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Vitamin Intake and Liver Cancer Risk: A Report From Two Cohort Studies in China

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Background Epidemiologic studies on the relationship between vitamin intake and liver cancer risk are sparse and inconsistent.

Methods We evaluated vitamin intake from diet and supplements and risk of liver cancer in 132 837 women and men from China who were recruited into the Shanghai Women's Health Study from 1997 to 2000 or the Shanghai Men's Health Study from 2002 to 2006. In-person interviews, using a validated food-frequency questionnaire, were conducted to collect data on dietary habits. Follow-up consisted of in-person surveys and record linkage. Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazard models with adjustment for potential confounders to compare liver cancer risk among participants with high vs low vitamin intake. All statistical tests were two-sided.

Results After excluding the first 2 years of follow-up, 267 participants (including 118 women and 149 men) developed liver cancer during an average of 10.9 (Shanghai Women's Health Study) or 5.5 (Shanghai Men's Health Study) years of follow-up. Dietary vitamin E intake was inversely associated with liver cancer risk (P_{trend} = .01), as was vitamin E supplement use (hazard ratio = 0.52, 95% confidence interval = 0.30 to 0.90). This association was consistent among participants with and without self-reported liver disease or a family history of liver cancer. Vitamin C and multivitamin use was associated with increased risk among participants with self-reported liver disease or family history of liver cancer, whereas intake of vitamin C and other vitamins from dietary sources was unrelated to liver cancer risk.

Conclusions Vitamin E intake, either from diet or supplements, may reduce the risk of liver cancer.

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Liver cancer is the fifth most common cancer in men and the seventh in women worldwide. Approximately 85% of liver cancers occur in developing countries, and 54% occur in China (1). Prognosis of liver cancer is poor with an overall 5-year survival rate of less than 15%, making it the third most common cause of cancer mortality worldwide (1,2).

Chronic infection with the hepatitis B virus (HBV) is the most important risk factor for liver cancer in humans, which is endemic in regions of Africa and Asia, especially in China (3–5). Chronic infection with hepatitis C virus (HCV) is another major risk factor for liver cancer and is more prevalent in developed countries where the rates of infection with HBV are relatively low (3–5). Other established etiological factors for liver cancer include long-term exposure to aflatoxin and chronic alcoholism leading to chronic liver disease (3–5). The former plays a prominent role in high-risk areas such as China and Africa (3–5). Other suspected potential risk factors for liver cancer include body fatness, diabetes and insulin resistance, and use of oral contraceptives (3–5).

Persistent inflammation caused by HBV or HCV infection can cause DNA damage, promote cancer cell growth, and is believed to be one mechanism involved in hepatocarcinogenesis (5). Dietary factors such as vitamin A and E, iron, copper, zinc, and selenium may influence susceptibility of the host to persistent infection (5,6) and thus reduce the risk of liver cancer. However, epidemiological studies evaluating the relationship between dietary factors and risk of liver cancer are few in number. In this study, we examined whether dietary vitamin intake or use of vitamin supplements was related to liver cancer risk in two large, population-based, prospective cohorts of women and men from China.

Materials and Methods

Study Population

Participants included in this study were enrolled in either the Shanghai Women's Health Study (SWHS) or the Shanghai Men's Health Study (SMHS). Details regarding the designs and methods used in these studies have been published elsewhere (7–10). Briefly, 74 941 women aged 40–70 years (response rate = 92.7%) at recruitment were enrolled in the SWHS between March 1, 1997 and May 31, 2000. SMHS recruitment was conducted from April 1, 2002

to June 30, 2006, and 61 491 men (response rate = 74.1%) aged 40–74 years with no history of cancer at recruitment were enrolled.

Participants were interviewed in person using a structured questionnaire to obtain information about demographic characteristics, lifestyle, dietary habits (including supplemental use of vitamins and calcium), medical history, occupational history, and physical activity. Anthropometrics, including weight, height, and circumferences of the waist and hips, were also measured at baseline. All participants provided written informed consent. Both studies were approved by the relevant Institutional Review Boards for human research at all participating institutes.

Assessment of Dietary Intake

Semi-quantitative food-frequency questionnaires (FFQs), designed to assess usual food intake, were implemented at the baseline survey and the first follow-up survey conducted 2–3 years after baseline (8,9). The SWHS FFQ included 77 food items, which included about 90% of commonly consumed food items in urban Shanghai in 1996 (8). The SMHS FFQ included 81 food items and covered 89% of the commonly consumed foods in Shanghai at the time of the baseline survey (9). During the in-person interviews, each participant was first asked, on average, how often he or she had consumed a specific food or food group during the 12-month time period before the interview (the possible categories were daily, weekly, monthly, yearly, or never), followed by a question on the amount consumed in liang (1 liang = 50 g) per unit of time. Each participant was also asked about whether he or she had taken vitamins A, B, C, or E; a multivitamin; or calcium supplements at least 3 times per week continuously for more than 2 months. Total energy and nutrient intakes for each food were calculated by multiplying the amount of food consumed by energy or nutrient content per gram of the food, as obtained from the Chinese Food Composition Tables (11). Total dietary intake of each nutrient was calculated by summing the nutrients from all food items reported in the FFQ. The validity and reproducibility of the questionnaires used in the SWHS and SMHS have been described elsewhere (8,9). The correlation coefficients for micronutrients between the FFQ and the means of twenty-four 24-hour dietary recalls (the recalls were conducted twice per month during a 12-month period) were Pearson r = 0.41–0.59 in women (8) and Spearman r = 0.33–0.58 in men (12 monthly 24-hour dietary recalls were implemented in the SMHS) (9).

Follow-up and Cancer Identification

Cohort members were followed for cancer occurrence through in-person follow-up surveys taking place every 2–3 years and annual record linkage with databases of the population-based Shanghai Cancer Registry, Shanghai Vital Statistics Registry, and Shanghai Resident Registry. For the SWHS, the response rates for the first (2000–2002), second (2002–2004), third (2004–2007), and fourth (2008–2011) in-person follow-up surveys were 99.8%, 98.7%, 96.7%, and 92.0%, respectively. For the SMHS, the response rates for the first (2004–2008) and second (2008–2011) follow-up surveys were 97.6% and 93.6%, respectively. All possible cancer diagnoses were verified through home visits and review of medical charts.

