Vitamin A and Prostate Cancer in Elderly Men: Enhancement of Risk

Laurence N. Kolonel,1 Jean H. Hankin, and Carl N. Yoshizawa

Epidemiology Program, Cancer Research Center, University of Hawaii, Honolulu, Hawaii 96813

ABSTRACT

Vitamin A intake was assessed from dietary histories on 452 men with prostate cancer and 899 population controls in Hawaii during the period 1977–1983. In the group of men <70 years of age, there were no significant associations of this nutrient with risk for prostate cancer. In the men ≥70 years, however, risk increased directly with the amount of vitamin A consumed (relative risk of 2.0 for the highest relative to the lowest intake quartile, and a significant linear trend, P < 0.01). The findings were similar for the various components of vitamin A but were somewhat stronger for total carotenoids than for total retinol. These results were generally consistent across the five ethnic groups and were not affected by statistical adjustment for dietary fat. Possible mechanisms for this risk enhancement by vitamin A in elderly men are proposed.

INTRODUCTION

Epidemiological studies of several different cancer sites have found reduced risks for cancer associated with increased consumption of vitamin A (1). However, two studies of prostate cancer reported an opposite effect. Graham et al. (2) found that the risk for prostate cancer increased directly with the level of intake of vitamin A in men at all ages, although the trend was stronger in those 70 years and older. Heshmat et al. (3) found higher mean intakes of vitamin A in cases compared with controls, but the differences were greater in younger men (ages 35–50 years). We recently carried out a larger case control study of prostate cancer in the multiethnic population of Hawaii. This study was designed to test dietary hypotheses related to fat, vitamin A, and trace elements, and used a more comprehensive dietary assessment than did previous studies. The findings from this study regarding vitamin A are reported here.

MATERIALS AND METHODS

For the period 1977–1983, all histologically confirmed cases of prostate cancer among Caucasian, Japanese, Chinese, Filipino, and Hawaiian men from the seven largest hospitals on the island of Oahu were identified through the Hawaii Tumor Registry. For each case, two population controls were sought in the same 5-year age group. Controls for the cases over age 65 were randomly selected from a 10% sample of all men on Oahu who were registered with the Health Care Finance Administration. Controls for cases under age 65 were selected by a random-digit dialing procedure, as described by Waksberg (4). The group matching on age for the controls assured overlapping distributions on this factor, but adjustment for age as a continuous variable was made in the analyses. Since ethnicity was not a matching factor in the design, there was some difference in ethnic distributions between cases and controls, reflecting the ethnic variation in prostate cancer incidence in Hawaii. The main differences were a higher proportion of Caucasians and a lower proportion of Filipinos among cases than controls. Ethnicity was included as an adjustment variable in all combined analyses.

RESULTS

The analyses were based on 452 cases and 899 controls. Of the original subjects identified (730 cases and 1202 controls), 241 had to be eliminated for various reasons (including relocation outside the study area, inability to be located, mental incompetence, death and no suitable surrogate for interview, unreliable information, etc.) and an additional 110 cases were eliminated because of physician refusal (usually related to concern for the emotional state of the patient or his immediate family members). Only 13.3% of cases and 11.1% of controls actually declined interview. These response rates did not differ appreciably between younger and older subjects.

Data were available on several factors which have been variously identified in previous epidemiological studies as possibly related to risk for the disease. Although more cases than controls gave a positive history of benign prostatic hypertrophy (17.5 versus 13.9%) and of prostate cancer in a first degree relative (2.0 versus 1.2%), neither association was statistically significant. In addition, we found no statistically significant differences between cases and controls on marital status, fertility, socioeconomic status, or obesity. Thus, these variables were not included in the models for the logistic regression analyses. Correlation coefficients (Pearson's product-moment) for vitamin A intake with both total fat and vitamin C were low (r = 0.3).

Mean weekly intakes of total vitamin A and its components
VITAMIN A AND PROSTATE CANCER IN ELDERLY MEN

In order to confirm the positive association in the older men and to look for consistency of effect, we repeated the analysis in the older group (≥70 years) for each of the study’s five ethnic groups separately. Since the carotene effect was somewhat stronger than the retinol effect in Table 2, the findings for total carotenes are shown in Table 3. For this analysis, the same quartile cut points were used for each ethnic group, and these were the same as for the previous combined analysis. However, because of the small size of the Chinese and Hawaiian samples, the results for these groups are by tertiles rather than quartiles, again based on the combined data set. These data indicate that the overall increase in risk associated with this nutrient was not a reflection of only one or two of the ethnic groups. As seen in the table, the risks are generally elevated in all groups except for the Hawaiians, although the trend is clearly monotonic and statistically significant only for the Caucasians. This same consistency of effect across ethnic groups was seen in the analyses for the other components in Table 2 (data not shown).

