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Vegetable-based dietary pattern and liver cancer risk: Results from the Shanghai Women's and Men's Health Studies

Wei Zhang,[1,2] Yong-Bing Xiang,[1,2,5] Hong-Lan Li,[1,2] Gong Yang,[3] Hui Cai,[3] Bu-Tian Ji,[4] Yu-Tang Gao,[2] Wei Zheng[3] and Xiao-Ou Shu[3]

[1]State Key Laboratory of Oncogene and Related Genes, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai; [2]Department of Epidemiology, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; [3]Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee; [4]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, USA

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Although dietary patterns, specific foods, and their constituents have been linked to cancer risk, the role of dietary patterns and specific food groups in liver cancer risk has not been investigated. In the Shanghai Women's Health Study (SWHS) and Shanghai Men's Health Study (SMHS), two cohort studies of 132 837 Chinese women and men, we evaluated the relationship between dietary patterns, food groups, and liver cancer risk. Through in-person interviews, dietary information intake over the preceding year was collected by using a validated food-frequency questionnaire. Cox regression model was used to estimate hazard ratios and 95% confidence intervals with adjustment for potential confounders. During an average follow-up of 10.9 (SWHS) or 5.5 (SMHS) years, 267 incident liver cancer cases were identified after the first 2 years of study enrolment. Three dietary patterns were derived by factor analysis. A vegetable-based dietary pattern was inversely associated with liver cancer; hazard ratios (95% confidence intervals) for the lowest to highest quartiles were: 1.00; 0.98 (0.71–1.35); 0.93 (0.67–1.29); and 0.58 (0.40–0.84); $P_{trend} = 0.01$. The association was stronger among participants with a history of chronic liver disease. Further analyses showed high intakes of celery, mushrooms, allium vegetables, composite vegetables (including asparagus lettuce and garland chrysanthemum), legumes and legume products were associated with reduced liver cancer risk (all $P_{trend} < 0.05$). Fruit- and meat-based dietary patterns were not associated with liver cancer risk. Our study suggests that a vegetable-based dietary pattern is associated with reduced liver cancer risk. (*Cancer Sci* 2013; 104: 1353–1361)

Approximately 749 000 new liver cancer cases occurred worldwide in 2008, 54% in China alone.[1] Chronic infection with HBV and HCV are two well-established risk factors for liver cancer in humans.[2,3] The former is the primary cause of liver cancer in China. Other risk factors include dietary aflatoxin exposure, excessive alcohol intake, obesity, and diabetes.[2,3]

Epidemiological evidence indicates that diet-related factors are related to most types of cancer both in developed and developing countries. Higher intake of fruit and vegetables probably reduces the risk for common cancers in humans because they are rich in natural antioxidant compounds. But the relationship between diet and liver cancer risk remains inconclusive. Higher intakes of vegetables,[4–12] fruits,[9–12] pork,[7] white meats,[12,13] fish,[11,14] wheat,[15] eggs,[10,12] milk,[10] and milk and yogurt combined[12] have been reported to lower liver cancer risk, whereas increased risk of liver cancer has been linked to excessive intake of red meat and animal protein,[13,16] eggs,[11] and milk.[17] In other words, dietary patterns represent a comprehensive picture of dietary intakes, as they may capture interactions between dietary components, as well as with other risk factors, thus providing a better understanding of the association between vegetable dietary pattern and liver cancer risk. However, this hypothesis has not yet been tested.

We report here on an investigation of vegetable dietary patterns and individual food item/groups in association with liver cancer risk among 132 837 Chinese women and men in urban Shanghai, China.

Materials and Methods

Study group. The current study is based on two ongoing, population-based, prospective cohort studies, the SWHS and the SMHS. Detailed descriptions of these studies have been published elsewhere.[18–20] Briefly, the SWHS includes 74 941 women aged 40–70 years who were recruited from seven urban communities of Shanghai between March 1997 and May 2000 (participation rate, 92%). The SMHS includes 61 491 men aged 40–74 years who were recruited from eight urban communities of Shanghai between April 2002 and June 2006 (participation rate, 74%). Both studies were approved by the Institutional Review Boards of all participating institutions. All participants provided written informed consent.

Both cohorts were followed for cancer incidence and all-cause mortality by in-person follow-up surveys carried out every 2–3 years and annual record linkages with databases at the population-based Shanghai Cancer Registry, Shanghai Vital Statistics, and Shanghai Resident Registry (all Shanghai, China). Response rates were 99.8%, 98.7%, 96.7%, and 92.0% for the first (2000–2002), second (2002–2004), third (2004–2007), and fourth (2008–2010) in-person follow-ups of the SWHS. The SMHS response rates were 97.6% for the first follow-up (2004–2008) and 93.6% for the second (2008–2011). Medical records and/or histological slides of cancer cases are collected to review and verify liver cancer diagnoses.

In-person interviews were carried out at baseline using structured questionnaires to obtain information on age, education and other sociodemographic characteristics, residential history, anthropometrics, medical history, lifestyle factors (smoking, alcohol consumption, tea consumption, ginseng use, etc.), dietary intakes, physical activity, occupational history, and family

[5]To whom correspondence should be addressed.
E-mail: ybxiang@shsci.org

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history of cancer. Reproductive history and hormone use were collected for women.

