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# Type 2 diabetes prevention diet and hepatocellular carcinoma risk in U.S. men and women

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## Abstract

**Background & Aims:** Adherence to a healthy diet has been associated with a reduced risk of type 2 diabetes (T2D). Hepatocellular carcinoma (HCC) may have overlapping mechanisms with T2D, such as inflammation and insulin resistance. Thus, we examined the association between a previously developed T2D prevention dietary pattern and HCC risk.

**Methods:** We followed 87,943 women in the Nurses' Health Study and 49,665 men in the Health Professionals Follow-up Study for up to 32 years. The dietary diabetes risk reduction score, which includes dietary glycemic index, cereal fiber, ratio of polyunsaturated to saturated fats, *trans* fat, sugar-sweetened beverages, nuts, coffee, and red and processed meat, was obtained using validated food frequency questionnaires and updated every 4 years. The Cox proportional hazards regression model was used to calculate multivariable hazard ratios (HRs) and confidence intervals (95%CIs).

**Results:** During over 1.9 million person-years, a total of 160 incident HCC cases were identified. The dietary diabetes risk reduction score was associated with a lower risk of HCC (top vs. bottom quartile; HR: 0.57, 95%CI: 0.34 to 0.95; $P_{trend}$=0.03). All of the individual food and beverage items were associated with risk of HCC in the expected direction, although the association was weaker than the overall dietary pattern.

**Conclusions:** Greater adherence to T2D prevention diet was associated with a lower risk of developing HCC among US men and women. Further studies are needed to confirm and extend our findings.

### Keywords

dietary diabetes risk reduction score; hepatocellular carcinoma; cohort study

## Introduction

Liver cancer is the third leading cause of cancer-related death globally.(1) Hepatocellular carcinoma (HCC) is the most common histological form of liver cancer.(2) In the US, the incidence of liver cancer has tripled since 1980, and over 42,220 adults were diagnosed in 2018.(3, 4) Accumulating evidence suggests that the incidence of HCC is approximately 2-fold higher in patients with type 2 diabetes (T2D) as compared with nondiabetic individuals, suggesting the importance of insulin resistance in the pathogenesis of HCC.(5-8)

Insulin resistance plays an important role in the development of T2D and nonalcoholic fatty liver disease (NAFLD), predisposing factors for HCC.(9-11) Serum levels of inflammatory markers, such as interleukin-6 and C-reactive protein are also elevated in diabetics and are associated with the risk of subsequent HCC.(12) Thus, an approach, such as a healthy diet, that can improve insulin sensitivity and reduce inflammation might be beneficial to prevent obesity,(13) T2D,(14) and liver cancer.(15) A dietary diabetes risk reduction score was developed for T2D prevention, which features high intakes of cereal fiber, polyunsaturated fats, nuts, and coffee; and low amounts of carbohydrates, trans fat, sweets, and red and processed meat.(16) Compared with other dietary patterns, such as the Alternate Healthy Eating Index-2010 (AHEI-2010)(17) and the Alternate Mediterranean Diet Score (AMED), (18) this T2D prevention dietary pattern captures the key dietary factors reported to be

associated with T2D. Adherence to this dietary pattern is essential to improve insulin sensitivity (19, 20) and to decrease the levels of inflammation(21) and metabolic disturbance.(22) Given that T2D and HCC are closely linked, we hypothesized that a T2D prevention dietary pattern might decrease the risk of developing HCC.

We tested this hypothesis by examining the association of the dietary diabetes risk reduction score with the risk of incident HCC among US men and women in two large cohort studies with long-term follow-up and repeated dietary measures.

## Methods

### Study population

Our study consisted of two large US cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).(23, 24) The NHS began in 1976 including 121,700 registered female nurses aged 30–55 years. The HPFS began in 1986 including 51,529 male health professionals aged 40–75 years. Demographics, lifestyle factors, and medical history were collected through self-administered questionnaires every two years. Follow-up rates for each cohort were over 90%. This study was approved by the Institutional Review Boards at Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health in Boston, MA, and those of participating registries as required.

