Serum Uric Acid Unrelated to Cancer Incidence in Humans

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ABSTRACT

We examined the hypothesis that low levels of serum uric acid are associated with elevated cancer risk. A subpopulation (163,830 members) of a large health maintenance organization was followed for a mean of 9.8 years after a multiphasic health checkup at which serum uric acid level was measured. Total cancer incidence as well as site-specific incidence (for lung, colon, and prostate cancer in men and lung, colon, breast, uterine, and cervical cancer in women) was ascertained from hospital discharge records and the Surveillance, Epidemiology, and End Results program in the San Francisco-Oakland Bay area. Age-adjusted cancer incidence was not elevated in the lower deciles of serum uric acid level. After adjusting for age, race, education, smoking, alcohol consumption, and body mass, using proportional hazards models, the risk of cancer was not elevated at lower levels of uric acid. Our results suggest that if increased risk of cancer is associated with low serum uric acid, this risk is associated with serum uric levels below those commonly seen in human populations.

INTRODUCTION

Humans and other primates have higher serum urate levels and lower hepatic uricase levels than lower mammalian species (1). Ames et al. (2) proposed that the antioxidant properties of uric acid may act to prevent formation of oxygen radicals and thereby protect against carcinogenesis. Oxygen radicals, produced in man during oxygen metabolism, are toxic to cell membranes, DNA, and RNA and may initiate carcinogenesis (2). High dietary levels of β-carotene, another antioxidant, has been associated with cancer rates lower than expected (3). It has been suggested that other antioxidants, such as vitamins C and E, may also protect against cancer (3).

Few epidemiological investigations have been conducted on the relation of serum uric acid to cancer in humans. Follow-up studies of Swedish men (4) and Finnish men and women (5) have found no association between uric acid levels and risk of cancer mortality, while a Dutch study (6) found a statistically significant inverse relation between serum uric acid level and lung cancer mortality in men monitored for 18 years. The same study found no relationship to total cancer mortality. This finding suggests that examination of specific cancers in relation to serum uric acid level may be worthwhile. We have examined cancer incidence in relation to serum uric acid levels for the three most common cancers in men and the five most common cancers in women. Our subjects were members of a large prepaid health plan who had their uric acid measured as part of a MHC. (7) An earlier study of cardiovascular disease in a small subset of this cohort had not revealed any relationship of cancer mortality with serum uric acid levels (6).

METHODS

Study Population.

The study population comprised members of the Kaiser Permanente Medical Care Program, Northern California Region. The Kaiser Permanente Medical Care Program is a large health maintenance organization whose members have demographic characteristics similar to those of the San Francisco Bay Area as enumerated by the U.S. Census (7). Members have full access to services in hospitals and clinics throughout the region. The computer-stored MHC, which has been offered to health plan members since 1964, included a blood sample and a detailed questionnaire with information on demographic characteristics, medical histories, and lifestyles. Uric acid was measured on an Auto-Analyzer (Technicon Company, White Plains, NY) from 1965 through 1968, and on an Auto-Chemist (AGA Corporation, Stockholm, Sweden) from 1969 through 1972. For this study we selected persons 20 years or older, examined from 1965 through 1972, and who had no known cancer prior to 7 months after their first examination in the study period. To eliminate a small number of extreme values which might have been technical errors we included only serum uric acid levels between 0.1 and 16.0 mg/dl. The final cohort comprised 75,283 men and 88,547 women with mean follow-up of 9.8 years (1,603,789 person-years of follow-up).

Follow-up. Incident cancers for persons in this cohort were ascertained from records of hospital discharges from 1960 through 1980 and from records of the Surveillance, Epidemiology, and End Results program in the San Francisco-Oakland Bay area from 1969 through 1980. To validate coded cancer diagnoses not previously reviewed by the Surveillance, Epidemiology, and End Results program or by our department in earlier studies, we reviewed a random sample of 500 codes. By a method previously described (8) we estimated that 89–99% of cancer diagnoses were accurately coded depending on the specific cancer site. A total of 3209 cancers in men and 4343 in women were ascertained for this study.

Each member of the cohort was monitored from 7 months following examination until the end of 1980, or until the member terminated membership in the health plan. When date of termination was not available from computer files, which were incomplete prior to 1976, a date halfway between the date of the last MHC and the beginning of 1976 was selected. Such assignments were necessary in about 12% of the cohort.

Statistical Methods. First, the incidence of any cancer (except non-melanomatous skin cancer) in the entire study population was determined for each sex-specific decile of serum uric acid level, adjusting for age by direct standardization, using the total study population as the standard. Next, we examined the potential to confound the cancer-uric acid association of variables that have been related to serum uric acid levels. Age, black and Asian race, education level, alcohol consumption (1–2 and 3+ drinks/day), current and ex-smoker, Quetelet index (weight/height² × 100), systolic and diastolic blood pressure, diuretic use, history of hypertension and gout, family history of gout, and serum levels of cholesterol, protein, creatinine, albumin, and hemoglobin were studied in relation to both serum uric acid levels and cancer, separately for men and women. The relationship of serum uric acid level to these possible covariables was examined in a 10% random sample of the cohort by regressing the level of serum uric acid on the possible confounders. Cancer risk was then examined in relation to the possible confounders by fitting proportional hazards models to the data from the 10% sample augmented by all of the cancer cases. Variables significantly related to serum uric acid and to cancer (P < 0.05) or strongly related to cancer were included in proportional hazards models fitted to the data from the entire study population (9).