Dietary intake assessment. Information of dietary intake over the preceding year was collected using validated FFQs at the baseline and first follow-up surveys (carried out 2–3 years after baseline).[18,19] The SWHS FFQ included 77 food items, covering approximately 90.0% of foods commonly consumed in urban Shanghai at enrolment; the SMHS FFQ included 81 food items, covering 88.8% of foods common in Shanghai at enrolment. These two FFQs are virtually identical with the following minor differences: (i) only the SWHS FFQ includes sweet potatoes; (ii) fresh soybeans, fresh peas, and fresh broad beans were combined into one category in the SWHS FFQ, but listed separately in the SMHS FFQ; and (iii) the SMHS FFQ includes garland chrysanthemum, shepherd's purse, clover, amaranth, pea shoots, and pig's ham hock, all of which are consumed in low amounts and were not included in the SWHS FFQ. The validity of the FFQs was evaluated previously; correlation coefficients for the main food groups as measured on the FFQ and averages from multiple 24-h dietary recalls ranged from 0.41 to 0.66 in the SWHS[18] and from 0.35 to 0.72 in the SMHS.[19] Only 3–7% of SWHS participants and 1.5–6.2% of SMHS participants were misclassified into extreme quartiles of food group intake. Daily total energy and nutrient intakes were derived from the FFQ by multiplying the amount of food consumed and its nutrient content based on the Chinese Food Composition Tables.[21]

Statistical analysis. The current analysis included follow-up data collected up to December 31, 2009. Liver cancer refers to cases with the ICD-9 diagnosis code 155.[22] During an average follow-up time of 10.9 years in the SWHS and 5.5 years in the SMHS, 355 incident cases of primary liver cancer were documented.

We excluded 2103 participants because of a history of cancer (1579 women) before study enrolment; or, during follow-up, a diagnosis of cancer *in situ* (61 women; 4 men), cancer that could not be confirmed (61 women; 23 men); or missing cancer type or diagnosis date (135 women; 133 men); or unreasonably high (>4000 kcal/day) or low (<500 kcal/day) energy intake (16 women; 91 men). To avoid the influence of preclinical disease on dietary habits, we further excluded 87 liver cancer cases (24 women; 63 men) diagnosed within 2 years of enrolment and 1405 participants (579 women; 826 men) who had fewer than 2 person-years of follow-up. After these exclusions, 132 837 participants, including 267 liver cancer cases, remained for the current analyses. Among them, 154 (57.7%) were primary malignant neoplasms (ICD-9 155.0), 46 (17.2%) were malignant neoplasms of the intrahepatic bile ducts (ICD-9 155.1), and 67 (25.1%) were unspecified malignant neoplasms of the liver (ICD-9 155.2).

As previously reported, dietary patterns were derived using factor analysis based on individual foods or food groups obtained directly from the FFQ.[23] Individual vegetable items in our study were classified into 13 food groups according to the system used in the Chinese Food Composition Tables, which was based on botanic similarity (Appendix 1).

To increase the accuracy of the dietary assessment, we used the averages of intakes derived from the two FFQs in the SWHS. 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. Because the vast majority of SMHS participants had a very short follow-up time after the second FFQ, only the information collected at baseline was included.

Three major dietary patterns were identified in our population: a vegetable-based diet, characterized by high intake of vegetables; a fruit-based diet, characterized by high intake of fresh fruits; and a meat-based diet, characterized by high intake of meat, poultry, and animal parts (heart, brain, tongue, intestine, etc.). These three patterns explain 79% of the variance in food intakes. [23] Associations of the three dietary patterns with selected baseline characteristics were assessed with adjustment for age and total energy intake[24] using the general linear model (continuous variables) or Cochran–Mantel–Haenszel statistics (categorical variables). Partial Pearson's correlation coefficients were calculated between dietary patterns and food group or nutrient intakes after adjustment for total energy intake.

Cox proportional-hazard regression models were used to estimate HRs and 95% CIs with age as the time scale and stratified on birth cohort (5-year categories). Dietary variables were classified into four categories based on the cohort-specific quartile distribution with the lowest quartile serving as the reference. Tests for linear trend were carried out by entering categorical variables as continuous parameters in the models.

Factors that were related to both liver cancer and the three dietary patterns were included in the analysis as covariates. These include: age at enrolment; BMI (weight [kg]/height [m^2]); total energy intake; sex; family income level; education level; family history of liver cancer in first-degree relatives; history of chronic viral hepatitis, chronic liver disease or cirrhosis, diabetes, and cholelithiasis or cholecystectomy; and vitamin C, vitamin E, or multivitamin supplement use. Further adjustment for ever smoking, ever drinking alcohol, marital status, and exercise participation did not materially alter our findings; therefore, we did not adjust for them in the final model.

Given that chronic viral hepatitis and liver cirrhosis are the major risk factors for liver cancer and may change dietary intake patterns, we carried out additional analyses stratified by history of chronic liver disease (defined as having viral hepatitis [ICD-9 code 070] or chronic liver disease and cirrhosis [ICD-9 code 571]) reported at baseline. Multiplicative interactions were evaluated using a likelihood ratio test by comparing the results with and without the interaction term in the models. We also carried out sensitivity analyses by excluding participants with a family history of liver cancer to address the potential influence of family dietary habits on risk estimates.

All statistical tests were two-sided, and P < 0.05 was considered statistically significant. Analyses were carried out with SAS version 9.2 software (SAS Institute, Cary, NC, USA).

Results

Cohort members who developed liver cancer were older and more likely to have a lower educational level, prior history of chronic viral hepatitis, chronic liver disease or cirrhosis, cholelithiasis or cholecystectomy, and family history of liver cancer compared with SWHS and SMHS participants that did not develop liver cancer. The SWHS cases were more likely to have higher BMI and lower vitamin E supplement use, whereas SMHS cases had lower family income, a history of diabetes, and high vitamin C and multivitamin supplement use. No differences in total energy intake, smoking habits, alcohol consumption, or regular physical activity in the preceding 5 years were noted (Table 1).