### Dietary assessments and computation of dietary diabetes risk reduction score

In the NHS, validated semi-quantitative FFQs were administered 9 times between 1980 and 2010.(24) In the HPFS, FFQs were administered 7 times between 1986 and 2010.(25) Each FFQ contained approximately 131 items except for the 1980 FFQ which included 61 items. For each FFQ, 9 response categories ranged from never or less than 1 time/month to ≥6 times/day. Nutrition intake was estimated by multiplying the consumption frequency of each food by the proportion of nutrients and then summing across the food items.

Consistent with a previous study from the same cohort,(16) dietary diabetes risk reduction score consisted of 8 dietary components, including dietary glycemic index (GI), cereal fiber, ratio of polyunsaturated to saturated fats (P:S), *trans* fat, sugar-sweetened beverages (SSBs), nuts, coffee, and red and processed meats. Scoring was based on quartiles of dietary intake: For favorable components, including cereal fiber, P:S ratio, nuts, and coffee, participants were assigned 1 to 4 points from the lowest quartile to the highest quartile, whereas scoring was reversed for unfavorable food items, including GI, *trans* fat, SSBs, and red and processed meat. Accordingly, the dietary diabetes risk reduction score ranged from 8 to 32, and a higher score indicated a healthier overall diet.

The validity and reproducibility of dietary data were comprehensively evaluated in these cohorts.(24, 26, 27) In the NHS, reasonable correlation coefficients between the FFQ and multiple dietary records were observed for fiber (0.56), carbohydrates (0.64), coffee (0.78), nuts and peanut butter (0.75), SSBs (0.84 for sugar-sweetened and diet sodas, 0.56 for other carbonated soft drinks, and 0.56 for fruit punch), total and specific types of fat (0.46–0.68), and red and processed meat (0.56 for hot dogs, 0.7 for bacon, 0.55 for other processed meat, 0.38 for hamburgers, and 0.46 for red meat). In the HPFS, the correlation coefficients for the

nutrients/foods mentioned above between the FFQs and multiple dietary records ranged from 0.29 to 0.90.

Information on potential HCC related factors was collected at baseline and throughout follow-up, including age, smoking status, aspirin use, T2D status, and physical activity. We also collected information and calculated intake of alcohol and total calories.(28) The race was inquired for one time in each cohort. Besides, the AHEI-2010 was assessed as an overall measure of diet quality, with higher scores reflecting better adherence to the dietary guidelines.(17)

## Ascertainment of hepatocellular carcinoma (HCC) and cirrhosis

Participants, who reported a new diagnosis of HCC in each cohort, were contacted for permission to obtain their medical records. Regarding possible unreported cancer cases, we further searched the State Cancer Registries and the National Death Index.(29) For deaths attributable to HCC, permissions were requested from next-of-kin to obtain medical records. Physicians reviewed medical records and confirmed the diagnosis, and further extracted all possible information on HCC cases, including the histological types of cancer (e.g., HCC vs. intrahepatic cholangiocarcinoma), the presence of underlying cirrhosis, and the presence of viral hepatitis (e.g., HBV/HCV infection). Additional HBV/HCV infection data was also available from a nested case-control study of liver cancer in the NHS and HPFS, derived from laboratory blood tests.(30) Cirrhosis was defined based on self-reported physician-diagnosed during the prior 2-year interval, and it was identified using the International Classification of Disease (ICD) $8^{th}$ code: 571.

