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A prospective study of dairy product intake and the risk of hepatocellular carcinoma in U.S. men and women

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Abstract

Although increasing dairy product intake has been associated with risk of several cancers, epidemiological studies on hepatocellular carcinoma are sparse and have yielded inconsistent results. We prospectively assessed the associations of dairy products (total, milk, butter, cheese, and yogurt) and their major components (calcium, vitamin D, fats, and protein) with the risk of

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hepatocellular carcinoma development among 51,418 men and 93,427 women in the Health Professionals Follow-up Study and the Nurses' Health Study. Diets were collected at baseline and updated every 2-4 years using validated food frequency questionnaires. Multivariable hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated using Cox proportional hazards regression model. During up to 32 years of follow-up, a total of 164 hepatocellular carcinoma cases were documented. After adjustment for most known hepatocellular carcinoma risk factors, higher total dairy product intake was associated with an increased risk of hepatocellular carcinoma (highest vs. lowest tertile, HR=1.85, 95%CI: 1.19-2.88; P_{trend}=0.009). For the same comparison, we observed significant positive associations of high-fat dairy (HR=1.81, 95%CI: 1.19-2.76; P_{trend}=0.008) and butter (HR=1.58, 95%CI: 1.06-2.36; P_{trend}=0.04) with hepatocellular carcinoma risk. There was a non-significant inverse association between yogurt intake and hepatocellular carcinoma risk (HR=0.72, 95%CI: 0.49-1.05; P_{trend}=0.26). Our data suggest that higher intake of high fat dairy foods was associated with higher, whereas higher yogurt consumption might be associated with lower risk of developing hepatocellular carcinoma among U.S. men and women.

Keywords

dairy products; milk; hepatocellular carcinoma; cancer; cohort study; cancer prevention

In the U.S., the incidence rate of liver cancer has tripled since 1980s, increasing sharply in the past 5 years among both men and women.[1, 2] The predominant histological form of primary liver cancer is hepatocellular carcinoma (HCC). However, over 35% of HCC cannot be explained by current known risk factors including chronic hepatitis B and C viruses (HBV/HCV) infections, excessive alcohol consumption, rare genetic disorders, obesity, and type 2 diabetes.[3] This suggests an important role of other factors including diet in HCC etiology in the U.S.[4]

Currently, per capita dairy products availability (milk equivalent) increased 9%, from 564 pounds in 1970 to 614 pounds in 2014 in the U.S.[5] The U.S. Department of Agriculture (USDA) recommends daily intake levels of 3 cup-equivalents for U.S. adults.[6] Despite the widespread use of dairy products, the relationship between dairy product intake and cancer risk remains inconclusive. Higher dairy product intake might be associated with a lower risk of colorectal cancer, but a higher risk of certain cancers. For example, men who consumed two or more cups of milk per day may double their risk of developing advanced prostate cancer compared to non-drinkers.[7] Similarly, women who consumed 4 or more cups of total dairy product a day may have a higher risk of serous ovarian cancer compared to women who consumed less than 2 cups a day.[8] Also, studies suggested that high dairy product intake may increase the levels of plasma insulin-like growth factor I (IGF-I).[9-12] The increased concentration of IGF-I, an important factor in the regulation of cell proliferation, differentiation, apoptosis, and carcinogenesis, might contribute to development of several cancers including HCC in experimental studies.[13, 14]

However, epidemiological studies,[15-21] particularly cohort studies,[15, 16] examining the associations between dairy products and risk of liver cancer, are limited, and have reported inconsistent results. In addition, it is unclear whether some compounds in dairy such as calcium, vitamin D, proteins, saturated fatty acids, and lactose, might be responsible for either inverse or positive associations between dairy product intake and HCC risk.[22] Only one study, to our knowledge, has comprehensively assessed the association of dairy products according to different food groups (total dairy, milk, cheese, and yogurt) and their components (calcium, vitamin D, fats, and protein) with HCC risk in European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.[15] The main findings from the EPIC study[15] suggested that higher consumption of dairy products could be associated with increased HCC risk. Hence, we prospectively investigated the associations between intakes of total dairy products, individual dairy products, and several major micro- and macronutrient components and the risk of incident HCC among U.S. adults.

