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High Dietary Intake of Vegetable or Polyunsaturated Fats is Associated With Reduced Risk of Hepatocellular Carcinoma

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Drs. Yang, Sui, and Zhang had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: all coauthors

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Abstract

Background & Aims: We investigated associations of intake of total fats, specific dietary fats, and fats from different food sources with risk of hepatocellular carcinoma (HCC) using data from the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

Methods: We analyzed data from a total of 138,483 women and men who participated in the NHS or HPFS. A validated semi-quantitative food frequency questionnaire was sent to NHS participants in 1980, 1984, 1986, and every 4 years thereafter; dietary information was collected from participants in the HPFS in 1986 and every 4 years thereafter. Multivariable hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards regression.

Results: After an average follow-up time of 26.6 years, 160 incident HCC cases were documented. Although there was a non-significant association between total fat intake and HCC, intake of vegetable fats reduced risk of HCC (HR for the highest vs lowest quartile, 0.61; 95% CI, 0.39–0.96; $P_{\text{trend}}=.02$), but not animal or dairy fats. Replacing animal or dairy fats with an equivalent amount of vegetable fats was associated with a lower risk of HCC (HR per 1 standard deviation, 0.79; 95% CI, 0.65–0.97). Among fat subtypes, monounsaturated and polyunsaturated fatty acids, including n-3 (HR, 0.63; 95% CI, 0.41–0.96; $P_{\text{trend}}=.14$) and n-6 polyunsaturated fatty acids (HR, 0.54; 95% CI, 0.34–0.86; $P_{\text{trend}}=.02$), were inversely associated with risk of HCC. Higher ratios of monounsaturated or polyunsaturated fat to saturated fat were inversely associated with HCC risk (all $P_{\text{trend}} .02$). In addition, when replacing saturated fats with monounsaturated or polyunsaturated fats, the HR per 1 standard deviation was 0.77 (95% CI, 0.64–0.92).

Conclusions: In an analysis of data from 2 large cohort studies, we found higher intake of vegetable fats and polyunsaturated fats to be associated with lower risk of HCC. Replacing animal or dairy fats with vegetable fats, or replacing saturated fats with monounsaturated or polyunsaturated fats, was associated with reduced risk of HCC.

Keywords

liver cancer; primary prevention; dairy fat; PUFAs

Introduction

In the United States, the incidence rate of hepatocellular carcinoma (HCC) has tripled since the 1980s, increasing sharply in the past 5 years among both men and women.^{1, 2} The increased incidence is particularly concerning due to poor prognosis of HCC, thereby

making prevention a key priority. Approximately 35% of HCC in the US, however, cannot be explained by currently known risk factors, including hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, excessive alcohol consumption, smoking, and metabolic disorders.³ Thus, identifying other modifiable factors such as diet to prevent development of HCC is crucial to decrease the morbidity and mortality of HCC.⁴

Dietary fats, which contain varying proportions of saturated and unsaturated (mono- and polyunsaturated) fats, have been suggested to play a role in hepatocarcinogenesis in experimental studies. For example, n-3 polyunsaturated fatty acids (PUFAs) may protect against HCC through the blockage of β -catenin and cyclooxygenase-2,⁵ or through their anti-inflammatory activity by inhibiting interleukin (IL)-1 and tumor necrosis factor (TNF) synthesis.^{6, 7} In addition, incorporation of n-3 PUFAs into cell membranes may alter the fluidity, structure and/or function of lipid rafts, which are crucial for downstream receptor signaling, controlling proliferation and apoptosis.^{8–10} Conversely, high intake of saturated fats and *trans* fatty acids has been associated with the development of non-alcoholic steatohepatitis (NASH) and its progression to fibrosis and cirrhosis,^{11, 12} which are known predisposing factors for HCC. Despite these data, epidemiological evidence^{13–18} regarding the association between dietary fat intake and HCC risk is limited and inconclusive. The association has been investigated in only three prospective^{13–15} and three case-control studies,^{16–18} with mixed results. Most of the studies were conducted among Europeans,^{14, 16–18} and only one¹⁵ was drawn from a US population. Furthermore, few studies^{13–15, 17} have examined the association by fat subtypes, and only one study¹⁴ has evaluated fats by food sources.

Therefore, we investigated the associations of total and specific dietary fats, and fats from different food sources with risk of developing HCC. We used data from two large ongoing US nationwide cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

Methods

Participants

Participants were selected from the NHS and HPFS. The rationale, design, and methodology of the 2 cohorts were published previously.^{19, 20} A flow chart of how we selected study population within the cohorts is presented in online Supplementary Figure 1. A total of 138,483 women and men were included in the final analysis. The Institutional Review Board at the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health approved this study, and those of participating registries as required.

