Relationship of Serum Uric Acid to Cancer Occurrence in a Prospective Male Cohort

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Abstract

Uric acid is a potent antioxidant and thus might protect against cancer. To test this hypothesis, we examined the relationship of serum uric acid to subsequent cancer incidence in a cohort of Japanese men in Hawaii. The study population consisted of 7889 men identified in the years 1965–1968 and followed by active hospital surveillance through November 1991. Cancer risk by serum uric acid level was analyzed using Cox proportional hazards regression with adjustment for age and, where indicated, smoking, alcohol use, and body mass index. No significant associations were seen for total cancer (1544 cases), or for cancers of the stomach (214), colon (272), rectum (105), lung (223), bladder (89), or hematopoietic system (77). For prostate cancer (293 cases), a positive association was found (relative risk for highest versus lowest quartile of serum uric acid = 1.5; 95% confidence interval 1.1-2.1; p for trend = 0.04). When the interval from examination to diagnosis was considered, this association was strongest for cases diagnosed in the first 10 years, was attenuated after 15 years, and disappeared completely after 20 years. The findings from this study do not support the hypothesis that uric acid protects against cancer occurrence.

Introduction

Abnormal levels of SUA frequently are found in cancer patients. These alterations generally have been attributed to the malignant process itself. Hyperuricemia in cancer patients (such as those with leukemia, lymphoma, or disseminated cancer) is thought to result from the increased nucleic acid turnover in the rapidly proliferating diseased tissue (1–3). Conversely, hypouricemia in cancer patients is thought to reflect increased renal secretion as a result of tubular damage or a tumor-related humoral factor (4–7).

However, because uric acid is an antioxidant and scavenger of singlet oxygen, it may play a role in cancer etiology by protecting against cancer occurrence (8, 9). Only a few epidemiological studies have tested this hypothesis, and the findings have been inconsistent (10–13). To further evaluate this association, we examined the relationship of SUA level to subsequent cancer incidence in a cohort of Japanese men in Hawaii.

Methods

The data were from the Japan-Hawaii Cancer Study, which is based on a cohort of 8006 Japanese-American men residing on the island of Oahu, Hawaii. This cohort was established in 1965 by the Honolulu Heart Program, and consisted of male Japanese volunteers from the Selective Service registration files who were living on Oahu and born between 1900 and 1919. These men were interviewed and examined between 1965 and 1968, at which time a blood sample was collected and tested for SUA levels. The interview included demographic and anthropometric information, medical history, physiological measurements, and other data.

Follow-up on the cohort has been maintained since that time by both active hospital surveillance on Oahu and by periodic linkage of the cohort with the statewide Hawaii Tumor Registry, a member of the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program. Each identified cancer case is confirmed histologically by examination of tissue obtained at surgery or by biopsy. On the basis of a 19-year follow-up survey of study subjects since their examination, only 1.3% of the men could not be located on Oahu. As a result, the surveillance for incidence cases of cancer should be nearly complete. The present analysis is based on follow-up through November 30, 1991.

Assay of SUA (nonfasting) was by the Auto-Analyzer N-13B method, using a phosphotungstic acid reagent. Details of this analytic method have been published previously (14). SUA measurement for each subject was based on a single sample, and was part of a larger test battery that included measurement of hematocrit as well as nonfasting serum cholesterol and triglyceride levels. A single laboratory, observing strict quality-control procedures, was used throughout the study.

The present analysis was based on total cancer incidence, as well as the incidence of the several specific cancers for which adequate numbers of cases were available: prostate, stomach, colon, rectum, lung, and hematopoietic tumors. The latter group was included because other reports had suggested that SUA might be associated with lymphomas and leukemias.

Of the original cohort of 8006 men, 35 were excluded because of missing SUA values and 82 had an existing cancer at the time of the initial examination. Thus, a total of 7889 men were included in the present analysis, of whom 2528
Serum Uric Acid and Cancer Incidence

Table 1  Mean level of serum uric acid by age at exam

<table>
<thead>
<tr>
<th>Age at exam</th>
<th>No. of men</th>
<th>Mean serum uric acid (mg/dl)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-49</td>
<td>1846</td>
<td>6.08</td>
<td>1.47</td>
</tr>
<tr>
<td>50-54</td>
<td>2751</td>
<td>6.04</td>
<td>1.51</td>
</tr>
<tr>
<td>55-59</td>
<td>1565</td>
<td>5.93</td>
<td>1.53</td>
</tr>
<tr>
<td>60-64</td>
<td>1308</td>
<td>5.85</td>
<td>1.52</td>
</tr>
<tr>
<td>65-69</td>
<td>419</td>
<td>6.04</td>
<td>1.54</td>
</tr>
</tbody>
</table>

Results

Mean SUA levels by 5-year age groups (45–69 years) are presented in Table 1. As seen in the table, mean levels decrease with age, except in the oldest group (age 65–69).

