

---

# **Association of Gamma-Glutamyltransferase and Cancer Incidence**

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

---

**Alexander M. Strasak, PhD<sup>1</sup>**

**Ruth M. Pfeiffer<sup>2</sup>, Martin Gregory<sup>3</sup>, Wolfgang Hilbe<sup>4</sup>, Jochen Klenk<sup>5</sup>, Larry J. Brant<sup>6</sup>, Willi Oberaigner<sup>7</sup>,  
Elfriede Ruttmann<sup>8</sup>, Hans Concini<sup>9</sup>, Günter Diem<sup>9</sup>, Karl P. Pfeiffer<sup>1</sup>, Hanno Ulmer<sup>1,9</sup>;**

**and the VHM&PP Study Group**

<sup>1</sup>Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Austria, <sup>2</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institute of Health, Bethesda, USA, <sup>3</sup>SAS Institute Inc., Heidelberg, Germany, <sup>4</sup>Department of Haematology and Oncology, Innsbruck Medical University, Austria, <sup>5</sup>Department of Epidemiology, University of Ulm, Germany, <sup>6</sup>Gerontology Research Center, National Institute on Aging, Baltimore, U.S.A., <sup>7</sup>Cancer Registry of Tyrol, Department of Clinical Epidemiology of the Tyrolean State, Hospitals Ltd, Innsbruck, Austria, <sup>8</sup>Department of Cardiac Surgery, Innsbruck Medical University, Austria, <sup>9</sup>Agency for Preventive and Social Medicine, Bregenz, Austria

**XVIII World Congress of Epidemiology 2008, Porto Alegre, Brazil**

---

# 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**<sup>1,3,4</sup>
- 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**<sup>5-12</sup>
  - GGT correlated with most **cardiovascular risk factors**<sup>13-16</sup>
  - Association of GGT with **chronic kidney disease**<sup>17</sup>
  - Independent role of GGT for **premature death from all causes**<sup>9,18,19</sup>

---

## 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.<sup>20-23</sup>
- A potentially interesting interpretation subsumes **GGT as a biomarker of exposure to certain cancer-causing xenobiotics** including persistent organic pollutants (POPs).<sup>24,25</sup>
- 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]<sup>29-31</sup>
  - **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<sup>32</sup> and has high completeness of recording.<sup>33</sup>
  - 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 <sup>1</sup>
Total number of visits	349,674
Number of GGT measurements, mean $\pm$ SD, (range)	3.8 $\pm$ 3.3 (1–19)
Age, mean $\pm$ SD (range), year	41.7 $\pm$ 15.9 (18–95)
Body-mass index, mean $\pm$ SD (median), kg/m <sup>2</sup>	24.2 $\pm$ 4.6 (23.3)
GGT, mean $\pm$ SD (median), U/L <sup>2</sup>	24.3 $\pm$ 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 $\pm$ SD (median), year	12.0 $\pm$ 5.6 (13.5)
Total person-years at risk	1,110,330
Incident cancers - no. (%)	4,884 (5.3)
Age at cancer diagnosis, mean $\pm$ SD (range), year	55.3 $\pm$ 13.8 (19–92)