Assessments of diet and other covariates and their validity

A validated semi-quantitative food frequency questionnaire (FFQ)^{19, 20} was sent in 1980, 1984, 1986, and every 4 years thereafter in the NHS. Likewise, dietary information was collected in 1986 and every 4 years thereafter using similar FFQs in the HPFS. A response rate of at least 90% has been achieved in most follow-up cycles in both NHS and HPFS.

Details on assessments of diet and other covariates, the validity of FFQ for measuring fat intake were described in the Supplementary Materials and Methods section.

Assessment of HCC

Details on HCC ascertainment as well as data on HBV/HCV infections were described in the Supplementary Materials and Methods section.

Statistical analyses

Person-years were calculated from the date of return of the baseline questionnaire to the diagnosis of HCC, date of death, loss to follow-up, or the end of the follow-up (June 1, 2012 for the NHS and January 31, 2012 for the HPFS), whichever came first. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox regression models with time-varying fat intake and covariates (i.e., person-year was assigned to the appropriate category for each variable at the beginning of every biennial follow-up questionnaire cycle). The models were stratified simultaneously by age and year of questionnaire return, enabling the finest possible control of confounding for age and secular trends. We presented HRs by both quartile categories and per 1-standard deviation (SD) increase of total and specific fats (grams/day). We pooled data from the two cohort studies because there was no significant heterogeneity in the association between fat consumption and HCC risk by cohort (all P -values > 0.05). Total and specific dietary fats were adjusted for energy using nutrient density model.²¹ To best reflect long-term diets and lifestyle, and to minimize within-person variability, we used the cumulative average of dietary intakes and other covariates whenever appropriate.²² We calculated the cumulative average intake of fats by averaging fat intake over time from 1980 for NHS and 1986 for HPFS to the current questionnaire cycle and updating data when information on fat intake was updated.

Details on covariate adjustments, proportional hazards assumption test, trend tests, substitution analyses, and secondary analyses are described in the Supplementary Materials and Methods sections. All statistical tests were 2-sided and performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Characteristics of participants.

Participants with higher consumption of total fats were younger, had higher BMI, engaged in less physical activity, consumed less alcohol, had higher prevalence of type 2 diabetes mellitus (T2D), were more likely to smoke, were less likely to use aspirin, and tended to have higher intake of coffee, compared to those with lower intake levels. Likewise, we observed similar pattern for both animal and dairy fats but not for vegetable fats except T2D (Table 1). These patterns were similar in both women (Supplementary Table 1) and men (Supplementary Table 2). Intake levels of % energy from animal fats decreased from 18.2% to 12.3% in men (1986–2010), and from 18.1% to 12.1% in women (1986–2010). While the consumption of % energy from vegetable fats increased in men from 13.2% to 19.5%, and in women from 14.1% to 19.2% (Supplementary Figure 2). Intake levels of other types of fats were generally stable during the study periods in two cohorts.

Total fats, their food sources and HCC.

After an average follow-up of 26.6 years (a total of 3,692,753 person-years in these cohorts), we identified 160 incident HCC cases. In multivariable-adjusted analysis, total fat intake was not significantly associated with HCC risk (comparing the highest to the lowest quartile categories, HR=0.76, 95% CI: 0.47–1.24, $P_{\text{trend}}=0.46$) (Table 2). According to food sources, intake of vegetable fats (HR=0.61, 95% CI: 0.39–0.96, $P_{\text{trend}}=0.02$), but not animal (HR=1.24, 95% CI: 0.74–2.07, $P_{\text{trend}}=0.33$) or dairy fats (HR=1.36, 95% CI: 0.84–2.19, $P_{\text{trend}}=0.13$) was associated with lower HCC risk. Similar results were found after mutual adjustments for vegetable, animal, and dairy fats (data not shown). When replacing animal or dairy fats with an equivalent amount of vegetable fats, the HR per 1-SD increase was 0.79 (95% CI: 0.65–0.97). The associations of animal or vegetable fats with HCC appeared stronger in men than those in women (Supplementary Table 3).

Fat subtypes and HCC.

