의학 석사 학위 논문

국민 건강보험공단 자료를 이용한 당화 상태에 따른 감마 글루타밀 전이효소 수준과 소화기암 발생의 상관 관계 분석

Association between gamma-glutamyltransferase level and risk of gastrointestinal cancer by glycemic status: A nationwide population-based study

2020년 2월

서울대학교 대학원

의학과 내과학 전공

홍 승 욱

A thesis of the Degree of Master

국민 건강보험공단 자료를 이용한 당화 상태에 따른 감마 글루타밀 전이효소 수준과 소화기암 발생의 상관 관계 분석

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October 2019

Department of Internal Medicine

Seoul National University College of Medicine,

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지도교수 김 주 성

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2019년 10월

서울대학교 대학원

의학과 내과학 전공

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2020년 1월

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위 원 _____ (인)

ABSTRACT

Association between gamma-glutamyltransferase level and risk of gastrointestinal cancer by glycemic status: A nationwide population-based study

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Introduction

Elevated serum gamma-glutamyltransferase (GGT) is associated with the risk of gastrointestinal cancer. However, it is not clear whether the relationship between GGT level and the risk of gastrointestinal cancer would be constant in accordance with the glycemic status. We aimed to assess the association between GGT level, glycemic status and the incidence of gastrointestinal cancer, respectively, and confirm the interaction between the two factors by stratified analysis.

Method

A total of 8,120,665 persons who received general medical check-up from January 2009 to December 2009 by the National Health Insurance Service were included. Subjects were classified according to quartile of GGT level (male: <21, 21-29, 30-47, and ≥48 U/L, female: <13, 13-15, 16-22, and ≥23 U/L) and incidence rates of esophageal, stomach, and colorectal cancer were analyzed for each group using Cox proportional hazards models. Stratified analyses were conducted by glycemic status; non-diabetes, impaired fasting glucose (IFG), and diabetes mellitus (DM).

Results

During the 8-year follow-up, 129,853 cases of gastrointestinal cancer newly occurred. The highest GGT quartile group had an increased risk of gastrointestinal cancer compared to the lowest (esophagus: HR= 2.408, 95%CI=2.184–2.654, stomach: HR=1.121, 95%CI=1.093-1.149, colorectal: HR=1.185, 95%CI =1.158-1.211). A significant association was revealed between the incidence of gastrointestinal cancer with IFG as well as DM. When analyzed stratified by glycemic status, effect of GGT was predominant regarding the risk of esophageal cancer. Meanwhile, the additional effect with GGT and diabetes were identified in the incidence of stomach and colorectal cancer

(stomach: HR=1.283, 95%CI=1.237-1.331, colorectal: HR=1.342, 95%CI=1.299-1.386, the highest GGT quartile in diabetes).

Conclusion

High GGT levels, IFG, and DM were respectively closely linked to the incidence of gastrointestinal cancer. The effect of GGT on the incidence of gastrointestinal cancer varied on the type of cancer and glycemic status.

Keywords: gamma-glutamyltransferase; diabetes; gastrointestinal neoplasm; cohort studies

Student Number: 2015-21977

CONTENTS

LIST OF TABLES AND FIGURES

colorectal cancer. DM: diabetes mellitus, IFG: impaired fasting glucose, Q1-4: GGT quartile level.

INTRODUCTION

Serum gamma-glutamyltransferase (GGT) is one of marker related to hepatic dysfunction and used as a surrogate marker that reflects excessive alcohol consumption.[1, 2] Several epidemiologic studies reported that elevated GGT level is associated with the incidence of various diseases including metabolic syndrome, diabetes mellitus (DM), cardiovascular disease and atrial fibrillation.[3-9] As evidence of a link between GGT rise and risk of cancer emerges, the clinical role of GGT is noted. In particular, the assertions that the elevated GGT level is associated with the risk of gastrointestinal cancer were proposed, but several studies showed different results depending on sex and type of cancer.[10-16] Hence, a further study with a large population is needed to establish the relationship GGT level and risk of gastrointestinal cancer.

DM is one of the growing chronic diseases, a number of epidemiologic studies examined the relationship between DM and the risk of gastrointestinal cancer.[17-20] A plenty of studies have tried to establish that an association between DM and the risk of gastrointestinal cancer.[17, 20] Although it is still controversial, several studies reported that DM is associated with an incident of gastrointestinal

cancer.[18, 19, 21] On the other hand, there is a lack of evidence on the association between impaired fasting

glucose (IFG), as prediabetes, and the risk of gastrointestinal cancer.

Therefore, we aimed to assess whether serum GGT level and glycemic status each contribute to the occurrence of gastrointestinal cancer through this large-scale study using the nationwide data. Another aim of this study is to evaluate indirectly whether the presence of additional interaction between two factors for the risk of gastrointestinal cancer by conducting the analysis stratified by glycemic status.

MATERIALS AND METHODS

Data sources

This population-based study is retrospectively conducted using database from the National Health Insurance Service (NHIS) in South Korea. The NHIS is one of the social security systems provided by the government and all Korean are obliged to enroll in. It serves to pay for the medical service to the health care provider, on behalf of the general population. All data related to the medical services guaranteed by the NHIS is stored in its database. The NHIS database collects the demographic data as well as the information regarding the medical services, including medications, hospitalization, and diagnoses identified by International Classification of Disease, Tenth Revision (ICD-10) codes of the subscribers. The NHIS recommends that subscribers undergo a general medical check-up biennially. General medical check-up includes the body measurement, chest-X ray, and blood chemistry test.

