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Association between Dietary Tomato Intake and the Risk of Hepatocellular Carcinoma: The Singapore Chinese Health Study

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ABSTRACT

Background: Intake of tomato and/or lycopene has been associated with reduced risk of several cancers, but there is no report on the association with risk of hepatocellular carcinoma (HCC).

Methods: The associations of tomato and lycopene consumption with risk of HCC were examined in the Singapore Chinese Health Study, a prospective cohort of 63,257 Chinese ages 45 to 74 years at enrollment. Diet was assessed using a validated semiquantitative food frequency questionnaire. Cox proportional hazard regression models were used to estimate HR and its 95% confidence interval (CI) of HCC with the consumption of tomato and lycopene among all cohort participants, and unconditional logistic regression was used to assess the association by hepatitis B surface antigen (HBsAg) positivity in a nested case–control study.

Results: After a mean follow-up of 17.6 years, 561 incident HCC cases were identified. Higher tomato intake was associated with lower risk of HCC after adjustment for potential confounders ($P_{trend} < 0.001$). Compared with the lowest quartile, HRs (95% CIs) of HCC for the second, third, and fourth quartile of tomato intake were 0.70 (0.56–0.88), 0.73 (0.58–0.92), and 0.63 (0.49–0.81). Among HBsAg-negative individuals, the inverse association remained ($P_{trend} = 0.03$). There was no association between lycopene intake and HCC risk ($P_{trend} = 0.54$).

Conclusions: Tomato intake may offer protection against the development of HCC, particularly among individuals without chronic infection with hepatitis B virus.

Impact: Tomato intake is a low-cost preventative measure against HCC that may help reduce risk due to increasing rates of nonalcoholic fatty liver disease.

Introduction

Liver cancer is predicted to be the sixth most commonly diagnosed cancer globally and fourth leading cause of cancer death in 2018 (1). Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancers (2). The major causes of HCC are hepatitis B virus (HBV), hepatitis C virus (HCV), excessive use of alcohol, nonalcoholic fatty liver disease (NAFLD), and to a less extent, aflatoxin (3–5).

Historically the incidence rate of liver cancer was low in the United States. However, it has been increasing during the past four decades with an annual rate of increase by 6% from 3.2 of 100,000 in 1975 to 11.2 of 100,000 in 2016 among white males (6). Furthermore, the prognosis of patients with liver cancer is poor with a 5-year survival rate at 18% overall. Liver cancer is the second most lethal tumor behind pancreatic cancer (2). Given the universal HBV vaccination and curative treatment for HCV, the rising incidence of HCC in the United States could be a consequence of increasing obesity and diabetes—the underlying causes for NAFLD, a major contributing factor for HCC (5). With the rapid increase in prevalence of obesity and diabetes globally (7), it is estimated that incidence of HCC due to NAFLD is expected to increase by 122% between 2016 and 2030 (2). Besides prevention and control of obesity, it is of vital importance to identify protective modifiable factors that can apply for primary prevention of HCC at a population level with low cost.

Tomato intake has been associated with a significantly reduced risk of prostate cancer and specifically in an Asian population (8), but overall associations between tomato intake and risk of various cancer types have been inconsistent. For example, tomato intake was associated with significantly lower risk of premenopausal breast cancer in Korean women, but was not associated in Japanese women (9, 10). Tomato intake has also been found to be associated with reduced risk of pancreatic cancer and ovarian cancer in U.S. populations (11, 12). Tomato contains high level of lycopene, which has been associated with reduced risk of prostate cancer (13). However, in prospective studies, whole tomato, as a food item, has been shown to have a greater protective effect than lycopene alone on prostate cancer (14). So far there is lack of epidemiologic data on the association between intake of tomato and/or lycopene and risk of HCC.

To fill the knowledge gap, we conducted a prospective study for the association between tomato and lycopene intake and risk of HCC in the Singapore Chinese Health Study, a prospective study of more than 60,000 middle-aged or older Chinese men and women in Singapore with up to 25 years of follow-up.

