Vegetable Consumption, Serum Retinol Level, and Risk of Hepatocellular Carcinoma

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ABSTRACT

A cohort of 8436 men in Taiwan was recruited with personal interview and blood sample collection between 1984 and 1986. During the 5-year follow-up period, 50 incident cases of hepatocellular carcinoma (HCC) were identified. Retinol levels were measured for 35 HCC patients whose serum samples were available and 140 matched controls randomly selected from cohort members without HCC. Lower vegetable intake was significantly associated with an increased risk of HCC after adjustment for other HCC risk factors (P = 0.006). The effect of low vegetable intake on HCC risk was limited to hepatitis B virus chronic carriers and cigarette smokers.

As compared with subjects who had a weekly vegetable consumption frequency of six or more meals, the multivariate-adjusted relative risk of HCC for subjects who had a frequency of less than six meals was 4.7 (95% confidence interval, 2.0–11.1; P = 0.0004) among chronic hepatitis B virus carriers and 3.8 (95% confidence interval, 1.7–8.5; P = 0.001) among cigarette smokers. There was an inverse dose-response relationship between the prediagnostic serum retinol level and the development of HCC (trend test, P = 0.003). The odds ratio of HCC for men with a retinol level in the lowest tertile was 9.0 (95% confidence interval, 2.1–39.1) compared with those with a level in the highest tertile. The relation remained after multivariate adjustment for cigarette smoking, habitual alcohol drinking, and either the seropositivity of hepatitis B virus surface antigen and/or anti-hepatitis C virus antibody or the past history of liver diseases through conditional logistic regression analysis. The association was more striking for men 55 years or younger and for those who smoked 10 or more cigarettes/day. There was a significant synergistic effect of hepatitis B virus surface antigen carrier status and low serum retinol level on the development of HCC. These data suggest a potential role of retinol in the chemoprevention of HCC.

INTRODUCTION

Liver cancer, largely HCC, is one of the major cancers in Africa and Asia (1). In Taiwan, liver cancer is the most common cancer in men and the second leading cancer in women (2). Because the disease is highly malignant with an extremely poor prognosis, emphasis should be placed on preventive measures. Chronic HBV infection has been well documented as a major cause of HCC on the basis of epidemiological, molecular biological, and animal studies (1). Many other possible etiological factors, including hepatitis C virus (3, 4), aflatoxin exposure (5, 6), alcohol drinking, cigarette smoking (7–10), and elevated serum level of endogenous testosterone (11), have also been documented to play roles in the development of HCC. However, very little attention has been paid to the potential role of dietary factors besides aflatoxins in human hepatocellular carcinogenesis (7, 12).

Many epidemiological studies have suggested that an increased consumption of vegetables may prevent the development of a wide range of cancers, including carcinomas of the lung, stomach, bladder, colon, and breast (13–18). Our previous publication-based cohort study in Taiwan also reported an inverse association between vegetable intake and HCC after controlling for potential confounders (7). There is a growing body of evidence from numerous in vitro and animal studies suggesting that many constituents in vegetables have potential anticancer activity (19). These compounds can block formation and activation of carcinogens, induce detoxifying enzymes, and suppress tumor promotion/progression.

Vegetables are the principal source of retinoids (20). Retinol (vitamin A) and its analogues have been shown to suppress chemically induced carcinogenesis by a variety of mechanisms in experimental studies (19, 21–26). In humans, despite a strong epidemiological evidence for an inverse relation between intake of vitamin A and cancer (13–18), results of the studies on the association between serum retinol levels and the risk of cancer have been inconsistent (27). Although one recent hospital-based case-control study in Taiwan has shown lower serum retinol levels in HCC cases than in controls (12), this finding is difficult to interpret because the serum retinol level of subjects was measured after the diagnosis of HCC and cancer might have affected their general nutritional status and serum retinol level.

The development of HCC is a process of multiple stages with a multifactorial etiology. Both viral and chemical carcinogens are involved in the pathogenesis of HCC. Nutritional status has long been regarded as an important factor modulating cancer susceptibility. HCC may serve as an ideal disease model for studying the role of nutritional factors in virus and chemical-induced carcinogenesis. To explore the multifactorial etiology of HCC, we have assembled a large-scale population-based cohort of male adults in Taiwan. Using this cohort as study base we have demonstrated significant associations of HCC risk with anti-HCV status, cigarette smoking, alcohol drinking, and elevated serum level of endogenous testosterone (4, 7, 10, 11). The primary focus of the present work was to investigate the associations with the development of HCC for the consumption of vegetables and the serum level of retinol, with emphasis on potential impacts of vegetable intake and serum retinol level on the risk of HBV- and cigarette smoking-related HCC.

