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ORIGINAL CONTRIBUTION

Consumption of soft drinks and juices and risk of liver and biliary tract cancers in a European cohort

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Abstract
Purpose The aim of the study was to assess associations between intake of combined soft drinks (sugar sweetened and artificially sweetened) and fruit and vegetable juices and the risk of hepatocellular carcinoma (HCC), intrahepatic bile duct (IHBC) and biliary tract cancers (GBTC) using data from the European Prospective Investigation into Cancer and Nutrition cohort of 477,206 participants from 10 European countries.
Methods After 11.4 years of follow-up, 191 HCC, 66 IHBC and 236 GBTC cases were identified. Hazard ratios and 95 % confidence intervals (HR; 95 % CI) were estimated with Cox regression models with multivariable adjustment (baseline total energy intake, alcohol consumption and intake pattern, body mass index, physical activity,

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level of educational attainment and self-reported diabetes status).

Results No risk associations were observed for IHBC or GBTC. Combined soft drinks consumption of >6 servings/week was positively associated with HCC risk: HR 1.83; 95 % CI 1.11–3.02, $p_{trend} = 0.01$ versus non-consumers. In sub-group analyses available for 91 % of the cohort artificially sweetened soft drinks increased HCC risk by 6 % per 1 serving increment (HR 1.06, 95 % CI 1.03–1.09, $n_{cases} = 101$); for sugar-sweetened soft drinks, this association was null (HR 1.00, 95 % CI 0.95–1.06; $n_{cases} = 127$, $p_{heterogeneity} = 0.07$). Juice consumption was not associated with HCC risk, except at very low intakes (<1 serving/week: HR 0.60; 95 % CI 0.38–0.95; $p_{trend} = 0.02$ vs. non-consumers).

Conclusions Daily intake of combined soft drinks is positively associated with HCC, but a differential association between sugar and artificially sweetened cannot be discounted. This study provides some insight into possible associations of HCC with sugary drinks intake. Further exploration in other settings is required.

Keywords Hepatocellular carcinoma · Biliary tract cancers · Soft drink · Fruit and vegetable juice · Prospective cohort

Abbreviations

HCC	Hepatocellular carcinoma
IHBC	Intrahepatic bile duct
HBV	Hepatitis B
HCV	Hepatitis C
T2D	Type 2 diabetes
NAFLD	Non-alcoholic fatty liver disease
GBTC	Biliary tract cancer
EBD	Extrahepatic bile duct cancer
GB	Gallbladder
AmpV	Ampulla of Vater
EPIC	European Prospective Investigation into Cancer and Nutrition
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
GGT	Gamma-glutamyl tranferase
AP	Liver-specific alkaline phosphatase
BMI	Body mass index

Introduction

Primary liver cancers are comprised of hepatocellular cancer (HCC) and cancers of the intrahepatic bile ducts (IHBC) [1]. Together, they are the seventh most common cancer worldwide [2] and the third cause of death from cancer in both sexes [3]. HCC represents the majority of primary liver cancers. Its risk factors include hepatitis B (HBV) and C (HCV) infections, aflatoxin exposure, tobacco smoking and heavy alcohol consumption mediated by liver cirrhosis [4, 5]. However, obesity, type 2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD) could

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also be contributing to the rising incidence of HCC [6–8]. A global increase has been also observed for the incidence of IHBC cancers, while for the extrahepatic bile duct (EBD) cancers, which are anatomically related to IHBC, there has been a decreasing trend worldwide [9]. The aetiology of IHBC cancer and cancers originating from biliary tract (GBTC), including: EBD, gallbladder (GB) and Ampulla of Vater (AmpV) cancers, is poorly understood. Obesity, diabetes mellitus, history of gallstones or cholecystitis have been proposed as possible risk factors for GBTC [8, 10].

Some dietary exposures may affect the development of cancers of the liver and biliary tract. For example, our own data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort show that daily increase in sugar intake by 50 g was associated with a significantly higher risk of HCC, and non-significant positive association with IHBC, but not GBTC [11]. Both soft drinks and some juices may contain high levels of sugars and could be related to HCC, IHBC or GBTC development directly or indirectly through associated diseases. Intake of soft drinks and fruit drinks has been linked to obesity, T2D and NAFLD [12–16]. It has also been shown that intake of soft drinks has increased progressively in the recent years. For example, in the USA, intake of sweetened beverages has increased by 60 % between 1977 and 2001 [17]. Also, an increase in prevalence of HCC and IHBC was observed in some developed countries; the annual incidence of HCC rose by 80 % in the last few decades [7]. Therefore, we hypothesise that intake of soft drinks and possibly juices could play a role in the development of HCC and maybe IHBC cancer.

To date, there have been no consensus in the literature regarding risk of various cancers and intake of soft drinks and/or juices [18–23], and associations for cancers of the liver and biliary tract have not been well studied. Given the rising consumption of sweetened non-alcoholic beverages and their likely link to several metabolic disorders that play a role in the development of these cancers, we present here an analysis of soft drinks and fruit and vegetable juices, in association with HCC, IHBC and GBTC in the EPIC cohort.

