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The role of serum uric acid as an antioxidant protecting against cancer: prospective study in more than 28 000 older Austrian women

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Background: It has been hypothesized that serum uric acid (SUA), via its antioxidant properties may protect against carcinogenesis. However, few epidemiological investigations have addressed this association and previous findings are inconsistent.

Patients and methods: We prospectively investigated the relation of SUA levels to subsequent cancer mortality in a large cohort of 28613 elderly Austrian women with a median follow-up of 15.2 years. Adjusted Cox proportional hazards models were calculated to evaluate SUA as an independently related factor to fatal cancer events.

Results: High SUA (>5.41 mg/dL) was independently associated with increased risk of total cancer mortality ($p<0.0001$); the adjusted hazard ratio for the highest versus lowest quartile of SUA was 1.27 (1.08–1.48). SUA levels were further positively related to deaths from malignant neoplasms of breast and female genital organs ($P = 0.02$) and nervous system and unspecified sites ($P = 0.02$). We found no evidence for an inverse relationship between SUA levels and risk of total or site-specific cancer mortality.

Conclusion: Our results are contrary to the proposed antioxidant and protective effect of SUA against cancer and rather suggest high SUA concentrations to be associated with outcome possibly reflecting more serious prognostic indication.

Key words: antioxidant, cancer mortality, carcinogenesis, epidemiology, older women, risk factor, serum uric acid

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introduction

Although recent studies found serum uric acid (SUA) to be an independent predictor for cardiovascular and total mortality in general populations [1–7], little is known about the role of SUA for cancer, particularly in women. It has been hypothesized that the antioxidant properties of SUA may play a crucial role in cancer etiology by preventing the formation of oxygen radicals, thereby protecting against carcinogenesis [8, 9]. It was further proposed that other antioxidants, such as vitamins C and E may also have a protective effect against cancer and high dietary levels of β-carotene, another antioxidant, have previously been associated with cancer rates lower than expected [10, 11]. Despite a lack of epidemiologic research in women, one study could demonstrate an inverse, though statistically non-significant relationship between SUA levels and cancer mortality in middle-aged men [12], fractionally supporting the assumed antioxidant and protective effect of SUA against cancer. Different investigations, partly containing both genders, found SUA concentrations to be entirely unrelated to cancer incidence and/or mortality after adjusting for potential confounding [11, 13–15]. Outright contradictory evidence in turn suggests a rather positive association between SUA and risk of fatal cancer, indicating that elevated levels of SUA may rather be considered a risk factor for cancer mortality and reduced life expectancy in general populations [1, 16, 17].

In the present study we prospectively investigated the association of SUA levels to risk of cancer mortality in a large cohort of 28 613 elderly Austrian women with 1552 incident cases, using health examination data from the Vorarlberg Health Monitoring and Promotion Programme (VHM&PP). To the best of our knowledge, this study is the first large scale investigation to explore the relation of SUA to cancer mortality in a general, apparently healthy population of older, post-menopausal women.

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patients and methods

study population

The VHM&PP [18–20] is a large, prospective, multicentre, population-based risk factor surveillance programme, located in Vorarlberg, the westernmost province of Austria. It is routinely performed by the Agency for Social and Preventive Medicine, and basically addresses all adults of the entire province. The programme routinely includes the recording of socio-demographic data, a physical examination with a fasting blood sample and consultation with a physician. From the outset in 1985, approximately two-thirds of the adult population of the province has participated in the programme. A more detailed description of the programme methodology has been reported elsewhere [18–20]. All participants signed informed consents to have personal data stored and processed. For this study, institutional review board approval was obtained by the Ethics Committee of the province of Vorarlberg.

Between 1985 and 2005, 99739 female adult Vorarlberg residents were enrolled in the VHM&PP cohort. However, as SUA routinely was determined only in all women aged ≥50 years at screening and not measured in women at younger ages, the current investigation was restricted to 28 613 female participants (age ≥50 years) with complete and valid data on SUA at enrolment. For the main analyses, we excluded study participants with follow-up periods <2 years (n = 1173), as it is unlikely that SUA predicts cancer death within such a short period of time. Thus, participants with fatal cancer events within the first 2 years after baseline SUA measurement were also barred from the main analyses.