According to fat subtypes, the HRs were 0.76 (95% CI: 0.47–1.25, $P_{\text{trend}}=0.32$) for monounsaturated and 0.71 (95% CI: 0.46–1.08, $P_{\text{trend}}=0.03$) for polyunsaturated fats. Although there is a null association between saturated fat intake and HCC risk, replacing saturated fats with an equivalent amount of monounsaturated or polyunsaturated fats was associated with lower risk of HCC (HR per 1-SD increase=0.77, 95% CI: 0.64–0.92). We found a non-significant association between cholesterol intake and HCC risk (HR=1.19, 95% CI: 0.74–1.92, $P_{\text{trend}}=0.18$). Both n-3 (HR=0.63, 95% CI: 0.41–0.96, $P_{\text{trend}}=0.14$) and n-6 PUFAs (HR=0.54, 95% CI: 0.34–0.86, $P_{\text{trend}}=0.02$) were statistically significantly associated with lower risk of HCC (Table 3). There is a null association between *trans* fats and HCC risk. When examining the ratios of polyunsaturated and/or monounsaturated fats to saturated fats (i.e., P:S, M:S, and [P+M]:S ratios) in relation to HCC risk, the P:S, M:S, and (P+M):S ratios were all associated with reduced risk of HCC. When we separately assessed the associations of specific dietary fats with HCC risk in women (Supplementary Table 4) and men (Supplementary Table 5), the results were similar to the pooled analyses.

Secondary analysis.

Among 105 HCC cases who have known information on hepatitis virus infections, 26 infected with HBV or HCV. We did not detect any statistically differential associations of total fats, fats from different food sources, or fat subtypes with the risk of viral and non-viral HCC, despite the insufficient statistical power due to the limited number of HCC cases (Supplementary Table 6). Similarly, when separately examining the associations with cirrhotic vs. non-cirrhotic HCC, there was no difference in the fat-HCC association (all $P_{\text{heterogeneity}} > 0.20$). There is no correlation between dietary fat intake and HBV/HCV infection status (all Spearman correlation coefficients were no more than 0.09). When we adjusted for the Alternative Healthy Eating Index-2010 score rather than the individual dietary factors in the models, the results were very similar to those in the main analysis. The associations were generally consistent in exploratory subgroups analysis defined by age, BMI, physical activity, smoking status, T2D, and regular aspirin use (Supplementary Table 7). When we used the absolute value of fat intake (not the energy adjusted value using

nutrient density model), the results remained almost the same with the main analysis (Supplementary Table 8).

Discussion

In two large, prospective cohort studies of US women and men, we found that intake of fats from vegetable but not animal or dairy, was inversely associated with HCC risk. In addition, increasing consumption of monounsaturated or polyunsaturated fats including both n-3 and n-6 PUFAs was associated with lower risk of developing HCC. Further, replacing animal or dairy fats with vegetable fats, or replacing saturated fats with monounsaturated or polyunsaturated fats, was associated with reduced risk of HCC. These findings, if validated, have important public health and clinical relevance.

To date, only six epidemiological studies have examined the association between dietary fat intake and risk of HCC with inconsistent findings.^{13–18} Three existing case-control studies^{16–18} of fats and HCC risk were all conducted in European populations. Among these studies, two^{17, 18} reported a null association between total fat intake and HCC risk, while a study¹⁶ showed a significant positive association (odds ratio [OR]=1.4). Only one hospital-based case-control study from Italy has investigated different types of fat intake, and showed that participants with higher intake of PUFAs, but not MUFAs or SFAs, had a significantly lower risk of HCC (OR=0.60).¹⁷

Beyond the above few case-controls studies, only three prospective studies exist on this topic. One cohort study within the National Institute of Health (NIH)-AARP Diet and Health cohort showed a statistically significant positive association (HRs per 5% increase in energy) for total (HR=1.10) and saturated fats (HR=1.38), a non-significant association for monounsaturated (HR=1.18), and a null association for polyunsaturated fats (HR=1.06).¹⁵ In another cohort study among Singapore Chinese showed similar patterns with HRs (the highest vs. lowest quartile) of 1.26 for total, 1.40 for saturated, and 0.90 for monounsaturated fats (all *P* values for trend across quartile categories were great than 0.05).¹³ In contrast, a study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort,¹⁴ showed a suggestive inverse HCC association for total fats (highest vs. lowest quartile category, HR=0.74, 95%CI: 0.45–1.23), monounsaturated fats (HR=0.53, 95%CI: 0.27–1.01), and polyunsaturated fats (HR=0.86, 95%CI: 0.55–1.35), and a null association for saturated or *trans* fats. That study¹⁴ also showed that total fats from animals were positively (HR=1.45), while fats from plant origin were inversely (HR=0.71) associated with HCC risk, although these associations did not reach statistical significance.¹⁴ Additionally, the EPIC study found a significant positive association between dairy fat intake and HCC risk (highest vs. lowest tertile, HR=1.63, 95%CI: 1.10–2.41).²³ Our findings were generally consistent those from the EPIC study.