Despite the lower risks associated with increased carotene intake levels in Hawaiians, none of these odds ratios, which are

### Table 1 Mean weekly vitamin A intake by prostate cancer cases and controls in Hawai‘i

<table>
<thead>
<tr>
<th>Vitamin A component (× 10^3)</th>
<th>Age group &lt;70 yr</th>
<th>Age group ≥70 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (N = 189)</td>
<td>Controls (N = 391)</td>
<td>Cases (N = 263)</td>
</tr>
<tr>
<td>Total vitamin A</td>
<td>77.2</td>
<td>83.5</td>
</tr>
<tr>
<td>Vitamin A (μg)</td>
<td>9.6</td>
<td>10.5</td>
</tr>
<tr>
<td>Carotenes (μg)</td>
<td>32.3</td>
<td>34.6</td>
</tr>
<tr>
<td>Beta-carotene (μg)</td>
<td>22.1</td>
<td>23.7</td>
</tr>
<tr>
<td>Other carotenes (μg)</td>
<td>10.2</td>
<td>10.9</td>
</tr>
</tbody>
</table>

* Adjusted for age and ethnicity by multiple covariance analysis.
* Includes supplement use.

### Table 2 Odds ratios* for prostate cancer by vitamin A intake level

<table>
<thead>
<tr>
<th>Intake quartile</th>
<th>Total vitamin A* (IU)</th>
<th>Total retinol* (μg)</th>
<th>Total carotenes</th>
<th>β-Carotene</th>
<th>Other carotenes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group ≥70 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (low)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>1.4 (0.9, 2.2)</td>
<td>1.0 (0.6, 1.5)</td>
<td>1.5 (1.0, 2.3)</td>
<td>1.2 (0.8, 1.9)</td>
<td>1.0 (0.9, 2.1)</td>
</tr>
<tr>
<td>3</td>
<td>1.3 (0.8, 2.0)</td>
<td>1.2 (0.8, 1.9)</td>
<td>1.6 (1.0, 2.5)</td>
<td>1.5 (0.9, 2.3)</td>
<td>1.4 (0.9, 2.2)</td>
</tr>
<tr>
<td>4 (high)</td>
<td>2.0 (1.3, 3.1)</td>
<td>1.4 (0.9, 2.1)</td>
<td>1.6 (1.0, 2.5)</td>
<td>1.5 (0.9, 2.3)</td>
<td>1.6 (1.0, 2.5)</td>
</tr>
<tr>
<td><em>P &lt; 0.01</em></td>
<td><em>P = 0.10</em></td>
<td><em>P = 0.08</em></td>
<td><em>P = 0.09</em></td>
<td><em>P = 0.08</em></td>
<td></td>
</tr>
<tr>
<td>Age group &lt;70 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (low)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>1.3 (0.8, 2.1)</td>
<td>0.8 (0.5, 1.4)</td>
<td>1.2 (0.7, 1.9)</td>
<td>1.5 (0.9, 2.4)</td>
<td>1.4 (0.9, 2.3)</td>
</tr>
<tr>
<td>3</td>
<td>1.0 (0.6, 1.6)</td>
<td>1.1 (0.7, 1.9)</td>
<td>1.1 (0.7, 1.8)</td>
<td>1.1 (0.7, 1.9)</td>
<td>1.1 (0.7, 1.8)</td>
</tr>
<tr>
<td>4 (high)</td>
<td>0.8 (0.5, 1.3)</td>
<td>0.9 (0.6, 1.5)</td>
<td>0.9 (0.5, 1.4)</td>
<td>1.0 (0.6, 1.6)</td>
<td>0.9 (0.5, 1.5)</td>
</tr>
<tr>
<td><em>P = 0.16</em></td>
<td><em>P = 0.82</em></td>
<td><em>P = 0.48</em></td>
<td><em>P = 0.55</em></td>
<td><em>P = 0.32</em></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age and ethnicity by multiple logistic regression analysis.
* Includes supplement use.
* Reference category.
* Numbers in parentheses, 95% confidence limits.
* Linear trend test.