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Materials and Methods

Study population

This study was conducted within the Singapore Chinese Health Study (SCHS), a population-based prospective cohort of 63,257 Chinese men and women ages 45 to 74 years at recruitment between April 1993 and December 1998. The cohort was drawn from permanent residents of Singapore who resided in government-built housing, where 86% of the Singapore population resided in. The enrollment criteria restricted study participants to two major dialect groups of Chinese in Singapore: the Hokkiens and Cantonese (15). All subjects provided written informed consent, and this study was approved by the Institutional Review Board at the National University of Singapore and the University of Pittsburgh.

Blood and urine samples were obtained from a 3% random sample of participants enrolled in SCHS from 1994 to 1999. From July 1999 to December 2003, all surviving cohort participants were contacted by telephone to provide updated information on their lifestyle characteristics such as alcohol use, tobacco use, body weight, physical activity, and medical history. At the telephone interview, each participant was asked if she/he was willing to donate biological samples. We also collected blood or buccal and urine samples from all consented participants during 2000 to 2005 period. Overall, 28,346 subjects (i.e., approximately 57% of eligible) agreed to provide blood for research.

Baseline and dietary assessment

Participants were interviewed at the time of enrollment by trained interviewers using a structured questionnaire. Interviews occurred in the participant's home where we collected information on demographic and lifestyle factors, such as dialect group, body weight and height, family history of cancer, medical history, current physical activity, lifetime tobacco use, menstrual/reproductive history (women only), and occupational exposures. The following formula was used to calculate the BMI: weight (in kilograms) divided by height (in meters) squared.

Details of the dietary assessment and validation of the food frequency questionnaire (FFQ) have been reported previously (16). Briefly, we used a validated semi-quantitative FFQ with 165 food items commonly consumed by the study population. For example, each participants was asked the average intake of raw and/or cooked tomatoes during the last year according to nine frequency categories: never or hardly ever, once a month, two to three times a month, once a week, two to three times a week, four to six times a week, once a day, and two or more times a day. We also asked the participants about their serving size of tomatoes as two wedges or less, three to four wedges, or five wedges or more. Total energy and dietary nutrients, including lycopene were estimated using the Singapore Food Composition Database that included 96 nutritional and nonnutritional values per 100 g of food and beverages (16).

Ascertainment of HCC cases

Deaths and cancer diagnosis among cohort patients were ascertained through the linkage analysis with the Singapore Registry of Births and Deaths and Singapore Cancer Registry, respectively. The Singapore Cancer Registry has been comprehensively collected information on cancer diagnosis since 1968 (17). As of December 31, 2015, only 56 participants (<0.1%) were lost to follow-up. HCC cases were defined by the International Classification of Diseases-Oncology, Second Edition (ICD-O-2) code C22. The present analysis included 561 incident cases of HCC after excluding 1,936 participants with a history of cancer at recruitment.

Case–control study of HCC

A nested case–control study was created within the biospecimen subcohort for serologic biomarker of hepatitis B infection. All 197 incident HCC cases diagnosed before December 31, 2015, who provided a baseline blood sample were included for this analysis. For each case, we randomly selected three controls (for the first 71 cases) or two controls (for the remaining 126 cases) within the cohort who provided a baseline blood sample and were alive and free of cancer at the date of HCC diagnosis of the index case. Control subjects were individually matched to the index case by age at enrollment (±3 years), gender, dialect groups (i.e., Hokkien, Cantonese), date of baseline interview (±2 years), and date of sample collection (±6 months).

Measurement of serologic marker of HBV

Serum samples of all subjects in the case–control study were tested for hepatitis B surface antigen (HBsAg) using a Commercialized Test Kit (Ausria, Abbott Laboratories) as described previously (18–20). Laboratory personnel were blinded on the case/control status of the test samples. Briefly, samples negative for HBsAg were further tested for the presence of antibodies to hepatis B core antigen (anti-HBc) and antibodies to hepatitis B surface antigen (anti-HBs; Corab and Ausab, Abbott Laboratories) on the first 302 samples. We did not measure anti-HBc and anti-HBs on the remaining 360 serum samples to save serum samples for other biomarker measurements.