SUBJECTS AND METHODS

Study Population. The cohort characteristics and method of cancer follow-up have been described previously (11). Briefly, between September 1984 and February 1986, all men 30 years old or older who were living in six townships of Taiwan and who did not have cancer were invited to participate in a prospective study for early detection of cancer. Each subject was personally interviewed by a well-trained nurse in local health centers of study townships. The standardized interview was based on a structured questionnaire covering sociodemographic characteristics, long-term habits of cigarette smoking and alcohol drinking, as well as personal and familial history of various chronic diseases. Information on dietary habits was obtained according to a food frequency questionnaire assessing each individual’s usual frequency of consuming meat and eggs, fresh vegetables, pickled foods, and fermented bean products. A total of 15 ml blood sample was also collected from each subject on April 14, 2017. © 1995 American Association for Cancer Research.
using a disposable needle and vacuum syringe. Serum samples were separated on the same day as blood collection. Two aliquots were frozen in deep freezers and transported in dry ice to the central laboratory at National Taiwan University College of Medicine. The serum samples were kept at −30°C until examination.

A total of 9691 subjects took part in this study. All participants were annually followed up for their health status by either personal home visit or telephone interview. In order to double validate the HCC occurrence and to trace the vital status of subjects lost in the follow-up, both computerized data files of the Death Certification System and National Cancer Registry System in Taiwan were also cross-checked and linked with identification profiles of this study annually. The analysis in this report was restricted to the cancer incidence during the follow-up period from September 1984 to December 1990. The average follow-up period per person was 5.4 years. Losses of follow-up (i.e., subjects for whom no death certificates had been found and who had not responded through routine follow-up) totaled 1049 (10.8%). Subjects for whom there were no data on vegetable consumption frequency in the baseline questionnaire (124 subjects) or no available serum samples for HBsAg assay (82 subjects) at the initial recruitment examination were excluded. A total of 8436 cohort members remained available for analysis in this study. Comparisons of data from subjects included in this study with those from subjects excluded showed that the two groups were comparable with respect to all demographic characteristics and distributions of potential HCC risk factors.

During the follow-up period, 50 incident liver cancer cases were identified. In about 40% of these cases the diagnosis was based on a confirmatory pathological examination, and in about 60% on elevated α-fetoprotein level (≥400 ng/ml) combined with at least one positive image on angiography, sonography, and/or computerized tomography scans.

Among the 50 incident liver cancer cases that occurred, 35 had available serum samples for analysis of retinol level. Comparison of risk factors associated with HCC showed similar distributions in these factors between the 35 liver cancer cases and the other 15 eligible cases without stored serum samples. To evaluate the association between serum retinol level and HCC, four controls matched by age [±5 years], date of questionnaire interview and blood collection, and area of residence were selected for each of the 35 cases with available serum samples. The controls were randomly selected from cohort members who were alive and free from cancers on the dates at diagnosis of liver cancer cases to whom they were matched.

Laboratory Analyses. All subjects in the study cohort were tested for HBsAg by reverse passive hemagglutination assay at the initial recruitment examination. HBsAg carrier status of all liver cancer cases developed during the follow-up period and the non-HCC controls in the nested case-control study on serum retinol and HCC was further validated by RIA using commercial kits (Abbott Laboratories, North Chicago, IL). For the 35 liver cancer cases and 140 matched controls with available serum samples for analysis of retinol level, anti-HCV was examined in duplicate by a second generation enzyme immunoassay (Abbott Laboratories). Positive samples from the first test were retested. Only repeatedly positive samples were considered as anti-HCV positive. Retinol levels were measured by HPLC according to the procedure described by Miller et al. (28). Serum samples for each case-control set were thawed in the dim light at room temperature and assayed on the same day. All laboratory personnel were unaware of disease status of subjects whose serum samples were tested.