Subjects and methods

Study design

EPIC is a large prospective multicentre study that aims to investigate the relationship between nutrition and cancer, as well as other chronic diseases. The rationale, study populations and data collection have been described previously [24]. Over 520,000 participants were enrolled from 23 centres in Denmark, France, Greece, Germany, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. Between 1992 and 1998, standardised lifestyle and personal history questionnaires, anthropometric data and blood samples were collected from most participants at recruitment, before disease onset or diagnosis. Blood samples are stored

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at the International Agency for Research on Cancer (IARC, Lyon, France; −196 °C, liquid nitrogen) for all countries except Denmark (−150 °C, nitrogen vapour) and Sweden (−80 °C freezers) where they are stored locally. All cohort members provided written informed consent. Approval for this study was obtained from the relevant ethical review boards of the participating institutions and from the IARC ethical review board (Lyon, France) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Case ascertainment

Overall, a total of 477,206 participants were included in this study after the following exclusions: 23,818 with prevalent cancer other than non-melanoma skin cancer, 4,380 with incomplete follow-up data or missing information on the date of diagnosis, 6,192 with missing dietary information, 60 with missing lifestyle information, and 9,596 those at the top or bottom 1 % of the distribution of the ratio of reported energy intake to energy requirement, and 78 with metastasis in the liver or ineligible histology code.

Cancer cases were identified using record linkage with regional cancer registries (Denmark, Italy, Netherlands, Norway, Spain, Sweden, UK; up to December 2006) or for France, Germany and Greece by health insurance records, contact with cancer or pathology registries or active follow-up (up to June 2010). Cancer cases were defined according to the 10th revision of International Classification of Diseases (ICD10): HCC (C22.0), IHBC (C22.1), GB (C23.9), AmpV (C24.1), EBD (C24.0, C24.8, C24.9). After a mean of 11.4 person years of follow-up, 191 HCC, 66 IHBC and 236 GBTC (87 GB, 54 AmpV, 95 EBD) cases were identified.

Dietary assessment and categories of intake

At enrolment, dietary intakes during the preceding 12 months were assessed based on validated country-specific dietary questionnaires designed to ensure high compliance and improved measures of local dietary habits [25]. Daily intakes of soft drinks and juices were determined in grams (g). Daily intakes of nutrients, alcohol and energy were calculated using standardised EPIC nutrient database [26]. The group of soft drinks included carbonated/soft/isotonic drinks and diluted syrups. Further classification of soft drinks into sugar sweetened and artificially sweetened was possible for participants (n = 424,123) in all centres except three: Italy (North and Ragusa), Sweden (Umeå). The group of juices comprise fruit, citrus and/or vegetable juices (including fresh and commercial juices, and nectars, with possible addition of sugars up to 20 % of the total weight of the finished product [27]), but the classification by commercial and natural juices was not possible.

For the purposes of the present analysis, the intakes of soft drinks and juices were also categorised into servings, defined to reflect current European intake customs. A serving of soft drinks was defined here as 330 g, equivalent to a volume of a soft drink can size in Europe (330 mL). For juices, one serving was considered as 200 g, equivalent to regular glass (200 mL) in Europe considered as a standard portion size for juices [28].

Nested case–control study

A nested case–control study of these cancer sites was also conducted as previously described [11]. For each HCC, IHBC or GBTC case, two controls free of cancer (other than non-melanoma skin cancer) were selected from the cohort by incidence density sampling and matched by study centre, sex, age (±1 year) at the time (±2 months) and time of the day (±3 h) of blood collection, fasting status (<3, 3–6, >6 h); for women further for menopausal status (pre-, peri-, post-menopausal), use of exogenous hormones (contraceptives or hormone replacement therapy) at blood collection (yes/no). Between the recruitment and 2006, there were 125 HCC cases identified for which blood samples were available for laboratory measurements. After the exclusion of cases and controls for whom laboratory measurements were not available due to missing sample or unsuccessful testing, the analyses included 121 HCC cases and their 241 matched controls. Additionally, the analyses were conducted for: 34 IHBC cases and their 67 controls, and 131 GBTC cases and 259 controls.

HBV and HCV status was assessed by measurement of the level of HBV surface antigen (HBsAg) or antibody to HCV (anti-HCV) with the use of relevant ARCHITECT chemiluminescent microparticle immunoassay (CMIA) (Abbott Diagnostics, France). Liver enzymes and other markers of liver function (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), liver-specific alkaline phosphatase (AP), albumin, bilirubin) were measured on the ARCHITECT c Systems™ (Abbott Diagnostics) according to the manufacturer's instructions. All laboratory analyses were performed by Centre de Biologie Republique Laboratory, Lyon, France.

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Statistical analyses

Cohort study

Comparisons of the baseline subject characteristics were done using the *t* test for continuous variables and the Chi-square test for categorical variables. Sex-, age- and centre-adjusted Pearson partial correlation coefficients were used to assess the correlations between dietary intakes of soft drinks (sugar sweetened and artificially sweetened) and juices and confounding factors in controls. Cox proportional hazard models with age as a timescale (age at recruitment and age of censoring or cancer diagnosis as entry and exit time, respectively) were used to calculate hazard ratio (HR) and 95 % confidence intervals (95 % CI) in order to estimate the association between soft drinks/juices and intakes and risks of HCC, IHBC, GBTC by defined categories, and as continuous variables (per number of servings a week) for all cancer and their subtypes.

In categorical analyses for both soft drinks and juices, non-consumers (reference category) were compared to either: (1) tertiles of intake among consumers, or (ii) categories of portions consumed per week: <1 (low consumers), 1–6 (regular consumers), >6 (high consumers). In the centres with available information (all centres excluding Umea, north Italy and Ragusa), analyses were also conducted stratified by sugar-sweetened and artificially sweetened soft drinks. To test for linear trend, median values to each category of intake and 0 g/day for non-consumers were assigned and entered into regression models.

