HHS Public Access

Author manuscript

Cancer Epidemiol. Author manuscript; available in PMC 2024 September 11.

Published in final edited form as:

Cancer Epidemiol. 2022 August ; 79: 102201. doi:10.1016/j.canep.2022.102201.

Sweetened beverage consumption and risk of liver cancer by diabetes status: a pooled analysis

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Abstract

Background: Consumption of sweetened beverages has been linked to several risk factors for liver cancer including diabetes. Studies investigating the role of sweetened beverage consumption and liver cancer, however, are limited. As persons with diabetes are advised against consumption of sugar, the objective of this study was to examine the role of sweetened beverage consumption and liver cancer risk by diabetes status.

Methods: Data from two U.S. cohorts: the NIH-AARP Diet and Health Study, and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial were harmonized and pooled. Hazard ratios

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Authors' Contributions:

Gieira S. Jones was involved in acquisition of the data, analysis and interpretation of the results, and drafting of the manuscript. Yesenia Ramirez was involved in data acquisition and review of manuscript. Linda M. Liao, Wen-Yi Huang, and Jessica L. Petrick were involved in interpretation of results and review of manuscript. Christian S. Alvarez, Wanshui Yang, and Xuehong Zhang were involved with critical review of the manuscript. Barry I. Graubard was involved with acquisition of the data, analysis and interpretation of the data and critical review of the manuscript. Katherine A. McGlynn was involved with study concept and design, interpretation of the results drafting of the manuscript, critical review of the manuscript and study supervision.

Disclosures: No conflicts to disclose

Declaration of Interest

The authors have no conflict of interest to report.

Credit Taxonomy

Gieira S. Jones: Methodology, Software, Formal analysis, Writing- original draft, visualization, Barry I. Graubard: Writing- Review & Editing, Methodology, Supervision, Yesenia Ramirez : Writing- Review & Editing, data curation, Linda M. Liao : Writing- Review & Editing, data curation, project administration, Wen-Yi Huang : Writing – Review & Editing, data curation, project administration, Christian S. Alvarez: Writing – Review & Editing, Wanshui Yang: Writing- Review & Editing, Xuehong Zhang: Writing- Review & Editing, Jessica L. Petrick: Writing – Review & Editing, Katherine A. McGlynn: Conceptualization, Writing- Review and Editing, Supervision, Funding acquisition

and 95%CI were estimated using Cox proportional hazard models stratified by median follow-up time.

Results: Among persons without diabetes, there were no statistical evidence of associations between liver cancer and consumption of sweetened beverages overall, sugar sweetened beverages (SSB), or artificially sweetened beverages (ASB). Sugar sweetened (SS) soda consumption, however, was associated with liver cancer in the first follow-up interval (HR:1.18. 95%CI: 1.03, 1.35). In contrast, among persons with diabetes, there were significant associations between liver cancer and consumption of sweetened beverages overall (HR: 1.12, 95%CI 1.01, 1.24), ASBs (HR: 1.13, 95% CI: 1.02, 1.25), soda overall (HR: 1.13, 95% CI: 1.00, 1.26) and artificially sweetened (AS) soda (HR: 1.13, 95% CI: 1.01, 1.27) in the first follow-up interval.

Conclusions: Increased soda consumption may be associated with risk of liver cancer. The results suggest that decreasing consumption of SS soda by persons without diabetes, and AS soda by persons with diabetes, could be associated with reduced liver cancer risk.

Keywords

Sweetened Beverages; diabetes; liver cancer

Introduction

Worldwide, liver cancer is the sixth most frequently occurring cancer and the third largest contributor to cancer mortality [1]. In the U.S., where 42,230 cases of liver cancer are predicted to occur in 2021 [2], a number of factors are known to increase risk. These factors include excessive alcohol consumption, hepatitis C virus (HCV), hepatitis B virus (HBV), cigarette smoking, non-alcoholic fatty liver disease, obesity, and type 2 diabetes [3, 4]. The combined population attributable fraction of these factors, however, is estimated at 59.5%, so 40.5% of risk remains poorly explained [5]. It is possible that dietary factors such as sweetened beverages are linked to liver cancer, as sweetened beverage consumption has been linked to non-alcoholic fatty liver disease, obesity, and type 2 diabetes [6–10].