Statistical analysis

Person-years of follow-up for each subject was calculated from the date of enrollment into the study to the date of HCC diagnosis, death, migration out of Singapore, or December 31, 2015, whichever occurred first. Quartiles of tomato and lycopene intake, respectively, were determined on the basis of their distributions among the entire cohort.

The differences in the distributions of baseline demographic and lifestyle factors between HCC cases and noncases were determined by Wilcoxon two-sample test (for continuous variables) or Kruskal–Wallis nonparametric test (for frequencies). Cox proportional hazards regression model was used to estimate HR and 95% confidence interval (CI) for the association between tomato or lycopene intake and HCC risk with adjustment for potential confounding variables. Covariates measured at baseline included in the model were age at recruitment (years), gender, dialect group (i.e., Cantonese, Hokkien), BMI (kg/m^2), education (i.e., no formal education/primary, secondary or higher), smoking status (i.e., never, light, heavy), alcohol intake (i.e., nondrinkers and light drinkers, heavy drinkers ≥7 drinks per week), year of enrollment (i.e., 1993–1995, 1996–1998), diabetes status (yes, no), physical activity (yes, no), and total energy intake (kCal/day). Heavy smokers were defined as those who began smoking before 15 years of age and smoked 13 or more cigarettes per day whereas all other smokers were considered as light smokers. Additional covariates such as intake of coffee and omega-6 polyunsaturated fatty acid did not alter the association between tomato or lycopene intake and HCC risk, thus the final results presented were not adjusted for these two covariates. Linear trend for HCC risk with levels of tomato or lycopene intake was tested on the basis of the ordinal values of their quartiles. Heterogeneity in the tomato-HCC risk associations between different groups of selected risk factors (i.e., gender, BMI, diabetes, smoking status) were tested by including product term of tomato intake and the risk factor in the Cox proportional hazards model.

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For the nested case–control study, logistic regression method was used to examine the association between tomato intake and HCC risk among individuals with available HBsAg status overall and among those negative for HBsAg.

All statistical analyses were performed using the SAS version 9.4 computer software (SAS Institute Inc.). All *P* values presented are two-sided. The *P* values that were less than 0.05 were considered to be statistically significant.

Results

After a mean (SD) follow-up of 17.6 (5.3) years for 61,321 participants, 561 incident HCC cases were identified. The median (25th percentile, 75th percentile) age of diagnosis was 71 years (65, 76).

Compared with those with lowest quartile, individuals in the highest quartile of tomato intake were younger, more likely to be men and attained higher level of education. They were also more likely to be nonsmokers, moderate alcohol drinkers, and physically more active. They had a lower prevalence of diabetes and higher levels of total energy and lycopene intake (**Table 1**). Compared with the rest of the cohort, HCC cases were older at recruitment, higher proportions of men, smokers, alcohol drinkers, and diabetes, but lower levels of education (**Table 2**).

High tomato intake was associated with a statistically significant decreased risk of HCC ($P_{trend} < 0.001$). Compared with the lowest quartile, HRs (95% CIs) of HCC for second, third, and fourth quartiles were 0.70 (0.56–0.88), 0.73 (0.58–0.92), and 0.63 (0.49–0.81), respectively, after adjustment for multiple potential founders (**Table 3**). Adjustment for additional risk factors including coffee intake and dietary omega-6 PUFA did not materially alter the results (data not shown). Lycopene intake was significantly correlated with tomato intake (the Spearman correlation coefficient = 0.49, $P < 0.001$). However, there was no association between lycopene intake and HCC risk ($P_{trend} = 0.54$; **Table 3**).

Stratified analyses were performed to assess the heterogeneity in the tomato–HCC risk association by selected risk factors for HCC including gender, history of type 2 diabetes, and levels of BMI, alcohol intake, and smoking status. The association between tomato intake and HCC was found only in nondiabetes participants ($P_{trend} < 0.001$) but no in diabetics participants ($P_{trend} = 0.38$) with $P_{heterogeneity} = 0.02$; Supplementary Table S1). Similarly, the association was stronger in men ($P_{trend} < 0.001$) than in women ($P_{trend} = 0.60$), but the $P_{heterogeneity}$ did not reach statistical significance (0.10). There was no statistically significant difference in the tomato–HCC risk association by levels of BMI (<25 or ≥25 kg/m^2; Supplementary Table S1), alcohol intake or cigarette smoking (data not shown).