Baseline characteristics of participants according to quartiles of the age- and energy-adjusted vegetable-based dietary pattern are presented in Table 2. Study participants in the highest quartile of the vegetable-based dietary pattern were younger, were more likely to have higher income, higher education, higher BMI, a history of diabetes, and a history of cholelithiasis or cholecystectomy, were regular exercisers and alcohol drinkers, and fewer were manual laborers. In addition, women in the highest quartile of the vegetable-based pattern were

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Table 1. Baseline characteristics of the Shanghai Women's (1997–2000) and Men's (2002–2006) Health Studies: Liver cancer cases compared with other cohort members

	Women			Men		
	Non-cases (n = 72 368)	Cases (n = 118)	P-value	Non-cases (n = 60 202)	Cases (n = 149)	P-value
Age at enrolment (years, mean ± SD)	52.4 ± 9.0	59.0 ± 8.8	<0.01	55.2 ± 9.7	59.4 ± 10.1	<0.01
BMI (kg/m^2, mean ± SE)	24.0 ± 0.0	24.7 ± 0.3	0.03	23.7 ± 0.0	23.3 ± 0.3	0.10
Total energy intake (kcal/day, mean ± SE)	1644.1 ± 1.3	1688.5 ± 32.1	0.17	1908.3 ± 1.9	1910.0 ± 38.7	0.97
Family income level, per person per year (%)						
Low	27.5	29.2	0.62	54.9	68.0	<0.01
Middle	38.9	44.9		35.4	24.8	
High	33.6	25.8		9.8	7.2	
Education level (%)						
Elementary school or less	21.1	29.4	<0.01	7.8	9.5	0.01
Middle school	37.3	29.2		33.0	31.9	
High school	28.0	32.9		35.7	43.9	
College or above	13.5	8.5		23.4	14.7	
Ever had chronic viral hepatitis (%)	2.6	27.1	<0.01	6.8	40.3	<0.01
Ever had chronic liver disease or cirrhosis (%)	0.8	3.2	<0.01	3.3	16.6	<0.01
Ever had diabetes (%)	4.2	6.2	0.16	6.1	8.7	0.01
Ever had cholelithiasis or cholecystectomy (%)	11.3	17.0	0.01	7.7	13.7	<0.01
Family history of liver cancer in first-degree relatives (%)	3.3	12.7	<0.01	3.5	11.7	<0.01
Ever smoker (%)	2.8	3.5	0.34	69.6	70.0	0.69
Ever drank alcohol (%)	2.3	1.9	0.98	33.6	25.9	0.72
Regular physical activity during past 5 years (%)	35.0	35.4	0.34	35.4	35.7	0.92
Vitamin C supplement use (%)	7.0	6.4	0.65	5.5	16.6	<0.01
Vitamin E supplement use (%)	10.9	7.0	0.06	4.5	6.1	0.66
Multivitamin supplement use (%)	7.1	7.0	0.56	7.5	13.6	0.01

All variables were standardized to age distribution at baseline survey. The general linear model for continuous variables and Cochran–Mantel–Haenszel statistics for categorical variables were used. BMI, body mass index; SD, standard deviation; SE, standard error.

Table 2. Baseline characteristics of study participants according to quartiles (Q) of the vegetable-based dietary pattern in the Shanghai Women's (1997–2000) and Men's (2002–2006) Health Studies

	Women			Men		
	Q1	Q4	P-value	Q1	Q4	P-value
Age at enrolment (years, mean ± sd)	52.6 ± 9.1	52.1 ± 8.8	<0.01	56.1 ± 10.3	54.3 ± 9.2	<0.01
Total energy intake (kcal/day, mean ± SE)	1726.6 ± 345.0	1699.6 ± 370.8	<0.01	1737.2 ± 452.4	2127.0 ± 494.5	<0.01
BMI (kg/m^2, mean ± SE)	23.7 ± 3.4	24.4 ± 3.4	<0.01	23.5 ± 3.1	24.1 ± 3.1	<0.01
Married (%)	89.6	87.6	<0.01	96.7	97.7	<0.01
Ever had chronic viral hepatitis (%)	2.5	2.8	0.20	7.1	6.8	0.08
Ever had chronic liver disease or cirrhosis (%)	0.8	0.9	0.28	2.9	3.9	<0.01
Ever had diabetes (%)	2.6	5.6	<0.01	3.6	8.5	<0.01
Ever had cholelithiasis or cholecystectomy (%)	10.1	12.4	<0.01	7.2	8.2	0.01
Family history of liver cancer in first-degree relatives (%)	3.2	3.3	0.80	3.6	3.6	0.89
Ever smoker (%)	2.8	3.0	0.05	71.6	68.5	<0.01
Ever drank alcohol (%)	2.0	2.8	<0.01	29.1	38.1	<0.01
Regular physical activity (%)	32.5	38.2	<0.01	30.6	38.9	<0.01
Family income level, per person per year (%)			<0.01			<0.01
Low	28.0	26.4		56.1	53.5	
Middle	38.4	39.5		34.4	36.1	
High	33.7	34.1		9.5	10.7	
Education level (%)			<0.01			<0.01
Elementary school or less	20.6	19.4		7.9	6.6	
Middle school	37.4	37.8		32.7	32.5	
High school	28.6	28.2		37.3	36.0	
College or above	13.4	14.6		22.1	24.9	
Occupation (%)			<0.01			<0.01
Professional	28.2	28.7		25.2	27.2	
Clerical	20.2	22.0		21.0	22.9	
Manual laborer	51.3	49.0		53.7	49.9	
Housewife	0.3	0.4				
Ever used oral contraceptives (%)	20.2	20.5	0.58			

All variables were adjusted for age and total energy intake. BMI, body mass index; SD, standard deviation; SE, standard error.

more likely to be smokers and have lower total energy intake, and they were less likely to be married. Men in the highest quartile of the vegetable-based pattern were more likely to be non-smokers, married, have higher total energy intake, and a history of chronic liver disease or cirrhosis. The fruit- and meat-based dietary patterns also varied according to socioeconomic and some lifestyle factors (data not shown).

