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Gamma-glutamyltransferase and risk of cancer in a cohort of 545,460 persons – the Swedish AMORIS study

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ABSTRACT

Background: Apart from using gamma-glutamyltransferase (GGT) as a predictor of diabetes, cardiovascular and chronic kidney disease, some evidence suggests GGT as an indicator of cancer risk. We aimed to study the association between GGT and cancer in a large Swedish cohort with 37,809 primary cancers.

Methods: In a cohort of 545,460 persons (aged >20 years) who had a measurement of GGT in the Apolipoprotein Mortality Risk (AMORIS) study, multivariate Cox proportional hazards regression was used to investigate categories of GGT (<18, 18–36,36–72, ⩾72 U/L) in relation to cancer risk. Stratified analyses were conducted by gender, levels of alanine aminotransferase (ALT) (</⩾50 U/L), glucose (</⩾6.11 mmol/L) and triglycerides (</⩾1.71 mmol/L).

Results: A positive association was found between categories of GGT and overall cancer risk (HR: 1.07 (95%CI: 1.04–1.09,), 1.18 (1.14–1.22), 1.32 (1.26–1.38) for the 2nd, 3rd and 4th categories compared to the 1st). Stratified analyses showed that for those with glucose ⩾6.11 mmol/L, the association between GGT and risk of prostate, breast and liver cancer became stronger (e.g. HR for GGT ⩾72 U/L and prostate cancer: 1.11 (0.98–1.26) and 1.35 (1.00–1.81) for glucose <6.11 and ⩾6.11 mmol/L, respectively). With pancreatic cancer, the association with GGT was weaker for those with elevated glucose levels compared to those with normal levels. No effects of ALT or triglyceride levels on risk were found.

Conclusion: We found evidence of associations between elevated GGT and risk of developing different cancers. The strength of this association may vary by glucose levels because

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hyperglycaemia can result in oxidative stress initiating damaging pathways of carcinogenesis.

1. Introduction

Apart from using gamma-glutamyltransferase (GGT) as a predictor of type 2 diabetes, cardiovascular and chronic kidney disease, there is some evidence to use GGT as an indicator of cancer risk.[1–4] The positive association between GGT levels and tumour incidence may be explained by the link between GGT and the cell redox state. GGT is a central enzyme in the glutathione (GSH) metabolism, a ubiquitous antioxidant thiol, and plays an important role in maintaining tissue oxidant/antioxidant balance, cellular defence, proliferation and protection against further oxidative stress.[5]

Evidence from observational studies for an association between GGT and cancer is limited, but two large prospective cohort studies based on 79,279 and 92,843 Austrian men and women showed elevated cancer risk for all GGT categories compared to normal low levels (<17.99 U/L).[3,4] This increased risk was found for malignant neoplasms of the digestive and respiratory tracts. For women, there was also a positive association for breast and female genital cancers together with lymphoma and haematopoietic cancer. In men there was also an increased risk for urinary tract cancers.[3,4] The association between GGT and breast cancer risk was studied in the British Guemsey Breast Cohort Study which included 4,714 women aged >32 years. There was only a positive association between GGT and breast cancer risk in premenopausal women.[6]

Even though these studies indicate that GGT might be involved in tumour biology, underlying mechanisms remain elusive and merit further studies. One of the pathways through which GGT and tumour development may be linked is hyperglycaemia because it can lead to overproduction of reactive oxygen species (ROS) by the mitochondrial electron-transport chain, which may be underlying the increased risk of malignancy in diabetics.[7] As there is currently only one large study population in which the association between GGT and cancer risk has been studied, we aimed to assess this association in a Swedish prospective cohort study with 37,809 primary cancers. Moreover, we wanted to ascertain whether liver dysfunction (as measured by alanine aminotransferase level) and metabolic abnormalities (based on glucose and triglycerides levels) may affect this association since hepatic disease and diabetes are potential confounders and effect-modifiers.

2. Methods

2.1. Study population and data collection

The Central Automation Laboratory (CALAB) database (1985–1996), includes data obtained from 351,487 men and 338,101 women, mainly from the greater Stockholm area. All individuals were either healthy individuals having clinical laboratory testing as part of a general health check-up or outpatients referred for laboratory testing. No individuals were inpatients at the time their blood samples were taken and none were excluded for disease symptoms or because of treatment. Apart from information on blood testing, no clinical data were included in the CALAB database.[8] This database was linked to several Swedish national registries such as the National Cancer Register and the Hospital Discharge Register by using the Swedish 10-digit personal identity number to provide information on socio-economic status (SES), vital status, cancer diagnosis and emigration. The linkage of national registers to the CALAB database is called the AMORIS study and it has been described in detail elsewhere.[8–14] This study complied with the Declaration of Helsinki and was approved by the ethics review board of the Karolinska Institute.

