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Glycemic index, glycemic load, dietary carbohydrate, and dietary fiber intake and risk of liver and biliary tract cancers in Western Europeans

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Background: The type and quantity of dietary carbohydrate as quantified by glycemic index (GI) and glycemic load (GL), and dietary fiber may influence the risk of liver and biliary tract cancers, but convincing evidence is lacking.
Patients and methods: The association between dietary GI/GL and carbohydrate intake with hepatocellular carcinoma (HCC; *N* = 191), intrahepatic bile duct (IBD; *N* = 66), and biliary tract (*N* = 236) cancer risk was investigated in 477 206 participants of the European Prospective Investigation into Cancer and Nutrition cohort. Dietary intake was assessed by country-specific, validated dietary questionnaires. Hazard ratios and 95% confidence intervals were estimated from proportional hazard models. HBV/HCV status was measured in a nested case–control subset.
Results: Higher dietary GI, GL, or increased intake of total carbohydrate was not associated with liver or biliary tract cancer risk. For HCC, divergent risk estimates were observed for total sugar = 1.43 (1.17–1.74) per 50 g/day, total starch = 0.70 (0.55–0.90) per 50 g/day, and total dietary fiber = 0.70 (0.52–0.93) per 10 g/day. The findings for dietary fiber were confirmed among HBV/HCV-free participants [0.48 (0.23–1.01)]. Similar associations were observed for IBD [dietary fiber = 0.59 (0.37–0.99) per 10 g/day], but not biliary tract cancer.

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Conclusions: Findings suggest that higher consumption of dietary fiber and lower consumption of total sugars are associated with lower HCC risk. In addition, high dietary fiber intake could be associated with lower IBD cancer risk.

Key words: biliary tract neoplasms, dietary carbohydrate, dietary fiber, glycemic index, hepatocellular carcinoma, liver neoplasms

introduction

Primary liver cancer (PLC; ranked sixth in incidence worldwide), a cancer grouping composed of hepatocellular (HCC) and intrahepatic bile duct (IBD) carcinomas, is highly malignant, usually diagnosed at late stages and often has very poor prognosis with limited treatment options [1]. The global geographic incidence trends are highest in developing regions and lowest in developed countries, reflecting the prevalence of two established risk factors—hepatitis B/C (HBV/HCV) and aflatoxin exposure. Recent data show that PLC rates are rapidly increasing in traditionally lower-risk industrialized countries [2–4] likely due to obesity, insulin resistance, metabolic, and hormonal changes which accompany the Western lifestyle and eventually lead to type 2 diabetes (T2D) and/or nonalcoholic fatty liver disease (NAFLD), a hepatic manifestation of the metabolic syndrome [5]. Biliary tract cancers (BTC; including cancers of the gallbladder, Ampulla of Vater and extrahepatic bile ducts) are another important grouping of tumors which, similar to PLC, have poorly understood etiology and are difficult to detect early and to treat [6, 7].

The type and amount of dietary carbohydrate are the main determinants of postprandial glucose and insulin responses [8]. Therefore, dietary glycemic index (GI) [9] and glycemic load (GL), measures of the glucose and insulin responses to different dietary carbohydrates, may play a role in liver carcinogenesis by increasing blood glucose, triglyceride, and cholesterol levels, insulin demand, and bioavailability of insulin-like growth factor-1 resulting in growth promotion and inhibition of apoptosis [10, 11]. This hypothesis is strengthened by the fact that diets with a high GI or GL are associated with an increased risk of obesity, T2D, gallbladder disease, hyperlipidemia [12], liver steatosis [13], and NAFLD [14], all of which may enhance susceptibility to HCC, IBD, and BTC [15–20] by increasing chronic and local inflammation and altering insulin and IGF signaling [21]. The liver is exposed to high concentrations of insulin because it is transported from the pancreas via the portal vein to the liver. Thus, deregulation of insulin-related pathways may promote liver or bile tract carcinogenesis. On the other hand, dietary fiber may prevent development of HCC, IBD, and BTC by beneficially influencing glycemic control, lipid profiles, and body weight [22, 23].

The association between GI, GL, and dietary carbohydrate in relation to HCC, IBD, and BTC risk has been investigated in only a few studies [24–30]. However, prospective evidence is limited to only one recent study reporting a null association for GI, and an inverse association for GL [30]. We, therefore, investigated the association between GI, GL, and dietary carbohydrate (including total sugar, starch, and dietary fiber) with HCC, IBD, and BTC risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

materials and methods

study design

EPIC is a multicenter prospective cohort study designed to investigate the association between environmental factors and incidence of chronic diseases. The rationale, study design, and methods of recruitment are detailed elsewhere [31], including baseline assessment of lifestyle factors (physical activity [32], alcohol drinking and smoking [31], anthropometrics [33], and diet [34]), which were collected from ∼520 000 individuals enroled between 1992 and 2000 in 23 centers throughout 10 European countries [31].

A total of 477 206 participants were included in the present analysis after an exclusion of 23 818 with prevalent cancer other than nonmelanoma skin cancer, 4380 with incomplete follow-up data or missing information on date of diagnosis, 6192 with missing dietary information, 60 with missing lifestyle information, and 9596 who were in the top or bottom 1% of the distribution of the ratio of reported total energy intake to estimated energy requirement, and 78 with metastasis in the liver or ineligible histology code.

All cohort members provided written informed consent. Ethical approval was obtained from the International Agency for Research on Cancer Ethics Review Committee and EPIC centers.

dietary measurement

Diet during the previous 12 months from recruitment into the study was assessed with validated country-specific dietary questionnaires (DQ) designed to ensure high compliance and better measures of local dietary habits [34]. Dietary intakes (in grams per day) of total carbohydrate and its components were estimated from the dietary instruments by using standardized country-specific food composition tables. The definitions of all nutrients including carbohydrate and the methods used to determine their values and standardize them across centers have been described elsewhere [35]. In order to improve comparability of dietary data across centers and to partially correct for dietary measurement error, a single standardized, computer-assisted 24-h dietary recall was obtained from an 8% stratified random sample ($N = 36\,900$) for calibration [36, 37].