Statistical Analyses. The person-time under observation for each subject was defined as the period of follow-up from recruitment to the date when he was affected with liver cancer or died from other causes or to the termination date of the follow-up, i.e., December 31, 1990. Cox's proportional hazards models were used to examine the association between vegetable consumption frequency and the risk of HCC with simultaneous control for multiple potential confounders. Conditional logistic models were used to derive the matched crude and multivariate-adjusted odds ratios associated with serum retinol level. Serum retinol levels of cases and controls were categorized according to the tertile of serum retinol levels of controls. Because there were only 35 liver cancer cases with serum retinol data, in the multivariate analysis the retinol level was dichotomized using the value of the first tertile for controls as the cutoff point. Tests for trend of matched odds ratios across tertiles were performed in conditional logistic regression by assigning scores of 3, 2, and 1, respectively, to the first (low), second (medium), and third (high) tertile of serum retinol level. In the stratified data analyses on serum retinol and HCC, relative risks were estimated by unmatched odds ratios. Mantel's χ² test for a trend was used to examine the dose-response relationship. Correlations between the weekly vegetable consumption frequency and the serum retinol levels were examined by Pearson's correlation coefficient. All statistical tests were based on two-tailed probability.

RESULTS

Among the 8436 men included in the study, 22.1% were younger than 40 years old, 50.8% were between 40 and 59 years, and the remaining 27.1% were 60 or more years old. There were 66.4% cohort members who had an educational level of elementary school and lower. HBsAg was detected in 13.0% of 8436 study subjects recruited.

Vegetable Intake and HCC Risk. Subjects who had a weekly vegetable consumption frequency of less than six meals had a significantly higher risk of developing HCC than those who had a vegetable consumption frequency of six meals a week or more after adjustment for age, HBsAg carrier status, habitual alcohol drinking, cigarette smoking, and past history of liver diseases (relative risk, 2.8; 95% CI = 1.3–5.8; P = 0.006). This association was observed in HBsAg carriers but not in noncarriers. Among HBsAg carriers, there was a 4.7-fold increase in risk of developing HCC for individuals who had a weekly vegetable consumption frequency of less than six meals as compared with those who had a higher weekly consumption frequency of vegetables (95% CI = 2.0–11.1; P = 0.0004) (Table 1).

Table 2 presents the multivariate-adjusted relative risk associated with vegetable consumption frequency by cigarette smoking status. The proportion of subjects with a lower vegetable consumption frequency was significantly higher in cigarette smokers (9.1%) than in nonsmokers (6.9%) (P = 0.001). Among smokers, lower intake was significantly associated with an increased risk of HCC (P = 0.001). The multivariate-adjusted relative risk of HCC for cigarette smokers who had a vegetable consumption frequency of less than six meals a week was 3.8 (95% CI = 1.7–8.5) compared with those who had a frequency of six meals or more a week. In contrast, there was essentially no association between vegetable intake and risk of HCC among nonsmokers.

Serum Retinol Levels and Risk of HCC. The means ± SD of ages for liver cancer cases and matched controls in the nested case-control study on serum retinol levels and HCC were 59.0 ± 9.6 and 59.0 ± 9.4 years, respectively. There were 3 liver cancer cases diagnosed within 1 year, 7 diagnosed between 1 and 2 years, and 25 cases diagnosed more than 2 years after blood collection. Liver cancer cases (60.0%) had a significantly higher HBsAg carrier rate than controls (6.4%). Anti-HCV was detected in 5 of 35 (14.3%) liver cancer cases and in only 4 of 140 (2.9%) matched controls.

Table 1 Multivariate-adjusted relative risk of HCC in relation to low vegetable consumption in a cohort of 8436 men in Taiwan

<table>
<thead>
<tr>
<th>Vegetable consumption (meals/wk)</th>
<th>HCC cases</th>
<th>Subject</th>
<th>Person-yr</th>
<th>Multivariate-adjusted relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥6</td>
<td>41</td>
<td>7,733</td>
<td>42,250.0</td>
<td>1.0*</td>
</tr>
<tr>
<td>&lt;6</td>
<td>9</td>
<td>703</td>
<td>3,511.6</td>
<td>2.8 (1.3–5.8)</td>
</tr>
<tr>
<td>HBsAg carriers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥6</td>
<td>25</td>
<td>1,010</td>
<td>5,487.5</td>
<td>1.0*</td>
</tr>
<tr>
<td>&lt;6</td>
<td>7</td>
<td>83</td>
<td>410.8</td>
<td>4.7 (2.0–11.1)</td>
</tr>
<tr>
<td>HBsAg noncarriers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥6</td>
<td>16</td>
<td>6,723</td>
<td>36,762.5</td>
<td>1.0*</td>
</tr>
<tr>
<td>&lt;6</td>
<td>2</td>
<td>620</td>
<td>3,100.8</td>
<td>1.2 (0.3–5.4)</td>
</tr>
</tbody>
</table>