As shown in Table 3, the vegetable-based dietary pattern was inversely associated with liver cancer risk (HRs [95% CIs] for lowest to highest quartiles: 1.00 [reference], 0.98 [0.71–1.35]; 0.93 [0.67–1.29]; and 0.58 [0.40–0.84]; P_{trend} = 0.01). Although the trend test and point estimates were only significant for men, the inverse association was consistent among both men and women. The test for multiplicative interaction between sex and the vegetable-based dietary pattern was not significant ($P_{interaction}$ = 0.09). Further analyses excluding individuals with a family history of liver cancer showed little change in the risk estimates (HRs [95% CIs] for the second to fourth quartiles: 0.93 [0.62–1.38]; 1.05 [0.71–1.55]; and 0.59 [0.38–0.94]; P_{trend} = 0.07, data not shown). We also carried out subgroup analyses by limiting the cases to primary malignant neoplasm of liver. Results were similar to those observed in the entire study population. The HRs (95% CIs) for the second to the fourth quartiles of the vegetable-based pattern were 0.72 (0.47–1.11), 0.76 (0.50–1.16), and 0.53 (0.33–0.85) (P_{trend} = 0.01, data not shown in table). The fruit- and meat-based dietary patterns were not associated with liver cancer risk.

We evaluated the association between dietary patterns and liver cancer risk further in stratified analyses by history of chronic liver disease (Table 4). The inverse association for the vegetable-based dietary pattern appeared to be stronger among participants with a history of chronic liver disease (HR [95% CI]: 0.34 [0.17–0.69]) than among participants without (HR [95% CI]: 0.78 [0.50–1.21]). Similar associations were found when the analyses were restricted to cases of primary malignant neoplasm of liver. The HRs (95% CIs) for participants with a history of chronic liver disease across the lowest to the highest quartiles of the vegetable-based pattern were 1.00 (reference), 0.93 (0.47–1.84), 0.83 (0.42–1.64), and 0.42 (1.18–0.94), respectively (P_{trend} = 0.04). The corresponding HRs (95% CIs) for participants without a history of chronic liver disease were 1.00 (reference), 0.63 (0.36–1.11), 0.75 (0.44–1.28), and 0.66 (0.37–1.16), respectively (P_{trend} = 0.19, data not shown in table). Again, the fruit- and meat-based dietary patterns were not associated with liver cancer risk in the stratified analyses.

Table 5 presents associations of liver cancer risk with intakes of total vegetables and vegetable subgroups. Total vegetable intake was significantly associated with reduced risk of liver cancer in participants with a history of chronic liver disease; HR (95% CIs) for highest compared with lowest quartile: 0.37 (0.18–0.75). Intakes of celery (P_{trend} = 0.03) and allium vegetables (P_{trend} < 0.01) were also inversely associated with liver cancer risk. Consumption of individual allium vegetables, including Chinese chives, garlic and garlic shoots, onions, and heads of garlic, were also inversely associated with risk (P_{trend} = 0.01, 0.02, <0.01, and 0.02, respectively; data not shown). Further analyses showed that the inverse association between celery and allium vegetable intakes were predominantly seen among individuals with a history of chronic liver disease (both $P_{interaction}$ = 0.04). Intake of legumes and legume products was inversely associated with risk (HRs [95% CIs] for lowest to highest quartiles: 1.00; 0.92 [0.66–1.28]; 0.73 [0.51–1.04]; and 0.72 [0.50–1.04]; P_{trend} = 0.04). Participants in the highest quartile of mushroom intake had significantly lower risk (HR [95% CI]: 0.66 [0.46–0.95] compared with the lowest quartile [P_{trend} = 0.03]). Intake of composite vegetables, including asparagus lettuce and garland chrysanthemum, was inversely associated with risk (HRs [95% CIs] for lowest to highest quartiles: 1.00; 0.90 [0.66–1.23]; 0.81 [0.58–1.12]; and 0.48 [0.33–0.71]; P_{trend} < 0.01). These associations did not vary by history of chronic liver disease ($P_{interaction}$ = 0.70 for legumes/legume products, 0.50 for mushrooms, and 0.96 for composite vegetables). As expected, the vegetable-based dietary pattern was correlated with intakes of dietary antioxidant vitamins, such as

Table 3. Hazard ratios for liver cancer risk by quartiles (Q) of dietary patterns in the Shanghai Women's (1997–2000) and Men's (2002–2006) Health Studies

