Joint Effects of Coffee Consumption and Serum Gamma-Glutamyltransferase on the Risk of Liver Cancer

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Only three Japanese prospective studies have suggested an inverse association between coffee drinking and liver cancer risk. No prospective studies on the association between serum gamma-glutamyltransferase (GGT) and liver cancer risk have been reported. We aimed to determine the single and joint associations of coffee consumption and serum GGT with the risk of primary liver cancer. Study cohorts included 60,323 Finnish participants who were 25-74 years of age and free of any cancer at baseline. During a median follow-up period of 19.3 years (interquartile range: 9.3-29.2 years), 128 participants were diagnosed with an incident liver cancer. The multivariable-adjusted (age, sex, alcohol consumption, education, smoking, diabetes and chronic liver disease at baseline and during follow-up, and body mass index) hazards ratios of liver cancer in participants who drank 0-1, 2-3, 4-5, 6-7, and ≥8 cups of coffee daily were 1.00, 0.66, 0.44, 0.38, and 0.32 (*P* for trend = 0.003), respectively. Further adjustment for serum GGT in subgroup analysis affected the results only slightly. The multivariable-adjusted and coffee-adjusted hazard ratio of liver cancer for the highest versus the lowest quartile of serum GGT was 3.13 (95% confidence interval = 1.22-8.07). The multivariable-adjusted inverse association between coffee consumption and liver cancer risk persisted when stratified by baseline factors: age more/less than 50 years, current smoker/never smoked/ever smoked, alcohol drinker/never drinker, obese/nonobese, and the highest/lowest three quartiles of serum GGT. A combination of very low coffee consumption and high level of serum GGT was associated with nearly nine-fold increased risk. *Conclusion*: Coffee drinking has an inverse and graded association with the risk of liver cancer. High serum GGT is associated with an increased risk of liver cancer. (HEPATOLOGY 2008;48:129-136.)

See Editorial on Page 7

Liver cancer is the third most common cause of death from cancer worldwide.[1] The incidence rate of liver cancer is high in western and central Africa, and southeastern and eastern Asia, low in most developed countries (except for Japan), and between in some southern European countries.[1] Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections have been identified as causative factors in more than 75% of cases worldwide and 85% of cases in less-developed countries.[1,2] However, the prevalence of HBV and HCV infections in most developed countries, except for Japan, Italy, and Greece, is low.[3,4]

Coffee is one of the most consumed beverages in the world. In last several years, three Japanese prospective studies have suggested an inverse association between cof-

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; MONICA, MONItoring trends and determinants of CArdiovascular disease; WHO, World Health Organization.

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Received January 10, 2008; accepted March 4, 2008.

Supported by grants from the Finnish Academy (108297 and 119681), and Special Research Funds of the Social Welfare and Health Board, City of Oulu.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.22320

Potential conflict of interest: Nothing to report.

fee drinking and liver cancer risk[5-7]; however, these studies did not control for HBV and HCV infections. Coffee drinking is also a relatively uncommon habit in Japan. Two recent meta-analyses based on these Japanese cohorts and five case-control studies has demonstrated that increased consumption of coffee may reduce the risk of liver cancer.[8,9] All studies in the two meta-analyses were conducted in Japan or southern Europe; therefore, the observed finding may not be generalizable to other populations. According to international statistics, Finns have a higher per capita coffee consumption (11.4 kg/year) than Japanese (3.2 kg/year), Americans (4.1 kg/year), Italians (5.8 kg/year), and other European populations (2.2-9.0 kg/year).[10] On the other hand, the prevalence of HBV and HCV infections among Finns is very low, <0.001% and 0.4%, respectively.[11] Furthermore, liver cancer is very rare in Finland compared to Japan and some other Asian countries.[1] Therefore, research into potential health effects of coffee in this population is of a particular interest.