Beverages can be sweetened by either sugar or by artificial sweeteners such as aspartame, sucralose, and saccharin. It is unclear, however, if either sugar sweetened beverages (SSB) or artificially sweetened beverages (ASB) contribute to liver cancer risk. A recent meta-analysis of one ASB, artificially sweetened (AS) soda, and gastrointestinal cancers reported that consumption associated with a 28% increase in liver cancer risk [11]. The literature on SSB consumption and liver cancer risk is also limited [12, 13]. In the U.S., where there is very high sweetened beverage consumption [14, 15], only one prospective study of sweetened beverage consumption and liver cancer has been reported [16].

Many persons with diabetes are advised to limit SSB consumption, therefore consumption can vary widely between persons with and without diabetes [17]. A U.S. national survey found that 34.7% of person without diabetes reported drinking sweetened beverages at least once per day, while only 22.0% of persons with diabetes reported drinking sweetened beverages at least once a day [17]. Based on the likelihood of different sweetened beverage

consumption exposure, the current study examined the relationship between sweetened beverage consumption and liver cancer risk by diabetes status.

Methods

Study population

The current study was a pooled analysis of the NIH-AARP Diet and Health Study (NIH-AARP) and the Prostate Lung, Colorectal and Ovarian cancer screening trial (PLCO) [18, 19]. Demographic, dietary, and lifestyle variables were harmonized between the two cohorts to assess risk of liver cancer. Study protocols for both the NIH-AARP and PLCO studies were approved by a National Cancer Institute institutional review board.

The NIH-AARP cohort study has been previously described [18]. In brief, during the years 1995–1996, participants were enrolled who resided in six states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Detroit, Michigan and Atlanta, Georgia). The study mailed AARP members aged 50–71 years old a baseline questionnaire to assess demographic characteristics, diet, medical history, lifestyle factors, and chronic disease status. After the exclusion of persons who withdrew from the study, had duplicate records, died before study entry, and who moved out of the 8 regions of the NIH-AARP catchment area before returning the questionnaire, the baseline cohort consisted of 566,398 participants. In the current analysis, additional criteria for exclusion included: persons whose data were collected from a proxy respondent (n= 15,760), reported a cancer diagnosis on baseline questionnaire (49,318), reported a history of cancer before entry (n= 2,028), and/or had zero follow up time (n=58), cancers ascertained by death report only (n= 4,268)). For the current analysis there were 494,966 NIH-AARP participants whose data were eligible for harmonization and analysis.

The PLCO study, a randomized controlled cancer screening trial, has been previously described [19]. In brief, the trial was conducted between 1993 and 2001 across 10 screening centers in the United States (Washington D.C.; Detroit, Michigan; Marshfield, Wisconsin; Honolulu, Hawaii; Birmingham, Alabama; Aurora, Colorado; Minneapolis, Minnesota; Pittsburgh, Pennsylvania; Boise, Idaho; and St. Louis, Missouri). The participants, men and women aged 55–74 years, were randomized to either a control arm or a screening arm. Baseline questionnaires collected demographic information, health history, dietary data, and lifestyle factors. There were 149,969 participants who completed the baseline questionnaire. The diet history questionnaire (DHQ), which was administered in 1998, collected intake information on multiple dietary items including alcohol, nutrient intake, supplement intake, daily grams and frequencies of food, and beverage intake. The current analysis included participants who completed the diet history questionnaire. Participants were ineligible for the current analysis if they failed to complete both the baseline and dietary questionnaires, had a history of any cancer prior to completion of the dietary questionnaire and no follow-up time after the completion of the dietary questionnaire (n= 48,360). There were 101,609 PLCO participants eligible to be included in the pooled analysis.

Exposure

The current study assessed frequency of consumption of both SSBs and ASBs. Specific beverage categories examined included soda, fruit punches (Hi-C, lemonade, and Kool-Aid) and fruit juices (orange/grapefruit juice, vegetable/tomato, other fruit juices/fruit juice mixtures). Sweetened beverage variables were derived by combining the frequency of consumed soda and frequency of consumed fruit punch. Reported beverage consumption was defined as frequency per day. The categories ranged from no consumption to 6+ times per day on both the PLCO and AARP dietary questionnaires.