A GI database was assembled from the published GI values [38–40], which were assigned in a standardized manner to carbohydrate-providing food items as described elsewhere [41] and in the Supplementary data, available at *Annals of Oncology* online. The overall dietary GL, which reflects the quantity and quality of carbohydrate in the diet, was calculated by multiplying the digestible carbohydrate content of a given food item by the quantity of that food item consumed per day and its GI value, and then summing the values for all food items. The overall GI, which reflects the average quality of carbohydrate consumed, was calculated by dividing the total GL by the total digestible daily carbohydrate consumption.

follow-up for cancer incidence and mortality

Vital status follow-up (98.5% complete) was collected by record linkage with regional and/or national mortality registries in all countries except Germany and Greece, where follow-up was based on active follow-up through study subjects or their next-of-kin. Cancer incidence was determined through record linkage with regional cancer registries (Denmark/Italy/Netherlands/Norway/Spain/Sweden/UK; complete up to

December 2006) or via the use of health insurance records, contacts with cancer and pathology registries, and/or active follow-up (France/Germany/Greece; complete up to June 2010).

case ascertainment

HCC was defined as tumor in the liver (C22.0 as per the 10th Revision of the International Statistical Classification of Diseases, Injury, and Causes of Death [42]). IBD carcinoma was defined as tumor in the IBDs (C22.1). BTC was defined as tumor in the gallbladder (C23.9), Ampulla of Vater (C24.1), and biliary tract (C24.0, C24.8 and C24.9). Cholangiocarcinoma was defined as tumor in the intra/extrahepatic bile ducts with morphology code '8160/3'. A total of 191 HCC, 66 IBD, and 236 biliary tract (gallbladder = 87, Ampulla of Vater = 54, and biliary tract = 95) cancer cases were included in the present analyses. Fifty-eight cholangiocarcinomas (intrahepatic = 48 and extrahepatic = 10) were also analyzed.

HBV and HCV seropositivity was measured in the nested within the EPIC cohort case–control study [including 290 cases (HCC = 122, IBD = 35 and BTC = 133) and 577 controls], the design of which has been previously described [43] and is detailed in the Supplementary data, available at *Annals of Oncology* online.

statistical analyses

The residual method was used to adjust for total energy by computing the residuals from a linear regression of dietary exposures of interest (all except GI since GI values reflect the physiological response to the consumption of the food item, but not its quantity) on total energy consumption with additional adjustment for center [44].

Cox proportional hazards models were used to calculate hazard ratio (HR) as estimates of relative risks and 95% confidence intervals (95% CI) for GI, GL, total carbohydrate, and total sugar, starch, and dietary fiber in relation to HCC, IBD, BTC, gallbladder, and cholangiocarcinoma risk. There was no violation of the proportional hazards assumption as checked by Schoenfeld residuals. Age was used as the underlying time variable, with entry and exit time defined as the subject's age at recruitment and age of censoring or cancer diagnosis, respectively. Dietary exposures of interest were included in models as continuous and as categorical variables, with quartile cut points based on sex-specific studywide energy adjusted (nonenergy adjusted for GI) all-cohort distributions. Results for IBD, cholangiocarcinoma, and gallbladder cancers are presented only for continuous dietary exposures due to low case numbers. To test dose responses, trend variables were assigned the sex-specific median values for overall quartiles of dietary exposures of interest. Heterogeneity of effects by sex and cancer subsites was assessed by χ^2 statistic.

Crude Cox models were stratified by study center to control for differences in follow-up procedures and questionnaire design, by age at recruitment (in 1-year categories), and by sex to allow for different baseline hazard rates, and adjusted for total energy intake. Multivariable models included the variables listed in Table 3.

calibration

Nutrient intakes and total energy intake were calibrated by utilizing a multivariable fixed-effects linear model in which 24-h recall values were regressed on the main DQ values for the calibration subsample of the EPIC cohort [45]. Individual predicted values for each dietary exposure of interest were computed from the calibration models. For all models, Cox regressions were fit with calibrated/predicted values on a continuous scale. The standard error of the calibrated coefficient was estimated by bootstrap sampling with 1000 repetitions to take into consideration the uncertainty related to measurement error correction [46].

effect modification

Effect modification on the multiplicative scale for potential effect modifying variables (including sex, body mass index, self-reported diabetes, smoking, baseline alcohol intake, and total dietary fat consumption) was tested by including the interaction terms formed by the product of modifying variable categories and the value of categories of nutrient intake. The statistical significance of interactions was assessed using likelihood ratio tests based on the models with and without the interaction terms.

nested case–control subset

Two conditional logistic models, with matching factors only and with adjustment for the same confounders as described above, were used to assess the strengths of association (incidence rate ratio, RR as estimated by odds ratio [47]; with 95% CI and tests for trend) among all and HBV/HCV negative individuals.

All statistical tests were two-sided, and P values < 0.05 were considered statistically significant. All statistical analyses were conducted using SAS version 9.2 software (SAS Institute, Inc., NC).

results

cohort study

A total of 5 415 385 person years of follow-up (mean = 11.4/maximum = 14.8 years) were contributed by 142 194 men and 335 012 women between 1992 and 2010. During this period, 191 HCC, 66 IBD, and 236 BTC cases were diagnosed (Table 1). The participants who developed HCC were more likely to be men, older, obese, current smokers, and to have higher baseline alcohol intake and diabetes (only for HCC) compared with participants who did not develop cancer. The participants who developed BTC were, at baseline, more likely to be women, be older, and have self-reported gallstones (Table 2).