METHODS

Study Cohort

We used data from 2 prospective cohort studies, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). Detailed descriptions of the 2 cohorts have been published elsewhere.[23, 24] Briefly, the NHS was composed of 121,700 U.S. female registered nurses aged 30 to 55 years, who lived in one of 11 states and completed a baseline questionnaire about their lifestyle and medical history in1976. The HPFS was composed of 51,529 U.S. male professionals aged 40 to 75 years, who returned a baseline questionnaire that inquired about detailed medical history, as well as lifestyle and usual dietary intake in 1986. In each cohort, questionnaires were administered biennially to collect updated information on medical history as well as lifestyle and behavioral risk factors for chronic diseases. The follow-up rates were greater than 90% in each cohort.

In this study, we defined baseline as 1980 for women (NHS) and 1986 for men (HPFS), when dairy product intake was first ascertained. After excluding participants with a history of cancer (except for non-melanoma skin cancer), or with no reports of dairy product intake, a total of 144,845 participants (51,418 men and 93,427 women) were included in this analysis.

Assessments of dairy products

In 1980, a 61-item FFQ was administered to the NHS participants to collect information on their usual intake of foods and beverages in the previous year. In 1984, 1986, and every 4 years thereafter, similar but expanded 131-item FFQs were sent to these participants to collect updated information on dietary intake. Using the similar expanded FFQ, dietary data were collected in 1986, and every 4 years thereafter from the HPFS participants.

In each FFQ, participants were asked how often, on average, they consumed each food of a standard portion size. There were 9 possible responses, which ranged from "never or less than once per month" to "6 or more times per day." Nutrient intake was calculated by multiplying the frequency of each food consumed by the nutrient content per serving of that food, and summing across all foods and beverages, using used the composition database from the USDA sources.[25] As previously reported,[26] questionnaire items on dairy products included "skim/low fat milk", "whole milk", "ice cream", "yogurt", "cottage/ricotta cheese", "cream cheese", "other cheese", "cream". From 1994 in both cohorts, yogurt consumption was separated into two items, "plain yogurt" (plain or with NutraSweet) and "flavored yogurt" (without NutraSweet). The standard serving size was 8 oz. glass for skim, low fat milk, or whole milk, tablespoons for cream, sour cream, ½ cup for sherbet or frozen yogurt, ice cream, cottage or ricotta cheese, 1 oz. for cream cheese or other cheese. Dairy products were categorized as high-fat dairy (whole milk, cream, sour cream, ice cream, cream cheese, and other cheese) and low-fat dairy (skimmed milk, sherbet, yogurt, and cottage cheese) in the analysis. We also assessed the association of each individual dairy product including milk (whole, skimmed), yogurt, cheese, butter, and ice cream in relation to HCC risk.

The reproducibility and validity of these FFQs have been reported in detail elsewhere.[27, 28] Briefly, the mean of correlation coefficients between FFQ and multiple dietary records were 0.62 both for low-fat dairy products and for high-fat dairy products,[27] and ranged from 0.57 (hard cheese) to 0.97 (yogurt) for other dairy products.[28]

Assessments of other factors

We also inquired information on age, height, weight, smoking status, physical activity (METS-hours/week), aspirin use, type 2 diabetes, and menopausal status and use of menopausal hormones (women only). In addition, alcohol use and coffee drinking were collected at baseline and updated almost every 4 years using the validated FFQs in each cohort. Detailed descriptions on the validity and reproducibility of these self-reported data such as body height and weight, and physical activity have been published elsewhere.[29, 30]