Table 2 shows the number of cases and the mean SUA level for selected cancer sites. There are no statistically significant differences between the mean levels for the cancer cases and noncases.

Table 3 shows odds ratios for cancer by quartile of SUA. These analyses were run with adjustment for age, first without and then with additional adjustment for the several potential confounders noted earlier in METHODS. Except for body mass index with colon cancer, alcohol with rectal cancer, cigarette smoking with lung and bladder cancers, and both smoking and alcohol consumption with all cancer sites combined, these additional adjustments had little effect on the observed risk ratios and thus are not included in the table. Only prostate cancer shows a significant linear trend (positive) in these data.

We considered the possibility that SUA levels may be altered by preexisting subclinical disease at the time of the SUA measurement. As shown in Table 4, removal of prostate cancer cases diagnosed in the first 2 years after examination did not eliminate the effect. (Similarly, the findings for the other cancer sites were unaffected by the removal of cases diagnosed in the first 2 years.) Because occult tumors are unusually common in prostate cancer and may be present for many years, we repeated the analysis eliminating all cases diagnosed up to 20 years after initial examination. The positive association persisted up to 10 years, was somewhat attenuated after 15 years, and disappeared completely after 20 years (Table 4).

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Uric acid is a powerful antioxidant quencher of singlet oxygen and is at least as potent as ascorbate (8). Indeed, one action of urate appears to be the stabilization of ascorbate in biological fluids (19). Because normal levels of SUA are substantially greater than those of ascorbate (8), SUA is potentially more important as an antioxidant in normal physiology. Nevertheless, we were unable to show any inverse association of SUA with cancer in this population of Japanese men in Hawaii. Instead, we found a positive association between antecedent SUA and subsequent development of prostate cancer within an interval of 10–15 years. A positive relationship was not found for SUA and any other cancer site examined.

Previous studies of the relationship of serum uric acid to cancer risk have yielded inconsistent findings. Some earlier investigations examined cancer mortality rather than incidence. Petersson and Trel
t (10) and Petersson et al. (20) found a positive association of SUA with total mortality (attributed entirely to cancer deaths, however) in a cohort of more than 7700 men in Malmo, Sweden. In their cohort, the association was limited to cases occurring in the first 2.5 years of follow-up, suggesting an effect of preclinical disease. They did not report the findings for specific cancer sites.

In a cohort of women, Levine et al. (11) found a positive association of SUA with total cancer mortality among the group who were 55–64 years of age, but no relationship in women at younger ages. No specific site seemed to account for this finding, nor did it appear to be a result of preclinical disease. In another study of women, Bengtson et al. (12) also found a positive association of SUA with total mortality, independent of age, body mass index, systolic blood pressure, smoking, serum cholesterol, triglycerides, creatinine, or calcium, etc. However, the increase in overall mortality could not be attributed to cancer per se.

In the only other report based on cancer incidence data in a prospective cohort, Hiatt and Fireman (13) found no association of SUA with cancer incidence after adjustment for age, race, education, smoking, alcohol intake, and body mass index. Their study, based on a cohort of 163,830 men and women, is the most comprehensive report to date on the relationship of SUA to cancer occurrence. Thus, although the literature is somewhat conflicting, there is little support for the hypothesis that SUA protects against cancer because of its antioxidant properties.

SUA levels are influenced both by endogenous production and by ingestion. It is estimated that perhaps up to 50%, but not more, of total SUA may be determined by diet (21). Such foods as organ meats (notably sweetbreads and liver), mussels, sardines, and sausages contain high amounts of purines that lead to the formation of uric acid (22, 23). In an earlier analysis on this cohort (24), we examined the relationship of foods and nutrients to prostate cancer risk. The only significant positive association with a food or food group was with seaweed, which is not an important source of uric acid. There was no association with meat intake or other major uric acid food sources. There were also no positive associations with any nutrients, including protein and fat.

The positive association between SUA and prostate cancer was an unexpected finding. Because the association was stronger when restricted to cases occurring in the first 10 years only (data not shown) and disappeared when cases occurring up to 20 years from SUA measurement were eliminated, it is possible that the SUA elevations reflect rapid cell turnover in preclinical diseased tissue. This explanation certainly could account for the elevated SUA levels that have been reported in patients who already have prostate cancer compared with controls (25). However, 20 years is an unusually long preclinical period for the manifestation of such an effect. Although the growth of occult prostate lesions may be particularly slow, it is somewhat difficult to conceive that the amount of abnormal prostate tissue present up to 20 years before clinical disease could yield sufficient cell turnover to generate elevations of SUA.

We considered possible biases in the data that might account for this finding. The blood specimen collections and the SUA measurement in the laboratory followed standard protocols and many other analyses of this dataset have yielded serum findings that are consistent with other reports in the literature (26–28). In addition, the number of prostate cases (a total of 293) was reasonably large, reducing the possibility that the finding occurred by chance.