For the present study, we selected all individuals aged >20 years whose GGT levels were measured at baseline (n = 545,460) and took the following information from the CALAB database: GGT (U/L), age at diagnosis, gender. Alanine aminotransferase (ALT) was measured in 537,272 persons while glucose (mmol/L) and triglycerides (mmol/L) were assayed in 516,190 and 520,771 persons, respectively. Follow-up started at time of measurement and ended at time of event (i.e. cancer diagnosis), death from any cause, emigration or end of follow-up (31st December 2002), whichever occurred first. From the other registries, we collected information regarding SES, history of circulatory or lung disease (ICD10: I00–I99 and J00–J99, respectively) prior to GGT measurement, cancer diagnosis and death. SES is based on occupational groups and classifies gainfully employed subjects into manual workers and non-manual employees, below designated as blue-collar and white-collar workers.[15] All subjects included in the analyses were free from benign neoplasms or cancer prior to their GGT measurements, according to the National Cancer Registry.

The quantitative determination of GGT was performed with an enzymatic colorimetric test using L-γ-glutamyl-3-carboxy-4-nitroanilide as donor substrate at a temperature of 37 °C, which is the reference method recommended by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).[1] ALT was measured with an enzymatic UV-test according to IFCC, including incubation with pyridoxal phosphate. The coefficient of variation was ⩽6.0% for both GGT and ALT. Glucose was measured enzymatically with a glucoseoxidase/peroxidase method and triglycerides were measured similarly with a glycerol–phosphate–oxidase after hydrolysis with lipoprotein lipase, as described previously.[9,16] All methods were fully automated with automatic calibration and performed at one accredited laboratory.[9]

2.2. Data analysis

Multivariate Cox proportional hazards regression was used to investigate categories of GGT (normal low <18 U/L, normal

high 18–36 U/L, elevated 36–72 U/L, highly elevated <72 U/L) as well as the log transformation of GGT in relation to cancer risk. The analysis was conducted for risk of cancer overall and adjusted for age, SES, gender and history of circulatory disease. Adjustment for history of lung disease did not alter our findings. Stratification by gender was performed to evaluate sex differences. To assess whether the association between GGT and cancer risk was modified by liver dysfunction, we stratified by ALT levels (</⩾50 U/L).[17] To compare our findings with other large prospective cohort studies,[3,4] this analysis was also performed for site-specific cancers grouped into neoplasms of the following organs: digestive (ICD7: 150–159), respiratory and intrathoracic (ICD7: 160–165), bone, connective tissue, soft tissue and skin (ICD7: 190, 191, 196, 197), breast and female genital organs (ICD7: 170–176), male genital organs (ICD7: 177–179), urinary organs (ICD7: 180,181), nervous system (ICD7: 192–195, 198), and lymphoid, haematopoietic and related tissue (ICD7: 200–207). The above analyses were also adjusted for glucose or triglycerides levels (continuous) in the subgroups with measurements of glucose or triglycerides, respectively. In the same sub-groups a stratified analysis by glucose or triglyceride levels was conducted based on the cut-offs according to the National Cholesterol Education Program (6.11 mmol/L or 1.71 mmol/L, respectively).[18] As we only observed differences in cancer risks between normal and high glucose levels, we further assessed the possible effect of glucose on the association between GGT and cancer risk, by conducting the glucose-stratified analysis for malignancies that had been associated with glucose levels previously (prostate, pancreatic, breast, liver and colon cancer).[19–21] A sensitivity analysis was conducted in which GGT measurements taken within two years prior to cancer diagnosis were deleted to detect reverse causation. All analyses were conducted with Statistical Analysis Systems (SAS) release 9.1.3 (SAS Institute, Cary, NC).

3. Results

37,809 persons developed cancer during follow-up (mean: 12.26 years). Most cancers developed in men (53.4%). The age distribution, at time of GGT measurement, of this study cohort is young (mean: 44 years) compared to the total Swedish population since most measurements were taken as part of health examinations done at company health check-ups. As a result, the majority of the study population (83.5%) was gainfully employed (Table 1).

