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A diet-wide association study for liver cancer risk: findings from a prospective cohort study in Chinese women

Jia-Yi Tuo[1,2,3], Qiu-Ming Shen[1,3], Zhuo-Ying Li[1,3], Jing-Yu Tan[1,2,3], Yu-Ting Tan[1,3], Hong-Lan Li[1,3] and Yong-Bing Xiang[1,2,3]

[1]State Key Laboratory of Systems Medicine for Cancer, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]School of Public Health, Shanghai Jiaotong University School of Medicine, Shanghai, China and [3]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China

Research Article

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Abbreviations:
SWHS, Shanghai women's health study; HCC, hepatocellular carcinoma; HBV, Hepatitis B virus; HCV, Hepatitis C virus; T2DM, type 2 diabetes mellitus; IL-6, interleukin-6; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; DWAS, Diet-wide association study; GWAS, genome-wide association studies; FDR, false discovery rate; FFQ, food frequency questionnaire; HR, hazard ratio; CI, confidence interval; PYs, person-years; BMI, body mass index; MET, metabolic equivalent; IQR, Inter quartile range; EPIC, European Prospective Investigation into Cancer and Nutrition; NIH-AARP, National Institutes of Health-American Association of Retired Persons Diet and Health Study cohort

Corresponding author:
Yong-Bing Xiang; Email: ybxiang@shsci.org

Abstract

Although dietary factors have been examined as potential risk factors for liver cancer, the evidence is still inconclusive. Using a diet-wide association analysis, our research evaluated the associations of 126 foods and nutrients on the risk of liver cancer in a Chinese population. We obtained the diet consumption of 72,680 women in the Shanghai Women's Health Study using baseline dietary questionnaires. The association between each food and nutrient and liver cancer risk was quantified by Cox regression model. A false discovery rate of 0.05 was used to determine the foods and nutrients which need to be verified. Totally 256 incident liver cancer cases were identified in 1,267,391 person-years during the follow-up duration. At the statistical significance level ($P \leq 0.05$), higher intakes of cooked wheaten foods, pear, grape and copper were inversely associated with liver cancer risk, while spinach, leafy vegetables, eggplant and carrots showed the positive associations. After considering multiple comparisons, no dietary variable was associated with liver cancer risk. Similar findings were seen in the stratification, secondary and sensitivity analyses. Our findings observed no significant association between dietary factors and liver cancer risk after considering multiple comparisons in Chinese women. More evidence is needed to explore the associations between diet and female liver cancer occurrence.

Introduction

Primary liver cancer ranked as the ninth most common cancer in women worldwide and the sixth main cause of cancer death in 2020.[1] Especially for women in China, liver cancer is more severe with the sixth cancer incidence and the fourth cancer mortality.[2] As the major histological type of liver cancer, hepatocellular carcinoma (HCC) accounts for 75–80% of all liver cancer cases.[3] Hepatitis B or C virus (HBV or HCV) infection and dietary aflatoxin intake are the most important causes of HCC, leading to over 80% cases.[4,5] In addition, the incidence and mortality rates of men were two to three folds of those of women, which is a stark sex discrepancy in most countries.[3] However, the precise cause of the disparities between men and women is still unknown. According to some researchers, men are more likely than women to be exposed to high-risk behaviours such as alcohol abuse, cigarette smoking, and HBV and/or HCV infection.[6] Hormones were also considered as a cause for sex difference in cancer development,[7] which could be related to serum interleukin-6 (IL-6) and adiponectin expression.[8,9]

