ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2021 January 14; 27(2): 143-232

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
January 14, 2021

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World J Gastroenterol 2021 January 14; 27(2): 176-188

DOI: 10.3748/wjg.v27.i2.176

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Repeatedly elevated γ-glutamyltransferase levels are associated with an increased incidence of digestive cancers: A population-based cohort study

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Author contributions: Kwak MS and Lee CH contributed to the conception and design of the study, interpretation of the data, and drafting of the manuscript; Han K and Kim DH contributed to the acquisition of the data, statistical analysis, table and figure creation and critical revision of the manuscript for important intellectual content.

Institutional review board statement: This study protocol was exempted from review by the Seoul National University Hospital Institutional Review Board because of the retrospective design of the study, and the researchers accessed only de-identified open clinical data for analytical purposes (No. H-1912-022-1085).

Informed consent statement: The subjects' information in the database was de-identified before the investigator accessed the data, thus informed consent was waived.

Conflict-of-interest statement: The authors declare no conflicts of

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Abstract

BACKGROUND

The association between elevated γ-glutamyltransferase (GGT) at a certain point and incident cancer has been suggested; however, no study has evaluated the association between repeatedly elevated GGT and cancer incidence.

AIM

To investigate the effects of repeatedly elevated GGT on the incidence of digestive cancers.

METHODS

Participants who had undergone health screening from 2009 to 2012 and 4 consecutive previous examinations were enrolled. GGT points were calculated as the number of times participants met the criteria of quartile 4 of GGT in four serial measurements (0-4 points). Multivariable Cox proportional hazard regression models were applied.

RESULTS

In total, 3559109 participants were included; among them, 43574 digestive cancers

interest for this article.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: South Korea

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: October 12, 2020
Peer-review started: October 12, 2020
First decision: November 23, 2020
Revised: December 5, 2020
Accepted: December 16, 2020
Article in press: December 16, 2020
Published online: January 14, 2021

P-Reviewer: Sharma K
S-Editor: Gao CC
L-Editor: A
P-Editor: Liu JH

developed during a median of 6.8 years of follow-up. The incidence of total digestive cancers increased in a dose-response manner in men [adjusted hazard ratio (aHR) compared with those with 0 GGT points = 1.28 and 95% confidence interval (CI) = 1.24-1.33 in those with 1 point; aHR = 1.40 and 95%CI = 1.35-1.46 in those with 2 points; aHR = 1.52 and 95%CI = 1.46-1.58 in those with 3 points; aHR = 1.88 and 95%CI = 1.83-1.94 in those with 4 points; *P* for trend < 0.001]. This trend was more prominent in men than in women and those with healthy habits (no smoking, no alcohol consumption, and a low body mass index) than in those with unhealthy habits.

CONCLUSION

Repeatedly elevated GGT levels were associated with an increased risk of incident digestive cancer in a dose-responsive manner, particularly in men and those with healthy habits. Repeated GGT measurements may be a good biomarker of incident digestive cancer and could help physicians identify high-risk populations.

Key Words: Gamma-glutamyltransferase; Cancer; Digestive organ; Serial exam; Incident cancer; Biomarker

Core Tip: We evaluate whether repeatedly elevated γ-glutamyltransferase (GGT) levels on four consecutive exams were associated with an increased incidence of digestive cancers using the population-based cohort data. In total, 3559109 participants were included with a median of 6.8 years of follow-up. Repeatedly elevated GGT levels on four consecutive exams were associated with an increased incidence of digestive cancers in a dose-response manner. This trend was more prominent in men than women and in those with healthy habits (no smoking, no alcohol consumption, and a low body mass index) than those with unhealthy habits.

Citation: Lee CH, Han K, Kim DH, Kwak MS. Repeatedly elevated γ-glutamyltransferase levels are associated with an increased incidence of digestive cancers: A population-based cohort study. *World J Gastroenterol* 2021; 27(2): 176-188
URL: https://www.wjgnet.com/1007-9327/full/v27/i2/176.htm
DOI: https://dx.doi.org/10.3748/wjg.v27.i2.176

INTRODUCTION

Gamma-glutamyltransferase (GGT) is the enzyme responsible for the extracellular catabolism of glutathione by catalyzing the transfer of the glutamyl residue from glutathione to an acceptor amino acid[1]. GGT is present on the external surface of most cells but is mainly present in biliary epithelial cells[2]. GGT is a well-known marker of hepatic dysfunction, cholestasis or excessive alcohol consumption[3]. However, elevated serum levels of GGT are also associated with various diseases, including non-hepatobiliary diseases, such as type 2 diabetes mellitus (DM)[4], obesity, dyslipidemia, metabolic syndrome[5], hypertension[4], chronic kidney disease[6] and cardiovascular disease[7].

Several studies have suggested that elevated serum levels of GGT are also associated with an increased incidence of digestive cancers. A population-based study showed that elevated serum GGT is associated with an increased risk of esophageal cancer[8]. Another population-based study in Korea showed that the baseline GGT had a dose-response association with incident cancers, including liver cancer and several gastrointestinal cancers[9]. A meta-analysis including 14 cohort studies showed that the overall cancer risk increased by 1.04 times per 5-U/L increment in serum GGT[10]. Nevertheless, most of these studies used a single measurement of GGT, although the GGT levels fluctuate over time. The within-subject biological variation in GGT was reported to be 13.8% (range, 3.9%-14.5%)[11]. Several other longitudinal follow-up studies also showed dynamic changes in GGT[12-14]. Furthermore, many factors affect

the level of GGT, such as age, sex, ethnicity, region, alcohol consumption, smoking, underlying diseases and drugs[15,16]. Therefore, a single measurement of GGT does not fully reflect the current status of GGT, limiting the understanding of the actual relationship between GGT and diseases. We hypothesized that multiple measurements of GGT over several years could mitigate the limitations of a single measurement. In this study, we investigated whether repeatedly elevated serum GGT levels on serial measurements over 3-4 years were associated with an increased risk of incident digestive cancer using population-based data.