Cox proportional hazards models were run as both crude (stratified by sex, age at recruitment in 1 year categories and study centre to account for differences in data collection, and adjusted for non-alcoholic energy intake using the standard method, i.e. by adding to the model [29]) and multivariable (additionally adjusted for a priori selected relevant confounders: smoking status and intensity of smoking (never; former smoker: quit <10 years ago, quit 11–20 years ago, quit >20 years ago; Current smoker: 1–15 cigarettes/day, 16–25 cigarettes/day, >25 cigarettes/day; other than cigarettes; current/former missing; unknown), alcohol intake at recruitment (g/day, continuous) and lifetime pattern of alcohol intake (never, former light, former heavy, light, never heavy, periodically heavy, always heavy drinkers, unknown); body mass index (BMI; kg/m^2, continuous), sex-specific physical activity (inactive, moderately active, active and missing), highest level of education attained (as a proxy for socio-economic status; none/primary, technical/professional, secondary, university or higher) and self-reported diabetes status (yes, no, missing)). Potential additional confounders considered but not included in the final model since they did not change the estimates by more than 10 % were: waist-to-hip ratio, level of intake of sugar from other sources other than sugar-sweetened beverages, meats, fish, fruit and vegetables. The associations were also studied mutually adjusting both the crude and multivariable models for the other type of studied beverage (i.e. for soft drinks and juices, sugar-sweetened and artificially sweetened soft drinks), as well as other non-alcoholic beverages intake; i.e. coffee and tea, since their intake may affect the intake of the beverages of interest or disease occurrence; however, they also did not appreciably modify the estimates and were not considered in the multivariable model. P for heterogeneity between estimates for individual exposures (i.e. soft drinks vs. juices and sugar-sweetened vs. artificially sweetened soft drinks) was tested. The difference of these associations in relation to HCC was assessed by inspecting the significance of the parameter related to the arithmetic difference of the two exposures in a model that also included their arithmetic sum.

Cubic spline regression models were computed to visualise the shape of association between soft drinks and juices intake and HCC or GBTC risk, controlling for the same confounders as in the multivariable model. The 5 cut points (knots) for the soft drinks and juices intake were determined corresponding to 10th, 25th, 50th, 75th and 90th percentile of intake expressed as number of servings (330-mL can, 200-mL glass) a week. For soft drinks that had more than 25 % non-consumers and therefore 10th and 25th percentile were equal to 0, only 4 knots were assigned at the level of intake: 0.00, 0.19, 1.82 and 4.58 cans/week. For juices, 5 knots were fitted at 0.00, 0.03, 0.69, 3.30 and 5.50 glasses a week. For better readability of the graph, the maximum was set as 99th percentile of intakes for soft drinks and juices (17.65 cans and 17.50 glasses a week, respectively).

Nested case–control subset

In the nested case–control study, odds ratio (OR) and 95 % CI were computed by conditional logistic regression for HCC, IHBC, GBTC combined and their subgroups. For HCC, the OR (95 % CI) was also computed for subjects with HBV/HCV-negative infection status. Two analysis models were run for continuous intake per serving of soft drinks and juices: (1) conditioned on the matching factors only and adjusted for non-alcoholic energy intake (crude model) and (2) multivariable adjustment for the same confounders as described for the cohort analyses. Because liver function may be altered in liver disease [30], the analyses per serving a week were also adjusted for liver function score (score: 0–6), based on the abnormal levels of liver function test (laboratory cut-offs: ALT > 55 U/L, AST > 34 U/L, GGT > 64 UL-men and > 36 U/L-women, AP > 150 U/L, albumin < 35 g/L, total bilirubin > 20.5 μmol/L). Interaction between soft