Outcome

Primary liver cancer was defined in accord with the Surveillance, Epidemiology and End Results (SEER) definition, based on ICD-O-3 topography codes C22.0 and C22.1, excluding morphology codes 9050–9055, 9140 and 9590–9992[20]. The follow-up time began at completion of the baseline questionnaire for the NIH-AARP Study and completion of the diet history questionnaire for the PLCO study. The end of study was defined as the first diagnosis of liver cancer, death, loss to follow-up or end of follow up which was December 31, 2011 for NIH AARP and December 31, 2017 for PLCO. The NIH-AARP study confirmed liver cancer diagnosis via linkage to state cancer registries. The PLCO study obtained cancer status via self-report and confirmed through medical record review and/or via linkage to the state cancer registries.

Statistical Analysis

Median and interquartile ranges were calculated for continuous covariates including age at baseline and total energy intake (kilocalories/day). Race/ethnicity, sex, alcohol use, and smoking were coded as categorical variables and reported as proportions. Categorical covariates were defined as follows: race/ethnicity (Non-Hispanic Whites, Non-Hispanic Blacks, Hispanic, Asian/Pacific Islanders), body mass index (underweight/normal, overweight, obese), sex (male, female), ever smoked cigarettes (yes, no), current alcohol consumption (yes, no), study cohort (NIH-AARP, PLCO), and reported as proportions. Diabetes status was self-reported at baseline for PLCO and NIH-AARP. Persons with diabetes have dietary restrictions for sugar consumption and therefore the analysis was stratified by diabetes status *a priori,* however a Wald test for interaction of sweetened beverage consumption and diabetes status was performed and did not support a statistical interaction between the variables (p-value =0.58). Participants whose caloric intake was outside of 3 standard deviations of the mean were removed from the analytic cohort (n= 42,210).

Cox proportional hazard models were used to estimate covariate adjusted hazard ratios (HR) for the association of sweetened beverage consumption with liver cancer. The proportional hazards assumptions were assessed using Schoenfeld residual tests and found to be violated. To address non-proportional hazards, Cox modeling was conducted separately for two follow-up intervals based on the median follow-up time (0–12 years follow-up time; 12 years follow-up time to end of follow-up). Beverage consumption was modeled as a continuous daily frequency variable (i.e., the absolute difference of (HR – 1) x 100% is the percent increase or decrease in the risk of liver cancer for HR's ≥ 1 or < 1, respectively,

for an increase of one consumption frequency per day). We used Wald tests of interaction to assess heterogeneity of the associations of sweetened beverage consumption and liver cancer risk between the two studies (PLCO vs NIH -AARP) and found no evidence of heterogeneity, p-value >0.05. Therefore, all Cox regression analyses combined the two samples with a main effect adjustment for study. All statistical analyses used two-sided p-values with $p<0.05$ without adjustment for multiple comparisons. All analyses were conducted in STATA 17 SE (College Station, TX).

Results

The pooled analytic cohort included a total of 553,874 participants, 506,389 of whom did not have diabetes, and 47,485 of whom had diabetes (Table 1). Among the persons without diabetes, 839 developed liver cancer, while among the persons with diabetes, 221 developed liver cancer. The median age was similar between the persons who developed liver cancer and those who did not. Persons who developed liver cancer, however, were more likely to be male, non-White, obese, and to report a history of smoking. Persons who developed liver cancer also reported higher total energy intakes at baseline.

Sweetened beverage consumption differed between persons with and without diabetes (chi-square p-value <0.01 [consumer vs non-consumer]). As shown in Table 2, the percentage of persons who drank any sweetened beverages was similar in both groups (persons without diabetes 91%, persons with diabetes 93%). Persons with diabetes, however, were more likely to report consumption of ASBs (81%) than persons without diabetes (50%). Similarly, consumption of AS soda was more common among persons with diabetes (79%) than persons without diabetes (47%), and SS soda consumption was less common among persons with diabetes (13%) than persons without diabetes (44%). Consumption of SS and AS fruit punch also varied by diabetes status, with greater consumption of AS punch among persons with diabetes, and greater consumption of SS punch among persons without diabetes. Patterns of orange/grapefruit, tomato/vegetable and other juice consumption did not vary greatly among persons with and without diabetes.