In our nested case–control study, overall 13% of study participants (36% in HCC cases and 4% in control subjects) tested positive for HBsAg. Chronic infection with HBV, that is, positive for HBsAg, was the most important causal factor for HCC in the study population, with an OR being 14.8 (95% CI, 7.8–28.1) compared with HBsAg-negative after adjustment for BMI, level of education, smoking status, diabetes, physical activity, total energy intake, and alcohol intake. To reduce or eliminate potential confounding effect of HBV infection on the association between tomato intake and HCC risk, we repeated analyses with adjustment for HBsAg status among all subjects and among HBsAg-negative individuals only in a nested case–control study that included 197 cases and 465 controls with available HBsAg serology. High intake of tomato was associated with a statistically significant decreased risk of HCC after adjustment for HBsAg serologic status and other potential confounders ($P_{trend} = 0.04$; **Table 4**). Among HBsAg-negative individuals, ORs (95% CIs) of HCC for second, third, and fourth quartiles of tomato intake were 0.56 (0.30–1.02), 0.54 (0.30–0.96), and 0.51 (0.28–0.94), respectively, compared with 1st quartile ($P_{trend} = 0.03$). There was no association between lycopene and HCC after adjustment for HBsAg status (Supplementary Table S2).

Discussion

In this large prospective cohort study, we found that tomato intake was inversely associated with the risk of HCC development that was independent of lycopene intake, suggesting that the protective effect is more likely due to compound(s) present in tomato other than lycopene. This inverse association was not explained by identified risk factors for HCC including chronic infection with HBV, alcohol intake, diabetes, and cigarette smoking, among others. The protective effect of

Table 1. Baseline characteristics by tomato intake, grams per day by quartile, the Singapore Chinese Healthy Study, 1993–2015.

Characteristics	First quartile (<1.95)	Second quartile (1.95–4.81)	Third quartile (4.81–8.83)	Fourth quartile (≥8.83)
Age, years, median (25th, 75th percentiles)	57 (51, 64)	56 (50, 63)	55 (49, 61)	54 (49, 61)
Female sex, *n* (%)	8,753 (57.2%)	8,740 (57.0%)	8,288 (53.9%)	8,247 (53.8%)
Cantonese dialect, *n* (%)	6,472 (42.3%)	6,795 (44.3%)	7,197 (46.8%)	7,861 (51.3%)
Education, secondary school or higher, *n* (%)	3,453 (22.6%)	3,857 (25.2%)	4,683 (30.5%)	5,443 (35.5%)
Body mass index, kg/m^2, median (25th, 75th percentiles)	23.11 (21.08, 24.46)	23.11 (21.10, 24.61)	23.11 (21.23, 24.73)	23.11 (21.10, 24.80)
Smoking status[a] (%)				
Never smoker	10,196 (66.7%)	10,689 (69.7%)	10,815 (70.3%)	10,883 (71.0%)
Light smoker	4,479 (29.3%)	3,999 (26.1%)	4,022 (26.2%)	3,934 (25.8%)
Heavy smoker	619 (4.0%)	640 (4.2%)	536 (3.5%)	509 (3.3%)
One or more alcoholic drinks per day, *n* (%)	759 (5.0%)	635 (4.1%)	692 (4.5%)	813 (5.3%)
Diabetes, *n* (%)	1,529 (10%)	1,503 (9.8%)	1,200 (7.8%)	1,237 (8.1%)
Any weekly physical activity[b], *n* (%)	4,313 (28.2%)	4,819 (31.4%)	5,343 (34.8%)	5,763 (37.60)
Total energy intake, kCal/day, median (25th, 75th percentiles)	1,285 (1,022, 1,625)	1,356 (1,101, 1,708)	1,526 (1,239, 1,890)	1,706 (1,362, 2,148)
Lycopene intake, mcg/day, median (25th, 75th percentiles)	192 (45, 719)	468 (183, 907)	856 (373, 1414)	1,328 (768, 2110)

Note: Chi-square test was used for categorical variables; Kruskal–Wallis test was used for continuous variables; all *P*-values <0.0001.