MATERIALS AND METHODS

National Health Insurance Service data source

We used the National Health Insurance Service (NHIS) database, which is managed by the Korean government. The NHIS covers almost all Koreans (97.2% of the Korean population)[8]. The NHIS supports annual or biennial standardized national health check-ups for all insured Koreans older than 40 years and employees older than 20 years. The NHIS contains information for each participant on their demographics, examinations, disease diagnosis codes claims according to the International Classification of Diseases (ICD-10), and treatments, including medication prescribed and procedures performed[17].

This study protocol was exempted from review by the Seoul National University Hospital Institutional Review Board because of the retrospective design of the study, and the researchers accessed only de-identified open clinical data for analytical purposes (H-1912-022-1085). Informed consent from participants was also waived by the Institutional Review Board of Seoul National University Hospital because of the retrospective nature of the study, and the researchers accessed only anonymous clinical data for analytical purposes.

Study population

We initially included participants who had undergone the Korean Health screening from 2009 to 2012. Among them, we selected participants who had 4 previous serial health screening examinations, as presented in Figure 1. Next, those with missing data were excluded. Participants who were diagnosed with any cancers at baseline were excluded based on C-codes and registration programs for serious diseases before the index date. The Korean government provides co-payment reductions for registered cancer patients. Only patients with a confirmed diagnosis of cancer after a thorough evaluation by a physician can be registered in this program.

Participants who died or had an event within 1 year ("lag period") were also excluded. The included participants were followed until December 2017.

Measurement of clinical variables and biochemical analysis

Standardized self-administered questionnaires were collected. They included questions on age (years), sex, alcohol consumption (amount and frequency), smoking (never, former and current), regular physical activity, yearly income, and underlying diseases, including malignancy. Heavy alcohol consumption was defined as > 21 standard drinks per week based on the self-administered questionnaire[18].

Body weight (kg) and height (m^2) were measured using an electronic scale, and the body mass index (BMI) was calculated as follows: BMI = body weight (kg)/height^2 (m^2). A BMI greater than 25 kg/m^2 was used to define the obese population in the subgroup analysis. The waist circumference (WC) was measured using a tape measure at the midpoint between the iliac crest and the lower costal margin by a well-trained examiner. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after 5 min of rest.

After overnight fasting, blood samples were collected from each participant and analyzed using a standardized laboratory method. The baseline laboratory examinations included GGT, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting glucose, aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

The diagnoses of hypertension, dyslipidemia and DM were defined using anthropometric measurements or laboratory data (SBP = 140 mmHg or DBP = 90 mmHg; total cholesterol level ≥ 240 mg/dL; fasting glucose level ≥ 126 mg/dL) or ICD codes (ICD I10 to I13 or I15; E78; E11 to E14) and medication use, including antihypertensive medication, dyslipidemia medication or insulin or oral hypoglycemic agents. In the subgroup analysis, the definition of chronic liver disease or liver

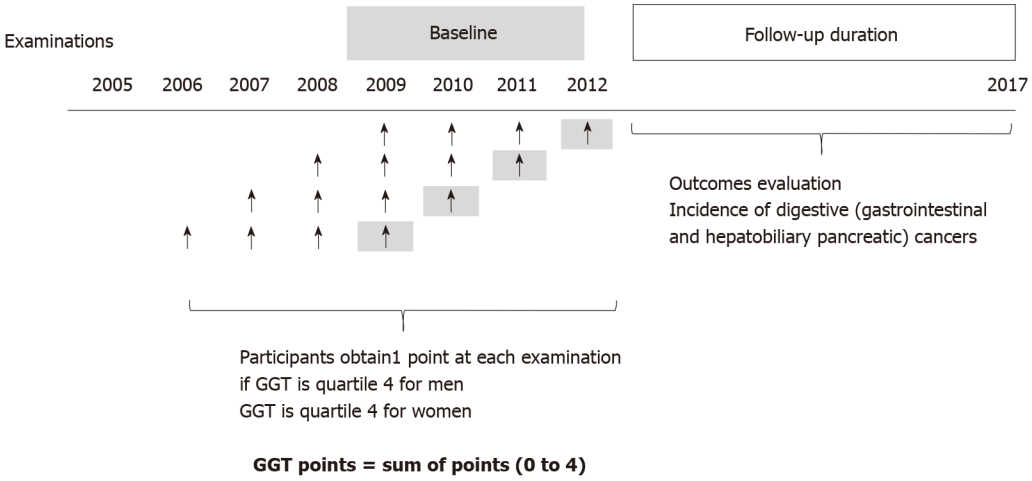

Figure 1 Definition of the γ-glutamyltransferase points and study design. The participants received one point if γ-glutamyltransferase (GGT) was in quartile 4 at each examination. The GGT points were defined as the sum of points of four examinations. GGT: Gamma-glutamyltransferase.

cirrhosis was based on ICD codes (B15-B19, K70.3, K74.6).

Definition of GGT points

Participants were assigned "GGT points" based on 4 consecutive examinations. They obtained 1 point if GGT was considered quartile 4 at each measurement. Participants who had GGT levels in quartile 4 in all four examinations received 4 GGT points; however, participants who had all GGT levels in quartiles 1-3 in the four examinations received 0 GGT points (Figure 1).

Outcomes

We evaluated the incidence of digestive cancers using the claim records of the NHIS during the follow-up period. The primary outcome was newly developed cancer in the gastrointestinal and hepatobiliary pancreas. Cancer was defined based on both the registration codes for serious diseases and the following ICD-10 codes: C15 (esophageal); C16 (stomach); C18-20 (colorectal); C22.0, 22.2, 22.3, 22.4, 22.7, and 22.9 (liver); C22.1, C23, and C24 (gallbladder and biliary tract); and C25 (pancreatic). Codes for reimbursement for serious diseases were also reviewed to reduce the error in studies with claims data; that is, both codes were required for the identification of cancer patients[19].

"Total digestive cancers" included both "gastrointestinal cancers" and "hepatobiliary pancreatic cancers". "Gastrointestinal cancers" included esophageal, stomach, and colorectal cancers. "Hepatobiliary pancreatic cancers" included liver, biliary (gallbladder and biliary tract), and pancreatic cancers.