When studying the association with overall cancer risk, a significant positive trend by categories of GGT was found for the total group as well as by gender (Table 2). Adjustment for glucose or triglyceride levels in the sub-groups with measurements of glucose or triglycerides did not alter the findings nor did excluding those who were diagnosed with cancer or died within two years after their GGT measurement (results not shown). Stratification by ALT levels did not alter our findings (Table 2).

Table 3 shows the association between GGT and different groups of cancer. A statistically significant positive association was found for neoplasms of digestive, respiratory, and urinary organs as well as breast and female and male genital organs. The hazard ratios (HRs) were the largest for cancer of digestive and respiratory organs (e.g. HR for log unit increase of GGT: 1.31 (95%CI: 1.27–1.35) and 1.30 (95%CI: 1.24–1.37) for digestive and respiratory cancer, respectively) (Table 3).

To assess effects of glucose and triglycerides on the association between GGT and cancer risk, we stratified the analyses conducted in Table 3, but only observed differences between normal and high glucose levels (Table 4 – Results for triglycerides not shown). As in Table 3, the results for those with normal glucose levels showed a positive association for all cancer groups studied apart from cancer of the bone, connective tissue, soft tissue and skin, the nervous system and lymphoid, haematopoietic and related tissue (Table 4). Amongst those with elevated glucose levels, results were similar, but the association became stronger for cancer of the breast, female and male genital organs (e.g. HR for log unit increase of GGT: 1.04 (95%CI: 1.00–1.09) and 1.15 (95%CI: 1.04–1.28) for male genital cancers in those with normal and high glucose levels, respectively).

The findings from Table 4 were studied in more detail for those cancers that have been previously associated with hyperglycaemia or diabetes (Table 5). A significant positive association was found between GGT levels and risk of prostate, pancreatic, breast, colon and liver cancer amongst those with normal glucose levels with the largest risk increase for pancreatic and liver cancer (HR for log unit increase in GGT: 1.36 (95%CI: 1.22–1.52) and 2.19 (95%CI: 1.98–2.42), respectively). Amongst those with elevated glucose levels, risk for prostate, breast and liver cancer became stronger (HR for log unit increase in GGT: 1.17 (95%CI: 1.05–1.30), 1.18 (95%CI: 1.02–1.35), 2.27 (95%CI: 1.89–2.72), respectively), whereas risk for pancreatic cancer decreased (HR for log unit increase in GGT: 1.36 (95%CI: 1.22–1.52) versus 0.89 (95%CI: 0.69–1.14)) and risk for colon cancer remained the same.

We also looked into an age-effect by stratifying the analysis for GGT and overall cancer risk by age groups (<30, 30–60, 60+ years), but did not find any differences (results not shown). In addition, we specifically studied the association between GGT levels and brain, liver and kidney cancers because these are organs with comparatively high GGT levels. We observed a significant association with GGT levels for liver and kidney cancer (HR for log unit increase in GGT: 2.22 (95%CI: 2.05–2.54) and 1.22 (95%CI: 1.11–1.34), respectively), but not for brain cancer (HR for log unit increase in GGT: 1.03 (95%CI: 0.94–1.13)).

4. Discussion

In the present study, high values of GGT (⩾18 U/L) were associated with an increased cancer risk compared to normal values (<18 U/L). Interestingly, the association remained after stratification by ALT levels. Moreover, cancer-site specific and stratified analysis by glucose levels showed that the positive associations between GGT and prostate, breast and liver cancer were stronger for those with glucose ⩾6.11 mmol/L than those with glucose <6.11 mmol/L. The opposite was found for pancreatic cancer.

GGT is involved in cell protection against oxidative stress since it is implicated in glutathione (GSH) transport.[5,22] GSH

Table 1 – Descriptive characteristics by cancer status.