## Statistical analyses

In the current study, the baseline was defined as 1980 for women and 1986 for men when validated FFQs were first administered. Participants were excluded if they had a history of cancer (except for non-melanoma skin cancer), implausible energy intake, or had missing information on the dietary diabetes risk reduction score at baseline, leaving 137,608 participants (87,943 women and 49,665 men) in the analyses. The person-years of the participant were calculated from the date of return of the baseline questionnaire to the date of HCC diagnosis, death, or the end of follow-up (June 1, 2012 in the NHS and January 31, 2012 in the HPFS), whichever occurred first. The Cox proportional hazards model, stratified by age (months) and study period (two-year interval), was used to estimate age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). To maximize the statistical power, we combined two cohorts to examine the association between the dietary diabetes risk reduction score and risk of HCC because there was no significant heterogeneity by gender ($P$=0.22). No violation of the proportional hazard assumption was found after testing an interaction term between the dietary diabetes risk reduction score and follow-up time ($P$=0.95). In the multivariable models, we adjusted for race (white or non-white), gender (female or male), physical activity (<3, 3-<27, ≥27 METS-hours/week), smoking status (never, past, or current), alcohol consumption (g/day, continuous), aspirin use (yes or no), body mass index (BMI, $kg/m^2$, continuous), and total calorie intake (kcal/day, tertiles). Because T2D could play a role between the dietary score and HCC, we have additionally adjusted for T2D as well as conducted analysis stratified by T2D. We calculated

the cumulative average of dietary diabetes reduction score to better represent long-term dietary habits and minimize within-person variations. The score was classified into quartiles with the lowest quartile as the reference group. Linear trend tests were performed using a median of each quartile as a continuous variable. As a secondary analysis, we further examined the associations of HCC with each component of dietary diabetes risk reduction score. We further performed similar analysis (as HCC) to examine the association of T2D dietary score with cirrhosis risk.

We conducted exploratory analyses by age, BMI, smoking status, alcohol consumption, physical activity, and aspirin use. We also performed several sensitivity analyses. First, analyses were performed after excluding HCC cases with known HBV/HCV infection. Second, the association of the dietary score with HCC was assessed separately by a history of pre-existing cirrhosis status (cirrhotic vs. non-cirrhotic HCC). Additionally, the Spearman correlation coefficient between the dietary diabetes risk reduction score and HBV/HCV infection status was calculated among participants with available data on chronic HBV/HCV infections. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, USA), and a *P* value less than 0.05 was considered to be statistically significant.

## Results

During 32 years of follow-up with over 1.9 million person-years, a total of 160 HCC cases were identified (85 women and 75 men). Among the 137,608 participants, those with higher dietary diabetes risk reduction scores were older and more likely to be physically active, use aspirin, and drink alcohol, have a higher AHEI-2010 score and lower BMI, but were less likely to be current smokers and have a history of T2D (Table 1). Similar patterns were observed in both women and men (Supplementary Table 1).

In the multivariable analyses, the dietary diabetes risk reduction score was associated with a statistically significant lower risk of HCC (the highest vs. lowest quartile; HR=0.57, 95%CI: 0.34 to 0.95; $P_{trend}$=0.03). These results remained essentially the same after further adjustment for T2D (Table 2). We further evaluated the associations between each dietary component of the dietary score and risk of HCC (Table 3). Generally, non-significant inverse associations were observed for cereal fiber, P:S ratio, nuts, coffee, whereas non-significant positive associations were observed for GI, *trans* fat, SSB, red and processed meats. When we separately assessed the associations of specific dietary components with HCC risk in each cohort, the results were similar to the pooled analyses (Supplementary Tables 2 and 3). Likewise, compared to participants with the lowest dietary score, the cirrhosis risk was lower in those with the highest dietary scores (HR=0.55, 95%CI: 0.34 to 0.90; $P_{trend}$=0.008) (Supplementary Table 4).