*Age, HBsAg carrier status, cigarette smoking, habitual alcohol drinking, and past history of liver diseases were also included in the regression model.

a Age, cigarette smoking, habitual alcohol drinking, and past history of liver diseases were also included in the regression model.
In univariate analysis, the risk of HCC increased monotonically with decreasing prediagnostic serum level of retinol (trend test, \( P = 0.003 \)). The matched odds ratios of developing HCC in the first tertile (low) to the third tertile (high) of retinol level were 9.0 (95% CI = 2.1—39.1), 3.0 (95% CI = 0.8—10.8) and 1.0, respectively (Table 3). This inverse dose-response relationship remained after exclusion of 10 matched case-control sets in which the cases were diagnosed within 2 years after blood collection (trend test, \( P = 0.032 \)). As compared with individuals with serum retinol levels in the high tertile, the matched odds ratio was 2.9 (95% CI = 0.6—14.7) and 7.0 (95% CI = 1.1—43.1), respectively, for individuals in medium and low tertile.

Conditional logistic regression analysis showed a strong association between low prediagnostic serum levels of retinol and increased risk of HCC after adjustment for the seropositivity of HBsAg and/or anti-HCV, cigarette smoking, and habitual alcohol drinking. The multivariate-adjusted odds ratio of HCC was 4.6 (95% CI = 1.0—20.7) for individuals with serum retinol levels in the low tertile compared with those having levels in medium or high tertiles (\( P = 0.048 \)). A similar result was observed when past history of liver diseases instead of HBsAg and/or anti-HCV seromarkers was included in the conditional logistic regression (odds ratio, 4.2; 95% CI = 1.4—12.2; \( P = 0.009 \)).

The odds ratio of HCC associated with decreased serum retinol level was more striking for men 55 years old or younger (Table 4). There was a significant inverse dose-response relationship between serum retinol level and HCC risk among men 55 years old or younger (trend test, \( P = 0.017 \)). However, no significant association of serum retinol level with HCC risk was observed for men older than 55 years.

Table 3 presents the combined effect of decreased serum retinol level and HBsAg carrier status on HCC risk. Although the analysis was based on a small number of HCC cases, the odds ratios suggested a strong synergistic effect between chronic HBV infection and decreased serum retinol levels. As compared with HBsAg noncarriers who had a serum retinol level in the highest tertile, the odds ratio associated with HCC was only 2.9 (95% CI = 0.1—46.5) for HBsAg carriers with serum retinol levels in the lowest tertile.

The association of serum retinol level with risk of HCC among HBsAg carriers and noncarriers are shown separately in Table 6. A significant inverse dose-response relationship between serum retinol level and HCC risk was observed for HBsAg carriers (trend test, \( P = 0.05 \)) but not for noncarriers. Table 7 presents the combined effect of decreased serum retinol level and serum retinol levels in the lowest tertile (odds ratio, 52.8; 95% CI = 7.6—488.4).

Table 2

<table>
<thead>
<tr>
<th>Vegetable consumption (meals/wk)</th>
<th>HCC cases</th>
<th>Subjecta</th>
<th>Person-yr</th>
<th>Multivariate-adjustedb relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers ≥6</td>
<td>26</td>
<td>5,007</td>
<td>27,176.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;6</td>
<td>8</td>
<td>501</td>
<td>2,467.4</td>
<td>3.8 (1.7—8.5)</td>
</tr>
<tr>
<td>Nonsmokers ≥6</td>
<td>15</td>
<td>2,723</td>
<td>15,055.7</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;6</td>
<td>1</td>
<td>201</td>
<td>1,038.2</td>
<td>0.9 (0.1—7.0)</td>
</tr>
</tbody>
</table>

*a There were four study subjects without cigarette smoking data. 