Cancers were coded by International Classification of Disease, Ninth Revision (ICD-9), codes. Tumors were grouped as primary malignant neoplasms (ICD-9 155.0), malignant neoplasms of the intrahepatic bile ducts (ICD-9 155.1), and unspecified malignant neoplasms of the liver (ICD-9 155.2) (12). The diagnosis of the cancers was confirmed via medical chart review by a panel of oncologists.

Statistical Analysis

Person-years of follow-up time were calculated for each participant from 2 years after the date of the baseline interview to the date of cancer diagnosis, death, date of loss to follow-up (if applicable), or December 31, 2009, whichever occurred first. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs), with age as the time scale. Dietary vitamin intakes were categorized by quartile distribution, with the lowest quartile serving as the reference group. Tests for linear trend were performed by assigning an ordinal value (1, 2, 3, and 4) to each quartile ($Q1$, $Q2$, $Q3$, and $Q4$) of exposure and treating it as a continuous variable in the regression model. In analyses of data from women and men combined, dietary intake variables were categorized on the basis of sex-specific quartile distributions. The proportional hazards assumption was examined by evaluation of the interaction between exposure and survival time in the models, and we found no violations of model assumptions.

Dietary information collected at baseline was used for the initial analysis. In the SWHS, we also used the average intake from the first FFQ (at baseline) and the second FFQ (conducted 2–3 years after baseline) in the analysis. For women who provided no second FFQ data (n = 5858, 8.1%) or who reported having diabetes, cardiovascular disease, or cancer diagnosed between the two FFQ surveys (n = 2237, 3.1%), only baseline dietary intake was used as the exposure. The vast majority of SMHS participants had a short follow-up time after the second FFQ. Thus, only the information collected in the first FFQ was included in the analysis.

In the multivariable analyses, we adjusted for the following potential confounding factors assessed at study recruitment: age (years entered as continuous variable); body mass index (calculated as weight in kg/m^2 as a continuous variable); fat intake (g/day, as a continuous variable); family income level (three categories: low [<5000 yuan/year in the SWHS and <12 000 yuan/year in the SMHS], medium [5000 to <10 000 yuan/year in the SWHS and 12 000 to <24 000 yuan/year in the SMHS], and high [>10 000 yuan/year in the SWHS and >24 000 yuan/year in the SMHS]); education level (four categories: elementary school or less, middle school, high school, and college or above); family history of liver cancer (yes or no); and history of viral hepatitis (yes or no), chronic liver disease or cirrhosis (yes or no), diabetes (yes or no), and cholelithiasis or cholecystectomy (yes or no). Smoking and alcohol consumption were not associated with liver cancer risk in our study populations; therefore, we did not adjust for them in the final model. The correlation coefficient between total energy intake and fat was r = 0.70, and adjustment for fat intake resulted in a much bigger change in risk estimates than adjustment for total energy. Therefore, fat intake was included in the final multivariable model. Analyses were conducted for the SWHS and SMHS separately and for the two cohorts combined when results did not vary statistically significantly by sex. We also conducted analyses restricted to participants who reported no use of any vitamin supplements at the baseline survey.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Inc, Cary, NC). All P values were calculated by two-sided tests and were considered statistically significant if P was less than .05. This study had 80% statistical power to identify

dietary risk/protective factors (comparing the highest vs the lowest quartiles of intake) for liver cancer with minimum hazard ratios of 1.64 (risk factor)/0.61 (protective factors) for women, 1.56 (risk factor)/0.64 (protective factors) for men, and 1.42 (risk factor)/0.70 (protective factors) for both sexes combined.

Results

We excluded 1844 participants from the SWHS and 174 participants from the SMHS from the analysis because of a diagnosis of cancer before enrollment (1579 women), loss to follow-up shortly after enrollment (8 women and 14 men), diagnosis of cancer in situ during follow-up (61 women and 4 men), cancer diagnosis that could not be confirmed (61 women and 23 men), and death from cancer with no cancer type or diagnosis date (135 women and 133 men) (data not shown). We also excluded 16 women and 91 men with extreme values for total energy intake (outside the range of 500–4000 kcal/d). We further excluded liver cancer patients (24 women and 63 men) diagnosed within 2 years of enrollment, because their dietary habits might have been influenced by preclinical symptoms, as well as the first two years of observation for the entire cohort from the analysis (ie, 1383 participants [571 women and 812 men] with less than 2 years of total observation were excluded from the study). After these exclusions, a total of 132 837 participants (72 486 women and 60 351 men) remained in the present study. During an average follow-up of 10.9 years in the SWHS and 5.5 years in the SMHS, 355 (142 women and 213 men) incident primary liver cancers were documented. Of these, 267 (118 women and 149 men) were diagnosed after the first 2 years of study enrollment. Among them, 154 (57.7%) were primary malignant neoplasms, 46 (17.2%) were malignant neoplasms of the intrahepatic bile ducts, and 67 (25.1%) were unspecified malignant neoplasms of the liver.

Age-standardized baseline characteristics of participants by liver cancer diagnosis status are presented in Table 1. Participants who developed liver cancer were older than participants who did not develop liver cancer. Participants who developed liver cancer were more likely to have a lower education level, a history of viral hepatitis, chronic liver disease and cirrhosis, cholelithiasis or cholecystectomy, and a family history of liver cancer in first-degree relatives compared with liver cancer-free study participants in both the SWHS and SMHS. Also, participants who developed liver cancer were more likely to have higher body mass index in the SWHS, whereas in the SMHS, they were more likely to have lower family income, a history of diabetes, and higher fat intake than those who remained liver cancer-free. No differences in total energy intake, smoking, or drinking habits between participants who developed liver cancer and those who remained liver cancer-free were observed.

