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Prospective study of the association of gamma-glutamyltransferase with cancer incidence in women

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Although several epidemiologic studies have shown that gamma-glutamyltransferase (GGT) is associated with cardiovascular disease and all-cause mortality, its relationship with cancer incidence remains widely unexplored. In experimental models the ability of cellular GGT to modulate crucial redox-sensitive functions has been established, and it may thus play a role in tumor progression. In the present study, we investigated the association of GGT with overall and site-specific cancer incidence in a population-based cohort of 92,843 Austrian women with 349,674 serial GGT measurements, prospectively followed-up for a median of 13.5 years. The relationship between GGT and cancer incidence was analyzed using adjusted Cox regression models with age as underlying time metric with age as underlying time metric including GGT concentrations at baseline and incorporating repeated GGT measurements as a time-dependent variable. During follow-up, 4,884 incidence cancers were observed. Compared to normal low GGT (<17.99 U/L), cancer risk was elevated for all other GGT categories (p for trend < 0.0001), with adjusted hazard ratios (95% confidence intervals) of 1.06 (0.99–1.13) for GGT levels between 18.00 and 35.99 U/L (normal high), 1.12 (1.02–1.22) for GGT levels between 36.00 and 71.99 U/L (elevated) and 1.43 (1.28–1.61) for highly elevated GGT (>72.00 U/L). Very similar results were seen when GGT was analyzed as a time-dependent variable. In cancer-site specific models, elevated GGT statistically significantly increased the risk for malignant neoplasms of digestive organs, the respiratory system/intrathoracic organs, breast and female genital organs and lymphoid and haematopoietic cancers (all, $p < 0.006$). Our study is the first to demonstrate in a large population-based cohort that high GGT levels significantly increased cancer risk in women.

Key words: gamma-glutamyltransferase; cancer incidence; risk factor; epidemiology; women

Gamma-glutamyltransferase (GGT), present on the external surface of most cells and in serum, is the enzyme responsible for the extracellular catabolism of glutathione (GSH), the main thiol antioxidant in mammalian cells.[1,2] In clinical practice, GGT is commonly used as a diagnostic test to assess liver dysfunction, and as a biological marker of excessive alcohol intake.[1,3,4] However, several recent epidemiologic studies have shown elevated GGT to independently influence morbidity and mortality from causes other than liver disease. Particularly, GGT was independently related to cardiovascular disease,[5–12] it correlated with most cardiovascular risk factors[13–16] and, more recently, an association with chronic kidney disease was found.[17] In addition, several large-scale studies indicate an independent role of GGT for premature death from all causes.[9,18,19]

The association of GGT with cancer incidence, however, remains largely unexplored. Several experimental models have elucidated the ability of cellular GGT to modulate crucial redox-sensitive functions, such as antioxidant/antitoxic defences and cellular proliferative/apoptotic balance, and its role in tumor progression, invasion and drug resistance has been proposed.[20–23] In addition, a potentially interesting interpretation subsumes GGT as a biomarker of exposure to certain cancer-causing xenobiotics, including persistent organic pollutants (POPs). Based on NHANES data, Lee and colleagues[24,25] recently showed that some environmental pollutants such as lead, cadmium, dioxins or organochlorine pesticides are positively and monotonically related to serum GGT levels in the general US population.

Previous studies of cancer mortality have produced contradicting results on the effects of GGT. Kazemi-Shirazi and colleagues[19] demonstrated a significant association of GGT levels and cancer death in a large, retrospective hospital-based study. In type 2 diabetic patients, Monami and colleagues[26] recently found an association between elevated GGT and cancer-related mortality; this relationship was confirmed in a multivariate analysis after adjustment for potential confounding. However, 2 other population-based studies,[9,27] conducted in males, failed to detect an association between GGT and fatal cancer events. We thus used data from a prospective, 19-year follow-up study in Austria, to investigate the association of GGT levels and cancer incidence. Among men, we recently found that elevated GGT levels were significantly associated with increased risk of overall cancer incidence and several site-specific malignancies.[28] In the present analysis, we focus on the association of GGT and cancer incidence in 92,843 women in the same cohort. To our knowledge, this is the first epidemiologic investigation of the association of GGT and cancer incidence in a large population-based cohort of women.