Ascertainment of hepatocellular carcinoma

In each cohort, participants were asked for written permission to obtain their medical records and pathological reports if they reported HCC on biennial questionnaires. For all deaths attributable to HCC, we requested permission from next-of-kin to review medical and pathological records. All possible cancer cases were further confirmed by a study physician who was blinded to exposure data and extracted information from the medical or pathological reports regarding the presence of underlying cirrhosis diagnosed by histopathology or by appropriate cross-sectional imaging, the presence of HBV or HCV infections, and the histological subtypes of the cancer. Additional data on HBV/HCV infection status were also available from a nested case-control study of HCC in the NHS/HPFS (26 HCC cases and 78 non-cases), which were derived from laboratory blood tests.[31] Considering potential unreported cancer deaths, we further searched state vital statistics records, the National Death Index.[32]

Statistical analyses

We calculated each individual's person-years from the date of return of the baseline questionnaire to the date of diagnosis of HCC, date of death, loss to follow-up, or the end of the follow-up (January 31, 2012 for the HPFS and June 1, 2012 for the NHS), whichever came first. Age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for dairy food intake in relation to the risk of HCC were calculated using time-varying Cox regression model. The model was stratified simultaneously by age and year of questionnaire return, enabling the finest possible control of confounding for age and secular trends. The adjusted covariates in the multivariable model included age, race, smoking, alcohol consumption, coffee drinking, body mass index (BMI), physical activity, aspirin use, type 2 diabetes (categories see footnote in tables). To best reflect long-term dietary habits and lifestyle, and minimize within-person variations, we used the cumulative average of dietary intakes (fiber and whole grains) and other covariates including smoking, alcohol consumption, coffee drinking, BMI, physical activity, aspirin use, and type 2 diabetes.[33] To maximize the statistical power, we combined two cohorts because we did not detect any significant heterogeneity between the two cohorts (P>0.05 for all heterogeneity tests of total dairy product intake by sex). We found no violation of proportional hazard assumption after testing an interaction term between total dairy product intake and follow-up time (P>0.05 for all tests). The trend tests were conducted using the median of each category of dairy as a continuous variable.

To evaluate the robustness of the results, we performed several sensitivity analyses. First, we conducted the analyses by excluding HCC cases with HBV/HCV infections. Second, we evaluated the associations with dairy products separately by a history of pre-existing cirrhosis status (i.e., cirrhotic vs. non-cirrhotic HCC), or by a history of chronic HBV/HCV infection status (i.e., viral and non-viral HCC). Third, because of a non-significant inverse association for yogurt and a positive association for non-yogurt dairy foods observed in the present study, we also mutually adjusted for yogurt and non-yogurt dairy foods in the analyses. Last, to evaluate to what extent the associations might be confounded by HBV/HCV infection status, we calculated Spearman correlation coefficients (r) between HBV/HCV infection status and total dairy food intake among participants with available data on chronic HBV/HCV infections. All statistical tests were 2-sided and performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Participants with higher total dairy intake were less likely to be current smokers and use aspirin, were more physically active, consumed less alcohol, and tended to have higher total intake of calcium, vitamin D, fat, and protein (Table 1). Similar patterns were observed in both men and women (Supplementary Table 1).

During up to 32 years of follow-up, we identified a total of 164 HCC cases. Comparing the top with bottom tertiles, the multivariable HRs were 1.85 for total dairy intake (95%CI: 1.19, 2.88; P_{trend}=0.009), 1.81 for high-fat dairy intake (95%CI: 1.19, 2.76; P_{trend}=0.008), and 1.18 for low-fat dairy intake (95%CI: 0.78, 1.78; P_{trend}=0.53) (Table 2). For the same comparisons, positive but mostly non-significant associations were observed for total milk intake (HR=1.23, 95%CI: 0.83, 1.83; P_{trend}=0.24), particularly skim milk (HR=1.36, 95%CI: 0.91, 2.03; P_{trend}=0.10), and butter intake (HR=1.58, 95%CI: 1.06, 2.36; P_{trend}=0.04). Interestingly, we observed a non-statistically significant inverse association of HCC risk with yogurt intake (HR=0.72, 95%CI: 0.49, 1.05; P_{trend}=0.26), and a positive association with total non-yogurt dairy (HR=2.01, 95%CI: 1.24, 3.25; P_{trend}=0.01). When stratified by sex, we observed similar results for both men and women (Supplementary Tables 2 and 3). We did not find any significant associations with fat, protein, calcium, or vitamin D either from dairy or from total diet in the combined cohorts (Table 3), or separately in men or women (Supplementary Tables 4 and 5).

