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γ-Glutamyltransferase and cancer risk: The Korean cancer prevention study

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Elevated serum γ-glutamyltransferase (GGT) is a marker of hepatic injury and is associated with risk of chronic disease. However, the value of GGT as a biomarker for cancer risk remains unclear. Therefore, we evaluated the association of serum GGT with cancer incidence among more than 1.6 million Koreans. We included 1,662,087 Koreans (1,108,121 men and 553,966 women aged 20–95 years) who received health insurance from the National Health Insurance Service and had a biennial medical evaluation between 1995 and 1998. Follow-up was through December 2012. Using Cox proportional hazards models, we adjusted for age, smoking status, alcohol consumption, exercise and body mass index after exclusion of early cases (cancer diagnosis or death within 5 years of starting follow-up) and estimated hazard ratios (HRs) of overall and organ-specific cancer incidence by GGT quintiles. During the 17-year follow-up, 129,087 new cancer cases occurred among the participants. Across levels of GGT, there was a positive gradient of HR and the highest quintile of GGT (≥60 IU/L) had the highest HR for all cancers in both men and women. By cancer site, the association was strongest for liver cancer, comparing the highest and lowest strata in men [HR, 6.67; 95% confidence interval (95%CI), 5.88–7.57] and in women (HR, 7.57; 95%CI, 6.41–8.94). Significant associations were also observed for cancers of the esophagus, larynx, stomach, colorectal, bile duct and lung in men and of the bile duct in women. Increased serum GGT level is independently associated with risk of cancer.

Serum γ-Glutamyltransferase (GGT) is a marker of hepatic injury; elevated levels can result from alcohol consumption, acute and chronic liver disease and oxidative stress.[1–3] Individuals with high levels of serum GGT are at increased risk of a wide range of disease outcomes, including diabetes and nonhepatic diseases compared with those having a level within normal limits.[4,5] Previous epidemiological studies have suggested that elevated serum GGT levels are associated with increased risk of dyslipidemia, obesity, hypertension, type 2 diabetes mellitus, metabolic syndrome and cardiovascular disease.[4–9] Several recent observational studies have found an association between elevated serum GGT levels and cancer incidence, but results have been inconsistent.[10–20] In addition, for specific cancers, including cancers of the breast,[11,13,14] cervix,[21] general female genital organs,[11] lymphoid tissue,[11,21] prostate,[14] liver,[14,15] as well as cancers in the digestive organs, respiratory system and intrathoracic organs and urinary organs,[11,12] conflicting results have been reported across studies.

Since serum GGT is a marker of oxidative stress, it may be a useful risk indicator beyond traditional risk factors for cancer.[22] Thus, quantifying the association of serum GGT levels with cause-specific cancer incidence may provide valuable information from clinical and public health perspectives. Therefore, the purpose of this study was to assess the association of serum GGT with cancer incidence among more than 1.6 million Koreans.

Key words: γ-Glutamyltransferase, cancer, cohort study
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Meterial and Methods

Study participants

The Korean Cancer Prevention Study (KCPS) is a prospective cohort study with a follow-up of 20 years. Information concerning the development of this cohort from participants in the National Health Insurance Service (NHIS) has been provided elsewhere.[23] In brief, the cohort was composed of government employees, teachers and their dependents who were insured by the NHIS from 1992 through 1999 and 20–95 years of age, had at least one medical examination, and completed a questionnaire during that time. Previously, the original KCPS included 1,329,525 Korean men and women 30–95 years of age who participated in a NHIS medical evaluation

What's new?

Elevated serum γ-Glutamyltransferase (GGT)—a marker of hepatic injury that is associated with risk of chronic disease—is also a marker of oxidative stress and may thus be a useful risk indicator beyond traditional risk factors for cancer. Recent studies have, however, yielded conflicting results and focused on the Western population. In this large prospective Asian cohort study, elevated serum GGT was associated with overall cancer incidence, and with increased risk of liver and bile duct cancer specifically, in both men and women. The findings offer a comprehensive update and warrant further study into the possible underlying biological mechanisms.

between 1992 and 1995 with biennial follow-up evaluations through the present.[23] However, for these analyses, we selected from those having a routine examination between 1995 and 1998. This specific time interval was selected since GGT testing began in 1995. The initial population included 1,962,700 participants aged 20 years between 1995 and 1998. The numbers of baseline enrollees by year were 275,268 in 1995, 1,262,354 in 1996, 206,441 in 1997 and 218,137 in 1998. All enrollees in the NHIS underwent standardized clinical examination at the local hospital. The new cohort included 921,058 members from the original cohort.