In exploratory analyses, we found that the inverse association with diabetes risk reduction score appeared generally similar in subgroups (Supplementary Table 5). In sensitivity analyses, similar results were observed after excluding HCC cases (n=26) with known HBV/HCV infection (top vs. bottom quartile, HR=0.58, 95%CI:0.33 to 1.00, $P_{trend}$=0.05) (Supplementary Table 6), for cirrhotic HCC(n=33) (HR=0.49, 95%CI: 0.16 to 1.49, $P_{trend}$=0.36), or non-cirrhotic HCC(n=63) (HR=0.49, 95%CI: 0.21 to 1.15, $P_{trend}$=0.05; *P*

$_{heterogeneity}$ > 0.99). The correlation coefficient between the dietary score and HBC/HCV infection status was −0.14.

## Discussion

After adjusting for major known risk factors for HCC, we found that the higher dietary diabetes risk reduction score, reflecting better adherence to a dietary pattern for T2D prevention, was independently associated with a significantly lower risk of developing HCC among US men and women. To our knowledge, the current study has demonstrated for the first time that eating a diet that facilitates the prevention of T2D might also aid in HCC prevention.

To date, limited epidemiological studies have examined the association of diet with HCC risk; most of these studies had focused on specific dietary components, such as meat,(31-33) sugar,(34, 35) or vegetables.(36) Compared to studies focusing on nutrients or individual food items, a dietary pattern may capture a more comprehensive picture of dietary intake, and enable examination of associations between overall diet and nutrition-related health outcomes. However, only a few studies have investigated the effects of dietary patterns on HCC risk.(37-40) Consistent with previous limited studies on dietary patterns,(37-40) we recently found that adherence to certain healthy dietary patterns such as AHEI-2010 might be associated with a reduced risk of HCC.(41) Our current results extended these findings and further demonstrated that adherence to a dietary pattern associated with T2D prevention might also reduce the risk of HCC.

The dietary diabetes risk reduction score captures the key nutrient components of the T2D prevention diet, including higher intake of cereal fiber, polyunsaturated fat, nuts, and coffee, but lower intake of food with higher GI, *trans* fat, SSBs, and red and processed meat. Of note, some of these components are shared by the dietary diabetes risk reduction score and other dietary patterns, such as AHEI-2010 and AMED, but there are some differences between these dietary patterns. For example, SSBs were found to be associated with an increased risk of T2D,(42, 43) but they are not considered in the AMED. Also, instead of including individual food components, such as fruit and vegetables, we used dietary GI because it allows us to capture all food items with a lower GI.(44)

While the mechanisms underlying the observed inverse associations between dietary diabetes risk reduction score and the risk of incident HCC requires more investigations, the T2D prevention dietary pattern has been linked to improved insulin sensitivity, modify gut microbiota, and reduced inflammation.(19, 21, 22, 45, 46) The beneficial effects can be partially explained by the healthy components of the dietary pattern. For instance, higher polyunsaturated fat consumption, which can be find in plant-based oils, nuts, and fish, could suppress hepatic lipogenesis and steatosis and insulin resistance via decreasing plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) and PCSK9 mRNA expression, a member of the proprotein convertase family which mainly synthesized in the liver.(47) Polyunsaturated fatty acids could also increase membrane fluidity, resulting in an improvement in insulin sensitivity and lower risk of T2D, (48) a risk factor for HCC. Additionally, experimental studies demonstrated that coffee and its bioactive components

modify gut microbiota by increasing the populations of *Bifidobacterium spp.* and suppressing the growth of *Escherichia coli* and *Clostridium spp.*(49, 50) Experimental animal models indicated a promoting effect of gut microbiota-driven inflammation in hepatocarcinogenesis, including a decreased abundance of *Bifidobacterium spp.* and increased level of *Escherichia coli* and *Clostridium spp.*(51, 52) Furthermore, the T2D prevention dietary pattern may lower HCC risk by decreasing intake and controlling appetite that could contribute to the maintenance of healthy body weight.(53, 54) Obesity is known to stimulate the increased production of inflammation markers, such as interleukin-6 (IL-6), IL-1, C-reactive protein, and tumor necrosis factor-α (TNF-α), resulting in a state of systematic inflammatory responses, which could play a role in hepatocarcinogenesis.(55) Also, previous evidence has suggested the higher intake of low-quality carbohydrates,(56) *trans fat,*(57) SSBs,(58) and red and processed meat (59) was associated with increased liver cancer risk, the inverse association that we observed between the dietary pattern and HCC risk might be partially through lower intake of these unfavorable foods or nutrients. Given the complex interactions among components, more studies are needed to illustrate the potential mechanisms through synergistic or antagonistic manner among multiple dietary components in the prevention of HCC.