In secondary analyses, after we excluded HCC cases with known chronic HBV or HCV infections (n=26), the overall results did not materially change (HR=2.24, 95%CI: 1.33, 3.77, P_{trend}=0.003 for total non-yogurt dairy; HR=0.67, 95%CI: 0.44, 1.02, P_{trend}=0.23 for yogurt). We found no correlation between dairy food intake and HBV (r=−0.05) or HCV (r=0.07) infection status in a subset of our cohorts (105 HCC cases and 78 non-cases). When examining HCC according to a history of cirrhosis, or hepatitis virus infection, we did not detect any differential associations of dairy product intake with cirrhotic and non-cirrhotic HCC risk, or with viral and non-viral HCC risk (all $P_{heterogenity}$>0.10). Last, the Spearman correlation coefficients between yogurt and other non-yogurt dairy food intake ranged from 0.01 to 0.26 (Supplementary Table 6). When we mutually adjusted for yogurt and non-yogurt dairy in the same model, we found very similar albeit slightly stronger associations for both yogurt (HR=0.70, 95%CI: 0.48, 1.03; P_{trend}=0.21) and non-yogurt dairy food intake (HR=2.01, 95%CI: 1.25, 3.25; P_{trend}=0.01).

DISCUSSION

In these two large prospective U.S. cohort studies, we found that higher intake of total dairy products might be associated with increased risk of HCC, and the association seemed to differ by types of dairy products consumed. Specifically, high-fat dairy and butter may be associated with higher, whereas yogurt intake may be associated with lower risk of incident HCC. We did not find any significant associations between fat, protein, lactose, calcium, or vitamin D from dairy products and risk of HCC. Given the popularity of dairy products consumption in the U.S.,[6] these findings warrants further confirmation.

Observational studies of dairy products and HCC risk are limited and have yielded inconsistent results. Among five existing case-control studies,[17-21] three reported an inverse[19-21] and one reported non-significant inverse[18] and one reported a positive[17] association between milk consumption and HCC. In contrast, among two existing cohort studies, one reported a positive,[15] and another reported a null association[16] between total dairy product intake and risk of HCC. This discrepancy could be partly due to the different study design (cohort vs. case-control study). Because of retrospective nature, case-control design was more likely to be affected by recall bias and reverse causality. In the EPIC cohort, 477,206 European men and women aged 20-85 years were followed-up for an average of 11 years with 191 HCC cases, higher total dairy intake (top vs. bottom tertile) was associated with a statistically significant 66% higher risk of HCC,[15] which was generally consistent with our findings. In the National Institutes of Health (NIH)-AARP cohort, 311 HCC cases were identified after an average of 7 years of follow-up among 293,907 men and 198,903 women. Higher total dairy intake (top vs. bottom quintile) was not significantly associated with the risk of HCC (HR=1.04).[16]

Several mechanisms might explain the possible positive associations between total dairy product intake and HCC risk. First, a number of experimental and observational studies[9-12] have found that intake of dairy products including both whole and skim milk, increased circulating concentrations of IGF-1. This effect was further confirmed by a meta-analysis of 15 cross-sectional studies and 8 randomized controlled trials.[34] High IGF-1 levels were reported to contribute to the development of certain cancers including HCC in experimental studies.[13, 14] Moreover, the liver is the major source of circulating IGF-1, and could be exposed to higher levels of this hormone compared to other organs. High IGF-1 may promote the growth of HCC both in vitro and in vivo.[35]