Data collection and study population

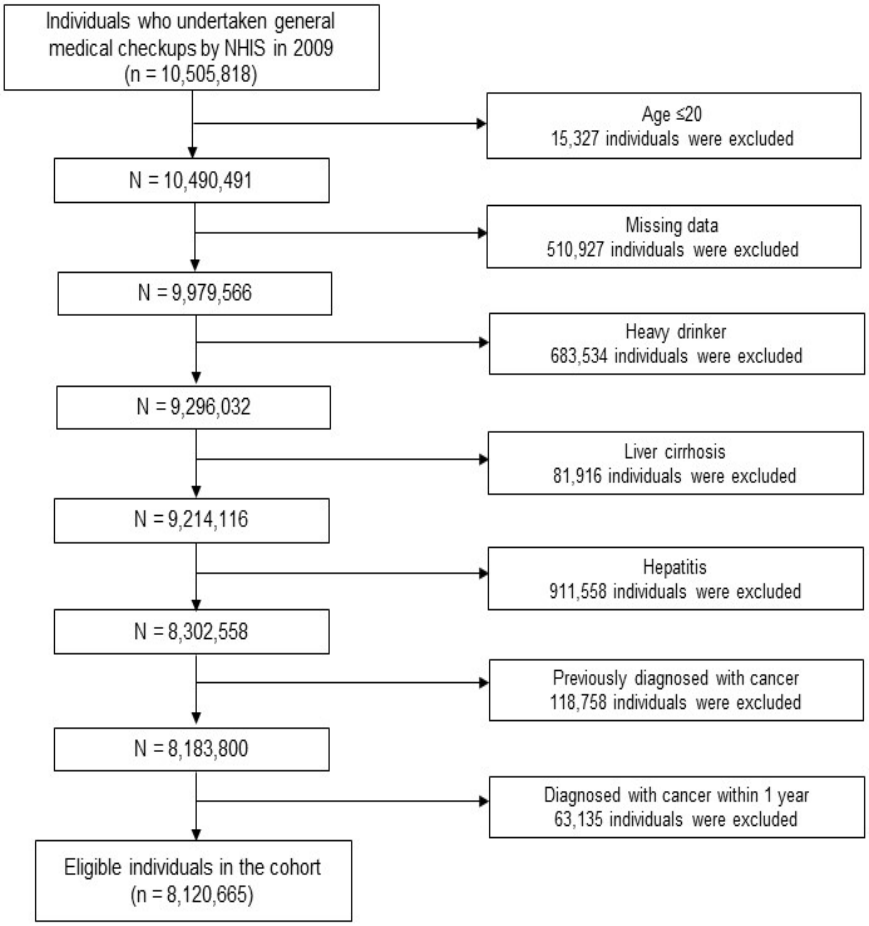
Demographic information including age, sex, and income was stored for all

participants who underwent general medical checkups in the NHIS database. The weight, height, and blood pressure for participants also were measured, and laboratory test including fasting blood glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGT level, and cholesterol was performed at the same day. A self-reporting questionnaire was used to assess the drinking habit, history of smoking, income, and exercise habit for the participants. The history of smoking was classified into three categories: (1) non-smoker; (2) ex-smoker; (3) current-smoker. Ex-smoker was defined as a person with more than 100 cigarette smoking experience, although smoking was currently ceased. The heavy drinker was defined as a person drinks more 30g of alcohol per day.

Adults over the age of 20 who underwent general medical checkup provided by the NHIS from January 2009 to December 2009 were qualified for the registration in this cohort. At the time of enrolment, the patients who had previously been diagnosed with cancer identified by ICD-10, regardless of the type, were excluded. To minimize disruption of pre-exiting factor to the incidence of gastrointestinal cancer, any type of cancer patients that diagnosed within one year of the time of enrollment were excluded from the cohort. The individuals diagnosed with liver cirrhosis (K703) or hepatitis (K746) were also excluded. To

avoid the confounding effect that excessive alcohol consumption on the gastrointestinal cancer incidence, individuals with heavy drinking was excluded in the cohort. The selection process of the study subjects was illustrated in Figure 1.

Figure 1. Flow chart of selection of study subjects.



Outcomes and ethical consideration

The members of the cohort were followed up until the occurrence of gastrointestinal cancer or December 31, 2017 (the end date of the study). Cases of newly diagnosed gastrointestinal cancer during follow-up period were identified by using ICD-10 codes in the NHIS database. Gastrointestinal cancer included esophagus, stomach and colorectal cancer, and their index date was the first cancer record. This study was approved by the Institutional Review Board at Seoul National University Hospital, and the requirement for informed consent was waived (IRB approved date: 2019.06.07, No. of IRB: E-1906-008-1036).

Statistical analysis

Data were expressed as mean ± SD for continuous variables and as number and proportions for categorical variables. Subjects were divided into 4 groups according to quartile of GGT level (male: first quartile [Q1], <21 U/L; second quartile [Q2], 21-29 U/L; third quartile [Q3], 30-47 U/L, and fourth quartile [Q4] ≥48 U/L, female: first quartile [Q1], <13 U/L; second quartile [Q2], 13-15 U/L, third quartile [Q3], 16-22 U/L, and fourth quartile [Q4], ≥23 U/L). To compare the difference among the groups, the Student t-test and ANOVA were used for continuous data and chi-square test for categorical data. The incidence rate of

gastrointestinal cancer was calculated by dividing the number of incident cases by the overall follow-up period and presented as per 10,000 person-year. To analyze the impact of glycemic status on the incidence of gastrointestinal cancer, subjects were categorized in accordance with fasting blood glucose (FBG) (Non-diabetes: FBG <100, prediabetes: 100≤ FBG <126, diabetes (DM): FBG≥126). The Cox proportional hazard model was used to evaluate the association GGT and risk of gastrointestinal cancer. In addition, stratified analyses were conducted by glycemic status. Two adjustment models were applied, model 1 was adjusted for age and sex, and model 2 was adjusted for age, sex, BMI, smoking, drinking, exercise, and income. The level of statistical significance was set at *P*-value < .05. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

A total of 8,120,665 persons were enrolled in this cohort. The eligible population was categorized into 4 groups by the quartile level of serum GGT. The baseline characteristics of the population in accordance with GGT quartiles are presented in Table 1. Compared with the other group (Q1-Q3), the more individuals who drink or smoke were assigned in the Q4 group. The proportion of persons with hypertension, hyperlipidemia, and metabolic syndrome gradually increased as the GGT quartile level increased. The level of FBG also increased with the GGT quartile increased.

Table1. Baseline characteristics by serum GGT level (*N* = 8,120,665)