Interestingly, we observed that the inverse association between the dietary pattern for T2D prevention and HCC risk was pronounced among individuals without T2D. However, no statistical evidence for interaction was found ($P_{interaction}$=0.13), which may be due to the limited number of HCC cases among participants with T2D (n=30). Of note, our results are consistent with previous studies.(38, 60) In the NIH-AARP Diet and Health study, another large cohort study, with over 500 HCC cases, the results of stratified analysis were similar. In addition, the difference that we observed in the subgroups may reflect some heterogeneity of the possible effect of dietary pattern on the development of HCC between health conditions. For example, compared with non-diabetics, participants with T2D are more likely to have nonalcoholic steatohepatitis or nonalcoholic fatty liver disease, two important predisposing factors for HCC.(61, 62) Also, for individuals with T2D, impaired glucose metabolism has been shown to accelerate HCC growth.(63) In this context, the protective role of the dietary pattern on HCC prevention might be diluted by other factors, such as medications use. In contrast, the possible beneficial effects of the T2D prevention dietary pattern on HCC may be more significant among those participants without T2D because metabolic disturbances (e.g., nonalcoholic steatohepatitis, impaired glucose, or insulin resistance) insulin resistance) may be at earlier more modifiable stanges. Taken together, further studies are necessary to confirm our findings and explore the potential mechanisms among individuals with T2D who have an altered metabolic state. Likewise, we found that the inverse association with higher dietary diabetes risk reduction score appeared slightly stronger in men, individuals being physically active, or with higher alcohol consumption. These observations might be due to chance and require further investigation.

Although the current study is well suited to assess the relationship between the dietary diabetes risk reduction score and HCC based on its prospective design, updated dietary measurements, and long-term follow-up, there are some limitations. First, the information on HBV/HCV infection status could not be obtained from all individuals in the full cohorts. However, among a subset of participants where we have such data, HBV/HCV infection

status showed no correlations with the dietary diabetes risk reduction score. Besides, results were very similar when we excluded the HCC cases with known chronic HBV/HCV infections. Second, chance findings cannot be ruled out due to limited HCC case numbers in the current study. Additionally, misclassification of dietary data was inevitable as with any observational study, but the FFQs used in this study have been extensively validated. Third, although many covariates were adjusted in the analysis, we cannot rule out the potential residual confounding. Last, the participants are primarily whites and results may not be generalizable to other racial/ethnic groups.

## Conclusions

In conclusion, we found that better adherence to T2D prevention diet is associated with lower risk of developing HCC among US men and women. Our findings should be interpreted with caution considering the limited number of HCC cases and lack of data on HBV/HCV infection in the full cohorts. More studies in high risk populations are warranted to confirm our results and elucidate underlying mechanisms. If our findings confirmed, the T2D prevention dietary pattern may serve as a possible strategy for HCC prevention.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations:

| | |
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| **T2D** | type 2 diabetes |
| **HCC** | hepatocellular carcinoma |
| **HR** | hazard ratio |
| **CI** | confidence interval |
| **NAFLD** | nonalcoholic fatty liver disease |
| **AHEI-2010** | Alternate Healthy Eating Index-2010 |