Second, dairy products are important source of dietary fat. Fat consumption might correlate with insulin resistance,[36] which could be associated with liver diseases and HCC.[37] Indeed, in a large U.S. cohort of 495,006 men and women with 338 HCC cases, fat intake was associated with a higher risk of HCC (highest vs. lowest quintile, HR=1.46, P_{trend}=0.045). In particular, saturated fat (highest vs. lowest quintile, HR=1.87, P_{trend}=0.009) and fat from dairy (same comparison, HR=1.57, P_{trend}=0.022), were associated with high risk of incident HCC.[38] However, we found that high-fat dairy, butter, and skim milk (but not whole milk) might be associated with high HCC risk, indicating that in addition to fat, other constitutes in dairy products may play a role in the possible dairy-HCC association. Similar to our results, several epidemiological studies[39-42] reported that only skim or low-fat milk, but not whole milk, was positively associated with the risk of prostate cancer. Taken together, our findings, if confirmed, might somewhat contradict the recommendation for cancer prevention that encourage choosing fat-free or low-fat dairy products in current dietary guidelines.[43] However, given the limited number of cases, future studies of dairy intake and HCC risk are warranted.

Third, animal studies showed probiotics as well as probiotic fermented dairy products such as yogurt may protect against aflatoxin B1 induced hepatic damage[44] and molecular alterations in hepatic cells[45] during hepatocellular carcinogenesis, and inhibit chemical induced liver tumors.[46] In addition, probiotics show a possible protective effect against hepatocarcinogenesis, through prevention of bile acid toxicity in the intestine and liver.[47] In line with this evidence, we found that yogurt (HR=0.72) was suggestively inversely associated with HCC risk. Similarly, results from EPIC cohort also reported a similar non-significant inverse association between yogurt and HCC among HBV- and HCV-free participants (HR=0.73).

The strengths of current study included two large cohorts of men and women, high rates of follow-up, and repeated measures of dietary and lifestyle data. There were also several limitations. First, misclassification of dairy product data exists as any observational study. However, the FFQs used in these studies had been validated against multiple diet records, and reasonable correlation coefficients between these assessments of dairy intake were observed.[27, 28] Second, we did not account for chronic HBV/HCV infections status in the full cohorts, which were important risk factors for HCC. However, the prevalence of HBV (~0.11%)[48] and HCV (~1.0%)[49] infections in the U.S. general population is low. Moreover, there is no correlation between dairy food intake and HBV/HCV infection status in a subset of our cohorts. Previous studies also found no correlations of obesity,[50] smoking habits,[31] and alcohol use,[31] and coffee intake[51] with HBV/HCV infection. Thus, our findings were less likely to be substantially confounded by hepatitis virus infection. Last, residual confounding was still possible, although we have adjusted for most known risk factors for HCC.

In summary, we found that the association between dairy intake and HCC risk appeared to depend on the types of dairy product consumed. High-fat dairy, skim milk, and butter intake were associated with higher and yogurt intake was suggestively associated with lower risk of HCC. Future studies that carefully consider HBV/HCV infection are needed to confirm our findings and to elucidate the underlying mechanisms.

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
IGF-I	insulin-like growth factor I
METS	metabolic equivalent tasks
NAFLD	nonalcoholic fatty liver disease
USDA	United States Department of Agriculture

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Novelty and Impact: In two large prospective U.S. cohort studies, we found that increased intake of non-yogurt dairy foods, particularly high fat dairy foods were associated with higher, whereas increased yogurt intake might be associated with lower risk of incident hepatocellular carcinoma. These findings could be of great importance for primary prevention against hepatocellular carcinoma give high consumption of dairy products in the U.S. population.

Table 1.