[a]Cigarette smoking: The "heavy" smokers were those who started to smoke before 15 years of age and smoked 13 or more cigarettes, all remaining ever smokers were defined as light smokers.

[b]Physical activity represents amount of strenuous physical activity and/or vigorous work.

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Table 2. Baseline characteristics by HCC status, the Singapore Chinese Healthy Study, 1993–2015.

Characteristics	HCC cases ($n = 561$)	Noncases ($n = 60{,}760$)
Age, years, median (25th, 75th percentiles)[a]	60 (53, 65)	55 (49, 62)
Female sex, *n* (%)[a]	156 (27.8%)	33,872 (55.8%)
Cantonese dialect, *n* (%)[a]	213 (38.0%)	28,112 (46.3%)
Education, secondary school or higher, *n* (%)	144 (25.7%)	17,292 (28.5%)
Body mass index, kg/m^2, median (25th, 75th percentiles)[a]	23.4 (22.0, 26.0)	23.1 (21.1–24.7)
Smoking status[b] (%)[a]		
Never smoker	281 (50.1%)	42,302 (69.6%)
Light smoker	232 (41.4%)	16,202 (26.7%)
Heavy smoker	48 (8.6%)	2,256 (3.7%)
One or more alcoholic drinks per day, *n* (%)[a]	53 (9.5%)	2,846 (4.7%)
Diabetes, *n* (%)[a]	85 (15.2%)	5,384 (8.9%)
Any weekly physical activity[c], *n* (%)	204 (36.4%)	20,034 (33.0%)
Tomato intake, grams/day, median (25th, 75th percentiles)[a]	3.85 (1.33, 7.76)	4.82 (1.98, 8.84)
Total energy intake, kCal/day, median (25th, 75th percentiles)	1,475 (1,172, 1,942)	1,460 (1,162, 1,853)
Lycopene intake, mcg/day, median (25th, 75th percentiles)	654 (237, 1313)	694 (265, 1365)

Note: Chi-square test was used for categorical variables; Wilcoxon two-sample test was used for continuous variables.
[a]*P*-values <0.0001.
[b]Cigarette smoking: The "heavy" smokers were those who started to smoke before 15 years of age and smoked 13 or more cigarettes, all remaining ever smokers were defined as light smokers.
[c]Physical activity represents amount of strenuous physical activity and/or vigorous work.

tomato intake against the development of HCC seemed more apparent in individuals without a history of type 2 diabetes at baseline. The protective effect of tomato intake on HCC risk remained even after excluding HBsAg-positive subjects. These results support the notion that tomato intake may be beneficial in reducing risk of non-HBV-related HCC, which is directly relevant to the United States where high prevalence of NAFLD is observed to be associated with increasing rate of HCC.

To our knowledge, the current analysis is the first effort to evaluate the association between tomato intake and HCC risk. This association, however, has been reported with the risk of several other cancer types including breast cancer in a case–control study of premenopausal women in Korea (9), cancer of the upper aerodigestive tract (including oral cavity, esophagus, larynx, and pharynx) in a case–control study in Uruguay (21), and prostate cancer in a prospective cohort in the United States (13). On the other hand, null associations between tomato intake and risk of prostate cancer have also been reported previously in multiple studies (22–25).

Experimental studies suggest that whole tomato rather than purified lycopene offer protective effect against liver injury and HCC development in rodents. In an alcoholic liver disease model, whole tomato powder significantly reduced the severity of alcohol-induced steatosis, hepatic inflammatory foci, and cytochrome P450 2E1 (CYP2E1) protein level in rats fed alcohol, whereas partial tomato extracts had no effect on these liver injury measures and purified lycopene greatly increased inflammatory foci (26). In the same report, the authors further examined the effect of whole tomato powder on the development of liver lesions induced by a chemical carcinogen, diethylnitrosamine (DEN), and found that the supplementation of whole tomato powder abolished the presence of preneoplastic foci of

Table 3. Association between daily dietary tomato intake, daily lycopene intake, and the risk of HCC, the Singapore Chinese Health Study, 1993–2015.