For the present study, we selected all individuals whose GGT levels were measured at baseline from 1995 through 1998 ($n = 1{,}930{,}736$). To avoid any bias due to preexisting disease in assessing the association of GGT with cancer risks, we excluded 1,273 participants who reported having any preexisting cancer as well as 25,059 participants who reported as having preexisting liver disease and 242,317 participants with missing information for key variables: smoking status, alcohol intake, exercise and body mass index. The final sample included 1,662,087 participants (1,108,121 men and 553,966 women). Since the study involved routinely collected data, informed consent for this study was not specifically obtained. The institutional review board of Yonsei University (Seoul, South Korea) approved the study.

Data collection

All enrollees in the NHIS underwent standardized examinations at local hospitals. In the 1995, 1996, 1997 and 1998 questionnaires, participants were asked to describe their cigarette smoking habit, along with other health habits including alcohol consumption. Total daily alcohol consumption was expressed as number of glasses per week, expressed as Korea's most popular alcoholic drink "Soju"; one glass of Soju contains about 12 g of ethanol. The completed questionnaires were reviewed and edited by trained staff and then entered into an electronic database.

Participants' weight and height were measured, and blood pressure was measured in the seating position. Fasting blood samples were obtained from participants and tested for routine clinical biochemistry including total cholesterol, fasting glucose, alanine aminotransferase (ALT) and asparate aminotransferase (AST) and GGT. Quality control of procedures was in accordance with the Korean Association of Laboratory Quality Control Standards.[24]

Follow-up and cancer outcomes

The follow-up period was up to 17 years, from January 1, 1996 until December 31, 2012. The principal outcome variables were cancer incidence by site, based on the national cancer registry data and hospitalization records from the medical insurance claims data. Although Korea has a national cancer registry, reporting was not complete during the time of follow-up. Consequently, hospital admission files were used to identify the first admission event for cancer.

Statistical analysis

For analysis, GGT values were stratified by quintiles: <12, 12–16, 17–23, 24–39 and ≥60 IU/L. In order to estimate the independent association of GGT with risk of cancer incidence, the Cox proportional hazard model was used. The model adjusted for age, age squared, smoking status, alcohol consumption, exercise, body mass index (BMI) and diabetes mellitus to estimate the independent association of GGT. To avoid the possibility of the reverse association between GGT levels and cancer risk, we excluded participants who received any cancer diagnosis or who died within 5 years of the starting point. For more detailed analyses of the dose-response trends, we also used restricted quadratic spline models with knots at serum GGT levels of 9, 12, 14, 17, 20, 24, 30 and 40 mg/dl. For the sensitivity analysis, to control the potential confounding caused by liver disease related factors, specifically alcohol consumption and viral hepatitis B (HBV), the data was further stratified into drinker and never drinker groups, and negative and positive HBV groups. All analyses were performed separately for men and women using SAS statistical software version 9.2 (SAS Institute, Cary, NC). All statistical tests were two-sided and statistical significance was determined as $p < 0.05$.

Results

The study population of 1,662,087 participants (1,108,121 men and 553,966 women) was largely middle aged (Table 1). As expected, new enrollees were younger than the original KCPS members.

Participant characteristics are shown in Table 2. Mean ages at study entry were 41.1 years in men and 41.4 years in

Table 1. General characteristics of study cohort participants, by membership in the original KCPS cohort and new enrollees, 1995–1998

	1995–1998 (n = 1,662,087)			
	Original KCPS cohort (n = 921,058)		New enrollees (n = 741,029)	
	Men	Women	Men	Women
Age, mean ± SD (years)	43.31 ± 9.96	46.61 ± 11.79	32.48 ± 10.10	34.54 ± 12.78
Body mass index, mean ± SD (kg/m^2)	23.25 ± 2.54	22.90 ± 3.08	23.14 ± 2.69	21.57 ± 2.99
Fasting glucose, mean ± SD (mg/dl)	90.67 ± 19.32	88.24 ± 18.37	88.97 ± 18.88	87.18 ± 18.77
Alcohol consumption, mean ± SD (g/day)	17.86 ± 32.09	0.22 ± 2.10	13.43 ± 21.47	0.95 ± 3.58
Smoking status				
Ex-smoker (%)	20.21	1.60	9.97	0.79
Current smoker (%)	58.71	3.33	61.86	1.32
Drinking status (ever; %)	78.04	14.99	75.62	24.00
Diabetes (yes; %)	2.82	2.30	2.33	2.19

women. Median GGT levels at study entry were 26 IU/L in men and 13 IU/L in women. At higher GGT levels, participants were older and heavier, and had higher diastolic blood pressure, higher fasting glucose, higher ALT and AST and higher prevalence of diabetes and hypertension. Men with elevated GGT levels were more likely to be smokers and more likely to consume alcohol (Table 2).