Several studies have revealed an inverse association between coffee consumption with serum levels of gamma-glutamyltransferase (GGT)[12,13] and alanine aminotransferase (ALT),[12,13] and with history of chronic liver disease[14] and liver cirrhosis.[15,16] Serum GGT and ALT have been widely used as indexes of liver injuries.[17] One of the isozymes of GGT, GGTII, has been considered as a valuable tumor marker in detecting small hepatocellular carcinoma (HCC) and a good supplementary marker to alpha fetoprotein in the diagnosis of HCC.[18] However, only a few studies have assessed if serum total GGT level is associated with risk of liver cancer, and none of them had investigated potential joint effects of coffee consumption and serum GGT with the risk of liver cancer. The aim of this study is to examine the single and joint associations of coffee consumption and serum GGT with the risk of primary liver cancer in a large prospective cohort.

Materials and Methods

Subjects. Seven independent cross-sectional population surveys were carried out in six geographic areas of Finland in 1972, 1977, 1982, 1987, 1992, 1997, and 2002.[19] In 1972 and 1977, a randomly selected sample making up 6.6% of the population born between 1913 and 1947 was drawn. Since 1982, the sample was stratified by area, gender, and 10-year age group according to the World Health Organization (WHO) MONICA (MONItoring trends and determinants of CArdiovascular disease) protocol.[20] The participation rate varied by year from 74%-88%.[19] The subjects included in the seven surveys were 25-64 years of age, and the 1997 and 2002 surveys also included subjects aged 65-74 years. Subjects who participated in more than one survey were included only in the first survey cohort. The total sample size of the seven surveys was 62,015. The final sample comprised 29,286 men and 31,037 women after excluding the participants with a history of any cancer ($n = 910$) at baseline, and the participants with incomplete data on any variables required for this analysis ($n = 782$). The participants gave an informed consent (verbal in 1972-1992 and signed in 1997 and 2002). These surveys were conducted according to the ethical rules of the National Public Health Institute, and the investigations were performed in accordance with the Declaration of Helsinki.

Baseline Measurements. A self-administered questionnaire was mailed to the participants to be completed at home and returned to the survey site. The questionnaire included questions on medical history, socioeconomic factors, smoking habits, and dietary habits. Education level, measured as the total number of school years, was divided into birth cohort–specific tertiles. The participants were classified as never smoked, ex-smokers, and current smokers. Data on diabetes at baseline and during follow-up were obtained from the questionnaire and completed by the National Hospital Discharge Register and National Social Insurance Institution's drug register. Data on chronic liver disease (chronic liver disease and cirrhosis) at baseline and during follow-up were obtained from the National Hospital Discharge Register.

The participants were asked, "How many cups of coffee do you drink daily? (1 cup of coffee equals 1 dL)".[21,22] Based on the validation study of the dietary questionnaire carried out in subgroups of the study population,[23] the correlations between the dietary questionnaire and food records for coffee were 0.89 in men and 0.85 in women. Coffee consumption was categorized into five categories: 0-1 cup, 2-3 cups, 4-5 cups, 6-7 cups, and ≥8 cups per day. Because questions on alcohol consumption were different between the first two surveys (1972 and 1977) and the latter surveys, the participants were categorized into abstainers and alcohol users. At the survey site, specially trained research nurses measured height and weight in light clothing and without shoes by using the standardized WHO MONICA protocol.[20] Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters.

Subgroup Measurements. More-detailed data on alcohol consumption, and measurement of serum GGT level were included in the surveys of 1982, 1987, 1992, 1997, and 2002 (n = 37,842). Ethanol consumption was categorized into four groups: none, 1-34, 35-209, ≥210