	No cancer N = 507,651 n(%)	Cancer N = 37,809 n(%)
Mean age (years) (SD)	43.47 (14.02)	55.30 (12.10)
Gender		
Men	271,056 (53.39)	20,086 (53.12)
Women	236,595 (46.61)	17,723 (46.88)
SES		
White collar	184,367 (36.32)	14,616 (38.66)
Blue collar	239,395 (47.16)	17,021 (45.02)
Not gainfully employed/missing	83,889 (16.52)	6172 (16.32)
History of circulatory disease (ICD-10:I00–I99)		
No	477,847 (94.13)	33,856 (89.54)
Yes	29,804 (5.87)	3953 (10.46)
History of lung disease (ICD-10:J00–99)		
No	31,454 (83.19)	448,245 (93.44)
Yes	6355 (16.81)	59,406 (11.70)
Glucose (mmol/L)[a]		
Mean (SD)	4.95 (1.24)	5.16 (1.44)
<6.11	452,203 (94.21)	32,999 (91.18)
⩾6.11	27,794 (5.79)	3194 (8.82)
Triglycerides (mmol/L)[b]		
Mean (SD)	1.31 (1.00)	1.42 (0.97)
<1.71	387,677 (80.04)	27,577 (75.67)
⩾1.71	96,651 (19.96)	8866 (24.33)
Mean follow-up time (years) (SD)	12.56 (3.91)	8.16 (4.64)
GGT (k U/L)		
Mean (SD)	27.05 (44.98)	30.45 (47.98)
Normal (<18)	260,968 (51.41)	16,784 (44.39)
Normal high (18–36)	167,804 (33.05)	13,679 (36.18)
Elevated (36–72)	55,815 (10.99)	5112 (13.52)
Highly elevated (>72)	23,064 (4.54)	2234 (5.91)
ALT (U/L)[c]		
Mean (SD)	26.95 (35.85)	25.71 (26.63)
<50	459,752 (91.97)	34,827 (93.20)
⩾50	40,153 (8.03)	2540 (6.80)

[a] Glucose was measured in a subgroup of 516,190 persons.
[b] Triglycerides were measured in a subgroup of 520,771 persons.
[c] Alanine aminotransferase was measured in a subgroup of 537,272 persons.

is continuously expelled by cells and GGT-mediated metabolism permits its continuous reintroduction into cells and mainly into mitochondria, a principal source of ROS through the electron transport chain.[23] Hence, increased GGT levels may reflect high levels of GSH turnover in response to intracellular oxidative stress. However, GGT has also been shown to have a pro-oxidative role since it is a source of low but continuous levels of ROS. Low levels of pro-oxidants may promote proliferation and modulate other functions such as immune response.[24] The persistent production of ROS as a consequence of increased GGT expression in tumour cells may contribute to genetic instability and tumour progression. Moreover, it was demonstrated that increased GGT activity is promoted by treatment with carcinogenic products in rodent epithelial cells, indicating that GGT is an early marker of neoplastic transformation.[25] Additionally, GGT expression is implicated in tumour progression as evidenced by experiments in nude mice demonstrating increased growth rate of tumour following GGT transfection.[26]

In the current study, a stronger association was observed between GGT and cancer risk when glucose levels were also elevated. Generally, hyperglycaemia and type II diabetes have been demonstrated to be associated with increased risk of several cancers including colon, prostate and pancreas.[27,28] It is not clear whether GGT levels were elevated in those studies, however, it is possible to speculate that the presence of two risk factors in individuals leads to a higher chance of developing neoplastic transformation. The mechanisms that are postulated to underlie hyperglycaemia and increased cancer risk involve pathways that lead to intracellular oxidative stress. It has been seen that hyperglycaemic state in susceptible cells leads to overproduction of ROS by the mitochondrial electron-transport chain, which may be underlying the

Table 2 – Hazard ratios (HR) and 95% Confidence Intervals (95%CI) for the risk of cancer by log and categories of GGT. All models were adjusted for gender, age, SES and history of circulatory disease.