Table 1 Baseline characteristics for HCC, IHBC and GBTC cases and non-cases

	HCC	IHBC	GBTC	Non-cases
Sex				
Male [*n* (%)]	127 (66.5)	33 (50.0)	89 (37.7)	141,945 (29.8)
Female [*n* (%)]	64 (33.5)	33 (50.0)	147 (62.3)	334,768 (70.2)
Age at recruitment (years) (mean ± SD)	59.6 ± 6.9	59.6 ± 7.7	58.1 ± 8.1	51.2 ± 9.9
BMI (kg/m^2) (mean ± SD)	28.0 ± 4.8	27.0 ± 4.2	26.6 ± 4.5	25.4 ± 4.3
Waist-to-hip ratio (mean ± SD)	0.94 ± 0.10	0.90 ± 0.10	0.87 0.10	0.84 ± 0.10
Smoking status, duration and intensity[a] [*n* (%)]				
Never smoker	53 (27.7)	28 (42.4)	110 (46.6)	205,157 (43.0)
Current smoker, occasional	14 (7.3)	3 (4.5)	11 (4.7)	40,046 (8.4)
Current smoker, 1–15 cigarettes/day	23 (12.0)	6 (9.0)	26 (11.0)	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)	8,647 (1.8)
Former smoker, quit ≤ 10 years ago	17 (8.9)	3 (4.5)	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)
Highest level of education attained[b] [*n* (%)]				
None	12(6.3)	3 (4.5)	12 (5.1)	20,909 (4.4)
Primary or secondary school	141 (73.8)	47 (71.2)	175(74.2)	325,492 (68.3)
University or higher	34 (17.8)	11 (16.7)	41 (17.4)	113,406 (23.8)
No. with diabetes at baseline[c] [*n* (%)]	22 (11.5)	2 (3.0)	16 (6.8)	12,478 (2.6)
No. with gallstones at baseline[d] [*n* (%)]	21 (11.0)	15 (22.7)	30 (12.7)	24,473 (5.1)
Physical activity[e] [*n* (%)]				
Inactive	18 (9.4)	8 (12.1)	29 1(2.3)	71,709 (15.0)
Moderately inactive	68 (35.6)	20 (30.3)	76 (32.2)	142,918 (30.0)
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)
Alcohol intake lifetime pattern[f, g] [*n* (%)]				
Never drinkers	8 (4.2)	3 (4.5)	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 (3.0)	3 (1.3)	1,979 (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 (0.8)	2,968 (0.6)
Alcohol at baseline (g/day)	20.3 ± 31.6	13.5 ± 18.4	11.9 ± 16.9	11.6 ± 16.8
Dietary intakes (mean ± SD)				
Soft drinks (g/day)	129.8 ± 280.3	66.1 ± 155.1	51.7 ± 113.9	76.8 ± 166.3
Juices (g/day)	78.0 ± 150.9	93.9 ± 134.6	58.8 ± 95.7	63.7 ± 108.9
Sugar (g/day)	108.6 ± 51.5	113.4 ± 46.8	99.4 ± 41.3	102.9 ± 43.8
Total energy[h] (kcal/day)	2,034.9 ± 647.3	2,069.1 ± 649.8	1,965.5 ± 595.9	1,990.5 ± 590.4

Number of persons with missing information: [a] HCC = 4, IHBC = 4, EBD = 8, non-cases = 15,742

[b] HCC = 4, IHBC = 5, EBD = 8, non-cases = 16,906

[c] Self- reported; HCC = 15, IHBC = 13, EBD = 13, non-cases = 36,823

[d] Self-reported; HCC = 50, IHBC = 18, EBD = 76, non-cases = 145,718

[e] HCC = 9, IHBC = 5, EBD = 17, non-cases = 66,228

[f] HCC = 37, IHBC = 10, EBD = 60, non-cases = 113,950

[g] Sex-specific categories: light drinker (women: 0–3 g/day, men: 0–6 g/day); heavy drinker (women ≥30 g/day, men ≥60 g/day)

[h] Total energy exempting alcohol

Table 2 HR (95 % CI) for HCC by categories of soft drink and juice consumption compared to non-consumers in the EPIC cohort

	PY	Cases	Median intake (5, 95 %) (g/day)	Crude Model[a]	Multivariable Model[b]
Soft drinks					
Non-consumers	2,044,390	78	0.0 (0.0, 0.0)	Reference	Reference
Tertile 1	1,058,798	30	6.7 (1.4, 23.0)	0.73 (0.47, 1.15)	0.82 (0.52, 1.29)
Tertile 2	1,097,448	31	50 (28.6, 103.5)	0.84 (0.53, 1.31)	0.94 (0.60, 1.48)
Tertile 3	1,061,657	52	216.8 (114.3, 827.0)	1.47 (1.00, 2.16)	1.46 (0.99, 2.16)
P_{trend}				*<0.01*	*0.01*
<1 can[c,d]/week	1,556,294	44	16.4 (1.4, 42.9)	0.79 (0.53, 1.19)	0.90 (0.60, 1.34)
1–6 cans/week	1,288,584	45	112.5 (50.7, 254.0)	0.98 (0.65, 1.46)	1.05 (0.70,1.57)
>6 cans/week	373,026	24	500 (295.2, 1155.6)	1.94 (1.19, 3.16)	1.83 (1.11, 3.02)
P_{trend}				*<0.01*	*0.01*
Per can/week[e]				1.06 (1.03, 1.08)	1.05 (1.02, 1.07)
Juices					
Non-consumers	1,137,774	51	0.0 (0.0, 0.0)	Reference	Reference
Tertile 1	1,391,106	49	6.6 (0.1, 15.7)	0.52 (0.32, 0.92)	0.57 (0.35, 0.92)
Tertile 2	1,396,782	41	42.9 (17.1, 78.6)	0.63 (0.39, 1.02)	0.77 (0.48, 1.25)
Tertile 3	1,336,632	50	142.0 (94.3, 452.6)	0.84 (0.53, 1.33)	0.98 (0.62, 1.55)
P_{trend}				*0.31*	*0.15*
<1 glass[c,d]/week	1,771,163	60	8.4 (0.3, 25.8)	0.54 (0.34, 0.85)	0.60 (0.38, 0.95)
1–6 glasses/week	1,875,327	52	76.8 (35.4, 450.0)	0.62 (0.39, 0.97)	0.75 (0.48, 1.18)
>6 glasses/week	478,030	28	273.8 (179.7, 650.5)	1.24 (0.72, 2.15)	1.38 (0.80, 2.38)
P_{trend}				*0.03*	*0.02*
Per glass/week[e]				1.03 (1.01, 1.06)	1.03 (1.01, 1.06)

[a] Crude Model: Cox proportional hazard model adjusted for non-alcoholic energy intake and stratified by age (1-year intervals), sex and study centre. *P* for linear trend was computed by assigning median values to each category of consumers and 0 g/day for non-consumers

[b] Multivariable Model: additionally adjusted for BMI, sex-specific physical activity, education level, alcohol at recruitment and alcohol intake pattern, smoking intensity, duration and history, diabetes status

[c] Can volume 330 mL, glass volume 200 mL

[d] In reference to non-consumers

[e] $p = 0.57$ for heterogeneity for associations for drinks and juices with HCC

drinks and juices intake and liver function score categories (no damage 0, possible damage 1–6), as well as BMI categories (BMI: <25 kg/m^2 normal weight, ≥25–30 kg/m^2 overweight, ≥30 kg/m^2 obese) was also studied. Where the interaction appeared significant, multivariable logistic regression additionally adjusted for matching criteria was run for the individual subgroups within the categories for the cancer risk and intake of soft drinks and juices.