Table 2 presents associations between dietary vitamins and liver cancer by quartiles of dietary vitamin intakes. Dietary intake

Table 1. Baseline characteristics of the Shanghai Women's (1997–2000) and Men's (2002–2006) Health Studies, comparing liver cancer patients with study participants who did not develop liver cancer

	Women			Men		
Characteristic*	**Participants who developed liver cancer (n=118)**	**Participants who did not develop liver cancer (n=72 368)**	***P*†**	**Participants who developed liver cancer (n=149)**	**Participants who did not develop liver cancer (n=60 202)**	***P*†**
Mean age at recruitment (SD), y	59.0 (8.8)	52.4 (9.0)	<.001	59.4 (10.1)	55.2 (9.7)	<.001
Mean body mass index (SE), kg/m^2	24.7 (0.3)	24.0 (0.0)	.03	23.3 (0.3)	23.7 (0.0)	.10
Mean total energy intake (SE), kcal/d	1688.5 (32.1)	1644.1 (1.3)	.17	1910.0 (38.7)	1908.3 (1.9)	.97
Mean fat intake (SE), g/d	30.5 (1.0)	29.6 (0.0)	.42	37.3 (1.3)	34.5 (0.1)	.03
Family income, per person per year, No. (%)			.62			.003
Low	44 (29.2)	19 894 (27.5)		103 (68.0)	33 032 (54.9)	
Middle	48 (44.9)	28 138 (38.9)		37 (24.8)	21 286 (35.4)	
High	26 (25.8)	24 336 (33.6)		9 (7.2)	5884 (9.8)	
Education level, No. (%)			<.001			.01
Elementary school or less	57 (29.4)	15 278 (21.1)		22 (9.5)	4702 (7.8)	
Middle school	22 (29.2)	27 015 (37.3)		48 (31.9)	19 892 (33.0)	
High school	34 (32.9)	20 273 (28.0)		57 (43.9)	21 498 (35.7)	
College or above	5 (8.5)	9802 (13.5)		22 (14.7)	14 110 (23.4)	
Ever had viral hepatitis, No. (%)	20 (27.1)	1873 (2.6)	<.001	51 (40.3)	4122 (6.8)	<.001
Ever had chronic liver disease or cirrhosis, No. (%)	5 (3.2)	582 (0.8)	<.001	24 (16.6)	1978 (3.3)	<.001
Ever had diabetes, No. (%)	12 (6.2)	3047 (4.2)	.16	20 (8.7)	3689 (6.1)	.01
Ever had cholelithiasis or cholecystectomy, No. (%)	28 (17.0)	8180 (11.3)	.01	24 (13.7)	4645 (7.7)	.004
Family history of liver cancer in first-degree relatives, No. (%)	12 (12.7)	2366 (3.3)	<.001	16 (11.7)	2133 (3.5)	<.001
Ever smoker, No. (%)	3 (3.5)	1993 (2.8)	.34	99 (70.0)	41 908 (69.6)	.69
Ever alcohol drinker, No. (%)	3 (1.9)	1632 (2.3)	.98	47 (25.9)	20 257 (33.6)	.72

* All variables were standardized to age distribution at baseline. SE = standard error.

† The general linear model was used to calculate *P* for continuous variables: age at recruitment, body mass index, total energy intake, fat intake. Cochran–Mantel–Haenszel statistics were used to calculate *P* for categorical variables: family income level (low income for <5000 yuan/year in the SWHS and <12 000 yuan/year in the SMHS; medium income for 5000 to <10 000 yuan/year in the SWHS and 12 000 to <24 000 yuan/year in the SMHS; and high income for >10 000 yuan/year in the SWHS and >24 000 yuan/year in the SMHS); education level (elementary school or less, middle school, high school, college or above); family history of liver cancer (yes or no); history of viral hepatitis (yes or no); history of chronic liver disease or cirrhosis (yes or no), history of diabetes (yes or no), and history of cholelithiasis or cholecystectomy (yes or no). All statistical tests were two-sided.

Table 2. Hazard ratios for liver cancer by quartiles of dietary vitamin intakes in the Shanghai Women's (1997–2000) and Men's (2002–2006) Health Studies