	Women		Men		Total	
	Cases (*n* = 118)	HR (95% CI)†	Cases (*n* = 149)	HR (95% CI)†	Cases (*n* = 267)	HR (95% CI)‡
Vegetable-based dietary pattern						
Q1	36	1.00	42	1.00	78	1.00
Q2	24	0.68 (0.40–1.14)	48	1.29 (0.85–1.96)	72	0.98 (0.71–1.35)
Q3	34	0.95 (0.59–1.52)	36	0.95 (0.60–1.49)	70	0.93 (0.67–1.29)
Q4	24	0.68 (0.40–1.14)	23	0.52 (0.31–0.89)	47	0.58 (0.40–0.84)
P for trend		*P* = 0.30		*P* = 0.01		*P* = 0.01
Fruit-based dietary pattern						
Q1	33	1.00	33	1.00	66	1.00
Q2	36	1.48 (0.91–2.40)	30	0.89 (0.54–1.46)	66	1.11 (0.78–1.56)
Q3	34	1.49 (0.90–2.47)	39	1.17 (0.72–1.88)	73	1.24 (0.88–1.74)
Q4	15	0.75 (0.40–1.43)	47	1.51 (0.92–2.46)	62	1.13 (0.78–1.64)
P for trend		*P* = 0.72		*P* = 0.06		*P* = 0.39
Meat-based dietary pattern						
Q1	39	1.00	38	1.00	77	1.00
Q2	30	0.99 (0.61–1.62)	41	1.14 (0.73–1.79)	71	1.02 (0.74–1.42)
Q3	26	1.08 (0.64–1.82)	30	0.96 (0.59–1.58)	56	0.95 (0.67–1.35)
Q4	23	1.18 (0.68–2.03)	40	1.36 (0.82–2.24)	63	1.18 (0.83–1.69)
P for trend		*P* = 0.54		*P* = 0.37		*P* = 0.51

†Adjusted for age, body mass index, total energy intake, family income level, education level, family history of liver cancer in first-degree relatives, history of chronic viral hepatitis, history of chronic liver disease or cirrhosis, history of diabetes, history of cholelithiasis or cholecystectomy, vitamin C and E and multivitamin supplement use, and mutual adjustment for three dietary patterns. ‡Additionally adjusted for sex.
CI, confidence interval; HR, hazard ratio; Q, quartile.

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Table 4. Hazard ratios for liver cancer risk by quartiles (Q) of dietary patterns in the Shanghai Women's (1997–2000) and Men's (2002–2006) Health Studies, stratified by history of chronic liver disease

	No history of chronic liver disease		History of chronic liver disease		*P* for interaction
	Cases (*n* = 183)	HR (95% CI)	Cases (*n* = 84)	HR (95% CI)	
Vegetable-based dietary pattern					
Q1	49	1.00	29	1.00	
Q2	49	1.03 (0.69–1.53)	23	0.94 (0.54–1.63)	
Q3	49	1.06 (0.71–1.58)	21	0.75 (0.43–1.33)	
Q4	36	0.78 (0.50–1.21)	11	0.34 (0.17–0.69)	
P for trend		0.36		<0.01	0.28
Fruit-based dietary pattern					
Q1	49	1.00	17	1.00	
Q2	50	1.18 (0.79–1.76)	16	0.84 (0.42–1.67)	
Q3	48	1.26 (0.84–1.90)	25	1.17 (0.62–2.24)	
Q4	36	1.05 (0.67–1.66)	26	1.17 (0.60–2.29)	
P for trend		0.67		0.44	0.55
Meat-based dietary pattern					
Q1	58	1.00	19	1.00	
Q2	42	0.86 (0.58–1.29)	29	1.47 (0.82–2.65)	
Q3	37	0.93 (0.61–1.41)	19	1.07 (0.56–2.05)	
Q4	46	1.38 (0.91–2.10)	17	0.89 (0.44–1.81)	
P for trend		0.20		0.58	0.17

Hazard ratio (HR) adjusted for age, sex, body mass index, total energy intake, family income level, education level, family history of liver cancer in first-degree relatives, history of diabetes, history of cholelithiasis or cholecystectomy, vitamin C and E and multivitamin supplement use, and mutual adjustment for three dietary patterns. CI, confidence interval; Q, quartiles.

vitamin A ($r = 0.50$), vitamin C ($r = 0.71$), and vitamin E ($r = 0.41$). Further adjustment for intakes of vitamin A, B1, B2, C, carotene, retinol, niacin, or folic acid did not materially change the associations (data not shown). However, after adjustment for dietary vitamin E intake, the inverse association between legumes and legume products and liver cancer risk was diminished (HRs [95% CIs] for lowest to highest quartiles: 1.00; 1.02 [0.71–1.48]; 0.89 [0.57–1.40]; and 0.91 [0.53–1.55]; $P_{trend} = 0.65$). Results of analyses limited to individuals with no family history of liver cancer at baseline were similar (data not shown). We also carried out analyses by restricting the cases to primary malignant neoplasm of liver. Similar associations were observed compared with those in the entire study population (data not shown in table).

No significant associations with liver cancer risk were observed for intakes of cruciferous, aquatic, cucurbitaceous, or solanaceous vegetables, tubers, spinach, carrots, or lotus root (all $P_{trend} > 0.05$).

Discussion

In this large, prospective study, we observed a clear, inverse association between a vegetable-based dietary pattern and liver cancer risk. This association was stronger among participants with a history of chronic liver disease. Inverse associations were also observed for total vegetable, celery, and allium vegetable consumption and were suggested for mushroom, composite vegetable, and legume and legume product consumption. Although estimates for total vegetables and liver cancer risk did not reach statistical significance, the inverse association patterns were consistent for both vegetable-based dietary pattern and intake of total vegetables.

Dietary pattern analysis has an advantage over analysis of individual food items and groups, in that it can capture interactions between foods and nutrients. The "prudent" dietary pattern (or "Mediterranean" or "vegetable–fruit" diet), characterized by high intakes of fruits, vegetables, legumes, and unrefined cereals, [25] and the "Western" pattern (or "Traditional" or "meat–sweet" diet) characterized by high intakes of red meat, high-fat foods, and refined grains, have been associated with risk of various cancers.[26–28] However, to our knowledge, no studies have evaluated the association of dietary patterns with liver cancer risk.