Statistical analysis

Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as means ± SD. For non-normally distributed variables, log transformation was performed, and geometric means were calculated. Group comparisons were performed using chi-squared tests for categorical variables and one-way analysis of variance for continuous variables.

The incidence rate of cancers was calculated as the number of events divided by the summation of person-years (per 1000). Multivariable Cox proportional hazards regression models were used to adjust covariates, and adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were presented. We also performed subgroup analyses according to the age, smoking status, alcohol consumption status, BMI, liver cirrhosis or hepatitis to evaluate whether there were effect modifications of the impact of GGT on cancer incidence in each subgroup.

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, United States) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided *P* value less than 0.05 was considered statistically significant.

RESULTS

The flowchart of the study enrolment is presented in Supplementary Figure 1. Among the total 3559109 included participants, 2569773 were men, and 989336 were women. More than half of both men (62.1%) and women (57.3%) had 0 GGT points. In other words, 37.9% of men and 42.7% of women had a high GGT level in at least one of the four time evaluations. In total, 10.1% of men and 15.5% of women had one point, 6.9% of men and 8.4% of women had 2 points, 7.1% of men and 7.1% of women had 3 points, and 13.8% of men and 11.7% of women had 4 points. Older age, current smoking, heavy drinking, hypertension, dyslipidemia, diabetes, high BMI, high waist circumference, elevated levels of fasting glucose, total cholesterol, triglycerides, AST, ALT and low physical activity were associated with increased GGT points in both men and women (P for trend < 0.001 for all; Table 1). The median follow-up duration was 6.8 years (5.3-7.4 years, mean 6.3 years). The univariate and multivariate analyses of the incidence of total digestive cancers, gastrointestinal cancers (esophageal, stomach and colorectal) and hepatobiliary pancreatic cancers according to the GGT points are presented in Table 2. The incidence of total digestive cancers increased as the GGT points increased. In men, the incidence of total digestive cancers increased in a dose-responsive manner as the GGT points increased compared with those who had 0 GGT points (aHR = 1.28, 95%CI = 1.24-1.33 in those with 1 GGT point; aHR = 1.40, 95%CI = 1.35-1.46 in those with 2 points; aHR = 1.52, 95%CI = 1.46-1.58 in those with 3 points; aHR = 1.88, 95%CI = 1.83-1.94 in those with 4 points; P for trend < 0.001). In women, this trend was similar, although the effect sizes were smaller than those in men (aHR = 0.99 and 95%CI = 0.93-1.06 in participants with 1 GGT point; aHR = 1.02 and 95%CI = 0.94-1.11 in those with 2 points; aHR = 1.11 and 95%CI = 1.02-1.21 in those with 3 points; aHR = 1.27 and 95%CI = 1.19-1.36 in those with 4 points; P for trend < 0.001).

This increasing trend according to the GGT points was consistent for each digestive cancer, including esophageal, stomach, colorectal, liver, pancreatic, and biliary cancers (Table 3 and Figure 2). In particular, this trend was the most prominent for liver cancer (6.89 times the increased risk), followed by esophageal cancer (3.07 times increased risk) in the 4-GGT-point group compared with the 0-point group in men. Similarly, the risk for liver cancers was mostly increased in women (aHR = 3.91 and 95%CI = 3.25-4.71 in those with 4 GGT points *vs* 0 points). However, no significant association was found between each type of gastrointestinal cancer and GGT points in women.

We performed subgroup analyses (Figure 3 and Supplementary Table 1). In men, the increasing trend in GGT points was consistent in all subgroups. This trend was most evident in those with healthy lifestyles (P for interaction < 0.001 among non-smokers; P for interaction < 0.001 among non-drinkers; P for interaction < 0.001 in the non-obese group) and those with hepatitis or liver cirrhosis (P for interaction < 0.001). There was no effect modification, with only one exception in the association of GGT points and cancer incidence among women. Only the presence of hepatitis or liver cirrhosis showed a significant interaction with the association between GGT points and liver cancer and stomach cancer incidence (aHR = 11.81, 95%CI = 6.95-20.07, P for interaction < 0.001; aHR = 1.94, 95%CI = 0.96-3.93, P for interaction = 0.043).

DISCUSSION

This large-scale population-based study showed that repeatedly elevated GGT levels (meeting the criteria of quartile 4) on four consecutive examinations over three years were associated with an increased incidence of digestive cancers, including esophageal, stomach, colorectal, liver, biliary and pancreatic cancers, during a median 6.8-year follow-up period. The higher was the number of GGT points, the higher was the risk of each cancer in a dose-response manner. The risk of liver cancer mostly increased as the GGT points increased. This trend was more prominent in men than in women and those with healthy habits (no smoking, no alcohol consumption, and a low BMI) than in those with unhealthy habits.

Several previous studies have shown an association between the GGT levels and incident digestive cancer. The Swedish Amoris cohort study showed the association between baseline GGT levels and the incidence of cancer, including liver cancer[20]. The Ohsaki cohort study in Japan showed the association of GGT levels and colorectal cancer incidence[21]. A meta-analysis including 1.7 million participants reported pooled relative risks of 1.32 (1.15-1.52) for overall cancers and 1.94 (1.35-2.79) for digestive cancers in the highest quartile *vs* the bottom third of baseline GGT levels[10]. However, these studies used a single measurement of GGT to investigate the relationship