In recent years, dietary factors have been extensively investigated as possible risk factors for liver cancer, but the evidence for the associations is still inconclusive, especially in men and women respectively. Many studies from the two large prospective cohorts - the Nurses' Health Study (NHS) for women and the Health Professionals Follow-up Study (HPFS) for men in America have been conducted to explore the dietary factors on liver cancer risk.[10–12] For example, processed red meat intake might be associated with a higher risk of HCC (HR = 2.36, 95% CI: 1.18–4.72), and an inverse association was found between poultry and HCC risk (HR = 0.53, 95% CI: 0.28–0.98); while there was a statistically significant association between fish and decreased HCC risk among women (HR = 0.52, 95% CI: 0.30–0.91).[12] The inconsistencies in the diet research among men and women may be related to their different dietary patterns and intake amounts, or various confounding factors related to liver cancer. However, most studies combined the male and female into their analyses, which could bias the results. In addition, many studies only focus on the association between one or several foods and nutrients and liver cancer, and are mainly conducted in America and Europe. Therefore, according to the differences in dietary cultures between China and other countries, and

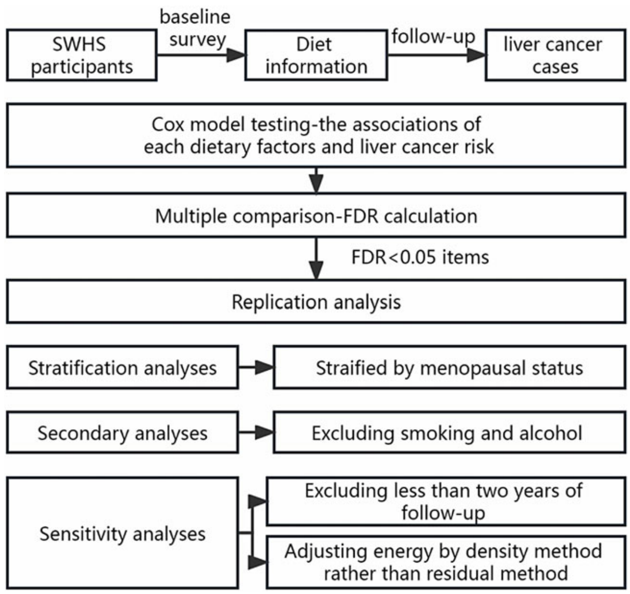

Figure 1. Study process of diet-wide association study analytical method to test associations between foods and nutrients intake and risk of liver cancer in the Shanghai Women's Health Study.

variations of eating habits for different sexes, it is worthy to conduct a high-quality epidemiologic study between diet and nutrition and liver cancer risk in Chinese women.

Similar to genome-wide association studies (GWAS), the diet-wide association study (DWAS) could estimate the association of each food and nutrient on health outcomes and perform multiple comparisons to identify the promising associations for further replication. The DWAS method has been used to find out the impact of diet on breast cancer, colorectal cancer and lung cancer,[13–15] while no studies have been conducted on liver cancer. Our study aims to provide high-quality evidence about the associations of foods and nutrients with the risk of liver cancer in Chinese female adults.

Materials and methods

Our study process of DWAS analytical method to test associations between foods and nutrients intake and risk of liver cancer, using dietary information from the cohort database of the Shanghai Women's Health Study (SWHS) has been presented (Figure 1).

Study population

From December 1996 to May 2000, the SWHS recruited 74,940 participants aged 40–70 and living in urban Shanghai. Previous reports had already revealed the study's design and rationale.[16] We have obtained written informed consent from all the participants. Each participant was questioned for a questionnaire to collect baseline demographic information, diet, lifestyle (such as smoking, alcohol drinking, and tea drinking), menstrual and reproductive condition, personal disease history and family history of cancer. Participants who met the following criteria were not allowed to participate in current study: (1) cancer in situ was discovered in follow-up (n = 135); (2) no cancer type or diagnosis date had been collected when the participant passed away from cancer (n = 244); (3) cancer at baseline (n = 1,598); (4) lost to follow-up after enrolling (n = 3); (5) diagnosis of cancer wasn't confirmed (n = 67); (5) values of total calorie intake were extremely low or high (<500 or >3,500 kcal/d) (n = 121); and (6) data of interested covariates was missing (n = 92). Finally, 72,680 participants were retained in current analysis. Informed consent has been obtained from all participants. This study was carried out in compliance with the Helsinki Declaration and was authorised by the Renji Hospital Ethics Committee of Shanghai Jiao Tong University School of Medicine (KY2019-197).