Sensitivity analyses and effect modification

In sensitivity analyses, the analyses were repeated excluding: (1) cases diagnosed prior to 2 years of follow-up in order to exclude for potential reverse-causation, (2) participants with self-reported diabetes at baseline due to possible diet modifications and (3) consumers with extreme intakes (the highest percentile).

Interaction between soft drinks and juices intake and sex, BMI and alcohol intake patterns was studied to consider potential effect modification. The statistical significance of associations was based on likelihood ratio tests on the models with and without interaction terms. All statistical analyses were performed with SAS 9.2 and considered statistically significant if $p < 0.05$.

Results

Participants and their lifestyle and diet

Participants who developed HCC were mainly men, older, physically active, less educated, and were more likely to have prevalent diabetes and gallstones, to be current smokers, and to be former or current heavy drinkers than the non-cases. They also had higher BMI and waist-to-hip ratio. IHBC

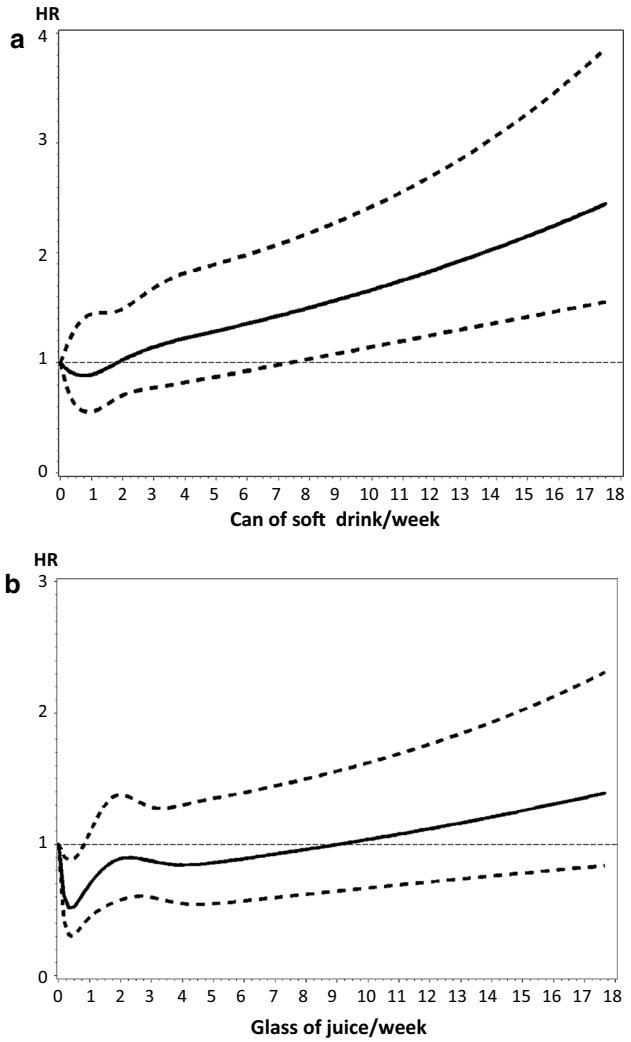

Fig. 1 Spline regression models for the intake of soft drinks (**a**) and juices (**b**) in relation hepatocellular carcinoma risk. Reference 0 mL/week. *Knots* correspond to 10th, 25th, 50th, 75th and 90th percentile of intake. The maximum corresponds to the 99th percentile. *Solid lines*- HR, *dashed lines*- 95 % CI

cases were equally distributed between the sexes and older then the non-cases and a higher proportion of them reported gallstones. Participants who developed GBTC were mostly women, less educated and were more likely to have diabetes and gallstones at baseline as compared to non-cases (Table 1).

Both daily consumers of soft drinks and juices were characterised by less healthy dietary pattern than non-consumers (higher consumption of sugar and confectionary, cakes and biscuits, and lower intake of legumes, fruits and vegetables, fish and shellfish), which was reflected in their higher intake of sugar (30 %), fat (5–6 %) and energy (10 %) (Online Resource 1). Self-reported diabetic subjects were more likely to consume daily artificially than sugar-sweetened soft drinks (5.5 vs. 1.9 %, respectively). In comparison, more non-diabetics consumed sugar-sweetened (2.8 %) than artificially sweetened soft drinks (1.6 %). Similar trend was observed for BMI categories; 4 % of obese subjects consumed daily artificially sweetened drinks vs. 1.6 % of those with normal weight. For sugar-sweetened drinks, the proportion was distributed equally between the BMI groups at the level of 3 %. Intake of soft drinks and juices positively correlated with dietary sugar ($r = 0.28$ and 0.34) and energy ($r = 0.10$ and 0.10). Similar coefficients were observed for sugar-sweetened group of soft drinks ($r_{sugar} = 0.33$ and $r_{energy} = 0.10$), but no correlation with these variables existed for artificially sweetened drinks. No correlation was observed between any type of the beverages and BMI, waist-to-hip ratio, physical activity level and alcohol intake at recruitment.