Table 1 Baseline characteristics according to the γ-glutamyltransferase points

	Total	GGT points[1]				
		0	1	2	3	4
Men	2569773	1595879	260084	177029	181702	355079
Age, yr	42.41 ± 10.53	41.64 ± 10.84	43.19 ± 10.47	43.31 ± 10.13	43.64 ± 9.82	44.19 ± 9.29
Smoking						
Non-smoker	720342 (28.03)	511103 (32.03)	65347 (25.13)	39900 (22.54)	37994 (20.91)	65998 (18.59)
Ex-smoker	662215 (25.77)	410064 (25.7)	70316 (27.04)	47571 (26.87)	47955 (26.39)	86309 (24.31)
Current	1187216 (46.2)	674712 (42.28)	124421 (47.84)	89558 (50.59)	95753 (52.7)	202772 (57.11)
Alcohol consumption						
No	720354 (28.03)	540201 (33.85)	64798 (24.91)	36701 (20.73)	32092 (17.66)	46562 (13.11)
Mild	1583612 (61.62)	952992 (59.72)	165116 (63.49)	114805 (64.85)	118787 (65.37)	231912 (65.31)
Heavy	265807 (10.34)	102686 (6.43)	30170 (11.6)	25523 (14.42)	30823 (16.96)	76605 (21.57)
Lowest quartile of yearly income (Q1)	399370 (15.54)	244182 (15.3)	42615 (16.39)	28596 (16.15)	28873 (15.89)	55104 (15.52)
Regular PA	790381 (30.76)	496084 (31.09)	80897 (31.1)	54551 (30.81)	55753 (30.68)	103096 (29.03)
BMI (kg/m^2)	24.19 ± 3.01	23.55 ± 2.79	24.71 ± 2.91	25.1 ± 2.98	25.34 ± 3.03	25.64 ± 3.13
WC (cm)	83.14 ± 7.56	81.48 ± 7.16	84.46 ± 7.22	85.43 ± 7.25	86.08 ± 7.33	86.96 ± 7.45
SBP (mmHg)	123.78 ± 12.99	122 ± 12.45	124.88 ± 12.85	125.93 ± 13.02	126.8 ± 13.23	128.37 ± 13.68
DBP (mmHg)	77.98 ± 9.17	76.71 ± 8.79	78.75 ± 9.07	79.51 ± 9.16	80.19 ± 9.32	81.27 ± 9.6
Hypertension	543619 (21.15)	249986 (15.66)	63584 (24.45)	48861 (27.6)	55827 (30.72)	125361 (35.31)
Dyslipidemia	394282 (15.34)	169026 (10.59)	47739 (18.36)	37512 (21.19)	42552 (23.42)	97453 (27.45)
Diabetes						
No	1747553 (68)	1178083 (73.82)	168406 (64.75)	108469 (61.27)	105608 (58.12)	186987 (52.66)
IFG	633865 (24.67)	343650 (21.53)	69127 (26.58)	50151 (28.33)	54139 (29.8)	116798 (32.89)
DM	188355 (7.33)	74146 (4.65)	22551 (8.67)	18409 (10.4)	21955 (12.08)	51294 (14.45)
Fasting glucose (mg/dL)	97.2 ± 22.15	94.38 ± 18.25	98.47 ± 22.98	100.13 ± 24.85	101.84 ± 26.59	105.13 ± 29.72
Total cholesterol (mg/dL)	195.09 ± 34.85	190.25 ± 32.83	198.57 ± 34.96	201.16 ± 35.5	202.95 ± 36.32	207.29 ± 37.85
LDL (mg/dL)	112.94 ± 32.32	112.28 ± 30.41	114.88 ± 33.13	114.76 ± 34.14	114.17 ± 35.16	112.95 ± 37.16
HDL (mg/dL)	52.16 ± 13.63	52.38 ± 13.38	51.6 ± 13.93	51.57 ± 14.01	51.58 ± 13.9	52.18 ± 14.14
Triglyceride (mg/dL)[2]	129.81 (129.72-129.9)	112.69 (112.6-112.78)	141.48 (141.19-141.77)	154 (153.61-154.38)	164.57 (164.16-164.98)	187.2 (186.86-187.54)
AST (IU/L)[2]	25.9 (25.89-25.91)	23.64 (23.63-23.65)	27.11 (27.08-27.15)	28.47 (28.43-28.51)	29.84 (29.79-29.89)	33.52 (33.47-33.56)
ALT (IU/L)[2]	26.41 (26.4-26.43)	22.44 (22.43-22.46)	29.54 (29.49-29.6)	32.15 (32.07-32.22)	34.42 (34.34-34.51)	40.07 (40-40.14)
GGT (U/L)[2]	36.3 (36.28-36.33)	24.79 (24.78-24.81)	43.21 (43.14-43.27)	53.64 (53.54-53.73)	66.15 (66.02-66.28)	107.44 (107.26-107.61)
Women	989336	566518	153299	83247	70183	116089
Age, yr	41.61 ± 11.55	39.36 ± 11.04	42.51 ± 11.54	44.13 ± 11.57	45.34 ± 11.47	47.33 ± 10.9
Smoking						
Non-smoker	950040 (96.03)	547422 (96.63)	147238 (96.05)	79376 (95.35)	66593 (94.88)	109411 (94.25)
Ex-smoker	16273 (1.64)	8976 (1.58)	2493 (1.63)	1454 (1.75)	1294 (1.84)	2056 (1.77)
Current	23023 (2.33)	10120 (1.79)	3568 (2.33)	2417 (2.9)	2296 (3.27)	4622 (3.98)
Alcohol consumption						