Assessment of dietary factors

At baseline of all cohort members, the dietary intake over the previous 12 months was collected using a validated semi-quantitative food frequency questionnaire (FFQ) with 71 food items, primarily about the average frequency (daily, weekly, monthly, yearly, or never) and amounts (1 liang = 50 g) per unit of time.[17] The FFQs of SWHS have fairly high validity and reproducibility as compared with multiple 24-h dietary recalls. The correlation coefficient for major food groups was 0.41–0.66 in the SWHS. The 2002 Chinese Food Composition Table [18] was used to calculate daily nutritional requirements based on the nutrient composition of each food. In the analysis, 126 dietary factors (88 foods/food groups and 38 nutrients) were included in total (Supplementary Tables S1 & S2).

Follow-up and case ascertainment

Every participant in the cohort was followed up every 3–4 years.[16] The data was synchronised yearly with the databases of the Shanghai Vital Statistics Registry, and the Shanghai Cancer Registry. In the past two decades, five follow-up surveys were done, with response rates of 99.7% from 2000 to 2002, 98.7% from 2002 to 2004, 94.9% from 2004 to 2006, 92.3% from 2007 to 2010, and 91.1% from 2012 to 2017. Each liver cancer diagnosis was supported by home visits, hospital medical reports, and reviews of medical records by clinical and pathological specialists.[18] The International Classification of Disease, the Ninth Revision was also used to code diseases, and liver cancer was defined as a primary malignant tumour with the code 155.[19] In this study, we censored the follow-up information on 31 December 2016.

Statistical analyses

In order to describe baseline characteristics, the entire cohort was separated into cases and non-cases of liver cancer. Continuous variables were reported as medians with interquartile ranges (IQRs), while categorical variables were described as counts with proportions. The Wilcoxon-Mann-Whitney test was used to compare continuous variables because of the skewed distribution, and the Chi-square test to compare categorical ones.

Cox proportional hazard regression models were used to estimate the association between each of the dietary factor and the risk of liver cancer in the cohort. The follow-up time (years) was chosen as the underlying time metric. And we determined the period from baseline to an event (i.e. liver cancer occurrence) or right-censoring (i.e. death, loss to follow-up, or Dec. 31, 2016), whichever came first, as person-years (PYs) to the event. The Schoenfeld residual method was used to validate the proportional hazards assumptions in Cox regression models,[20] and no indication of a violation of these assumptions was found. Foods and nutrients were adjusted for energy intake using the residual approach[21] and Z was transformed to reflect the associations per one standard deviation (SD) increase in dietary consumption. Hazard ratios (HRs) and 95% confidence intervals (CIs) were

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presented by both quartile categories and per 1-SD increment of the dietary items. All models were adjusted for age at entry (years, continuous), calorie intake (kcal/d, continuous), body mass index (BMI) (4 categories: <18.5 kg/m^2, 18.5–23.9 kg/m^2, 24–27.9 kg/m^2, ≥28 kg/m^2),[22] physical activity (multiplying the weekly hours spent on specific physical activities (including stairs climbing, housework, walking, cycling to and from work, and walking and cycling except for transportation for work) in the past 1 year by their corresponding metabolic equivalent (MET) values and cumulating the total weekly MET (MET hour/week, continuous), education (4 categories: elementary school and below, middle school, high school, and college and above), menopause status (yes/no), smoking status (defined as 'ever smoked at least 1 cigarette/day for more than 6 months continuously', yes/no), alcohol drinking status (defined as 'ever drank alcohol at least 3 times/week for more than 6 months continuously', yes/no), family history of liver cancer (yes/no), medical history of chronic hepatitis (yes/no) and type 2 diabetes mellitus (T2DM) (yes/no).