Characteristics of participants according to total dairy products in pooled Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)

	Total dairy products		
	Tertile 1	Tertile 2	Tertile 3
Age (year) *	62.5(11.9)	62.8(11.9)	62.8(12.0)
White, %	94.8	97.6	98.2
Physical activity, METS-hours/week	20.0(22.6)	21.3(22.2)	22.4(24.3)
Body mass index, kg/m^2	25.1(4.1)	25.3(4.1)	25.4(4.4)
Smoking status, pack-years	13.5(19.3)	12.2(18.5)	12.9(19.9)
Regular aspirin use, %	35.8	38.2	38.0
Type 2 diabetes, %	5.0	5.1	5.2
Food and nutrient intakes			
High-fat dairy products, serving/day	0.6(0.3)	1.1(0.5)	2.1(1.5)
Low-fat dairy products, serving/day	0.5(0.4)	1.0(0.6)	1.7(1.2)
Milk, serving/day	0.3(0.3)	0.8(0.5)	1.6(1.0)
Total cheese, serving/day	0.4(0.2)	0.6(0.3)	0.9(0.7)
Yogurt, serving/day	0.1(0.1)	0.1(0.2)	0.2(0.3)
Butter, serving/day	0.1(0.2)	0.2(0.4)	0.7(1.0)
Alcohol, g/day	8.0(12.2)	7.7(11.1)	7.6(11.4)
Total coffee intake, cups/day	2.0(1.6)	2.1(1.6)	2.2(1.7)
Total fat, g/day	64.1(12.8)	63.9(11.6)	64.8(12.0)
Fat from dairy products, g/day	8.7(3.5)	12.2(4.0)	16.5(6.3)
Total protein, g/day	78.1(15.5)	79.5(14.0)	80.9(14.6)
Protein from dairy products, g/day	10.2(4.5)	15.2(5.4)	20.2(8.4)
Total vitamin D, IU/day	349(263)	381(230)	421(227)
Vitamin D from dairy products, IU/day	58(50)	99(64)	153(100)
Total calcium, mg/day	790(355)	933(327)	1086(359)
Calcium from dairy products, mg/day	292(140)	445(172)	613(275)

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.

Intake of dairy products and risk of hepatocellular carcinoma in pooled Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)*

	Dairy products, HR (95% CI)			P_{trend}
	Tertile 1	Tertile 2	Tertile 3	
Total dairy products				
No. of cases (n=164)	36	56	72	
Age-adjusted model**	1 (Reference)	1.49 (0.98, 2.26)	1.91 (1.28, 2.86)	0.002
Multivariable-adjusted model¶	1 (Reference)	1.49 (0.97, 2.30)	1.85 (1.19, 2.88)	0.009
High-fat dairy products				
No. of cases (n=164)	38	55	71	
Age-adjusted model**	1 (Reference)	1.48 (0.98, 2.25)	1.94 (1.31, 2.88)	0.001
Multivariable-adjusted model¶	1 (Reference)	1.45 (0.95, 2.21)	1.81 (1.19, 2.76)	0.008
Low-fat dairy products				
No. of cases (n=160)	44	57	59	
Age-adjusted model**	1 (Reference)	1.21 (0.81, 1.79)	1.20 (0.81, 1.78)	0.41
Multivariable-adjusted model¶	1 (Reference)	1.23 (0.83, 1.84)	1.18 (0.78, 1.78)	0.53
Milk (whole + skim or low-fat milk)				
No. of cases (n=164)	47	50	67	
Age-adjusted model**	1 (Reference)	1.01 (0.68, 1.51)	1.29 (0.89, 1.88)	0.14
Multivariable-adjusted model¶	1 (Reference)	1.01 (0.68, 1.52)	1.23 (0.83, 1.83)	0.24
Whole milk				
No. of cases (n=149)	59	36	54	
Age-adjusted model**	1 (Reference)	0.93 (0.57, 1.53)	1.07 (0.73, 1.57)	0.59
Multivariable-adjusted model¶	1 (Reference)	0.92 (0.56, 1.50)	1.01 (0.69, 1.50)	0.79
Skim or low-fat milk				
No. of cases (n=158)	44	49	65	
Age-adjusted model**	1 (Reference)	1.06 (0.71, 1.60)	1.38 (0.94, 2.02)	0.08
Multivariable-adjusted model¶	1 (Reference)	1.07 (0.71, 1.62)	1.36 (0.91, 2.03)	0.10
Yogurt				
No. of cases (n=148)	74	29	45	
Age-adjusted model**	1 (Reference)	0.54 (0.35, 0.84)	0.70 (0.48, 1.02)	0.19
Multivariable-adjusted model¶	1 (Reference)	0.54 (0.35, 0.85)	0.72 (0.49, 1.05)	0.26
Total cheese (cottage cheese + cream cheese + other cheeses)				
No. of cases (n=163)	52	52	59	
Age-adjusted model**	1 (Reference)	0.97 (0.66, 1.43)	1.05 (0.72, 1.52)	0.78
Multivariable-adjusted model¶	1 (Reference)	0.92 (0.62, 1.36)	0.88 (0.59, 1.31)	0.54
Cottage cheese				