The discrepancy among previous studies of fats and HCC risk remains unknown. The potential reverse causality and recall bias in retrospective case-control design may partly explain the inconsistent findings between case-control and cohort studies. We postulate that the inconsistent findings within the cohort studies^{13–15, 17} could be at least, in part, due to the different intake levels and food sources of fats among different study populations. For

example, for total dietary fats, the average intake levels for participants in our cohorts were similar with those in the NIH-AARP cohort,¹⁵ but lower than those in the EPIC,¹⁴ and higher than those from the Singapore cohort.¹³ Additionally, the main food sources of monounsaturated fats within NIH-AARP are meats and meat products (over 20%). Unlike NIH-AARP cohort, the main food sources of monounsaturated fats in our cohorts are olive oil and nuts (~20%), which were similar to those in EPIC study. The vegetable (plant) fats including fats from olive oil and nuts were shown to be associated with lower risk of HCC in the current study. Given the limited number of HCC cases and inconsistent results in previous studies,^{13–18} more studies are warranted to confirm our findings, ideally with pooled analysis across cohorts in different populations.

There seemed a slightly stronger association of some types of fat with HCC risk in men than those in women. For example, the associations for animal and vegetable fats appeared much stronger in men compared to those in women, although the *P* for heterogeneity between the genders did not reach statistical significance. These possible differential associations might be due to chance. Alternatively, it could be partly explained by different intake levels in women and men. For example, intake levels of % energy from animal fats in men were lower than those in women, while men have higher consumption of % energy from vegetable fats than those in women.

Interestingly, we found both n-3 and n-6 PUFAs were associated with lower risk of HCC. It is known that dietary n-3 PUFAs can exert anti-inflammatory effects on acute and chronic inflammatory reactions,^{6, 7} and alter the composition of cellular phospholipid membranes,^{8–10} which in turn could affect membrane or membrane-bound receptor functions, thereby controlling proliferation and apoptosis. Furthermore, n-3 PUFAs may inhibit HCC growth in mice,⁵ and supplementation with n-3 PUFAs showed beneficial effects on patients with NAFLD in randomized controlled clinical trials (RCTs) such as decreasing alanine aminotransferase, total cholesterol, and triglyceride, and increasing high-density lipoprotein cholesterol.^{24, 25}

There was a discrepancy between the evidence from experimental studies and human clinical trials, in terms of the role of n-6 PUFAs in cancer development and prognosis. Experimental studies suggested that increasing dietary intake of n-6 PUFAs arachidonic acid (ARA) or its precursor linoleic acid (LA) may increase inflammation, because ARA is a precursor to many potent pro-inflammatory mediators such as prostaglandins and leukotrienes, and higher n-6 PUFAs intake may also inhibit anti-inflammatory effect of n-3 PUFAs.²⁶ Nonetheless, human clinical trials^{27–29} have found that increased intake of ARA or LA does not increase the concentrations of many inflammatory markers including IL-1 β , TNF- α , and IL-6. Moreover, observational studies^{30, 31} and a meta-analysis of 15 RCTs³² have suggested that ARA and LA may be linked to reduced inflammation. In line with findings from clinical trials, our findings support the hypothesis that a high n-6 PUFAs diet may prevent against HCC development. In contrast, the only prospective study that investigated specific PUFAs in relation to HCC risk, conducted among Singapore Chinese, showed a significant positive association of n-6 PUFAs and the ratio of n-6 PUFAs to n-3 PUFAs with the risk of HCC.¹³ The reasons for these different findings remains unclear, which requires further investigations.

Strengths of the present study include the prospective design, measurements of fat intake from various food sources, high follow-up rates, and validated HCC outcome. In addition, utilizing the repeated measures of dietary fat intake and other covariates during the follow-up periods may better represent long-term dietary habits and lifestyle, and reduce the within-person variability.

Our study has several limitations. First, despite an average follow-up of 26.6 years in the two cohorts, the number of incident HCC cases is relatively small. So, there might have been chance findings. Second, as other observational studies, measurement errors in fat intake and other dietary factors cannot be ruled out. However, FFQs used in these cohorts have showed good reproducibility and validity for measuring dietary fats and other dietary factors.

19, 20, 33–35 Third, the data on liver fibrosis and cirrhosis as well as other chronic liver diseases such as chronic HBV/HCV infections were not available in the full cohorts. Therefore, we cannot adjust for or conduct stratified analyses by these factors in the analysis, although HBV/HCV infection status was not correlated with total or specific fat intake, indicating that our results are not likely to be substantially confounded by HBV or HCV infection status. In addition, we cannot investigate the fat-HCC association in high-risk populations such as patients with cirrhosis or patients with chronic HBV/HCV infections. Although we did not find any differential association of intake of dietary fats with cirrhotic and non-cirrhotic HCC or with viral and non-viral HCC, the insufficient statistical power may limit our ability to make a firm conclusion. Future studies that investigate the association between fat intake and HCC among patients with liver diseases such as cirrhosis or chronic HBV or HCV infections are warranted. Likewise, we did not adjust for medication use such as metformin or statins since we did not collect these data at baseline. While no correlation between statin use and dietary fat intake was observed, indicating that statin use is unlikely to confound the observed fat-HCC association. Last, our cohorts consist mainly of white US health professionals and the results may not be generalizable to other racial/ethnic groups or to persons of different socio-economic status.