We calculated the false discovery rate (FDR) for each food and nutrient to account for multiple comparisons in the analysis, which is the proportion of expected false positives to all positive associations, or the percentage of findings drawn from the null distribution at a specific significance level.[23] To compute the value of FDR, we generated a 'null distribution' of regression test statistics through random assignment of the case status and both the case status and time to event, run the Cox proportional hazards model, and gathered the corresponding P value over 1,000 permutations.[24] Dietary factors with an FDR < 0.05 would be retained for republication.[25]

Priori exploratory stratification analyses were conducted to evaluate the associations of dietary factors on liver cancer risk among participants with different menopausal statuses (yes vs. no). The secondary analyses comprised the participants without smoking and alcohol drinking, in order to eliminate the potential role of smoking and alcohol drinking. In addition, sensitivity analyses were also conducted, such as (1) all participants with a follow-up time of less than two years were excluded; (2) dietary nutrients were adjusted by the energy density method rather than the residual method to examine the robustness of the results.[21]

The results were deemed statistically significant when the two-sided P values were less than 0.05. All of the analyses were conducted using the R software (version 4.0.5).

Data availability statement

The data will be available on request pending approval by the scientific committee of the relevant institutes.

Results

From the baseline survey to the end of 2016, there was a total of 1,267,391 person-years (average of 17.44 years) of follow-up in which 256 female participants were newly diagnosed with liver cancer. The incidence density of liver cancer was 20.20 cases per 100,000 PYs, and the cumulative incidence proportion was 0.35% during the follow-up period. Compared with non-cases, liver cancer cases were more likely to be older, overweight, lower-educated, postmenopausal, and had a family history of liver cancer, self-reported medical histories of chronic hepatitis and T2DM (Table 1). The baseline dietary items intake levels in the cohort have also been presented (Supplementary Table S3).

Of the 126 dietary factors that were evaluated in SWHS, higher intakes of four factors (cooked wheaten foods, pear, grape, copper) were associated with a low risk of liver cancer at the statistical significance level ($P < 0.05$), while the other four factors (spinach, leafy vegetables, eggplant, carrots) were positively associated with liver cancer risk. Cooked wheaten foods and pear also had inverse linear trends with the risk of liver cancer ($P_{trend} < 0.05$). However, no dietary factor retained an association with liver cancer risk after correcting for multiple comparisons (minimum FDR = 0.252) (Figure 2 & Supplementary Table S4).

Exploratory stratification analyses according to menopausal status have been conducted in the recruited women. For the 8 statistically significant dietary variables in the main analyses, only carrots among premenopausal women, and cooked wheaten foods, pear, copper and spinach among postmenopausal women still had the HRs at the statistical significance level ($P < 0.05$). While no associations were observed after correcting for multiple comparisons in both the premenopausal and postmenopausal women (Supplementary Table S5).

In the secondary analyses, after excluding the participants with smoking or alcohol drinking, we observed that all the statistically significant HRs of the 8 factors in the main analysis still existed ($P < 0.05$). After correcting for multiple comparisons, the dietary factors still had no associations with liver cancer risk (minimum FDR = 0.252) (Supplementary Table S6).

As for the sensitivity analyses, we excluded participants with less than 2 years of follow-up, and found that the statistically significant HRs of the factors in main analyses still existed except for carrots, while disappeared after correcting for multiple comparisons (minimum FDR = 0.084) (Supplementary Table S7). The results of dietary nutrients using the energy density method were similar to the energy residual method except for copper (Supplementary Table S8).

Discussion

In this study, we used the DWAS approach to systematically evaluate the association between dietary intakes of 126 foods and nutrients and the risk of liver cancer in Chinese women. At the statistical significance level ($P < 0.05$), cooked wheaten foods, pear, grape and copper were inversely associated with liver cancer risk, while spinach, leafy vegetables, eggplant and carrots showed the positive associations. After considering multiple comparisons, no dietary variable was associated with liver cancer risk (FDR > 0.05). Similar results were observed in the stratification, secondary and sensitivity analyses.