Table 1. Baseline Characteristics by Volume of Coffee Consumption*

Characteristic	Daily Coffee Consumption (Cups/Day)					*P* Value
	0–1	2–3	4–5	6–7	≥8	
Men						
Number of participants	2999	5430	7892	6732	6233	
Age (years)	44.3	45.6	45.4	45.9	43.8	<0.001
BMI (kg/m2)	26.2	26.4	26.4	26.5	26.6	<0.001
Education (years)	10.2	10.1	9.7	9.1	8.8	<0.001
Serum GGT (U/L)†	45.1	42.1	36.7	32.4	33.9	<0.001
Alcohol drinker (%)	60	72	68	64	62	<0.001
Current smoking (%)	24	29	38	45	60	<0.001
History of diabetes (%)	3	3	3	3	2	0.82
Incident diabetes during follow-up (%)	7	7	7	7	7	0.70
History of chronic liver disease (%)	0.4	0.3	0.1	0.1	0.1	0.014
Incident chronic liver disease during follow-up (%)	1.3	1.0	0.6	0.3	0.5	<0.001
Women						
Number of participants	3151	7251	10,099	6994	3542	
Age (years)	40.8	45.2	45.9	45.9	43.8	<0.001
BMI (kg/m2)	25.8	25.9	26.0	26.5	26.8	<0.001
Education (years)	10.5	10.5	10.0	9.5	9.2	<0.001
Serum GGT (U/L)†	25.4	22.3	19.8	19.3	19.3	<0.001
Alcohol drinker (%)	42	45	39	31	34	<0.001
Current smoking (%)	11	14	17	19	33	<0.001
History of diabetes (%)	3	2	2	2	2	0.19
Incident diabetes during follow-up (%)	7	7	6	6	6	0.13
History of chronic liver disease (%)	0.1	0.2	0.1	0.1	0.0	0.28
Incident chronic liver disease during follow-up (%)	0.5	0.4	0.4	0.2	0.3	0.14

*Data shown are means or percentages; all data, except age, adjusted for age and study year; P value statistical significance represents P value from the ANOVA.
†This analysis only included surveys of 1982, 1987, 1992, 1997, and 2002.

g/week in men; none, 1-34, 35-139, ≥140 g/week in women. GGT was determined from fresh venous blood serum samples using a kinetic method (Oy Medix Biochemica AB, Kauniainen, Finland) based on the recommendation of the European Committee for Clinical Laboratory Standards in the same central laboratory at the Finnish National Public Health Institute.

Prospective Follow-Up. All types of cancer cases were identified through the population-based country-wide Finnish Cancer Registry since 1953. The subjects with cancer diagnosed before the baseline surveys were excluded. The registries are estimated to be of high accuracy and coverage for the studied cancer types.[24] The survey cohorts were followed through computer-based register linkage to June 30, 2006, for liver cancer diagnosis, emigration, or death, whichever occurred first. The time at risk was calculated from the beginning of the follow-up at the survey dates (the time at risk was calculated from 2 years after the survey dates in the analyses excluding the liver cancer cases during the first 2 years of follow-up) to the end of the follow-up. In the present analyses, primary liver cancer comprised all types of primary liver cancer (HCC, cholangiocarcinoma, adenocarcinoma, and primary liver cancer with unspecified histology).

Statistical Analyses. Differences in risk factors based on different levels of coffee consumption were tested using the General Linear Model after adjustment for age and study year (Table 1). The single and joint associations between coffee consumption and serum GGT level at baseline on the risk of primary liver cancer were analyzed by using Cox proportional hazards models. Different levels of coffee consumption or serum GGT were included in the models as dummy variables, and the significance of the trend over different categories of coffee consumption or serum GGT was tested in the same models by giving an ordinal numeric value for each dummy variable. The proportional hazards assumption in the Cox model was assessed with graphical methods and with models including time-by-covariate interactions.[25] In general, all proportionality assumptions were appropriate. Incident diabetes and chronic liver disease during follow-up were used as time-dependent covariates in Cox models. The reference category 0-1 cup/day was chosen rather than the non–coffee drinking category because the risk of liver cancer did not differ between coffee drinkers with one cup daily and coffee abstainers (hazard ratio [HR] was 0.97). Thus, the reference group contained larger numbers of participants, making the statistical comparisons more stable. Because none of the interactions between sex and coffee consumption and serum GGT level on the risk of liver cancer were statistically significant, men and women were combined in the analyses. To avoid the potential bias of

