memo (2011) Vol. 4: 50–54
DOI 10.1007/s12254-011-0249-4
Printed in Austria

memo
magazine of european medical oncology

Associations of serum uric acid and gamma-glutamyltransferase with cancer in the Vorarlberg Health Monitoring and Promotion Programme (VHM&PP) – a short review

M. Edlinger[1], G. Nagel[2], W. Hilbe[3], G. Diem[4], H. Concin[4], Alexander M. Strasak[1], H. Ulmer[1]

[1]Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria
[2]Institute of Epidemiology, Ulm University, Ulm, Germany
[3]Department of Haematology and Oncology, Innsbruck Medical University, Innsbruck, Austria
[4]Agency for Preventive and Social Medicine, Bregenz, Austria

Received 17 February 2011; accepted 4 March 2011

The Vorarlberg Health Monitoring and Promotion Programme (VHM&PP), based on prospectively gathered, repeated routine health examination data from a cohort of more than 175,000 adults, is one of the largest ongoing population-based risk factor surveillance programmes worldwide. Among others, the so far widely unknown associations of serum uric acid (SUA) and gamma-glutamyltransferase (GGT) with cancer were investigated. Both SUA and GGT are known to be related to the metabolic syndrome and furthermore considered as markers of oxidative stress. After controlling for several confounding factors, it was found that elevated SUA levels were statistically significantly related to overall cancer mortality and several site-specific malignancies in both men and women. Additionally, a J-shaped effect of SUA levels on risk of overall cancer incidence appeared in men, with significantly increased cancer risk at high levels of SUA. Likewise, in accordance with some experimental evidence, among men and women elevated GGT increased cancer risk overall and for several lifestyle-related malignancies. On the basis of these findings, and considering the routine measurement in clinical practice, SUA and GGT might function as a valuable marker to identify patients with an increased risk to develop malignant diseases.

Keywords: Serum uric acid, gamma-glutamyltransferase, cancer, prospective cohort study, epidemiology

Introduction

Increased serum uric acid (SUA) concentrations have consistently been reported to be associated with the progression of cardiovascular diseases. It has been documented to be higher in patients with coronary heart disease [1]. Much controversy exists, however, whether SUA is causally involved in cardiovascular diseases [2], although SUA is indeed associated with many of the established cardiovascular risk factors, including hypertension, dyslipidaemia, obesity and excessive alcohol consumption [3]. However, to date little is known regarding the role of SUA in relation to cancer. On the basis of experimental models, it has been hypothesised that the antioxidant properties of SUA may play an important role in cancer aetiology by preventing the formation of oxygen radicals, thereby protecting against carcinogenesis [4]. The few available epidemiological findings are inconsistent [5, 6]. Some studies demonstrated an inverse relationship between SUA and cancer mortality, partly supporting the assumed antioxidant properties and protective effect of SUA on cancer. Other studies found SUA concentrations to be unrelated to cancer incidence after adjusting for potential confounding factors. There are also findings suggesting a positive association with cancer incidence, indicating that elevated SUA should rather be considered as a risk factor, at least for certain types of cancer.

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 [7]. Evidence from a large-scale population study indicates a perceptible increase in GGT during the past few decades, with a strong secular trend [8]. Apart from its well-established clinical use as an indicator of hepatobiliary diseases and a marker of excessive alcohol intake, several recent studies have suggested elevated GGT to be a risk factor of various other outcomes. Specifically, it was reported that GGT is related to the occurrence of cardiovascular disease [9], to most cardiovascular risk factors, including diabetes, hypertension, dyslipidaemia and metabolic syndrome [10], and is independently associated with cardiovascular mortality [11]. The association of GGT with cancer, however, remains largely unexplored to date. Several experimental models have elucidated the ability

Correspondence: Michael Edlinger, MSc, MSc, Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Schöpfstraße 41, 6020 Innsbruck, Austria.
E-mail: michael.edlinger@i-med.ac.at

of cellular GGT to modulate crucial redox-sensitive functions, such as antioxidant and antitoxic defences and cellular proliferative and apoptotic balance, and its role in tumour progression, invasion, and drug resistance has been proposed [12]. In addition, a potentially interesting interpretation subsumes GGT as a biomarker of exposure to certain cancer-causing xenobiotics, including persistent organic pollutants. Environmental pollutants such as lead, cadmium, dioxins, or organochlorine pesticides are positively related to serum GGT levels in the general US population [13].