	Both sexes combined		Women		Men		
Dietary vitamin intakes*	**No. of participants who developed liver cancer (n=267)**	**HR (95% CI)†**	**No. of women who developed liver cancer (n=118)**	**HR (95% CI)‡**	**No. of men who developed liver cancer (n=149)**	**HR (95% CI)‡**	$P_{interaction}$
Vitamin A, μgRE/d							.74
≤468.966 (462.845)	72	1.00 (reference)	37	1.00 (reference)	35	1.00 (reference)	
≤617.907 (634.149)	68	1.04 (0.74 to 1.46)	29	0.95 (0.58 to 1.58)	40	1.16 (0.73 to 1.85)	
≤796.609 (852.917)	65	0.99 (0.70 to 1.41)	25	0.86 (0.50 to 1.49)	40	1.15 (0.72 to 1.84)	
>796.609 (852.917)	62	0.88 (0.60 to 1.29)	27	0.93 (0.52 to 1.68)	35	0.88 (0.52 to 1.46)	
P_{trend}		.51		.73		.62	
Retinol, μg/d							.08
≤98.325 (91.003)	74	1.00 (reference)	44	1.00 (reference)	31	1.00 (reference)	
≤150.280 (142.157)	60	0.93 (0.66 to 1.33)	25	0.75 (0.45 to 1.26)	35	1.21 (0.74 to 1.99)	
≤212.153 (201.105)	63	0.99 (0.69 to 1.44)	19	0.63 (0.35 to 1.17)	44	1.45 (0.88 to 2.37)	
>212.153 (201.105)	70	1.12 (0.74 to 1.68)	30	1.10 (0.58 to 2.05)	40	1.27 (0.73 to 2.23)	
P_{trend}		.56		.99		.32	
Carotene, μg/d							.99
≤1977.268 (1963.557)	70	1.00 (reference)	34	1.00 (reference)	36	1.00 (reference)	
≤2695.501 (2851.723)	71	1.11 (0.80 to 1.55)	31	1.04 (0.63 to 1.70)	40	1.19 (0.76 to 1.88)	
≤3574.449 (3987.903)	65	0.99 (0.70 to 1.40)	28	0.96 (0.57 to 1.61)	37	1.05 (0.66 to 1.68)	
>3574.449 (3987.903)	61	0.87 (0.61 to 1.25)	25	0.82 (0.47 to 1.42)	36	0.92 (0.57 to 1.50)	
P_{trend}		.38		.46		.64	
Vitamin B1, mg/d							.05
≤0.733 (0.863)	81	1.00 (reference)	41	1.00 (reference)	40	1.00 (reference)	
≤0.869 (1.048)	69	0.89 (0.64 to 1.24)	23	0.58 (0.34 to 0.99)	46	1.20 (0.77 to 1.85)	
≤1.027 (1.260)	56	0.72 (0.50 to 1.04)	31	0.78 (0.46 to 1.33)	25	0.63 (0.37 to 1.08)	
>1.027 (1.260)	61	0.65 (0.42 to 1.01)	23	0.48 (0.24 to 0.98)	38	0.79 (0.45 to 1.40)	
P_{trend}		.03		.10		.14	
Vitamin B2, mg/d							.14
≤0.658 (0.729)	75	1.00 (reference)	45	1.00 (reference)	30	1.00 (reference)	
≤0.831 (0.930)	59	0.87 (0.61 to 1.24)	23	0.59 (0.34 to 1.00)	36	1.27 (0.77 to 2.09)	
≤1.019 (1.151)	67	1.00 (0.69 to 1.45)	24	0.64 (0.36 to 1.16)	43	1.48 (0.89 to 2.47)	
>1.019 (1.151)	66	0.90 (0.57 to 1.41)	26	0.63 (0.30 to 1.32)	40	1.25 (0.68 to 2.29)	
P_{trend}		.82		.21		.39	
Niacin, mg/d							.31
≤11.321 (12.825)	81	1.00 (reference)	40	1.00 (reference)	41	1.00 (reference)	
≤13.439 (15.532)	70	0.93 (0.67to 1.30)	29	0.78 (0.47 to 1.30)	42	1.09 (0.70 to 1.70)	
≤15.977 (18.729)	51	0.66 (0.45 to 0.97)	19	0.58 (0.31 to 1.06)	32	0.75 (0.46 to 1.23)	
>15.977 (18.729)	65	0.73 (0.47 to 1.13)	31	0.88 (0.44 to 1.77)	34	0.63 (0.35 to 1.14)	
P_{trend}		.06		.41		.07	
Folic acid , μg/d							.76
≤226.762 (258.319)	75	1.00 (reference)	39	1.00 (reference)	36	1.00 (reference)	
≤278.804 (324.190)	56	0.78 (0.55 to 1.11)	26	0.72 (0.43 to 1.19)	30	0.86 (0.52 to 1.40)	
≤339.372 (404.452)	70	0.95 (0.67 to 1.34)	27	0.74 (0.44 to 1.26)	43	1.15 (0.72 to 1.82)	
>339.372 (404.452)	66	0.77 (0.53to 1.13)	26	0.62 (0.34 to 1.14)	40	0.90 (0.54 to 1.49)	
P_{trend}		.33		.14		.97	
Vitamin C, mg/d							.78
≤59.928 (61.165)	75	1.00 (reference)	32	1.00 (reference)	43	1.00 (reference)	
≤82.153 (86.829)	67	0.96 (0.69 to 1.34)	31	1.16 (0.70 to 1.92)	36	0.85 (0.55 to 1.33)	
≤109.963 (119.799)	73	1.08 (0.77 to 1.51)	33	1.27 (0.76 to 2.13)	40	0.97 (0.63 to 1.51)	
>109.963 (119.799)	52	0.71 (0.48 to 1.04)	22	0.87 (0.47 to 1.58)	30	0.63 (0.38 to 1.04)	
P_{trend}		.18		.83		.13	
Vitamin E, mg/d							.08
≤9.977 (10.531)	82	1.00 (reference)	44	1.00 (reference)	38	1.00 (reference)	
≤12.785 (13.877)	65	0.80 (0.57 to 1.11)	30	0.70 (0.43 to 1.13)	35	0.90 (0.56 to 1.44)	
≤16.176 (17.937)	57	0.66 (0.46 to 0.94)	16	0.35 (0.19 to 0.64)	41	0.97 (0.61 to 1.55)	
>16.176 (17.937)	63	0.60 (0.40 to 0.89)	28	0.49 (0.26 to 0.90)	35	0.68 (0.40 to 1.17)	
P_{trend}		.01		.003		.24	
Vitamin E alpha, mg/d							.99
≤3.043 (3.116)	83	1.00 (reference)	40	1.00 (reference)	43	1.00 (reference)	
≤4.012 (4.164)	67	0.84 (0.60 to 1.17)	31	0.90 (0.55 to 1.47)	36	0.81 (0.51 to 1.27)	
≤5.071 (5.436)	59	0.77 (0.54 to 1.10)	25	0.79 (0.45 to 1.40)	34	0.76 (0.47 to 1.23)	
>5.071 (5.436)	58	0.65 (0.43 to 0.98)	22	0.63 (0.32 to 1.26)	36	0.67 (0.40 to 1.13)	
P_{trend}		.04		.19		.14	

Table 2. (Continued)

Dietary vitamin intakes*	Both sexes combined: No. of participants who developed liver cancer (n=267)	Both sexes combined: HR (95% CI)†	Women: No. of women who developed liver cancer (n=118)	Women: HR (95% CI)‡	Men: No. of men who developed liver cancer (n=149)	Men: HR (95% CI)‡	$P_{interaction}$
Vitamin E beta and gamma, mg/d							.69
≤2.947 (2.949)	82	1.00 (reference)	42	1.00 (reference)	40	1.00 (reference)	
≤4.039 (4.289)	63	0.78 (0.56 to 1.09)	28	0.67 (0.41 to 1.09)	35	0.89 (0.56 to 1.41)	
≤5.421 (5.914)	57	0.65 (0.46 to 0.92)	22	0.48 (0.28 to 0.84)	35	0.79 (0.50 to 1.27)	
>5.421 (5.914)	65	0.62 (0.43 to 0.91)	26	0.47 (0.26 to 0.86)	39	0.74 (0.45 to 1.23)	
P_{trend}		.01		.01		.20	
Vitamin E delta, mg/d							.83
≤2.502 (2.679)	81	1.00 (reference)	40	1.00 (reference)	41	1.00 (reference)	
≤3.466 (3.906)	63	0.79 (0.56 to 1.10)	28	0.69 (0.42to 1.12)	35	0.87 (0.55to 1.38)	
≤4.711 (5.432)	56	0.64 (0.45 to 0.92)	24	0.54 (0.31 to 0.92)	32	0.72 (0.45to 1.16)	
>4.711 (5.432)	67	0.67 (0.46 to 0.97)	26	0.49 (0.27 to 0.88)	41	0.81 (0.50to 1.32)	
P_{trend}		.02		.01		.30	

* Cut points for the quartiles of vitamin intakes used in analyses of data from the Shanghai Men's Health Study are shown in parentheses. In analyses of data from women and men combined, dietary intake variables were categorized on the basis of sex-specific quartile distributions. RE = retinol equivalent.