	GGT quartile				
	Q1	Q2	Q3	Q4	
	N = 2,001,551	*N* = 2,029,189	*N* = 2,099,258	*N* = 1,990,667	*P*-value
Age (years)*	43.75 ± 14.75	45.93 ± 14.36	47.87 ± 13.83	49.28 ± 12.9	<.0001
Sex, Men (%)	1,047,272 (52.32)	1,026,998 (50.61)	1,105,896 (52.68)	1,054,248 (52.96)	<.0001
Waist circumference (cm)*	76.34 ± 8.1	78.36 ± 8.66	80.92 ± 8.91	83.5 ± 8.88	<.0001
Body mass index (kg/m^2)*	22.37 ± 2.71	23.1 ± 2.96	24.02 ± 3.16	24.97 ± 3.34	<.0001
Exercise (%)	1,036,622 (51.79)	1,044,128 (51.46)	1,074,483 (51.18)	1,000,684 (50.27)	<.0001
Smoking status (%)					<.0001
Non-smoker	1,330,105 (66.45)	1,308,008 (64.46)	1,272,410 (60.61)	1,140,435 (57.29)	
Ex-smoker	259,333 (12.96)	269,649 (13.29)	294,621 (14.03)	261,707 (13.15)	
Current smoker	412,113 (20.59)	451,532 (22.25)	532,227 (25.35)	588,525 (29.56)	
Low income (%)	425,064 (21.24)	429,320 (21.16)	440,156 (20.97)	425,771 (21.39)	<.0001
Drinker (%)	783,461 (39.14)	876,698 (43.2)	997,037 (47.49)	1,060,510 (53.27)	<.0001
Hypertension (%)	290,349 (14.51)	403,676 (19.89)	564,871 (26.91)	713,722 (35.85)	<.0001
Dyslipidemia (%)	165,360 (8.26)	272,186 (13.41)	420,969 (20.05)	577,006 (28.99)	<.0001
Metabolic syndrome (%)	218,539 (10.92)	371,250 (18.3)	607,707 (28.95)	869,756 (43.69)	<.0001
Fasting glucose (mg/dl)*	92.13 ± 16.49	94.07 ± 18.82	97.15 ± 22.32	102.55 ± 27.88	<.0001

*Value was presented with mean ± SD.

Association between serum GGT level and the incidence of gastrointestinal cancer

During the follow-up period, 3,792 cases of esophageal cancer, 57,932 cases of stomach cancer, and 68,789 cases of colorectal cancer were incident, respectively. For each type of cancer, the number of incident cases, the incident rate, and the adjusted HR according to the GGT quartile level were shown in Table 2. In both of two adjustment models, the risk of gastrointestinal cancer significantly increased with a gradual rise of the serum GGT level, regardless of the type of cancer. The Q4 groups had a significantly higher risk of occurrence gastrointestinal cancer compared to the Q1 groups (esophagus: HR=2.408, 95%CI=2.184–2.654, stomach: HR=1.121, 95%CI=1.093-1.149, colorectal: HR=1.185, 95%CI =1.158-1.211) (Figure 2a-c).

Table 2. Incidence of gastrointestinal cancer according to serum GGT level

Cancer site		GGT quartile				*P* for trend
		Q1	Q2	Q3	Q4	
Esophagus	Cases, n	671	780	945	1,396	
	Incidence rate[1]	0.46	0.53	0.62	0.97	
	HR (95% CI)[2]	1*	1.194 (1.077-1.324)	1.403 (1.270-1.549)	2.415 (2.200-2.651)	<0.001
	HR (95% CI)[3]	1*	1.218 (1.098-1.351)	1.445 (1.305-1.559)	2.408 (2.184-2.654)	<0.001
Stomach	Cases, n	12,406	13,530	15,470	15,886	
	Incidence rate[1]	8.52	9.17	10.15	11.04	
	HR (95% CI)[2]	1*	1.028 (1.003-1.053)	1.073 (1.048-1.099)	1.172 (1.144-1.200)	<0.001
	HR (95% CI)[3]	1*	1.012 (0.987-1.037)	1.042 (1.017-1.068)	1.121 (1.093-1.149)	<0.001
Colorectal	Cases, n	13,749	15,802	18,953	20,265	
	Incidence rate[1]	9.45	10.72	12.45	14.09	
	HR (95% CI)[2]	1*	0.983 (0.918-1.052)	1.075 (1.010-1.145)	1.209 (1.139-1.284)	<0.001
	HR (95% CI)[3]	1*	1.03 (1.007-1.054)	1.091 (1.067-1.116)	1.185 (1.158-1.212)	<0.001

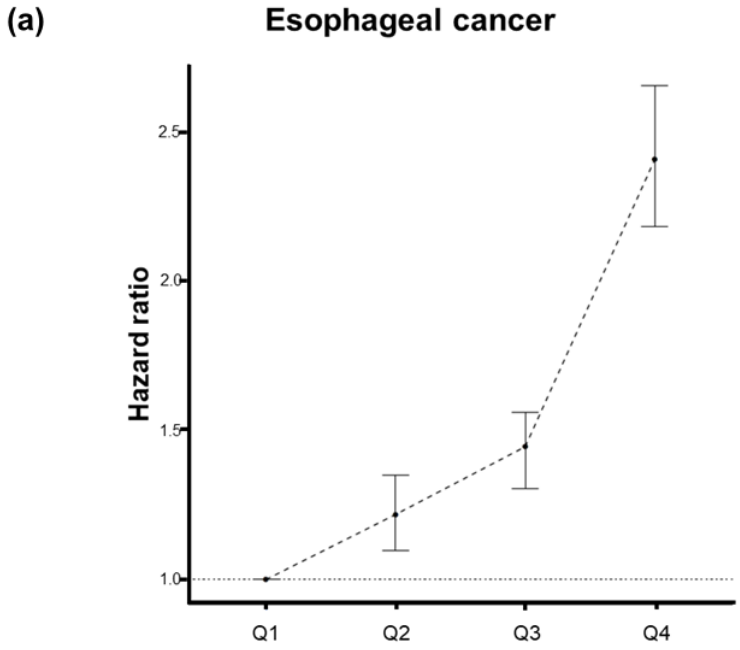
*Reference value

[1]Per 10,000 person-year,

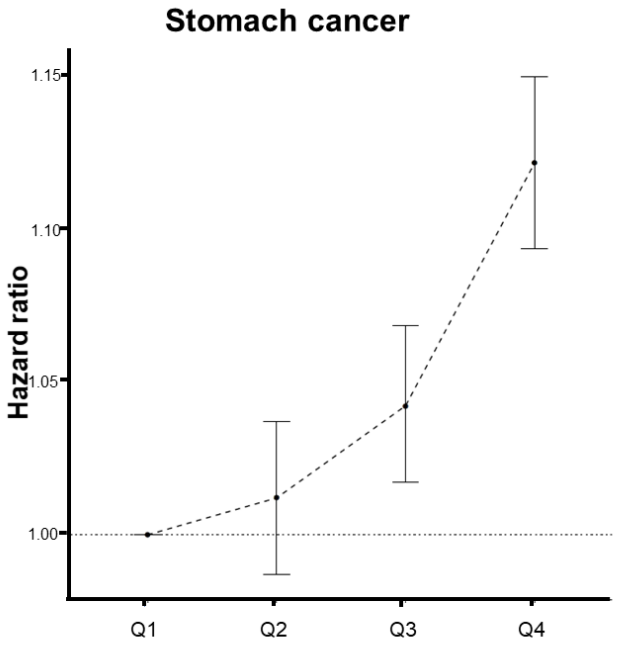
[2] Model 1: Adjusted for age, sex,

[3] Model 2: Adjusted for age, sex, BMI, smoking, drinking, exercise, income.