Soft drink intake and the risk of HCC

Compared to non-consumers, the highest tertile of soft drinks consumers showed a borderline significant higher risk of HCC after adjustment for confounders (HR 1.46, 95 % CI 0.99–2.16; $p_{trend} = 0.01$), and no significant associations were observed for the first and the second tertile of consumers (Table 2).

Consumption of more than six (6 × 330 mL) cans per week of soft drinks was significantly associated with higher risk of HCC after adjustment for confounders, as compared to non-consumers (HR 1.83, 95 % CI 1.11–3.02; $p_{trend} = 0.01$); no significant associations were observed for lower intakes (Table 2).

In continuous analyses, the increment of 330 mL of soft drinks a week was significantly positively associated with the risk of HCC after adjustment for confounders (HR 1.05, 95 % CI 1.02–1.07) (Table 2). Spline regression analyses by an increase in a serving a week showed a linear mostly positive association with HCC that appeared significant for daily and higher consumption of soft drinks (Fig. 1a).

In additional analyses by the type of drinks (sugar-sweetened vs. artificially sweetened), each additional serving of artificially sweetened soft drink was positively associated with HCC risk (HR 1.06, 95 % CI 1.03–1.09, $n_{cases} = 101$), while for sugar-sweetened soft drinks, this association was null (HR 1.00, 95 % CI 0.95–1.06, $n_{cases} = 127$). The difference between both estimates was borderline significant ($p_{heterogeneity} = 0.07$).

Juice intake and the risk of HCC

Compared to non-consumers, the lowest tertile of juice intake was significantly associated with reduced HCC risk in both crude (HR 0.52, 95 % CI 0.32–0.92; $p_{trend} = 0.31$) and multivariable models (HR 0.57, 95 % CI 0.35–0.92; $p_{trend} = 0.15$), while no significant association was observed for the second and third tertile of consumers (Table 2).

Table 3 Hazard ratios and 95 % CI for IHBC and GBTC and its subsites associated with one serving increment per week in the consumption of soft drinks and juices in the EPIC cohort

	IHBC ($N = 66$) HR (95 % CI)	GBTC			All GBTC ($N = 236$) HR (95 % CI)
		EBD ($N = 95$) HR (95 % CI)	GB ($N = 87$) HR (95 % CI)	AmpV ($N = 54$) HR (95 % CI)	
Soft drinks					
Crude[a]	0.99 (0.91, 1.07)	0.95 (0.86, 1.04)	0.91 (0.80, 1.03)	1.02 (0.95, 1.10)	0.96 (0.91, 1.00)
Multivariable[b]	0.97 (0.90, 1.06)	0.94 (0.86, 1.03)	0.89 (0.79, 1.01)	1.02 (0.95, 1.10)	0.96 (0.90, 1.00)
Juices					
Crude	1.04 (1.00, 1.08)	1.01 (0.96, 1.06)	0.97 (0.91, 1.04)	0.97 (0.87, 1.08)	0.99 (0.95, 1.03)
Multivariable	1.04 (1.00, 1.08)	1.01 (0.96, 1.06)	0.97 (0.91, 1.04)	0.97 (0.88, 1.08)	0.99 (0.95, 1.03)

Serving for soft drinks corresponds to 330 mL and for juices to 200 mL

IHBC intrahepatic bile duct, *GBTC* biliary track, *EBD* extrahepatic bile duct, *GB* gallbladder, *AmpV* Ampulla of Vater cancers

[a] Crude Model adjusted for non-alcoholic energy intake and stratified by age(1-year intervals), sex and study centre

[b] Multivariable Model: additionally adjusted for BMI, sex-specific physical activity, education level, alcohol at recruitment and alcohol intake pattern, smoking intensity, duration and history, diabetes status (IHBC) and gallstones history (GBTC and their subtypes)

When considering intake as serving categories in relation to non-consumers, consumption of less than a 200-mL glass a week was associated with lower HCC risk in multivariable model (HR 0.60, 95 % CI 0.38–0.95; $p_{trend} = 0.02$), and when only consumers were considered, a positive trend ($p_{trend} = 0.004$) was observed for higher consumption. The highest category of intake was non-significantly positively associated with HCC risk (HR 1.38, 95 % CI 0.80–2.38; $p_{trend} = 0.02$) (Table 2).

In continuous analyses, the increase in intake of one serving (200 mL) of juice a week was positively associated with the risk of HCC (HR 1.03, 95 % CI 1.01–1.06) (Table 2). In spline regression analyses, the association for juices was negative and significant only for intakes lower than one glass a week (Fig. 1b).

Sensitivity analyses and effect modification for HCC risk and soft drinks and juices intake

Exclusion of persons diagnosed with HCC within the first 2 years from recruitment did not change the findings for either exposure (data not shown). When only non-diabetic individuals were studied, the HRs were similar to whole cohort estimates, but weaker, probably due to lower sample size of this sub-cohort. Excluding participants with the 1 % highest intakes of soft drinks and juices did not modify the results for juices, but the association for the highest tertile for soft drinks was attenuated (HR 1.35, 95 % CI 0.87–2.10).