With indications of potential effects of SUA and GGT, possibly involving oxidative stress, in this review we summarise the findings from VHM&PP regarding SUA and GGT in relation to cancer.

Study population

To analyse the associations of SUA and GGT with cancer, prospective longitudinal health examination data from the Vorarlberg Health Monitoring and Promotion Programme (VHM&PP) have been used. VHM&PP is one of the world's largest population-based risk factor surveillance programmes. The cohort was initiated in 1985 and conducted by the Agency for Social and Preventive Medicine in Vorarlberg, Austria. A detailed description of the programme methodology has been reported elsewhere [14].

All adults in the region were invited to participate through a combination of different measures, including written invitations, television, radio and newspaper reports, leading to a total of more than 175,000 study participants and over two million person-years of follow-up [15] (Tab. 1). Active follow-up, with repeated longitudinal routine health examinations of study participants, is performed through a recall-system of written biennial re-invitation letters. Costs are covered by the participant's compulsory health insurance. Informed consent to store and process the data is obtained from all participants at each examination and research approval has been given by the relevant ethical committee.

Data that are recorded include height, weight, systolic and diastolic blood pressure, smoking and occupational status, and from fasting blood samples SUA, GGT, total serum cholesterol, triglycerides and blood glucose. In analyses applying more than one measurement of the exposure variable, only those values before the cancer diagnosis date were used. Additional sensitivity analyses were performed to rule out possible reverse causation (i.e. preclinical disease causing higher laboratory values). Information regarding morbidity and mortality is provided by the local health authority. Nearly all cancers (97%) were histologically confirmed [16, 17].

So far, many research questions have been addressed, concerning risk factors, cardiovascular disease, all-cause mortality, cancer, as well as trends (see Fig. 1). Including the studies stemming from the cooperation within the so-called Metabolic syndrome and Cancer project [18–28], the number of publications produced currently exceeds well over 30, with more to come. Here we review the results of the studies on SUA and GGT in relation to cancer.

Tab. 1: Several (baseline) characteristics of the Vorarlberg Health Monitoring and Promotion Programme (1985–2003)