Exposure	Persons	Person-year	Cases	HR (95% CI)[a]
Tomato intake (g/day)				
First quartile (<1.95)	15,294	260,526	186	1.00
Second quartile (1.95–4.81)	15,328	270,490	132	0.70 (0.56–0.88)
Third quartile (4.81–8.83)	15,373	278,375	134	0.73 (0.58–0.92)
Fourth quartile (≥8.83)	15,326	274,100	109	0.63 (0.49–0.81)
P_{trend}				0.0004
Continuous scale (g/day)				0.98 (0.97–0.99)
Lycopene intake (mcg/day)				
First quartile (<263)	15,248	256,499	152	1.00
Second quartile (263–691)	15,296	271,024	134	0.90 (0.71–1.14)
Third quartile (691–1,361)	15,362	276,941	143	0.93 (0.73, 1.17)
Fourth quartile (≥1,361)	15,415	279,027	132	0.91 (0.71, 1.18)
P_{trend}				0.5444
Continuous scale (mcg/day)				1 (1, 1)

[a]Adjusted for age, gender, dialect, BMI, education, smoking status, alcohol intake, year of enrollment, diabetes status, physical activity, and total energy intake.

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Table 4. Association between tomato intake (g/day) and HCC by HBsAg serology, Singapore Chinese Health Study, 1993–2015.

	Cases	Controls	OR (95% CI)
Tomato intake overall[a]			
First quartile (<1.95)	63	104	1.00[a]
Second quartile (1.95–4.81)	40	108	0.51 (0.28–0.93)
Third quartile (4.81–8.83)	57	130	0.58 (0.33–1.03)
Fourth quartile (≥8.83)	37	123	0.52 (0.29–0.94)
P_{trend}			0.0409
Tomato intake stratified by HBV status			
HBsAg (−)			
First quartile (<1.95)	41	100	1.00[b]
Second quartile (1.95–4.81)	26	101	0.56 (0.30–1.02)
Third quartile (4.81–8.83)	33	127	0.54 (0.30–0.96)
Fourth quartile (≥8.83)	27	118	0.51 (0.28–0.94)
P_{trend}			0.0300
HBsAg (+)			
First quartile (<1.95)	22	4	1.00[b]
Second quartile (1.95–4.81)	14	7	0.21 (0.04–1.21)
Third quartile (4.81–8.83)	24	3	0.90 (0.14–5.79)
Fourth quartile (≥8.83)	10	5	0.29 (0.05–1.64)
P_{trend}			0.3590
$P_{interaction}$, HBsAg and tomato intake			0.75

[a]Conditional logistic regression that retained case–control pairs where controls were matched to cases on age, gender, date of interview, dialect group, and date of sample collection. Model was adjusted for BMI, education, smoking status, alcohol intake, diabetes status, physical activity, total energy intake, and HBsAg serology.

[b]Unconditional logistic regression adjusted for age, gender, dialect, education, BMI, smoking status, alcohol intake, year of enrollment, diabetes status, physical activity, and total energy intake.

altered hepatocytes in DEN-injected mice that were also fed alcohol (26). In a separate report, tomato extract was shown to more greatly decrease CYP2E1, inflammatory foci, and mRNA expression of proinflammatory cytokines (e.g., TNFα, IL1β, and IL12) in the liver of a high-fat diet-induced nonalcohol steatohepatitis (NASH) promoted DEN-initiated hepatocarcinogenesis in rats than purified lycopene (27). Tomato intake may also decrease risk of HCC through increased gut microbial diversity, as NASH is related to gut dysbiosis and progression to HCC (28, 29). In β-carotene-15, 15′-oxygenase (BCO1) and β-carotene-9′, 10′-oxygenase (BCO2) knockout mice assigned to high-fat diet with or without tomato powder for 24 weeks, tomato powder significantly reduced the incidence of HCC by 67% along with decreased hepatic inflammatory foci (30). Taken together, these experimental data suggested that tomato rather than lycopene offered protective effect against the promoting effect of alcohol and high-fat diet on chemical carcinogen induced carcinogenesis. Our study results are consistent with these experimental studies.