† The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by using Cox proportional hazard models with adjustment for sex (men or women), age (y, continuous variable), body mass index (kg/m^2, continuous variable), fat intake (g/d, continuous variable), family income level (low, medium, and high), education level (elementary school or less, middle school, high school, college or above), family history of liver cancer (yes or no), history of viral hepatitis (yes or no), history of chronic liver disease or cirrhosis (yes or no), history of diabetes (yes or no), and history of cholelithiasis or cholecystectomy (yes or no).Two-sided P_{trend} values were calculated by assigning an ordinal value (1, 2, 3, 4) to each quartile (*Q*1, *Q*2, *Q*3, and *Q*4) of exposure and treating it as a continuous variable in the regression models.

‡ HRs and 95% CIs were calculated by using Cox proportional hazard models with adjustment for age (y, continuous variable), body mass index (kg/m^2, continuous variable), fat intake (g/d, continuous variable), family income level (low, medium, and high), education level (elementary school or less, middle school, high school, college or above), family history of liver cancer (yes or no), history of viral hepatitis (yes or no), history of chronic liver disease or cirrhosis (yes or no), history of diabetes (yes or no), and history of cholelithiasis or cholecystectomy (yes or no).

Table 3. Hazard ratios for liver cancer by vitamin and calcium supplement use in the Shanghai Women's (1997–2000) and Men's (2002–2006) Health Studies*

Vitamin supplement	Women: No. of women who developed liver cancer (n=118)	Women: HR (95% CI)*	Men: No. of men who developed liver cancer (n=149)	Men: HR (95% CI)*	Both sexes combined: No. of participants who developed liver cancer (n=267)	Both sexes combined: HR (95% CI)†
Vitamin B						
No	111	1.00 (reference)	136	1.00 (reference)	247	1.00 (reference)
Yes	7	1.19 (0.50 to 2.84)	13	1.01 (0.52 to 1.97)	20	1.07 (0.63 to 1.82)
Vitamin C						
No	107	1.00 (reference)	128	1.00 (reference)	235	1.00 (reference)
Yes	11	1.65 (0.82 to 3.33)	21	2.20 (1.30 to 3.74)	32	1.96 (1.29 to 2.98)
Vitamin E						
No	111	1.00 (reference)	139	1.00 (reference)	250	1.00 (reference)
Yes	7	0.41 (0.18 to 0.96)	10	0.70 (0.34 to 1.45)	17	0.52 (0.30 to 0.90)
Multivitamin						
No	111	1.00 (reference)	128	1.00 (reference)	239	1.00 (reference)
Yes	7	1.00 (0.45 to 2.21)	21	1.84 (1.13 to 2.98)	28	1.45 (0.96 to 2.19)
Calcium						
No	93	1.00 (reference)	142	1.00 (reference)	234	1.00 (reference)
Yes	25	0.88 (0.56 to 1.41)	8	0.80 (0.38 to 1.67)	33	0.87 (0.59 to 1.28)

* The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by using Cox proportional hazard models with adjustment for age (y, continuous variable), body mass index (kg/m^2, continuous variable), fat intake (g/d, continuous variable), family income level (low, medium, and high), education level (elementary school or less, middle school, high school, college or above), family history of liver cancer (yes or no), history of viral hepatitis (yes or no), history of chronic liver disease or cirrhosis (yes or no), history of diabetes (yes or no), history of cholelithiasis or cholecystectomy (yes or no), dietary vitamin E intake (cut points for the quartiles of vitamin E intake in the SWHS were ≤9.977, ≤12.785, ≤16.176, and >16.176 and in the SMHS were ≤10.531, ≤13.877, ≤17.937, and >17.937), and additionally, mutually adjusted for vitamin C supplement use (yes or no), vitamin E supplement use (yes or no), and multivitamin supplement use (yes or no).

† The HRs and 95% CIs were calculated by using Cox proportional hazard models with adjustment for sex (male or female), age (y, continuous variable), body mass index (kg/m^2, continuous variable), fat intake (g/d, continuous variable), family income level (low, medium, and high), education level (elementary school or less, middle school, high school, college or above), family history of liver cancer (yes or no), history of viral hepatitis (yes or no), history of chronic liver disease or cirrhosis (yes or no), history of diabetes (yes or no), history of cholelithiasis or cholecystectomy (yes or no), dietary vitamin E intake (cut points for the quartiles of vitamin E intake in the SWHS were ≤9.977, ≤12.785, ≤16.176, and >16.176 and in the SMHS were ≤10.531, ≤13.877, ≤17.937, and >17.937), and additionally, mutually adjusted for vitamin C supplement use (yes or no), vitamin E supplement use (yes or no), and multivitamin supplement use (yes or no).

of vitamin E was inversely associated with liver cancer risk (lowest to the highest quartiles: HR =1.00 [reference], HR = 0.80 [95% CI = 0.57 to 1.11], HR = 0.66 [95% CI = 0.46 to 0.94], and HR = 0.60 [95% CI = 0.40 to 0.89]; P_{trend} = .01). Similar associations were found for subtypes of vitamin E, including alpha-tocopherol, beta- and gamma-tocopherol, and delta-tocopherol (P_{trend} = .04, .01, and .02, respectively).The inverse association patterns were consistent for both women and men, but trend tests and point estimates were only statistically significant for women. The test for multiplicative interaction between sex and vitamin E intake, however, indicated that sex does not influence the association between vitamin E and liver cancer. Further analyses excluding individuals who reported use of any vitamin supplement at the baseline survey showed that vitamin E intake was consistently associated with reduced risk of liver cancer (second to the fourth quartiles: HR = 0.68 [95% CI = 0.47 to 0.99], HR = 0.59 [95% CI = 0.39 to 0.88], and HR = 0.55 [95% CI = 0.35 to 0.85]; P_{trend} = .004, data not shown in table) among non–vitamin supplement users.

Increasing quartiles of vitamin B1 intake were associated with a statistically significant, reduced risk of liver cancer (P_{trend} = .03).The associations between vitamin B1 and risk of liver cancer (P_{trend}= .31) diminished after further adjustment for vitamin E intake (data not shown). No statistically significant associations were observed for other dietary vitamin intakes (all P_{trend} > .05).