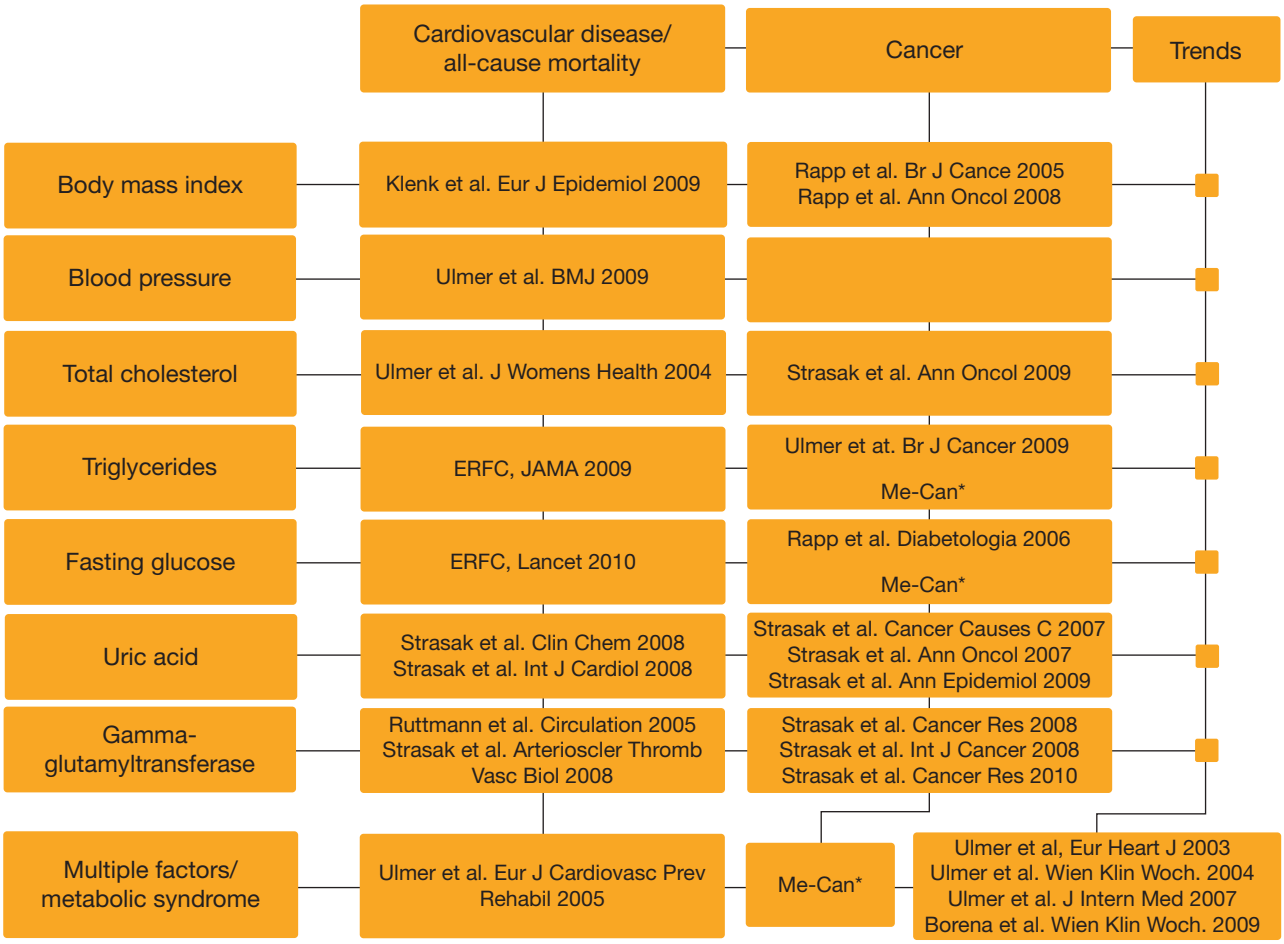
	Female	Male
Number of participants	94,805	80,224
Age (years), mean (s)	41.2 (15.9)	41.2 (14.7)
Smoking status		
Never	78.5%	69.9%
Ever	21.5%	30.1%
Body mass index		
<25 kg/m^2	64.7%	50.7%
25 to <30 kg/m^2	24.2%	39.5%
≥30 kg/m^2	11.1%	9.8%
Serum uric acid (mg/dl), mean (s)	4.5 (1.3)	5.7 (1.3)
Gamma-glutamyltransferase (units/l), median	17.9	28.6
Inter-quartile range	12.5–25.1	19.7–44.8
Follow-up (years)		
Median	13.6	12.6
Person-years at risk	1,144,823	910,870
Number of subjects with incident cancer of which:	4506	4945
Breast, female genital organs	2272	–
Male genital organs	–	1857
Digestive organs	1013	1123
Bone, connective tissue, soft tissue, skin	433	445
Lymphoid, haematopoietic, related tissue	296	271
Respiratory system	216	747
Urinary organs	210	423
Nervous system, unspecified sites	66	79
Cancer incidence (per 1000 person-years)	3.9	5.4
Number of cancer deaths	1562	1922

s Standard deviation.