Material and methods

Study population

The Vorarlberg Health Monitoring and Promotion Program [VHM&PP][29–31] is one of the world's largest ongoing population-based risk factor surveillance programs. The cohort was initiated in 1985 and is conducted by the Agency for Social and Preventive Medicine in Vorarlberg, the westernmost province of Austria. All adults in the region are invited to participate by a combination of different measures including written invitations, television, radio and newspaper reports. Active follow-up of study participants is

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performed through a recall-system of written biennial reinvitation letters. Sociodemographic data are recorded, and a voluntary physical examination is conducted regularly in a standardized manner by trained local physicians and internists. During the exam, a fasting blood sample is taken. Costs are covered by the participant's (compulsory) health insurance. A more detailed description of the program methodology has been reported elsewhere.[29]

Between 1985 and 2003, 94,628 female Vorarlberg residents (aged >18 years) were enrolled in the VHM&PP cohort. Approximately 75% of participants had 2 or more routine health examinations. After excluding 1,734 participants (1.8%) with a history of malignancies prior to enrolment or with no GGT measurements, the current investigation was restricted to 92,894 healthy female participants. To eliminate possible effects of severe preclinical disease, we further excluded participants with baseline GGT values >600 U/L ($n = 51$), resulting in a total of 92,843 women with 349,674 serial GGT measurements eligible for analyses.

All participants signed informed consents to have personal data stored and processed. For our study, institutional review board approval was obtained by the Ethics Committee of the province of Vorarlberg.

Data collection

Measurements of height, weight, smoking status (current, former, never) and GGT levels are routinely obtained for each study participant. Women in the study had between 1 and 19 GGT measurements available for analysis. Individuals who reported smoking of at least one cigarette per day during the year before examination were classified as current smokers. Occupational status (blue collar, white collar or self-employed) was determined by the insurance number of participants and used as a surrogate measure of socioeconomic status. Participants who were retired at baseline were classified according to their former occupation, and housewives were classified according to their husband's job.

Cancer ascertainment

Cancers were identified by the Vorarlberg cancer registry, which has been accepted for IARC publication since 1993[32] and has high completeness of recording.[33] Nearly all cancers (96.7%) were histologically confirmed. Cohort data were linked with the Vorarlberg Death Index to identify deaths and to calculate person-years at risk. For statistical analyses, cancers were grouped into the following subgroups according to the International Classification of Diseases, 9th and 10th Revision [ICD-9, ICD-10][34]: Malignant neoplasms of digestive organs (ICD-9 150-157; ICD-10 C15-C25), respiratory system and intrathoracic organs (ICD-9 160-165; ICD-10 C30-C39), bone, connective tissue, soft tissue and skin (ICD-9 170-173; ICD-10 C40-C49), breast and female genital organs (ICD-9 174,179-184; ICD-10 C50-58), urinary organs (ICD-9 188-189; ICD-10 C64-68), nervous system and unspecified sites (ICD-9 190-199; ICD-10 C69-C72) and lymphoid, haematopoietic and related tissue (ICD-9 200-208; ICD-10 C81-C96).

Laboratory measurements

Two central laboratories that underwent regular internal and external quality procedures enzymatically determined GGT concentrations on fasting blood samples. Within 60 to 240 min after venous blood sample collection from a cubital vein, serum was obtained by centrifugation for 15 min at 4,000 rotations per min. Subsequently, GGT concentrations were measured at 37°C and were given as units per liter (U/L). To check calibration, 3 daily control samples were included. If average values of the control samples of each run were not within 3% of the true value, the run was repeated. Day-by-day variation had to be within 5%.