We examined colon, lung, and prostate cancer among men and...
cervical, uterine, breast, colon, and lung cancer in women. Serum uric acid level was included as a continuous variable in an initial set of proportional hazards models. To focus on the consequences of low levels of uric acid and to eliminate associations attributable to possible effects of preclinical cancer on uric acid level, a second series of models which included indicators of low (3-3.9 mg/dl in men and 2-2.9 mg/dl in women) and very low uric acid levels (<3 mg/dl in men and <2 mg/dl in women), were fitted to data on all persons with no history of cancer up to 2 years after examination. This second series of models also included a variable for quantity smoked by current smokers.

We stratified all multivariate models by month of MHC to adjust for changes in procedures and equipment over the duration of the study. The log-likelihood function was computed separately for each stratum of the study population that took the MHC during the same month, and the computed likelihoods were summed across strata to yield an overall likelihood that was maximized to obtain parameter estimates (10). Thus, each time a cancer was diagnosed in a member of the study population, that person was compared with all other persons of the same sex who had the MHC in the same month as the cancer case and who remained in the health plan free of cancer when the cancer of the case was diagnosed.

RESULTS

The mean ± SD of serum uric acid levels in this cohort was 5.97 ± 1.34 mg/dl for men and 4.62 ± 1.22 mg/dl for women. Age was positively associated with serum uric acid level in both sexes. Each increase of 10 years was associated with a rise of 0.20 mg/dl among women and 0.04 mg/dl among men. The age-adjusted cancer incidence among men was slightly higher in the highest decile of serum uric acid; otherwise cancer incidence was unrelated to uric acid decile (Fig. 1).

In addition to age, the variables most significantly (P< 0.001) associated with serum uric acid level in both sexes were alcohol consumption of 3 or more drinks/day, Quetelet index, hypertensive blood pressure, diuretic use, family history of gout, and serum levels of protein, creatinine, and albumin. Also significantly (P < 0.001) associated were Asian race, history of gout, and cholesterol level in men, and alcohol consumption of 1–2 drinks/day and hemoglobin levels in women. Of these variables only Quetelet index, alcohol consumption, and race were significantly associated with the risk of cancer in either men or women and were chosen as covariates in subsequent analyses. Smoking status and level of education were also selected for inclusion in subsequent models because they are frequently found to be strongly associated with cancer risk. The mean levels of serum uric acid for these selected possible confounders are presented in Table 1.

### Table 1 Serum uric level in relation to selected variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>5.88 ± 1.23*</td>
<td>4.20 ± 1.02</td>
</tr>
<tr>
<td>40–59</td>
<td>5.96 ± 1.32</td>
<td>4.59 ± 1.20</td>
</tr>
<tr>
<td>60+</td>
<td>6.03 ± 1.41</td>
<td>5.06 ± 1.28</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>5.94 ± 1.28</td>
<td>4.47 ± 1.15</td>
</tr>
<tr>
<td>Black</td>
<td>5.84 ± 1.36</td>
<td>4.35 ± 1.24</td>
</tr>
<tr>
<td>Asian</td>
<td>6.09 ± 1.33</td>
<td>4.46 ± 1.10</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>5.88 ± 1.35</td>
<td>4.52 ± 1.21</td>
</tr>
<tr>
<td>Some college</td>
<td>5.95 ± 1.27</td>
<td>4.41 ± 1.13</td>
</tr>
<tr>
<td>College graduate</td>
<td>5.98 ± 1.24</td>
<td>4.38 ± 1.08</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>5.99 ± 1.29</td>
<td>4.49 ± 1.18</td>
</tr>
<tr>
<td>Ex</td>
<td>6.04 ± 1.31</td>
<td>4.50 ± 1.16</td>
</tr>
<tr>
<td>Current</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 pack/day</td>
<td>5.87 ± 1.27</td>
<td>4.36 ± 1.12</td>
</tr>
<tr>
<td>1–2 packs/day</td>
<td>5.79 ± 1.27</td>
<td>4.40 ± 1.14</td>
</tr>
<tr>
<td>2+ packs/day</td>
<td>5.92 ± 1.34</td>
<td>4.50 ± 1.20</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinker</td>
<td>5.79 ± 1.32</td>
<td>4.51 ± 1.21</td>
</tr>
<tr>
<td>Moderate</td>
<td>5.90 ± 1.26</td>
<td>4.40 ± 1.12</td>
</tr>
<tr>
<td>Heavy</td>
<td>6.19 ± 1.37</td>
<td>4.82 ± 1.29</td>
</tr>
<tr>
<td>Quetelet (kg/m² × 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21</td>
<td>5.41 ± 1.20</td>
<td>4.09 ± 0.99</td>
</tr>
<tr>
<td>21–26.9</td>
<td>5.80 ± 1.23</td>
<td>4.41 ± 1.10</td>
</tr>
<tr>
<td>27+</td>
<td>6.35 ± 1.35</td>
<td>5.05 ± 1.30</td>
</tr>
<tr>
<td>Menopause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4.25 ± 1.05</td>
<td>4.78 ± 1.25</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± SD.