HCC, IBD, and cholangiocarcinoma

GI, GL, and total carbohydrate were not associated with HCC risk (Table 3). Of the specific carbohydrate that was examined in relation to HCC, a positive association was observed for total sugar (for high versus low quartile, HR = 1.88, 95% CI 1.16–3.03; P_{trend} = 0.008). Conversely, an inverse HCC risk was observed for higher intakes of total starch (HR = 0.59, 95% CI 0.35–0.99, P_{trend} = 0.014) and dietary fiber (HR = 0.51, 95% CI 0.31–0.83, P_{trend} = 0.013). Further adjustment for dietary fiber made no material difference in risk estimates for GI, GL, total carbohydrate, and sugar; however, for total starch, multivariable-adjusted risk estimates were slightly attenuated across quartiles (HR_{Q2} = 0.88, 95% CI 0.60–1.31, HR_{Q3} = 0.64, 95% CI 0.39–1.04, HR_{Q4} = 0.70, 95% CI 0.40–1.23, P_{trend} = 0.110) and per 50 g/day (HR = 0.77, 95% CI 0.59–1.02).

The calibrated continuous models results suggested possibly stronger associations between these dietary exposures and HCC risk (HR = 1.45, 95% CI 1.01–2.09 per 50 g/day of sugar; HR = 0.71, 95% CI 0.43–1.16 per 50 g/day of starch; HR = 0.65, 95% CI 0.42–0.96 per 10 g/day of fiber). Sex did not modify any of the associations (all P values for heterogeneity > 0.10). The results for IBD and cholangiocarcinoma are presented in Table 4.

Table 1. Size of the EPIC cohort, numbers of cancer cases, and distribution of dietary glycemic load, total carbohydrate, starch, sugar and dietary fiber intakes, by subcohort EPIC cohort study, 1992–2010

Country	Cohort size	Total no. of PY	Mean (5th–95th percentiles)		No. of cancer cases						Mean (5th–95th percentiles) among all cohort participants				
			Age at recruitment, years	No. of years of follow-up	HCC	IBD	GB	Amp V	Other BTC[a]	CCA	Glycemic load (unit/day)	Glycemic index (unit/day)	Total starch (g/day)	Total sugar (g/day)	Total dietary fiber (g/day)
France	67 382	704 125	52.7 (44.2–65.3)	10.5 (4.1–12.0)	3	5	5	3	5	5	127 (62–209)	55.8 (47.2–62.7)	122 (51–214)	103 (50–170)	22.6 (12.5–35.1)
Italy	44 528	515 974	50.5 (37.8–63.2)	11.6 (9.1–14.2)	29	4	11	8	10	3	149 (72–249)	56.5 (50.3–63.1)	161 (66–288)	100 (47–173)	22.3 (11.9–36.1)
Spain	39 995	493 614	49.2 (36.8–62.9)	12.3 (9.5–14.5)	9	3	13	4	6	1	122 (61–200)	55.9 (47.9–62.9)	128 (54–223)	89 (41–151)	24.6 (13.0–39.5)
UK general population	29 503	354 318	57.6 (43.6–73.4)	12.0 (10.1–14.6)	17	13	1	6	1	14	131 (71–210)	56.1 (51.3–60.9)	104 (54–169)	127 (62–217)	22.2 (11.6–35.8)
UK health conscious	45 880	510 590	43.9 (23.8–70.7)	11.1 (9.2–13.4)	1	2	5	2	4	3	130 (73–204)	55.5 (50.6–60.5)	111 (57–178)	122 (61–204)	26.0 (13.1–43.1)
The Netherlands	36 501	443 852	49.0 (25.6–66.2)	12.2 (10.1–14.6)	4	1	7	7	8	1	132 (73–216)	57.2 (51.1–63.0)	113 (58–193)	116 (57–195)	23.0 (13.5–34.6)
Greece	26 018	251 170	53.1 (33.0–72.4)	9.7 (3.6–13.5)	16	7	2	2	7	4	106 (59–167)	55.0 (49.4–60.5)	94 (49–158)	84 (38–144)	21.8 (12.6–34.0)
Germany	48 569	495 614	50.6 (36.7–63.6)	10.2 (5.5–12.7)	37	13	11	2	21	10	124 (65–204)	54.0 (48.9–58.7)	112 (57–183)	107 (43–207)	21.6 (12.0–34.0)
Sweden	48 672	669 944	52.0 (30.2–68.8)	13.8 (7.6–16.8)	29	7	24	6	14	5	136 (73–221)	57.1 (51.4–62.6)	139 (75–233)	99 (44–173)	19.9 (10.1–32.9)
Denmark	54 989	625 098	56.7 (50.7–64.2)	11.4 (7.6–13.2)	44	10	7	11	19	11	130 (73–204)	55.3 (49.8–60.5)	117 (62–187)	103 (47–187)	25.0 (13.2–39.7)
Norway	35 169	351 086	48.1 (41.6–54.9)	10.0 (10.0–10.1)	2	1	1	3	0	1	112 (63–164)	58.1 (52.8–63.0)	108 (58–159)	76 (36–126)	20.6 (11.3–30.9)
Total	47 7206	541 5385	51.2 (33.4–66.3)	11.4 (6.9–14.8)	191	66	87	54	95	58	128 (67–210)	56.0 (49.7–62.1)	121 (57–211)	103 (46–183)	22.8 (12.1–36.7)

[a]Other BTC include biliary tract cancers, excluding cancers in the Ampulla of Vater and gallbladder.

PY, person-years; HCC, hepatocellular carcinoma; IBD, intrahepatic bile duct cancer; BTC, biliary tract cancer; GB, gallbladder cancer; Amp V, Ampulla of Vater; CCA, cholangiocarcinoma; SD, standard deviation; p5, fifth percentile; p95, 95th percentile.