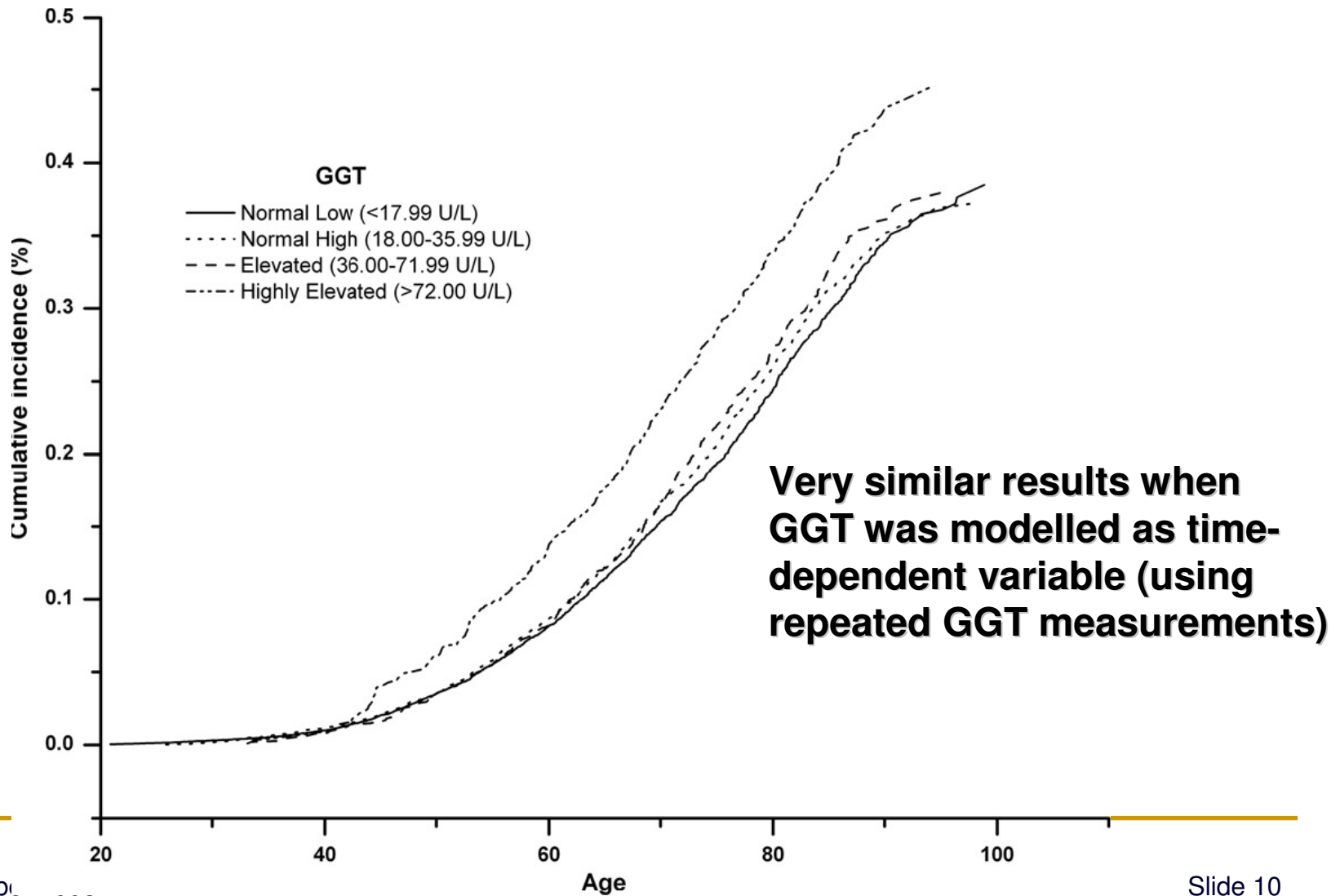
<sup>1</sup>Participants with baseline GGT concentrations  $>600$  U/L or with history of malignancies prior to enrolment were excluded.–<sup>2</sup>GGT values are shown as averages of each participant during individual follow-up and before eventual cancer diagnoses. All other characteristics pertain 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)				<i>p</i> for trend <sup>2</sup>
	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)	
	( <i>n</i> = 53,506)	( <i>n</i> = 28,915)	( <i>n</i> = 7,364)	( <i>n</i> = 3,058)	
All Cancers ( <i>n</i> = 4,884)					
Events - no. (%)	1991 (3.7)	1902 (6.6)	645 (8.8)	346 (11.3)	
HR (95% CI) <sup>3</sup>	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 ( <i>n</i> = 1,079)					
Events - no. (%)	415 (0.8)	412 (1.4)	157 (2.1)	95 (3.1)	
HR (95% CI) <sup>3</sup>	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 ( <i>n</i> = 226)					
Events - no. (%)	77 (0.1)	99 (0.3)	26 (0.4)	24 (0.8)	
HR (95% CI) <sup>3</sup>	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 ( <i>n</i> = 423)					
Events - no. (%)	188 (0.4)	158 (0.5)	50 (0.7)	27 (0.9)	
HR (95% CI) <sup>3</sup>	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 ( <i>n</i> = 2,278)					
Events - no. (%)	949 (1.8)	885 (3.1)	303 (4.1)	141 (4.6)	
HR (95% CI) <sup>3</sup>	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 ( <i>n</i> = 220)					
Events - no. (%)	84 (0.2)	91 (0.3)	35 (0.5)	10 (0.3)	
HR (95% CI) <sup>3</sup>	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 ( <i>n</i> = 100)					
Events - no. (%)	49 (0.1)	31 (0.1)	13 (0.2)	7 (0.2)	
HR (95% CI) <sup>3</sup>	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 ( <i>n</i> = 325)					
Events - no. (%)	141 (0.3)	130 (0.4)	31 (0.4)	23 (0.8)	
HR (95% CI) <sup>3</sup>	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