measurements

Measurements of height, weight, blood pressure, total cholesterol, blood glucose, SUA and smoking status (current, former, never) routinely were obtained for each participant. Women 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 was included in the models as a surrogate measure of socioeconomic status. Participants who were retired at baseline were classified according to their former occupation and housewife's according to their husband's occupation. Two central laboratories undergoing regular internal and external quality procedures performed SUA measurements on fasting blood samples on a RXL (DADE). Subsequently, subjects were stratified according to quartiles of SUA distribution with cut-off values ranging from 3.70 (lowest quartile), 4.50, 5.40 to ≥5.41 mg/dL (highest quartile).

end points

By the end of 2005, 5702 deaths were recorded in our database, of which 1552 (27.2%) were cancer related deaths. Date and cause of death information was provided by the local health authority and was linked in the database with the use of a validated procedure. All deaths were identified from death certificates that were confirmed by authorized physicians only. For analyses, cancer deaths were grouped into the following subgroups according to the *International Classification of Diseases*, 9th and 10th revision (ICD-9, ICD-10):

(i) malignant neoplasms of digestive organs (ICD-9 150–157; ICD-10 C15–C25);
(ii) respiratory system and intrathoracic organs (ICD-9 160–165; ICD-10 C30–C39);
(iii) bone, connective tissue, soft tissue and skin (ICD-9 170–173; ICD-10 C40–C49);
(iv) breast and female genital organs (ICD-9 174,179–184; ICD-10 C50–58);
(v) urinary organs (ICD-9 188–189; ICD–10 C64–68);
(vi) nervous system and unspecified sites (ICD-9 190–199; ICD-10 C69–C72);
(vii) lymphoid, haematopoietic and related tissue (ICD-9 200–208; ICD-10 C81–C96).

statistical analysis

Cox proportional hazards models, adjusted for age, body-mass index, smoking status, occupational status and year of examination were used to compute hazard ratios with 95% confidence intervals (CI) for the association of SUA with cancer mortality. In addition, hazard ratios (95% CI) were estimated for unit increases of SUA and significance testing was performed with a Wald χ^2 test on SUA unit changes as well. Subgroup analyses for site-specific cancer deaths, age groups and according to time intervals between baseline SUA screening and subsequent mortality (i.e. 5 and 10 years) were performed with the same Cox models. The proportional hazards assumption was checked and found to be fulfilled for all models. Significance testing of age as an effect modifier for the relation between SUA and cancer mortality was done through the assessment of interaction terms in the models. Probability values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS 14.0 (Chicago, Illinois).

results

characteristics of study population

Demographic and clinical characteristics of the study cohort are shown in Table 1. The total cohort consisted of 28 613 apparently healthy older female Austrian adults with complete and valid data on SUA, prospectively followed up for a median time of 15.2 years, with a total time at risk of 387 731 person years. Mean age at study entry was 62.3 years; total mortality was 19.9% and cancer mortality corresponded to 5.4%. Baseline SUA measurements were approximately normally distributed, ranging from 1.1 to 14.0 mg/dL with a mean ± SD of 4.6 ± 1.3 mg/dL.

association of SUA with cancer mortality

The relationship between baseline SUA levels and subsequent cancer mortality in participants with at least 2 years of follow-up, is shown in Table 2 and Figure 1. In adjusted Cox proportional hazards models, high SUA levels were significantly associated with increased risk of total cancer mortality (P < 0.0001); the hazard ratio (95% CI) for the highest versus lowest quartile of SUA was 1.27 (1.08–1.48). Regarding the association of SUA levels with site-specific cancer mortality, we found an independent, positive association with deaths from malignant neoplasms of breast and female genital organs (P = 0.02) and malignant neoplasms of nervous system and unspecified sites (P = 0.02); the hazard ratios (95% CI) for the highest versus lowest quartile of SUA were 1.25 (0.94–1.67) and 1.99 (1.01–3.91), respectively. We did not detect any significant inverse relationship between SUA levels and subsequent mortality from any site-specific cancer. To eliminate possible effects of very old participants, likely to confound the relationship of SUA levels and risk of cancer mortality, we excluded all subjects aged >75 years for a subgroup analysis. However, all associations that were significant in the main analysis remained unchanged in terms of statistical significance when reanalysed.