Findings

An overview of the most important results from VHM&PP regarding the association of SUA and GGT with consequent cancer is presented in Tab. 2. Strong effects (hazard ratio [HR] ≥ 1.50) at elevated SUA levels were observed for lymphoid, haematopoietic and related tissue cancers and for a malignant neoplasm of the respiratory system and of the urinary organs among males. For GGT strong effects were found for a malignant neoplasm of the digestive organs and of the respiratory system among both females and males, and also of the urinary organs among males. In the other tumour sites the effects of SUA and GGT were only moderate (HR between 1.00 and 1.50) or statistically not significant.

Other findings concerned a clear dose-response relationship of increased male cancer mortality with increasing level of SUA. Among participants aged less than 65 years, the relationship was even more pronounced. When considering the time interval between the baseline SUA measurement and date of cancer death, SUA levels were more predictive of deaths occurring 10 years or more after the baseline measurement compared to deaths within 10 years [29]. In another



*** Me-Can: Metabolic syndrome and Cancer project, a cooperation of VHM&PP with six other population-based cohorts in Sweden and Norway [18–28]**

Fig. 1: Overview of risk factors and outcomes investigated in Health Monitoring and Promotion Programme (VHM&PP)

Tab. 2: Overview of the relationships, expressed as hazard ratios[a], of serum uric acid and gamma-glutamyltransferase with consequent site-specific cancer incidence in the Vorarlberg Health Monitoring and Promotion Programme (1985–2003) [29–34]

	Serum uric acid[b]		Gamma-glutamyltransferase[c]	
	Female	Male	Female	Male
Breast, female genital organs	<1.50	–	<1.50	–
Male genital organs	–	n.s.	–	n.s.
Digestive organs	n.s.	<1.5	≥1.50	≥1.50
Bone, connective tissue, soft tissue, skin	n.s.	n.s.	n.s.	n.s.
Lymphoid, haematopoietic, related tissue	n.s.	≥1.50[d]	<1.50	n.s.
Respiratory system	n.s.	≥1.50	≥1.50	≥1.50
Urinary organs	n.s.	≥1.50[d]	n.s.	≥1.50
Nervous system, unspecified sites	<1.50	n.s.	n.s.	n.s.

n.s. not significant.
[a]Based on highest *versus* lowest category or on per log(GGT)-unit increase.
[b]Cancer mortality and partly also incidence as endpoint.
[c]Cancer incidence as endpoint.
[d]Based on penalised splines.

study focused on elderly women, high SUA levels were also significantly associated with increased total cancer mortality [30]. It was also found that the dose-response association of SUA with overall cancer incidence among males was not linear. There seemed to be a J-shaped effect of SUA, with statistically significantly increased risks in the upper third of the SUA distribution and moderately increased risks at low levels [31].

The analysis of the association of baseline GGT and risk of overall cancer incidence among men yielded an estimated risk increase of 58% per GGT log-unit. Estimates for the association of GGT, modelled as average concentration during individual follow-up, yielded that even moderately elevated values (60 units/l) are significantly associated with increased overall cancer incidence. This risk was substantially larger at higher GGT levels. Age modified the association, with a markedly stronger relation in participants below the age of 65 years [32]. In women, compared to the normal low GGT levels the cancer incidence was elevated for the other GGT categories, with a risk increase of 43% for the highest category [33]. The incidence of invasive cervical cancer was also significantly higher for elevated GGT levels, with up to a tripled risk for very high GGT concentrations (≥72.00 units/l). In contrast, associations between GGT serum levels and cervical intraepithelial neoplasia III risk were not significant [34].

Conclusion

The results from VHM&PP are contrary to the proposed antioxidant and protective effect of SUA against cancer in both men and women. High SUA concentrations seem to be independently associated with increased cancer risk and it is suggested that high SUA is a valuable long-term surrogate parameter for a life-style at risk of developing cancer.