Cancer incidence

During the 17 years of follow-up, 90,069 incident cancer cases occurred among men and 39,018 among women. After exclusion of early cases (cancer occurring within 5 years of the starting point), 74,201 incident cancer cases occurred among men and 32,796 among women. We observed positive linear trends in cancer incidence with increased GGT levels for colorectal, bile duct and lung cancers in men (Table 3). An association of GGT level with esophageal, laryngeal, stomach, colorectal, bile duct and lung cancer incidence was observed in the highest GGT level group (≥40 IU/L). The association between serum GGT and liver cancer was strong [hazard ratio (HR), 6.6; 95% confidence interval (95%CI), 5.8–7.5]. However, serum GGT level was negatively associated with leukemia incidence.

In women, positive linear trends were observed in incidence of bile duct cancer. Although the association of GGT level with brain cancer was not statistical significant, positive linear trends were observed (Table 4). Similar to men, we found a strong significant association between increased serum GGT levels and liver cancer in women (HR, 7.6; 95%CI, 6.4–8.9).

In restricted quadratic spline models, the risks of all cancers and liver cancer increased with increasing serum GGT levels in men and women (Fig. 1).

When stratifying by other variables (*i.e.,* BMI age and exercise), the association for liver cancer remained in both men and women. However, associations with site-specific cancers were attenuated in the high BMI (≥25 kg/m^2) and the younger group (<60 years; Supporting Information eTables 1 and 2).

Sensitivity analysis

To control potential confounding by alcohol consumption, the data was further stratified into drinker and never drinker groups. When considering using fractional polynomials, all-cancer incidence rates showed a linear trend in both drinker and never drinker groups with increasing GGT levels (Fig. 2). The risk of liver cancer associated with elevated serum GGT level was not modified by alcohol consumption. In men, we also assessed the association of serum GGT level with cancer risk considering smoking and alcohol consumption as potential modifiers and alcohol consumption in women. We observed significant associations with all cancer and liver cancer incidence regardless of smoking and drinking status. When stratified by HVB antigen, the association of increased serum GGT levels with risk of liver cancer incidence was significant in both the HBV antigen negative and positive groups (Supporting Information eTable 4).

Discussion

In this large prospective cohort study, elevated serum GGT levels are associated with overall cancer incidence in men and women, including those who are self-reported non-drinkers and nonsmokers. One strength of this study is the size of the cohort, nearly 1.7 million, matching that of a recent meta-analysis that included 14 cohort studies.[20] In terms of site-specific cancer incidence, elevated serum GGT was significantly associated with increased risk of esophageal, laryngeal, stomach, colorectal and lung cancer in men. In both men and women, elevated serum GGT levels were associated with increased risk of liver and bile duct cancer. Although serum GGT is a marker of alcohol intake, it is notable that elevated serum GGT levels are associated with

Table 2. Baseline characteristics by GGT level[1], KCPS1995–1998, $n = 1{,}662{,}087$