Table 1. Characteristics of study population, VHM&PP 1985–2005

Characteristic	All participants	Serum Uric Acid (Quartiles)			
		1 (≤3.70 mg/dL)	2 (3.71–4.50 mg/dL)	3 (4.51–5.40 mg/dL)	4 (≥5.41 mg/dL)
	(n = 28 613)	(n = 7 404)	(n = 7 611)	(n = 6 976)	(n = 6 622)
Age, mean ± SD (range), y	62.3 ± 8.8 (50.0–95.3)	60.4 ± 8.1 (50.0–91.4)	61.3 ± 8.5 (50.0–95.3)	62.5 ± 8.7 (50.0–93.3)	65.2 ± 9.3 (50.0–94.1)
Age >75 y– no. (%)	3 073 (10.7)	475 (6.4)	633 (8.3)	782 (11.2)	1 183 (17.9)
Current smoking – no. (%)	2 536 (8.9)	618 (8.3)	705 (9.3)	662 (9.5)	551 (8.3)
BMI, mean ± SD (median), kg/m^2	26.5 ± 4.6 (25.9)	24.9 ± 3.9 (24.4)	25.9 ± 4.3 (25.2)	27.0 ± 4.5 (27.0)	28.4 ± 5.0 (27.8)
Glucose, mean ± SD (median), mg/dL	96.1 ± 30.1 (90.0)	94.8 ± 32.6 (89.0)	94.5 ± 28.5 (89.0)	95.5 ± 27.7 (91.0)	99.3 ± 31.5 (93.0)
Serum uric acid, mean ± SD (median), mg/dL	4.6 ± 1.3 (4.5)	3.1 ± 0.5 (3.2)	4.2 ± 0.2 (4.2)	5.0 ± 0.3 (4.9)	6.4 ± 0.9 (6.2)
Total cholesterol, mean ± SD (median), mg/dL	246.1 ± 46.6 (243.0)	240.1 ± 43.9 (237.0)	245.0 ± 45.5 (242.0)	248.8 ± 46.8 (245.0)	251.2 ± 49.6 (248.0)
Systolic blood pressure, mean ± SD (median), mm Hg	145.2 ± 22.5 (140.0)	140.0 ± 21.4 (140.0)	143.1 ± 21.9 (140.0)	146.6 ± 22.5 (145.0)	151.8 ± 22.7 (150.0)
Diastolic blood pressure, mean ± SD (median), mm Hg	85.1 ± 11.1 (84.0)	83.1 ± 10.7 (80.0)	84.5 ± 10.7 (80.0)	85.9 ± 11.2 (85.0)	87.2 ± 11.3 (85.0)
Total mortality – no (%)	5 702 (19.9)	1 128 (15.2)	1 278 (16.8)	1 443 (20.7)	1 853 (28.0)
cardiovascular/cerebrovascular deaths – no. (%)	2 874 (10.0)	515 (7.0)	636 (8.4)	725 (10.4)	998 (15.1)
cancer related deaths – no. (%)	1 552 (5.4)	354 (4.8)	371 (4.9)	396 (5.7)	431 (6.5)
other death cause – no. (%)	1276 (4.5)	259 (3.5)	271 (3.6)	322 (4.6)	424 (6.4)
Follow-up, mean ± SD (median), years	13.6 ± 6.0 (15.2)	14.6 ± 5.8 (17.0)	13.7 ± 6.0 (15.5)	13.3 ± 6.0 (14.6)	12.4 ± 6.1 (13.4)
Person years at risk	387 731	108 333	104 367	92 776	82 255

BMI indicates body mass index.

In order to further investigate possible effects of preclinical disease at time of SUA measurement, also likely to confound our results by altering SUA concentrations [21–23], in a lag analysis, we classified all 1552 cancer deaths according to their time of incidence, into those occurring (i) within 5 years, (ii) after 5 or more years, and (iii) after 10 or more years after baseline SUA measurement. We found the association between SUA levels and risk of total cancer mortality to be most pronounced in deaths occurring within 5 years after SUA measurement [HR for the highest versus lowest quartile of SUA 1.39 (0.99–1.94), $P = 0.02$], remaining stable for deaths occurring 5 or more years after SUA screening [HR 1.27 (1.07–1.51), $P = 0.002$], but entirely vanishing in deaths occurring 10 or more years after baseline SUA measurement [HR 1.09 (0.88–1.35), $P = 0.67$]. Again, we are unable to report any significant inverse relationship between SUA, and risk of total or site-specific cancer mortality in all time intervals analysed.