	Total HR(95%CI)	Men HR(95%CI)	Women HR(95%CI)
Total group	*N* = 545460	*N* = 291142	*N* = 254318
Log GGT	1.12 (1.10–1.14)	1.16 (1.13–1.18)	1.12 (1.10–1.15)
GGT (U/L) quartiles			
Normal (<18)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Normal high (18–36)	1.07 (1.04–1.09)	1.08 (1.04–1.11)	1.10 (1.08–1.14)
Elevated (36–72)	1.18 (1.14–1.22)	1.20 (1.15–1.25)	1.23 (1.16–1.30)
Highly elevated (>72)	1.32 (1.26–1.38)	1.40 (1.33–1.48)	1.25 (1.15–1.36)
P-value for trend	<0.001	<0.001	<0.001
Normal ALT (<50 U/L)	*N* = 494,579	*N* = 253,132	*N* = 241447
Log GGT	1.13 (1.11–1.15)	1.16 (1.14–1.19)	1.13 (1.10–1.16)
GGT (k U/L) quartiles			
Normal (<18)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Normal high (18–36)	1.07 (1.05–1.10)	1.08 (1.04–1.11)	1.11 (1.07–1.15)
Elevated (36–72)	1.20 (1.16–1.25)	1.21 (1.16–1.27)	1.23 (1.16–1.31)
Highly elevated (>72)	1.36 (1.28–1.44)	1.42 (1.33–1.53)	1.25 (1.12–1.39)
P-value for trend	<0.001	<0.001	<0.001
High ALT (⩾50 U/L)	*N* = 42693	*N* = 34082	*N* = 8611
Log GGT	1.15 (1.10–1.21)	1.16 (1.10–1.23)	1.13 (1.04–1.22)
GGT (k U/L) quartiles			
Normal (<18)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Normal high (18–36)	1.00 (0.83–1.20)	1.18 (0.92–1.50)	0.88 (0.66–1.17)
Elevated (36–72)	1.09 (0.92–1.31)	1.26 (0.99–1.60)	1.08 (0.81–1.42)
Highly elevated (>72)	1.28 (1.07–1.53)	1.49 (1.17–1.89)	1.14 (0.87–1.50)
P-value for trend	<0.001	<0.001	0.042

Table 3 – Hazard ratios (HR) and 95% Confidence Intervals (95%CI) for the risk of different cancer types by log and categories of GGT. All models were adjusted for gender, age, SES and history of circulatory disease.

Site-specific cancer	Normal low (<18 U/L)	Normal high (18–36 U/L)	Elevated (36–72 U/L)	Highly elevated (>72 U/L)	*P*-value for trend	Log GGT
Digestive organs (n = 7,077)						
Events – *n*(%)	2761(39.01)	2640 (37.30)	1072 (15.15)	604 (8.53)		
HR (95%CI)	1.00 (Ref)	1.16 (1.09–1.22)	1.36 (1.26–1.46)	1.95 (1.78–2.13)	<0.001	1.31 (1.27–1.35)
Respiratory system and intrathoracic organs (n = 3,108)						
Events – *n*(%)	1162 (37.39)	1218 (39.19)	484 (15.57)	244 (7.85)		
HR (95%CI)	1.00 (Ref)	1.24 (1.14–1.34)	1.39 (1.25–1.55)	1.78 (1.55–2.05)	<0.001	1.30 (1.24–1.37)
Bone, connective tissue, soft tissue and skin (n = 3,444)						
Events – *n*(%)	1595 (46.31)	1264 (36.70)	413 (11.99)	172 (4.99)		
HR (95%CI)	1.00 (Ref)	0.95 (0.88–1.03)	0.90 (0.80–1.00)	0.96 (0.82–1.12)	0.088	0.95 (0.90–1.01)
Breast and female genital organs (n = 8,577)						
Events – *n*(%)	5245 (61.15)	2381 (27.76)	715 (8.30)	239 (2.79)		
HR (95%CI)	1.00 (Ref)	1.08 (1.03–1.13)	1.28 (1.19–1.39)	1.09 (0.96–1.25)	<0.001	1.10 (1.06–1.14)
Urinary organs (n = 2755)						
Events – *n*(%)	1006 (36.52)	1118 (40.58)	462 (16.77)	169 (6.13)		
HR (95%CI)	1.00 (Ref)	1.15 (1.05–1.25)	1.31 (1.17–1.46)	1.22 (1.03–1.44)	<0.001	1.13 (1.07–1.20)
Nervous system (n = 2,307)						
Events – *n*(%)	1163 (50.41)	786 (34.07)	262 (11.36)	96 (4.16)		
HR (95%CI)	1.00 (Ref)	1.05 (0.96–1.15)	1.08 (0.94–1.24)	1.00 (0.81–1.24)	0.401	1.02 (0.96–1.09)
Lymphoid, haematopoietic and related tissue (n = 2,655)						
Events – *n*(%)	1183 (44.56)	975 (36.72)	343 (12.92)	154 (5.80)		
HR (95%CI)	1.00 (Ref)	1.00 (0.91–1.09)	1.00 (0.89–1.13)	1.15 (0.97–1.36)	0.331	1.00 (0.94–1.06)
Male genital organs (n = 6,445)						
Events – *n*(%)	2117 (32.85)	2783 (43.18)	1112 (17.25)	433 (6.72)		
HR (95%CI)	1.00 (Ref)	1.03 (0.97–1.09)	1.10 (1.02–1.18)	1.13 (1.02–1.25)	0.003	1.07 (1.03–1.12)

Table 4 – Hazard ratios (HR) and 95% Confidence Intervals (95%CI) for the risk of different cancer types by log and categories of GGT amongst persons with normal and high glucose levels. All models were adjusted for gender, age, SES and history of circulatory disease.