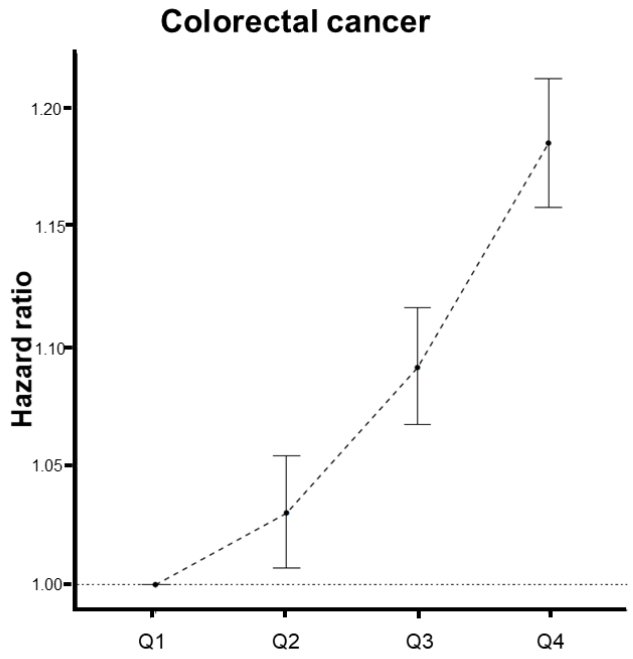
Figure 2. Association between serum GGT quartile level and incidence of gastrointestinal cancer (a) esophageal cancer, (b) stomach cancer, (c) colorectal cancer. Q1-4: GGT quartile level.



(b)


Stomach cancer
Hazard ratio
1.15
1.10
1.05
1.00
Q1
Q2
Q3
Q4

(c)


Colorectal cancer
Hazard ratio
1.20
1.15
1.10
1.05
1.00
Q1
Q2
Q3
Q4

Association between glycemic status and the incidence of gastrointestinal cancer

For each gastrointestinal cancer, the number of cancer incident cases and incidence rate stratified the glycemic status were presented in Table 3. The glycemic status was categorized as non-DM, prediabetes, and DM. Compared to the non-DM group, the risk of incidence of each gastrointestinal cancer was higher than in both IFG and DM group. (Esophagus, IFG; HR=1.198, 95%CI=1.113-1.290, DM; HR= 1.278, 95%CI=1.170-1.397) (Figure 3a), (Stomach, IFG; HR=1.050, 95%CI=1.030-1.071, DM; HR= 1.181, 95%CI=1.154-1.210) (Figure 3b), (Colorectal, IFG; HR=1.089, 95%CI=1.069-1.108, DM; HR= 1.217, 95%CI=1.191-1.244) (Figure 3c).

Table 3. Incidence of gastrointestinal cancer according to glycemic status

Cancer site		Glycemic status		
		Non-DM	IFG	DM
Esophagus	Cases, n	1,996	1,122	674
	Incidence rate[1]	0.48	0.87	1.44
	Model 1, HR (95% CI)[2]	1*	1.155 (1.074-1.243)	1.168 (1.070-1.276)
	Model 2, HR (95% CI)[3]	1*	1.198 (1.113-1.290)	1.278 (1.170-1.397)
Stomach	Cases, n	32,862	18,214	10,951
	Incidence rate[1]	7.93	11.74	20.03
	Model 1, HR (95% CI)[2]	1*	1.056 (1.036-1.077)	1.191 (1.164-1.220)
	Model 2, HR (95% CI)[3]	1*	1.050 (1.030-1.071)	1.181 (1.154-1.210)
Colorectal	Cases, n	39,604	18,214	10,951
	Incidence rate[1]	9.57	14.14	23.60
	Model 1, HR (95% CI)[2]	1*	1.109 (1.089-1.128)	1.246 (1.220-1.274)
	Model 2, HR (95% CI)[3]	1*	1.089 (1.069-1.108)	1.217 (1.191-1.244)

*Reference value

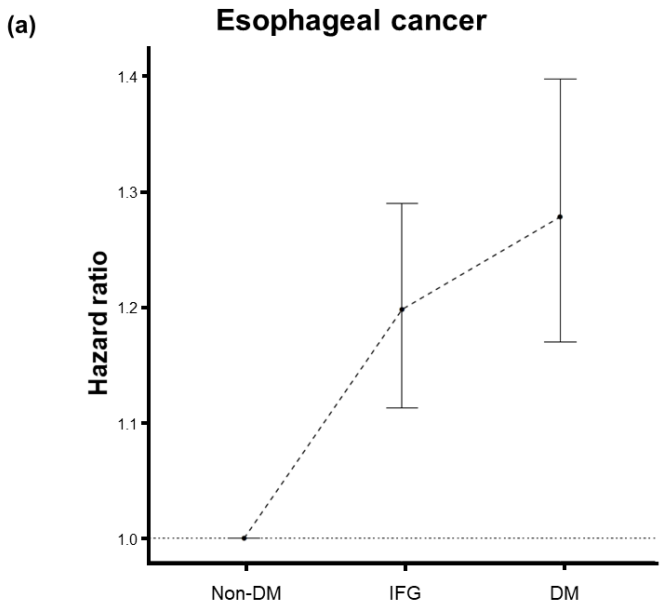
[1]Per 10,000 person-year,

[2]Adjusted for age, sex,

[3]Adjusted for age, sex, BMI, smoking, drinking, exercise, income.

DM: Diabetes Mellitus, IFG: Impaired fasting glucose.

Figure 3. Associated between glycemic status and incidence of gastrointestinal cancer (a) esophageal cancer, (b) stomach cancer, (c) colorectal cancer. DM: diabetes mellitus, IFG: impaired fasting glucose.