The cooked wheaten foods always include noodles and steamed bread, which are rich in starch. However, the literature evidence for the association between cooked wheaten foods and risk of liver cancer is sparse, and only a few focused on starch and liver cancer risk. Polesel J and his colleagues recruited 185 HCC patients and 412 controls and found that the highest vs. lowest tertile of OR was 1.70 for starch on HCC development ($P_{trend} > 0.05$).[26] In contrast, a prospective study from the European Prospective Investigation into Cancer and Nutrition (EPIC) found that 50g/d increment of total starch intake was associated with a lower risk of HCC (RR = 0.70, 95% CI: 0.55–0.90) among European people.[27] However, these studies didn't figure out the dietary associations among female participants. Our study showed the inverse association between cooked wheaten foods and female liver cancer risk, which disappeared after correcting for multiple comparisons. More

Table 1. Baseline demographic and lifestyle characteristics between liver cancer cases and non-cases (Shanghai Women's Health Study, 1996–2016)

	Overall (n = 72,680)	Non-cases (n = 72,424)	Liver cancer cases (n = 256)	*P* value
Age at entry (years, IQR)	50.27 (16.44)	50.24 (16.42)	60.83 (14.56)	<0.001
BMI (kg/m^2, IQR)	23.73 (4.44)	23.72 (4.43)	24.70 (5.26)	<0.001
Physical activity (MET hours/week, IQR)	100.45 (57.10)	100.45 (57.10)	102.39 (54.90)	0.918
Calorie intake (kcal/d, IQR)	1,634.10 (494.46)	1,634.32 (494.35)	1,583.62 (469.37)	0.071
Education (*n*, %)				<0.001
Elementary school and below	15,489 (21.31)	15,381 (21.24)	108 (42.19)	
Middle school	27,060 (37.23)	26,996 (37.27)	64 (25.00)	
High school	20,315 (27.95)	20,255 (27.97)	60 (23.44)	
College and above	9,816 (13.51)	9,792 (13.52)	24 (9.38)	
Menopausal status (*n*, %)				<0.001
Yes	35,496 (48.84)	35,299 (48.74)	197 (76.95)	
No	37,184 (51.16)	37,125 (51.26)	59 (23.05)	
Smoking status (*n*, %)				0.189
Yes	2,006 (2.76)	1,995 (2.75)	11 (4.30)	
No	70,674 (97.24)	70,429 (97.25)	245 (95.70)	
Alcohol drinking status (*n*, %)				0.602
Yes	1,628 (2.24)	1,624 (2.24)	4 (1.56)	
No	71,052 (97.76)	70,800 (97.76)	252 (98.44)	
Family history of liver cancer (*n*, %)				<0.001
Yes	2,383 (3.28)	2,357 (3.25)	26 (10.16)	
No	70,297 (96.72)	70,067 (96.75)	230 (89.84)	
Medical history of chronic hepatitis (*n*, %)				<0.001
Yes	1,865 (2.57)	1,829 (2.53)	36 (14.06)	
No	70,815 (97.43)	70,595 (97.47)	220 (85.94)	
Medical history of T2DM (*n*, %)				<0.001
Yes	3,122 (4.30)	3,097 (4.28)	25 (9.77)	
No	69,558 (95.70)	69,327 (95.72)	231 (90.23)	

Note: Values were medians (IQR) for continuous variables and count (proportion) for categorical variables. Compare continuous variables using the Wilcoxon-Mann-Whitney test because of the skewed distribution, and compare categorical ones using $\chi 2$ test.
Abbreviations: IQR, inter quartile range; BMI, body mass index; MET, metabolic equivalent; SWHS, Shanghai Women's Health Study; T2DM, type 2 diabetes mellitus.

