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의학석사 학위논문

Association between  
Coffee and Green Tea  
Consumption and All-cause and  
Cause-specific Death

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# Abstract

## Association between Coffee and Green Tea Consumption and All-cause and Cause- specific Death

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**Background:** Both coffee and green tea are popular beverages worldwide. However, the effect of these beverages on death remains unclear. Therefore, we aimed to investigate the association between coffee and green tea drinking and all-cause and cause-specific death.

**Materials and Methods:** The Korean Multi-center Cancer Cohort (KMCC) study, a population-based prospective cohort study, commenced from 1993 to 2005. Death was ascertained by means of linkage to Nationwide Death Certificate database in Korea until December 31, 2014. We used 11,877 individuals (4,615 men and

7,262 women) for analysis. The risks of all-cause, cancer, cardiovascular disease and other particular caused death were assessed by estimating hazard ratios (HRs) and their 95% confidence intervals (95% CIs) using cox proportional hazard model adjusted for potential confounders such as age, sex, cigarette smoking, alcohol consumption, body mass index and comorbidity index (consisted of history of bronchopneumonia, chronic liver disease, hypertension, ischemic heart diseases, stroke and diabetes).

**Results:** 2,326 participants (1,331 men and 995 women) died until the end point of follow-up (December 31, 2014). Multivariate adjusted HRs (95% CIs) for all-cause death were 0.91 (0.81 – 1.03) for 2–4 cups of coffee/month, 0.79 (0.69 – 0.91) for 2–6 cups of coffee/week, 0.83 (0.75 – 0.92) for  $1 \leq$  cup of coffee/day ( $p$  for trend  $< 0.001$ ) compared with those who drank  $\leq 1$  cup of coffee/month. Corresponding to green tea, multivariate adjusted HRs (95% CIs) were 0.94 (0.84–1.06), 0.82 (0.70–0.96) and 0.76 (0.63–0.93) ( $p$  for trend  $< 0.001$ ). Inverse association were also observed between coffee drinking

and death due to chronic liver disease. As compared person who drank  $\leq 1$  cup of coffee/month, multivariate adjusted HRs (95% CIs) for chronic liver disease related death were 0.88 (0.44–1.77) for 2–4 cups of coffee/month, 0.47 (0.18–1.22) for 2–6 cups of coffee/week, 0.51 (0.27–0.97)  $1 \leq$  cup of coffee/day. Neither coffee nor green tea drinking were not significantly associated with cancer death.

**Conclusions:** Our community based prospective cohort study suggested that coffee and green tea drinking was associated with reduced risk of all-cause death. Furthermore, coffee drinking was inversely associated with chronic liver disease related death.

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**Keywords:** death, all-cause death, cause-specific death, cancer death, cardiovascular disease death, coffee, green tea

**Student Number:** 2014 – 25059

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# 1. Introduction

## 1.1 Components of coffee and green tea

Coffee and green tea are two of the most popular beverages around the world (1–3). However, the role of these beverages to health are still controversial because they have both harmful and beneficial aspects to our body (4, 5).

These beverages contains many functional components such as caffeine, polyphenols, and phenolic acids (6–10). In general, 95–200 mg of caffeine can be contained in 8–oz cup of brewed caffeinated coffee. Even decaffeinated coffee can contain 5–15 mg in 8–oz cup (11) and 8–oz cup of green tea can contains 240–320 mg of polyphenols (7). Concentration of these components varies by material characteristics (species, genetic characteristics), agricultural growing methods (traditional, organic), types of beverages (instant, roasted), roasting degree, brewing methods (boiled, filtered) (6, 7, 11, 12).

Caffeine, one of the main components of coffee and green tea is involved in increasing blood pressure (13), increasing plasma cholesterol, biomarkers for inflammation(14), insulin resistance

(15), and serum lipid concentration (16). They were known as cardio metabolic risk factors. Central nervous system stimulation and lower bone density were also known as adverse effects of caffeine (17). Moreover, intake high dose of caffeinated coffee can cause headache, tremulousness, anxiety, and trouble in sleep (6). However, caffeine have beneficial aspects such as weight control (18), associated with lower risk of depression (19), Alzheimer's dementia (20, 21) and Parkinson's disease (22–24). Also, catechins which is in polyphenols are abundant in coffee and green tea (8, 25). They have antioxidative properties that are concerned of inhibiting DNA damage and tumor promotion *in vitro* and *in vivo* (9, 26–29).

## 1.2 The relationship between coffee and green tea and death

### 1.2.1 The relationship between coffee and green tea and all-cause death

Association between coffee and green tea consumption and the risk of all-cause death have been investigated. Several prospective studies and meta-analysis studies have reported that consumption of coffee or green tea and all-cause mortality were inversely associated (30–36).

However, their dose response relationship is still controversial whether they have linear association or not (33, 36).

### 1.2.2 The relationship between coffee and green tea and cause-specific death

Association between coffee and green tea drinking and cause-specific death have been investigated. Especially, the main cause of death from cancer and cardiovascular disease (CVD) have been comparatively investigated (30–32, 34–36). Recent studies have shown that inverse association between coffee and green tea drinking and death from CVD (30–32, 34–36). On the other hand, no significant association between coffee or green tea consumption and death from cancer are observed through several studies (30–32, 34, 36).

However, most of previous studies are limited to death due to all-cause, cancer and CVD. Studies about the relationship between coffee and green tea drinking and more detailed reasons of death such as endocrine disease, digestive disease, neurological disease were lacking. Moreover, most of previous studies were conducted in America, Japan but the association between coffee and green tea and all-cause, and cause-specific death are different according to geographical regions and nations



(36, 37).

## 1.3 Objectives

We examined the association of coffee and green tea drinking with death in Korean community based prospective cohort study. More detailed our objectives were as followed.