The findings also show that elevated GGT is significantly associated with increased cancer risk in men. In addition, for the first time in a large population-based cohort a significant association between high GGT levels and increased cancer risk in women was shown. This is in accordance with recent research on breast cancer risk [35]. In addition, the findings from VHM&PP further suggest GGT to be involved in the progression of premalignant cervical lesions to invasive cancer.

Besides for the detection of alcohol consumption and being a general marker of liver dysfunction and congestion, several other issues are possibly involved in the variation of GGT levels, such as metabolic syndrome, medication, oxidative stress, and persistent organic pollutants. Likewise, SUA might act as a proxy for unhealthy diet and alcohol consumption. Both GGT and SUA can then be seen as markers of an unfavourable lifestyle related to cancer.

An important limitation in VHM&PP is that the number of cancer cases permitted the study of only broad malignancy categories. Also, routine SUA determination was only done in older women (50 years and above), thereby restricting the power and the generalisability of some results.

Whether these findings concerning possible SUA and GGT effects might lead to optimised cancer screening, remains to be answered. A precondition of each screening method is a relevant intervention that would influence the clinical course for the patient. Certain modifiable risk factors and simple markers seem to be involved so thereby various options in the field of prevention might become available. In addition, it should be considered that measurement of SUA and GGT in a healthy population might function as a prognostic tool to identify patients with an increased risk to develop malignant diseases.

Conflict of interest
The authors declare that there is no conflict of interest.

References

[1] Beard JT. Serum uric acid and coronary heart disease. Am Heart J, 106: 397–400, 1983.
[2] Koenig W, Meisinger C. Urid acid, type 2 diabetes, and cardiovascular diseases: fueling the common soil hypothesis? Clin Chem, 54: 231–233, 2008.
[3] Conen D, Wietlisbach V, Bovet P, Shamlaye C, Riesen W, Paccaud F, Burnier M. Prevalence of hyperuricemia and relation of serum uric acid with cardiovascular risk factors in a developing country. BMC Public Health, 4: 9, 2004.
[4] Ames BN, Cathcart R, Schweirs E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci U S A, 78: 6858–6862, 1981.
[5] Hiatt RA, Fireman BH. Serum uric acid unrelated to cancer incidence in humans. Cancer Res, 48: 2916–2918, 1988.
[6] Kolonel LN, Yoshizawa C, Nomura AM, Stemmermann GN. Relationship of serum uric acid to cancer occurrence in a prospective male cohort. Cancer Epidemiol Biomarkers Prev, 3: 225–228, 1994.
[7] Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci, 38: 263–355, 2001.
[8] Lee DH, Ha MH, Kam S, Chun B, Lee J, Song K, Boo Y, Steffen L, Jacobs DR Jr. A strong secular trend in serum gamma-glutamyltransferase from 1996 to 2003 among South Korean men. Am J Epidemiol, 163: 57–65, 2006.
[9] Pompella A, Emdin M, Passino C, Paolicchi A. The significance of serum gamma-glutamyltransferase in cardiovascular diseases. Clin Chem Lab Med, 42: 1085–1091, 2004.
[10] 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, 27: 127–133, 2007.
[11] Ruttmann E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H. The Vorarlberg health monitoring and promotion programme study group. γ-Glutamyltransferase as a risk factor for cardiovascular disease mortality, an epidemiological investigation in a cohort of 163 944 Austrian adults. Circulation, 112: 2130–2137, 2005.
[12] Pompella A, De Tata V, Paolicchi A, Zunino F. Expression of gamma-glutamyltransferase in cancer cells and its significance in drug resistance. Biochem Pharmacol, 71: 231–238, 2006.
[13] Lee DH, Jacobs DR Jr. Association between serum concentrations of persistent organic pollutants and γ glutamyltransferase: results from the National Health and Examination Survey 1999–2002. Clin Chem, 52: 1825–1827, 2006.
[14] Ulmer H, Kelleher C, Diem G, Concin H. Long-term tracking of cardiovascular risk factors among men and women in a large population-based health system: the Vorarlberg Health Monitoring & Promotion Programme. Eur Heart J, 24: 1004–1013, 2003.
[15] Klenk J, Nagel G, Ulmer H, Strasak A, Concin H, Diem G, Rapp K; the VHM&PP Study Group. Body mass index and mortality: results of a cohort of 184,697 adults in Austria. Eur J Epidemiol, 24: 83–91, 2009.
[16] Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (eds.). Cancer incidence in five continents, vol. VIII. IARC Scientific Publication No. 155, Lyon, 2002.
[17] Oberaigner W, Vittadello F. Cancer mapping in Alpine regions 1996–2000. Pro Literatur Verlag, Mammendorf, 2006.
[18] Stocks T, Rapp K, Bjørge T, Manjer J, Ulmer H, Selmer R, Lukanova A, Johansen D, Concin H, Tretli S, Hallmans G, Jonsson H, Stattin P. Blood glucose and risk of incident and fatal cancer in the Metabolic syndrome and Cancer project (Me-Can): analysis of six prospective cohorts. PLoS Med, 6(12): e1000201, 2009. doi:10.1371/journal.pmed.1000201.