No statistically significant interactions were observed between categories of soft drink intake and sex ($p = 0.200$), BMI category ($p = 0.126$) or alcohol intake pattern ($p = 0.912$) nor categories of juices intake and sex ($p = 0.568$), BMI category ($p = 0.617$) or alcohol intake pattern ($p = 0.745$).

Table 4 OR and 95 % CI for HCC associated with one serving increment per week in the consumption of soft drinks and juices in the nested case–control study within the EPIC cohort

	Cases	Controls	OR (95 % CI)
Soft drinks			
Crude Model[a]	121	241	1.21 (1.09, 1.35)
Multivariable Model[b]			1.18 (1.04, 1.34)
Multivariable Model + liver function score			1.22 (1.05, 1.40)
Multivariable Model + hepatitis status[c]			1.19 (1.04, 1.37)
Multivariable model for hepatitis-free individuals	84	162	1.22 (1.04, 1.44)
Juices			
Crude Model	121	241	1.03 (0.97, 1.09)
Multivariable Model			1.01 (0.93, 1.09)
Multivariable Model + liver function score			1.04 (0.95, 1.13)
Multivariable Model + hepatitis status			0.99 (0.90, 1.08)
Multivariable model for hepatitis-free individuals	84	162	1.00 (0.90, 1.12)

Serving for soft drinks corresponds to 330 mL and for juices to 200 mL

[a] Crude Model: matching factors only and adjusted for non-alcoholic energy intake

[b] Multivariable Model: crude model additionally adjusted for BMI, sex-specific physical activity, education level, alcohol at recruitment and alcohol intake pattern, smoking intensity, duration and history, diabetes status

[c] Liver function score (1–6) was calculated according to the cut-off values for: ALT > 55 U/L, AST > 34 U/L, GGT > 64 UL-men and 36 U/L-women, AP > 150 U/L, albumin < 35 g/L, total bilirubin > 20.5 μmol/L

Intake of juices and soft drinks and the risk of IHBC, GBTC and its subtypes

The risk of IHBC in an adjusted model per 200 mL increase in juice intake a week was higher by 4 % (HR 1.04, 95 % CI 1.00–1.08). The increment of a serving of soft drink or juice a week was not significantly associated with GBTC subtypes (Table 3).

No significant associations were observed for tertiles of soft drinks or juices consumers in relation to non-consumers and the risk of GBTC. Also, when the intakes were treated as serving categories of soft drinks compared to non-consumers, no associations were found (data not shown). For each additional 330 mL of soft drink a week, a borderline inverse association was observed with all GBTC combined (HR 0.96, 95 % CI: 0.91–1.00). A mostly negative, although not significant, association was observed based on cubic splines for soft drinks or juice and GBTC risk (data not shown).

Nested case–control study

In a nested case–control subset, each additional can of soft drink a week increased the risk of HCC (OR 1.18, 95 % CI 1.04–1.34). These results were maintained in hepatitis-free individuals or after adjustment for hepatitis status or liver function score (Table 4). There was no significant association for soft drinks and the risk of IHBC or GBTC (data not shown).

For HCC, an interaction was observed between increase in one portion of soft drink intake and liver function score category ($p = 0.028$). Stratified analyses by liver function score category revealed a significantly higher risk of HCC by soft drink intake in the suggested liver damage subgroup (score 1–6) (OR 1.46, 95 % CI 1.04–2.03), while in the group with no liver damage, this association was not significant (OR 1.15, 95 % CI 0.87–1.51) (data not shown). There was no interaction between soft drink intake and either BMI ($p = 0.296$) or alcohol intake pattern ($p = 0.362$).

Drinking an additional glass of juice a week was not associated with HCC risk (OR 1.00, 95 % CI 0.93–1.08) (Table 4). There was no significant association for juices and the risk of IHBC or GBTC (data not shown). No interaction was observed between juice intake and liver function score ($p = 0.862$), alcohol intake pattern ($p = 0.055$) or BMI category ($p = 0.195$).

Discussion

There was a positive association between consumption of soft drinks and HCC risk, which was present in continuous analyses and for the highest categories of intake in the cohort, but also in the nested case–control subset after adjustment for hepatitis status and liver function score. In subgroup analyses by soft drink category, per serving increase in artificially sweetened but not sugar-sweetened soft drinks, this association was significant. Each increment of a serving of soft drink was associated with lower overall GBTC risk, but no significant associations were observed when the intakes were treated as categories. No significant associations existed in the cohort for regular or high juice consumers and risk of HCC. Compared to non-consumers, an intake of up to one serving of juice per week was associated with an inverse HCC risk, but for each additional serving of juice, there was a positive association with HCC and IHBC risk.

Previously reported findings from the EPIC cohort have shown that high sugar intakes are positively significantly associated with HCC risk and not significantly with IHBC, but inversely associated with GBTC [11]. Soft drinks contain 55–130 g of total sugar per litre [31]. However, most commercial and some natural fruit juices may also be characterised by high sugar levels, i.e. 3–112 g/L [32]. Therefore, we hypothesised that intakes of high in sugar beverages may be linked to development of HCC and possibly IHBC. In this study, only soft drinks showed a positive association with HCC, but we could not distinguish between commercial and natural juices. The observed link between intake of soft drinks and HCC could be mediated through some conditions associated with HCC, such as obesity [33, 34]. In observational studies, positive association for soft drinks intake and obesity is mainly observed for extreme categories of intake [35]. In this study, a positive association with HCC exists only for high soft drinks consumers, but interestingly BMI did not appear as an important confounder for this association; addition of BMI to the model did not considerably modify the risk estimates, and no interaction was observed between BMI categories and intakes of combined soft drinks.