In univariate analysis, the risk of HCC increased monotonically with decreasing prediagnostic serum level of retinol (trend test, \( P = 0.003 \)). The matched odds ratios of developing HCC in the first tertile (low) to the third tertile (high) of retinol level were 9.0 (95% CI = 2.1—39.1), 3.0 (95% CI = 0.8—10.8) and 1.0, respectively (Table 3). This inverse dose-response relationship remained after exclusion of 10 matched case-control sets in which the cases were diagnosed within 2 years after blood collection (trend test, \( P = 0.032 \)). As compared with individuals with serum retinol levels in the high tertile, the matched odds ratio was 2.9 (95% CI = 0.6—14.7) and 7.0 (95% CI = 1.1—43.1), respectively, for individuals in medium and low tertile.

Conditional logistic regression analysis showed a strong association between low prediagnostic serum levels of retinol and increased risk of HCC after adjustment for the seropositivity of HBsAg and/or anti-HCV, cigarette smoking, and habitual alcohol drinking. The multivariate-adjusted odds ratio of HCC was 4.6 (95% CI = 1.0—20.7) for individuals with serum retinol levels in the low tertile compared with those having levels in medium or high tertiles (\( P = 0.048 \)). A similar result was observed when past history of liver diseases instead of HBsAg and/or anti-HCV seromarkers was included in the conditional logistic regression (odds ratio, 4.2; 95% CI = 1.4—12.2; \( P = 0.009 \)).

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Table 5 presents the combined effect of decreased serum retinol level and HBsAg carrier status on HCC risk. Although the analysis was based on a small number of HCC cases, the odds ratios suggested a strong synergistic effect between chronic HBV infection and decreased serum retinol levels. As compared with HBsAg noncarriers who had a serum retinol level in the highest tertile, the odds ratio associated with HCC was only 2.9 (95% CI = 0.1—46.5) for HBsAg carriers with serum retinol levels in the lowest tertile (odds ratio, 52.8; 95% CI = 7.6—488.4).
DISCUSSION

Taiwan is a hyperendemic area of HBV infection with a HBsAg carrier rate as high as 15–20% (3, 8). HBV has been well documented as the most important determinant of HCC in Taiwan (1–3, 7, 8). Although a majority of HCC cases are attributable to chronic HBV infection, HCC is not an inevitable consequence of chronic infection with HBV. There are only a fraction of chronic HBV carriers who are affected with HCC during their lifetime. The onset age of HCC among chronic HBV carriers also varies over a wide range from younger than 10 to older than 80 years old. These facts indicate that other environmental risk factors and individual susceptibility are contributory to the occurrence of HCC among HBV carriers.

Our previous studies have demonstrated a significant synergistic effect of HBsAg carrier status with HCV infection (3), alcohol drinking, and cigarette smoking on the development of HCC (8). This study showed a 4.7-fold increased risk of HCC for HBsAg carriers who had a weekly vegetable consumption frequency of less than six meals compared with those who had a frequency of six or more meals after adjustment for other HCC risk factors. Based on the population attributable risk percentage estimated in this study, increasing intake for vegetables may result in an approximate 20% reduction of HCC among HBsAg carriers. In contrast, low vegetable consumption does not appear to be a significant risk factor of HCC for HBsAg noncarriers. There was also a much higher HCC risk associated with low prediagnostic serum level of retinol for HBsAg carriers than for noncarriers in this study. The relative risk of developing HCC for HBsAg carriers with serum retinol levels in the lowest tertile was 18 times higher than the risk for HBsAg carriers having levels in the highest tertile. These results provide the most important evidence thus far for the interaction of chronic HBV infection with nutritional factors in the development of HCC.

Dietary vitamin A deficiency enhances tobacco carcinogenesis in experimental animals (23). Previous prospective study has also shown that the relative risk of lung cancer in relation to dietary intake of provitamin A which can be metabolic precursors of retinol in vivo depends on cigarette smoking status (13). According to our data, lower vegetable consumption was significantly associated with an increased risk of HCC among cigarette smokers, but this association was not present in nonsmokers. The relative HCC risk associated with low serum retinol levels for men who smoked 10 or more cigarettes/day was much more striking than that for those who smoked less than 10 cigarettes a day or never smoked. These data are compatible with previous animal study and implicate that low intake of vegetables and/or low serum retinol may render cigarette smokers more susceptible to hepatocarcinogenesis.