### Table 3 Odds ratios* for prostate cancer by carotenoid intake level and ethnicity in men ≥70 years of age

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Caucasian (71;107)</th>
<th>Japanese (103;193)</th>
<th>Filipino (40;122)</th>
<th>Hawaiian (21;27)</th>
<th>Chinese (28;59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intake quartile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (low)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>1.0 (0.4, 2.4)</td>
<td>1.8 (0.8, 3.9)</td>
<td>2.7 (1.0, 7.5)</td>
<td>0.3 (0.1, 1.4)</td>
<td>2.2 (0.8, 6.4)</td>
</tr>
<tr>
<td>3</td>
<td>1.1 (0.5, 2.6)</td>
<td>1.6 (0.8, 3.5)</td>
<td>3.4 (1.1, 10.7)</td>
<td>0.4 (0.1, 1.9)</td>
<td>1.6 (0.5, 5.4)</td>
</tr>
<tr>
<td>4 (high)</td>
<td>2.5 (1.0, 6.3)</td>
<td>2.1 (1.0, 1.1)</td>
<td>1.1 (0.4, 3.4)</td>
<td><em>P = 0.03</em></td>
<td><em>P = 0.10</em></td>
</tr>
</tbody>
</table>

* Adjusted for age by multiple logistic regression analysis.
* Includes β-carotene and other carotenoids.
* Reference category.
* Numbers in parentheses, number of cases; number of controls.
* Intake categorized into tertiles.
* Numbers in parentheses, 95% confidence limits.
* Linear trend test.

For cases and controls are shown in Table 1. For men under 70 years of age (43% of the study sample), consumption levels are lower for the cases than for the controls, although none of these differences is statistically significant. For the older men, however, mean intakes are greater for the cases than for the controls. For total vitamin A, this difference is statistically significant, and for the carotene components, the difference is of borderline significance, but for retinol the difference is not significant.

Table 2 shows the odds ratios based on multiple logistic regression for increasing levels (quartiles) of intake of the various vitamin A components. In the younger men (<70 years), there are no significantly reduced or elevated risks and no significant trends. In the older men, however, there is a significant trend of increasing risks with total vitamin A intake, and the odds ratio for the fourth quartile (2.0) is also significantly elevated. The analyses for the components of total vitamin A show similar relationships, although the findings for total carotenoids are somewhat stronger than for total retinol. An analysis of vitamin C did not result in any significantly elevated or reduced risks and no significant trends for either of the two age groups.

In order to confirm the positive association in the older men and to look for consistency of effect, we repeated the analysis in the older group (≥70 years) for each of the study’s five ethnic groups separately. Since the carotene effect was somewhat stronger than the retinol effect in Table 2, the findings for total carotenes are shown in Table 3. For this analysis, the same quartile cut points were used for each ethnic group, and these were the same as for the previous combined analysis. However, because of the small size of the Chinese and Hawaiian samples, the results for these groups are by tertiles rather than quartiles, again based on the combined data set. These data indicate that the overall increase in risk associated with this nutrient was not a reflection of only one or two of the ethnic groups. As seen in the table, the risks are generally elevated in all groups except for the Hawaiians, although the trend is clearly monotonic and statistically significant only for the Hawaiians. This same consistency of effect across ethnic groups was seen in the analyses for the other components in Table 2 (data not shown). Despite the lower risks associated with increased carotene intake levels in Hawaiians, none of these odds ratios, which are

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based on very small numbers, is statistically significant.

In order to examine more carefully the interaction of age with the vitamin A-prostate cancer association, we repeated the analyses of Table 2 for different 5-year age categories. The direct association between vitamin A and prostate cancer was not present in any age group below 70 years and showed a progressive increase in magnitude with age above 70 years. We also looked separately at vitamin A supplement use. Vitamin A supplements (only retinol during the period of this study) were used by 43.8% of cases and 42.6% of controls, and these rates did not differ significantly between the younger and older groups of subjects.

Because dietary fat was also positively associated with prostate cancer risk in our study (data not shown), we repeated the analyses of Table 2 with further adjustment for dietary fat. However, none of the odds ratios was significantly altered by this additional adjustment. We also repeated the analyses of Table 2 eliminating those subjects who were interviewed by proxy (15.0% of cases; 10.9% of controls), and the results were virtually unchanged.

**DISCUSSION**

The results of this study clearly indicate a differential effect of dietary vitamin A on prostate cancer risk according to the age of the subjects. In the study by Graham et al. (2), a similar, positive association was seen, and although it was present in both younger (<70 years) and older (≥70 years) men, the dose-response trend was statistically significant only in the older group. On the other hand, Heshmat et al. (3) found the association to be stronger in younger men, based on a dichotomization of the study population at 50 years. In contrast, our study clearly shows the effect to be restricted to older men. As noted previously, when we examined the data in 5-year age groups, the vitamin A effect first appeared in the 70- to 74-year group and then persisted, with a progressive increase in magnitude, to the oldest group.

It does not seem likely that an artifact in our data is responsible for this age-related effect. To create the result we see, not only would there have to be a difference in reporting of dietary histories between younger and older men, but within the older group, there would have to be a differential response between cases and controls. Furthermore, we have used the same methodology in other studies, notably a case control study of vitamin A and lung cancer (10), in which we found an inverse association between vitamin A intake and cancer that was equally evident in younger and older men.