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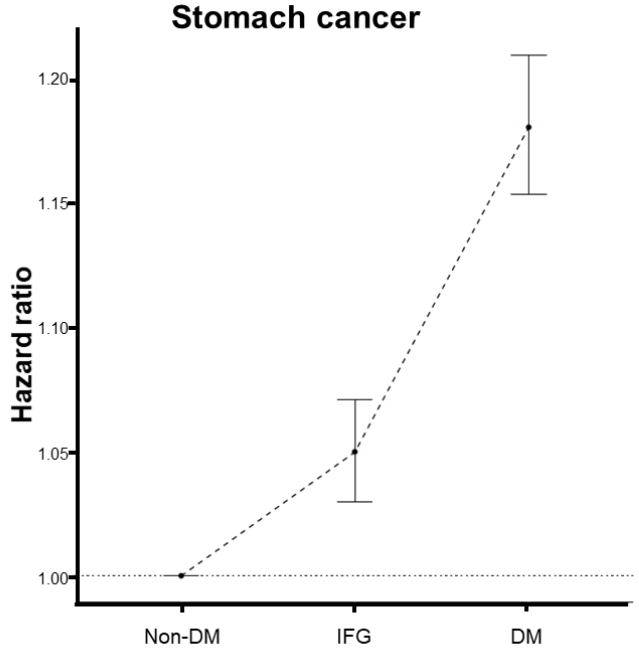
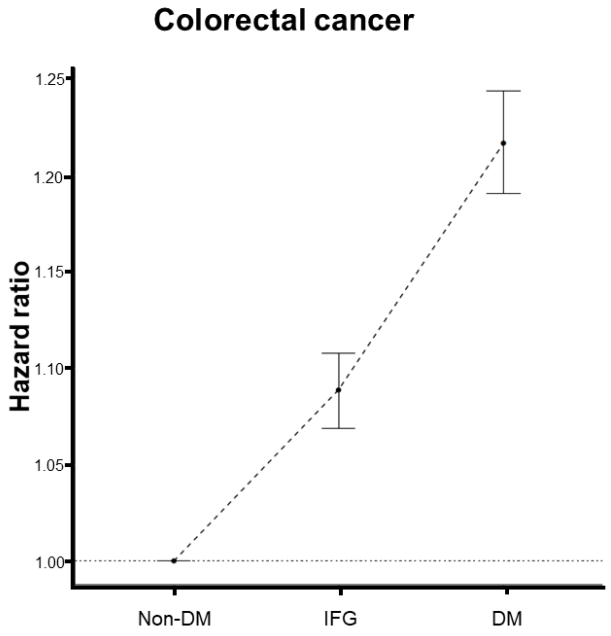

Stomach cancer
Hazard ratio
1.20
1.15
1.10
1.05
1.00
Non-DM
IFG
DM

(c)


Colorectal cancer
Hazard ratio
1.25
1.20
1.15
1.10
1.05
1.00
Non-DM
IFG
DM

Association incidence of gastrointestinal cancer and serum GGT level stratified by glycemic status

To evaluate association the risk of gastrointestinal cancer and serum GGT level according to the glycemic status, the stratified analyses by glycemic status were conducted. The subjects were stratified into non-DM, prediabetes, and DM groups by the glycemic status, and each group was divided into Q4 groups and other groups (Q1-3) according to serum GGT level. After setting Q1-3 groups in non-DM to reference group, the HR of the occurrence in gastrointestinal cancer was estimated for each group (Table 4).

The risk of esophageal cancer in the Q4 groups was higher than that in the Q1-3 groups regardless of glycemic status. Besides, the Q4 groups of non-DM and prediabetes showed a higher risk in the incident of esophageal cancer than the Q1-3 group of DM. (non-DM/Q4, HR:1.98, 95%CI:1.799-2.180; prediabetes/Q4, HR:2.089, 95%CI:1.873-2.331; DM/Q1-3, HR:1.168, 95%CI:1.037-1.316) (Figure 4a). Regarding the stomach cancer, Q4 group of DM had the highest risk (HR:1.283, 95%CI: 1.237-1.331). Similar risks were shown in Q4 group of prediabetes and Q1-3 group of DM (prediabetes/Q4, HR:1.129, 95%CI:1.094-1.165; DM/Q1-3, HR:1.164, 95%CI:1.130-1.199) (Figure 4b). In colorectal

cancer, the risk of occurrence was highest in the Q4 group of DM (HR:1.342, 95%CI:1.299-1.386), and similar in the Q4 group of prediabetes (HR:1.214, 95%CI:1.180-1.248) and in the Q1-3 group of DM (HR:1.193, 95%CI:1.161-1.227) (Figure 4c).

Table 4. Association incidence of gastrointestinal cancer and serum GGT level stratified by glycemic status

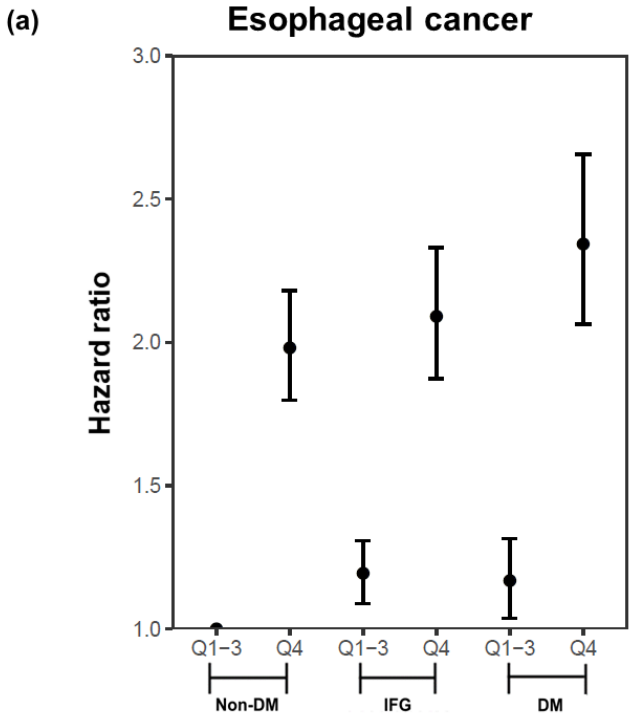
Glycemic status	GGT level	Cancer site					
		Esophagus		Stomach		Colorectal	
		Incidence rate[1]	HR (95% CI)[2]	Incidence rate[1]	HR (95% CI)[2]	Incidence rate[1]	HR (95% CI)[2]
Non-DM	Q1-Q3	0.41	1*	7.68	1*	9.11	1*
	Q4	0.76	1.98 (1.799-2.180)	9.02	1.077 (1.049-1.105)	11.44	1.093 (1.068-1.119)
IFG	Q1-Q3	0.77	1.193 (1.088-1.309)	11.71	1.043 (1.019-1.067)	13.61	1.067 (1.044-1.090)
	Q4	1.09	2.089 (1.873-2.331)	11.90	1.129 (1.094-1.165)	15.41	1.214 (1.180-1.248)
DM	Q1-Q3	1.32	1.168 (1.037-1.316)	21.51	1.164 (1.130-1.199)	24.17	1.193 (1.161-1.227)
	Q4	1.60	2.341 (2.063-2.656)	18.01	1.283 (1.237-1.331)	22.85	1.342 (1.299-1.386)

*Reference value

[1]Per 10,000 person-year, [2]Adjusted for age, sex, BMI, smoking, drinking, exercise, income.