Table 2. Selected baseline demographic and lifestyle characteristics of cancer cases and noncases, EPIC cohort study, 1992–2010

Baseline characteristics	Hepatocellular carcinoma (*N* = 191)	Intrahepatic bile duct cancer (*N* = 66)	Biliary tract cancer (*N* = 236)	Noncases (*N* = 476 713)
Men (*N*, %)	127 (66.5)	33 (50.0)	89 (37.7)	141 945 (29.8)
Women (*N*, %)	64 (33.5)	33 (50.0)	147 (62.3)	334 768 (70.2)
Age at recruitment (years)	59.6 (6.9)	59.6 (7.7)	58.1 (8.1)	51.2 (9.9)
Smoking status and intensity (*N*, %)				
Never smoker	53 (27.8)	28 (42.4)	110 (46.6)	205 157 (43.0)
Current smoker, occasional	14 (7.3)	3 (4.6)	11 (4.7)	40 046 (8.4)
Current smoker, 1–15 cigarettes/day	23 (12.0)	6 (9.1)	26 (11)	55 258 (11.6)
Current smoker, 16–25 cigarettes/day	24 (12.6)	4 (6.1)	17 (7.2)	29 822 (6.3)
Current smoker, >25 cigarettes/day	14 (7.3)	1 (1.5)	5 (2.1)	8647 (1.8)
Former smoker, quit ≤10 years ago	17 (8.9)	3 (4.6)	15 (6.4)	45 552 (9.6)
Former smoker, quit 11–20 years ago	18 (9.4)	9 (13.6)	29 (12.3)	38 923 (8.2)
Former smoker, quit >20 years ago	24 (12.6)	8 (12.1)	15 (6.4)	37 566 (7.9)
No. with diabetes (*N*, %)[a]	22 (11.5)	2 (3.0)	16 (6.8)	12 478 (2.6)
No. with gallstones (*N*, %)[b]	21 (11.0)	15 (22.7)	30 (12.7)	24 473 (5.1)
Anthropometric factors (mean, SD)				
Height (cm)	168.4 (10.1)	166.4 (9.8)	166.3 (9.2)	166 (8.9)
Weight (kg)	79.7 (17.2)	75.1 (15.1)	73.6 (14)	70.2 (13.7)
Body mass index (kg/m^2)	28.0 (4.8)	27.0 (4.2)	26.6 (4.5)	25.4 (4.3)
Waist-to-hip ratio	0.94 (0.1)	0.90 (0.1)	0.87 (0.1)	0.84 (0.1)
Total physical activity (*N*, %)[c]				
Inactive	18 (9.4)	8 (12.1)	29 (12.3)	71 709 (15)
Moderately inactive	68 (35.6)	20 (30.3)	76 (32.2)	142 918 (30)
Moderately active	78 (40.8)	28 (42.4)	92 (39.0)	156 660 (32.9)
Active	18 (9.4)	5 (7.6)	22 (9.3)	39 198 (8.2)
Education (*N*, %)				
None/primary	88 (46.1)	31 (47)	99 (42.0)	142 818 (30.0)
Technical/professional	53 (27.8)	14 (21.2)	50 (21.2)	106 176 (22.3)
Secondary	12 (6.3)	5 (7.6)	38 (16.1)	97 407 (20.4)
University or higher	34 (17.8)	11 (16.7)	41 (17.4)	113 406 (23.8)
Lifetime pattern of alcohol intake (*N*, %)				
Never drinkers	8 (4.2)	3 (4.6)	12 (5.1)	28 136 (5.9)
Former light drinkers	12 (6.3)	6 (9.1)	9 (3.8)	15 030 (3.2)
Former heavy drinkers	10 (5.2)	2 (3)	3 (1.3)	1979 (0.4)
Light drinkers	23 (12.0)	10 (15.2)	39 (16.5)	87 806 (18.4)
Never heavy drinkers	63 (33.0)	25 (37.9)	94 (39.8)	184 436 (38.7)
Periodically heavy drinkers	32 (16.8)	9 (13.6)	17 (7.2)	42 408 (8.9)
Always heavy drinkers	6 (3.1)	1 (1.5)	2 (0.9)	2968 (0.6)
Daily dietary intake (mean, SD)				
Total energy (kcal)[d]	2180.4 (689.2)	2166.6 (664.8)	2051.4 (623.5)	2074 (619.2)
Glycemic index	56.0 (4.0)	55.9 (2.9)	56.0 (3.8)	56.0 (3.9)
Glycemic load (unit)	131.1 (48.1)	131.7 (45.6)	125.9 (43.3)	128.2 (44.6)
Total carbohydrate (g)	233.1 (80.8)	234.4 (77.2)	223.6 (72.4)	228 (74.4)
Total starch (g)	117.6 (45.7)	115.2 (46.6)	120.1 (48.7)	120.9 (49.0)
Total sugar (g)	108.6 (51.5)	113.4 (46.8)	99.4 (41.3)	102.9 (43.8)
Total dietary fiber (g)	21.1 (8.0)	21.4 (6.6)	22.1 (8.0)	22.8 (7.7)
Alcohol (g)	20.8 (31.1)	13.9 (18.5)	12.3 (17.1)	11.9 (17.1)

Missing values were not excluded from percentage calculations; therefore, the sum of percent across subgroups may not add up to 100%. The number of noncases includes only cohort subjects without liver cancer.

Categorical variables are presented as numbers and percentages, continuous variables are presented as mean and standard deviations, adjusted for age and center except for age at recruitment, which was adjusted for center only.

[a]Self-reported data. Number of participants with missing data on diabetes status: HCC = 17, IBD = 13, EBD = 15, noncases = 39 143.

[b]Self-reported data. Number of participants with missing data on gallstones status: HCC = 17, IBD = 18, EBD = 77, noncases = 146 938.

[c]Total physical activity categories were sex specific.

[d]Total energy consumption was strongly correlated with total dietary GL (Spearman's partial correlation coefficient, $\rho = 0.81$), dietary carbohydrate intake ($\rho = 0.81$), but weakly with overall GI ($\rho = 0.10$), after adjustment for study center, sex, and age. After additional adjustment for total energy, total dietary carbohydrate was strongly correlated with GL ($\rho = 0.94$), weakly with GI ($\rho = 0.19$), and inversely with total fats ($\rho = -0.60$); GI with GL ($\rho = 0.48$); GL with total sugar ($\rho = 0.42$), total starch ($\rho = 0.68$), and total fiber ($\rho = 0.33$); and GI with total sugar ($\rho = -0.27$), total starch ($\rho = 0.52$), and total fiber ($\rho = -0.03$). All correlation coefficients were statistically significant ($P < 0.0001$).