	GGT (IU/L)				
Characteristics	**<12**	**12–16**	**17–23**	**24–39**	**≥40**
Men	***N* = 93,451**	***N* = 171,520**	***N* = 230,319**	***N* = 299,741**	***N* = 313,090**
Age (years)	38.3 (13.3)	38.9 (12.8)	40.1(12.4)	41.6(11.9)	43.5(10.9)
Body mass index (kg/m^2)	22.1(2.3)	22.5 (2.4)	22.9 (2.5)	23.7 (2.7)	24.4 (2.8)
Systolic blood pressure (mmHg)	119.2 (14.0)	120.0 (14.2)	121.4 (14.6)	123.5 (15.2)	127.3 (16.4)
Diastolic blood pressure (mmHg)	76.4 (10.1)	77.0 (10.2)	78.0 (10.4)	79.7 (10.7)	82.4 (11.3)
Fasting glucose (mg/dl)	88.0 (16.4)	88.4 (17.0)	89.5 (18.7)	91.3 (20.6)	96.5 (27.0)
Total cholesterol (mg/dl)	171.1 (31.4)	176.9 (32.1)	183.3 (33.3)	190.7 (35.0)	198.9 (39.4)
Log GGT	1.0 (0.1)	1.1 (0.0)	1.3 (0.0)	1.5 (0.1)	1.8 (0.2)
Log ALT	1.3 (0.1)	1.4 (0.1)	1.4 (0.1)	1.4 (0.1)	1.5 (0.2)
Log AST	1.2 (0.2)	1.3 (0.2)	1.3 (0.2)	1.4 (0.2)	1.5 (0.2)
Alcohol intake (g/day)	6.7 (13.9)	8.0 (15.2)	9.9 (17.4)	13.5 (21.0)	23.3 (29.3)
Smoking status (%)					
Nonsmoker	38.7	36.1	33.0	29.0	22.6
Exsmoker	12.4	12.9	13.6	14.1	13.7
Current smoker					
1–10 cig	9.8	9.8	9.5	9.2	9.0
−11–20 cig	30.7	32.2	33.6	35.5	38.6
>20 cig	8.4	9.1	10.3	12.2	16.1
Exercise (%)	61.7	61.1	59.8	58.2	57.1
Type 2 diabetes (%)	2.0	2.1	2.6	3.5	6.8
Hypertension (%)	19.0	20.9	24.1	29.5	40.0
Women	*N* = 230,628	*N* = 152,302	*N* = 96,246	*N* = 54,958	*N* = 19,832
Age (years)	38.2 (13.0)	40.9 (14.0)	44.3 (14.4)	47.8 (14.0)	50.7 (13.0)
Body mass index (kg/m^2)	21.7 (2.7)	22.2 (3.1)	22.9 (3.3)	23.7 (3.4)	24.3 (3.5)
Systolic blood pressure (mmHg)	114.3 (15.2)	116.8 (16.7)	119.5 (18.2)	122.7 (19.5)	125.5 (20.5)
Diastolic blood pressure (mmHg)	73.0 (10.8)	74.6 (11.4)	76.3 (12.0)	78.4 (12.4)	79.9 (12.8)
Fasting glucose (mg/dl)	86.5 (14.7)	87.9 (17.5)	90.4 (22.3)	94.5 (28.9)	99.5 (34.9)
Total cholesterol (mg/dl)	179.4 (34.9)	186.1 (36.7)	192.5 (38.8)	199.8 (41.3)	207.2 (44.5)
Log GGT	0.9 (0.1)	1.1 (0.0)	1.3 (0.0)	1.5 (0.1)	1.8 (0.2)
Log ALT	1.3 (0.1)	1.3 (0.1)	1.3 (0.1)	1.4 (0.2)	1.5 (0.2)
Log AST	1.1 (0.2)	1.2 (0.2)	1.3 (0.2)	1.3 (0.2)	1.5 (0.3)
Alcohol intake (g/day)	0.6 (2.7)	0.7 (3.1)	0.8 (3.7)	1.0 (4.9)	1.6 (7.4)
Smoking status (%)					
Nonsmoker	97.9	97.1	95.8	94.4	92.1
Exsmoker	0.7	1.0	1.2	1.5	1.9
Current smoker					
1–10 cig	0.8	1.1	1.7	2.2	3.1
11–20 cig	0.5	0.7	1.1	1.7	2.4
>20 cig	0.1	0.1	0.2	0.3	0.5
Exercise (%)	24.4	25.4	25.7	26.1	25.6
Type 2 diabetes (%)	1.5	2.4	4.1	6.8	11.2
Hypertension (%)	12.5	17.1	22.8	29.6	35.4

[1]Data are expressed as mean (SD) unless otherwise indicated.
Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase.

Table 3. Hazard ratio (HR, 95%CI)[1] of total and site-specific cancer incidence according to GGT level in men, excluding first 5-year follow-up, KCPS 1995–2012