In conclusion, our findings add to previous studies suggesting that substitution of vegetable fats for animal or dairy fats, or substitution of monounsaturated or polyunsaturated fats for saturated fats was associated with lower risk of HCC among US adults. Future prospective studies that carefully consider HBV/HCV infections, ideally combining results from multiple cohorts among different populations are warranted. In addition, the underlying biological mechanisms that are responsible for the potential fat-HCC association remain to be further elucidated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper:

BMI	body mass index
CI	confidence interval
EPIC	European Prospective Investigation into Cancer and Nutrition
FFQ	food frequency questionnaire
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
IL	interleukin
METS	metabolic equivalent tasks
MUFAs	monounsaturated fatty acids
NAFLD	nonalcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NHS	Nurses' Health Study
PUFAs	polyunsaturated fatty acids
SFAs	saturated fatty acids
TNF	tumor necrosis factor

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What You Need to Know

Background:

Dietary fats, which contain varying proportions of saturated and unsaturated fats, have been proposed to contribute to hepatocarcinogenesis.

Findings:

In an analysis of data from the Nurses' Health Study and Health Professionals Follow-up Study, we found higher intake of vegetable fats and polyunsaturated fats to be associated with lower risk of hepatocellular carcinoma. Replacing animal or dairy fats with vegetable fats, or replacing saturated fats with monounsaturated or polyunsaturated fats, was also associated with reduced risk of hepatocellular carcinoma.

Implications for patient care:

Patients at risk for hepatocellular carcinoma should consider replacing animal and dairy fats in their diet with vegetable fats, and replacing saturated fats with monounsaturated or polyunsaturated fats.

Age-adjusted characteristics of participants according to fat intake in the Nurses' Health Study (1980–2012) and the Health Professionals Follow-up Study (1986–2012)^a