---

# Discussion I

- **First epidemiologic 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<sup>28</sup>** 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.<sup>39</sup>
  - 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 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.<sup>40,41</sup>
  - GGT has been shown to inversely correlate with levels of several antioxidants, which are known to lower incidence of several cancers.<sup>44,45</sup>
- **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](mailto: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.

---

# References I

1. Whitfield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci* 2001;38:263–355.
2. Meister A. Metabolism and transport of glutathione and other gammaglutamyl compounds. In: Larsson A, Orrenius S, Holmgren A, Mannervik B, eds. *Functions of glutathione: biochemical, toxicological and clinical aspects*. New York: Raven Press, 1983;1–22.
3. Rollason JG, Pincherle G, Robinson D. Serum gammaglutamyltranspeptidase in relation to alcohol consumption. *Clin Chim Acta* 1972;39:75–80.
4. Skinner HA, Holt S, Schuller R, Roy J, Israel Y. Identification of alcohol abuse using laboratory tests and a history of trauma. *Ann Intern Med* 1984;101:847–51.
5. Pompella A, Emdin M, Passino C, Paolicchi A. The significance of serum gamma-glutamyltransferase in cardiovascular diseases. *Clin Chem Lab Med* 2004;42:1085–91.
6. Ruttman E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H; and the Vorarlberg Health Monitoring and Promotion Program Study Group. G Glutamyltransferase as a risk factor for cardiovascular disease mortality. An epidemiological investigation in a cohort of 163944 Austrian adults. *Circulation* 2005;112:2130–7.
7. Meisinger C, D€oring A, Schneider A, L€owel H; KORA Study Group. Serum gamma-glutamyltransferase is a predictor of incident coronary events in apparently healthy men from the general population. *Atherosclerosis* 2006;189:297–302.
8. Hozawa A, Okamura T, Kadowaki T, Murakami Y, Nakamura K, Hayakawa T, Kita Y, Nakamura Y, Okayama A, Ueshima H; NIPPON DATA90 Research Group. Gamma-Glutamyltransferase predicts cardiovascular death among Japanese women. *Atherosclerosis* 2007;194:498–504.
9. Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamyltransferase: determinants and association with mortality from ischemic heart diseases and all cause. *Am J Epidemiol* 1995;142:699–708.
10. Jousilahti P, Rastenyte D, Tuomilehto J. Serum gamma-glutamyl transferase, self reported alcohol drinking, and the risk of stroke. *Stroke* 2000;31:1851–5.
11. Bots ML, Salonen JT, Elwood PC, Nikitin Y, Freire de Concalves A, Inzitari D, Sivenius J, Trichopoulou A, Tuomilehto J, Koudstaal PJ, Grobbee DE. Gamma-glutamyltransferase and risk of stroke: the EUROSTROKE project. *J Epidemiol Community Health* 2002;56(suppl 1):25–9.
12. Lee DH, Silventoinen K, Hu G, Jacobs DR, Jr, Jousilahti P, Sundvall J, Tuomilehto J. Serum gamma-glutamyltransferase predicts non-fatal myocardial infarction and fatal coronary heart disease among 28838 middle-aged men and women. *Eur Heart J* 2006;27:2170–6.
13. Lee DS, Evans JC, Robins SJ, Wilson PW, Albano I, Fox CS, Wang TJ, Benjamin EJ, D'Agostino RB, Vasan RS. Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol* 2007;27:127–33.
14. Rantala AO, Lilja M, Kauma H, Savolainen MJ, Reunanen A, Kesaniemi YA. Gamma-glutamyl transpeptidase and the metabolic syndrome. *J Intern Med* 2000;248:230–8.
15. Lee DH, Ha MH, Kim JR, Gross M, Jacobs DR, Jr. Gamma-glutamyltransferase, alcohol, and blood pressure. A four year follow-up study. *Ann Epidemiol* 2002;12:90–6.