High consumption of vegetables has been associated with reduced liver cancer risk in three Asian cohort studies and two case–control studies.[4–12] In a cohort of 8436 men in Taiwan, participants consuming vegetables at <6 meals per week had significantly higher liver cancer risk compared with those consuming vegetables at ≥6 meals per week. This association was more evident in HBV carriers.[4] We also observed the inverse association between total vegetables and liver cancer risk was stronger among participants with a history of chronic liver disease. Two prospective studies carried out in Japan found a similar association. One study found that intakes of total vegetables, green-yellow vegetables, and green leafy vegetables were inversely associated with risk of hepatocellular carcinoma.[5] Another found that high intake of green-yellow vegetables was associated with reduced liver cancer mortality among Japanese atomic bomb survivors.[8] A case–control study carried out in northern Italy reported that lower combined fruit and vegetable consumption was associated with increased liver cancer risk.[6] Another Italian study found a non-significant inverse association of vegetable intake and hepatocellular carcinoma risk.[12] However, two case–control studies from Greece[29,30] reported no association between vegetable consumption and liver cancer risk, although they involved only 97[29] and 65[30] cases. The retrospective and hospital-based designs of previous studies are major limitations. Allium vegetable intake has been linked to lower risk of several types of cancer, including cancers of the esophagus,[3,31,32] stomach,[3,32,33] and colon/rectum,[3,34] but no reports have focused on liver cancer. Data linking consumption of celery, mushrooms, and composite vegetables to cancer are lacking. However, consumption of these foods is relatively low in Western societies.

Vegetables are major sources of vitamins, minerals, dietary fiber, and other bioactive compounds.[3, 33] The vegetable-based dietary pattern in our previous study showed strong positive correlations with dietary vitamins, such as vitamin A, C, and E. However, adjustment for dietary vitamins A and C

Table 5. Hazard ratios for liver cancer risk by quartiles of vegetable group intakes in the Shanghai Women's (1997–2000) and Men's (2002–2006) Health Studies, stratified by history of chronic liver disease

	Total		No history of chronic liver disease		History of chronic liver disease		P for interaction
	Cases	HR (95% CI)†	Cases (n = 183)	HR (95% CI)‡	Cases (n = 84)	HR (95% CI)‡	
Total vegetables (g/day)							
≤196.74 (213.30)	73	1.00	47	1.00	26	1.00	
≤275.32 (307.69)	62	0.91 (0.64–1.28)	43	1.06 (0.70–1.62)	19	0.67 (0.37–1.22)	
≤376.04 (429.95)	77	1.15 (0.82–1.61)	52	1.33 (0.88–2.01)	25	0.84 (0.47–1.49)	
>376.04 (429.95)	55	0.73 (0.49–1.07)	41	1.06 (0.66–1.69)	14	0.37 (0.18–0.75)	
P for trend		P = 0.30		P = 0.55		P = 0.02	P = 0.31
Cruciferous vegetables (g/day)							
≤58.60 (61.14)	71	1.00	48	1.00	23	1.00	
≤87.41 (97.29)	77	1.14 (0.82–1.57)	55	1.22 (0.83–1.80)	22	0.99 (0.55–1.78)	
≤122.81 (148.55)	57	0.83 (0.58–1.19)	39	0.85 (0.55–1.31)	18	0.80 (0.43–1.51)	
>122.81 (148.55)	62	0.83 (0.58–1.19)	41	0.84 (0.54–1.29)	21	0.79 (0.43–1.47)	
P for trend		P = 0.14		P = 0.20		P = 0.37	P = 0.94
Solanaceous vegetables (g/day)							
≤22.65 (15.93)	74	1.00	50	1.00	24	1.00	
≤41.54 (30.80)	60	0.88 (0.62–1.24)	41	0.95 (0.63–1.44)	19	0.71 (0.38–1.32)	
≤69.89 (55.87)	54	0.81 (0.56–1.16)	38	0.93 (0.60–1.43)	16	0.58 (0.30–1.12)	
>69.89 (55.87)	79	1.14 (0.81–1.61)	54	1.37 (0.90–2.08)	25	0.81 (0.44–1.49)	
P for trend		P = 0.56		P = 0.18		P = 0.47	P = 0.94
Cucurbitaceous vegetables (g/day)							
≤25.61 (21.01)	80	1.00	57	1.00	23	1.00	
≤42.48 (38.61)	60	0.79 (0.56–1.10)	40	0.80 (0.53–1.20)	20	0.78 (0.42–1.43)	
≤65.87 (64.84)	68	0.91 (0.65–1.27)	50	1.03 (0.70–1.53)	18	0.68 (0.36–1.28)	
>65.87 (64.84)	59	0.74 (0.52–1.06)	36	0.73 (0.47–1.14)	23	0.79 (0.42–1.49)	
P for trend		P = 0.19		P = 0.35		P = 0.43	P = 0.58
Legumes and legume products (not including water content)							
≤15.69 (25.53)	74	1.00	51	1.00	23	1.00	
≤22.62 (37.70)	69	0.92 (0.66–1.28)	44	0.90 (0.60–1.36)	25	1.00 (0.56–1.79)	
≤31.56 (53.60)	58	0.73 (0.51–1.04)	40	0.78 (0.51–1.19)	18	0.64 (0.34–1.21)	
>31.56 (53.60)	66	0.72 (0.50–1.04)	48	0.82 (0.53–1.27)	18	0.59 (0.30–1.17)	
P for trend		P = 0.04		P = 0.30		P = 0.06	P = 0.70
Tubers (g/day)							
≤3.84 (2.57)	75	1.00	52	1.00	23	1.00	
≤9.40 (7.72)	73	1.04 (0.75–1.45)	48	1.00 (0.67–1.50)	25	1.01 (0.56–1.82)	
≤18.52 (15.44)	49	0.95 (0.66–1.39)	33	0.90 (0.57–1.41)	16	1.05 (0.54–2.03)	
>18.52 (15.44)	70	1.12 (0.79–1.59)	50	1.17 (0.77–1.78)	20	0.98 (0.51–1.86)	
P for trend		P = 0.62		P = 0.55		P = 0.96	P = 0.90
Aquatic vegetables (g/day)							
≤4.84 (3.70)	78	1.00	56	1.00	22	1.00	
≤9.35 (7.86)	63	0.89 (0.63–1.24)	40	0.81 (0.54–1.22)	23	1.11 (0.61–2.01)	
≤16.43 (15.01)	70	1.00 (0.72–1.39)	45	0.95 (0.63–1.42)	25	1.16 (0.64–2.11)	
>16.43(15.01)	56	0.73 (0.51–1.05)	42	0.85 (0.56–1.30)	14	0.56 (0.28–1.12)	
P for trend		P = 0.17		P = 0.6		P = 0.16	P = 0.31
Celery (g/day)							
≤2.87 (1.74)	82	1.00	48	1.00	34	1.00	
≤5.94 (5.22)	81	1.05 (0.77–1.43)	58	1.39 (0.94–2.04)	23	0.62 (0.36–1.06)	
≤11.37 (11.34)	53	0.75 (0.53–1.07)	37	0.98 (0.64–1.52)	16	0.48 (0.26–0.88)	
>11.37 (11.34)	51	0.73 (0.51–1.05)	40	1.12 (0.73–1.74)	11	0.30 (0.15–0.60)	
P for trend		P = 0.03		P = 0.98		P < 0.01	P = 0.04
Allium vegetables (g/day)							
≤3.69 (6.73)	98	1.00	60	1.00	38	1.00	
≤6.45 (11.70)	56	0.62 (0.45–0.87)	36	0.66 (0.44–1.00)	20	0.57 (0.33–0.99)	
≤11.12 (20.03)	61	0.68 (0.49–0.95)	44	0.83 (0.56–1.24)	17	0.47 (0.26–0.84)	
>11.12 (20.03)	52	0.56 (0.39–0.80)	43	0.81 (0.53–1.22)	9	0.24 (0.11–0.51)	
P for trend		P < 0.01		P = 0.44		P < 0.01	P = 0.04

