Association of Gamma-Glutamyltransferase and Cancer Incidence

A Prospective Population-based 19-year Follow-Up Study in 92,843 Austrian Women

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Background I

- In clinical practice, **Gamma-Glutamyltransferase (GGT)** is commonly used as a **diagnostic test to assess liver dysfunction**, and as a **biological marker of excessive alcohol intake**[1,3,4]

- Several epidemiologic studies have shown **elevated GGT to further independently influence morbidity and mortality from causes other than liver disease**

  - GGT independently related to **cardiovascular disease**[5–12]
  - GGT correlated with most **cardiovascular risk factors**[13–16]
  - Association of GGT with **chronic kidney disease**[17]
  - Independent role of GGT for **premature death from all causes**[9,18,19]

Background II

- **The association of GGT with cancer remains largely unexplored to date!**

- Several **experimental models** elucidated the **ability of cellular GGT to modulate crucial redox-sensitive functions**, such as antioxidant/antitoxic defences and its role in tumour progression, invasion and drug resistance has been proposed.[20–23]

- A potentially interesting interpretation subsumes **GGT as a biomarker of exposure to certain cancer-causing xenobiotics** including persistent organic pollutants (POPs).[24,25]

- Strasak et al. Cancer Res. 2008: First epidemiologic investigation to demonstrate an independent association between elevated GGT and cancer incidence in men from the general population

Study Aims

- **To investigate the association of GGT with risk of overall and site-specific cancer incidence in a large prospective population-based cohort of apparently healthy women**

Methods I – Study Population

- **Vorarlberg Health Monitoring and Promotion Program** [VHM&PP][29-31]
  - **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 longitudinal follow-up of study participants with repeated routine health examinations** is performed through a recall-system of written biennial re-invitation letters.

Methods II – Data Collection & Cancer Ascertainment

- Measurements of **height, weight, smoking status** (current, former, never) and **serum GGT** levels are routinely obtained for each study participant.

- **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.

- 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 linked with the **Vorarlberg Death Index** to identify deaths and to calculate person years at risk.

Methods III – Statistical Analyses

- **Cox proportional hazards models including (1) baseline log-GGT and (2) log-GGT as time-dependent variable** were used to estimate hazard ratios and their 95% confidence intervals for the association of GGT with overall and site-specific cancer incidence.

- Since GGT levels change with age and age also strongly influences cancer risk, **age was used as underlying time metric in the main analyses**

- **All models adjusted** for body-mass index (BMI), smoking status (never/former/current), year of entry into the cohort (in quartiles) and occupational status (3 categories), measured at baseline.