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| **AMED** | Alternate Mediterranean Diet Score |
| **NHS** | Nurses' Health Study |
| **HPFS** | Health Professionals Follow-up Study |
| **FFQ** | food frequency questionnaire |
| **MET** | metabolic equivalent of task |
| **GI** | glycemic index |
| **P:S** | ratio of polyunsaturated to saturated fats |
| **SSBs** | sugar-sweetened beverages |
| **HBV** | hepatitis B virus |
| **HCV** | hepatitis C virus |
| **BMI** | body mass index |
| **IL-6** | interleukin-6 |
| **IL-1** | interleukin-1 |
| **TNF-α** | tumor necrosis factor-α |
| **CLD** | chronic liver disease |

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**WHAT IS KNOWN**

- T2D and HCC may share overlapping mechanisms, such as inflammation and insulin resistance.
- Health eating is a modifiable factor in type 2 diabetes (T2D) and cancer prevention.

**WHAT IS NEW HERE**

- Adherence to a T2D prevention dietary pattern is associated with lower risk of HCC.
- Diet improves insulin sensitivity and inflammation, serving as a possible way in HCC prevention.

**Table 1.**

Age-standardized characteristics of participants according to quartiles of dietary diabetes risk reduction score in the pooled Nurses' Health Study and Health Professionals Follow-up Study

| | Dietary diabetes risk reduction score | | | |
|---|---|---|---|---|
| | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** |
| Age (year) * | 57.8(12.0) | 61.3(11.8) | 64.0(11.5) | 66.9(10.7) |
| White, % | 96.2 | 96.9 | 97.1 | 97.5 |
| Body mass index, kg/m$^2$ | 25.8(4.6) | 25.5(4.3) | 25.2(4.0) | 24.7(3.7) |
| Physical activity, METS-hours/week | 18.1(23.0) | 19.2(21.9) | 21.4 (22.4) | 26.1(25.2) |
| Type 2 diabetes, % | 5.6 | 5.5 | 5.0 | 4.1 |
| Regular aspirin use, % | 34.6 | 36.7 | 37.9 | 38.0 |
| Smoking status | | | | |
| Past smoking, % | 28.9 | 34.9 | 40.2 | 46.9 |
| Current smoking, % | 13.2 | 13.1 | 11.0 | 8.1 |
| Food and nutrient intakes | | | | |
| Alcohol (g/day) | 6.3(10.7) | 7.7(11.8) | 8.3(11.8) | 8.8(11.4) |
| Glycemic index, GI | 54.5(2.7) | 53.0(3.1) | 51.9(3.1) | 50.6(2.9) |
| Cereal fiber (g/day) | 3.7(1.9) | 4.3(2.3) | 5.1(2.8) | 6.1(3.4) |
| Ratio of polyunsaturated to saturated fats, P:S | 0.43(0.11) | 0.48(0.13) | 0.54(0.16) | 0.66(0.20) |
| Trans fat (% energy) | 2.0(0.6) | 1.9 (0.6) | 1.6(0.5) | 1.3(0.5) |
| Sugar-sweetened beverage intake (servings/week) | 4.7(5.3) | 2.5(3.4) | 1.4(2.2) | 0.6(1.1) |
| Nut intake (servings/week) | 0.6(1.0) | 0.9(1.4) | 1.2(1.8) | 1.9(2.5) |
| Coffee intake (cups/day) | 1.5(1.5) | 2.1(1.6) | 2.3(1.6) | 2.5(1.6) |
| Red and processed meat intake (servings/day) | 1.7(0.8) | 1.3(0.7) | 1.0(0.5) | 0.6(0.4) |
| Alternate Healthy Eating Index-2010, AHEI-2010 | 42.9(7.7) | 48.3(7.6) | 53.8(7.9) | 61.7(8.4) |

Values were means (SD) or percentages and were standardized to the age distribution of the study population.

METS, Metabolic equivalent tasks.

* Value was not age adjusted.