Table 3. Hazard ratios and 95% confidence intervals for hepatocellular carcinoma and BTC, by quartiles of GI and energy-adjusted GL, total carbohydrate, and other carbohydrate components, EPIC cohort study, 1992–2010

Dietary variables[a]	No. of person-years	Hepatocellular carcinoma			Biliary tract cancer		
		No. of cases	Crude[b] HR (95%CI)	Multivariable[c] HR (95%CI)	No. of cases	Crude[b] HR (95%CI)	Multivariable[c] HR (95%CI)
Glycemic index							
Quartile 1	1 329 767	55	1.00 (ref.)	1.00 (ref.)	62	1.00 (ref.)	1.00 (ref.)
Quartile 2	1 350 399	46	0.86 (0.58–1.28)	0.95 (0.64–1.42)	47	0.77 (0.53–1.13)	0.78 (0.53–1.15)
Quartile 3	1 366 382	42	0.83 (0.55–1.25)	0.90 (0.59–1.36)	73	1.26 (0.89–1.80)	1.29 (0.91–1.84)
Quartile 4	1 368 837	48	1.11 (0.73–1.69)	1.09 (0.71–1.66)	54	1.04 (0.70–1.53)	1.06 (0.71–1.57)
P_{trend} [d]			*0.779*	*0.832*		*0.340*	*0.295*
Uncalibrated, per 5 units/day			0.97 (0.78–1.20)	0.98 (0.80–1.21)		1.05 (0.87–1.27)	1.06 (0.88–1.28)
Calibrated, per 5 units/day			0.97 (0.61–1.55)	1.04 (0.71–1.51)		1.28 (0.84–1.96)	1.23 (0.85–1.79)
Glycemic load							
Quartile 1	1 319 793	53	1.00 (ref.)	1.00 (ref.)	53	1.00 (ref.)	1.00 (ref.)
Quartile 2	1 3547 53	51	0.93 (0.62–1.39)	1.15 (0.76–1.74)	56	0.99 (0.67–1.46)	0.99 (0.67–1.48)
Quartile 3	1 369 788	41	0.78 (0.50–1.21)	1.03 (0.64–1.64)	68	1.18 (0.80–1.73)	1.20 (0.80–1.79)
Quartile 4	1 371 051	46	0.86 (0.54–1.37)	1.19 (0.72–1.97)	59	1.06 (0.69–1.61)	1.08 (0.69–1.69)
P_{trend} [d]			*0.381*	*0.639*		*0.596*	*0.545*
Uncalibrated, per 50 units/day			0.88 (0.65–1.20)	1.12 (0.81–1.56)		0.93 (0.69–1.25)	0.92 (0.67–1.27)
Calibrated, per 50 units/day			0.71 (0.39–1.28)	1.19 (0.64–2.21)		0.91 (0.51–1.61)	0.97 (0.50–1.87)
Total carbohydrate							
Quartile 1	1 318 461	58	1.00 (ref.)	1.00 (ref.)	56	1.00 (ref.)	1.00 (ref.)
Quartile 2	1 361 296	42	0.67 (0.44–1.01)	0.84 (0.55–1.29)	55	0.89 (0.60–1.30)	0.87 (0.59–1.30)
Quartile 3	1 373 975	42	0.67 (0.44–1.03)	0.92 (0.58–1.46)	65	0.97 (0.66–1.43)	0.96 (0.64–1.44)
Quartile 4	1 361 653	49	0.75 (0.48–1.18)	1.06 (0.64–1.75)	60	0.93 (0.61–1.41)	0.92 (0.59–1.44)
P_{trend} [d]			*0.220*	*0.769*		*0.872*	*0.861*
Uncalibrated, per 100 g/day			0.86 (0.58–1.27)	1.25 (0.81–1.93)		0.88 (0.60–1.28)	0.84 (0.55–1.28)
Calibrated, per 100 g/day			0.68 (0.35–1.32)	1.24 (0.57–2.69)		0.76 (0.40–1.45)	0.80 (0.37–1.75)
Total sugar							
Quartile 1	1 338 111	37	1.00 (ref.)	1.00 (ref.)	63	1.00 (ref.)	1.00 (ref.)
Quartile 2	1 354 070	50	1.18 (0.77–1.82)	1.46 (0.94–2.27)	49	0.66 (0.45–0.96)	0.66 (0.45–0.97)
Quartile 3	1 364 409	54	1.36 (0.88–2.10)	1.77 (1.12–2.78)	65	0.83 (0.57–1.20)	0.83 (0.57–1.22)
Quartile 4	1 358 794	50	1.42 (0.90–2.24)	1.88 (1.16–3.03)	59	0.79 (0.53–1.16)	0.78 (0.52–1.18)
P_{trend} [d]			*0.110*	*0.008*		*0.448*	*0.472*
Uncalibrated, per 50 g/day			1.31 (1.06–1.61)	1.43 (1.17–1.74)		0.89 (0.71–1.11)	0.88 (0.70–1.11)
Calibrated, per 50 g/day			1.48 (1.03–2.14)	1.45 (1.01–2.09)		0.86 (0.58–1.27)	0.90 (0.60–1.33)
Total starch							
Quartile 1	1 315 988	66	1.00 (ref.)	1.00 (ref.)	59	1.00 (ref.)	1.00 (ref.)
Quartile 2	1 343 230	52	0.74 (0.51–1.07)	0.84 (0.57–1.23)	51	0.82 (0.56–1.21)	0.81 (0.55–1.20)
Quartile 3	1 372 299	34	0.47 (0.30–0.74)	0.56 (0.36–0.90)	60	0.98 (0.67–1.45)	0.98 (0.66–1.45)
Quartile 4	1 383 868	39	0.49 (0.30–0.80)	0.59 (0.35–0.99)	66	1.16 (0.76–1.75)	1.14 (0.75–1.75)
P_{trend} [d]			*0.001*	*0.014*		*0.395*	*0.429*
Uncalibrated, per 50 g/day			0.62 (0.49–0.78)	0.70 (0.55–0.90)		1.03 (0.82–1.29)	1.03 (0.81–1.29)
Calibrated, per 50 g/day			0.35 (0.21–0.58)	0.71 (0.43–1.16)		1.06 (0.63–1.78)	1.11 (0.67–1.86)
Total fiber							
Quartile 1	1 369 061	68	1.00 (ref.)	1.00 (ref.)	61	1.00 (ref.)	1.00 (ref.)
Quartile 2	1 337 796	44	0.59 (0.40–0.86)	0.70 (0.47–1.04)	59	0.94 (0.65–1.35)	0.93 (0.64–1.34)
Quartile 3	1 343 820	50	0.63 (0.43–0.92)	0.75 (0.50–1.13)	60	0.91 (0.63–1.32)	0.88 (0.60–1.29)
Quartile 4	1 364 708	29	0.39 (0.25–0.63)	0.51 (0.31–0.83)	56	0.86 (0.58–1.28)	0.83 (0.55–1.26)