First, we investigated association between frequency of coffee and green tea drinking ( $\leq 1$  cup/month, 2–4 cups/month, 2–6 cups/week,  $1 \leq$  cup/day) and death from all-cause, cancer, CVD, and non-cancer non-CVD death. Second, we investigated association between frequency of coffee and green tea drinking ( $\leq 1$  cup/month, 2–4 cups/month, 2–6 cups/week,  $1 \leq$  cup/day) and particular cause-specific death (digestive, endocrine, neurological disease related death as well as other underlying cause of death).

## 2. Methods and Materials

### 2.1 Study design and study population

Korean Multi-center Cancer Cohort (KMCC) as a community based prospective cohort study commenced between 1993 and 2005. The details of KMCC study had been described previously (38). The KMCC consisted of 20,585 participants who lived in urban and rural area including Haman, Chungju, Uljin and Youngil in Korea. Information on lifestyle, diet and history of disease were obtained from structured questionnaire by well-trained interviewers and anthropometric factors such as height and weight were measured directly using standard methods.

Among 20,585 participants, we excluded subjects who were enrolled in 1994, 1998, and 1999 (n=4,670). During these periods, there were no questionnaire items about frequency of both beverages drinking. We excluded subjects without information on frequency of both beverages drinking (n=4,036). Then we excluded subjects without information on frequency of each of coffee and green tea analysis respectively (coffee: n=16, green tea: n=160). Unfortunately, in 1993 and 1995, information

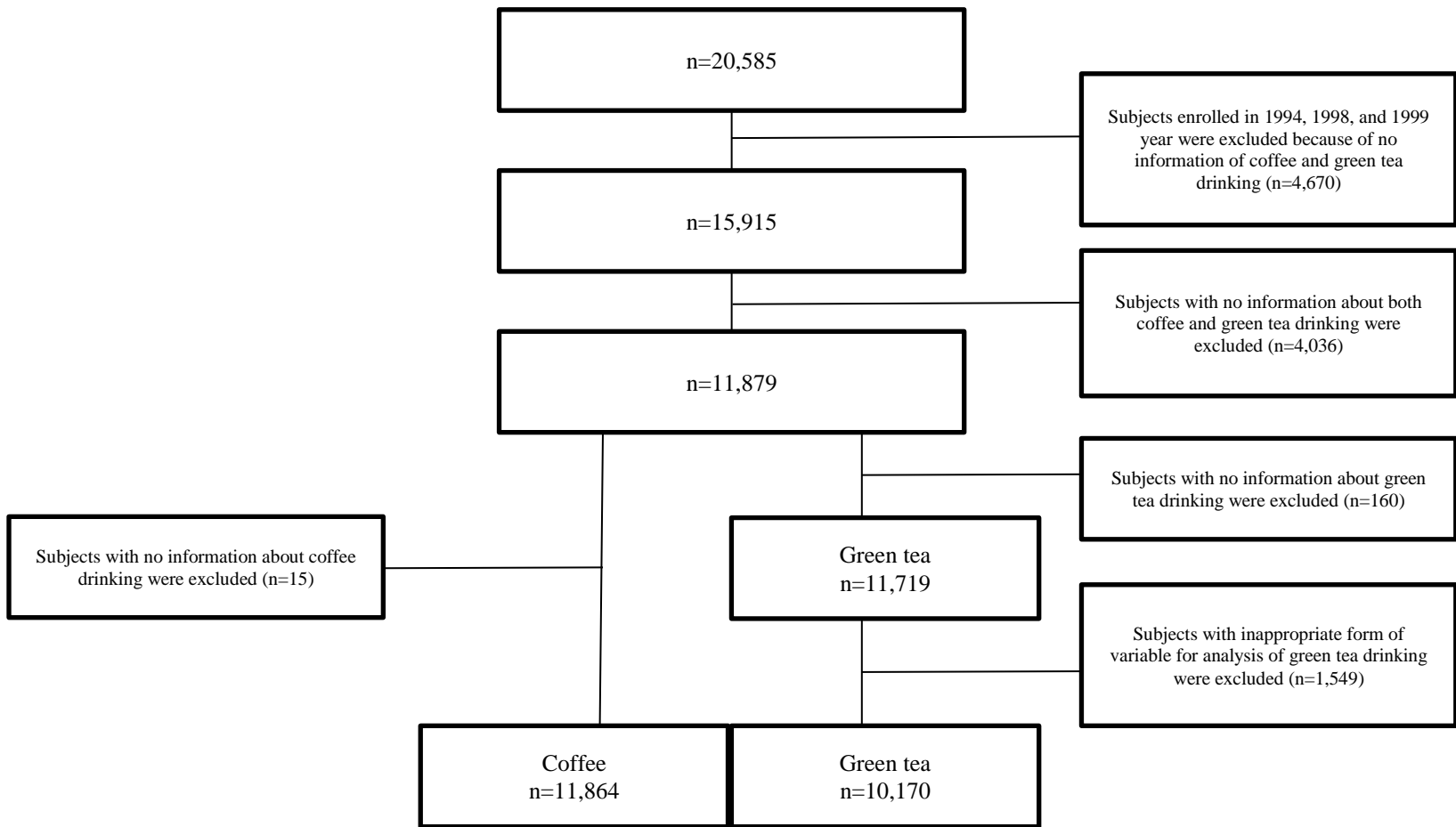
on green tea drinking was ineligible to present study because this information was obtained at once from questionnaire on two beverages (green tea and ginseng tea), so we could not distinguish green tea or ginseng tea drinking during these periods. Thus we excluded those subjects (n=1,549). Finally, we used 11,864 and 10,170 subjects for each analysis on coffee and green tea drinking (table 1 and figure 1).

The KMCC study was approved by the Institutional Review Boards of Seoul National university Hospital (H-0110-084-002).