	No	661884 (66.9)	383621 (67.72)	103332 (67.41)	55147 (66.25)	45838 (65.31)	73946 (63.7)
	Mild	318233 (32.17)	179199 (31.63)	48446 (31.6)	26984 (32.41)	23345 (33.26)	40259 (34.68)
	Heavy	9219 (0.93)	3698 (0.65)	1521 (0.99)	1116 (1.34)	1000 (1.42)	1884 (1.62)
Lowest quartile of yearly income (Q1)		365612 (36.96)	181102 (31.97)	61625 (40.2)	35775 (42.97)	31499 (44.88)	55611 (47.9)
Regular PA		270758 (27.37)	155736 (27.49)	42388 (27.65)	22839 (27.44)	18923 (26.96)	30872 (26.59)
BMI (kg/m^2)		22.45 ± 3.22	21.79 ± 2.82	22.56 ± 3.15	23.14 ± 3.39	23.64 ± 3.53	24.36 ± 3.71
WC (cm)		73.52 ± 8.28	71.77 ± 7.42	73.86 ± 8.07	75.36 ± 8.49	76.6 ± 8.78	78.47 ± 9.09
SBP (mmHg)		116.17 ± 13.59	114.11 ± 12.72	116.63 ± 13.55	118.33 ± 14.04	119.76 ± 14.23	121.91 ± 14.56
DBP (mmHg)		72.92 ± 9.26	71.68 ± 8.83	73.17 ± 9.25	74.2 ± 9.46	75.08 ± 9.54	76.39 ± 9.73
Hypertension		130992 (13.24)	45016 (7.95)	21361 (13.93)	15255 (18.32)	15700 (22.37)	33660 (28.99)
Dyslipidemia		128796 (13.02)	45810 (8.09)	21112 (13.77)	14928 (17.93)	15084 (21.49)	31862 (27.45)
Diabetes							
	No	805990 (81.47)	489351 (86.38)	124149 (80.98)	64211 (77.13)	51316 (73.12)	76963 (66.3)
	IFG	148818 (15.04)	68823 (12.15)	24264 (15.83)	15071 (18.1)	14042 (20.01)	26618 (22.93)
	DM	34528 (3.49)	8344 (1.47)	4886 (3.19)	3965 (4.76)	4825 (6.87)	12508 (10.77)
Fasting glucose (mg/dL)		91.41 ± 16.31	89.21 ± 12.41	91.39 ± 15.32	93.13 ± 17.79	94.99 ± 20.38	98.8 ± 25.3
Total cholesterol (mg/dL)		190.33 ± 34.94	185.48 ± 32.85	191.82 ± 35.03	195.68 ± 35.98	198.31 ± 36.74	203.37 ± 37.76
LDL (mg/dL)		110.02 ± 31.3	106.75 ± 29.16	111.38 ± 31.72	113.91 ± 33.05	115.34 ± 33.97	118.18 ± 35.21
HDL (mg/dL)		60.82 ± 15.16	61.63 ± 14.7	60.57 ± 15.3	59.93 ± 15.73	59.3 ± 15.65	58.74 ± 16.1
Triglyceride (mg/dL)[2]		85.34 (85.25-85.42)	76.5 (76.4-76.59)	87.69 (87.47-87.91)	95.8 (95.47-96.13)	103.29 (102.89-103.69)	115.13 (114.78-115.49)
AST (IU/L)[2]		21.38 (21.36-21.39)	20.06 (20.05-20.08)	21.64 (21.61-21.67)	22.58 (22.54-22.63)	23.6 (23.55-23.66)	25.95 (25.89-26)
ALT (IU/L)[2]		16.82 (16.81-16.84)	14.74 (14.73-14.76)	17.38 (17.34-17.41)	19.11 (19.05-19.17)	20.85 (20.78-20.92)	24.6 (24.53-24.67)
GGT (U/L)[2]		17.53 (17.51-17.54)	13.52 (13.51-13.53)	18.15 (18.12-18.18)	21.94 (21.89-21.99)	26.28 (26.21-26.35)	39.57 (39.46-39.69)

[1]Participants receive 1 point at each examination if γ-glutamyltransferase (GGT) is in the highest quartile at each examination. GGT points were calculated as the sum of points at 4 consecutive examinations.

[2]Geometric mean. Categorical variables are expressed as numbers (%); continuous variables are expressed means ± SD. PA: Physical activity; BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; IFG: Impaired fasting glucose; DM: Diabetes mellitus; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyltransferase.

between GGT and the risk of digestive cancers. A single measurement of GGT has limitations, as described above in the introduction. Our study showed that repeated measurements have the benefit of mitigating the limitations of a single measurement of GGT in the screening of those at risk of cancer. In the current study, 37.9% of men and 42.7% of women had a high GGT level in at least one of four measurements. Among them, 27% of men (10.1% of men in total) and 36% of women (15.5% of women in total) had a high GGT level only once. Thus, most of them would have been classified into a low-level GGT group if they had undergone a single measurement during that period. Additionally, participants who had 2 or more GGT points had a higher risk of incident digestive cancer than those with 1 GGT point who had a high GGT level only once. A dose-response relationship was found between the GGT points and risk of incident digestive cancer. Those with 1 GGT point did not show a higher risk of cancer than those with 0 GGT points, but those with higher GGT points showed a higher risk of cancer than those with 0 GGT points for several cancers. (*e.g.*, biliary and pancreatic cancers in women, as shown in Table 3). In one study, the GGT levels were measured several times; however, the main outcome was the association between only the baseline GGT and site-specific cancers, and the changing status of GGT was not fully evaluated. Moreover, alcohol consumption, which is the most important confounder, was not adjusted[22,23] In the current study, we adjusted for various major

Table 2 Incidence of all digestive cancers, gastrointestinal cancers (including esophagus, stomach and colorectal cancers), and hepatobiliary pancreatic cancers (including liver, biliary tract and pancreas) according to the γ-glutamyltransferase points