Statistical analyses

Cox proportional hazards models were used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) for the association of GGT with overall and site-specific cancer incidence. As GGT levels change with age, and age also strongly influences cancer risk, age was used as the time scale for the analysis.[35] Follow-up for a woman started at her age at enrolment in the cohort and ended at cancer diagnosis or at censoring. Censoring events were death, end of study, loss to follow-up and emigration. First, we computed adjusted HRs with 95% CIs using baseline GGT levels as a categorical variable, using the groups <17.99 U/L (normal low), 18.00–35.99 U/L (normal high), 36.00–71.99 U/L (elevated) and >72.00 U/L (highly elevated). A test for log-linear trend was performed. The proportional hazards assumption was checked using Schoenfeld residuals[36] and visual inspection of the hazard plots. To accommodate repeated GGT measurements, we also fitted time-dependent Cox proportional hazards models[36] models with time-varying GGT levels and adjustment for baseline subject characteristics. All models were adjusted for body-mass index (BMI) in 4 categories, smoking status (never/former/current), year of entry into the cohort (in quartiles) and occupational status (3 categories), measured at baseline. We repeated all analyses on the calendar time scale, additionally adjusting for age, in a sensitivity analyses. We evaluated whether the GGT-cancer relationship was modified by BMI and smoking using stratified analyses. Two-sided p-values <0.05 were considered statistically significant. All statistical analyses were conducted using SPSS 15.0 and SAS 9.1 statistical software.

TABLE I – CHARACTERISTICS OF STUDY POPULATION, VHM&PP 1985–2003

All female VHM&PP participants, 1985–2003	94,628
Participants with complete and valid data on GGT	92,894
Eligible participants for analyses	92,843[1]
Total number of visits	349,674
Number of GGT measurements, mean ± SD, (range)	3.8 ± 3.3 (1–19)
Age, mean ± SD (range), year	41.7 ± 15.9 (18–95)
Body-mass index, mean ± SD (median), kg/m^2	24.2 ± 4.6 (23.3)
GGT, mean ± SD (median), U/L[2]	24.3 ± 26.2 (17.9)
Current or former smoker (%)	21.5
Occupational status	
Blue collar (%)	36.9
White collar (%)	54.9
Self-employed (%)	8.2
Follow-up, mean ± SD (median), year	12.0 ± 5.6 (13.5)
Total person-years at risk	1,110,330
Incident cancers - no. (%)	4,884 (5.3)
Age at cancer diagnosis, mean ± SD (range), year	55.3 ± 13.8 (19–92)

[1]Participants with baseline GGT concentrations >600 U/L or with history of malignancies prior to enrolment were excluded.–[2]GGT values are shown as averages of each participant during individual follow-up and before eventual cancer diagnoses. All other characteristics pertain to baseline values (*i.e.* measurements at first visit).

Results

Characteristics of study population

Demographic and clinical characteristics of the study population are shown in Table I. Median follow-up time was 13.5 years with a total of 1,110,330 person-years. Most participants (93.3%) were followed-up for at least 2 years after baseline GGT measurement and 65.8% had follow-up times of 10 or more years. Mean age at study entry was 41.7 years. During follow-up, 4,884 (5.3%) incident cancers were observed. On average, 3.8 GGT measurements were obtained for each participant (range 1–19). Baseline GGT levels ranged from 3.0 to 590.7 U/L, with a median of 17.9 U/L.

TABLE II – OVERALL AND SITE-SPECIFIC CANCER INCIDENCE ACCORDING TO GGT CATEGORIES MEASURED AT BASELINE, VHM&PP 1985–2003[1]

