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Vitamin A and Prostate Cancer in Elderly Men: Enhancement of Risk[1]

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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 carotenes 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.

Each participant was interviewed at home, using a detailed questionnaire that included demographic, medical, social, occupational, and dietary information. The dietary assessment method has been described at length elsewhere (5), and was based on a quantitative history approach in which both frequency of consumption and portion size were determined. Usual intake of more than 100 food items during a typical month (or year for seasonal fruits) prior to disease onset in the cases was recorded as well as use of vitamin supplements. The same information during a corresponding time period was obtained from the controls. Proxy interviews were conducted for those subjects who were too ill to be interviewed or who had died and for whom a suitable substitute was available (usually the spouse). Data were collected from both cases and controls during the period 1980–1983.

The intake of vitamin A (and other nutrients) was computed from our food composition data base. To estimate intake levels of the separate components of vitamin A (retinol, β-carotene, and other carotenes), we used formulas published by the Food and Agriculture Organization and the National Research Council (6, 7). Mean intakes for cases and controls, statistically adjusted for age and ethnicity, were calculated using multiple covariance analysis (8). Multiple logistic regression analysis (9) was used to compute odds ratios for the vitamin A components, statistically adjusted for age and ethnicity. For these analyses, quartiles (or tertiles for certain small subsamples) of average weekly intake were obtained from the combined cases and controls, and binary indicator variables were used to compute the odds ratios. A test for linear trend in the logit of risk was performed by comparing twice the difference in log-likelihoods for models with and without a trend variable, based on a χ^2 distribution with 1 degree of freedom. The trend variable assumed the values of the quartile (or tertile) midpoints of the appropriate nutrient. The data were analyzed separately for men younger than 70 years and men 70 years or older. This was an *a priori* decision based on the report of Graham *et al.* (2) in which stronger associations for dietary variables were found for men ≥70 years.

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

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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 carotenes 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 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 Hawaii*[a]

Vitamin A component ($\times 10^3$)	Age group <70 yr			Age group ≥70 yr		
	Cases ($N = 189$)	Controls ($N = 391$)	P	Cases ($N = 263$)	Controls ($N = 508$)	P
Total vitamin A[b] (IU)	77.2	83.5	0.20	87.9	78.2	0.03
Retinol[b] (μg)	9.6	10.5	0.36	9.8	8.6	0.19
Carotenes (μg)	32.3	34.6	0.30	39.2	35.2	0.05
Beta-carotene (μg)	22.1	23.7	0.30	27.2	24.3	0.05
Other carotenes (μg)	10.2	10.9	0.30	12.0	10.9	0.08

[a] Adjusted for age and ethnicity by multiple covariance analysis.
[b] Includes supplement use.

Table 2 *Odds ratios*[a] *for prostate cancer by vitamin A intake level*

Intake quartile	Total vitamin A[b]	Total retinol[b]	Total carotenes	β-Carotene	Other carotenes
			Age group ≥70 yr		
1 (low)[c]	1.0	1.0	1.0	1.0	1.0
2	1.4 (0.9, 2.2)[d]	1.0 (0.6, 1.5)	1.5 (1.0, 2.3)	1.2 (0.8, 1.9)	1.4 (0.9, 2.1)
3	1.3 (0.8, 2.0)	1.2 (0.8, 1.9)	1.6 (1.0, 2.5)	1.5 (0.9, 2.3)	1.4 (0.9, 2.2)
4 (high)	2.0 (1.3, 3.1)	1.4 (0.9, 2.1)	1.6 (1.0, 2.5)	1.5 (0.9, 2.3)	1.6 (1.0, 2.5)
	$P < 0.01$[e]	$P = 0.10$	$P = 0.08$	$P = 0.09$	$P = 0.08$
			Age group <70 yr		
1 (low)	1.0	1.0	1.0	1.0	1.0
2	1.3 (0.8, 2.1)	0.8 (0.5, 1.4)	1.2 (0.7, 1.9)	1.5 (0.9, 2.4)	1.4 (0.9, 2.3)
3	1.0 (0.6, 1.6)	1.1 (0.7, 1.9)	1.1 (0.7, 1.8)	1.1 (0.7, 1.9)	1.1 (0.7, 1.8)
4 (high)	0.8 (0.5, 1.3)	0.9 (0.6, 1.5)	0.9 (0.5, 1.4)	1.0 (0.6, 1.6)	0.9 (0.5, 1.5)
	$P = 0.16$	$P = 0.82$	$P = 0.48$	$P = 0.55$	$P = 0.32$

[a] Adjusted for age and ethnicity by multiple logistic regression analysis.
[b] Includes supplement use.
[c] Reference category.
[d] Numbers in parentheses, 95% confidence limits.
[e] Linear trend test.

Table 3 *Odds ratios*[a] *for prostate cancer by carotene*[b] *intake level and ethnicity in men ≥70 years of age*

Intake quartile	Ethnic group				
	Caucasian (71;107)[c]	Japanese (103;193)	Filipino (40;122)	Hawaiian (21;27)	Chinese (28;59)
1 (low)[d]	1.0	1.0	1.0	1.0[e]	1.0[e]
2	1.0 (0.4, 2.4)[f]	1.8 (0.8, 3.9)	2.7 (1.0, 7.5)	0.3 (0.1, 1.4)	2.2 (0.8, 6.4)
3	1.1 (0.5, 2.6)	1.6 (0.8, 3.5)	3.4 (1.1, 10.7)	0.4 (0.1, 1.9)	1.6 (0.5, 5.4)
4 (high)	2.5 (1.0, 6.3)	2.1 (1.0, 1.1)	1.1 (0.4, 3.4)		
	$P = 0.03$[g]	$P = 0.10$	$P = 0.73$	$P = 0.26$	$P = 0.47$

[a] Adjusted for age by multiple logistic regression analysis.
[b] Includes β-carotene and other carotenes.
[c] Numbers in parentheses, number of cases; number of controls.
[d] Reference category.
[e] Intake categorized into tertiles.
[f] Numbers in parentheses, 95% confidence limits.
[g] Linear trend test.

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 prostatic 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 carotenes (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 yet 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 carotenes. Because carotenes 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.

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 demonstrating infiltrative characteristics, may be greater in high risk Blacks than in other high risk populations (19).

The implications for cancer prevention of opposing effects of a particular dietary component on different cancer sites are 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.

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