---

## References II

16. Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M, Blomhoff R, Jacobs DR, Jr. Gamma-glutamyltransferase and diabetes—a 4 year follow-up study. *Diabetologia* 2003;46:359–64.
17. Ryu S, Chang Y, Kim DI, Kim WS, Suh BS. Gamma-glutamyltransferase as a predictor of chronic kidney disease in nonhypertensive and nondiabetic Korean men. *Clin Chem* 2007;53:71–7.
18. Brenner H, Rothenbacher D, Arndt V, Schuberth S, Fraisse E, Fliedner TM. Distribution, determinants, and prognostic value of gammaglutamyltransferase for all-cause mortality in a cohort of construction workers from southern Germany. *Prev Med* 1997;26:305–10.
19. Kazemi-Shirazi L, Endler G, Winkler S, Schickbauer T, Wagner O, Marsik C. Gamma glutamyltransferase and long-term survival: is it just the liver? *Clin Chem* 2007;53:940–6.
20. Pompella A, Corti A, Paolicchi A, Giommarelli C, Zunino F. Gamma-glutamyltransferase, redox regulation and cancer drug resistance. *Curr Opin Pharmacol* 2007;7:360–6.
21. Pompella A, De Tata V, Paolicchi A, Zunino F. Expression of gamma-glutamyltransferase in cancer cells and its significance in drug resistance. *Biochem Pharmacol* 2006;71:231–8.
22. Franzini M, Corti A, Lorenzini E, Paolicchi A, Pompella A, De Cesare M, Perego P, Gatti L, Leone R, Apostoli P, Zunino F. Modulation of cell growth and cisplatin sensitivity by membrane gammaglutamyltransferase in melanoma cells. *Eur J Cancer* 2006;42:2623–30.
23. Dominici S, Valentini M, Maellaro E, Del Bello B, Paolicchi A, Lorenzini E, Tongiani R, Comporti M, Pompella A. Redox modulation of cell surface protein thiols in U937 lymphoma cells: the role of gamma-glutamyl transpeptidase-dependent H<sub>2</sub>O<sub>2</sub> production and S-thiolation. *Free Radic Biol Med* 1999;27:623–35.
24. Lee DH, Lim JS, Song K, Boo Y, Jacobs DR, Jr. Graded associations of blood lead and urinary cadmium concentrations with oxidativestress related markers in the U.S. population: results from the thirdNational Health and Nutrition Examination Survey. *Environ Health Perspect* 2006;114:350–4.
25. Lee DH, Jacobs DR, Jr. Association between serum concentrations of persistent organic pollutants and gamma glutamyltransferase: results from the National Health and Examination Survey 1999–2002. *Clin Chem* 2006;52:1825–7.
26. Monami M, Balzi D, Lamanna C, Melani C, Cocca C, Lotti E, Fedeli A, Masotti G, Marchionni N, Mannucci E. Prognostic value of serum liver enzymes levels in type 2 diabetic patients. *Diabetes Metab Res Rev* 2007;23:625–30.
27. Petersson B, Trelle E, Henningsen NC, Hood B. Risk factors for premature death in middle aged men. *BMJ* 1984;288:1264–8.
28. Strasak AM, Rapp K, Brant LJ, Hilbe W, Gregory M, Oberaigner W, Ruttman E, Concin H, Diem G, Pfeiffer KP, Ulmer H; VHM&PP Study Group. Association of gamma-glutamyltransferase and risk of cancer incidence in men: a prospective study. *Cancer Res*, in press. AQ2
29. Ulmer H, Kelleher C, Diem G, Concin H. Long-term tracking of cardiovascular risk factors among men and women in a large populationbased health system: the Vorarlberg Health Monitoring & Promotion Programme. *Eur Heart J* 2003;24:1004–13.