	Gamma-glutamyltransferase (GGT)					
	Normal low (<17.99 U/L)	Normal high (18.00–35.99 U/L)	Elevated (36.00–71.99 U/L)	Highly elevated (>72.00 U/L)	*p* for trend[2]	Hazard ratio per GGT unit increase
	(*n* = 53,506)	(*n* = 28,915)	(*n* = 7,364)	(*n* = 3,058)		
All Cancers (*n* = 4,884)						
Events - no. (%)	1991 (3.7)	1902 (6.6)	645 (8.8)	346 (11.3)		
HR (95% CI)[3]	1.00 (Ref)	1.06 (0.99, 1.13)	1.12 (1.02, 1.22)	1.43 (1.28, 1.61)	<0.0001	1.002 (1.001, 1.003)
Site-specific cancers						
Malignant neoplasms of digestive organs (*n* = 1,079)						
Events - no. (%)	415 (0.8)	412 (1.4)	157 (2.1)	95 (3.1)		
HR (95% CI)[3]	1.00 (Ref)	0.96 (0.84, 1.11)	1.10 (0.91, 1.32)	1.57 (1.25, 1.97)	0.002	1.003 (1.001, 1.004)
Malignant neoplasms of respiratory system and intrathoracic organs (*n* = 226)						
Events - no. (%)	77 (0.1)	99 (0.3)	26 (0.4)	24 (0.8)		
HR (95% CI)[3]	1.00 (Ref)	1.34 (0.99, 1.82)	1.10 (0.70, 1.73)	2.31 (1.45, 3.68)	0.006	1.004 (1.001, 1.006)
Malignant neoplasms of bone, connective tissue, soft tissue and skin (*n* = 423)						
Events - no. (%)	188 (0.4)	158 (0.5)	50 (0.7)	27 (0.9)		
HR (95% CI)[3]	1.00 (Ref)	0.98 (0.79, 1.22)	0.98 (0.71, 1.36)	1.30 (0.86, 1.96)	0.48	1.002 (0.999, 1.004)
Malignant neoplasms of breast and female genital organs (*n* = 2,278)						
Events - no. (%)	949 (1.8)	885 (3.1)	303 (4.1)	141 (4.6)		
HR (95% CI)[3]	1.00 (Ref)	1.11 (1.01, 1.22)	1.21 (1.06, 1.38)	1.35 (1.13, 1.61)	<0.0001	1.002 (1.001, 1.003)
Malignant neoplasms of urinary organs (*n* = 220)						
Events - no. (%)	84 (0.2)	91 (0.3)	35 (0.5)	10 (0.3)		
HR (95% CI)[3]	1.00 (Ref)	1.03 (0.76, 1.40)	1.18 (0.79, 1.76)	0.80 (0.41, 1.54)	0.96	1.001 (0.997, 1.004)
Malignant neoplasms of nervous system and unspecified sites (*n* = 100)						
Events - no. (%)	49 (0.1)	31 (0.1)	13 (0.2)	7 (0.2)		
HR (95% CI)[3]	1.00 (Ref)	0.77 (0.48, 1.22)	1.02 (0.54, 1.92)	1.29 (0.58, 2.89)	0.81	1.001 (0.995, 1.007)
Malignant neoplasms of lymphoid, haematopoietic and related tissue (*n* = 325)						
Events - no. (%)	141 (0.3)	130 (0.4)	31 (0.4)	23 (0.8)		
HR (95% CI)[3]	1.00 (Ref)	1.05 (0.98, 1.12)	1.11 (1.01, 1.21)	1.40 (1.25, 1.58)	<0.0001	1.002 (1.001, 1.003)

[1]Participants with baseline GGT concentrations >600 U/L or with history of malignancies prior to enrolment were excluded. GGT measurements at first visit were used in the analyses.–[2]*p*-values for log-linear trend were calculated using baseline GGT categories as an ordinal variable in a fixed-effects Cox proportional hazards model, adjusted for body-mass index, smoking status, occupational status and year of entry into the cohort.–[3]Hazard ratios (95% confidence intervals) from Cox proportional hazards models adjusted for body-mass index, smoking status, occupational status and year of entry into the cohort.

Association of baseline GGT with overall and site-specific cancer incidence

The association of baseline GGT with risk of overall cancer incidence, estimated from adjusted Cox regression models, is shown in Table II and Figure 1. Compared to normal low GGT (<17.99 U/L), overall cancer risk was elevated for all other GGT categories, with adjusted HRs and corresponding 95% CIs of 1.06 (0.99, 1.13) for GGT levels between 18.00 and 35.99 U/L (normal high), 1.12 (1.02, 1.22) for GGT levels between 36.00 and 71.99 U/L (elevated) and 1.43 (1.28, 1.61) for highly elevated GGT (>72.00 U/L). The estimates exhibit a clear dose-response relationship (*p* for trend < 0.0001). This trend is also clearly apparent in Figure 1, which plots the cumulative crude incidence estimated from the Cox model for the 4 baseline GGT categories.