	GGT, IU/L						
	<12	12–16	17–23	24–39	≥40		
Type of cancer	*N* = 93,451	*N* = 171,520	*N* = 230,319	*N* = 299,741	*N* = 313,090	*p* trend	Per 1SD
All cancers							
Incidence rate[2]	480.13	501.52	526.73	576.54	692.60		
HR (95%CI)	1.0	1.04 (1.01–1.08)	1.09 (1.06–1.13)	1.18 (1.14–1.22)	1.46 (1.41–1.51)	<0.0001	1.09 (1.08–1.09)
Esophagus							
Incidence rate[2]	8.90	6.12	8.66	11.85	23.12		
HR (95%CI)	1.0	0.80 (0.59–1.09)	1.00 (0.76–1.31)	1.24 (0.95–1.60)	2.16 (1.68–2.79)	<0.0001	1.14 (1.12–1.16)
Larynx							
Incidence rate[2]	5.63	3.41	5.58	7.35	9.62		
HR (95%CI)	1.0	0.67 (0.46–0.97)	0.94 (0.67–1.31)	1.16 (0.84–1.58)	1.69 (1.24–2.30)	<0.0001	1.10 (1.07–1.13)
Stomach							
Incidence rate[2]	113.23	116.76	123.59	128.74	145.39		
HR (95%CI)	1.0	0.99 (0.92–1.07)	1.04 (0.97–1.12)	1.07 (1.00–1.15)	1.22 (1.14–1.30)	<0.0001	1.04 (1.03–1.05)
Colorectal							
Incidence rate[2]	72.67	73.59	80.06	86.77	100.01		
HR (95%CI)	1.0	1.01 (0.92–1.11)	1.04 (0.95–1.13)	1.09 (1.00–1.18)	1.25 (1.15–1.36)	<0.0001	1.04 (1.02–1.05)
Liver							
Incidence rate[2]	28.68	34.90	40.71	60.45	131.40		
HR (95%CI)	1.0	1.34 (1.16–1.55)	1.71 (1.49–1.96)	2.67 (2.35–3.04)	6.59 (5.81–7.48)	<0.0001	1.20 (1.20–1.21)
Bile duct							
Incidence rate[2]	13.24	13.81	14.17	15.96	17.59		
HR (95%CI)	1.0	1.08 (0.85–1.36)	1.06 (0.85–1.32)	1.23 (0.99–1.52)	1.37 (1.10–1.69)	<0.0001	1.09 (1.06–1.12)
Pancreas							
Incidence rate[2]	17.88	16.23	17.77	18.49	20.69		
HR (95%CI)	1.0	0.93 (0.76–1.14)	1.01 (0.83–1.21)	1.04 (0.87–1.25)	1.14 (0.95–1.36)	<0.0001	1.05 (1.03–1.08)
Lung							
Incidence rate[2]	82.73	85.81	91.01	94.34	100.91		
HR (95%CI)	1.0	1.01 (0.92–1.11)	1.09 (1.00–1.19)	1.10 (1.01–1.20)	1.25 (1.14–1.36)	<0.0001	1.05 (1.04–1.06)
Prostate							
Incidence rate[2]	51.14	59.37	54.98	56.49	49.00		
HR (95%CI)	1.0	1.14 (1.02–1.27)	1.07 (0.96–1.19)	1.04 (0.94–1.15)	0.95 (0.85–1.06)	<0.0001	0.94 (0.91–0.96)
Kidney							
Incidence rate[2]	12.17	12.44	13.53	14.20	15.36		
HR (95%CI)	1.0	0.96 (0.78–1.19)	1.03 (0.84–1.25)	1.06 (0.88–1.28)	1.12 (0.92–1.36)	0.7250	1.01 (0.97–1.04)
Bladder							
Incidence rate[2]	20.10	20.87	24.08	24.18	26.07		
HR (95%CI)	1.0	1.02 (0.85–1.22)	1.11 (0.94–1.32)	1.12 (0.95–1.32)	1.06 (0.90–1.25)	0.5547	1.01 (0.98–1.04)
Brain							
Incidence rate[2]	5.17	5.72	4.52	4.89	5.88		
HR (95%CI)	1.0	0.99 (0.73–1.35)	0.94 (0.70–1.27)	1.03 (0.77–1.38)	1.21 (0.90–1.62)	0.1675	1.04 (0.99–1.09)
Leukemia							
Incidence rate[2]	6.79	4.80	7.15	12.98	6.15		
HR (95%CI)	1.0	0.67 (0.50–0.90)	0.91 (0.70–1.19)	0.88 (0.68–1.13)	0.90 (0.69–1.17)	0.6750	1.01 (0.96–1.07)

[1]Adjusted for age, age square, smoking status, alcohol intake, exercise, body mass index and diabetes mellitus.
[2]Age adjusted rate per 100,000 person-years.

Table 4. Hazard ratio (HR, 95%CI)[1] of total and site-specific cancer incidence according to GGT level in women, exclusion of first 5-year follow-up, KCPS 1995–2012