	Total fat			Animal fat			Vegetable fat			Dairy fat		
	Quartile 1	Quartile 4	Quartile 1	Quartile 4	Quartile 1	Quartile 4	Quartile 1	Quartile 4	Quartile 1	Quartile 4	Quartile 1	Quartile 4
Age, years ^b	66.0(11.5)	58.4(12.0)	67.3(11.0)	57.4(11.9)	59.7(12.4)	64.17(11.5)	63.7(12.1)	60.8(12.1)				
White, %	95.6	97.4	96.2	96.9	95.5	97.9	94.3	98.2				
Body mass index, kg/m ²	24.7(3.8)	25.8(4.5)	24.4(3.7)	25.8(4.5)	25.3(4.2)	25.1(4.2)	25.0(4.1)	25.3(4.3)				
Physical activity, METS-hours/week	25.4(25.4)	18.9(23.3)	25.4(25.1)	19.1(25.0)	22.6(26.9)	20.3(21.4)	22.4(23.9)	20.1(23.5)				
Type 2 diabetes, %	4.0	5.6	3.8	5.5	4.6	5.0	5.1	4.7				
Regular aspirin use, %	38.0	34.5	38.0	32.8	35.1	37.7	38.0	35.1				
Past smoking, %	39.9	34.5	40.6	32.5	35.0	39.1	38.6	35.5				
Current smoking, %	9.4	14.9	7.7	15.4	14.0	10.4	11.8	13.8				
Food and nutrient intake												
Alcohol, g/day	9.5(14.1)	6.2(9.3)	8.0(12.2)	7.4(11.1)	9.9(14.6)	6.1(9.0)	8.6(13.1)	7.2(10.6)				
Total coffee intake, cups/day	1.9(1.5)	2.4(1.8)	1.8(1.5)	2.3(1.8)	2.0(1.7)	2.2(1.7)	2.0(1.6)	2.2(1.7)				
Total fat (% of energy)	26.3(3.4)	40.8(4.1)	28.1(5.1)	39.1(5.2)	31.4(7.8)	36.4(5.1)	31.9(7.2)	36.0(5.6)				
Animal fat (% of energy)	15.2(4.1)	26.0(7.2)	13.5(3.0)	27.8(5.8)	23.1(8.5)	18.0(5.0)	18.4(7.5)	23.7(6.2)				
Vegetable fat (% of energy)	11.1(3.3)	14.8(5.2)	14.6(4.5)	11.3(4.0)	8.3(2.1)	18.4(2.8)	13.5(4.5)	12.3(4.1)				
Dairy fat (% of energy)	5.4(2.3)	7.7(3.8)	5.0(2.0)	8.3(4.0)	7.1(3.8)	6.0(2.5)	3.5(1.0)	10.5(2.8)				
Saturated fat (% of energy)	9.2(1.9)	15.0(2.8)	9.2(1.9)	15.1(2.7)	12.2(3.9)	12.1(2.6)	10.6(3.2)	14.2(2.8)				
Monounsaturated fat (% of energy)	10.0(1.6)	16.3(2.2)	10.8(2.3)	15.5(2.7)	12.2(3.7)	14.4(2.3)	12.9(3.5)	13.6(2.5)				
Polyunsaturated fat (% of energy)	5.0(1.0)	6.5(1.5)	5.8(1.5)	5.6(1.3)	4.6(0.9)	7.1(1.2)	6.0(1.4)	5.5(1.3)				
Trans fat (% of energy)	1.3(0.5)	2.1(0.6)	1.4(0.6)	1.9(0.6)	1.4(0.6)	2.0(0.7)	1.7(0.7)	1.7(0.5)				
N-3 PUFAs (% of energy)	0.62(0.17)	0.68(0.18)	0.66(0.18)	0.63(0.16)	0.59(0.16)	0.71(0.18)	0.67(0.18)	0.63(0.15)				
N-6 PUFAs (% of energy)	4.3(1.0)	5.7(1.6)	5.2(1.4)	4.8(1.3)	3.8(0.9)	6.4(1.2)	5.2(1.4)	4.8(1.3)				
N-6 PUFAs:n-3 PUFAs ratio	7.3(1.8)	8.9(2.8)	8.4(3.0)	7.9(2.1)	6.8(1.7)	9.7(2.8)	8.2(2.6)	8.0(2.1)				
M:S ratio	1.1(0.2)	1.1(0.2)	1.2(0.2)	1.0(0.1)	1.0(0.1)	1.2(0.2)	1.3(0.2)	1.0(0.1)				
P:S ratio	0.59(0.20)	0.47(0.17)	0.68(0.19)	0.39(0.12)	0.43(0.17)	0.63(0.18)	0.63(0.21)	0.42(0.12)				
(M+P):S ratio	1.7(0.4)	1.6(0.3)	1.9(0.4)	1.4(0.2)	1.5(0.3)	1.9(0.3)	1.9(0.4)	1.4(0.2)				

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

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METS, Metabolic equivalent tasks; PUFAs, polyunsaturated fatty acids; M:S, monounsaturated fat to saturated fat; P:S, polyunsaturated fat to saturated fat; (M+P):S, (monounsaturated fat and polyunsaturated fat) to saturated fat.

^qValue was not age adjusted.

HRs and 95% CIs for hepatocellular carcinoma by quartiles of energy-adjusted^a dietary intake of total fats and their food sources in the Nurses' Health Study (1980–2012) and the Health Professionals Follow-up Study (1986–2012)

	Quartile 1	HR (95% CI)			HR (95% CI) Per 1-SD increase	P _{trend}
		Quartile 2	Quartile 3	Quartile 4		
Total fat						
Number of cases	52	41	39	28	160	
Age-adjusted model ^b	1 (Reference)	0.90 (0.59–1.35)	0.96 (0.63–1.46)	0.86 (0.54–1.39)	0.98 (0.82–1.17)	0.85
Multivariable-adjusted model ^c	1 (Reference)	0.85 (0.56–1.28)	0.88 (0.57–1.34)	0.76 (0.47–1.24)	0.93 (0.78–1.12)	0.46
Animal fat						
Number of cases	42	47	41	30	160	
Age-adjusted model ^b	1 (Reference)	1.37 (0.90–2.08)	1.42 (0.92–2.20)	1.41 (0.86–2.31)	1.18 (0.97–1.44)	0.10
Multivariable-adjusted model ^c	1 (Reference)	1.29 (0.85–1.97)	1.25 (0.80–1.96)	1.24 (0.74–2.07)	1.11 (0.90–1.37)	0.33
Vegetable fat						
Number of cases	46	46	29	39	160	
Age-adjusted model ^b	1 (Reference)	0.82 (0.54–1.24)	0.47 (0.29–0.75)	0.61 (0.39–0.95)	0.80 (0.67–0.96)	0.01
Multivariable-adjusted model ^c	1 (Reference)	0.81 (0.53–1.23)	0.47 (0.29–0.76)	0.61 (0.39–0.96)	0.80 (0.67–0.97)	0.02
Dairy fat						
Number of cases	34	44	46	36	160	
Age-adjusted model ^b	1 (Reference)	1.31 (0.84–2.05)	1.50 (0.96–2.34)	1.34 (0.84–2.15)	1.13 (0.96–1.33)	0.13
Multivariable-adjusted model ^c	1 (Reference)	1.34 (0.85–2.10)	1.55 (0.99–2.42)	1.36 (0.84–2.19)	1.13 (0.96–1.33)	0.13
Animal and dairy fat						
Number of cases	37	52	43	28	160	
Age-adjusted model ^b	1 (Reference)	1.71 (1.12–2.62)	1.69 (1.08–2.64)	1.41 (0.85–2.35)	1.18 (0.99–1.42)	0.07
Multivariable-adjusted model ^c	1 (Reference)	1.63 (1.06–2.49)	1.54 (0.98–2.42)	1.29 (0.77–2.18)	1.14 (0.94–1.38)	0.18

