 0.49; 95% CI, 0.12, 1.89). 각각 녹차와 복부비만을 독립적으로 보았을 경우, 녹차의 경우 상호작용을 고려한 경우와 비슷한 결과를 보였으나 복부비만의 경우 위험요인으로 모든 보정의 예에서 유의성을 보이지 않았다.

결론 : 소공성경색에 대해 녹차와 복부비만이 상호작용을 가지는 것으로 보이나, 모든 혼란요인을 통제한 상태에서는 유의성을 잃었다. 상호작용을 잃은 이유에 대해서는, 만성적인 질환인 소공성경색이 단 하나의 요인, 즉 녹차의 섭취나 복부비만 등의 요인에 의해 유의수준을 가질 정도의 위험요인으로 작용하기는 어렵다고 볼 수도 있으며, 또 하나는 소공성경색의 위험인자로 보정된 고혈압 및 지질인자 등이 위험인자가 아닌 중간인자로서 작용을 할 수 있다는 점을 고려할 때, 과잉보정의 문제를 생각할 수 있다.

한편, 독립적으로 녹차와 복부비만이 소공성경색에 미치는 영향을 분석한 경우, 녹차가 상호작용에 미치는 요인이 큰 것으로 보인다. 녹차만의 경우와 녹차와 복부비만 상호작용의 경우 모두, 위의 제기된 문제를 고려하여 좀더 명확한 인과관계, 혹은 보호인자로서의 작용을 확실히 규명하기 위해서는, 잘 계획되고, 대규모의, 그리고 전향적인 연구가 필요할 것으로 생각되며, 앞으로 유전역학적인 연구도 수행하여, 환경적인 요인뿐만 아니라 유전적인 요인까지 고려한 상호작용에 대해 연구가 필요하겠다.

주요어: 환자대조군 연구, 뇌졸중, 소공성경색, 녹차, 복부비만