Table 3 presents associations between vitamins B, C, and E; multivitamins; and calcium supplements and liver cancer risk with adjustment for dietary vitamin E and other potential confounders. Only one liver cancer patient reported regular use of single vitamin A supplements. Thus, vitamin A supplement data are not presented. Vitamin E supplement use was associated with reduced risk of liver

Table 4. Hazard ratios for liver cancer by quartiles of selected vitamin intakes in the Shanghai Women's (1997–2000) and Men's (2002–2006) Health Studies, stratified by self-reported liver disease and/or family history of liver cancer

	Participants without self-reported liver disease and family history of liver cancer (n=176)		Participants with self-reported liver disease or family history of liver cancer (n=91)		
Vitamin intakes*	**No. of cancers**	**HR (95% CI)†**	**No. of cancers**	**HR (95% CI)†**	**$P_{interaction}$‡**
Vitamin E, mg/d§					.84
≤9.977 (10.531)	59	1.00 (reference)	23	1.00 (reference)	
≤12.785 (13.877)	41	0.74 (0.49 to 1.11)	24	0.95 (0.53 to 1.69)	
≤16.176 (17.937)	37	0.64 (0.42 to 1.00)	20	0.69 (0.37 to 1.28)	
>16.176 (17.937)	39	0.58 (0.35 to 0.95)	24	0.64 (0.33 to 1.23)	
P_{trend}		.02		.12	
Vitamin E, mg/d§,‖					.54
≤9.977 (10.531)	54	1.00 (reference)	17	1.00 (reference)	
≤12.785 (13.877)	37	0.75 (0.49 to 1.15)	9	0.51 (0.23 to 1.15)	
≤16.176 (17.937)	31	0.62 (0.39 to 0.99)	11	0.54 (0.25 to 1.18)	
>16.176 (17.937)	30	0.52 (0.30 to 0.88)	15	0.67 (0.31 to 1.42)	
P_{trend}		.01		.32	
Vitamin E supplement use§					.19
No	168	1.00 (reference)	82	1.00 (reference)	
Yes	8	0.50 (0.23 to 1.10)	9	0.59 (0.27 to 1.28)	
Vitamin C supplement use§					.01
No	165	1.00 (reference)	70	1.00 (reference)	
Yes	11	1.21 (0.61 to 2.37)	21	3.39 (1.94 to 5.92)	
Multivitamin supplement use in men					.06
No	79	1.00 (reference)	49	1.00 (reference)	
Yes	7	1.28 (0.58 to 2.84)	14	2.64 (1.40 to 4.99)	

* Cut points for the quartiles of vitamin intakes used in analyses of data from the Shanghai Women's Health Study along with the cut points for the Shanghai Men's Health Study are shown in parentheses. In analyses of data from women and men combined, dietary intake variables were categorized on the basis of sex-specific quartile distributions.

† The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by using Cox proportional hazard models with adjustment for age (y, continuous variable), body mass index (kg/m^2, continuous variable), fat intake (g/d, continuous variable), family income level (low, medium, and high), education level (elementary school or less, middle school, high school, college or above), history of diabetes (yes or no), history of cholelithiasis or cholecystectomy (yes or no), and mutually adjusted for vitamin E intake (cut points for the quartiles of vitamin E intake in the SWHS were ≤9.977, ≤12.785, ≤16.176, and >16.176 and in the SMHS were ≤10.531, ≤13.877, ≤17.937, and >17.937), vitamin E supplement (yes or no), vitamin C supplement (yes or no), and multivitamin supplement use (yes or no). P_{trend} was calculated by assigning an ordinal value (1, 2, 3, 4) to each quartile (*Q*1, *Q*2, *Q*3, and *Q*4) of exposure and treating it as a continuous variable in the regression models.

‡ $P_{interaction}$ was calculated by introducing an interaction term between the exposure and self-reported liver disease and/or family history of liver cancer in the regression model. All *P* values were two-sided.

§ The HRs and 95% CIs were calculated by using Cox proportional hazard models with adjustment for sex (male or female), age (y, continuous variable), body mass index (kg/m^2, continuous variable), fat intake (g/d, continuous variable), family income level (low, medium, and high), education level (elementary school or less, middle school, high school, college or above), history of diabetes (yes or no), history of cholelithiasis or cholecystectomy (yes or no), and mutually adjusted for vitamin E intake (cut points for the quartiles of vitamin E intake in the SWHS were ≤9.977, ≤12.785, ≤16.176, and >16.176 and in the SMHS were ≤10.531, ≤13.877, ≤17.937, and >17.937), vitamin E supplement (yes or no), vitamin C supplement (yes or no), and multivitamin supplement use (yes or no).

‖ Individuals who had used any vitamin supplement before enrollment were excluded from the analysis.

cancer (ever use vs never use: HR = 0.52, 95% CI = 0.30 to 0.90), and this inverse association was more evident among women (HR = 0.41, 95% CI = 0.18 to 0.96). Use of vitamin C supplement, on other hand, was associated with increased liver cancer risk (HR = 1.96, 95% CI = 1.29 to 2.98), and the association in men was more evident among smokers (HR = 2.69, 95% CI = 1.38 to 5.24; data not shown). In addition, multivitamin supplement use had a statistically significant association with increased risk of liver cancer in men (HR = 1.84, 95% CI = 1.13 to 2.98) but not in women (HR = 1.00, 95% CI = 0.45 to 2.21). This association in men appeared to be stronger among nonsmokers (HR = 2.16, 95% CI = 1.03 to 4.53) than among smokers (HR = 1.53, 95% CI = 0.79 to 2.98; data not shown). No statistically significant associations were observed between use of vitamin B or calcium supplement and risk of liver cancer.

We also analyzed associations between dietary vitamin E intake and vitamin C, E, and multivitamin supplement use with liver cancer risk stratified by history of liver disease (viral hepatitis, chronic liver disease, or cirrhosis) and family history of liver cancer because these conditions may change an individual's dietary pattern or other lifestyle factors (Table 4). The associations with vitamin E either from diet or supplements were consistent among participants with and without self-reported liver disease or family history of liver cancer, and the association appeared to be slightly stronger among participants who reported no liver disease or family history of liver cancer, although the test for multiplicative interaction was not statistically significant. Associations with vitamin C and multivitamin supplement use in men were predominantly seen among individuals with self-reported liver disease or family history of liver cancer ($P_{interaction}$ = .01 and .06, respectively).