DM: Diabetes Mellitus, IFG: Impaired fasting glucose.

Figure 4. Association incidence of gastrointestinal cancer and serum GGT level stratified by glycemic status (a) esophageal cancer, (b) stomach cancer, (c) colorectal cancer. DM: diabetes mellitus, IFG: impaired fasting glucose, Q1-4: GGT quartile level.



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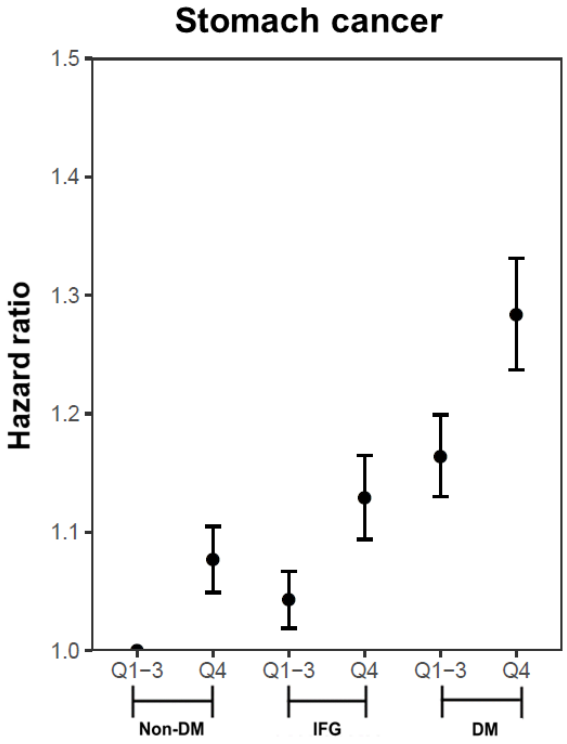
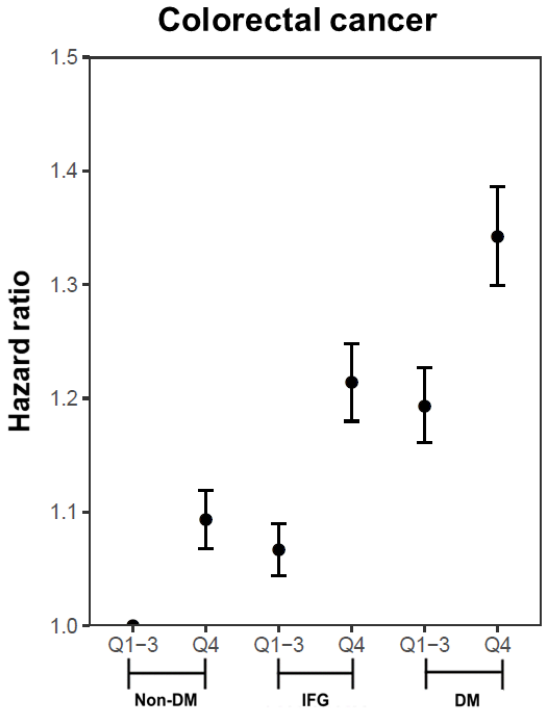

Stomach cancer
Hazard ratio
1.5
1.4
1.3
1.2
1.1
1.0
Q1−3
Q4
Q1−3
Q4
Q1−3
Q4
Non-DM
IFG
DM

(c)


Colorectal cancer
Hazard ratio
1.5
1.4
1.3
1.2
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Q1−3
Q4
Q1−3
Q4
Q1−3
Q4
Non-DM
IFG
DM

DISCUSSION

The findings of this large-scale study indicate that elevated serum GGT level is significantly associated with the risk in gastrointestinal cancer, and the risk of cancer gradual increases as the level of GGT increase. Moreover, the risk of gastrointestinal cancer in the DM group, even the IFG group, is significantly higher than that in the non-DM group. To evaluate the interaction between the GGT level and the glycemic status contribute to the risk of gastrointestinal cancer, the stratified analysis was conducted in accordance with the glycemic status. Regarding the incidence of stomach and colorectal cancer, the additional effect of two factors was indirectly shown, but an elevated GGT level was the dominant factor in esophageal cancer. To the best of our knowledge, this is the first large-scale study to confirm the association of gastrointestinal cancer incidence with the glycemic status as well as an elevated GGT level and to reveal the interaction of two factors.

Previous epidemiologic studies have identified a significant correlation between an elevated GGT level and the incidence of gastrointestinal cancer. In cohort studies from Austria and Sweden revealed high GGT levels were

associated with the risk of gastrointestinal cancer, and another study from Korea founded high GGT levels had a connection in risk of esophagus, stomach, and colorectal cancer, but only in men.[10, 12-14] In addition, a meta-analysis indicated that an elevated GGT level has a significant connection to risk of gastrointestinal cancer.[11] Although the biological mechanism regarding the association of an elevated GGT level and the risk of gastrointestinal cancer is still not clear, the result of this large-scale study was mostly consistent with that of the previous epidemiologic studies. Hence, it may be strong evidence of the need for further study to address the predictive role of serum GGT in gastrointestinal cancer.

Several previous studies have tried to investigate an association between DM and the risk of gastrointestinal cancer.[17, 22-27] A cohort study in the U.K. claimed that only colon cancer of the gastrointestinal tract is associated with DM,[27] and a study in the U.S. showed that a significant correlation between DM and colon cancer incidence only in men.[23] On the other hand, the link between DM and the occurrence of stomach or esophageal cancer is still controversial.[17-19, 28] Despite no information regarding anti-diabetic drugs or Hb A1c in this study, since more participants were included than previous studies, our finding that DM is associated with developing of gastrointestinal cancer deserves to be interesting

for the clinician. Moreover, it is an impressive result that subjects with IFG have a significantly higher risk of developing gastrointestinal cancer than healthy ones. A few studies have reported that IFG itself increases the risk of liver and colorectal cancer.[29-31] Our result that IFG increases the risk of esophageal and stomach cancer, including colorectal cancer is a novel finding. After all, insulin resistance is a plausible mechanism that links glycemic status and cancer incidence.[32] Based on our findings, further studies are needed to investigate the relationship between glycemic status and risk of gastrointestinal cancer.

The influence of high GGT level and glycemic status on the occurrence of gastrointestinal cancer, respectively, differed by the site of cancer. Regarding esophageal cancer, the influence of high GGT level was overwhelming. Meanwhile, the additional effect of high GGT level and glycemic status, which contributed to the risk of stomach and colorectal cancer, was indirectly revealed. Our findings indicate that individuals with high GGT levels should consider the precise screening of esophageal cancer, regardless of glycemic status. In addition, patients with DM, or IFG and high GGT levels, had a higher risk of developing stomach and colorectal cancer than a healthy person. Therefore, it is required to develop a model that can precisely estimate an individual's risk of developing

gastrointestinal cancer, and appropriated screening strategies are needed.