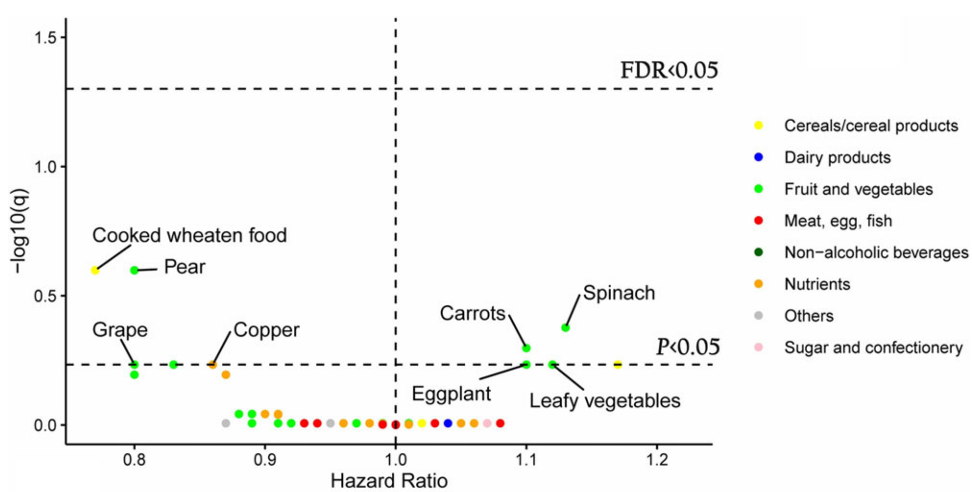

Figure 2. Volcano plot showing results from the diet-wide association study regarding the association between 126 dietary factors and liver cancer risk in the Shanghai Women's Health Study. The y-axis shows the false discovery rate (FDR) adjusted *P* values in –log10 scale from the Cox proportional hazards regression models for each dietary factor. The x-axis shows the estimated HR for each dietary factor per 1-SD increase in daily consumption. The dashed horizontal line represents the level of significance corresponding to FDR of 0.05 and *P* value of 0.05. The models were adjusted for age, BMI, calorie intake, physical activity, education, menopause status, smoking, alcohol drinking, family history of liver cancer, medical history of chronic hepatitis and type 2 diabetes mellitus.

epidemiologic studies are needed to evaluate the potential role of cooked wheaten foods in female liver cancer occurrence.

In general, vegetables and fruits are low in fat and calories, and rich in vitamins, minerals, and dietary fibre, which have been found to be inversely associated with cardiovascular disease, diabetes, and stroke.[(28–30)] However, a recent meta-analysis including 12 studies reported that vegetables were associated with low risk of liver cancer (Summary RR = 0.70, 95% CI: 0.56–0.87; $I^2 = 79.1\%$), while fruits had no association with liver cancer risk (Summary RR = 0.93, 95% CI: 0.80–1.09; $I^2 = 46.8\%$).[(31)] The inverse associations between fruits and liver cancer risk could be observed in some case-control studies.[(32,33)] In our study, we found the positive associations between vegetables (spinach, leafy vegetables, eggplant and carrots) and female liver cancer risk, and fruits (pear and grape) had the statistically significant HRs on decreasing the risk. However, no factors retained the associations after correcting for multiple comparisons. Longer follow-up times and more cases of liver cancer are warranted to affirm the possible effect of vegetables and fruits on the development of female liver cancer.

Copper is an essential micronutrient for human life, and shellfish and animal liver are good food sources for dietary copper.[(34)] Many reviews indicated that copper has a redox property, and could protect the basic elements of the cell, including lipids, protein, and DNA, from in situ produced reactive oxygen species and oxygen free radicals, which could be useful for people's physical health.[(35)] However, few studies observed the associations between dietary copper and liver cancer risk. Our study found an inverse association between consumption of dietary copper and liver cancer risk while disappeared after correcting for multiple comparisons. The association of copper on liver cancer is still required more reliable epidemiological evidence.