**Table 1.** Variables collection years

<b>Variables</b>	<b>Year</b>												
	<b>1993</b>	<b>1994</b>	<b>1995</b>	<b>1996</b>	<b>1997</b>	<b>1998</b>	<b>1999</b>	<b>2000</b>	<b>2001</b>	<b>2002</b>	<b>2003</b>	<b>2004</b>	<b>2005</b>
Frequency of coffee drinking	O	X	O	O	O	X	X	O	O	O	O	O	O
Frequency of green tea drinking	X <sup>1</sup>	X	X <sup>1</sup>	O	O	X	X	O	O	O	O	O	O

<sup>1</sup>. Information was obtained from questionnaire which had frequency of both green tea and ginseng tea drinking



**Figure 1.** Selection process for study population

## 2.2 Follow up and outcome ascertainment

Participants were followed from baseline (1993–2005) until the date of death or the end point of follow up (December 31 2014). Death and underlying cause of death were ascertained through linkage with Nationwide Death Certificate database in Korea. To conduct analysis on cause specific death, we classify by underlying cause of death according to International Classification of Disease, 10th Revision (ICD–10): cancer (C00–C99), cardiovascular disease (I00–I99), stroke (I60–I69), ischemic heart disease (I20–I25), non–cancer non–cardiovascular disease (A00–B99, D00–H95, J00–Z99), digestive disease (K00–K95), chronic liver disease (K70–K77), endocrine disease (E00–E89), diabetes (E10–E14), neurological disease (G00–G99) and Parkinson's disease (G20).

## 2.3 Assessment of exposure and potential confounding factors

Frequency of coffee and green tea drinking was obtained from self-reported questionnaire at baseline. We did not have information on type of beverages. According to one company report, among total sale of coffee, instant coffee was decreased 53.7% to 33.7% and coffee by coffee shops was increased 28% to 46.8% from 2007 to 2014 in Korea (39). Moreover, import of coffee bean and green bean was increased but import of instant coffee was decreased from 1996 to 2015 (40).

Our baseline questionnaire also included information about age, sex, cigarette smoking, alcohol consumption and history of disease and so on. Cigarette smoking was divided as never smoker (less than 400 cigarettes smoking per lifetime), former smokers (400 and more cigarettes smoking per lifetime but person who do not smoke at baseline), and current smokers (400 and more cigarettes smoking per life time and person who smoke at baseline). Alcohol consumption was divided as never drinker, former drinker (ever drank but person who do not drink at



baseline) and current drinker (ever drank and person who drink at baseline). History of disease was divided as never (never diagnosed specific disease), current patient (ever diagnosed specific disease and person who had this disease at baseline), past patient (ever diagnosed specific disease but person who did not have this disease at baseline) and patient with unknown morbid state (ever diagnosed specific disease but unknown whether they had this disease or not at baseline). BMI ( $\text{Kg/m}^2$ ) was calculated from height and weight measured directly using the physical examination at base line.

## 2.4 Statistical analysis

Baseline characteristics of study participants according to vital status (alive and death) and frequency consumption of beverages ( $\leq 1$ cup/month, 2–4 cups/month, 2–6 cups/week, and  $\geq 1$ cup/day) were estimated by Chi square test for categorical variables, t-test and analysis of variance (ANOVA) test for continuous variables.

To assess the relationship between frequency of coffee and green tea drinking and all-cause and cause specific death, we calculated HRs and their 95% CI using cox proportional hazard model. The lowest category ( $\leq 1$ cup/month) of frequency of those beverages drinking was used as reference group. HRs was calculated by adjusting for potential confounders such as age at baseline (continuous variable), sex (men and women), cigarette smoking (above 400 cigarette: never, former and current), alcohol consumption (yes and no), body mass index ( $< 23$ ,  $23-25$  and  $25 < \text{Kg/m}^2$ ), comorbidity index (0, 1 and  $\geq 2$ ). We selected adjustment variables by backward elimination methods. The comorbidity index was calculated by sum of history of

diseases (bronchopneumonia, chronic liver disease, hypertension, ischemic heart diseases, stroke and diabetes) with positive association with all-cause death using cox proportional hazard model. Never diagnosed or missing value were counted 0 (score) and ever diagnosed were counted 1 (score).

In our statistical analysis,  $P$ -values were 2-tailed and the differences at less than 0.05 were considered statistically significant. All statistical analyses were performed using Statistical Analysis System software package (SAS) 9.4 for windows (SAS Institute, Cary, NC, USA).

## 3. Results

### 3.1 Baseline characteristics of study participants

Baseline characteristics of study participants according to frequency of beverage consumptions were presented in table 2. Subjects who drank coffee more than twice a month were more consisted of male. Coffee drinker were also more likely to be younger, be more obese, be more educated, consume more smoke, and alcohol. However, they were less likely to be have history of diseases (all  $P < 0.001$ ) (Table 2).

Green tea drinker with more than twice a month were more consisted of male compared with once or less a month. People who drank green tea tended to be younger, be more obese, be more educated, and consume more alcohol (all  $P < 0.001$ ). Current smoker in persons who drank green tea more than twice a month were lesser than persons with once or less a month but value was not statistically significant ( $P = 0.057$ ). High consumption of green tea was more likely to have history of disease ( $P = 0.033$ ) (Table 2).

**Table 2.** Baseline characteristics of the study subjects according to frequency of green tea drinking in the Korean Multi-center Cancer Cohort (KMCC), 1993-2004