CI, confidence interval; HR, hazard ratio; SD, standard deviation.

The median values (% of energy) for each quartile category were 26.8, 31.8, 35.3, 40.4 for total fat, 13.7, 18.4, 21.8, 27.6 for animal fat, 8.7, 12.0, 14.4, 17.7 for vegetable fat, and 3.6, 5.3, 6.9, 9.8 for dairy fat.

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^aTotal and specific dietary fats were adjusted for energy using nutrient density model (ref. 23).

^bAdjusted for age (months, continuous).

^cAdjusted for age (months, continuous), gender (women, men), race (white, non-white), physical activity (<3, 3-27, 27 METS-hours/week), body mass index (kg/m², continuous), smoking status (never, past, current smoking), aspirin use (no, yes), type 2 diabetes (no, yes), alcohol intake (<5, 5-15, 15 g/day), total coffee intake (<2, 2-4, 4 cups/day), and total calorie intake (kcal/day, tertile).

Table 3.

HRs and 95% CIs for hepatocellular carcinoma by quartiles of energy-adjusted^a intake of specific fats in the Nurses' Health Study (1980–2012) and the Health Professionals Follow-up Study (1986–2012)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	HR (95% CI) Per 1-SD increase	P _{trend}
Saturated fat						
Number of cases	49	50	34	27	160	
Age-adjusted model ^b	1 (Reference)	1.24 (0.83–1.84)	1.01 (0.65–1.57)	1.02 (0.63–1.67)	1.08 (0.89–1.30)	0.45
Multivariable-adjusted model ^c	1 (Reference)	1.17 (0.78–1.75)	0.91 (0.58–1.43)	0.92 (0.55–1.52)	1.03 (0.84–1.26)	0.77
Monounsaturated fat						
Number of cases	48	47	38	27	160	
Age-adjusted model ^b	1 (Reference)	1.08 (0.72–1.62)	0.98 (0.64–1.50)	0.85 (0.53–1.38)	0.96 (0.80–1.15)	0.64
Multivariable-adjusted model ^c	1 (Reference)	1.02 (0.68–1.54)	0.90 (0.58–1.39)	0.76 (0.47–1.25)	0.91 (0.75–1.10)	0.32
Polysaturated fat						
Number of cases	51	41	29	39	160	
Age-adjusted model ^b	1 (Reference)	0.72 (0.47–1.09)	0.53 (0.33–0.83)	0.75 (0.49–1.14)	0.84 (0.71–1.00)	0.05
Multivariable-adjusted model ^c	1 (Reference)	0.71 (0.47–1.07)	0.51 (0.32–0.81)	0.71 (0.46–1.08)	0.83 (0.69–0.99)	0.03
Trans fat						
Number of cases	45	52	30	33	160	
Age-adjusted model ^b	1 (Reference)	1.29 (0.86–1.92)	0.81 (0.51–1.29)	1.08 (0.68–1.70)	0.98 (0.81–1.19)	0.83
Multivariable-adjusted model ^c	1 (Reference)	1.23 (0.82–1.85)	0.77 (0.48–1.24)	1.04 (0.65–1.67)	0.96 (0.78–1.18)	0.70
Cholesterol						
Number of cases	47	38	40	35	160	
Age-adjusted model ^b	1 (Reference)	0.91 (0.59–1.39)	1.18 (0.77–1.82)	1.36 (0.85–2.16)	1.22 (1.00–1.49)	0.05
Multivariable-adjusted model ^c	1 (Reference)	0.85 (0.55–1.31)	1.06 (0.69–1.64)	1.19 (0.74–1.92)	1.16 (0.93–1.44)	0.18
N-3 PUFAs						
Number of cases	49	32	37	42	160	
Age-adjusted model ^b	1 (Reference)	0.58 (0.37–0.91)	0.64 (0.41–0.99)	0.67 (0.44–1.02)	0.91 (0.77–1.06)	0.22