This cohort study was a large-scale study with nearly 8.1 million participants. However, this study had several limitations. First, since only the baseline values of GGT and fasting glucose were collected, it is limited to assess the lowering effect of GGT or fasting glucose on the occurrence of gastrointestinal cancer. In addition, the diagnosis of DM is likely to be inaccurate because DM was defined based on the result of a single fasting glucose test without further tests. Although patients with hepatitis and liver cirrhosis were excluded in the study, the residual confounding is concerned because other data of liver enzymes were not adjusted. Finally, it requires careful interpretation to evaluate the interaction between GGT level and glycemic status by the stratified analysis. Since several studies reported that high GGT level is associated with insulin resistance,[33, 34] it needed complete control of one value to evaluate the interaction between two factors. However, an indirect method called the stratified analysis was conducted, it may be a limitation to the interpretation of the results.

In conclusion, this large-scale study demonstrated an elevated GGT level is associated with the risk of gastrointestinal cancer and the risk increases gradually with the GGT level. Additionally, it showed that the change of glycemic status

including IFG as well as DM is related to the incidence of gastrointestinal cancer. Further studies are required to assess the effect of sequential change in GGT level and glycemic status on the occurrence of gastrointestinal cancer. Despite there are some limitations, this study would be meaningful evidence for clinicians to warrant a customized strategy for screening of gastrointestinal cancer according to GGT level, and glycemic status.

REFERENCES

1. Teschke R, Rauen J, Neuefeind M, Petrides AS, Strohmeyer G. Alcoholic liver disease associated with increased gamma-glutamyltransferase activities in serum and liver. *Advances in experimental medicine and biology* 1980;**132**: 647-54.
2. Whitfield JB. Gamma glutamyl transferase. *Critical reviews in clinical laboratory sciences* 2001;**38**: 263-355.
3. Melvin JC, Rodrigues C, Holmberg L, Garmo H, Hammar N, Jungner I, Walldius G, Lambe M, Jassem W, Van Hemelrijck M. Gamma-glutamyl transferase and C-reactive protein as alternative markers of metabolic abnormalities and their associated comorbidites: a prospective cohort study. *International journal of molecular epidemiology and genetics* 2012;**3**: 276-85.
4. Kunutsor SK, Abbasi A, Adler AI. Gamma-glutamyl transferase and risk of type II diabetes: an updated systematic review and dose-response meta-analysis. *Annals of epidemiology* 2014;**24**: 809-16.
5. Franzini M, Scataglini I, Ricchiuti A, Fierabracci V, Paolicchi A, Pompella A, Dell'Omo G, Pedrinelli R, Corti A. Association between plasma gamma-glutamyltransferase fractions and metabolic syndrome among hypertensive patients. *Scientific reports* 2017;**7**: 12003.
6. Lee SR, Choi EK, Han KD, Cha MJ, Oh S. Association between gamma-glutamyltransferase level and incidence of atrial fibrillation: A nationwide population-

based study. *International journal of cardiology* 2017;**245**: 149-55.

7. Nano J, Muka T, Ligthart S, Hofman A, Darwish Murad S, Janssen HLA, Franco OH, Dehghan A. Gamma-glutamyltransferase levels, prediabetes and type 2 diabetes: a Mendelian randomization study. *International journal of epidemiology* 2017;**46**: 1400-9.
8. Wang S, Zhang J, Zhu L, Song L, Meng Z, Jia Q, Li X, Liu N, Hu T, Zhou P, Zhang Q, Liu L, et al. Association between liver function and metabolic syndrome in Chinese men and women. *Scientific reports* 2017;**7**: 44844.
9. Ndrepepa G, Colleran R, Kastrati A. Gamma-glutamyl transferase and the risk of atherosclerosis and coronary heart disease. *Clinica chimica acta; international journal of clinical chemistry* 2018;**476**: 130-8.
10. Van Hemelrijck M, Jassem W, Walldius G, Fentiman IS, Hammar N, Lambe M, Garmo H, Jungner I, Holmberg L. Gamma-glutamyltransferase and risk of cancer in a cohort of 545,460 persons - the Swedish AMORIS study. *European journal of cancer (Oxford, England : 1990)* 2011;**47**: 2033-41.
11. Kunutsor SK, Apekey TA, Van Hemelrijck M, Calori G, Perseghin G. Gamma glutamyltransferase, alanine aminotransferase and risk of cancer: systematic review and meta-analysis. *International journal of cancer* 2015;**136**: 1162-70.
12. Mok Y, Son DK, Yun YD, Jee SH, Samet JM. gamma-Glutamyltransferase and cancer risk: The Korean cancer prevention study. *International journal of cancer* 2016;**138**: 311-9.
13. Strasak AM, Pfeiffer RM, Klenk J, Hilbe W, Oberaigner W, Gregory M, Concin H,

Diem G, Pfeiffer KP, Ruttmann E, Ulmer H. Prospective study of the association of gamma-glutamyltransferase with cancer incidence in women. *International journal of cancer* 2008;**123**: 1902-6.

14. Strasak AM, Rapp K, Brant LJ, Hilbe W, Gregory M, Oberaigner W, Ruttmann E, Concin H, Diem G, Pfeiffer KP, Ulmer H. Association of gamma-glutamyltransferase and risk of cancer incidence in men: a prospective study. *Cancer research* 2008;**68**: 3970-7.
15. Choi YJ, Lee DH, Han KD, Yoon H, Shin CM, Park YS, Kim N. Elevated serum gamma-glutamyltransferase is associated with an increased risk of oesophageal carcinoma in a cohort of 8,388,256 Korean subjects. *PloS one* 2017;**12**: e0177053.
16. Tsuboya T, Kuriyama S, Nagai M, Hozawa A, Sugawara Y, Tomata Y, Kakizaki M, Nishino Y, Tsuji I. Gamma-glutamyltransferase and cancer incidence: the Ohsaki cohort study. *Journal of epidemiology* 2012;**22**: 144-50.
17. Miao ZF, Xu H, Xu YY, Wang ZN, Zhao TT, Song YX, Xu HM. Diabetes mellitus and the risk of gastric cancer: a meta-analysis of cohort studies. *Oncotarget* 2017;**8**: 44881-92.
18. Xu B, Zhou X, Li X, Liu C, Yang C. Diabetes mellitus carries a risk of esophageal cancer: A meta-analysis. *Medicine* 2017;**96**: e7944.
19. Petrick JL, Li N, Anderson LA, Bernstein L, Corley DA, El Serag HB, Hardikar S, Liao LM, Liu G, Murray LJ, Rubenstein JH, Schneider JL, et al. Diabetes in relation to Barrett's esophagus and adenocarcinomas of the esophagus: A pooled study from the International Barrett's and Esophageal Adenocarcinoma Consortium. *Cancer* 2019.