	Coffee (N=11,864)				<i>P</i> -value <sup>1</sup>	Green tea (N=10,170)				<i>P</i> -value <sup>1</sup>
	≤1 cup /month (N=4,534)	2-4 cups /month (N=1,513)	2-6 cups /week (N=1,443)	≥1 cup /day (N=4,374)		≤1 cup /month (N=5,633)	2-4 cups /month (N=2,133)	2-6 cups /week (N=1,353)	≥1 cup /day (N=1,051)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (year)	59.7 (10.5)	59.0 (10.9)	56.7 (11.4)	54.8 (11.6)	<0.001	58.6 (11.1)	56.9 (11.7)	55.2 (11.5)	53.8 (11.9)	<0.001
	N (%)	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)	N (%)	
Male	1,337 (29.5)	603 (39.9)	614 (42.6)	2,053 (46.9)	<0.001	2,074 (36.8)	854 (40.0)	573 (42.4)	464 (44.2)	<0.001
BMI > 25 Kg/m <sup>2</sup>	1,308 (28.9)	433 (28.6)	443 (30.7)	1,531 (35.0)	<0.001	1,776 (31.5)	660 (30.9)	456 (33.7)	400 (38.1)	<0.001
Education ≥ 12 years	248 (5.5)	80 (5.3)	154 (10.7)	679 (15.5)	<0.001	370 (6.6)	221 (10.4)	265 (19.6)	262 (24.9)	<0.001
Current cigarette smokers	825 (18.2)	371 (24.5)	353 (24.5)	1,429 (32.7)	<0.001	1,413 (25.1)	527 (24.7)	301 (22.3)	233 (22.2)	0.057
Current alcohol drinkers	1,223 (27.0)	585 (38.7)	624 (43.2)	1,796 (41.1)	<0.001	1,924 (34.2)	796 (37.3)	521 (38.5)	426 (40.5)	<0.001
Comorbidity index <sup>2</sup> ≥ 2	217 (4.8)	57 (3.8)	45 (3.1)	165 (3.8)	<0.001	254 (4.5)	83 (3.9)	57 (4.2)	61 (5.8)	0.033

Abbreviation: SD, standard deviation;

<sup>1</sup> *P*-values were calculated by chi-square test for categorical variables and analysis of variance (ANOVA) test for continuous variables.

<sup>2</sup> Comorbidity index (0, 1 and ≥2) included bronchopneumonia, chronic liver disease, hypertension, ischemic heart diseases, stroke, and diabetes.

### 3.2 Association between frequency of coffee drinking and all-caused and cancer, CVD, non-cancer non-CVD mortality

An inverse association between coffee drinking and all-caused death were observed in multivariate adjusted HRs (table 3). As compared with group with lowest coffee drinking, multivariate adjusted HRs (95% CIs) for all-caused death were as followed: 0.91 (0.81–1.03) for 2–4 cups/month, 0.79 (0.69–0.91) for 2–6 cups/week, 0.83 (0.75–0.92) for  $1 \leq$  cups/day, and  $p$ -trend $<0.001$ .

We were not observed any significant results in between coffee drinking and cancer death. As compared with reference group, HRs (95% CIs) were as followed: 0.81 (0.64–1.02) for 2–4 cups/month, 0.95 (0.75–1.20) for 2–6 cups/week, 0.87 (0.73–1.03) for 1 cup $\leq$ /day, and  $p$ -trend=0.171 (table 3)

As compared group with lowest frequency of coffee drinking, multivariate adjusted HRs (95% CI) between coffee drinking and CVD death were as followed: 1.24 (0.98–1.57) for 2–4 cups/month; 0.70 (0.50–0.97) for 2–6 cups/week; 0.94 (0.76–

1.16) for 1 cup $\leq$ /day;  $p$ -trend=0.254 (table 3)

Non-cancer non CVD death and coffee drinking were statistically significant. As compared with reference group, HRs (95% CIs) were as followed: 0.84 (0.71–1.01) for 2–4 cups/month, 0.73 (0.59–0.90) for 2–6 cups/week, 0.76 (0.65–0.88) for 1 cup $\leq$ /day,  $p$ -trend<0.001 (table 3)

### 3.3 Association between frequency of green tea drinking and all-caused and cancer, CVD, non-cancer non-CVD mortality

Green tea drinking were also inversely associated with all-cause mortality in table 3. Multivariate adjusted HRs for all-cause death were as followed: 0.94 (0.84–1.06) for 2–4 cups/month, 0.82 (0.70–0.96) for 2–6 cups/week, 0.76 (0.63–0.93) for  $1 \leq$  cup/day, and  $p$ -trend $<0.001$  compared with reference group.

We were not observed any significant results in between green tea drinking and cancer death [multivariate adjusted HRs (95% CIs): 1.10 (0.91–1.35) for 2–4 cups/month; 1.05 (0.81–1.35) for 2–6 cups/week; 0.94 (0.69–1.28) for  $1 \leq$  cup/day;  $p$ -trend: 0.965;] (table 3).

As compared group with lowest frequency of green tea drinking, multivariate adjusted HRs (95% CI) between green tea drinking and CVD death were as followed: 0.79 (0.62–1.01) for 2–4 cups/month; 0.62 (0.43–0.90) for 2–6 cups/week; 0.65 (0.43–1.00) for  $1 \leq$  cup/day;  $p$ -trend=0.002; (table 3).

Multivariate adjusted HRs (95% CI) between green tea drinking



and non-cancer non-CVD death, as compared with group with lowest frequency of green tea drinking, were as followed: 0.92 (0.77–1.08) for 2–4 cups/month; 0.78 (0.61–0.98) for 2–6 cups/week; 0.70 (0.52–0.94) for  $1 \leq \text{cup/day}$ ;  $p\text{-trend}=0.003$ ; (table 3).

**Table 3.** Association between frequency of coffee or green tea drinking and death from all-cause, cancer, cardiovascular disease, and non-cancer non-CVD in the Korean Multi-center Cancer Cohort (KMCC) with the baseline of 1993-2005 by the follow-up of 2014