Site-specific cancer	Normal low (<18 U/L)	Normal high (18–36 U/L)	Elevated (36–72 U/L)	Highly elevated (>72 U/L)	*P*-value for trend	Log GGT
Normal glucose levels (<6.11 mmol/L)						
Digestive organs (n = 5,927)						
Events – *n*(%)	2490 (42.01)	2219 (37.44)	797 (13.45)	421 (7.10)		
HR (95%CI)	1.00 (Ref)	1.15 (1.09–1.22)	1.31 (1.20–1.42)	1.98 (1.78–2.19)	<0.001	1.30 (1.25–1.35)
Respiratory system and intrathoracic organs (n = 2,606)						
Events – *n*(%)	1063 (40.79)	1037 (39.79)	352 (13.51)	154 (5.91)		
HR (95%CI)	1.00 (Ref)	1.24 (1.13–1.35)	1.30 (1.15–1.47)	1.62 (1.37–1.92)	<0.001	1.27 (1.19–1.34)
Bone, connective tissue, soft tissue and skin (n = 3,050)						
Events – *n*(%)	1478 (48.46)	1114 (36.52)	334 (10.95)	124 (4.07)		
HR (95%CI)	1.00 (Ref)	0.97 (0.89–1.05)	0.90 (0.80–1.02)	0.96 (0.80–1.16)	0.148	0.95 (0.90–1.01)
Breast and female genital organs (n = 7,810)						
Events – *n*(%)	4985 (63.83)	2095 (26.82)	558 (7.14)	172 (2.20)		
HR (95%CI)	1.00 (Ref)	1.06 (1.01–1.12)	1.22 (1.12–1.33)	1.08 (0.92–1.25)	<0.001	1.08 (1.04–1.13)
Urinary organs (n = 2,367)						
Events – *n*(%)	919 (38.83)	971 (41.02)	354 (14.96)	123 (5.20)		
HR (95%CI)	1.00 (Ref)	1.15 (1.05–1.27)	1.26 (1.11–1.43)	1.25 (1.04–1.52)	<0.001	1.15 (1.08–1.22)
Nervous system (n = 2,083)						
Events – *n*(%)	1083 (51.99)	708 (33.99)	221 (10.61)	71 (3.41)		
HR (95%CI)	1.00 (Ref)	1.07 (0.97–1.18)	1.11 (0.96–1.29)	1.02 (0.79–1.29)	0.209	1.04 (0.97–1.12)
Lymphoid, haematopoietic and related tissue (n = 2,339)						
Events – *n*(%)	1091 (46.64)	863 (36.90)	269 (11.50)	116 (4.96)		
HR (95%CI)	1.00 (Ref)	1.01 (0.92–1.11)	0.98 (0.85–1.12)	1.20 (0.99–1.46)	0.334	0.99 (0.92–1.06)
Male genital organs (n = 5,556)						
Events – *n*(%)	1959 (35.26)	2421 (43.57)	872 (15.69)	304 (5.47)		
HR (95%CI)	1.00 (Ref)	1.01 (0.95–1.07)	1.06 (0.98–1.15)	1.08 (0.96–1.22)	0.086	1.04 (1.00–1.09)
High glucose levels (⩾6.11 mmol/L)						
Digestive organs (n = 780)						
Events – *n*(%)	173 (22.18)	296 (37.95)	193 (24.74)	118 (15.13)		
HR (95%CI)	1.00 (Ref)	1.12 (0.92–1.35)	1.31 (1.06–1.61)	1.55 (1.22–1.96)	<0.001	1.20 (1.10–1.31)
Respiratory system and intrathoracic organs (n = 330)						
Events – *n*(%)	66 (20.00)	115 (34.85)	89 (26.97)	60 (18.18)		
HR (95%CI)	1.00 (Ref)	1.08 (0.79–1.46)	1.42 (1.03–1.96)	1.85 (1.30–2.64)	<0.001	1.32 (1.16–1.51)
Bone, connective tissue, soft tissue and skin (n = 267)						
Events – *n*(%)	73 (27.34)	108 (40.45)	58 (21.72)	28 (10.49)		
HR (95%CI)	1.00 (Ref)	0.96 (0.71–1.29)	0.94 (0.66–1.33)	0.89 (0.57–1.38)	0.584	0.96 (0.81–1.13)
Breast and female genital organs (n = 478)						
Events – *n*(%)	159 (33.26)	169 (35.36)	102 (21.34)	48 (10.04)		
HR (95%CI)	1.00 (Ref)	1.10 (0.88–1.37)	1.67 (1.30–2.15)	1.36 (0.99–1.89)	0.001	1.19 (1.07–1.33)
Urinary organs (n = 272)						
Events – *n*(%)	53 (19.49)	108 (39.71)	80 (29.41)	31 (11.40)		
HR (95%CI)	1.00 (Ref)	1.21 (0.87–1.69)	1.54 (1.08–2.19)	1.18 (0.76–1.85)	0.112	1.09 (0.93–1.27)
Nervous system (n = 148)						
Events – *n*(%)	45 (30.41)	58 (39.19)	28 (18.92)	17 (11.49)		
HR (95%CI)	1.00 (Ref)	0.96 (0.65–1.42)	0.83 (0.51–1.34)	0.91 (0.52–1.61)	0.549	0.94 (0.76–1.17)
Lymphoid, haematopoietic and related tissue (n = 214)						
Events – *n*(%)	55 (25.70)	80 (37.38)	54 (25.23)	25 (11.68)		
HR (95%CI)	1.00 (Ref)	0.96 (0.68–1.36)	1.14 90.77–1.67)	1.00 (0.62–1.61)	0.691	1.11 (0.94–1.32)
Male genital organs (n = 606)						
Events – *n*(%)	108 (17.82)	245 (40.43)	169 (27.89)	84 (13.86)		
HR (95%CI)	1.00 (Ref)	1.17 (0.94–1.47)	1.31 (1.03–1.68)	1.33 (1.00–1.77)	0.022	1.15 (1.04–1.28)