We also considered the possibility of a bias as a result of the use of medications to lower SUA. If SUA actually protects against prostate cancer, then the lowering of SUA levels could increase risk. Thus, if a substantial proportion of the men with high SUA levels subsequently reduced their levels by medical intervention, a positive association of SUA with prostate cancer could be seen. We had data on the use

![Table 4](https://example.com/table4.png)

**Table 4** Relative risk of prostate cancer by quartile of serum uric acid at entry and interval to diagnosis

<table>
<thead>
<tr>
<th>Interval to diagnosis</th>
<th>Serum uric acid level (mg/dl)</th>
<th>No. of cases</th>
<th>Relative risk (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 yr</td>
<td>≤5.0</td>
<td>60</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.1–6.0</td>
<td>94</td>
<td>1.5 (1.1–2.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.1–7.0</td>
<td>69</td>
<td>1.4 (1.0–2.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥7.1</td>
<td>65</td>
<td>1.6 (1.1–2.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>&gt;5 yr</td>
<td>≤5.0</td>
<td>58</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.1–6.0</td>
<td>89</td>
<td>1.4 (1.0–2.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.1–7.0</td>
<td>66</td>
<td>1.4 (1.0–1.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥7.1</td>
<td>64</td>
<td>1.6 (1.1–2.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;10 yr</td>
<td>≤5.0</td>
<td>53</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.1–6.0</td>
<td>80</td>
<td>1.4 (1.0–2.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.1–7.0</td>
<td>60</td>
<td>1.3 (0.9–2.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥7.1</td>
<td>56</td>
<td>1.5 (1.0–2.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt;15 yr</td>
<td>≤5.0</td>
<td>42</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.1–6.0</td>
<td>56</td>
<td>1.2 (0.8–1.8)</td>
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</tr>
<tr>
<td></td>
<td>6.1–7.0</td>
<td>43</td>
<td>1.2 (0.8–1.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥7.1</td>
<td>45</td>
<td>1.5 (1.0–2.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>&gt;20 yr</td>
<td>≤5.0</td>
<td>22</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.1–6.0</td>
<td>21</td>
<td>0.8 (0.5–1.5)</td>
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</tr>
<tr>
<td></td>
<td>6.1–7.0</td>
<td>15</td>
<td>0.8 (0.4–1.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥7.1</td>
<td>16</td>
<td>0.9 (0.5–1.8)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**Discussion**

Measurement of SUA is a routine procedure with repeatable results in clinical laboratories. Although short-term fluctuations in SUA levels occur within individuals, these differences are not significant and there is no diurnal pattern (18). Average levels are higher in males than in females but the levels do not increase with age, as confirmed in our data (Table 1).

Uric acid is a powerful antioxidant quencher of singlet oxygen and is at least as potent as ascorbate (8). Indeed, one action of urate appears to be the stabilization of ascorbate in biological fluids (19). Because normal levels of SUA are substantially greater than those of ascorbate (8), SUA is potentially more important as an antioxidant in normal physiology. Nevertheless, we were unable to show any inverse association of SUA with cancer in this population of Japanese men in Hawaii. Instead, we found a positive association between antecedent SUA and subsequent development of prostate cancer within an interval of 10–15 years. A positive relationship was not found for SUA and any other cancer site examined.

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of such medications from a subsequent examination of these men approximately 6 years after the SUA measurements. Only a small proportion (6.5%) took any uric acid-lowering drugs. Although prostate cancer occurred in a higher proportion of the men who took these medications (4.6%) compared with the men who did not (3.9%), this difference was not statistically significant and seems unlikely to account for the overall positive association.

If elevated SUA is a true risk factor for prostate cancer, it may be an indirect reflection of the metabolism of androgens (particularly testosterone and its derivative dihydrotestosterone), which have been implicated in prostate cancer risk (29). These hormones are associated with increases in muscle mass, and we showed earlier a positive association between muscle mass of the upper arm and prostate cancer risk (30). If increased muscle mass results in greater tissue turnover and DNA catabolism, then serum levels of uric acid could be increased by this mechanism. Although we know of no direct evidence that muscle mass is associated with SUA level, it is of note that men with higher SUA levels than women and that men with an endomorphic somatotype tend to have higher values than men with an ectomorphic somatotype (18).

In an earlier multiethnic case-control study in Hawaii (31), we found that the intake of carotenoids (which, like uric acid, are also antioxidants) was positively associated with prostate cancer risk. In that study, we isolated the finding to a greater consumption by the cases of papaya, a fruit containing significant amounts of β-cryptoxanthin (32). It has been shown that retinoids and carotenoids can have tumor-promoting, as well as tumor-inhibiting, effects on cancer in animal models (33). Although uric acid also might have such opposite effects, we know of no evidence in this regard.

In conclusion, the present findings do not support the hypothesis that SUA protects against cancer occurrence. The positive association with prostate cancer may be related to preclinical disease, but merits further study.

Acknowledgments
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