GGT points	Number	Event	Duration	IR per 1000	Age-adjusted	Model 1	Model 2	Model 3
					IR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Men								
Total digestive cancer								
0	1595879	17789	10257993.68	1.734	3.20 (3.14, 3.26)	1 (reference)	1 (reference)	1 (reference)
1	260084	4058	1667865.93	2.433	4.19 (3.88, 4.52)	1.40 (1.36, 1.45)	1.30 (1.26, 1.34)	1.28 (1.24, 1.33)
2	177029	2982	1133122.25	2.632	4.70 (4.25, 5.19)	1.52 (1.46, 1.58)	1.43 (1.38, 1.49)	1.40 (1.35, 1.46)
3	181702	3341	1161757.06	2.876	5.06 (4.63, 5.53)	1.66 (1.60, 1.72)	1.57 (1.51, 1.62)	1.52 (1.46, 1.58)
4	355079	8106	2250566.91	3.602	6.36 (6.14, 6.59)	2.08 (2.03, 2.13)	1.96 (1.91, 2.01)	1.88 (1.83, 1.94)
P for trend						< 0.001	< 0.001	< 0.001
Gastrointestinal cancer								
0	1595879	14709	10263671.88	1.433	2.64 (2.59, 2.69)	1 (reference)	1 (reference)	1 (reference)
1	260084	3023	1669790.42	1.810	3.11 (2.87, 3.37)	1.26 (1.22, 1.31)	1.17 (1.12, 1.22)	1.12 (1.08, 1.17)
2	177029	2169	1134702.18	1.912	3.39 (3.03, 3.78)	1.33 (1.28, 1.40)	1.26 (1.20, 1.32)	1.18 (1.13, 1.24)
3	181702	2372	1163597.98	2.039	3.55 (3.21, 3.93)	1.42 (1.36, 1.49)	1.34 (1.28, 1.40)	1.24 (1.19, 1.30)
4	355079	5075	2256426.45	2.249	3.94 (3.76, 4.12)	1.57 (1.52, 1.62)	1.48 (1.43, 1.53)	1.34 (1.29, 1.39)
P for trend						< 0.001	< 0.001	< 0.001
Hepatobiliary pancreatic cancer								
0	1595879	5616	10294767.52	0.546	1.01 (0.98, 1.03)	1 (reference)	1 (reference)	1 (reference)
1	260084	1584	1675373.07	0.945	1.62 (1.49, 1.76)	1.73 (1.64, 1.83)	1.60 (1.52, 1.70)	1.65 (1.56, 1.75)
2	177029	1217	1138317.76	1.069	1.92 (1.73, 2.13)	1.96 (1.84, 2.09)	1.86 (1.75, 1.98)	1.93 (1.82, 2.06)
3	181702	1399	1167524.64	1.198	2.13 (1.95, 2.34)	2.20 (2.07, 2.33)	2.08 (1.96, 2.21)	2.18 (2.05, 2.32)
4	355079	4109	2262184.82	1.816	3.22 (3.13, 3.32)	3.34 (3.20, 3.47)	3.16 (3.04, 3.29)	3.35 (3.21, 3.50)
P for trend						< 0.001	< 0.001	< 0.001
Women								
Total digestive cancer								
0	566518	3367	3558510.54	0.946	1.81 (1.77, 1.85)	1 (reference)	1 (reference)	1 (reference)
1	153299	1124	959235.81	1.172	1.75 (1.65, 1.86)	1.24 (1.16, 1.33)	1.00 (0.93, 1.07)	0.99 (0.93, 1.06)
2	83247	694	519023.27	1.337	1.80 (1.63, 1.98)	1.42 (1.30, 1.54)	1.03 (0.95, 1.12)	1.02 (0.94, 1.11)
3	70183	682	435747.09	1.565	1.95 (1.78, 2.15)	1.66 (1.53, 1.80)	1.12 (1.03, 1.22)	1.11 (1.02, 1.21)
4	116089	1431	714960.09	2.002	2.25 (2.15, 2.35)	2.12 (1.99, 2.26)	1.30 (1.22, 1.38)	1.27 (1.19, 1.36)
P for trend						< 0.001	< 0.001	< 0.001
Gastrointestinal cancer								
0	566518	2891	3559398.08	0.812	1.55 (1.51, 1.59)	1 (reference)	1 (reference)	1 (reference)
1	153299	913	959636.19	0.951	1.43 (1.33, 1.53)	1.17 (1.09, 1.26)	0.95 (0.88, 1.03)	0.95 (0.88, 1.02)
2	83247	548	519282.68	1.055	1.44 (1.28, 1.61)	1.30 (1.19, 1.43)	0.96 (0.88, 1.05)	0.95 (0.87, 1.04)
3	70183	526	436048.99	1.206	1.51 (1.34, 1.69)	1.49 (1.36, 1.63)	1.03 (0.93, 1.13)	1.01 (0.92, 1.11)
4	116089	1006	715795.75	1.405	1.58 (1.49, 1.68)	1.74 (1.62, 1.86)	1.08 (1.01, 1.17)	1.06 (0.98, 1.14)
P for trend						< 0.001	0.052	0.232
Hepatobiliary pancreatic cancer								
0	566518	884	3565741.17	0.248	0.47 (0.45,0.49)	1 (reference)	1 (reference)	1 (reference)

1	153299	337	961504.59	0.350	0.53 (0.48, 0.57)	1.42 (1.25, 1.60)	1.11 (0.98, 1.25)	1.10 (0.97, 1.25)
2	83247	238	520353.15	0.457	0.58 (0.52, 0.66)	1.85 (1.60, 2.13)	1.29 (1.12, 1.49)	1.29 (1.11, 1.49)
3	70183	241	437047.77	0.551	0.69 (0.62, 0.77)	2.23 (1.94, 2.57)	1.44 (1.25, 1.66)	1.43 (1.23, 1.65)
4	116089	608	717322.51	0.848	0.95 (0.91, 0.99)	3.44 (3.10, 3.81)	1.98 (1.78, 2.20)	1.95 (1.74, 2.18)
P for trend						< 0.001	< 0.001	< 0.001

Model 1: Unadjusted model. Model 2: Age-adjusted model. Model 3: Age, smoking, drinking, income, hypertension, diabetes, dyslipidemia, body mass index, and physical activity-adjusted model. IR: Incidence rate; HR: Hazard ratio; CI: confidence interval; GGT: Gamma-glutamyltransferase.

confounders, including alcohol consumption and physical activity, in a nationwide, population-based, large-scale study.

The underlying biological mechanisms of the effect of repeatedly elevated levels of GGT and cancer incidence cannot be fully explained considering the epidemiologic study design of this study. GGT is a marker of oxidative stress[24]. The involvement of the pro-oxidant activity of GGT can serve as an additional source of endogenous reactive oxygen species in cancer cells. This activity can contribute to persistent oxidative stress, modulate important redox-sensitive processes, affect the proliferation and apoptosis of cells, and cause genomic instability and carcinogenesis[25,26]. This mechanism might explain the possible role of GGT in cancer incidence.

The association between GGT and total digestive cancer incidence was more prominent in men than in women, and the association between GGT and gastrointestinal cancers was present in only men. The cause might be the higher level of GGT in men than in women, as presented in other studies[9,20,21,27]. The GGT levels were lower in women than in men (mean 17.5 *vs* 36.3) in this study; thus, the relative effect sizes were smaller in women than in men. Another plausible explanation is that a sex effect modification may exist regarding the association between GGT and cancer incidence. The sex-related variability of the effect of GGT on cancer incidence may be due to sex-specific genetic variations or mutations or sex-specific responses to exposed carcinogens or environmental factors[27,28].