increased risk of malignancy in diabetics.[7] Moreover, it is thought that in vascular endothelial cells, glucose-induced activation of sorbitol accumulation and nuclear factor-B activation can be prevented by reducing the levels of mitochon-

Table 5 – Glucose-stratified hazard ratios (HR) and 95% Confidence Intervals (95%CI) for the risk of different cancer types by log and categories of GGT. All models were adjusted for gender, age, SES and history of circulatory disease.

	Normal low (<18 U/L)	Normal high (18–36 U/L)	Elevated (36–72 U/L)	Highly elevated (>72 U/L)	P-value for trend	Log GGT
Glucose < 6.11 mmol/L						
Prostate cancer (n = 5,293)						
Events – n(%)	1835 (34.67)	2319 (43.81)	848 (16.02)	291 (1.64)		
HR (95%CI)	1.00 (Ref)	1.03 (0.97–1.09)	1.11 (1.02–1.20)	1.11 (0.98–1.26)	0.009	1.06 (1.01–1.11)
Pancreatic cancer (n = 746)						
Events – n(%)	299 (40.08)	286 (38.34)	111 (14.88)	50 (6.70)		
HR (95%CI)	1.00 (Ref)	1.27 (1.07–1.50)	1.56 (1.25–1.96)	2.01 (1.48–2.72)	<0.001	1.36 (1.22–1.52)
Breast cancer (n = 5,626)						
Events – n(%)	3606 (64.10)	1499 (2.68)	389 (6.91)	132 (2.35)		
HR (95%CI)	1.00 (Ref)	1.07 (1.00–1.13)	1.20 (1.08–1.34)	1.17 (0.99–1.40)	<0.001	1.08 (1.03–1.13)
Liver cancer (n = 563)						
Events – n(%)	182 (32.33)	200 (35.52)	88 (15.63)	93 (16.52)		
HR (95%CI)	1.00 (Ref)	1.53 (1.24–1.88)	2.16 (1.67–2.81)	6.50 (5.03–8.41)	<0.001	2.19 (1.98–2.42)
Colon cancer (n = 2,168)						
Events – n(%)	988 (45.57)	810 (37.36)	272 (12.55)	98 (4.52)		
HR (95%CI)	1.00 (Ref)	1.08 (0.98–1.19)	1.15 (1.00–1.32)	1.19 (0.97–1.47)	0.014	1.09 (1.02–1.17)
Glucose ⩾6.11 mmol/L						
Prostate cancer (n = 586)						
Events – n(%)	103 (17.58)	236 (40.27)	167 (28.50)	80 (13.65)		
HR (95%CI)	1.00 (Ref)	1.19 (0.94–1.50)	1.37 (1.07–1.76)	1.35 (1.00–1.81)	0.013	1.17 (1.05–1.30)
Pancreatic cancer (n = 120)						
Events – n(%)	37 (30.83)	45 (37.50)	22 (18.33)	16 (13.33)		
HR (95%CI)	1.00 (Ref)	0.88 (0.51–1.22)	0.68 (0.40–1.16)	0.93 (0.51–1.69)	0.477	0.89 (0.69–1.14)
Breast cancer (n = 311)						
Events – n(%)	107 (34.41)	101 (32.48)	69 (22.19)	34 (10.93)		
HR (95%CI)	1.00 (Ref)	0.97 (0.74–1.27)	1.66 (1.22–2.25)	1.42 (0.97–2.10)	0.003	1.18 (1.02–1.35)
Liver cancer (n = 99)						
Events – n(%)	12 (12.12)	26 (26.26)	26 (26.26)	35 (35.35)		
HR (95%CI)	1.00 (Ref)	1.55 (0.78–3.07)	2.92 (1.46–5.84)	7.68 (3.94–14.95)	<0.001	2.27 (1.89–2.72)
Colon cancer (n = 248)						
Events – n(%)	58 (23.39)	97 (39.11)	72 (29.03)	21 (8.47)		
HR (95%CI)	1.00 (Ref)	1.11 (0.80–1.54)	1.50 (1.05–2.13)	0.85 (0.51–1.40)	0.494	1.06 (0.90–1.25)

drial ROS.[29] Levels of ROS can be decreased by an inhibitor of electron transport chain complex, such as manganese superoxide dismutase, suggesting that hyperglycaemia may be directly involved in oxidative stress.[29] Interestingly, the stronger association between GGT and cancer risk for high glucose levels was observed (with exception from skin cancer) for cancer of origin in epithelial tissue. However, to our knowledge there is no current theory to explain this.