discussion

The purpose of the present study, involving more than 28 000 predominantly healthy, older Austrian women, was to evaluate the role of SUA as an antioxidant possibly protecting against cancer. Instead of an inverse relationship of SUA levels and risk of subsequent cancer mortality, we found older female individuals with baseline SUA values ≥5.41 mg/dL to have a 27% greater risk for all fatal cancer events in comparison to women with SUA concentrations ≤3.70 mg/dL. This risk increased to nearly 100% for deaths from malignant neoplasms of the nervous system and unspecified sites. Our results strongly weigh against the proposed antioxidant properties and protective effect of SUA on cancer [8,9], rather suggesting that high SUA concentrations may independently be associated with outcome possibly reflecting more serious prognostic indication. Although not addressed in the present study, we also observed strikingly increased cardiovascular mortality in study participants with high SUA levels (Table 1) and the threshold for this outcome was located in the median value of SUA.

In line with our results, Levine and colleagues [1] reported a positive association of SUA levels with total cancer mortality among females aged 55–64, persisting also after adjustment for multiple risk factors. Conversely, in a cohort of elderly subjects from Italy, Mazza and colleagues [6], in univariate analysis found that SUA could protect against cancer by influencing the toxic and carcinogenic effects of oxygen radicals, although the authors did not conduct sex specific analysis in women. Nevertheless, in multivariate analysis SUA lost a predictive role on cancer mortality. Similarly, Hiatt and Fireman [11] found SUA to be entirely unrelated to cancer incidence in a large cohort of women from the US after adjusting for important confounding factors. To our knowledge, there are no other published epidemiologic reports on the relation of SUA and cancer in women.

Although Bozkir and colleagues [15] recently reported SUA levels of lung cancer patients to be significantly lower than those of healthy controls, markedly elevated levels of SUA were

Table 2. Cancer mortality according to quartiles of SUA in participants with at least 2 years of follow-up, VHM&PP 1985-2005 †

	Serum uric acid (SUA)					*P* for unit increase
	1 (≤3.70 mg/dL)	2 (3.71–4.50 mg/dL)	3 (4.51–5.40 mg/dL)	4 (≥5.41 mg/dL)	Total per unit increase	
	(*n* = 7 195)	(*n* = 7 298)	(*n* = 6 682)	(*n* = 6 265)	(*n* = 27 440)	
Total cancer mortality						
Events, no. (%)	337 (4.7)	349 (4.8)	371 (5.6)	396 (6.3)	1453 (5.3)	
HR (95% CI)‡	1.00 (Ref)	1.02 (0.88–1.19)	1.14 (0.98–1.33)	1.27 (1.08–1.48)	1.08 (1.03–1.12)	<0.0001
Mortality from site–specific cancers						
Malignant neoplasm of digestive organs						
Events, no. (%)	125 (1.7)	116 (1.6)	125 (1.9)	138 (2.2)	504 (1.8)	
HR (95% CI)‡	1.00 (Ref)	0.91 (0.70–1.17)	1.02 (0.79–1.31)	1.18 (0.91–1.53)	1.05 (0.98–1.13)	0.19
Malignant neoplasm of respiratory system and intrathoracic organs						
Events, no. (%)	35 (0.5)	32 (0.4)	41 (0.6)	32 (0.5)	140 (0.5)	
HR (95% CI)‡	1.00 (Ref)	0.96 (0.58–1.57)	1.37 (0.86–2.20)	1.26 (0.75–2.12)	1.11 (0.97–1.27)	0.13
Malignant neoplasm of bone, connective tissue, soft tissue and skin						
Events, no. (%)	4 (0.1)	13 (0.2)	10 (0.1)	5 (0.1)	32 (0.1)	
HR (95% CI)‡	1.00 (Ref)	2.96 (0.95–9.21)	2.08 (0.62–7.01)	1.30 (0.33–5.07)	0.97 (0.72–1.31)	0.86
Malignant neoplasm of breast and female genital organs						
Events, no. (%)	103 (1.4)	102 (1.4)	104 (1.6)	115 (1.8)	424 (1.5)	
HR (95% CI)‡	1.00 (Ref)	1.00 (0.75–1.32)	1.10 (0.83–1.46)	1.25 (0.94–1.67)	1.09 (1.01–1.18)	0.02
Malignant neoplasm of urinary organs						
Events, no. (%)	13 (0.2)	27 (0.4)	15 (0.2)	24 (0.4)	79 (0.3)	
HR (95% CI)‡	1.00 (Ref)	1.92 (0.99–3.73)	0.94 (0.43–2.04)	1.52 (0.74–3.09)	1.01 (0.84–1.20)	0.94
Malignant neoplasm of nervous system and unspecified sites						
Events, no. (%)	16 (0.2)	15 (0.2)	16 (0.2)	28 (0.4)	75 (0.3)	
HR (95% CI)‡	1.00 (Ref)	0.95 (0.46–1.97)	1.11 (0.54–2.29)	1.99 (1.01–3.91)	1.22 (1.03–1.46)	0.02
Malignant neoplasm of lymphoid, haematopoietic and related tissue						
Events, no. (%)	30 (0.4)	34 (0.5)	40 (0.6)	35 (0.6)	139 (0.5)	
HR (95% CI)‡	1.00 (Ref)	1.16 (0.71–1.90)	1.38 (0.85–2.25)	1.23 (0.73–2.07)	1.04 (0.91–1.19)	0.55