In stratified analyses, we found the protective effect of tomato intake against the development of HCC to be more pronounced in individuals without a history of type 2 diabetes at baseline. As type 2 diabetes itself is a strong risk factor for HCC (5), the protective association between tomato intake and HCC may not be as apparent among those who have diabetes at baseline because they are already at high risk for liver disease, such as NAFLD. In addition to finding that HBsAg was not a confounder of the association between tomato intake and HCC, we found a protective effect among those both HBsAg-negative and positive with suggestion of a stronger protective effect among those HBsAg-positive. Although chance findings are possible and we have little power to detect an association among such small groups, future studies should examine tomato and the intensity of traditional risk factors for the association with HCC among HBsAg-positive individuals.

Strengths of our study include a prospective study design that would minimize the potential impact of underlying disease progression on exposure (i.e., tomato intake), which could result in reversal causality. A large sample size with up to 25 years of follow-up provided a large number of incident HCC cases and sufficient statistical power for our study. The parallel examination for tomato and lycopene intake provided direct comparison for their associations with HCC risk, and clearly demonstrated that tomato rather than lycopene had significant protective effect against HCC development. In our study, about 29% of dietary lycopene is from tomato products. Other major sources of lycopene include watermelon and honeydew melon (47%) and noodle and pasta grant products (12%). The FFQ used in our study was developed and validated specifically for this population and is internally consistent and reproduceable (16). The comprehensive question also provided information on established risk factors for HCC as covariates which were adjusted for in our statistically analysis. More importantly, HBsAg status was determined on a subset of HCC cases and their matched controls through a nested case–control study within our cohort. The repeated analysis among HBsAg-negative individuals showed the similar protective effect of tomato intake against the development of HCC, which completely ruled out potential confounding effect of HBV infection.

Our study also has some limitations. A possible limitation was misclassification of tomato exposure since the intake of tomato was assessed only once at baseline and subject might have changed their tomato intake during follow-up or the subject did not accurately recall their tomato intake at baseline. However, such measurement error would likely result in nondifferential misclassification, leading to an underestimated tomato–HCC risk association. Another limitation was that our estimation of lycopene intake was derived from the FFQ, and the estimated dietary lycopene was only moderately correlated with biological level of lycopene (the correlation coefficient between dietary and serum lycopene was reported to be 0.30 in men and 0.19 in women (31)). Thus, dietary lycopene may not reflect *in vivo* exposure, which could lead to the null association with cancer risk. The current version of the Food Composition Table provided a limited number of nutritive and nonnutritive compounds, which limited our ability to identify if other compounds in tomato such as apolycopenoids, minerals, and phenolic compounds might be responsible for the observed inverse association between tomato intake and HCC risk. We also would like to acknowledge that nonsignificant association between tomato intake and HCC risk among HBsAg-positive subjects was due to a small sample size and lack of statistical power.

In conclusion, to our knowledge, our study is the first to show evidence of a protective effect of tomato intake against the development of HCC in a large prospective cohort. This inverse association was independent of other known confounding factors. Future studies are warranted to identify possible compounds present in tomato other than lycopene. If confirmed, high consumption of tomato may be cheap and effective approach for primary prevention of HCC.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C.E. Thomas, H.N. Luu, J-M. Yuan
Development of methodology: C.E. Thomas, H.N. Luu, W-P. Koh, J-M. Yuan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J-M. Yuan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.E. Thomas, H.N. Luu, R. Wang, A. Jin, W-P. Koh, J-M. Yuan
Writing, review, and/or revision of the manuscript: C.E. Thomas, H.N. Luu, W-P. Koh, J-M. Yuan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.N. Luu, J. Adams-Haduch, W-P. Koh, J-M. Yuan
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