In cancer-site specific models, highly elevated baseline GGT statistically significantly increased risk of malignant neoplasms of digestive organs (*p* for trend 0.002), the respiratory system/intrathoracic organs (*p* for trend 0.006), breast and female genital organs (*p* for trend < 0.0001) and lymphoid and haematopoietic cancers (*p* for trend < 0.0001) with HRs of 1.57 (1.25, 1.97), 2.31 (1.45, 3.68), 1.35 (1.13, 1.61) and 1.40 (1.25, 1.58) for the highest (>72.00 U/L) *versus* lowest (<17.99 U/L) category of GGT, respectively (Table II). Significance of associations did not change when GGT was used as a continuous variable in the Cox models (Table II).

To eliminate possible confounding of our findings by severe preclinical disease (*i.e.* undiagnosed cancers at time of enrolment), we repeated all analyses excluding (*i*) the first year of follow-up after entry into the cohort, resulting in *n* = 4,505 incident cancers and (*ii*) participants diagnosed with malignancies within the first 2 years after enrolment (*n* = 633). Statistical significance of the above findings did not change (data not shown). In a further re-analysis, we adjusted all Cox models for the number of GGT measurements during follow-up (used in 4 categories: <5, 5–9, 10–14, >14). The effects of GGT levels on cancer risk did not change substantially; however, having more GGT measurements was associated with a significantly lower cancer risk, possibly

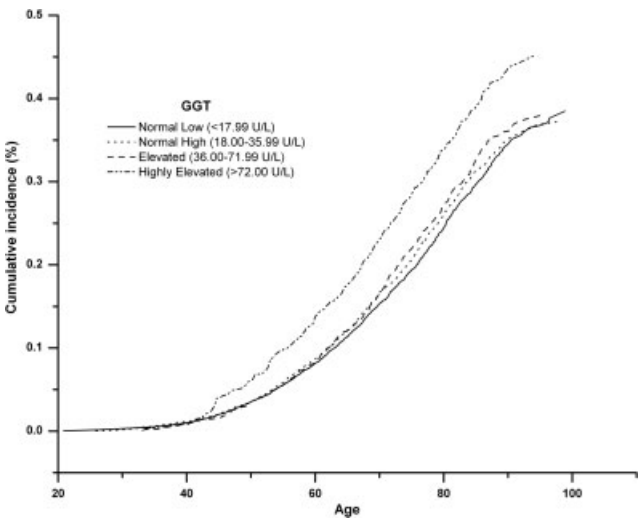

FIGURE 1 – Adjusted cumulative overall cancer incidence according to baseline GGT levels among 92,843 female Austrian adults (mean age 41.7 years) in the VHM&PP. Curves were estimated at the average values of covariates using Cox proportional hazards models adjusted for body-mass index, smoking status, occupational status and year at entry into the cohort.

indicating more censoring due to other diseases. When analyses were repeated on the calendar time scale, additionally adjusting for age, results were very similar (data not shown). Stratification by BMI or smoking status did not indicate interactions of GGT by those variables.

Association of time-dependent GGT with overall and site-specific cancer incidence

Analyses where all GGT measurements were included using time-dependent covariates in an extended Cox regression confirmed the findings for the association of baseline GGT with overall cancer incidence. Compared to the normal low GGT category (<17.99 U/L) the HRs (with 95% CIs) from the time-dependent Cox model were 1.07 (1.00, 1.14) for the normal high category, 1.13 (1.03, 1.24) for the elevated GGT category and 1.44 (1.29, 1.62) for the highly elevated GGT group. When GGT was modeled with a trend, the HR was 1.10 (1.07, 1.14; $p < 0.0001$). When we repeated the cancer site-specific analyses with GGT levels as a time-dependent covariate, results did not change (data not shown).

Discussion

This is the first study to investigate the association of GGT and risk of cancer incidence in women from a large population-based cohort. We found elevated GGT concentrations (>72.00 U/L) to significantly increase risk of overall cancer incidence and for several site-specific cancers. Our estimates proved to be stable under several modeling strategies and after exclusion of participants diagnosed with malignancies within the first 2 years after enrolment, strongly indicating an independent role of GGT on carcinogenesis.