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Table 5 (continued)

	Total		No history of chronic liver disease		History of chronic liver disease		*P* for interaction
	Cases	HR (95% CI)†	Cases (n = 183)	HR (95% CI)‡	Cases (*n* = 84)	HR (95% CI)‡	
Mushrooms (g/day)							
≤2.82 (2.44)	92	1.00	65	1.00	27	1.00	
≤5.88 (5.70)	60	0.71 (0.51–0.99)	46	0.85 (0.58–1.25)	14	0.44 (0.23–0.86)	
≤10.83 (12.04)	60	0.73 (0.52–1.03)	39	0.80 (0.53–1.20)	21	0.58 (0.32–1.06)	
>10.83 (12.04)	55	0.66 (0.46–0.95)	33	0.72 (0.46–1.13)	22	0.57 (0.31–1.05)	
P for trend		*P* = 0.03		*P* = 0.13		*P* = 0.13	*P* = 0.50
Spinach (g/day)							
≤1.18 (1.22)	99	1.00	70	1.00	29	1.00	
≤3.07 (3.18)	55	0.74 (0.53–1.03)	32	0.61 (0.40–0.93)	23	1.02 (0.58–1.78)	
≤5.85 (7.95)	58	0.71 (0.51–0.99)	38	0.68 (0.45–1.01)	20	0.76 (0.42–1.36)	
>5.85 (7.95)	55	0.92 (0.65–1.30)	43	1.03 (0.69–1.54)	12	0.67 (0.33–1.35)	
P for trend		*P* = 0.36		*P* = 0.82		*P* = 0.18	*P* = 0.19
Carrots (g/day)							
≤0.03 (0.00)	93	1.00	62	1.00	31	1.00	
≤0.69 (0.79)	49	0.99 (0.70–1.41)	32	0.93 (0.60–1.44)	17	1.07 (0.58–1.99)	
≤3.62 (3.30)	55	0.79 (0.56–1.10)	41	0.89 (0.59–1.32)	14	0.55 (0.29–1.04)	
>3.62 (3.30)	70	0.95 (0.69–1.32)	48	1.00 (0.67–1.48)	22	0.78 (0.44–1.40)	
P for trend		*P* = 0.49		*P* = 0.89		*P* = 0.17	*P* = 0.47
Composite vegetables (g/day)							
≤0.06 (1.74)	90	1.00	63	1.00	27	1.00	
≤0.71 (4.33)	73	0.90 (0.66–1.23)	49	0.90 (0.62–1.31)	24	0.88 (0.51–1.54)	
≤2.25 (8.59)	64	0.81 (0.58–1.12)	45	0.86 (0.58–1.26)	19	0.71 (0.39–1.30)	
>2.25 (8.59)	40	0.48 (0.33–0.71)	26	0.50 (0.31–0.80)	14	0.47 (0.24–0.90)	
P for trend		*P* < 0.01		*P* = 0.01		*P* = 0.02	*P* = 0.96
Lotus root (g/day)							
≤0.02 (0.00)	107	1.00	73	1.00	34	1.00	
≤0.30 (0.60)	54	1.12 (0.80–1.57)	42	1.21 (0.82–1.79)	12	0.79 (0.40–1.57)	
≤1.56 (1.81)	53	0.93 (0.66–1.31)	33	0.88 (0.58–1.34)	20	1.00 (0.56–1.78)	
>1.56 (1.81)	53	0.83 (0.59–1.17)	35	0.83 (0.55–1.26)	18	0.81 (0.44–1.49)	
P for trend		*P* = 0.25		*P* = 0.28		*P* = 0.63	*P* = 0.47