The observation of a direct association between vitamin A and prostate cancer is consistent in all three epidemiological studies that attempted to assess the intake of this nutrient per se. Furthermore, a recent updated analysis of the data from a very large prospective cohort of men in Japan revealed that the previously reported protective effect of green and yellow vegetables (11) did not persist in men older than 74 years, among whom the trend was in the opposite direction (12). Although two other studies suggested a possible protective effect (13, 14), these investigations only reported the frequency of consumption of certain foods (particularly carrots) and did not separately analyze the data for the older men.

Although this apparent enhancement effect of vitamin A on prostate cancer risk in older men requires further study, the enhancement of carcinogenesis by vitamin A in animal models is well known (15–17). This effect appears to influence tumor progression rather than the early stages of carcinogenesis (18). Prostatic carcinoma is unique among human cancers in that the prevalence of occult tumors is remarkably high. In high risk populations, such as Swedes or Caucasians and Blacks in the United States, the prevalence may exceed 40% in men above the age of 70 years (19, 20). The age-specific incidence curve in such populations is exponential in shape, with a marked increase in the slope above age 70. Thus, if vitamin A causes progression of occult tumor foci so that they are more likely to become clinically manifest, then this effect would be most apparent in the elderly men.

The mechanism for such an effect is not yet established. However, in rats, and possibly in man, vitamin A appears to play a role in testosterone synthesis (21). If vitamin A increases endogenous levels of this hormone, which may mediate the development of prostate cancer (22), this effect may be more significant in older men whose natural levels of testosterone are declining. Zumoff et al. (23) have even proposed that the etiology of prostate cancer may be different in older and younger men.

Other mechanisms for this enhancement of prostate cancer risk by vitamin A can be suggested. One possibility is an interaction of vitamin A with zinc, which may play a role in the development of prostate cancer (24, 25). Another is a direct effect of vitamin A on the proliferation of prostatic epithelial cells. In a recent study (26), human prostate tissue obtained at surgery for benign prostatic hypertrophy was grown in defined medium in the presence of epidermal growth factor or insulin as mitogens. Under these conditions, retinyl acetate inhibited cell proliferation (or had no effect) at very low concentrations, but greatly enhanced proliferation at higher concentrations, suggesting a possible regulatory effect controlled by dose.

An alternative explanation for the increased risk associated with vitamin A needs to be considered. This is the possibility that vitamin A actually does protect against prostate cancer. If men with low intakes of vitamin A develop their disease at younger ages, then there would be a selection of men with higher vitamin A consumption in the older patients. This would result in an apparent direct association between vitamin A intake and prostate cancer. Two observations in our data argue against this explanation: (a) we should have found an inverse association with vitamin A in the younger ages, whereas we did not; (b) we should have seen a difference in the stage distribution at diagnosis between younger and older cases, since the higher vitamin A intake in the older patients would presumably contribute to slower progression of the disease. In fact, we found no difference between the two groups in the proportion of localized tumors (66.9% in men ≥70 years versus 67.4% in men <70 years), and the proportion of distant tumors was actually greater in the older men (21.7 versus 14.4%).

The inhibitory effect of vitamin A on human cancer (most notably demonstrated for lung cancer in epidemiological studies) presumably occurs because of its effect on the early stages of promotion. One cannot clearly attribute this effect to either retinol (and its role in epithelial cell differentiation) or carotenoids (and their role in deactivating reactive chemical species) although the epidemiological evidence on lung cancer seems to favor a carotene effect (27). Similarly, one cannot deny attribute the enhancement effect on prostatic carcinoma to only one of these constituents, since ours is the only report which has as yet examined these components separately. Nevertheless, our findings are stronger for the carotenoids. Because carotenoids constitute the major portion of vitamin A intake for older persons in our population, however, the tendency to see stronger effects for this component may be misleading.
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The finding by Heshmat et al. (3) of a risk enhancement effect of vitamin A in both younger and older men (but actually greater in the younger men) needs to be explained. Their study was carried out among Blacks in the United States who have the highest reported incidence of this cancer in the world (28). The prevalence of occult tumors below age 50, especially lesions (but actually greater in the younger men) needs to be explained. Their study effect of vitamin A in both younger and older men (but actually obvious. Hence, it will be important to clarify any such effects and to weigh the corresponding risks before major dietary recommendations for cancer can be made to the general public.

ACKNOWLEDGMENTS

The authors thank the physicians and staff of the following hospitals for their support of this study: Kaiser Medical Center; Kuakini Medical Center; Queen's Medical Center; Straub Clinic and Hospital; St. Francis Hospital; Castle Memorial Hospital; and Wahiawa General Hospital.

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