[19] Bjørge T, Stocks T, Lukanova A, Tretli S, Selmer R, Manjer J, Rapp K, Ulmer H, Almquist M, Concin H, Hallmans G, Jonsson H, Stattin P, Engeland A. Metabolic syndrome and endometrial carcinoma. Am J Epidemiol, 171: 892–902, 2010.
[20] Häggström C, Stocks T, Rapp K, Bjørge T, Lindkvist B, Concin H, Engeland A, Manjer J, Ulmer H, Selmer R, Tretli S, Hallmans G, Jonsson H, Stattin P. Metabolic syndrome and risk of bladder cancer: prospective cohort study in the Metabolic syndrome and Cancer project (Me-Can). Int J Cancer, 2010. doi:10.1002/ijc.25521.
[21] Bjørge T, Lukanova A, Jonsson H, Tretli S, Ulmer H, Manjer J, Stocks T, Selmer R, Nagel G, Almquist M, Concin H, Hallmans G, Häggström C, Stattin P, Engeland A. Metabolic syndrome and breast cancer in the Me-Can (Metabolic syndrome and Cancer) project. Cancer Epidemiol Biomarkers Prev, 19: 1737–1745, 2010.
[22] Stocks T, Borena W, Strohmaier S, Bjørge T, Manjer J, Engeland A, Johansen D, Selmer R, Hallmans G, Rapp K, Concin H, Jonsson H, Ulmer H, Stattin P. Cohort profile: the Metabolic syndrome and Cancer project (Me-Can). Int J Epidemiol, 39: 660–667, 2010.
[23] Johansen D, Stocks T, Jonsson H, Lindkvist B, Bjørge T, Concin H, Almquist M, Häggström C, Engeland A, Ulmer H, Hallmans G, Selmer R, Nagel G, Tretli S, Stattin P, Manjer J. Metabolic factors and the risk of pancreatic cancer: a prospective analysis of almost 580,000 men and women in the Metabolic syndrome and Cancer project. Cancer Epidemiol Biomarkers Prev, 19: 2307–2317, 2010.
[24] Nagel G, Concin H, Bjørge T, Rapp K, Manjer J, Hallmans G, Diem G, Häggström C, Engeland A, Almquist M, Jonsson H, Selmer R, Stocks T, Tretli S, Ulmer H, Stattin P, Lukanova A. Metabolic syndrome and rare gynecological cancers in the Metabolic syndrome and Cancer project (Me-Can). Ann Oncol, 2010 [Epub ahead of print].
[25] Stocks T, Lukanova A, Bjørge T, Ulmer H, Manjer J, Almquist M, Concin H, Engeland A, Hallmans G, Nagel G, Tretli S, Veierød MB, Jonsson H, Stattin P. Metabolic factors and the risk of colorectal cancer in 580,000 men and women in the Metabolic syndrome Cancer project (Me-Can). Cancer [Epub ahead of print], 2010.
[26] Borena W, Stocks T, Jonsson H, Strohmaier S, Nagel G, Bjørge T, Manjer J, Hallmans G, Selmer R, Almquist M, Häggström C, Engeland A, Tretli S, Concin H, Strasak A, Stattin P, Ulmer H. Serum triglycerides and cancer risk in the metabolic syndrome and Cancer (Me-Can) collaborative study. Cancer Causes Control, 2010. doi:10.1007/s10552-010-9697-0