	Coffee					Green tea				
	≤1 cup /month	2-4 cups /month	2-6 cups /week	1 cup ≤ /day	<i>p</i> -trend	≤1 cup /month	2-4 cups /month	2-6 cups /week	1 cup ≤ /day	<i>p</i> -trend
PYs	59,953	20,415	18,710	54,875		70,290	27,721	16,544	12,163	
<b>All-caused death (ICD-10: A00-Z99)</b>										
Death	1,045	357	241	679		1,118	406	182	115	
HR <sup>1</sup> (95% CI)	1.00	0.91 (0.81-1.03)	<b>0.79 (0.69-0.91)</b>	<b>0.83 (0.75-0.92)</b>	<b>&lt;0.001</b>	1.00	0.94 (0.84-1.06)	<b>0.82 (0.70-0.96)</b>	<b>0.76 (0.63-0.93)</b>	<b>&lt;0.001</b>
<b>Cancer death (ICD-10: C00-C99)</b>										
Death	302	97	93	245		326	142	72	45	
HR <sup>1</sup> (95% CI)	1.00	0.81 (0.64-1.02)	0.95 (0.75-1.20)	0.87 (0.73-1.03)	0.171	1.00	1.10 (0.91-1.35)	1.05 (0.81-1.35)	0.94 (0.69-1.28)	0.965
<b>Cardiovascular disease (CVD) death (ICD-10: I00-I99)</b>										
Death	241	99	42	151		277	80	32	23	
HR <sup>1</sup> (95% CI)	1.00	1.24 (0.98-1.57)	0.70 (0.50-0.97)	0.94 (0.76-1.16)	0.254	1.00	0.79 (0.62-1.01)	<b>0.62 (0.43-0.90)</b>	<b>0.65 (0.43-1.00)</b>	<b>0.002</b>
<b>Non-cancer non-CVD death (ICD-10: A00-B99, D00-H95, J00-Z99)</b>										
Death	502	161	106	283		515	184	78	47	
HR <sup>1</sup> (95% CI)	1.00	0.84 (0.71-1.01)	<b>0.73 (0.59-0.90)</b>	<b>0.76 (0.65-0.88)</b>	<b>&lt;0.001</b>	1.00	0.92 (0.77-1.08)	<b>0.78 (0.61-0.98)</b>	<b>0.70 (0.52-0.94)</b>	<b>0.003</b>

Abbreviation: PYs, person-years; HR, hazard ratio; CI, confidence interval;

<sup>1</sup>. Adjusted age, sex, cigarette smoking (above 400 cigarettes: never, former, and current), alcohol consumption (never, former, and current), body mass index (<23, 23-25, 25-30 kg/m<sup>2</sup>), comorbidity index (0, 1 and ≥2)

### 3.4 Association between frequency of coffee drinking and detailed cause-specific mortality

Table 4 presented the result of association between coffee and other particular cause specific death.

Coffee consumption appeared to be potentially associated with endocrine disease related death. As compared with group with lowest frequency of coffee drinking, multivariate adjusted HRs (95% CI) between coffee drinking and digestive related death were as followed: 0.79 (0.44–1.42) for 2–4 cups/month, 0.52 (0.25–1.11) for 2–6 cups/week, 0.65 (0.40–1.07) for 1 cup  $\leq$ /day,  $p$ -trend=0.057 (table 4)

Moreover, we observed significant association between coffee drinking and chronic liver disease death. As compared group with lowest frequency of coffee drinking, multivariate adjusted HRs (95% CI) between coffee drinking and chronic liver disease death were as followed: 0.88 (0.44–1.77) for 2–4 cups/month, 0.47 (0.18–1.22) for 2–6 cups/week, 0.51 (0.27–0.97) for 1 cup  $\leq$ /day,  $p$ -trend=0.023 (table 4)

Potential association was also observed between coffee drinking

and Parkinson's disease death. HRs (95% CI) as followed: 1.10 (0.41–2.90) for 2–4 cups/month; 0.52 (0.12–2.32) for 2–6 cups/week; 0.31 (0.09–1.09) for  $1 \leq \text{cup/day}$ ;  $p$ -trend=0.051 (table 4).

However, we did not observe significant results in endocrine and diabetes related death (table 4).

**Table 4.** Association between frequency of coffee drinking and cause-specific death in the Korean Multi-center Cancer Cohort (KMCC) with the baseline of 1993-2005 by the follow-up of 2014

	Coffee				<i>p</i> -trend
	≤1 cup /month	2-4 cups /month	2-6 cups /week	1 cup ≤ /day	
<b>Digestive disease death (K00-K95)</b>					
Death	45	15	8	27	
HR <sup>1</sup> (95% CI)	1.00	0.79 (0.44-1.42)	0.52 (0.25-1.11)	<b>0.65 (0.40-1.07)</b>	<b>0.057</b>
<b>Chronic liver disease death (K70-K77)</b>					
Death	28	11	5	15	
HR <sup>1</sup> (95% CI)	1.00	0.88 (0.44-1.77)	0.47 (0.18-1.22)	<b>0.51 (0.27-0.97)</b>	<b>0.023</b>
<b>Endocrine disease death (E00-E89)</b>					
Death	50	15	6	26	
HR <sup>1</sup> (95% CI)	1.00	0.91 (0.51-1.64)	0.48 (0.20-1.12)	0.71 (0.43-1.16)	0.101
<b>Diabetes (E10-E14)</b>					
Death	45	14	4	23	
HR <sup>1</sup> (95% CI)	1.00	0.99 (0.54-1.82)	0.37 (0.13-1.03)	0.71 (0.42-1.20)	0.104
<b>Neurological disease death (G00-G99)</b>					
Death	32	8	6	11	
HR <sup>1</sup> (95% CI)	1.00	0.66 (0.30-1.45)	0.73 (0.30-1.76)	<b>0.53 (0.26-1.07)</b>	<b>0.076</b>
<b>Parkinson's disease death (G20)</b>					
Death	14	6	2	3	
HR <sup>1</sup> (95% CI)	1.00	1.10 (0.41-2.90)	0.52 (0.12-2.32)	<b>0.31 (0.09-1.09)</b>	<b>0.051</b>

Abbreviation: HR, hazard ratio; CI, confidence interval;

<sup>1</sup>. Adjusted age, sex, cigarette smoking (above 400 cigarettes: never, former, and current), alcohol consumption (never, former, and current), body mass index (<23, 23-25, 25< kg/m<sup>2</sup>), comorbidity index (0, 1 and ≥2)

### 3.5 Association between frequency of green tea drinking and detailed cause-specific mortality

Table 5 presented the result of association between green tea drinking and other particular cause specific death.