20. Qi J, He P, Yao H, Song R, Ma C, Cao M, Cui B, Ning G. Cancer risk among patients with type 2 diabetes: A real-world study in Shanghai, China. *Journal of diabetes* 2019.
21. Dixon JL, Copeland LA, Zeber JE, MacCarthy AA, Reznik SI, Smythe WR, Rascoe PA. Association between diabetes and esophageal cancer, independent of obesity, in the United States Veterans Affairs population. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus* 2016;**29**: 747-51.
22. Valent F. Diabetes mellitus and cancer of the gastrointestinal organs: An Italian population-based cohort study. *Journal of diabetes and its complications* 2015;**29**: 1056-61.
23. Ma Y, Yang W, Song M, Smith-Warner SA, Yang J, Li Y, Ma W, Hu Y, Ogino S, Hu FB, Wen D, Chan AT, et al. Type 2 diabetes and risk of colorectal cancer in two large U.S. prospective cohorts. *British journal of cancer* 2018;**119**: 1436-42.
24. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Archives of internal medicine* 2006;**166**: 1871-7.
25. Tseng CH, Tseng FH. Diabetes and gastric cancer: the potential links. *World journal of gastroenterology* 2014;**20**: 1701-11.
26. Xu HL, Tan YT, Epplein M, Li HL, Gao J, Gao YT, Zheng W, Shu XO, Xiang YB. Population-based cohort studies of type 2 diabetes and stomach cancer risk in Chinese men and women. *Cancer science* 2015;**106**: 294-8.
27. de Jong R, Peeters P, Burden AM, de Bruin ML, Haak HR, Masclee AAM, de Vries F, Janssen-Heijnen MLG. Gastrointestinal cancer incidence in type 2 diabetes mellitus;

results from a large population-based cohort study in the UK. *Cancer epidemiology* 2018;**54**: 104-11.

28. Fujishiro M, Ishihara H. Controversy regarding gastric cancer and diabetes. *Journal of gastroenterology* 2016;**51**: 80-1.
29. Jung KJ, Kim MT, Jee SH. Impaired fasting glucose, single-nucleotide polymorphisms, and risk for colorectal cancer in Koreans. *Epidemiology and health* 2016;**38**: e2016002.
30. Feng X, Wang G, Li N, Lyu Z, Chen S, Wei L, Chen Y, Xie S, Yang W, Yin J, Cui H, Chen H, et al. The association between fasting blood glucose and the risk of primary liver cancer in Chinese males: a population-based prospective study. *British journal of cancer* 2017;**117**: 1405-11.
31. Liu T, Wang W, Cui H, Sun M, Wang Y, Liu X, Cao L, Liu H, Liu S. Elevated fasting serum glucose levels increase the risk of hepatocellular carcinoma: A prospective cohort study. *Medicine* 2019;**98**: e16369.
32. Arcidiacono B, Iiritano S, Nocera A, Possidente K, Nevolo MT, Ventura V, Foti D, Chiefari E, Brunetti A. Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. *Experimental diabetes research* 2012;**2012**: 789174.
33. Arase Y, Heianza Y, Hara S, Ohmoto-Sekine Y, Amakawa K, Tsuji H, Ogawa K, Saito K, Kodama S, Ikeda K, Kumada H, Kobayashi T, et al. Potential impact of joint association of alanine aminotransferase and gamma-glutamyltransferase on insulin resistance in Japan: The Toranomon Hospital Health Management Center Study 19 (TOPICS 19). *Hepatology research : the official journal of the Japan Society of Hepatology* 2015;**45**: 247-58.

34. Wei D, Chen T, Gao Y, Tian H. Serum Gamma-Glutamyltransferase and Ferritin are Related to Insulin Resistance: A Population-Based Study. *Clinical laboratory* 2015;**61**: 1157-61.

국문 초록

배경: 감마 글루타밀 전이효소의 상승과 소화기암의 발생 위험은 관련성이 있다. 그러나 혈당 장애가 동반된 환자에게서 감마 글루타밀 전이효소와 소화기암의 위험도의 상관관계는 명확하지 않다. 우리는 본 연구를 통해 감마 글루타밀 전이효소 수치와 혈당장애가 각각 소화기암 발생에 미치는 관련성을 평가하고, 계층화 분석을 통해 두 요인 사이에 상호작용에 대해 알아보고자 한다.

방법: 2009년 1월부터 12월까지 국민 건강보험 공단에서 제공하는 일반 건강검진을 받은 총 8,120,665의 대상자가 본 연구에 포함되었다. 대상자는 감마 글루타밀 전이효소의 4분위 값에 따라 구분하였고 각 그룹에 대해 식도, 위 그리고 대장직장암의 발생율을 조사하였다. 또한 혈당 장애를 비당뇨, 공복혈당장애, 그리고 당뇨군으로 구분하여 계층화 분석을 시행하였다.

결과: 8년 동안의 추적관찰 기간동안 총 129,853 건의 소화기암이 발생하였다. 감마 글루타밀 전이효소가 가장 높았던 군은 낮은 군에 비해 소화기암 발생의 위험이 높았다. (식도암: 위험비 = 2.403, 95% 신뢰구간 = 2.184−2.654, 위암: 위험비 = 1.121, 95% 신뢰구간 =

1.093–1.149, 대장직장암: 위험비 = 1.185, 95% 신뢰구간 = 1.158–1.211). 당뇨뿐 아니라 공복혈당장애를 가진 대상자도 소화기암의 발생 위험이 높았다. 혈당 장애에 따라 계층화 분석을 하였을 때, 감마 글루타밀 전이효소의 효과는 식도암에서 우세하였다. 반면 위암과 대장암의 발생에 있어서는 감마 글루타밀 전이효소의 상승과 혈당장에 상승 작용이 확인되었다.

결론: 높은 감마 글루타밀 전이효소의 수치와 공복혈당 장애 그리고 당뇨는 각각 소화기암 발생과 유의한 관련성이 있다. 높은 글루타밀 전이효소의 효과는 혈당 장애와 암종에 따라 달라진다.

주요어: 감마 글루타밀 전이효소; 소화기암; 코호트 연구; 당뇨

학 번: 2015–21977