	GGT, IU/L						
	<12	12–16	17–23	24–39	≥40		
Type of cancer	***N* = 230,628**	***N* = 152,302**	***N* = 96,246**	***N* =54,958**	***N* = 19,832**	***p* trend**	**Per 1SD**
All cancers							
Incidence rate[2]	374.71	389.89	399.54	415.78	459.38		
HR (95%CI)	1.0	1.02 (0.99–1.05)	1.03 (1.00–1.07)	1.08 (1.04–1.12)	1.21 (1.15–1.28)	<0.0001	1.10 (1.08–1.13)
Esophagus							
Incidence rate[2]	0.94	2.03	0.79	0.91	2.12		
HR (95%CI)	1.0	2.58 (1.34–4.98)	1.18 (0.53–2.66)	1.23 (0.50–3.00)	1.89 (0.66–5.39)	0.8227	1.05 (0.68–1.61)
Larynx							
Incidence rate[2]	0.43	0.42	0.33	0.16	0.35		
HR (95%CI)	1.0	1.30 (0.50–3.40)	0.50 (0.13–1.89)	0.45 (0.09–2.17)	1.00 (0.20–4.93)	0.6331	1.08 (0.78–1.51)
Stomach							
Incidence rate[2]	55.14	53.73	60.09	54.21	52.48		
HR (95%CI)	1.0	0.98 (0.90–1.06)	1.07 (0.98–1.17)	1.02 (0.92–1.13)	0.95 (0.82–1.11)	0.9388	1.00 (0.93–1.08)
Colorectal							
Incidence rate[2]	50.42	49.72	57.11	51.67	51.45		
HR (95%CI)	1.0	1.00 (0.91–1.09)	1.10 (1.01–1.21)	1.03 (0.92–1.14)	1.12 (0.96–1.29)	0.2242	1.05 (0.97–1.12)
Liver							
Incidence rate[2]	14.01	19.22	21.68	33.25	93.04		
HR (95%CI)	1.0	1.53 (1.30–1.80)	1.76 (1.49–2.08)	2.77 (2.34–3.27)	7.55 (6.39–8.93)	<0.0001	1.32 (1.29–1.35)
Bile duct							
Incidence rate[2]	6.13	10.31	10.00	13.11	12.55		
HR (95%CI)	1.0	1.30 (1.03–1.64)	1.29 (1.00–1.65)	1.60 (1.24–2.07)	1.87 (1.35–2.58)	<0.0001	1.21 (1.12–1.31)
Pancreas							
Incidence rate[2]	12.07	14.28	13.16	14.63	14.07		
HR (95%CI)	1.0	1.15 (0.95–1.39)	1.19 (0.97–1.45)	1.31 (1.06–1.62)	1.26 (0.94–1.69)	0.3313	1.06 (0.94–1.21)
Lung							
Incidence rate[2]	36.50	34.57	37.09	38.14	26.63		
HR (95%CI)	1.0	0.97 (0.87–1.09)	1.02 (0.91–1.15)	1.02 (0.89–1.16)	0.77 (0.63–0.95)	0.1339	0.92 (0.81–1.03)
Breast							
Incidence rate[2]	54.07	56.87	56.14	59.82	59.92		
HR (95%CI)	1.0	1.03 (0.97–1.10)	1.00 (0.93–1.08)	1.07 (0.98–1.17)	1.02 (0.89–1.18)	0.0113	1.09 (1.02–1.16)
Cervix							
Incidence rate[2]	11.95	12.35	13.10	9.88	14.84		
HR (95%CI)	1.0	1.02 (0.88–1.19)	1.11 (0.93–1.31)	0.89 (0.71–1.11)	1.10 (0.82–1.49)	0.6905	1.03 (0.89–1.20)
Kidney							
Incidence rate[2]	6.00	5.76	5.05	5.06	7.28		
HR (95%CI)	1.0	0.95 (0.76–1.20)	0.88 (0.67–1.14)	0.87 (0.64–1.18)	1.20 (0.81–1.78)	0.0683	1.14 (0.99–1.31)
Bladder							
Incidence rate[2]	5.58	6.91	4.80	6.41	5.55		
HR (95%CI)	1.0	0.97 (0.74–1.26)	0.80 (0.59–1.09)	1.15 (0.84–1.56)	0.85 (0.53–1.38)	0.4695	0.90 (0.66–1.21)
Brain							
Incidence rate[2]	4.42	5.19	5.77	5.64	6.75		
HR (95%CI)	1.0	1.21 (0.92–1.59)	1.31 (0.98–1.75)	1.32 (0.94–1.85)	1.53 (0.97–2.40)	0.0159	1.18 (1.03–1.35)

Table 4. Hazard ratio (HR, 95%CI) of total and site-specific cancer incidence according to GGT level in women, exclusion of first 5-year follow-up, KCPS 1995–2012 (Continued)

	GGT, IU/L						
	<12	12–16	17–23	24–39	≥40		
Type of cancer	***N* = 230,628**	***N* = 152,302**	***N* = 96,246**	***N* =54,958**	***N* = 19,832**	***p* trend**	**Per 1SD**
Leukemia							
Incidence rate[2]	3.37	3.92	4.57	4.74	3.63		
HR (95%CI)	1.0	1.06 (0.81–1.40)	1.24 (0.92–1.67)	1.15 (0.80–1.65)	1.07 (0.62–1.85)	0.3311	1.11 (0.90–1.37)

[1]Adjusted for age, age square, smoking status, alcohol intake, exercise, body mass index and diabetes mellitus.
[2]Age adjusted rate per 100,000 person-years.