High GGT levels are known to be associated with hepatic and hepatobiliary diseases. By stratifying the association between GGT and cancer risk by ALT levels, we aimed to identify whether this association operates via a mechanism that is independent of liver dysfunction. The liver enzyme ALT is a biomarker known to be specific for liver damage as it mainly appears in the liver and its levels increase when there is injury to the liver. This enzyme is involved in the citric acid cycle and is of clinical relevance in patients with liver and hepatobiliary pathology.[30] Since our stratified analysis did not show any difference by ALT levels, this suggested that GGT is directly linked to tumourigenesis, independent of liver dysfunction.

A major strength of the present analysis lies in the large number of persons with prospective measurements of GGT available in the AMORIS database, all measured at the same laboratory. Use of national registers provided virtually complete follow-up for each person as well as detailed information on cancer diagnosis, time of death and emigration. Furthermore, information on both exposure and outcome was obtained independently and assessed in an accurate manner. The AMORIS population was selected by analysing blood samples from health check-ups in non-hospitalised individuals. The AMORIS cohort is similar to the general working population of Stockholm County in terms of SES and ethnicity. During the study period all-cause mortality was about 14% lower in the AMORIS population than in the general population of Stockholm County when taking age, gender and calendar year into account.[31] This selection of a healthy cohort does, however, not affect the internal validity of our study. There were no repeated measurements for GGT available nor was there information on tumour severity or possible confounders such as alcohol consumption or other liver toxic products.

Conclusion

This large prospective cohort study indicates that there is an association between GGT and tumour development, over and above liver dysfunction. Moreover, our data suggest that the strength of the association between GGT and cancer varies by glucose levels. Both findings call for further investigations into biological mechanisms underlying possible links between GGT and cancer.

Conflict of interest statement

None declared.

Role of funding organisations

The funding organisations had no influence in the design and conduct of the study, collection, management, analysis and interpretation of data, and preparation, review or approval of the manuscript. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

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