Results I – Characteristics of Study Population

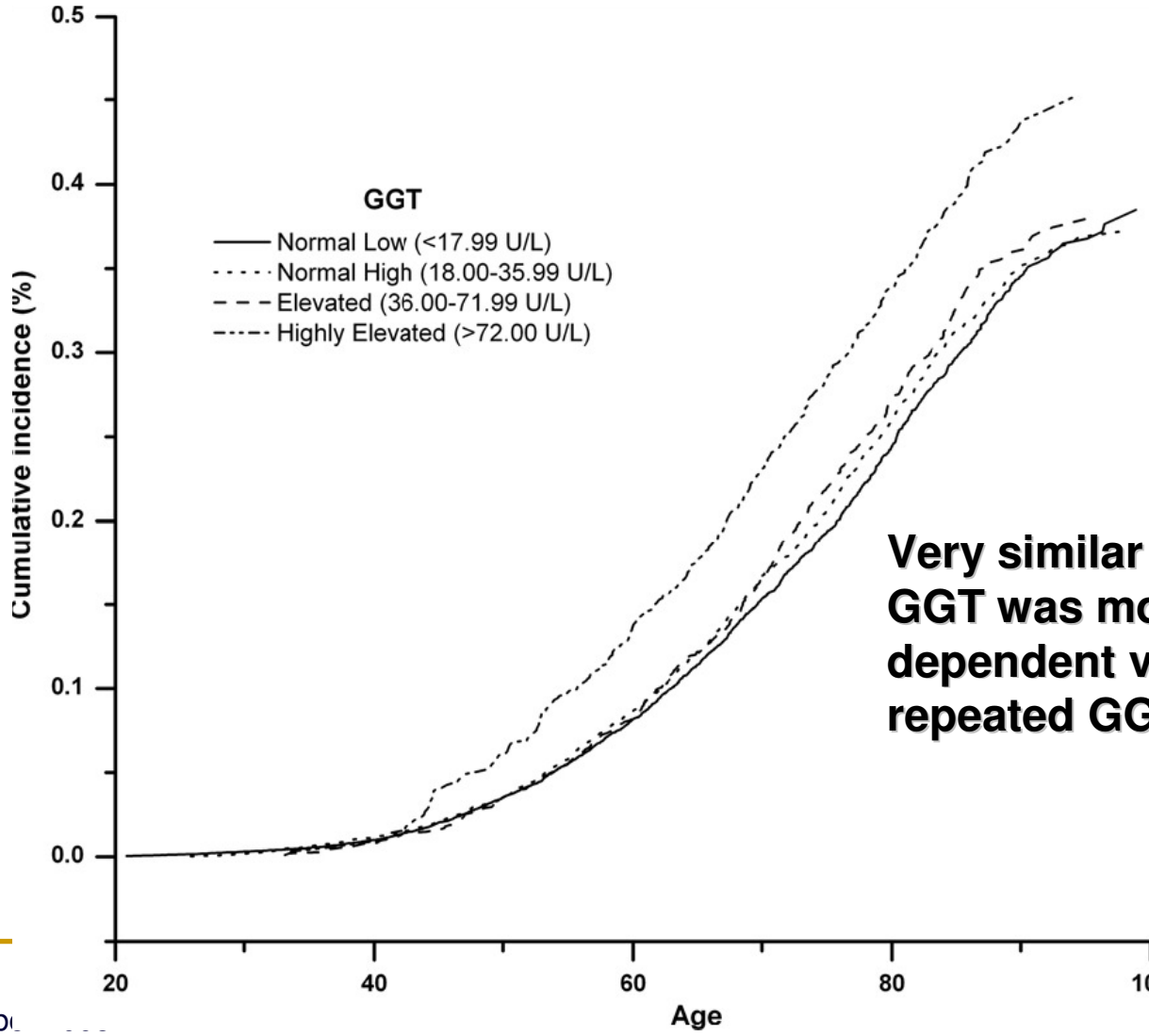
All female VHM&PP participants, 1985–2003	94,628
Participants with complete and valid data on GGT	92,894
Eligible participants for analyses	92,843[1]
Total number of visits	349,674
Number of GGT measurements, mean ± SD, (range)	3.8 ± 3.3 (1–19)
Age, mean ± SD (range), year	41.7 ± 15.9 (18–95)
Body-mass 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 II – Association of GGT Categories with Overall and Site-Specific Cancer Incidence

	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]
	(*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
Site-specific cancers					
Malignant neoplasm 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
Malignant neoplasm 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
Malignant neoplasm 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
Malignant neoplasm 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
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
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
Malignant neoplasm 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

Results III - Association of GGT Categories with Overall Cancer Incidence



Very similar results when GGT was modelled as time-dependent variable (using repeated GGT measurements)

Discussion I

- **First epidemiolgic investigation to demonstrate an independent association between serum GGT and cancer incidence in women from the general population**
  - Estimates proved to be stable **after exclusion of participants diagnosed with malignancies within the first 2 years** after enrolment

- **Results largely agree with findings we recently reported from men in the same cohort**[28] strongly indicating an independent role of GGT on carcinogenesis!

Discussion II – Potential Limitations of Study

- **Information on some risk and confounding factors was not available**, including physical activity, diet, and alcohol consumption.
  - Rate of chronic drinkers among women in our cohort less than 5% based on the results of 2 random health surveys.[39]
  - 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.
- **Data on drug prescriptions/medication use and prevalent health conditions not routinely collected in our cohort**.

Discussion III – Conclusion

- **The underlying biological mechanisms causing elevated GGT to increase incidence of cancer overall and for several anatomic sites need further study!**
  - GGT is 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]
  - GGT has been shown to inversely correlate with levels of several antioxidants, which are known to lower incidence of several cancers.[44,45]
- **GGT as a new and sensitive marker for a life-style at increased risk for the development of cancer???**

Thank you for your attention!

Questions, Comments, etc.: alexander.strasak@i-med.ac.at

For details see: Strasak et al. Prospective Study of the Association of Gamma-Glutamyltransferase with Cancer Incidence in Women. Int J Cancer 2008.

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