Continued

Table 3.. *Continued*

Dietary variables[a]	No. of person-years	Hepatocellular carcinoma			Biliary tract cancer		
		No. of cases	Crude[b] HR (95%CI)	Multivariable[c] HR (95%CI)	No. of cases	Crude[b] HR (95%CI)	Multivariable[c] HR (95%CI)
P_{trend} [d]			*<0.001*	*0.013*		*0.461*	*0.369*
Uncalibrated, per 10 g/day			0.58 (0.44–0.76)	0.70 (0.52–0.93)		0.92 (0.72–1.16)	0.89 (0.69–1.14)
Calibrated, per 10 g/day			0.43 (0.28–0.66)	0.65 (0.42–0.96)		0.79 (0.53–1.15)	0.74 (0.49–1.10)

[a]All dietary variables, except for glycemic index, were energy adjusted by residual method. Quartile cut points were based on studywide energy-adjusted sex-specific nutrient intake distributions. Medians of sex-specific quartiles of energy adjusted by residual method (except GI) nutrients were: GI (men), Q1 = 52.2, Q2 = 55.6, Q3 = 57.8, Q4 = 61.2 units/day; GI (women), Q1 = 50.7, Q2 = 54.6, Q3 = 57.0, Q4 = 60.5 units/day; GL (men), Q1 = 111.0, Q2 = 136.8, Q3 = 154.0, Q4 = 185.8 units/day; GL (women), Q1 = 92.2, Q2 = 112.2, Q3 = 125.8, Q4 = 151.1 units/day; total carbohydrate (men), Q1 = 201.7, Q2 = 243.0, Q3 = 270.2, Q4 = 317.3 g/day; total carbohydrate (women), Q1 = 170.3, Q2 = 202.5, Q3 = 225.0, Q4 = 263.0 g/day; total sugar (men), Q1 = 68.1, Q2 = 97.0, Q3 = 119.1, Q4 = 159.9 g/day; total sugar (women), Q1 = 63.6, Q2 = 87.7, Q3 = 106.5, Q4 = 140.0 g/day; total starch (men), Q1 = 93.9, Q2 = 125.5, Q3 = 150.5, Q4 = 195.8 g/day; total starch (women), Q1 = 76.9, Q2 = 100.8, Q3 = 117.9, Q4 = 153.3 g/day; total dietary fiber (men), Q1 = 16.5, Q2 = 21.7, Q3 = 25.7, Q4 = 33.3 g/day; total dietary fiber (women), Q1 = 15.6, Q2 = 19.9, Q3 = 23.2, Q4 = 29.8 g/day.

[b]Stratified by age (1-year intervals), sex, and center and adjusted for total energy intake (continuous).

[c]Additionally adjusted for sex-specific physical activity level (inactive, moderately inactive, moderately active, active, and missing), education (none/primary school, technical/professional school, secondary school, university degree, and unknown), body mass index (kg/m^2; continuous), smoking status and intensity (never, former <10 and ≥10 years, current (<15, 15–24 and ≥25 cigarettes/day, other than cigarettes, and unknown), self-reported diabetes status (yes, no, and unknown), baseline alcohol intake (g/day; continuous), and lifetime alcohol intake pattern (never drinkers, former light drinker, former heavy drinkers, light drinkers, never heavy drinkers, periodically heavy drinkers, always heavy drinkers, and unknown). Other potential confounders examined, but not included in the model since their inclusion did not change the effect estimates by more than 10% were waist-to-hip ratio, total dietary fat, intake of meat, fruits and vegetables, and coffee consumption; for BTC and gallbladder cancer, self-reported history of gallstones.

EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; CI, confidence interval; BTC, biliary tract cancer, GI, glycemic index; GL, glycemic load.

[d]*P*-value for trend test.

Table 4. Multivariable-adjusted[a] hazard ratios and 95% confidence intervals for intrahepatic bile duct, cholangiocarcinoma, and gallbladder cancers by increase in intake of GI and energy-adjusted GL, total carbohydrate, and other carbohydrate components, EPIC cohort study, 1992–2010

Dietary variables[b]	Intrahepatic bile duct cancer (*N* = 66)	Cholangiocarcinoma (*N* = 58)	Gallbladder cancer (*N* = 87)
Glycemic index, per 5 units/day	1.05 (0.73–1.52)	1.04 (0.70–1.54)	1.08 (0.80–1.47)
Glycemic load, per 50 units/day	0.89 (0.50–1.56)	0.83 (0.45–1.51)	0.97 (0.57–1.67)
Total carbohydrate, per 100 g/day	0.81 (0.39–1.68)	0.70 (0.33–1.50)	1.02 (0.50–2.07)
Total sugar, per 50 g/day	1.12 (0.77–1.63)	0.93 (0.62–1.41)	0.95 (0.64–1.41)
Total starch, per 50 g/day	0.75 (0.48–1.17)	0.87 (0.54–1.41)	1.16 (0.80–1.69)
Total fiber, per 10 g/day	0.59 (0.37–0.95)	0.67 (0.41–1.09)	1.09 (0.73–1.63)

[a]Stratified by age (1-year intervals), sex, and center and adjusted for total energy intake (continuous), for sex-specific physical activity level (inactive, moderately inactive, moderately active, active, and missing), education (none/primary school, technical/professional school, secondary school, university degree, and unknown), body mass index (kg/m^2; continuous), smoking status and intensity (never, former <10 and ≥10 years, current (<15, 15–24, and ≥25 cigarettes/day, other than cigarettes, and unknown), self-reported diabetes status (yes, no, and unknown), baseline alcohol intake (g/day; continuous), and lifetime alcohol intake pattern (never drinkers, former light drinker, former heavy drinkers, light drinkers, never heavy drinkers, periodically heavy drinkers, always heavy drinkers, and unknown).