Table 2. Hazard Ratios of Liver Cancer by Volume of Coffee Consumption

Characteristic	Daily Coffee Consumption (Cups/Day)					*P* Value for Trend
	0–1	2–3	4–5	6–7	≥8	
Total (n = 60,323)						
Number of participants	6150	12,681	17,991	13,726	9775	
Numbers of liver cancer	20	30	33	28	17	
Person-years	96,777	210,816	333,673	283,191	192,010	
Age, sex, and study year adjusted HR (95% CI)	1.00	0.68 (0.39–1.21)	0.46 (0.26–0.81)	0.42 (0.24–0.76)	0.40 (0.21–0.76)	0.012
Multivariate adjusted HR (95% CI)*	1.00	0.66 (0.37–1.16)	0.44 (0.25–0.77)	0.38 (0.21–0.69)	0.32 (0.16–0.62)	0.003
Men (n = 29,286)						
Number of participants	2999	5430	7892	6732	6233	
Numbers of liver cancer	16	21	17	15	13	
Person-years	48,992	90,517	138,663	127,477	116,396	
Age and study year adjusted HR (95% CI)	1.00	0.69 (0.36–1.33)	0.37 (0.19–0.74)	0.34 (0.17–0.70)	0.36 (0.17–0.76)	0.006
Multivariate adjusted HR (95% CI)*	1.00	0.68 (0.35–1.31)	0.35 (0.18–0.71)	0.31 (0.15–0.63)	0.28 (0.13–0.61)	0.001
Women (n = 31,037)						
Number of participants	3151	7251	10 099	6994	3542	
Numbers of liver cancer	4	9	16	13	4	
Person-years	47,785	120,299	195,010	155,714	75,614	
Age and study year adjusted HR (95% CI)	1.00	0.71 (0.22–2.32)	0.66 (0.22–1.99)	0.64 (0.20–1.98)	0.49 (0.12–1.99)	0.90
Multivariate adjusted HR (95% CI)*	1.00	0.62 (0.19–2.04)	0.60 (0.20–1.82)	0.58 (0.19–1.82)	0.41 (0.10–1.70)	0.82

*Adjusted for age, sex (men and women combined analysis only), study year, alcohol consumption, education, smoking, diabetes and chronic liver disease at baseline and during follow-up, and BMI.

early liver cancer due to an elevated serum GGT or change in coffee drinking habit, additional analyses were carried out excluding the subjects who were diagnosed with liver cancer and/or those who died from any causes during the first 2 years of follow-up. Statistical significance was considered to be $P < 0.05$. All statistical analyses were performed with SPSS for Windows 15.0 (SPSS Inc., Chicago, IL).

Results

The median coffee consumption daily was 5.0 cups (interquartile range: 3.0-6.0 cups). After adjustment for age and study year, coffee consumption was directly associated with BMI and smoking and inversely associated with education and serum GGT (Table 1).

During a median follow-up period of 19.3 years (interquartile range: 9.3-29.2 years), 128 participants were diagnosed with an incident primary liver cancer. The multivariable-adjusted (age, sex, alcohol consumption, education, smoking, diabetes and chronic liver disease at baseline and during follow-up, and BMI) HRs of liver cancer in participants who drank 0-1, 2-3, 4-5, 6-7, and ≥8 cups of coffee daily were 1.00, 0.66, 0.44, 0.38, and 0.32 (*P* for trend = 0.003), respectively (Table 2 and Fig. 1). After exclusion of the participants who were diagnosed with chronic liver disease at baseline (n = 84) and who were diagnosed with liver cancer (n = 8) and/or those who died from any causes (n = 478) during the first 2 years of follow-up, multivariable-adjusted HRs of liver cancer in participants who drank 0-1, 2-3, 4-5, 6-7, and ≥8 cups of coffee daily were 1.00, 0.66, 0.43, 0.42, and 0.35 (*P* for trend = 0.013), respectively.