Cut-off points for quartiles of vegetable intake in the Shanghai Men's Health Study are shown in parentheses. †Additionally adjusted for history of chronic viral hepatitis, history of chronic liver disease or cirrhosis. ‡Adjusted for age, sex, body mass index, total energy intake, family income level, education level, family history of liver cancer, history of diabetes, history of cholelithiasis or cholecystectomy, vitamin C and E and multivitamin supplement use, and mutual adjustment for these dietary patterns. CI, confidence interval; HR, hazard ratio.

did not change the associations. Adjustment for dietary vitamin E weakened the association between legume and legume product consumption and liver cancer risk, but the association for the vegetable-based dietary pattern and several other vegetable groups persisted. These results suggest that other biochemical components in these vegetables may be responsible for the observed association. For instance, allium vegetables (onions, leeks, garlic, etc.) are rich in flavonols, diallyl sulphides, and organosulfur compounds,[3,35] mushrooms contain polysaccharides, especially lentinan,[34] and celery is a major dietary source of apigenin and luteolin. Evidence is emerging from cell culture and animal model experiments that these phytochemicals and other yet-to-be-identified bioactive components may have cancer-inhibitory effects through their antioxidative properties, modulation of phase I and II enzymes, stimulation of the immune system, or inhibition of mutagenesis and DNA adducts.[3,35–40] A recent study evaluated effects of dietary dry bean on 84 hepatic expressions of stress and toxicity-related genes in rats and found six up- or downregulated genes, including *CYP3A11*, *CYP7A1*, *FMO1*, *GSTM1*, *MIF*, and *UGT1A6*, may exert cancer-preventive effects in liver.[41] It is worth noting that the preventive effects of the vegetable-based pattern or total vegetables on liver cancer were strengthened when participants were limited to those who had a history of chronic liver disease in our study. Further research is needed to understand the mechanisms underlying these associations.

Strengths of our study include the population-based, prospective study design, high response rates, use of a validated FFQ, and adjustment for a wide range of potential confounders. There are some limitations in the present study. First, a lack of data on HBV/HCV infection and aflatoxin exposure. However, HCV infection and aflatoxin exposure are very low in Shanghai.[42] Although history of chronic viral hepatitis, chronic liver disease, or cirrhosis could capture some information related to HBV or HCV infection, this method of determining exposure to chronic viral infection is less than optimal. Second, although family income level and education were adjusted in our analyses, we cannot completely rule out the possibility of residual confounding from socioeconomic status. Third, several epidemiologic studies have evaluated the potential association between coffee consumption and liver cancer risk. However, coffee consumption was not common at baseline time of our cohorts. We did not collect information on coffee consumption in our survey questionnaires and thus were unable to evaluate its potential effects on the risk of liver cancer. Fourth, similar to all nutritional epidemiology studies, measurement errors in dietary assessment is always a concern and may attenuate the true association. Fifth, the temporal difference of baseline data collection between men and women may result in dietary differences, which may account for some of the minor sex differences observed. Finally, although the study was based on two cohorts of more than 132 837 Chinese people, the case sample size for some of the subgroup analyses was relatively small.

In summary, a vegetable-based dietary pattern, total vegetable intake, and consumption of celery, mushrooms, allium vegetables, composite vegetables, and legumes and legume products were inversely associated with liver cancer risk. The inverse association appeared to be stronger among participants with a history of chronic liver disease. Our findings, if confirmed, could have a significant impact on prevention of liver cancer, the third leading cause of cancer deaths worldwide.

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Disclosure Statement

The authors have no conflict of interest.

Abbreviations

BMI	body mass index
CI	confidence interval
FFQ	food-frequency questionnaire
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
ICD-9	International Classification of Disease, 9th Revision
SD	standard deviation
SE	standard error
SMHS	Shanghai Men's Health Study
SWHS	Shanghai Women's Health Study

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Appendix: 1

Composition of vegetable food groups

Food group	Food items included
Cruciferous vegetables	Greens, Chinese greens; green cabbage; Chinese cabbage, bok choy cabbage; cauliflower; white radish; white turnip; shepherd’s purse
Solanaceous vegetables	Eggplant; fresh red and green peppers; tomatoes
Cucurbitaceous vegetables	Wax gourds; cucumbers; luffa
Legumes and legume products	Soy milk, powdered soy milk; bean curd; fried bean curd, vegetarian chicken, bean curd cake and other kinds of bean products, excluding fresh bean curd; dried soybeans; mung beans, red beans, and other dried beans; soybean sprouts; mung bean sprouts; snow pea shoots; baby soy beans; fresh peas; fresh broad beans; yard long beans; green beans (four-season beans); hyacinth beans/snow peas (dutch peas); peanuts
Tubers	Potatoes; sweet potatoes
Aquatic vegetables	Wild rice stems; bamboo shoots
Celery	Celery
Allium vegetables	Green onions; Chinese chives; garlic and garlic shoots; onions; heads of garlic
Mushrooms	Fresh mushrooms, fresh xianggu mushroom; black and white edible tree fungi; dried xianggu mushroom
Spinach	Spinach
Carrots	Carrots
Composite vegetables	Asparagus lettuce; garland chrysanthemum
Lotus root	Lotus root