Another interesting finding is that GGT points had a greater association with incident digestive cancer in the subgroup with a healthy lifestyle (no smoking, no alcohol consumption, no obesity) than in the subgroup with an unhealthy lifestyle, although the difference in each site-specific cancer should be considered. The risk of cancer was the highest in liver cancer, followed by esophageal cancer according to the GGT points in men. Because these two cancers are well-known alcohol-associated cancers, some may hypothesize that the association between GGT points and cancer may be attributable to residual confounding by alcohol intake. A previous study in Japan showed a positive association between GGT and alcohol-related cancers among only current drinkers[21]. However, another study conversely showed an association between baseline GGT and cancer incidence regardless of the drinking and smoking status[9]. Our study found similar results to the latter and even showed a highly prominent association between GGT and cancer in the never smoker and no drinking groups. The exact underlying mechanism of this phenomenon is unknown. However, one possible explanation is that the effect of GGT points on cancer incidence might have been weakened by other well-known cancer risk factors in participants with unhealthy habits. This result suggests that elevated GGT, which can be detected using an inexpensive and simple test is a risk factor in those without other commonly known cancer risk factors, such as smoking, alcohol or obesity. Additional attention should be given to patients with repeatedly elevated GGT levels on serial examinations, particularly those who are not smokers, heavy alcohol consumers or obese.

CONCLUSION

Our nationwide population-based study showed an association between repeatedly elevated GGT and the incidence of digestive cancers in a dose-response manner, even after adjustment for major confounders, including alcohol consumption. A single measurement of serum GGT is an easy and inexpensive test but has limitations; thus, repeated measurements could provide more useful information in the health screening setting. The repeated measurement of GGT may be a good biomarker for predicting cancer incidence and could help physicians identify those at high-risk for digestive

Table 3 Incidence of site-specific digestive cancers according to the γ-glutamyltransferase points based on four consecutive examinations

	Esophagus		Stomach		Colorectal		Liver		Biliary		Pancreas	
	IR per 1000	HR (95%CI)	IR per 1000	HR (95%CI)	IR per 1000	HR (95%CI)	IR per 1000	HR (95%CI)	IR per 1000	HR (95%CI)	IR per 1000	HR (95%CI)
Men												
0	0.037	1 (reference)	0.772	1 (reference)	0.757	1 (reference)	0.215	1 (reference)	0.126	1 (reference)	0.293	1 (reference)
1	0.073	1.78 (1.45, 2.18)	0.968	1.12 (1.06, 1.19)	0.938	1.09 (1.03, 1.15)	0.505	2.39 (2.21, 2.59)	0.203	1.46 (1.29, 1.64)	0.389	1.18 (1.08, 1.28)
2	0.082	1.99 (1.58, 2.51)	1.011	1.18 (1.10, 1.25)	0.984	1.14 (1.07, 1.21)	0.624	3.13 (2.87, 3.41)	0.203	1.49 (1.30, 1.72)	0.392	1.19 (1.08, 1.32)
3	0.103	2.43 (1.97, 3.00)	1.063	1.22 (1.15, 1.29)	1.051	1.19 (1.12, 1.27)	0.727	3.74 (3.45, 4.06)	0.203	1.49 (1.30, 1.72)	0.425	1.27 (1.15, 1.40)
4	0.134	3.07 (2.61, 3.62)	1.127	1.26 (1.21, 1.33)	1.209	1.34 (1.28, 1.40)	1.293	6.89 (6.49, 7.32)	0.257	1.91 (1.72, 2.12)	0.501	1.48 (1.37, 1.59)
Women												
0	0.005	1 (reference)	0.319	1 (reference)	0.534	1 (reference)	0.067	1 (reference)	0.065	1 (reference)	0.150	1 (reference)
1	0.007	1.00 (0.42, 2.39)	0.345	0.87 (0.77, 0.99)	0.651	0.99 (0.90, 1.08)	0.114	1.41 (1.12, 1.77)	0.102	1.12 (0.88, 1.42)	0.186	0.97 (0.81, 1.14)
2	0.008	0.92 (0.31, 2.74)	0.390	0.89 (0.77, 1.04)	0.720	0.99 (0.89, 1.11)	0.150	1.70 (1.32, 2.20)	0.138	1.30 (0.99, 1.70)	0.238	1.10 (0.90, 1.34)
3	0.009	1.01 (0.34, 3.02)	0.462	0.98 (0.84, 1.14)	0.804	1.03 (0.92, 1.16)	0.199	2.14 (1.66, 2.74)	0.162	1.36 (1.03, 1.78)	0.279	1.18 (0.96, 1.44)
4	0.014	1.38 (0.61, 3.12)	0.542	1.04 (0.92, 1.17)	0.924	1.06 (0.97, 1.17)	0.396	3.91 (3.25, 4.71)	0.203	1.45 (1.16, 1.80)	0.354	1.32 (1.13, 1.55)

Multivariate analysis was adjusted for age, smoking, drinking, income, hypertension, diabetes, dyslipidemia, body mass index and physical activity. IR: Incidence rate; HR: Hazard ratio; CI: Confidence interval.

cancers, even in those with healthy habits.

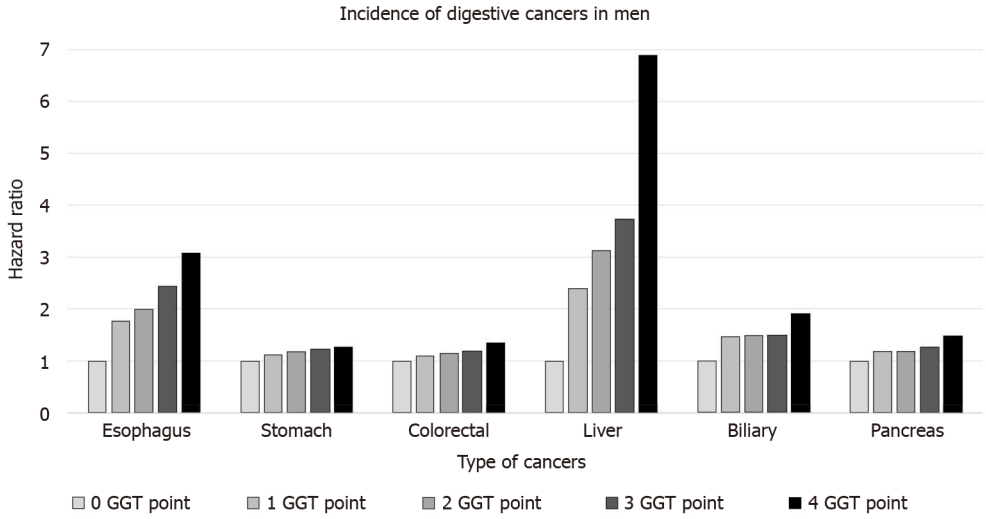

Figure 2 Incidence of site-specific digestive cancers according to the γ-glutamyltransferase points based on four consecutive examinations in men. GGT: Gamma-glutamyltransferase.