When the analysis was restricted to surveys from 1982 to 2002 (n = 37,842), more-detailed data on alcohol consumption and measurement of serum GGT level were available. During a median follow-up period of 14.3 years (interquartile range: 6.4-19.4 years), 60 participants were diagnosed with an incident primary liver cancer. The multivariable-adjusted and GGT-adjusted HRs of liver cancer in participants who drank 0-1, 2-3, 4-5, 6-7, and ≥8 cups of coffee daily were 1.00, 0.53 (95% confidence

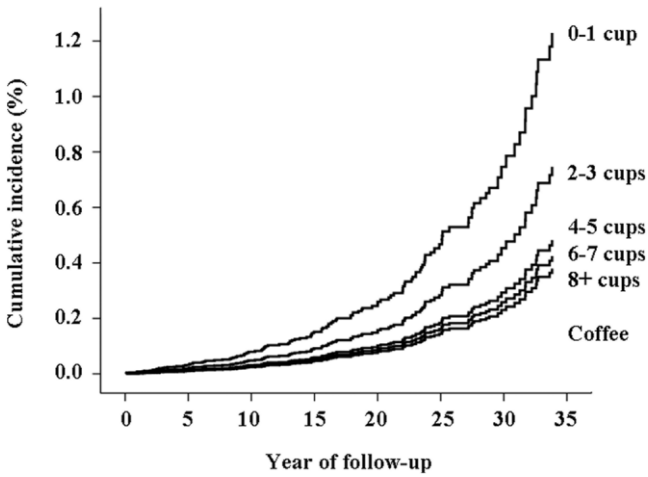

Fig. 1. The cumulative incidence curve of liver cancer by volume of coffee consumption. Adjusted for age, sex, study year, alcohol consumption, education, smoking, diabetes and chronic liver disease at baseline, and BMI.

Table 3. Hazard Ratios of Liver Cancer by Quartiles of Serum GGT*

Characteristic	Quartiles of Serum GGT				*P* Value for Trend
	1	2	3	4	
Number of participants	10,102	9086	9050	9604	
Numbers of liver cancer	7	13	15	25	
Person-years	177,092	119,651	106,266	104,466	
Age, sex, and study year adjusted HR (95% CI)	1.00	2.15 (0.84-5.48)	2.47 (0.96-6.32)	4.03 (1.63-9.97)	0.020
Multivariate adjusted HR (95% CI)†	1.00	2.19 (0.86-5.59)	2.53 (0.99-6.48)	4.17 (1.67-10.4)	0.018
Multivariate adjusted HR (95% CI)‡	1.00	2.02 (0.79-5.14)	2.13 (0.82-5.51)	3.13 (1.22-8.07)	0.12

*This analysis only included surveys of 1982, 1987, 1992, 1997, and 2002. Cut-points for quartile of GGT were 13, 19, and 31 U/L.
†Adjusted for age, sex, study year, alcohol and coffee consumptions.
‡Adjusted for the above variables and for education, smoking, diabetes and chronic liver disease at baseline and during follow-up, and BMI.

interval [CI] 0.26-1.12), 0.41 (95% CI 0.20-0.86), 0.29 (95% CI 0.12-0.70), and 0.22 (95% CI 0.07-0.63) (*P* for trend = 0.018), respectively.

A statistically significant positive association was found between serum GGT and liver cancer risk (Table 3 and Fig. 2). The multivariable-adjusted and coffee-adjusted HR of liver cancer for the highest versus the lowest quartile of serum GGT was 3.13 (95% CI 1.22-8.07). Exclusion of the participants who were diagnosed with chronic liver disease at baseline (n = 74) and who were diagnosed with liver cancer (n = 7) and/or those who died from any causes (n = 280) during the first 2 years of follow-up, did not change this association (HR 2.91, 95% CI 1.04-8.15).