Inverse associations were observed for primary malignancies of the liver (ICD-9 1.55.0) and dietary vitamin E intake (second to fourth quartiles of dietary intake: HR = 0.80 [95% CI = 0.52 to 1.24]; HR = 0.63 [95% CI = 0.39 to 1.01]; and HR = 0.50 [95% CI = 0.29 to 0.87]; P_{trend} = .009) and use of vitamin E supplements (HR = 0.37 [95% CI = 0.17 to 0.81]) (data not shown). Similar results were observed for malignancies of the intrahepatic bile ducts (ICD-9 155.1) and dietary vitamin E intake (second to fourth quartiles of dietary intake: HR = 0.37 [95% CI = 0.15 to 0.89], HR = 0.35 [95% CI = 0.14 to 0.88], and HR = 0.51 [95% CI = 0.20 to 1.26]; P_{trend} = .10) and vitamin E supplement use (HR = 0.68, 95% CI = 0.21 to 2.20) (data not shown). No statistically significant associations were found for unspecified malignancies of the liver (ICD-9 155.2) and dietary vitamin E intake (second to fourth quartiles of dietary intake: HR = 1.34 [95% CI = 0.66 to 2.72], HR = 1.16 [95% CI = 0.55 to 2.43], and HR = 1.02 [95% CI = 0.45 to 2.30]; P_{trend} = .93) and for vitamin E supplement use (HR = 0.92, 95% CI = 0.32 to 2.61) (data not shown). Similarly, the increased risk associated with vitamin C and multivitamin supplement use was primarily observed for primary malignancies of the liver (ICD-9 155.0; data not shown). However, it should be noted that the statistical power for these subgroup analyses was low because of the reduced sample size.

Discussion

In this large, prospective study of women and men from China, we found that higher intakes of vitamin E from both diet and supplements were inversely associated with the risk of liver cancer, although the association was not statistically significant when data from only men were analyzed. This association was consistently observed among individuals with and without self-reported liver disease or family history of liver cancer. On the other hand, use of vitamin C and multivitamin supplements in men was statistically significantly associated with an increased risk of liver cancer among individuals with self-reported liver disease or family history of liver cancer.

Vitamin E, a fat-soluble vitamin, occurs in eight different forms (alpha-, beta-, gamma-, and delta-tocopherol and alpha-, beta-, gamma-, and delta-tocotrienol). Each form has slightly different biological properties, but all are antioxidants (13,14). In our study, all subtypes of vitamin E intake were inversely associated with liver cancer risk in the overall study population including both men and women. Numerous experimental studies have suggested that vitamin E may prevent DNA damage, enhance DNA repair, prevent lipid peroxidation, inhibit the activation of carcinogens, and boost the immune system (5,13,14,17–20). Epidemiological research and clinical trials in humans have investigated the effects of dietary or supplemental vitamin E intake or serum tocopherol on risk of various cancers, including lung, esophageal, breast, colon, bladder, and prostate cancers, but have yielded inconsistent results (3,5,20,21). Vitamin E supplement use has been shown to significantly improve liver function in patients infected with viral hepatitis (22,23). To our knowledge, only two epidemiological studies, both using a case–control study design, have evaluated dietary micronutrient intakes and liver cancer risk (15,16). A hospital-based case–control study conducted in Greece, involving 97 case patients with hepatocellular carcinoma and 128 control subjects reported a null association for dietary intake of vitamin E and other micronutrients (15). Another hospital-based case–control study conducted in Italy, including 185 hepatocellular carcinoma case patients and 412 cancer-free control subjects, showed an inverse association for β-carotene intake (odds ratio = 0.48, 95% CI = 0.24 to 0.93) and nonstatistically significant association with vitamin E intake (odds ratio = 0.77, 95% CI = 0.40 to 1.49) (16). However, these studies were limited by small sample size and by their retrospective and hospital-based study designs. In our study, dietary and supplement use information was prospectively collected, and we excluded the first 2 years of observation after study enrollment. We found a clear, inverse dose–response relation between dietary vitamin E intake and liver cancer risk, an association that was independent of supplement use and that appeared to be slightly stronger among participants who reported no liver disease or family history of liver cancer. Similarly, vitamin E supplement use was also associated with reduced risk of liver cancer. Therefore, our study provides strong evidence suggesting that vitamin E intake, either from dietary sources or supplements, reduces the risk of liver cancer. It should be noted that the association among men did not reach statistical significance, although no interaction between sex and vitamin E intake was observed. Given that there is no biological evidence supporting a sex-specific effect for vitamin E, we consider the small difference between men and women in the risk estimate association with dietary vitamin E intake to be a random fluctuation due to the relatively few liver cancer cases included in the study.

Vitamin C is a water-soluble vitamin. Results from experimental animal studies on vitamin C intake and liver cancer have been

inconsistent (17,24–26). Some studies have found that supplemental vitamin C inhibits hepatocarcinogenesis (14,24), whereas other studies have found no effect (14,25). An enhancement of hepatocarcinogenesis in animals administered higher amounts of vitamin C was also reported (17,26). Only one epidemiological study investigated the association between vitamin C from dietary sources and liver cancer risk (27). In that population-based prospective study of 19 998 Japanese individuals, dietary vitamin C seemed to be associated with nonsignificantly increased risk of liver cancer (lowest to the highest tertiles: HR = 1.00 [reference], HR = 1.74 [95% CI = 1.0 to 3.1], and HR = 1.38 [95% CI = 0.80 to 2.40]). The association was stronger among current smokers. In our study, we found that vitamin C supplement use was associated with increased liver cancer risk in men, 69% of whom were ever smokers, and the association was more pronounced among smokers. Similarly, we found that multivitamin supplement use was associated with increased risk of liver cancer in men. We also found that the vitamin C and multivitamin supplement association was stronger among participants with self-reported liver disease or family history of liver cancer. Because participants with liver disease or family history of liver cancer are more likely to take vitamin supplements than those without these conditions, the possibility of reverse causation is indicated. More studies are warranted to further evaluate the effect of vitamin supplement use on liver cancer, particularly the biological mechanisms behind the observed interactions with sex and liver disease.

Few participants (less than 17.5%) in our population use vitamin supplements, and the food supply in China is not fortified with vitamins and minerals. Thus, our study population provides a unique opportunity to evaluate associations with dietary vitamin intakes. Other strengths of our study include the prospective and population-based study design and the high participation and follow-up rates. Furthermore, validated dietary questionnaires were used in our study, and repeated dietary information from the SWHS was applied.