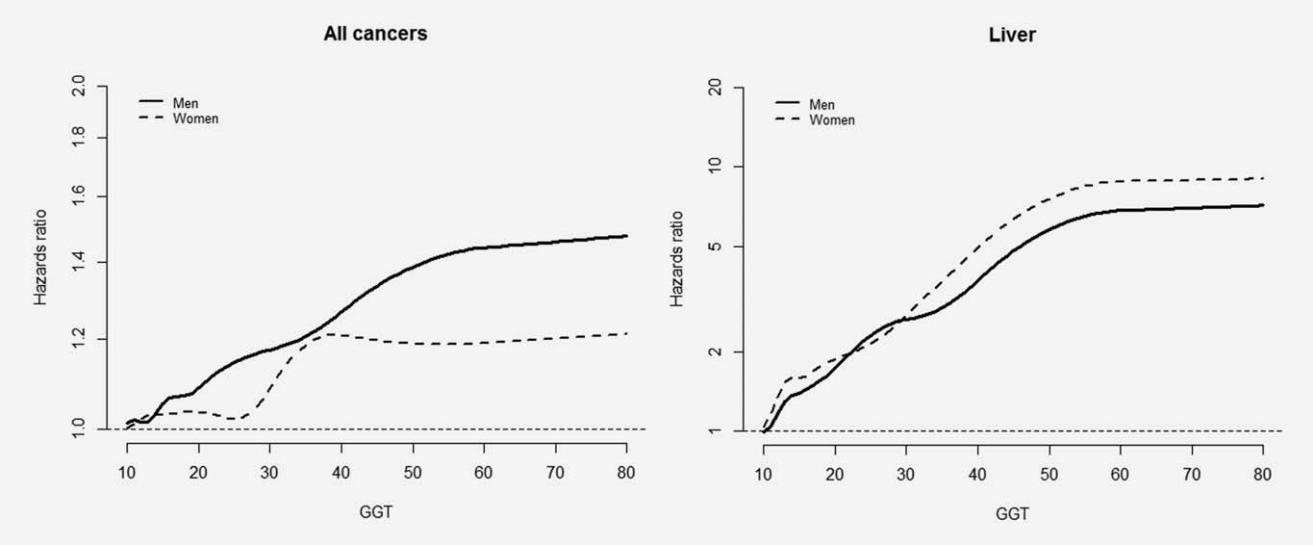

Figure 1. Hazard ratio of all cancers and liver cancer incidence in men and women.

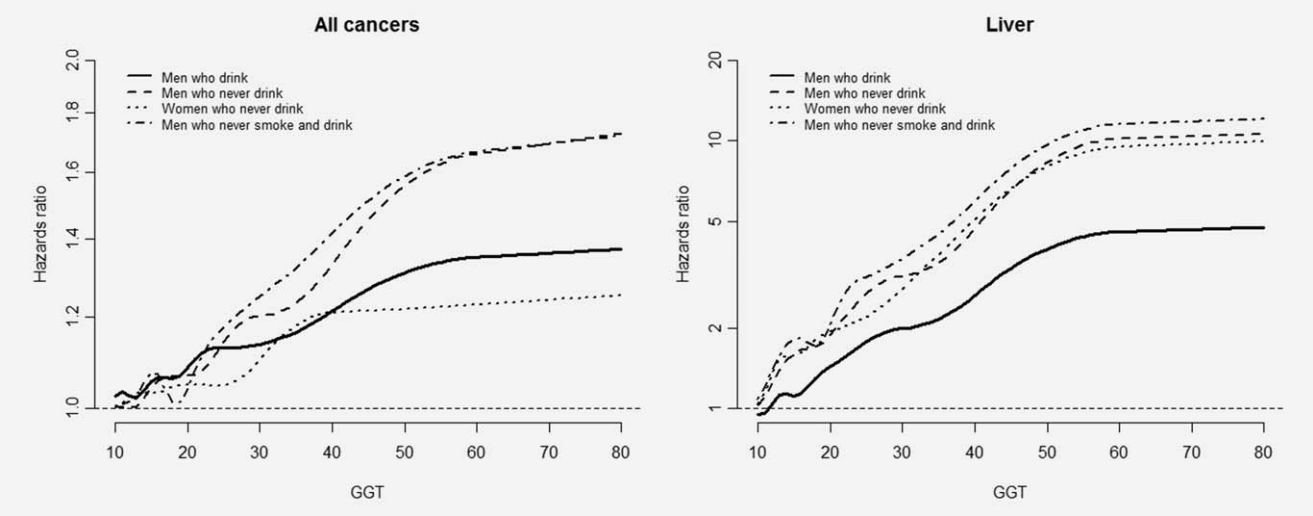

Figure 2. Hazard ratio of all cancers and liver cancer incidence by drinking and smoking status.

risk for cancer in those self-reported as not drinking or smoking and after adjustment for alcohol intake in those who do drink.