	Dairy products, HR (95% CI)			P_{trend}
	Tertile 1	Tertile 2	Tertile 3	
No. of cases (n=152)	46	59	47	
Age-adjusted model **	1 (Reference)	1.20 (0.81, 1.76)	0.82 (0.55, 1.24)	0.17
Multivariable-adjusted model ¶	1 (Reference)	1.15 (0.78, 1.71)	0.75 (0.49, 1.15)	0.08
Cream cheese				
No. of cases (n=138)	52	39	47	
Age-adjusted model **	1 (Reference)	0.97 (0.64, 1.49)	1.03 (0.69, 1.54)	0.87
Multivariable-adjusted model ¶	1 (Reference)	0.95 (0.62, 1.47)	0.94 (0.63, 1.42)	0.78
Cream				
No. of cases (n=140)	43	44	53	
Age-adjusted model **	1 (Reference)	1.08 (0.70, 1.65)	1.36 (0.90, 2.04)	0.12
Multivariable-adjusted model ¶	1 (Reference)	1.06 (0.69, 1.63)	1.32 (0.87, 2.00)	0.17
Ice cream				
No. of cases (n=158)	46	48	64	
Age-adjusted model **	1 (Reference)	0.98 (0.65, 1.47)	1.25 (0.85, 1.83)	0.16
Multivariable-adjusted model ¶	1 (Reference)	0.96 (0.64, 1.45)	1.21 (0.81, 1.80)	0.24
Butter				
No. of cases (n=150)	42	45	63	
Age-adjusted model **	1 (Reference)	1.29 (0.84, 1.99)	1.67 (1.12, 2.48)	0.02
Multivariable-adjusted model ¶	1 (Reference)	1.28 (0.83, 1.97)	1.58 (1.06, 2.36)	0.04

* We created the median values of each tertile categories for total dairy products (1.1, 2.0, 3.5 serving/day), high-fat dairy products (0.4, 0.9, 2.0 serving/day), low-fat dairy products (0.2, 0.9, 1.9 serving/day), milk (0.1, 0.7, 1.6 serving/day), whole milk (0, 0, 0.3 serving/day), skim or low-fat milk (0.02, 0.5, 1.4 serving/day), yogurt (0, 0.1, 0.2 serving/day), total cheese (0.2, 0.5, 0.9 serving/day), cottage cheese (0, 0.1, 0.3 serving/day), cream cheese (0, 0.04, 0.1 serving/day), cream (0, 0.1, 0.3 serving/day), ice cream (0.02, 0.1, 0.3 serving/day), and butter (0, 0.1, 0.7 serving/day) in pooled NHS and HPFS.

CI, confidence interval; **HR**, hazard ratio.