†Study participants with fatal cancer events within the first 2 years after baseline SUA measurement or follow-up periods <2 years were excluded from the main analyses.

‡Hazard ratios (95% CI) from Cox proportional hazards models adjusted for age, body-mass index, smoking status, occupational status and year of examination.

frequently observed in cancer patients and have been attributed to the malignant process itself, resulting from the increased nucleic acid turnover in the rapidly proliferating diseased tissue [21–23]. As the observed positive association of SUA with risk of total cancer mortality in our cohort was strongest, when only considering cases occurring within 5 years after baseline SUA measurement, it cannot be ruled out that our results may residually be confounded by such effects of severe preclinical disease (i.e. cancer morbidity) at time of SUA measurement. Contrawise, considering that our cohort was a general, apparently healthy, female population, rather than a sick hospital sample, this effect should be of minor ponderosity on our results.

Our study had several strengths and potential limitations. Major strengths were the prospective design, the large sample size, length of follow-up, and the standardized protocol. In addition, examinations were performed by experienced physicians only. Even though information on major risk factors was collected, our study was unable to account for additional factors that further might have residually confounded the relationship between SUA and cancer mortality, and large scale epidemiological investigations in general cannot certainly answer the underlying biological mechanisms. Additionally, despite the large size of our cohort, fatal events in single subgroups were relatively infrequent, possibly causing type II errors. Finally, data on preclinical disease and cancer morbidity was not available in our database.

In summary, this study aimed to investigate the role of SUA as an antioxidant, protecting against cancer, in a large central European population-based cohort of apparently healthy older women. Our results are contrary to the proposed antioxidant effect of SUA against cancer and rather indicate high SUA concentrations to be independently associated with outcome possibly reflecting more serious prognostic indication, though not necessarily specific to cancer mortality. However, the presence of elevated SUA suggests the clinical importance of monitoring and intervention on this basis.

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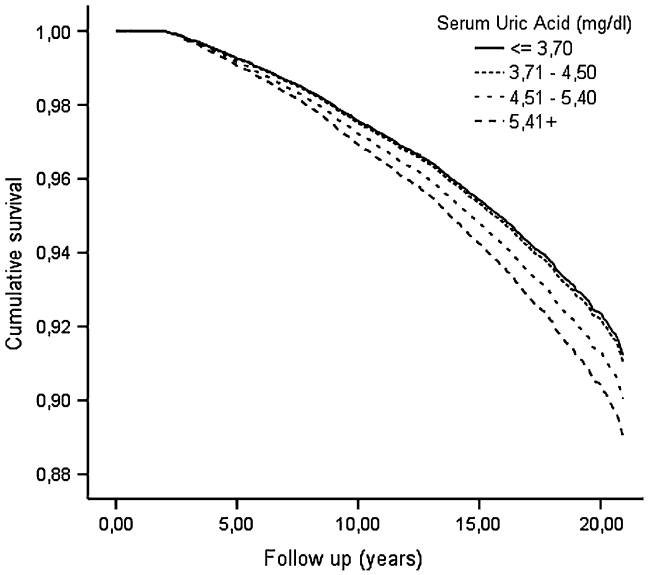

Figure 1. Adjusted cumulative survival from all cancers according to quartiles of SUA among 27 440 elderly female Austrian adults in the VHM&PP estimated at the average values of covariates. Study participants with fatal cancer events within the first 2 years after baseline SUA measurement or follow-up periods <2 years were excluded. Survival curves were calculated with Cox proportional hazards models adjusted for age, body-mass index, smoking status, occupational status and year of examination.

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