As shown in Table 3, the analysis of persons without diabetes found no statistical evidence of an overall association between consumption of sweetened beverages and liver cancer (HR: 1.05, 95%CI: 0.97, 1.14). Similarly, there was no statistical evidence of an association between overall consumption of soda and liver cancer (HR: 1.07, 95%CI: 0.98, 1.17). SS soda consumption, however, was associated with an increased risk of liver cancer in the first follow-up interval (HR: 1.18, 95%CI: 1.03, 1.35). In addition, orange/grapefruit juice was associated with a reduced risk of liver cancer in the first follow-up interval. There were no other statistically significant associations among persons without diabetes, either within the first follow-up interval or the second follow-up interval.

The analysis that examined sweetened beverage consumption and liver cancer risk among persons with diabetes is shown in Table 4. Overall sweetened beverage consumption was associated with increased risk of liver cancer risk in the first follow-up interval (HR: 1.12, 95%CI: 1.01, 1.24). Stratification into consumption of SSBs and ASBs, however, found a significant association with ASB consumption (HR: 1.13, 95%CI: 1.02–1.25), but not with

SSB consumption (HR: 0.90, 95%CI: 0.56–1.44). This same pattern was observed for soda consumption. The significant association observed for overall soda consumption and liver cancer (HR: 1.13, 95%CI; 1.00 1.26) was evident for AS soda (HR: 1.13, 95%CI: 1.01, 1.27), but not for SS soda (HR: 0.90, 95%CI: 0.47, 1.70). There were no other statistically significant associations evident among persons with diabetes in either time interval.

To further examine the possibility of reduced risk with increasing follow-up time, we conducted more detailed analyses over four follow-up time intervals: 0 to <=6 yrs., 6 to <= 12 yrs., 12 to <=18 yrs., and 18+ yrs. The analyses found, among persons with diabetes, an indication of decreasing HR's for all sweetened beverage consumption of HR: 1.20 (95%CI: 1.04, 1.38), HR: 1.06 (95%CI: 0.92, 1.02), HR: 0.77 (95%CI: 0.57, 1.00) and 0 cases, respectively. The HR's for the persons without diabetes were approximately constant over the same time intervals (data not shown).

Discussion

In the current study of pooled data from two U.S. cohorts, soda consumption was found to be associated with an increased risk of liver cancer in the first follow-up interval. Among persons without diabetes, SS soda consumption was linked to liver cancer, while among persons with diabetes, AS soda consumption was linked to liver cancer. In addition, orange juice/grapefruit juice consumption was found to be associated with reduced risk of liver cancer among people without diabetes in the first follow up interval.

The study findings add to a growing literature on the role of sweetened dietary factors in liver cancer [11–13]. Several prior studies have looked specifically at sweetened beverage consumption. A multi-center case-control study of persons with cirrhosis in France reported that soda consumption was significantly associated with hepatocellular carcinoma, the dominant histologic type of liver cancer [13]. The study, however, grouped SS and AS soda into a single variable for analysis, thus making it is difficult to determine their separate effects. The European Prospective Investigation into Cancer and Nutrition (EPIC) study also examined soda consumption and observed a significantly increased risk of liver cancer at the highest level of consumption (HR: 1.83, 95%CI, 1.11, 3.02) but found no significant association with juice consumption (HR: 1.38, 95%CI, 0.80, 2.38) [12]. A subset analysis in the EPIC study found, however, that ASBs were significantly associated with liver cancer (HR: 1.06, 95%CI, 1.03, 109), but SSBs were not (HR: 1.00, 95%CI, 0.95, 1.06). Neither of the two European studies stratified the participants on diabetes status. In the EPIC study, all persons reported lower overall sweetened beverage consumption than was observed in the current study. This difference in consumption patterns in Europe and the U.S. may be related to differences in results between the current study and the EPIC study. One prior U.S. study also examined SSB consumption and liver cancer [16]. In a pooled analysis of data from the Nurses' Health Study and the Health Professionals Follow-up Study, there was no significant relationship between SSB consumption and risk of liver cancer. The analysis did not specifically examine soda or type of soda, however. A recent meta-analysis of ASB and liver cancer, which included only the EPIC study and the U.S. study, reported an overall risk of liver cancer (HR: 1.28, 95%CI, 1.03, 1.58) [11].

In the current study, the significant associations with liver cancer were observed only during the first follow-up interval. Why the risk didn't persist after the median time of follow-up is not clear but could be related to changes in beverage consumption habits over time. This hypothesis couldn't be examined, however, as repeated dietary consumption questionnaires were not administered in either of the cohorts. It is also possible that our study results were affected by differential depletion of susceptible persons over time, a phenomenon which might be more likely to occur among the participants with diabetes [21].