[27] Edlinger M, Strohmaier S, Jonsson H, Bjørge T, Manjer J, Borena WT, Häggström C, Engeland A, Tretli S, Concin H, Nagel G, Selmer R, Johansen D, Stocks T, Hallmans G, Stattin P, Ulmer H. Metabolic syndrome and risk of brain tumour in the large population-based Me-Can cohort study. 2010. [Submitted].
[28] Borena W, Strohmaier S, Lukanova A, Jonsson H, Lindkvist B, Bjørge T, Edlinger M, Stocks T, Nagel G, Manjer J, Engeland A, Selmer R, Häggström C, Tretli S, Concin H, Hallmans G, Stattin P, Ulmer H. Metabolic risk factors and primary liver cancer in a large prospective study of 578,700 adults. 2010. [Submitted].
[29] Strasak AM, Rapp K, Hilbe W, Oberaigner W, Ruttmann E, Concin H, Diem G, Pfeiffer KP, Ulmer H; the VHM&PP Study Group. Serum uric acid and risk of cancer mortality in a large prospective male cohort. Cancer Causes Control, 18: 1021–1029, 2007.
[30] Strasak AM, Rapp K, Hilbe W, Oberaigner W, Ruttmann E, Concin H, Diem G, Pfeiffer KP, Ulmer H, on behalf of the VHM&PP Study Group. The role of serum uric acid as an antioxidant protecting against cancer: prospective study in more than 28,000 older Austrian women. Ann Oncol, 18: 1893–1897, 2007.
[31] Strasak AM, Lang S, Kneib T, Brant LJ, Klenk J, Hilbe W, Oberaigner W, Ruttmann E, Kaltenbach L, Concin H, Diem G, Pfeiffer KP, Ulmer H; the VHM&PP Study Group. Use of penalized splines in extended Cox-type additive hazard regression to flexibly estimate the effect of time-varying serum uric acid on risk of cancer incidence: a prospective, population-based study in 78,850 men. Ann Epidemiol, 19: 15–24, 2009.
[32] Strasak AM, Rapp K, Brant LJ, Hilbe W, Gregory M, Oberaigner W, Ruttmann E, Concin H, Diem G, Pfeiffer KP, Ulmer H; the VHM&PP Study Group. Association of γ-glutamyltransferase and risk of cancer incidence in men: a prospective study. Cancer Res, 68: 3970–3977, 2008.
[33] Strasak AM, Pfeiffer RM, Klenk J, Hilbe W, Oberaigner W, Gregory M, Concin H, Diem G, Pfeiffer KP, Ruttmann E, Ulmer H; the VHM&PP Study Group. Prospective study of the association of gamma-glutamyltransferase with cancer incidence in women. Int J Cancer, 123: 1902–1906, 2008.
[34] Strasak AM, Goebel G, Concin H, Pfeiffer RM, Brant LJ, Nagel G, Oberaigner W, Concin N, Diem G, Ruttmann E, Gruber-Moesenbacher U, Offner F, Pompella A, Pfeiffer KP, Ulmer H; the VHM&PP Study Group. Prospective study of the association of serum γ-glutamyltransferase with cervical intraepithelial neoplasia III and invasive cervical cancer. Cancer Res, 70: 3586–3593, 2010.
[35] Fentiman IS, Allen DS. γ-Glutamyl transferase and breast cancer risk. Br J Cancer, 103: 90–93, 2010.