Potential association between green tea drinking and death from stroke were observed in table 5. Multivariate adjusted HRs (95% CI), as compared with reference group, were as followed: 0.66 (0.45–0.97) for 2–4 cups/month, 0.58 (0.34–0.99) for 2–6 cups/week, 0.79 (0.46–1.38) for 1cup≤/day,  $p$ -trend=0.036

Green tea consumption appeared to be potentially associated with death from endocrine related disease and diabetes. As compared group with lowest frequency of green tea drinking, multivariate adjusted HRs (95% CI) between green tea drinking and endocrine related disease death were as followed 0.65 (0.36–1.20) for 2–4 cups/month, 0.35 (0.13–0.97) for 2–6 cups/week, 0.54 (0.19–1.51) for 1cup≤/day,  $p$ -trend=0.023 (table 5) As compared group with lowest frequency of green tea drinking, multivariate adjusted HRs (95% CI) between green tea drinking and diabetes related death were as followed 0.67 (0.36–

1.26) for 2–4 cups/month, 0.29 (0.09–0.94) for 2–6 cups/week,  
0.61 (0.22–1.72) for 1cup  $\leq$ /day,  $p$ -trend=0.035 (table 5)

**Table 5.** Association between frequency of green tea drinking and cause-specific death in the Korean Multi-center Cancer Cohort (KMCC) with the baseline of 1993-2005 by the follow-up of 2014

	Green tea				<i>p</i> -trend
	≤1 cup /month	2-4 cups /month	2-6 cups /week	1 cup ≤ /day	
<b>CVD death (I00-I99)</b>					
Death	277	80	32	23	
HR <sup>1</sup> (95% CI)	1.00	0.79 (0.62-1.01)	<b>0.62 (0.43-0.90)</b>	<b>0.65 (0.43-1.00)</b>	<b>0.002</b>
<b>Stroke death (I60-I69)</b>					
Death	135	33	15	14	
HR <sup>1</sup> (95% CI)	1.00	<b>0.66 (0.45-0.97)</b>	<b>0.58 (0.34-0.99)</b>	0.79 (0.46-1.38)	<b>0.036</b>
<b>Ischemic heart disease death (I20-I25)</b>					
Death	67	23	10	3	
HR <sup>1</sup> (95% CI)	1.00	0.96 (0.60-1.54)	0.84 (0.43-1.65)	0.36 (0.11-1.16)	0.127
<b>Endocrine disease death (E00-E89)</b>					
Death	54	13	4	4	
HR <sup>1</sup> (95% CI)	1.00	0.65 (0.36-1.20)	<b>0.35 (0.13-0.97)</b>	0.54 (0.19-1.51)	<b>0.023</b>
<b>Diabetes death (E10-E14)</b>					
Death	49	12	3	4	
HR <sup>1</sup> (95% CI)	1.00	0.67 (0.36-1.26)	<b>0.29 (0.09-0.94)</b>	0.61 (0.22-1.72)	<b>0.035</b>

Abbreviation: HR, hazard ratio; CI, confidence interval;

<sup>1</sup>. Adjusted age, sex, cigarette smoking (above 400 cigarettes: never, former, and current), alcohol consumption (never, former, and current), body mass index (<23, 23-25, 25< kg/m<sup>2</sup>), comorbidity index (0, 1 and ≥2)



## 4. Discussion

### 4.1 Summary of the results

In this large, community based, prospective Korean cohort study, inverse association were observed between consumption of both coffee and green tea and all-cause death. Compared with subjects who drank 1 or less cup of coffee and green tea per month, 2–6 cups of coffee per week and 1 and more cup of green tea per day had 21% and 24% risk reduction for all-cause mortality. We also observed inverse association between coffee drinking and chronic liver disease specific death. Neither coffee nor green tea intake had no significant risk reduction for cancer death.

## 4.2 Interpretation of the results and comparison with prior studies

### 4.2.1 Association between coffee drinking and all-cause death

We found that coffee drinking was inversely associated with all-cause death. Our finding was consistent with prior cohort studies (31, 41–43). The negative association was reported from previous studies with stratified analysis by sex (30, 44). The National Institutes of Health-AARP Diet and Health Study reported that 4–5 cups /day of coffee intake was associated with reduced risk of total death for men (12%) and women (16%) among 33,731 men and 18,784 women with 50– 71 years during 5,148,760 person years (30). Japan Collaborative Cohort Study for Evaluation of Cancer Risk was conducted on 46,465 men and 64,327 women with 40–79 years. This study concluded that coffee drinking was associated with reduced risk of all-cause mortality in both sex (44). Three studies showed that the effect of coffee drinking for all caused death was different in men and women (45–47). Four meta-analysis were also reported reverse

association between coffee consumption and all-cause mortality (32, 33, 37, 48).

However, positive association of coffee drinking with total mortality was observed by two cohort studies (49, 50). The Aerobics Center Longitudinal Study cohort reported that coffee drinking was positively associated with total death in men but they did not observed significant results in women (49). The other cohort study was conducted in 1992. As compared with lowest group (<1 cup/day), HR (95% CI) for middle group (1–2 cups/day) and highest group (3 and more cups/day) was 1.15 (1.05–1.26) and 1.28 (1.12–1.47) (50).

No association between coffee drinking and all caused mortality was also reported by several previous studies (51–53).

## 4.2.2 Association between green tea drinking and all-cause death

The inverse association between green tea intake and all-cause death was consistent with prior studies (34, 43, 54–56). Among 40,530 persons with 40–79 years. The Ohsaki National Health Insurance Cohort Study, population-based prospective cohort study reported that the highest frequency group for green tea drinking (5 or more cups per day) had the lowest HR for all causes death in both men (HR=0.88; 95% CI 0.79–0.98) and women (HR=0.77; 95% CI 0.67–0.89) compared with lowest frequency group for green tea drinking (less than 1 cup per day) (34). Two meta-analysis also recently reported negative association between green tea consumption and all caused death (35, 36).