**Table 2.**

Dietary diabetes risk reduction score and risk of hepatocellular carcinoma in Nurses' Health Study and Health Professionals Follow-up Study

| | Dietary diabetes risk reduction score, HR (95% CI) | | | | $P_{trend}$ |
|---|---|---|---|---|---|
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | |
| **Women (NHS)** | | | | | |
| Number of cases | 14 | 19 | 28 | 24 | |
| Age-adjusted * | 1 (Ref) | 0.91 (0.45 to 1.83) | 0.76 (0.39 to 1.46) | 0.68 (0.34 to 1.36) | 0.22 |
| Multivariable-adjusted ** | 1 (Ref) | 0.95 (0.47 to 1.93) | 0.83 (0.42 to 1.64) | 0.78 (0.38 to 1.62) | 0.45 |
| Multivariable-adjusted ¶ | 1 (Ref) | 0.95 (0.47 to 1.93) | 0.82 (0.42 to 1.62) | 0.78 (0.37 to 1.61) | 0.44 |
| **Men (HPFS)** | | | | | |
| Number of cases | 19 | 19 | 27 | 10 | |
| Age-adjusted * | 1 (Ref) | 0.75 (0.39 to 1.41) | 0.75 (0.42 to 1.35) | 0.38 (0.18 to 0.82) | 0.02 |
| Multivariable-adjusted ** | 1 (Ref) | 0.75 (0.39 to 1.44) | 0.79 (0.43 to 1.45) | 0.40 (0.18 to 0.87) | 0.03 |
| Multivariable-adjusted ¶ | 1 (Ref) | 0.73 (0.38 to 1.41) | 0.78 (0.43 to 1.44) | 0.39 (0.18 to 0.86) | 0.03 |
| **Pooled** | | | | | |
| Number of cases | 33 | 38 | 55 | 34 | |
| Age-adjusted * | 1 (Ref) | 0.83 (0.52 to 1.33) | 0.75 (0.49 to 1.17) | 0.54 (0.33 to 0.89) | 0.01 |
| Multivariable-adjusted ** | 1 (Ref) | 0.82 (0.51 to 1.32) | 0.77 (0.49 to 1.21) | 0.57 (0.34 to 0.95) | 0.03 |
| Multivariable-adjusted ¶ | 1 (Ref) | 0.82 (0.51 to 1.31) | 0.77 (0.49 to 1.20) | 0.57 (0.34 to 0.95) | 0.03 |

CI, confidence interval; HR, hazard ratio; Ref, reference group.

*Adjusted for age (in months) and study period (two-year interval).

**Adjusted for age (in months), study period (two-year interval), gender (women, men), race (White, non-White), physical activity (3, 3-<27, ≥27 METS-hours/week), smoking status (never, past, current), body mass index (kg/$m^2$, continuous), aspirin use (yes, no), alcohol intake (g/day, continuous), and total calorie intake (kcal/day, tertiles).

¶Multivariable-adjusted model**+ type 2 diabetes (yes, no).

**Table 3.**

Associations between components in dietary diabetes risk reduction score and risk of hepatocellular carcinoma in the pooled Nurses' Health Study and Health Professionals Follow-up Study