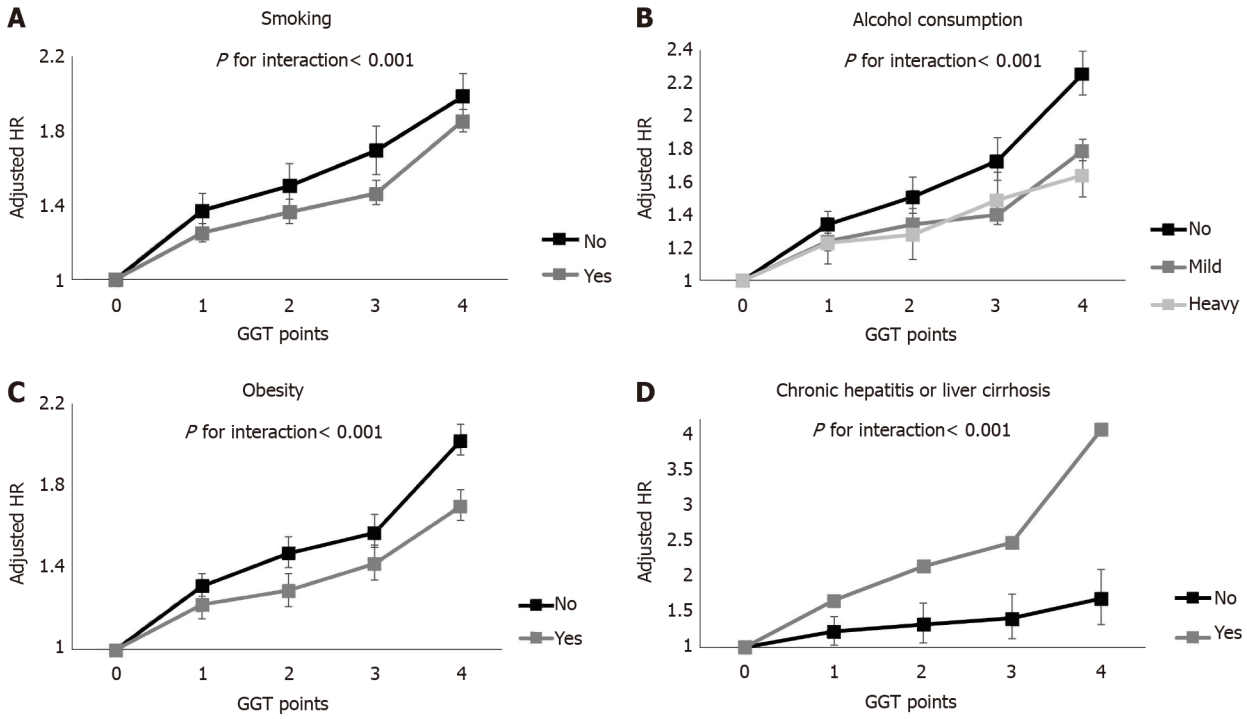

Figure 3 Subgroup analysis of the association of γ-glutamyltransferase points and the total digestive cancer incidence. A: Smoking (no smoking *vs* ever smoking); B: Alcohol consumption; C: Obesity (body mass index ≥ 25); D: Chronic hepatitis or liver cirrhosis in men. GGT: Gamma-glutamyltransferase; HR: hazard ratio.

ARTICLE HIGHLIGHTS

Research background

The association between elevated γ-glutamyltransferase (GGT) at a certain point and incident cancer has been suggested; however, no study has studied the association between repeatedly elevated GGT and cancer incidence.

Research motivation

GGT levels are not fixed but dynamic, and many factors affect the level of GGT. Therefore, a single measurement of GGT does not fully reflect the current status of GGT, limiting the understanding of the actual relationship between GGT and diseases. We hypothesized that multiple measurements of GGT over several years could

mitigate the limitations of a single measurement.

Research objectives

To elucidate whether repeatedly elevated GGT levels, which are commonly practiced in routine health examinations, can be used as a biomarker of subsequent incidence of digestive cancer.

Research methods

A population-based longitudinal cohort study was conducted with the participants who had undergone health screening from 2009 to 2012 and 4 consecutive previous examinations. GGT points were calculated as the number of times participants met the criteria of quartile 4 of GGT in four serial measurements (0-4 points). Multivariable Cox proportional hazard regression models were applied.

Research results

Among 3559109 participants, 43574 digestive cancers developed during a median of 6.8 years of follow-up. The incidence of total digestive cancers increased according to GGT points in a dose-response manner in men [adjusted hazard ratio (aHR) compared with those with 0 GGT points = 1.28 and 95% confidence interval (CI) = 1.24-1.33 in those with 1 point; aHR = 1.40 and 95%CI = 1.35-1.46 in those with 2 points; aHR = 1.52 and 95%CI = 1.46-1.58 in those with 3 points; aHR = 1.88 and 95%CI = 1.83-1.94 in those with 4 points; P for trend < 0.001]. This trend was more prominent in men than in women and those with healthy habits (no smoking, no alcohol consumption, and a low body mass index) than in those with unhealthy habits.

Research conclusions

Repeatedly elevated GGT levels were associated with an increased risk of incident digestive cancer in a dose-responsive manner, particularly in men and those with healthy habits.

Research perspectives

Repeated GGT measurements may be a good biomarker of incident digestive cancer and could help physicians identify high-risk populations.

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