There are several potential mechanisms by which increased SSB consumption could increase liver cancer risk. In the U.S., SSB consumption contributes a third of added sugars to the diet [14]. Prior clinical studies have suggested that a high glycemic index derived from carbohydrates may increase insulin resistance and hyperinsulinemia [22]. Insulin is mitogenic and consistently elevated levels of insulin could promote carcinogenesis [23, 24]. SSBs may also promote cancer by predisposing to health conditions that are risk factors for liver cancer, such as non-alcoholic fatty liver disease, type 2 diabetes, and obesity [25]. In particular, obesity is associated with increased inflammation in adipose tissues, and inflammatory cellular environments are known mediators for cancer progression [25, 26]. In addition, it has been suggested that consumers of sweetened beverages may have an increased risk of liver cancer, and liver cancer risk factors, due to circadian rhythm disruption [25, 27–30].

Why increased AS soda consumption would be related to liver cancer among persons with diabetes isn't clear. Animal studies have indicated ASs such as aspartame, sucralose and saccharin may be linked to cancer [31, 32]. However epidemiological studies have not been able to substantiate these hypotheses for some sweeteners (aspartame) and have conflicting results for other sweeteners [23, 33]. Studies have reported that AS soda consumption is related to increased abdominal obesity [34], which has been associated with an increased risk of liver cancer [35]. In addition, studies have reported that ASs can alter the composition of the gut microbiota, which could directly affect hepatic health via the portal vein communication [36].

Among the persons without diabetes, orange/grapefruit juice consumption was associated with reduced liver cancer risk in the earlier follow-up interval. Animal studies provide some support for such a relationship as rodent models have reported a relationship between alpha-carotene and reduced liver cancer development [37, 38]. Prior human studies that examined juice consumption have not reported any associations with liver cancer, but the studies have not conducted their analysis by juice type [12, 13]. An alternative explanation for the association is that orange juice consumption served as a marker of an overall healthier diet, or a marker of breakfast consumption [39]. While orange juice is naturally high in sugar, most individuals consume only small amounts and generally only consume it with breakfast [39]. As eating breakfast may be correlated with a healthier diet or healthier lifestyle, consumption of orange/grapefruit may simply be a proxy variable.

A major strength of the current study is that the results were based on pooling data from two large prospective studies which resulted in a large sample size. Both cohorts had been in follow-up for a sufficiently long period of time that a sizeable number of liver cancer

cases had developed and the exposure variables from the food frequency questionnaires were calculated in the same manner in both cohorts. In addition to these strengths, the current study also had several limitations. The analyses were based on sweetened beverage consumption at one time point as no information on consumption either before or after that time point was available. In addition, there was no information on the volume of each beverage consumed and, for some tea and coffee variables, frequency of consumption could not be easily harmonized between the two studies and so these variables could not be included. In addition, diabetes was self-reported, there was no distinction between type 1 and type 2 diabetes, and date of diagnosis was not collected. As the vast majority of diabetes in U.S. adults is type 2 diabetes (90–95%), the inability to distinguish between type 1 and type 2 is unlikely to have introduced major bias. Finally, the study did not have information on HBV or HCV status and therefore adjustments could not be made for these risk factors. However, HBV and HCV are unlikely to be confounders in the current analysis as there is little evidence that they are associated with sweetened beverage consumption.

In summary, our large U.S. based study suggests that development of liver cancer may be associated with consumption of SS soda among persons without diabetes, and AS soda among persons with diabetes. Further examinations of the relationships in other populations are warranted as beverage consumption is a modifiable factor which could have health benefits beyond a reduction in risk of liver cancer.

Financial Support:

National Cancer Institute Intramural Research Program

Abbreviations:

SSB	sweetened beverages

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Highlights

- Sugar sweetened soda is associated with increased liver cancer risk among persons without diabetes.
- Artificially sweetened soda is associated with increased liver cancer risk among persons with diabetes.
- The risk of liver cancer was evident in the first 12 years of follow-up.

Table 1.