Our results agree with recent epidemiologic findings from a retrospective hospital-based study,[19] reporting a 2.4-fold risk increase for cancer death in women in the highest GGT quintile, in comparison to normal low GGT in Austrian women aged 33–66 years. Our results further agree largely with findings we recently reported on men from the same cohort.[28] Among men, increased baseline GGT levels were also significantly associated with increased risk of cancer overall, malignant neoplasms of digestive organs and the respiratory system/intrathoracic organs. However, there were several differences between the genders, in addition to cancers of the breast and female genital organs: while we found increased risk of lymphoid and haematopoietic cancers among women, this association was not seen for men. Among men, but not among women, risk of cancers of the urinary organs was also significantly associated with elevated GGT levels.

A limitation of our investigation was that information on several risk and confounding factors was not available, including physical activity, diet, and, most notably, alcohol consumption. Chronic and excessive alcohol consumption considerably increases the risk for cancer of the organs and tissues of the respiratory tract and the upper digestive tract, liver, colon, rectum and breast.[37] The lack of adjustment for alcohol consumption could have affected our earlier findings on cancer incidence in men,[28] including the incidence of lymphoid and haematopoietic malignancies, as alcohol consumption has been associated with a lower risk of non-Hodgkin lymphoma.[38] However, we do not expect the association of GGT and cancer risk among women to be impacted strongly by the lack of adjustment for alcohol consumption, as the rate of chronic drinkers among women was less than 5% based on the results of 2 random health surveys in our population.[39] Moreover, in that subsample, based on self-reported data, only a weak, age-adjusted correlation of 0.09 ($p = 0.089$) of GGT with the average number of alcohol units per week was observed. A further limitation of the present study is that data on drug prescriptions/medication use and prevalent health conditions including diabetes mellitus, liver and renal disease that can enhance the risk of cancer were not routinely collected in our cohort.

The underlying biological mechanisms causing elevated GGT to increase incidence of cancer overall and for several sites need further study. Experimental evidence has elucidated the ability of cellular GGT to modulate crucial redox-sensitive functions, such as antioxidant/antitoxic defences and cellular proliferative/apoptotic balance, and its role in tumor progression, invasion and drug resistance has repeatedly been suggested.[20–23] GGT is constitutively expressed in several organs and is often significantly increased in malignant or premalignant lesions, where it is considered a factor conferring growth and survival advantages for the rapidly dividing neoplastic cells.[40,41] The ability of cellular GGT to affect the catabolism of extracellular GSH potentially reflects on several aspects of cell metabolism, especially through the modulation of redox status at cell surfaces and H_2O_2 production. It has been speculated[24,25] that GSH might have an important function in conjugating xenobiotics such as lead, cadmium, dioxins or organochlorine pesticides to facilitate their excretion in the urine or bile, by rendering them more water-soluble. Since cellular GGT is indispensable for metabolism of extracellular GSH, higher serum GGT plausibly reflects increased cellular GGT activity to metabolize extracellular GSH conjugates. Thus, serum GGT might increase with increasing exposure to xenobiotics which need to be conjugated to GSH.[24,25] In an experiment with carcinogen-treated rats, Stark and coworkers[42] found that metabolism of GSH by GGT in preneoplastic liver foci can initiate an oxidative process leading to a radical-rich environment and to oxidative damage. Such damage may contribute to the processes by which cells within such foci progress to malignancy. GGT has also been shown to be inversely correlated with levels of several antioxidants, including β-carotene, α-carotene, β-cryptoxanthin and α-Tocopherol,[43] which are known to lower incidence of several cancers.[44,45]

In summary, the present, prospective, long-term study aimed to investigate the association of GGT and risk of cancer incidence in a large population-based cohort of more than 92,000 apparently healthy Austrian women across a wide age range. Our results, for the first time demonstrate that elevated GGT is significantly related to increased risk of overall cancer incidence and several site-specific cancers. Although our findings need to be confirmed in other populations, they strongly suggest the clinical importance of monitoring and intervention based on the presence of elevated GGT.

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