	HR (95% CI)				HR (95% CI) Per 1-SD increase	P_{trend}
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Multivariable-adjusted model ^c	1 (Reference)	0.57 (0.36–0.90)	0.62 (0.40–0.96)	0.63 (0.41–0.96)	0.89 (0.75–1.04)	0.14
N-6 PUFAs						
Number of cases	50	32	47	31	160	
Age-adjusted model ^b	1 (Reference)	0.56 (0.36–0.87)	0.83 (0.55–1.24)	0.57 (0.36–0.89)	0.83 (0.69–0.98)	0.03
Multivariable-adjusted model ^c	1 (Reference)	0.55 (0.35–0.86)	0.80 (0.53–1.21)	0.54 (0.34–0.86)	0.81 (0.68–0.97)	0.02
N-6 PUFAs:n-3 PUFAs ratio						
Number of cases	38	43	47	32	160	
Age-adjusted model ^b	1 (Reference)	1.08 (0.70–1.68)	1.20 (0.78–1.84)	0.89 (0.55–1.42)	0.92 (0.77–1.09)	0.32
Multivariable-adjusted model ^c	1 (Reference)	1.09 (0.70–1.70)	1.21 (0.78–1.87)	0.92 (0.57–1.48)	0.92 (0.78–1.10)	0.39
P:S ratio						
Number of cases	31	49	38	42	160	
Age-adjusted model ^b	1 (Reference)	1.18 (0.75–1.87)	0.80 (0.49–1.30)	0.77 (0.47–1.24)	0.77 (0.64–0.92)	0.005
Multivariable-adjusted model ^c	1 (Reference)	1.18 (0.74–1.87)	0.81 (0.49–1.33)	0.81 (0.49–1.32)	0.78 (0.64–0.94)	0.009
M:S ratio						
Number of cases	36	43	38	43	160	
Age-adjusted model ^b	1 (Reference)	1.04 (0.67–1.63)	0.82 (0.52–1.29)	0.78 (0.50–1.23)	0.81 (0.69–0.96)	0.02
Multivariable-adjusted model ^c	1 (Reference)	1.03 (0.66–1.62)	0.82 (0.52–1.30)	0.79 (0.50–1.26)	0.81 (0.68–0.97)	0.02
(M+P):S ratio						
Number of cases	32	50	40	38	160	
Age-adjusted model ^b	1 (Reference)	1.27 (0.81–1.99)	0.85 (0.53–1.37)	0.69 (0.43–1.12)	0.78 (0.65–0.93)	0.005
Multivariable-adjusted model ^c	1 (Reference)	1.27 (0.81–1.99)	0.85 (0.53–1.37)	0.71 (0.44–1.17)	0.78 (0.65–0.94)	0.008

CI, confidence interval; HR, hazard ratio; PUFAs, polyunsaturated fatty acids; M:S, monounsaturated fat to saturated fat; (M+P):S, (monounsaturated fat and polyunsaturated fat) to saturated fat; SD, standard deviation.

The median values (% of energy) for each quartile category were 8.9, 11.3, 13.0, 15.5 for saturated fat, 10.1, 12.2, 13.7, 16.1 for monounsaturated fat, 4.4, 5.3, 6.1, 7.2 for polyunsaturated fat, 1.1, 1.6, 1.9, 2.4 for *trans* fat, 0.5, 0.6, 0.7, 0.8 for n-3 PUFAs, 3.7, 4.6, 5.4, 6.5 for N-6 PUFAs, 6.1, 7.4, 8.5, 10.2 for n-6 PUFAs:N-3 PUFAs ratio, 0.35, 0.46, 0.55, 0.71 for P:S ratio, 0.95, 1.06, 1.14, 1.30 for M:S ratio, and 1.3, 1.5, 1.7, 2.0 for (M+P):S ratio.

^aDietary fats were adjusted for energy using nutrient density model (ref. 23).

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Adjusted for age (months, continuous).
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^c Adjusted for age (months, continuous), gender (women, men), race (white, non-white), physical activity (<3, 3-~27, 27 METS-hours/week), body mass index (kg/m², continuous), smoking status (never, past, current smoking), aspirin use (no, yes), type 2 diabetes (no, yes), alcohol intake (<5, 5-~15, 15 g/day), total coffee intake (<2, 2-~4, 4 cups/day), and total calorie intake (kcal/day, tertile).