However, other cohort studies reported that green tea drinking and all caused mortality was not associated (45, 51, 57).

### 4.2.3 Association between coffee drinking and CVD death

Studies about association between coffee drinking and CVD were conducted previously but their association was still controversial. Previous studies reported negative association (30–32, 41, 42, 46, 57, 58), positive association (59), and null association (43, 48–51, 53, 60, 61).

One study conducted meta-analysis on 13 prospective studies. This study reported that coffee consumption was negatively associated with CVD related death. As compared with person who drink coffee less than one cup per day, RRs (95% CIs) were 0.89 (0.86–0.91) for 1 cup/day, 0.81 (0.77–0.85) for 2 cups/day, 0.79 (0.74–0.84) for 3 cups/day, 0.80 (0.74–0.86) for 4 cups/day, 0.82 (0.75–0.90) for 5 cups/day, 0.85 (0.75–0.95) for 6 cups/day, 0.87 (0.76–1.00) for 7 cups/day, 0.90 (0.76–1.06) for 8 cups/ day (32). Singapore Chinese Health Study showed that coffee drinking was associated with reduced risk of CVD death in never smoker but these are not statistically significant in smoker among 52,584 Chinese men and women. In 2009, the Japan Collaborative Cohort Study for Evaluation of

Cancer Risk suggested that coffee consumption at 3 and more cups per day was associated with increased risk of CVD death in Women. HRs and their 95% CIs were as followed: 0.87 (0.62–1.23) for 1–6 cups/week, 0.77 (0.55–0.99) for 1–2 cups/day, 2.30 (1.31–4.02)  $\geq 3$  cups/day (59).

#### 4.2.4 Association between green tea drinking and CVD death

Inverse association between green tea drinking and CVD death was reported by previous studies (34, 36, 51, 54–56, 59). In the Ohsaki Study, 5 or more cup of green tea drinking per day was inversely associated with death from CVD (adjusted HR 0.74 95% CI 0.62–0.89) compared with less than 1 cup drinking per day. As well as, according to subtype analysis in CVD death, significant risk reduction was observed in death from stroke (adjusted HR for 5 or more cups/day 0.63 95% CI 0.49–0.82) but null association was observed between green tea drinking and death from coronary heart disease (adjusted HR for 5 or more cups/day 0.86 95% CI 0.59–1.26) (34).

However, two cohort studies reported that no association between tea drinking and CVD death (43, 57).

#### 4.2.5 Association between coffee drinking and cancer death

Several studies about association between coffee drinking and cancer mortality have been conducted previously. Nine prospective cohort studies and one meta-analysis study was reported that they had no association between coffee drinking and total cancer death (30, 41–43, 45, 46, 48, 50, 53, 57). The National Institutes of Health–AARP Diet and Health Study as a large prospective cohort study conducted on 229,119 men and 173,141 women from 1995 to 2008. This study showed that coffee consumption had no association with total cancer death in both men and women (30). One meta-analysis study on 11 prospective studies suggested null association between coffee consumption and death from cancer (48).

Negative association between coffee drinking and total cancer death were also reported previously (31, 44, 58). Moreover, some studies reported negative association between coffee drinking and particular cancer death. One study was conducted using three large prospective cohorts (the Nurses' Health Study, the Nurses' Health Study II and Health Professionals Follow-up



Study). This study reported that 3.1–5.0 cups of coffee consumption per day could reduce 49% risk of ovarian cancer death in never smokers (31). Similarly, another cohort study showed that coffee drinking was inversely associated with colorectal cancer death among women (58).

In contrast, positive association between coffee drinking and total cancer death was suggested from one cohort study (60) and one meta-analysis study (32).

#### 4.2.6 Association between green tea drinking and cancer death

In our study, we did not observe any association between green tea drinking and cancer death. Many previous studies suggested null association between green tea drinking and cancer mortality (34, 36, 45, 48, 54, 55).

Only one study reported that tea consumption could reduce risk of cancer death.  $\geq 2$  cups of green tea drinking per day was negatively associated with cancer death was observed among multi-ethnic urban population from Northern Manhattan study. (43).

#### **4.2.7 Association between coffee and green tea drinking and cause-specific death**

Our study suggested negative association between coffee drinking and chronic liver disease death. Multiethnic Cohort Study (MEC) conducted on 215,000 men and women from 1993 to 1996 by Veronica Wendy Setiawan in USA. This population-based prospective study reported that person who consumed 2–3 cups and  $\geq 4$  cups coffee per day had 46% and 71% risk reduction for chronic liver disease death respectively (62). The Singapore Chinese Health Study reported coffee or green tea consumption had no association with total cirrhosis mortality but negative association were observed between coffee consumption and non-viral hepatitis related cirrhosis mortality among 63,274 persons (63).

To our knowledge, there is no study regarding association between green tea drinking and endocrine disease or diabetes related death. However, several meta-analysis studies reported that tea drinking could reduce the risk of type 2 diabetes (64–67).

Corresponding to green tea, the NIH-AARP Diet and Health Study reported that 6 cups and more per day of coffee consumption associated with lower risk of death due to diabetes in Men but this result was not consistent in women (30). Moreover, the European Prospective Investigation into Cancer and Nutrition (EPIC) study in 10 European countries reported that caffeinated coffee consumption was inversely associated with type 2 diabetes but decaffeinated coffee drinking was no association (68). The Nurses' Health Study (NHS) was constructed in 1976 among 121,701 women with 30–55 years. This study reported that caffeinated and decaffeinated coffee consumption inversely associated with type 2 diabetes (69).