---

## References III

30. Strasak AM, Rapp K, Hilbe W, Oberaigner W, Ruttman E, Concin H, Diem G, Pfeiffer KP, Ulmer H; VHM&PP Study Group. Serum uric acid and risk of cancer mortality in a large prospective male cohort. *Cancer Causes Control* 2007;18:1021–9.
31. Strasak AM, Rapp K, Hilbe W, Oberaigner W, Ruttman E, Concin H, Diem G, Pfeiffer KP, Ulmer H; VHM&PP Study Group. The role of serum uric acid as an antioxidant protecting against cancer: prospective study in more than 28000 older Austrian Women. *Ann Oncol* 2007;18:1893-7.
32. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. *Cancer incidence in five continents*, vol. VIII. Lyon, France: International Agency for Research on Cancer, 2003. ISBN 92832 21559.
33. Oberaigner W, Vittadello F. *Cancer mapping in alpine regions 1996–2000*. Mammendorf: Pro Literature Verlag, 2006.
34. World Health Organization. *International classification of diseases (ICD)*. Available at: <http://www.who.int/classifications/icd/en>.
35. Thiebaut AC, Benichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med* 2004; 23:3803–20.
36. Therneau TM, Grambsch PM. *Modeling survival data: extending the Cox model*. New York: Springer, 2000.
37. Seitz HK, Becker P. Alcohol metabolism and cancer risk. *Alcohol Res Health* 2007;30:38–41, 44–7.
38. Morton LM, Zheng T, Holford TR, Holly EA, Chiu BC, Costantini AS, Stagnaro E, Willett EV, Dal Maso L, Serraino D, Chang ET, Cozen W, et al. Alcohol consumption and risk of non-Hodgkin lymphoma: a pooled analysis. *Lancet Oncol* 2005;6:469–76.
39. Ulmer H, Diem G, Bischof HP, Ruttman E, Concin H. Recent trends and sociodemographic distribution of cardiovascular risk factors: results from two population surveys in the Austrian WHO CINDI demonstration area. *Wien Klin Wochenschr* 2001;113:573–9.
40. Hanigan MH, Pitot HC. Gamma-glutamyltranspeptidase—its role in hepatocarcinogenesis. *Carcinogenesis* 1985;6:165–72.
41. Hanigan MH, Gallagher BC, Townsend DM, Gabarra V. Gamma-glutamyl transpeptidase accelerates tumor growth and increases the resistance of tumors to cisplatin in vivo. *Carcinogenesis* 1999;20:553–9.
42. Stark AA, Russell JJ, Langenbach R, Pagano DA, Zeiger E, Huberman E. Localization of oxidative damage by a glutathione-gammaglutamyl transpeptidase system in preneoplastic lesions in sections of livers from carcinogen-treated rats. *Carcinogenesis* 1994;15:343–8.
43. Lee DH, Gross MD, Jacobs DR, Jr. Association of serum carotenoids and tocopherols with gamma-glutamyltransferase: the Cardiovascular Risk Development in Young Adults (CARDIA) Study. *Clin Chem* 2004;50:582-8.
44. Gey KF. Prospects for the prevention of free radical disease, regarding cancer and cardiovascular disease. *Br Med Bull* 1993;49:679–99.
45. Comstock GW, Bush TL, Helzlsouer K. Serum retinol,  $\beta$ -carotene, vitamin E, and selenium as related to subsequent cancer of specific sites. *Am J Epidemiol* 1992;135:115–21.