** Adjusted for age (in months).

¶ Adjusted for age (in months), gender (women, men), race (White, non-White), physical activity (<3, 3-<27, ≥27 METS/week), body mass index (<25, 25-<27.5, 27.5-<30, ≥30 kg/m^2), pack-years of smoking (0, 1-<10, ≥10 pack-years), alcohol intake (<5, 5-<15, ≥15 g/day), total coffee intake (≤1, 2-3, ≥4 cups/day), total calorie intake (kcal/day, tertile), aspirin use (no, yes), and type 2 diabetes (no, yes).

Table 3.

Intake of fat, protein, vitamin D and calcium and risk of hepatocellular carcinoma in pooled Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)

	HR (95% CI)			
	Tertile 1	Tertile 2	Tertile 3	P_{trend}
Total fat				
No. of cases (n=160)	64	52	44	
Age-adjusted model *	1 (Reference)	0.95 (0.66, 1.38)	1.04 (0.70, 1.54)	0.86
Multivariable-adjusted model ¶	1 (Reference)	0.87 (0.60, 1.27)	0.92 (0.62, 1.38)	0.68
Fat from dairy products				
No. of cases (n=160)	44	67	49	
Age-adjusted model *	1 (Reference)	1.60 (1.09, 2.34)	1.35 (0.90, 2.04)	0.20
Multivariable-adjusted model ¶	1 (Reference)	1.62 (1.10, 2.39)	1.34 (0.88, 2.03)	0.24
Total protein				
No. of cases (n=160)	56	51	53	
Age-adjusted model *	1 (Reference)	0.89 (0.61, 1.30)	1.03 (0.71, 1.50)	0.82
Multivariable-adjusted model ¶	1 (Reference)	0.85 (0.58, 1.24)	0.89 (0.60, 1.31)	0.59
Protein from dairy products				
No. of cases (n=160)	48	63	49	
Age-adjusted model *	1 (Reference)	1.20 (0.82, 1.75)	0.94 (0.63, 1.40)	0.65
Multivariable-adjusted model ¶	1 (Reference)	1.27 (0.86, 1.86)	0.96 (0.64, 1.45)	0.73
Total vitamin D				
No. of cases (n=160)	34	69	57	
Age-adjusted model *	1 (Reference)	1.50 (0.99, 2.26)	1.10 (0.71, 1.69)	0.86
Multivariable-adjusted model ¶	1 (Reference)	1.55 (1.02, 2.36)	1.21 (0.78, 1.88)	0.77
Vitamin D from dairy products				
No. of cases (n=160)	48	45	67	
Age-adjusted model *	1 (Reference)	0.83 (0.55, 1.25)	1.20 (0.83, 1.74)	0.20
Multivariable-adjusted model ¶	1 (Reference)	0.86 (0.57, 1.30)	1.25 (0.86, 1.83)	0.15
Total calcium				
No. of cases (n=160)	41	56	63	
Age-adjusted model *	1 (Reference)	1.09 (0.72, 1.63)	0.99 (0.66, 1.48)	0.85
Multivariable-adjusted model ¶	1 (Reference)	1.20 (0.80, 1.81)	1.16 (0.77, 1.75)	0.57
Calcium from dairy products				
No. of cases (n=160)	47	57	56	
Age-adjusted model *	1 (Reference)	1.11 (0.76, 1.64)	1.10 (0.74, 1.62)	0.68
Multivariable-adjusted model ¶	1 (Reference)	1.16 (0.78, 1.72)	1.14 (0.77, 1.69)	0.57

CI, confidence interval; **HR**, hazard ratio.

*Adjusted for age (in months).

¶Adjusted for age (in months), gender (women, men), race (White, non-White), physical activity (<3, 3-<27, ≥27 METS/week), body mass index (<25, 25-<27.5, 27.5-<30, ≥30 kg/m^2), pack-years of smoking (0, 1-<10, ≥10 pack-years), alcohol intake (<5, 5-<15, ≥15 g/day), total coffee intake (≤1, 2-3, ≥4 cups/day), total calorie intake (kcal/day, tertile), aspirin use (no, yes), and type 2 diabetes (no, yes).