[b]All dietary variables, except for glycemic index, were energy-adjusted by residual method.

biliary tract cancers

None of the dietary exposure variables of interest were statistically significantly associated with BTC risk (Table 3). Sex did not modify any of the associations (all *P* values for heterogeneity > 0.10). The results did not differ by subsite (gallbladder versus other BTC; all *P* values for heterogeneity >0.30). Findings for continuous dietary exposures in relation to gallbladder cancer are presented in Table 4.

sensitivity analyses and effect modifications

The findings did not change considerably for any of the cancer sites after exclusion of the first 3 and 6 years of follow-up.

The results for HCC did not change substantially after excluding persons with self-reported diabetes; and for BTC cancer, after excluding persons with self-reported gallstones. We did not observe any statistically significant multiplicative interactions (data not shown).

by food source and groups

The results of analyses by food source (Supplementary Tables S1 and S2, available at *Annals of Oncology* online) showed that fiber from cereals and cereal products was statistically significantly inversely associated with HCC risk (HR = 0.78, 95% CI 0.64–0.96 per 5 g/day; P_{trend} = 0.012), after mutual adjustment for fiber from other food sources. Fiber from vegetable (HR = 0.79, 95% CI 0.55–1.15 per 5 g/day; P_{trend} = 0.424) or other sources (HR = 0.90, 95% CI 0.75–1.08 per 5 g/day; P_{trend} = 0.221), but not from fruits (HR = 1.06, 95% CI 0.83–1.35 per 5 g/day; P_{trend} = 0.854), were also inversely, but statistically nonsignificantly, associated with HCC risk. Additionally, sugar from nonalcoholic beverages (HR = 1.11, 95% CI 1.04–1.19 per 10 g/day; P_{trend} = 0.011) were associated with a high risk for HCC. Similar associations were observed for IBD, but not BTC (data not shown). In analyses by food groups, cereal and cereal products (for high versus low quartile, HR = 0.47, 95% CI 0.28–0.79; P_{trend} = 0.006) were statistically significantly associated with lower HCC risk. A similar association, but weaker, was observed for IBD (for high versus low quartile, HR = 0.80, 95% CI 0.36–1.77; P_{trend} = 0.435), but not BTC (for high versus low quartile, HR = 1.03, 95% CI 0.65–1.64; P_{trend} = 0.680).

Table 5. Incidence rate ratios and 95% confidence intervals for HCC and BTC, by quartiles of GI and energy-adjusted GL, total carbohydrate, and other carbohydrate components among HBV and HCV free individuals, within the EPIC nested case–control study, 1992–2006

Dietary variables[b]	Hepatocellular carcinoma (Ca = 84/Co = 162)	Biliary tract cancer (Ca = 124/Co = 241)
Glycemic index, per 5 units/day	1.08 (0.65–1.80)	1.08 (0.75–1.55)
Glycemic load, per 50 units/day	0.87 (0.32–2.35)	1.30 (0.63–2.71)
Total carbohydrate, per 100 g/day	0.70 (0.19–2.61)	1.31 (0.54–3.19)
Total sugar, per 50 g/day	1.40 (0.75–2.61)	1.32 (0.88–1.97)
Total starch, per 50 g/day	0.50 (0.23–1.08)	0.86 (0.54–1.39)
Total fiber, per 10 g/day	0.48 (0.23–1.01)	0.84 (0.53–1.33)

[a]All dietary variables, except for glycemic index, were energy-adjusted by residual method.

[b]Conditional logistic model, matching factors were age at blood collection (±1 year), sex, study center, time of the day at blood collection (±3 h interval), and fasting status at blood collection (<3, 3–6, and >6 h); among women, additionally by menopausal status (pre-, peri-, and postmenopausal), and hormone replacement therapy use at time of blood collection (yes/no), and adjusted for total energy intake.

[c]Additionally adjusted for sex-specific physical activity level (inactive, moderately inactive, moderately active, active, and missing), education (none/primary school, technical/professional school, secondary school, university degree, and unknown), body mass index (kg/m^2; continuous), smoking status and intensity (never, former <10 and ≥10 years, current (<15, 15–24, and ≥25 cigarettes/day, other than cigarettes, and unknown), self-reported diabetes status (yes, no, and unknown), baseline alcohol intake (g/day; continuous), and lifetime alcohol intake pattern (never drinkers, former light drinker, former heavy drinkers, light drinkers, never heavy drinkers, periodically heavy drinkers, always heavy drinkers, and unknown).

EPIC, European Prospective Investigation into Cancer and Nutrition; Ca, cases; Co, controls; OR, odds ratio; CI, confidence interval; HCC, hepatocellular carcinoma; BTC, biliary tract cancers; GI, glycemic index; GL, glycemic load.

nested case–control subset

Cancer cases were diagnosed, on average, 5 years (standard deviation = 2.9) after blood collection. Thirty-one percent, 3%, and 5% of HCC, IBD, and BTC cases, respectively, had either an HBV or HCV infection, or both. The corresponding percents for matched controls were 4%, 6%, and 6% (Supplementary Table S3, available at *Annals of Oncology* online).