Demographic characteristics of the NIH-AARP Diet and Health Study and the PLCO study participants

	Persons without diabetes		Persons with diabetes	
	Non-case	**Liver Cancer**	**Non-case**	**Liver Cancer**
N	505,550	839	47,264	221
Person-Years	6,710,651	7672	546,416	1,963
Age at baseline, (IQR)	62.4 (8.8)	64.0 (7.6)	63.7 (8.2)	64.1 (7.0)
Total energy intake, (IQR)	1618.9 (830.7)	1709.8 (916.3)	1606.1 (856.5)	1659.2 (857.3)
Sex, (%)				
Male	278,667 (55.1)	607 (72.3)	30,505 (64.5)	175 (79.2)
Female	226,883 (44.9)	232 (27.7)	16,759 (35.5)	46 (20.8)
Race/Ethnicity, (%)				
Non-Hispanic White	464,259 (93.1)	729 (88.2)	40,476 (87.4)	184 (84.0)
Non-Hispanic Black	16,798 (3.4)	35 (4.2)	3,443 (7.4)	6 (2.7)
Hispanic	8,557 (1.7)	24 (2.9)	1,316 (2.8)	21 (9.6)
Asian /Pacific Islander	9,131 (1.8)	39 (4.7)	1,096 (2.4)	8 (3.7)
Ever smoke, (%)				
No	194,058 (39.6)	243 (30.0)	15,468 (33.9)	68 (31.5)
Yes	295,840 (60.4)	566 (70.0)	30,185 (66.1)	148 (69.5)
Alcohol use, (%)				
No	116,436 (23.1)	245 (29.4)	20,404 (43.3)	89 (40.3)
Yes	387,125 (76.9)	589 (70.6)	26,669 (56.7)	132 (59.7)
Body mass index, (%)				
Underweight/Normal	185,545 (37.5)	221 (27.2)	8,470 (18.4)	37 (17.2)
Overweight	211,042 (42.7)	346 (42.5)	18,460 (40.1)	91 (42.3)
Obese	98,178 (19.8)	246 (30.3)	19,090 (41.5)	87 (40.5)

*Columns do not sum to total because of missing data

Table 2.

Frequency of sweetened beverage consumption among study participants by diabetes status

	Persons without diabetes				
			times per day		
	0	Any	<1	1–2	>2
Sweetened Beverages					
All	45076 (9%)	461313 (91%)	339261 (67%)	62565 (12%)	59487 (12%)
Sugar sweetened	217503 (43%)	288886 (57%)	244897 (48%)	25480 (5%)	18509 (4%)
Artificially sweetened	254282 (50%)	252107 (50%)	174603 (35%)	36823 (7%)	40681 (8%)
Soda					
All	58383 (11%)	448006 (88%)	339390 (67%)	54825 (11%)	53791 (11%)
Sugar sweetened	284059 (56%)	222330 (44%)	186705 (37%)	20366 (4%)	15259 (3%)
Artificially sweetened	266376 (53%)	240013 (47%)	167672 (33%)	34387 (7%)	37954 (7%)
Fruit Punch					
All	288007 (56%)	225582 (45%)	211395 (42%)	7284(1%)	6903 (1%)
Sugar sweetened	332639 (66%)	173750 (34%)	165762 (32%)	4556 (1%)	3432 (1%)
Artificially sweetened	442693 (87%)	63696 (13%)	57757 (11%)	2642 (1%)	3297 (1%)
Juices					
Orange/Grapefruit	42826 (8%)	463563 (92%)	333483 (66%)	114378 (23%)	15702 (3%)
Tomato/Vegetable	158053 (31%)	348336 (69%)	339971 (67%)	6970 (1%)	1395 (1%)
Other	127494 (25%)	378895 (75%)	347818 (69%)	23531 (5%)	7546 (1%)
	Persons with diabetes				
			times per day		
	0	**Any**	**<1**	**1–2**	**>2**
Sweetened Beverages					
All	3382 (7%)	44103 (93%)	24850 (52%)	7169 (15%)	12084 (26%)
Sugar sweetened	35017 (74%)	12468 (26%)	10786 (22%)	823 (2%)	859 (2%)
Artificially sweetened	8947 (19%)	38538 (81%)	20886 (44%)	6336 (13%)	11316 (24%)
Soda					
All	4325 (9%)	43160 (91%)	25779 (54%)	6291 (13%)	11090 (24%)
Sugar sweetened	41114 (87%)	6371 (13%)	5333 (11%)	527 (1%)	511 (1%)
Artificially sweetened	9970 (21%)	37515 (79%)	21192 (45%)	5793 (12%)	10530 (22%)
Fruit Punch					
All	28509 (60%)	18976 (40%)	16527 (35%)	913(2%)	1536(3%)
Sugar sweetened	38609 (81%)	8876 (19%)	8213 (17%)	305 (1%)	358 (1%)
Artificially sweetened	36424 (77%)	11061 (23%)	9283 (20%)	628 (1%)	1150 (2%)
Juices					
Orange/Grapefruit	6375 (13%)	41110 (87%)	30351 (64%)	9322 (20%)	1437 (3%)
Tomato/Vegetable	16186 (34%)	31299 (66%)	30165 (63%)	949 (2%)	185 (1%)
Other	16683 (35%)	30802 (65%)	28801(61%)	1510 (3%)	491 (1%)