There was much controversy about the relation between cigarette smoking and HCC risk in the past. However, most recent studies have implicated that cigarette smoking is a major nonviral risk factor for HCC (7–9). The biological mechanism by which cigarette smoking acts in the development of HCC is not completely known. An increased expression of neu oncoprotein was found to be correlated with cigarette smoking during hepatocarcinogenesis in our previous nested case-control study (10). In this study, cigarette smokers had a lower intake of vegetables than nonsmokers. A higher proportion of HCC cases who smoked 10 or more cigarettes/day had a lower prediagnostic serum retinol level than those who smoked less than 10 cigarettes/day or never smoked. It was also observed that low serum retinol levels were correlated with low consumption of vegetables. These results implicate that the low intake of vegetables and thus a low serum level of retinol may also be important in the induction of HCC by cigarette smoking.

The measurement of vegetable intake in this study might be subject to potential errors in reliability or validity. However, since this study was based on a prospective study design, the biased assessment of vegetable consumption may not be associated with the disease status. In other words, any misclassification of vegetable consumption status in this study was likely to be random and only lead to an underestimate of any true association. Although there was no established mechanism for the association between low vegetable consumption and HCC, many nutritional constituents present in vegetables have been shown to modulate the multistage process of carcinogenesis (19). Retinol occurs naturally only in certain foods of animal origin. The principal sources of retinol in most people are dark green leafy vegetables and certain yellow and red fruits and vegetables rich in various kinds of carotenoids that can be converted to retinol by the human body (20). Retinol and its synthetic analogues (defined as retinoids) are involved in a broad spectrum of physical and pathological events (19, 21, 22). A wealth of data have been available on the modulatory roles of retinoids in chemical carcinogenesis and their cancer chemoprevention properties (19, 21–26). Retinol exerts a hormone-like control of normal cellular differentiation and proliferation in essentially all epithelia (22), decreases the expression of certain oncoproteins (24), inhibits cells from DNA damage, and modulates the metabolism of chemical carcinogens (23, 25, 26). Dietary supplementation with retinoids has been shown to decrease the frequency of spontaneous and chemical carcinogen-induced HCC in experimental animals (29, 30).

Serum retinol levels are of particular interests because they provide the closest approximation to the exposure of retinol at the cellular level that are currently available. This study revealed a significant inverse association between prediagnostic serum retinol level and HCC risk. Although the serum retinol levels of subjects in this study were determined before the clinical diagnosis of HCC was made, early HCC may influence the serum retinol levels due to changes in dietary habits or physical conditions of HCC patients with early symptoms. Only three HCC cases occurred within the first year of follow-up. More than 70% of the HCC cases in this study were diagnosed more than 2 years after blood collection. The association between serum retinol level and HCC risk was unchanged after exclusion of patients with HCC diagnosed within 2 years after blood collection. This suggests that there may be little influence of the preclinical cancer on serum levels of retinol in this study.

On the other hand, human liver is the storehouse for vitamin A. Abnormal liver function may result in changing the retinol levels in liver tissues and blood. Most HCC patients in Taiwan are chronic HBV carriers. Chronic hepatitis, liver cirrhosis, and HCC may be successive sequela of chronic HBV infection. Because lower serum retinol levels remained significantly associated with a higher risk of HCC after adjustments were made for past history of liver diseases or for HBsAg and/or anti-HCV seromarkers, it is unlikely that the inverse association of serum retinol level with HCC observed in this study was a result of chronic liver diseases.

The relative HCC risk associated with low serum retinol levels was more striking for men 55 years or younger than for men older than 55 years old. Whether low serum retinol may shorten the induction period of hepatocarcinogenesis and thus accelerate the development of HCC requires further study. There is a remarkable geographic variation in HCC incidence throughout the world. High risk areas cluster in tropical Africa and Southeast Asia where HCC commonly affects young individuals (1). In these areas, not only are chronic HBV infection and aflatoxin exposure very prevalent but there are also malnourishing conditions. In addition to chronic HBV infection and aflatoxin exposure, dietary deficiency has also long been regarded as a risk factor of HCC in these areas.
However, there have been relatively few epidemiological studies to examine the association between dietary factors other than aflatoxins and HCC. In this study, a significant role of low serum retinol level was observed in the development of HBV-related HCC. This finding suggests that dietary modification may be important for HCC control in high incidence areas. Our previous in vitro study has also observed that retinol was a potent inhibitor of the formation of aflatoxin B1-DNA adducts (31). Whether serum retinol may play a role in aflatoxin-induced HCC deserves further evaluation.

REFERENCES

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