### Table 2 Relative risk of cancer at selected sites in relation to serum uric acid level adjusted for age, race, level of education, smoking status, alcohol consumption, and body mass

<table>
<thead>
<tr>
<th>Cancer</th>
<th>n</th>
<th>Relative risk/1 mg/dl increase of uric acid (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any site</td>
<td>2721</td>
<td>1.04 (1.01, 1.07)</td>
</tr>
<tr>
<td>Lung</td>
<td>519</td>
<td>0.97 (0.92, 1.06)</td>
</tr>
<tr>
<td>Colon</td>
<td>310</td>
<td>1.07 (0.98, 1.17)</td>
</tr>
<tr>
<td>Prostate</td>
<td>491</td>
<td>1.05 (0.98, 1.12)</td>
</tr>
<tr>
<td>Breast</td>
<td>1215</td>
<td>1.04 (0.99, 1.09)</td>
</tr>
<tr>
<td>Uterus</td>
<td>469</td>
<td>0.98 (0.90, 1.16)</td>
</tr>
<tr>
<td>Cervix</td>
<td>452</td>
<td>0.95 (0.87, 1.04)</td>
</tr>
</tbody>
</table>

Adjustment of the cancer-uric acid associations for these covariates using Cox regression yielded results similar to those apparent in Fig. 1. Serum uric acid level, modeled as a continuous variable, was not related to cancer in the predicted direction for either sex. At the 5 common sites in women and the 3 common sites in men, slight associations were found in both directions, but none of these was statistically significant (Table 2). The upper bounds of the 95% confidence intervals suggest that a 1 mg/dl rise in serum uric acid levels is not associated with more than a 17% fall in cancer risk at any of the sites studied.

Closer examination of persons with low serum uric acid levels (5.7% of the study population) and with very low serum uric acid levels (0.7%) found that neither low nor very low serum uric acid levels were associated with significantly increased risk for any cancer among persons who remained free of cancer for at least 2 years following examination (Table 3). Relative risks were generally small and not significant. Of the 20 relative risks we evaluated only 3 were greater than 1.5: lung in men and uterine in women at very low uric acid levels and colon cancer in men at low levels of uric acid.

Fig. 1. Age-adjusted cancer incidence by decile of serum uric acid level.
DISCUSSION

We found little evidence to support the hypothesis advanced by Ames et al. (2) that low uric acid is a risk factor for cancer. The data used to test this hypothesis were collected prospectively, the cohort was very large, and there was sufficient power to rule out substantial effects of serum uric acid level on cancer risk in both sexes, even for specific cancer sites. We are concerned that the mean levels of serum uric acid in our study population were higher than in other populations (11) by almost 1 mg/dl perhaps because of differences in the measurement techniques. However, the relationship of serum uric acid level to other variables such as race, body size, alcohol consumption, hypertension, and hemoglobin level are similar to those found by other population-based studies (11, 12).

Our results confirm those of a large cohort study of mortality in middle-aged men in Sweden (4) which found a small but significant direct relationship to overall cancer mortality (18 deaths) in men. This relationship was confined to “early deaths” that occurred within the first 2.5 years after baseline and could thus have been due to the effects of the cancer on serum uric acid levels rather than vice versa. Another prospective study of 3195 men and 3155 women in Finland showed that cancer mortality was higher with each lower level of uric acid level, but the variation in the rates by serum uric acid level was not statistically significant.

One study in the Netherlands recorded mortality in 672 men aged 47–66 years during over 10 years of follow-up and found that lower levels of serum uric acid were associated with lung cancer mortality but not with total cancer mortality. After controlling for age and smoking, the relationship of serum uric acid to lung cancer was significant. An association of serum uric acid level with lung cancer would be biologically plausible under the Ames hypothesis, since the high oxygen environment of lung tissue could be more susceptible to the carcinogenic activity of oxygen radicals. Our analysis, in which we adjusted for body mass, education, alcohol use, age, and smoking, failed to demonstrate a relationship of over-all cancer incidence (or lung cancer in particular) to serum uric acid levels. When we restricted our lung cancer cases to those occurring 2 years after the examination, no elevated risk was apparent until levels below 3 mg/dl for men. At these very low levels there were so few people that we are unable to rule out the possibility that the elevated risk was due to chance. In general, other cancers did not show this hypothesized relationship with low serum uric acid.

This epidemiological study does not speak directly to the presence of antioxidant properties of uric acid and how they influence the toxic and carcinogenic effects of oxygen radicals. An increased risk of cancer may exist at levels of serum uric acid below those we could examine. However, together with previous studies our results suggest that an inhibitory effect of uric acid on carcinogenesis cannot be demonstrated in epidemiological investigations, even in large human populations.

REFERENCES

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