Table 3.

Hazard ratios for associations of beverage consumption and risk of liver cancer among persons without diabetes

		≤12 years of follow-up		12+ years of follow-up	
		cases	**non-cases**	**cases**	**non-cases**
		587	**5,05,802**	**252**	**3,59,702**
		HR	**95%CI**	**HR**	**95%CI**
Sweetened beverages					
	All	1.05	(0.97, 1.14)	0.92	(0.79, 1.06)
	Regular	1.12	(0.99, 1.28)	0.80	(0.61, 1.05)
	Diet	1.01	(0.92, 1.11)	0.99	(0.86, 1.15)
Soda					
	All	1.07	(0.98, 1.17)	0.92	(0.79, 1.08)
	Regular	1.18	(1.03, 1.35)	0.84	(0.62, 1.13)
	Diet	1.00	(0.90, 1.11)	0.98	(0.83, 1.15)
Fruit punch					
	All	0.98	(0.78, 1.24)	0.88	(0.59, 1.31)
	Regular	0.89	(0.62, 1.29)	0.60	(0.29, 1.27)
	Diet	1.06	(0.80, 1.41)	1.11	(0.74. 1.65)
Juices					
	Orange/Grapefruit	0.77	(0.65, 0.92)	1.02	(0.82, 1.27)
	Tomato/Vegetable	1.19	(0.89. 1.59)	1.01	(0.58, 1.77)
	Other	0.94	(0.74, 1.18)	1.13	(0.85. 1.50)

*Beverages was defined as a continuous variable (times/day)

**Adjusted for age at baseline, sex, race/ethnicity, body mass index, smoking, alcohol use, study, total energy intake (kcal/day)

Table 4.

Hazard ratios for association of beverage consumption and risk of liver cancer among persons with diabetes

	≤12 years of follow-up		12+ years of follow-up	
	cases	**non-cases**	**cases**	**non-cases**
	158	**47,327**	**63**	**26,664**
	HR	**95%CI**	**HR**	**95%CI**
Sweetened beverages				
All	1.12	(1.01, 1.24)	0.77	(0.59, 1.00)
Sugar sweetened	0.90	(0.56, 1.44)	0.43	(0.11, 1.76)
Artificially sweetened	1.13	(1.02, 1.25)	0.82	(0.64, 1.05)
Soda				
All	1.13	(1.00, 1.26)	0.75	(0.56, 1.00)
Sugar sweetened	0.90	(0.47, 1.70)	0.61	(0.15, 2.45)
Artificially sweetened	1.13	(1.01, 1.27)	0.78	(0.59, 1.03)
Fruit punch				
All	1.13	(0.89, 1.43)	0.87	(0.48, 1.55)
Sugar sweetened	0.90	(0.43, 1.88)	0.04	(0.00, 11.47)
Artificially sweetened	1.17	(0.92, 1.48)	1.01	(0.61. 1.69)
Juices				
Orange/Grapefruit	1.21	(0.99, 1.49)	0.89	(0.54, 1.46)
Tomato/Vegetable	0.92	(0.47. 1.78)	0.72	(0.19, 2.75)
Other	0.95	(0.56, 1.61)	1.23	(0.69, 2.20)

*Beverages was defined as a continuous variable (times/day)

**Adjusted for age at baseline, sex, race/ethnicity, body mass index, smoking, alcohol use, study, total energy intake (kcal/day)