In stratification analyses, only carrots among premenopausal women, and cooked wheaten foods, pear, copper and spinach among postmenopausal women still had the HRs at the statistical significance level, while all disappeared after correction. The reason might be related to female sex hormones. Premenopausal women have higher levels of oestrogen, and animal studies have found that oestrogen could combine with oestrogen receptor α and suppress the production of IL-6 to decrease liver carcinogenesis.[(8)] And compared with postmenopausal women, the potential role of diet on liver cancer could be reduced among premenopausal women. More studies are needed to verify the condition.

Most cohort studies like the EPIC and the National Institutes of Health-American Association of Retired Persons Diet and Health Study cohort (NIH-AARP) evaluated dietary factors on liver cancer risk among all the participants rather than only women. Fortunately, the NHS recruited 138,483 women in America and showed that white meat, fish, n-3 PUFA were all associated with the low risk of female liver cancer,[(11,12)] which were not observed in our study. Except for the sample size of cases, the reason could be attributed to the different dietary patterns between the Chinese and American people - in the NHS, white meat, plant, olive oil and nuts were the main food sources of fat[(11)]; whereas in the participants of the SWHS, the main food source of fat were red meat and meat products, and people always considered cooked wheaten foods and rice as their staple food.[(36)]

Our study is the first to systematically estimate the association between a wide set of dietary factors with female liver cancer risk in Asia. The cohort additionally had a large scale of population with liver cancer cases. Moreover, a number of known risk variables for liver cancer from our earlier research have been included into our multivariable analysis, including BMI, physical activity, education, menopause status, smoking status, alcohol drinking status, family history of liver cancer, medical history of chronic hepatitis and T2DM, to reduce the effect of potential confounders. However, there are still several limitations. Firstly, the data on diet were only obtained from the baseline, and the changes over time are needed to take into account. Secondly, the items in the multivariable model weren't adjusted for the other relative dietary components, which still needs careful conclusion. Thirdly, the data of HBV or HCV infection was lacked in the participants, which could limits the interpretation and understanding of the associations and even pathogenesis of dietary factors on liver cancer. Although, the medical history of hepatitis or chronic liver diseases was used to adjust in the multivariable models instead which could reduce the potential effect of HBV or HCV infection. We still need to collect the complete information of HBV or HCV infection for further analysis. Fourthly, diet aflatoxin exposure, the significant cause of liver cancer, wasn't considered in our investigation. Moreover, the number of cases of several reproductive factors were small in our study, so the findings need to be interpreted with caution. And because our prospective cohort primarily consisted of urban Chinese adult women, it should be cautious to generalise the findings to a larger population, such as those living in rural areas. In addition, external verification and high-quality epidemiologic studies are needed to assess the reliability and stability of our findings. Finally, we lacked pertinent information regarding specific cases of hepatocellular carcinoma and other sites, and around 25% of primary liver cancer patients had unclear sites,[(37)] so we used the combined cases in our analysis. For additional investigation, the specific histological subtype of liver cancer would be needed.

Conclusions

In summary, no significant association was observed between dietary factors and female liver cancer risk after considering multiple comparisons. The possible associations of cooked wheaten foods, pear, grape, copper, spinach, leafy vegetables, eggplant and carrots on female liver cancer before correction warrant further investigations based on longer follow-up times, large number of cases and more high-quality research.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/jns.2024.86

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Authorship. Y-BX designed research and obtained funding; J-YT, Q-MS, Z-YL, J-YT, Y-TT, H-LL, and Y-BX conducted the study; J-YT, H-LL, and Y-BX analysed the data and interpreted the results; J-YT and Y-BX prepared and wrote the first draft; All authors reviewed and approved the final version of the paper; and Y-BX has primary responsibility for final content.

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Competing of interests. The authors have declared no potential conflicts of interest.

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