| | Components in dietary diabetes risk reduction score, HR (95% CI) | | | | $P_{trend}$ |
|---|---|---|---|---|---|
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | |
| **Glycemic index (GI)** | | | | | |
| Number of cases | 32 | 48 | 39 | 41 | |
| Age-adjusted * | 1 (Ref) | 1.40 (0.89 to 2.19) | 1.18 (0.74 to 1.89) | 1.45 (0.91 to 2.30) | 0.19 |
| Multivariable-adjusted ** | 1 (Ref) | 1.45 (0.92 to 2.27) | 1.25 (0.78 to 2.01) | 1.54 (0.96 to 2.48) | 0.12 |
| **Cereal fiber** | | | | | |
| Number of cases | 33 | 39 | 46 | 42 | |
| Age-adjusted * | 1 (Ref) | 0.87 (0.54 to 1.40) | 0.83 (0.52 to 1.31) | 0.65 (0.40 to 1.05) | 0.07 |
| Multivariable-adjusted ** | 1 (Ref) | 0.93 (0.57 to 1.50) | 0.92 (0.57 to 1.49) | 0.79 (0.48 to 1.31) | 0.34 |
| **P:S** | | | | | |
| Number of cases | 31 | 49 | 38 | 42 | |
| Age-adjusted * | 1 (Ref) | 1.18 (0.75 to 1.87) | 0.80 (0.49 to 1.30) | 0.77 (0.47 to 1.24) | 0.10 |
| Multivariable-adjusted ** | 1 (Ref) | 1.23 (0.77 to 1.95) | 0.85 (0.52 to 1.39) | 0.85 (0.52 to 1.39) | 0.23 |
| **Trans fat** | | | | | |
| Number of cases | 44 | 53 | 28 | 35 | |
| Age-adjusted * | 1 (Ref) | 1.32 (0.88 to 1.97) | 0.76 (0.47 to 1.22) | 1.10 (0.70 to 1.74) | 0.86 |
| Multivariable-adjusted ** | 1 (Ref) | 1.27 (0.85 to 1.90) | 0.72 (0.44 to 1.17) | 1.07 (0.67 to 1.70) | 0.74 |
| **SSBs** | | | | | |
| Number of cases | 38 | 41 | 43 | 38 | |
| Age-adjusted * | 1 (Ref) | 0.97 (0.62 to 1.51) | 1.09 (0.70 to 1.69) | 1.23 (0.78 to 1.95) | 0.27 |
| Multivariable-adjusted ** | 1 (Ref) | 1.02 (0.65 to 1.60) | 1.14 (0.73 to 1.78) | 1.26 (0.79 to 2.01) | 0.29 |
| **Nut intake** | | | | | |
| Number of cases | 43 | 37 | 35 | 45 | |
| Age-adjusted * | 1 (Ref) | 0.84 (0.54 to 1.31) | 0.75 (0.48 to 1.17) | 0.84 (0.55 to 1.28) | 0.63 |
| Multivariable-adjusted ** | 1 (Ref) | 0.85 (0.54 to 1.33) | 0.76 (0.48 to 1.20) | 0.85 (0.55 to 1.33) | 0.72 |
| **Coffee intake** | | | | | |
| Number of cases | 38 | 49 | 44 | 29 | |
| Age-adjusted * | 1 (Ref) | 0.98 (0.64 to 1.51) | 1.01 (0.65 to 1.56) | 0.77 (0.47 to 1.25) | 0.31 |
| Multivariable-adjusted ** | 1 (Ref) | 0.93 (0.60 to 1.42) | 0.90 (0.57 to 1.40) | 0.67 (0.41 to 1.11) | 0.12 |
| **Red and processed meat** | | | | | |
| Number of cases | 35 | 40 | 53 | 32 | |
| Age-adjusted * | 1 (Ref) | 1.25 (0.79 to 1.97) | 1.84 (1.19 to 2.82) | 1.36 (0.83 to 2.21) | 0.10 |
| Multivariable-adjusted ** | 1 (Ref) | 1.16 (0.73 to 1.84) | 1.67 (1.08 to 2.60) | 1.18 (0.71 to 1.96) | 0.33 |

HR, Hazard Ratio; CI, Confidence Interval; Ref, reference group; P:S, ratio of polyunsaturated to saturated fats; SSBs, sugar-sweetened beverages.

*Adjusted for age (in months) and study period (two-year interval).

** Adjusted for age (in months), study period (two-year interval), gender (women, men), race (White, non-White), physical activity (3, 3-<27, ≥27 METS-hours/week), smoking status (never, past, current), body mass index (kg/$m^2$, continuous), aspirin use (yes, no), alcohol intake (g/day, continuous), and total calorie intake (kcal/day, tertiles).