Our study also has some limitations. First, the follow-up time for SMHS participants is relatively short. Thus, the statistical power for subgroup analyses was low. Second, although we took into consideration participants' history of hepatitis and liver cirrhosis in our analyses, we cannot completely rule out confounding from unmeasured confounders such as HBV infection, HCV infection, and aflatoxin exposure, although HCV infection and aflatoxin exposure are very low in Shanghai (28). Third, we did not collect information on the specific doses of the vitamin supplements in our study. Doses for vitamins E and C vary substantially among the supplements commonly available on the Chinese market, from 50 to 1000 international units (IU) for vitamin E and 60–1000 mg for vitamin C. This precluded us from evaluating the effect of vitamin supplement dose on risk of liver cancer. Fourth, measurement errors in dietary intake assessment introduced by the FFQ, which are most likely nondifferential, may have attenuated estimates for the dietary associations. Last, given the multiple comparisons carried out in the current study, a chance finding cannot be ruled out. However, the consistent pattern observed for dietary vitamin E intake and supplemental vitamin E use, and for men and women, argue against a chance finding.

In summary, in these two population-based cohort studies of 132 837 women and men, we found that high intake of vitamin E either from diet or supplements was related to lower risk of liver cancer in middle-aged or older people from China. The positive associations with use of vitamin C and multivitamin supplements may be a reflection of reverse causation. If confirmed, these findings could open a new venue for prevention of liver cancer, the third most common cause of death worldwide.

References

1. Ferlay J, Shin HR, Bray F, et al. *GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10* [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. http://globocan.iarc.fr. Accessed December 4, 2011.
2. Sankaranarayanan R, Swaminathan R, Lucas E. *Cancer Survival in Africa, Asia, the Caribbean and Central America (SurvCan)*. IARC Scientific Publications vol. 162, ISBN 978-92-832-2162-3. Lyon, France: International Agency for Research on Cancer; 2011.
3. London WT, McGlynn KA. Liver cancer. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*. 3rd ed. New York, NY: Oxford University Press; 2006:763–786.
4. Chuang SC, La Vecchia C, Boffetta P. Liver cancer: descriptive epidemiology and risk factors other than HBV and HCV infection. *Cancer Lett.* 2009;286(1):9–14.
5. World Cancer Research Fund/American Institute for Cancer Research (AICR). *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: AICR; 2007.
6. Puertollano MA, Puertollano E, De Cienfuegos GA, et al. Dietary antioxidants: immunity and host defense. *Curr Top Med Chem.* 2011;11(14):1752–1766.
7. Zheng W, Chow WH, Yang G, et al. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. *Am J Epidemiol.* 2005;162(11):1123–1131.
8. Shu XO, Yang G, Jin F, et al. Validity and reproducibility of the food frequency questionnaire used in the Shanghai Women's Health Study. *Eur J Clin Nutr.* 2004;58(1):17–23.
9. Villegas R, Yang G, Liu D, et al. Validity and reproducibility of the food-frequency questionnaire used in the Shanghai Men's Health Study. *Br J Nutr.* 2007;97(5):993–1000.
10. Cai H, Zheng W, Xiang YB, et al. Dietary patterns and their correlates among middle-aged and elderly Chinese men: a report from the Shanghai Men's Health Study. *Br J Nutr.* 2007;98(5):1006–1013.
11. Yang G, Wang G, Pan X. *Chinese Food Composition Tables*. Beijing, China: Peking University Medical Press; 2002.
12. World Health Organization. *International Classification of Diseases, ninth revision (ICD-9)*. Geneva, Switzerland: World Health Organization; 1977.
13. Ju J, Picinich SC, Yang Z, et al. Cancer-preventive activities of tocopherols and tocotrienols. *Carcinogenesis*. 2010;31(4):533–542.
14. Pekmezci D. Vitamin E and immunity. *Vitam Horm*. 2011;86:179–215.
15. Kuper H, Tzonou A, Lagiou P, et al. Diet and hepatocellular carcinoma: a case-control study in Greece. *Nutr Cancer*. 2000;38(1):6–12.
16. Polesela J, Talaminia R, Montella M, et al. Nutrients intake and the risk of hepatocellular carcinoma in Italy. *Eur J Cancer*. 2007;43(16):2381–2387.
17. Samandari E, Visarius T, Zingg JM, et al. The effect of gamma-tocopherol on proliferation, integrin expression, adhesion, and migration of human glioma cells. *Biochem Biophys Res Commun*. 2006;342(4):1329–1333.
18. Reiter E, Jiang Q, Christen S, et al. Anti-inflammatory properties of alpha- and gammatocopherol. *Mol Aspects Med.* 2007;28(5–6):668–691.
19. Constantinou C, Papas A, Constantinou AI, et al. Vitamin E and cancer: an insight into the anticancer activities of vitamin E isomers and analogs. *Int J Cancer*. 123(4):739–752.
20. Glauert HP, Calfee-Mason K, Stemm DN, et al. Dietary antioxidants in the prevention of hepatocarcinogenesis: a review. *Mol Nutr Food Res.* 2010;54(7):875–896.
21. Gaziano JM, Glynn RJ, Chrieten WG, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2009;301(1):52–62.
22. Von Herbay A, Stahl W, Niederau C, et al. Vitamin E improves the aminotransferase status of patients suffering from viral hepatitis C: a

randomized, double-blind, placebo-controlled study. *Free Radic Res.* 1997;27(6):599–605.
23. Andreone P, Fiorino S, Cursaro C, et al. Vitamin E as treatment for chronic hepatitis B: results of a randomized controlled pilot trial. *Antiviral Res.* 2001;49(2):75–81.
24. Shamaan NA, Kadir KA, Rahmat A, et al. Vitamin C and aloe vera supplementation protects from chemical hepatocarcinogenesis in the rat. *Nutrition*. 1998;14(11–12):846–852.
25. Iverson F, Campbell J, Clayson D, et al. Effects of antioxidants on aflatoxin-induced hepatic tumors in rats. *Cancer Lett*. 1987;34(2):139–144.
26. Takabatake M, Shibutani M, Dewa Y, et al. Concurrent administration of ascorbic acid enhances liver tumor-promoting activity of kojic acid in rats. *J Toxicol Sci*. 2008;33(2):127–140.
27. Kurahashi N, Inoue M, Iwasaki M, et al. Vegetable, fruit and antioxidant nutrient consumption and subsequent risk of hepatocellular carcinoma: a prospective cohort study in Japan. *Br J Cancer*. 2009;100(1):181–184.
28. Yuan JM, Ross RK, Stanczyk FZ, et al. A cohort study of serum testosterone and hepatocellular carcinoma in Shanghai, China. *Int J Cancer*. 1995;63(4):491–493.

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