Previous studies have addressed the relationship between serum GGT level and cancer risk and generally found positive associations. Furthermore, several studies reported a

positive dose–response relationship between serum GGT level and overall cancer risk.[11–16,20] Our findings are consistent with previous studies reporting a dose-response relationship of overall cancer with elevated serum GGT level. Particularly, the association is strongest for liver cancer, a site for which the predominant risk factors, alcohol consumption and hepatitis, increase GGT. For site-specific cancers, associations of high GGT level with cancer-specific incidence are inconsistent across the previous studies. Large cohort studies from Austria and Sweden have shown associations for risk of cancer in the digestive organs, the respiratory system and intrathoracic organs and the urinary organs in men and women.[11,12,14] However, the category of all digestive organs was grouped such that the association of GGT with liver cancer was not examined separately from those of other digestive organs. In addition, a meta-analysis has shown a strong association between high GGT levels and cancer of digestive organs,[20] which is consistent with the significant associations between high GGT levels and stomach, colorectal, liver and bile duct cancer incidence in men in our study. However, the results were not consistent in women in our study.

In clinical practice, serum GGT is an indicator of liver disease and a marker of alcohol intake.[1,3] That a strong positive association was observed in alcohol-related cancer incidence may indicate that the associations were attributable to residual confounding by alcohol intake. In a previous study, there was a positive relationship between GGT and alcohol-related cancers only among current drinkers.[15] In our study, however, increased GGT levels were associated with increased risk of esophageal, stomach, colorectal, liver and lung cancers in both drinker and nondrinker groups.

We observed strong association between high GGT levels and risk of liver cancer in both men and women. A strong association between high GGT and liver cancer incidence has been previously shown.[10,15] In Korea, hepatitis B infection is common and an important cause of liver cancer.[23] Hepatitis B infection is a direct causal the risk factor for liver cancer.[25–27] To examine whether the association of GGT level is independently associated with occurrence of liver cancer, we analyzed the association between serum GGT and liver cancer according to hepatitis B infection status. In both negative and positive HVB antigen groups, increased serum GGT levels were associated with risk for liver cancer, thereby reflecting an independent association.

Although the biological mechanism underlying the association of increased serum GGT levels with risk of cancer is not clear, several processess may be involved. First, increased serum GGT may be affected by the serum concentration of persistent organic pollutants (POPs),[28] hence an elevated serum GGT may be a marker of exposure to environmental pollutants including POPs.[28,29] Certainly the mechanism by which POPs may increase risk for cancers remains unclear, is epidemiologic study suggests an association between POPs and cancer risk.[30] Also, with increased GGT levels in tumor cells, there is persistent production of reactive oxidant species (ROS). Thus, increased GGT levels can (or may) drive tumor progression.[31] Thus, serum GGT may be a diagnostic or prognostic marker of cancer and suggest strategies of prevention and management from both clinical and public health perspectives.

The present study design was prospective and a very large study population was selected from the general population of Korea. However, this study has several limitations. First, we did not collect repeated measurements for GGT and therefore could not determine changes in GGT level, and their association with cancer incidence. Second, the outcome definition was based on ICD-10 codes of hospitalization data. Therefore, we acknowledge the possibility that there could be some misclassification of primary site. Another limitation is reliance on self-reported tobacco and alcohol use, collected at only a single time point. Misclassification is unavoidable for the resulting exposure variables and hence we are concerned about residual confounding by tobacco and alcohol, which may contribute to the association observed for esophageal and laryngeal cancers.

In conclusion, serum GGT level is associated with overall cancer incidence and more strongly with cancers of a few sites, particularly cancer of the liver. The evidence does not support using GGT level as a general marker for identifying those at high risk for cancer. Thus, further studies are required, particularly to investigate the relation between longitudinal change in GGT and overall and site-specific cancer incidence. There is a need for further research on the association of serum GGT level with the risks of specific cancers incidence in the general population. In addition, there is a need for further investigations on biological mechanisms contributing to the association between serum GGT and cancer incidence.

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