Table 4 shows multivariable-adjusted HRs of liver cancer at different levels of coffee consumption among different subpopulations. No significant interactions were found between the age groups (25-49 versus 50-74 years), smokers versus nonsmokers, alcohol drinkers versus nondrinkers, and BMI levels (<30 versus >30 kg/m^2). In our surveys of 1987, 1992, 1997, and 2002 that collected details about different types of coffee consumption (n = 28,771), the inverse trend between coffee drinking and liver cancer risk was found in both filtered coffee drinkers and pot-boiled coffee drinkers (data not shown).

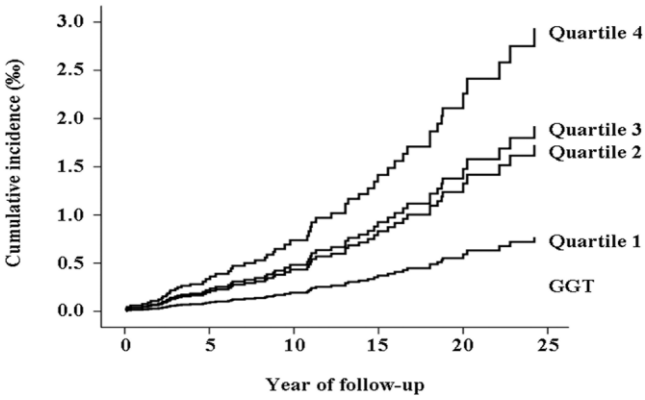

Fig. 2. The cumulative incidence curve of liver cancer by quartiles of GGT. Adjusted for age, sex, study year, alcohol and coffee consumption, education, smoking, diabetes and chronic liver disease at baseline, and BMI.

The joint association of coffee consumption and serum GGT with the risk of liver cancer is shown in Fig. 3. Multivariable-adjusted inverse association between coffee consumption and liver cancer risk was found in participants at the highest quartile of serum GGT (*P* for trend = 0.011) and combined quartiles 1-3 of serum GGT (*P* for trend = 0.10). In comparison with persons who drank at least 6 cups of coffee daily and had serum GGT in the quartiles 1-3 (reference group), subjects who drank 0-1 cup of coffee and were at the highest quartile of serum GGT showed about 9.2 times increased risk for the development of liver cancer. There were no statistically significant interactions between coffee consumption and serum GGT on the risk of liver cancer ($P > 0.25$).

Discussion

The results of our large population-based prospective study found a significant inverse association between coffee drinking and the risk of primary liver cancer. High level of serum GGT, measured by the highest quartile of serum GGT, increased the risk of primary liver cancer. Nevertheless, the inverse association between coffee consumption and the risk of liver cancer was consistent in the subjects at any level of serum GGT.

Two recent meta-analyses based on three Japanese cohorts and five case-control studies (two from Japan, two from Italy, and one from Greece) have demonstrated that increased consumption of coffee may reduce the risk of liver cancer.[8,9] Because all studies included in the two meta-analyses were conducted in populations at high risk of liver cancer, it is not known to what extent the observed findings may be generalizable to other populations. In Japan and Italy, about 90% and 80% of liver cancers are estimated to be attributable to HCV and HBV infections.[2,26,27] In this study, we have no information available on history of HCV and HBV infections; however,

Table 4. Hazard Ratios of Liver Cancer According to Coffee Consumption Stratified by Age, Smoking, Alcohol Consumption, and BMI