In multivariable adjusted analyses limited to HBV and HCV negative participants (Table 5), dietary GI and GL, total carbohydrate, starch, and sugar were not associated with risk of HCC and BTC. Whereas higher total fiber intake, was associated with lower HCC risk (for high versus low quartile, RR = 0.26, 95% CI 0.08–0.80, P_{trend} = 0.022; per 10 g/day, RR = 0.48, 95% CI 0.23–1.01), but only weakly and statistically nonsignificantly with BTC risk (for high versus low quartile, RR = 0.83, 95% CI 0.41–1.67; P_{trend} = 0.420; per 10 g/day, RR = 0.84, 95% CI 0.53–1.33). Consideration of all nested case–control subjects but with adjustment for HBV/HCV status resulted in similar findings (data not shown).

discussion

In this large prospective study, a higher intake of total dietary fiber and a lower intake of dietary sugar were associated with decreased risk of HCC and possibly of IBD, but not BTC risk. Calibration of nutrient intakes to account for potential measurement error strengthened the associations, but they remained statistically significant only for dietary sugar and fiber with HCC. Consideration of food sources of dietary fiber showed that cereal fiber and cereal products were statistically significantly associated with lower HCC risk. No statistically significant effect modifications of the dietary exposures were observed for either cancer site. In a nested case–control subset, restriction of analyses to participants without HBV/HCV infections showed a statistically significant inverse association between dietary fiber and HCC risk.

The role of dietary GI, GL, and total dietary carbohydrate in liver carcinogenesis has been little studied, with most of the evidence coming from case–control settings [24–26, 48] with retrospective evaluation of diet, which is particularly problematic among individuals with HCV/HBV infections since they are more likely to change their diets before cancer diagnosis. The only prospective evidence to date originates from the NIH-AARP Diet and Health Study and suggests an inverse GL–liver cancer association and, similarly to our findings, the null results for GI [30]. No prospective epidemiologic studies have investigated the association between dietary GI and/or GL and BTC risk, and only few case–control studies have reported on carbohydrate intake with inconsistent results [28, 29]. Despite a biologically plausible link of HCC, IBD, and BTC with high-GL and high-GI diets, our study shows null results for these cancers.

No published studies have reported on the association between dietary sugar and starch and HCC and/or IBD risk. Our results suggest a positive association for dietary sugar with HCC risk. In HBV/HCV-negative participants, these associations were in similar directions but no longer significant. A positive association observed for HCC could be in part explained by the increased fructose consumption, which may underlie the development of NAFLD [49]. The previous epidemiologic evidence for an association of total dietary sugar with BTC is inconclusive and derived from case–control studies [27, 50–52]. In our study, no significant associations were observed for BTC.

Limited epidemiologic evidence supports the hypothesis that dietary fiber and its main sources (cereals, vegetables, and fruits) reduce the risk of HCC, IBD, and BTC [28, 29, 53–55]. Our study has suggested a possible inverse association between total dietary fiber consumption and HCC and IBD cancer risk, which was further confirmed among HBV/HCV-negative participants. Also, a potential beneficial effect of total dietary fiber on BTC risk, though not statistically significant, was suggested. In general, our data support the World Cancer Research Fund conclusion about possible beneficial role of cereals consumption in liver carcinogenesis [17], which could be in large part due to their high-fiber content.

The potential mechanisms by which diets high in fiber could lower HCC, IBD, and BTC risk may relate to reduction in subjective appetite and energy intake, maintenance of normal body weight [23], or beneficial effects on postprandial glucose level and blood lipid profile [22]. Fiber's hypocholesterolemic action is mediated by a lower absorption of intestinal bile acid in the colon resulting in higher fecal bile acid loss and *de novo* synthesis of bile acids from cholesterol in the liver, and hence reduced blood total and low-density lipoprotein cholesterol concentrations, which might be involved in hepatocarcinogenesis. Therefore, the protective effects of dietary fiber in liver and biliary tract carcinogenesis are biologically plausible and require further study.

The major advantages of this study are its prospective design, which eliminates differential recall of diet between cancer cases and noncases, large size, and careful selection of cancer cases based on tumor morphology, histology, and behavior to ensure the inclusion of only first primary tumors. This study is the first to incorporate biomarkers of HBV/HCV infection into the analysis of prospective cohort, thus confirming the findings in a hepatitis-free population.

Limitations are the following: (i) diet was assessed only at baseline and may not have accounted for potential dietary changes during follow-up and may not have included a period of exposure relevant to cancer initiation; (ii) dietary measurement errors may have occurred, but these were addressed to some extent by the application of the calibration method; (iii) since measurement errors of Food Frequency Questionnaire and 24-h recall are likely correlated, the effect estimates observed in our study could possibly underestimate the true associations; (iv) the reference GI values were obtained mainly from Australian, British, and US foods for a limited number of food items, therefore a potential variation in processing and cooking methods [38], as well as food choices and dietary practices in different European countries may not have been fully accounted for. Dietary fiber, and other dietary exposures, might be susceptible to confounding since high intake of fiber in general reflects a healthier lifestyle such as being physically active, lower alcohol consumption, and not smoking. In our models, we have adjusted for other determinants of healthy lifestyle; however, the presence of possible residual confounding may not be ruled out, especially for such risk factors as self-reported history of diabetes and gallstones. No data were available on sclerosing cholangitis, a risk factor for IBD and BTC, on incidence of T2D and gallstones, and on exposure to aflatoxins, which is uncommon in Western Europe [56]. Finally, the small sample size for some cancer sites (e.g. cholangiocarcinoma), particularly within a nested case–control subset, did not allow performing some multivariable analyses and stratification by potential effect modifying factors.

In conclusion, this large and comprehensive study has shown no association of overall GI, total GL, and total dietary carbohydrate with HCC, IBD, and BTC risk. The results also have suggested a possible positive association for dietary sugar with HCC, but not IBD or BTC risk. In addition, our findings have shown that high dietary fiber intake is associated with lower HCC and IBD risk among all and HBV/HCV-free participants, whereas the inverse association for BTC was not statistically significant.

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ER is the overall coordinator of the EPIC study. All authors contributed to recruitment, data collection/acquisition, biological sample collection, follow-up and/or management of the EPIC cohort, as well as the interpretation of the present findings and approval of the final version for publication.

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disclosure

The authors have declared no conflicts of interest.

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