Previous cohort study about association between coffee drinking and neurological disease death was published in 2015. This study reported that increment of one cup of coffee per day was inversely associated with death from neurologic disease ( $P < 0.05$ ) (31). Moreover, prospective study regarding Parkinson's disease and coffee and tea drinking was conducted in Finns in 1982, 1987, 1992 and 1997 among 14,293 men and

15,042 women. This large population-based study coffee reported that daily consumption of coffee and tea was inversely associated with development of Parkinson's disease in both sexes. As compared 0 cup of coffee per day, multivariate adjustment HR (95%CI) for 1–2 cups, and  $\geq 3$  cups of coffee per day was followed: 0.53 (0.31–0.92); 0.40 (0.23–0.71);  $p$ -trend=0.005; For tea, multivariate adjustment HR (95%CI) for 1–2 cups, and  $\geq 3$  cups of tea per day in comparison to the reference group (0 cup of tea per day), was followed: 1.02 (0.74–1.41) 0.41 (0.20–0.83);  $p$  for trend=0.038; (70)

### 4.3 Possible mechanisms

Coffee and tea contains many bioactive compounds (6–10). Especially, polyphenols in coffee and green tea was known as antioxidant (4, 7). For example, one study reported that epigallocatechin-3-gallate, most active polyphenols, could improve mitochondrial function (7, 71). A randomized controlled trial in china of 240 subjects with mild to moderate hypercholesterolemia who received a once-daily theaflavin-enriched green tea extract (375mg) had lower level of total cholesterol and low-density lipoprotein cholesterol by 11.3 ( $\pm 0.9$ ) percent and 16.4 ( $\pm 1.1$ ) (both  $P < 0.01$ ) respectively compared to placebo group (72). Moreover, catechin intake was associated with mortality from ischemic heart disease (73). (–)–Epigallocatechin-3-gallate could significantly reduce infarct area in a rat model of transient focal cerebral ischemia (74).

Several studies reported that caffeine consumption was associated with Parkinson's disease (75–78). One experimental study reported that caffeine could reduce development of Parkinson's disease thorough A(2A) antagonist in 1-methyl-4-

phenyl-1,2,3,6-tetrahydropyridine Parkinson's disease mouse  
model(78).

#### 4.4 Limitations and strength of our study

This study had several limitations. First, information on the consumption of both coffee and green tea were obtained by self-reported at baseline. Thus, there could not reflect long-term or changed pattern of consumption appropriately. Second, we don't have information on the type of beverage (canned, instant, caffeinate and decaffeinate) and process of beverage preparation (boiled and filtered). In present study, we could not distinguish type of coffee although Korean consumed coffee mix (instant coffee with sugar and cream) than espresso in 1990s. However, one cohort study conducted subgroup analysis according to additive of coffee (no additive coffee, cream or whole milk only, low-fat milk only, nondairy creamer, sugar or honey only, lightener and sweetener, and other). This study reported that coffee consumption was inversely associated with all-cause death as compared with non-coffee drinker regardless of additive. Only one sub group (sugar-free sweetener only) was observed non-significantly (33).

However, our study has several strengths. First, KMCC is a



community based prospective cohort study so we could minimize recall bias and selection bias. Second, KMCC collected information about various epidemiological factors. We could control potential confounders by adjustment for these factors.

## 4.5 Conclusion

In conclusion, consumption of coffee and green tea was associated with lower risk of all-cause death our community based prospective cohort study in Korea. Moreover, coffee drinking was associated with reduced risk of chronic liver disease death. The relationship between coffee and green tea drinking and cause-specific death such as endocrine disease, digestive disease and neurological disease related death need to be studied in prospective studies with larger participants and longer follow up periods.

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## 초 록

**서론:** 커피와 녹차는 전세계적으로 인기 있는 음료이나 이들과 모든 원인 사망 및 사인 별 사망 사이의 관계에 대해서는 아직 명확하게 밝혀져 있지 않다. 따라서 본 연구에서는 커피와 녹차 섭취와 그 빈도에 따른 모든 원인 사망 및 사인 별 사망 사이의 연관성을 파악하고자 한다.

**방법:** 본 연구에서는 커피와 녹차 섭취와 모든 원인 사망과 사인 별 사망 (암, 심혈관계 질환, 심혈관계 외 질환) 사이 연관성 분석을 시행하였다. 본 연구 분석에는 한국인다가관암코호트 자료 (Korean Multi-center Cancer cohort, KMCC) 의 11,877 명(남성 4,615명, 여성 7,262명)을 사용하였다. 일반인구집단의 특성 비교에는 chi-square test를 사용하였고 연관성 분석에서는 cox proportional hazard model 을 사용하여 adjusted hazard ratios, adjusted HRs 와 95% 신뢰구간 (confidence interval, CI)을 산출하였다.

**결과:** 2014년까지 추적 관찰한 결과, 1,331명의 남성과 995명의 여성의 사망을 확인 하였다. 월 1회 미만의 커피 섭취 군과 비교하여 월 2-4회 커피 섭취 군의 전원인 사망의 adjusted HR 값 (95% 신뢰구간)은 0.91 (0.81 - 1.03) 이었고, 주 2-6회 섭취하는 군은

0.79 (0.69 - 0.91), 하루 1회 이상 섭취하는 군은 0.83 (0.75 - 0.92) 이었다 ( $p$  for trend<0.001). 녹차를 월 1회 미만 섭취하는 군에 비해 월 2-4회 섭취하는 군의 adjusted HR (95% 신뢰구간) 은 0.94 (0.84-1.06), 주 2-6회 섭취하는 군은 0.82 (0.70-0.96), 하루 1회 이상 섭취하는 군은 0.76 (0.62-0.93) 으로 나타났다 ( $p$  for trend<0.001). 또한 커피 섭취는 만성 간 질환으로 인한 사망과 역의 상관관계를 가졌다. 반면 커피와 녹차 섭취와 암으로 인한 사망 사이 유의한 결과를 관찰하지 못하였다.

**결론:** 본 연구에서는 커피와 녹차 섭취는 모든 원인 사망 위험 감소와 연관성을 보였고 커피 섭취는 만성 간 질환으로 인한 사망의 위험 감소와 연관성을 가지는 것을 확인하였다.

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**주요어:** 사망, 모든 원인 사망, 사인 별 사망, 암 사망, 심혈관계 질환 사망, 커피, 녹차

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