Characteristic	Daily Coffee Consumption (Cups/Day)					P Value for Trend	*P* Value for Interaction
	0–1	2–3	4–5	6–7	≥8		
Age (year)							>0.75
25–49	1.00	0.38 (0.15–0.94)	0.41 (0.18–0.93)	0.30 (0.12–0.73)	0.24 (0.09–0.66)	0.036	
50–74	1.00	0.79 (0.37–1.68)	0.40 (0.18–0.87)	0.41 (0.19–0.90)	0.38 (0.16–0.94)	0.034	
Smoking							>0.25
Never or ever	1.00	0.83 (0.42–1.66)	0.43 (0.21–0.88)	0.34 (0.16–0.75)	0.27 (0.10–0.78)	0.005	
Current	1.00	0.22 (0.07–0.68)	0.31 (0.13–0.78)	0.32 (0.13–0.79)	0.29 (0.12–0.71)	0.036	
Alcohol consumption							>0.75
Never drinker	1.00	0.59 (0.26–1.33)	0.46 (0.22–0.97)	0.36 (0.16–0.79)	0.35 (0.14–0.85)	0.088	
Alcohol drinker	1.00	0.62 (0.27–1.39)	0.32 (0.13–0.77)	0.36 (0.15–0.88)	0.29 (0.11–0.79)	0.042	
BMI (kg/m2)							>0.75
<30	1.00	0.61 (0.31–1.21)	0.48 (0.25–0.93)	0.39 (0.19–0.78)	0.32 (0.15–0.71)	0.036	
≥30	1.00	0.53 (0.19–1.48)	0.24 (0.08–0.72)	0.29 (0.10–0.85)	0.29 (0.09–0.99)	0.077	

This analysis included all surveys (n = 60,323); adjusted for age, sex, study year, education, smoking, diabetes and chronic liver disease at baseline and during follow-up, BMI, other than the variable for stratification.

the prevalence of HBV and HCV infections among the general population is very low in Finland (<0.001% and 0.4%, respectively)[11] compared with the prevalence in Japan (1.5% and 1.5%-2.3%) and Italy (>3% and 2.2%).[3,4,28] The incidence of liver cancer is lower in Finland and other mostly developed countries than in Japan and Italy.[1] Both the low prevalence of HBV and HCV infections and high coffee consumption may contribute to the low liver cancer incidence in Finland compared with that in Japan and Italy.

Serum GGT is a plasma membrane enzyme and is mainly secreted by hepatic Kupffer cells and endothelial cells of the bile duct in healthy adults.[18] Total serum GGT can be divided into 13 isoenzymes, and GGTII has been considered as a useful tumor marker complementary to alpha fetoprotein for diagnosis of small HCC.[18] The effects of regular daily coffee consumption on liver enzymes have been studied in several studies, and an inverse association between coffee consumption and serum GGT level and other liver enzymes (ALT and alkaline phosphatase) was found.[12,13] Serum GGT level has been widely used as a marker of liver cirrhosis,[17] because elevation of GGT could be an expression of excess deposition of fat in liver (hepatic steatosis), and was also associated with both inflammation and oxidative stress, and they might play a major role in pathological conditions such as inflammation and diabetes.[29] The present study is, to our knowledge, the first large prospective study to suggest that a high level of serum total GGT is a risk factor for primary liver cancer. Unfortunately, we did not determine any of the GGT isoenzymes, which might make the association even stronger.

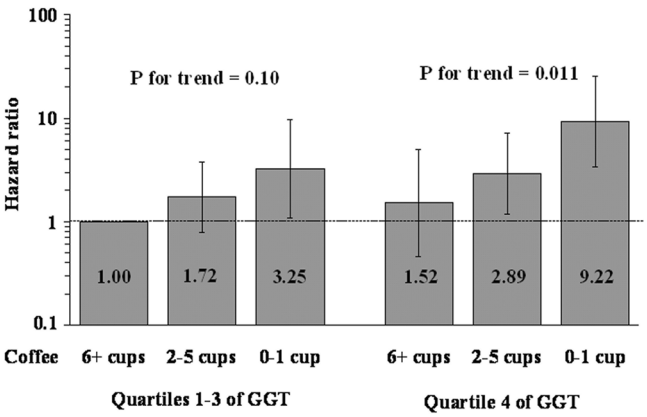

Fig. 3. Hazard ratio of liver cancer by joint effect of coffee consumption and serum GGT. Adjusted for age, sex, study year, alcohol consumption, education, smoking, diabetes and chronic liver disease at baseline and during follow-up, and BMI.