Higher risk of HCC in daily consumers of soft drinks could be also related to adverse effects of their high sugar content on lipid and glucose metabolism [36]. Soft drinks, high in both glucose and fructose, result in a rapid increase in blood glucose and insulin levels at the intermediate level between the responses observed for pure glucose and fructose [37]. Fructose is rapidly taken up by the liver and favours de novo lipogenesis which may lead to hepatic lipid accumulation and finally to NAFLD [38]. Soft drink intake was significantly associated with an increased risk for NAFLD [39]. Taking into account that nearly three quarters of patients infected with HCV and half of HBV positive patients exhibit liver steatosis, of which 10–20 % develop NAFLD [40], we repeated the analysis in a case–control subset excluding hepatitis positive individuals and

additionally adjusting for liver function score, an indicator of liver dysfunction. We found that each increment of a portion of soft drink was associated with increased risk of HCC by 20 %, independently of hepatitis status. However, observed interaction between liver function score and soft drink intake in relation to HCC risk may indicate that liver damage may play a role in HCC development associated with soft drinks intake.

Interestingly, when we investigated these associations further, after categorising soft drinks into sugar sweetened and artificially sweetened in the subset of centres where this data were available (91 % of the cohort), only for the artificially sweetened soft drinks, the association was positive. Similar findings were previously reported in the EPIC cohort and its French sub-cohort for the association between soft drinks and juices and diabetes risk; 350 mL increment of artificially sweetened soft drink had stronger effect on increased risk of developing diabetes than sugar-sweetened soft drink, while juice intake was not associated with diabetes [8, 41]. Indeed, a recent study in mice reported an effect of non-caloric artificial sweeteners on intestinal microbiota composition leading to induction of glucose intolerance [42], but the findings require further confirmation in humans. Diabetes could be another important intermediate factor between HCC risk and soft drinks consumption. The intake of soft and fruit drinks is associated with increased risk of T2D [12, 35]. This may imply that: (1) components other than sugar present in diet/reduced-sugar soft drinks, such as sweetening agent or colourants, could be associated with the risk of HCC; (2) artificially sweetened beverages, in general considered as healthier since they do not contain sugar, could be more frequently consumed by individuals with some existing underlying disorders, for example diabetes or obesity, and (3) diabetes/obesity might have been a consequence of high intake of sugary drinks in the past. Indeed in our cohort, self-reported diabetic subjects or obese individuals consumed daily more frequently artificially sweetened than sugar-sweetened soft drinks.

It can also be hypothesised that the group of high consumers of soft drinks would be characterised by less healthy dietary pattern. Data from an American dietary survey 1999–2002 indicated that soft drinks are more frequently consumed in the fast food dietary cluster, but less often by individuals characterised by a diet high in vegetables [43]. In this study, high consumers of both soft drinks and juices had less healthy dietary intakes and higher alcohol, sugar and energy content of their diet. The adjustment for some food components that may affect risk of liver and biliary track cancers (e.g. intake of meat, fish, fruit and vegetables) did not modify the outcomes, but we cannot rule out a confounding effect of other dietary components.

The nature of the association between juice and HCC risk may also vary according to different thresholds of intake. Juices are considered as healthier dietary choices due to their antioxidant, minerals, vitamins, phytochemicals and fibre content [44], as compared to soft drinks with poor nutritional quality. Fibre and polyphenols are known for their protective role against cancers in different sites [45], including HCC [11, 46]. Our results may suggest that at lower consumption, the beneficent effect of some juice components is present, whereas at very high levels of consumption, the sugar content of juices may override the potentially protective role of other components of juices. This could be supported by the observation that when only consumers were considered, increasing risk of HCC was observed with higher category of intake.

Strengths of the present study include its prospective multicentre design that included a diverse European population with different habits of drinks and juices intakes [47]. Availability of detailed lifestyle and health status information made it possible to control for multiple confounders. Additionally, biochemical measurements of hepatitis status and liver enzymes enabled to control for the key risk factors for HCC. We were able to distinguish between multiple morphologic sites of liver and biliary tract cancers.

The study has some limitations. Liver and biliary tract cancers are relatively rare; a small sample size was available for analysis. The dietary and lifestyle data were collected only at baseline; it is possible that participants modified their dietary intakes during the follow-up. To control for potential diet modification, we conducted sensitivity analyses excluding cases identified within the first two years of follow-up. We were not able to distinguish between different kinds of juice (e.g. natural juices or nectars with added sugar) as well as the type of sugar or sweetener in the beverages, which made it difficult to assess the effect of added sugar or type of artificial sweetener used on the diet–disease relationship. Given the small study size which is even further reduced in the subgroup analyses, it is possible that these results were obtained by chance. So, confirmation from other settings and populations is necessary.

In conclusion, our results indicate that high consumption (one or more cans a day) of all combined soft drinks may increase the risk of HCC, but not GBTC. Interestingly, this association was mainly driven by the subgroup of artificially sweetened soft drinks. A modest consumption of juices may be associated with a lower risk of HCC, but this effect disappears at higher levels of consumption. The findings could be important for public health concerning dietary recommendations in cancer prevention. However, more research is required to determine whether the observations presented here are indeed real, and whether they are related directly to higher sugar intake, higher intake of artificial sweeteners or to other dietary or lifestyle patterns or HCC-associated disease status associated with consumption of soft drinks and juices.

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