Several previous studies have found an inverse association between coffee drinking and the risk of chronic liver disease[14] and liver cirrhosis,[15,16] which are strongly related to the risk of liver cancer.[30] Therefore, it could be hypothesized that coffee drinking might decrease liver cancer risk partly through coffee's protective effect on the risk of chronic liver disease. In this study, the inverse association between coffee consumption and liver cancer risk, as well as the positive association between serum GGT and liver cancer risk, did not change after excluding the subjects with chronic liver diseases at baseline and who were diagnosed with liver cancer during the first 2 years of follow-up. Moreover, this inverse association between coffee consumption and liver cancer risk was consistent in the subjects at any level of serum GGT.

Several other putative mechanisms behind the association of coffee drinking and serum GGT on liver cancer risk have also been proposed. Coffee contains many compounds, such as chlorogenic acid, which may have the

potential to influence glucose metabolism processes to prevent hyperglycemia, and consequently oxidative stress. Part of this effect on the glycemic status is due to the favorable effects of chlorogenic acid on the liver.[21] Animal studies have also shown that coffee and chlorogenic acid have a direct inhibitory effect on carcinogenic potential in the liver.[31] Caffeine is another major component of coffee, and in one animal study, caffeine levels were inversely related to liver injury.[32] Recently, our studies[21,29] found that coffee consumption may decrease type 2 diabetes risk; however, a raised serum GGT level may increase the risk of type 2 diabetes.[33] Another meta-analysis indicated a positive association between diabetes and HCC risk.[34] Thus, the protective effects of coffee consumption on liver cancer risk may be mediated through a reduced risk of type 2 diabetes, but on the other hand, the harmful effect of serum GGT on liver cancer risk may be mediated through an increased risk of type 2 diabetes.

The habit of coffee consumption among the Finns is somewhat different from other Western populations. The majority of Finns drink coffee daily, with an average cup size of about 1-1.3 dL. In this study, only 6.9% of Finns (n = 4183) reported no coffee consumption and 3.3% of Finns (n = 1967) reported consumption of one cup of coffee a day among the 60,323 participants. The use of decaffeinated coffee is not popular in Finland. In our surveys of 1987, 1992, 1997, and 2002 which collected details about different types of coffee consumption among coffee drinkers (n = 26,707), 86% of participants used filtered coffee, 11% of participants drank pot-boiled coffee without filtering, 2% of participants drank instant coffee, and only 0.8% of the people drank decaffeinated or noncaffeinated coffee. The type of coffee did not modify the risk of liver cancer.

There are several strengths and limitations in our study. Our study is population-based and comprises a large number of participants from a homogeneous population. The median follow-up, 19.3 years, was long without any loss of follow-up. A limitation of our study was that we used self-reported data on coffee intake only at baseline. However, the misclassification of exposure during the follow-up is most probably not systematically related to the outcome, but may weaken the observed association. Second, we did not assess the effect of caffeine on the risk of liver cancer because we did not have available information about other main sources of caffeine, that is, the consumption of cola beverages and chocolate. Third, we had no data on history of either HBV or HCV infections at baseline, but it is known that the prevalence of these infections are very low in Finland. Because our data allowed for only a dichotomized measure of alcohol consumption in the whole sample, we may not be able to fully control for the effect of this variable on the risk of liver cancer. In order to evaluate the impact of this shortcoming, we performed separate subgroup analyses (surveys of 1982, 1987, 1992, 1997, and 2002) in the multivariable-adjusted model of a dichotomized measure of alcohol consumption compared with another multivariable-adjusted model of four categories of alcohol consumption. In general, the relative risk between coffee consumption and liver cancer was not influenced substantially or systematically. In addition, we cannot completely exclude the effects of residual confounding due to measurement error in the assessment of confounding factors or some unmeasured factors.

In conclusion, this study confirmed a significant inverse association between coffee drinking and the risk of primary liver cancer. High levels of serum GGT, measured by the highest quartile of serum GGT, significantly increased the risk of primary liver cancer. The biological mechanisms behind the association of coffee consumption with the risk of liver cancer are not understood at present. It would be interesting to find out whether the modification of coffee drinking would modify the risk of liver cancer in people positive for either HBV or HCV infection.

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