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Association of sugary beverages with survival among patients with cancers of the upper aerodigestive tract

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Abstract

Purpose—The role of consumption of added sugars in cancers of the upper aerodigestive tract (UADT) is unclear. We examined associations between sugary beverages and susceptibility to UADT cancer as well as overall survival among UADT cancer patients.

Methods—The association between dietary added sugar and susceptibility to UADT cancers or overall survival among 601 UADT cancer cases was evaluated using data from a population-based case–control study conducted in Los Angeles County. Unconditional logistic regression was used to estimate odds ratios and 95 % confidence intervals (CI) for cancer susceptibility, and Cox regression was used to estimate hazards ratios (HRs) with 95 % CIs for survival, adjusting for relevant confounders.

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Compliance with ethical standards

Conflict of interest The authors do not have any financial or other conflicts of interest to disclose.

Informed consent Informed consent was obtained from all individual participants included in the study.

Research involving human subjects All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results—A total of 248 deaths were observed during follow-up (median 12.1 years). A positive association was observed with consumption of grams of sugar from beverages, including soft drinks and fruit juices, and poorer survival among UADT cancer cases (aHR, Q4 vs. Q1:1.88; 95 % CI 1.29, 2.72; *p* for trend = 0.002), as well as servings of sugary beverages (aHR, Q4 vs. Q1: 95 % CI 1.97, 95 % CI 1.32–2.93). This was due largely to consumption of sugars from soft drinks. Particularly, high consumption of sugary beverages was associated with poorer survival among esophageal cancer cases, driven by squamous cancers. No association was observed between sugary beverages and cancer susceptibility.

Conclusion—These findings suggest that consumption of sugary beverages may decrease survival associated with UADT cancers. Additional studies should be conducted to examine survival among cancer patients consuming high amounts of added or refined sugars. Such studies may highlight prognostic factors for UADT cancers.

Keywords

Sugary beverages; Head and neck cancers; Cox regression; Survival; Case; control

Introduction

Dietary and lifestyle factors play an important role in cancers of the head and neck. Tobacco smoking, alcohol drinking, and red or processed meat may increase risk or progression, while other factors such as high consumption of fruit and vegetables may reduce risk [1–3]. However, the identification of additional etiologic and preventive factors is necessary. It has been suggested that dietary sugars play a role in the development and progression of chronic disease. Of particular relevance is high-fructose corn syrup, commonly added to processed foods and sweetened beverages, consumption of which has increased dramatically since 1950 [4]. Sugar-sweetened beverages and desserts contain concentrated fructose without the vitamins, micronutrients, and fiber found in fruits and vegetables [5], whereby cell integrity is preserved in a fiber-rich matrix, slowing the rate of sugar absorption. Dietary added sugar and high-fructose corn syrup have been strongly correlated with metabolic syndrome [6–8], which is characterized by increased triglycerides, LDL cholesterol, blood pressure, and uric acid [9]. It appears that dietary added sugars might trigger chronic inflammation, promoting these disease conditions.

There are not many reports on the association between intake of dietary added sugar and cancer. There is some evidence of a role for sweet foods and beverages in breast cancer risk [10], and a recent study demonstrated that increased glucose uptake initiates oncogenic signaling pathways for breast cancer promotion [11]. Additionally, a possible association with pancreatic cancer risk has been observed in prospective studies [12–14], particularly with consumption of sodas or soft drinks, and associations have been reported in case–control studies [15–17]. Interestingly, fructose was shown to induce proliferation of pancreatic cancer cells in vitro [18]. This occurred through fructose-mediated induction of transketolase, an enzymatic regulator of the pentose phosphate pathway. Hence, high fructose and sucrose intake may play an important role in oncogenesis [19].

There is clearly a need to elucidate the role of added sugars in other cancers. We analyzed the association between sugars from beverages and incidence of various cancers of the upper aerodigestive tract (UADT) as well as overall survival among cancer cases in a population-based case–control study of residents of Los Angeles County.

Methods

Study population

The UCLA Cancer Study was a population-based case–control study of lung and UADT cancers diagnosed among residents ages 18–65 of Los Angeles County [20]. The study was conducted between 1999 and 2004. UADT cancer cases, including oral, pharyngeal, laryngeal, and esophageal cancers, were identified through the rapid ascertainment system of the Cancer Surveillance Program (CSP) for Los Angeles County. Cases were contacted by mail and asked to participate, after notifying the physician of record. There were 601 UADT cancer cases including 338 oropharyngeal cancers, 90 laryngeal cancers, 108 esophageal cancers, and 48 nasopharyngeal cancers. There were a total of 497 squamous cancers, 74 adenocarcinomas (all of esophageal origin), and 30 cases of a distinct pathology. Vital status was obtained through the social security death index. Histology and anatomic site were determined using the International Classification of Disease-Oncology (ICD-O) recommendations. For the majority of cases (89 %), interviews were conducted within 6 months post-diagnosis. Controls were free of lung and UADT cancers and identified from a census within the neighborhood of cases. A total of 1,040 controls were recruited. Trained interviewers administered standardized questionnaires collecting information on demographics, diet history, behavioral, and other risk factors such as tobacco smoking, alcohol drinking, family history, physical activity, and occupational and environmental exposures.

Estimation of sugar consumption

Participants were asked about frequency of consumption for a specified serving size over the past year in the food section of the questionnaire. The food frequency questionnaire (FFQ), described previously [21], was based on the National Cancer Institute's "Brief Block FFQ" [22], and inquired about diet history over the last 12 months, corresponding to the year prior to interview, and was expanded to include additional fruit and vegetable items. Intake of sugars from beverages was assessed from the "beverages" and "fruits" sections of the questionnaire. Two categories of sugary beverages were considered to capture the sugars present in these drinks: SB1, representing the sum in grams of sugars from soft drinks and fruit juices, and SB2, representing the sum in grams of sugars from soft drinks, fruit juices, and sugar added to tea, coffee, or cereal. Participant responses for consumption frequency were used to obtain a composite value of grams of sugar per day for each item, which was calculated using the United States Department of Agriculture National Nutrient Database for Standard Reference (http://ndb.nal.usda.gov/).

Statistical analyses

Dietary intake of sugars was analyzed using the high/low values, separated by the median, or quartile distribution representing sugar consumption in grams per day among cases (for

analysis of survival)—SB1 cut points, (Q1) 0.71, (Q2) 11.81, (Q3) 40.00, SB2 cut points, (Q1) 3.04, (Q2) 20.76, (Q3) 45.29— or among controls (for analysis of UADT cancer susceptibility): SB1 cut points, (Q1) 0.71, (Q2) 9.11, (Q3) 26.97, SB2 cut points, (Q1) 2.67, (Q2) 14.83, (Q3) 36.18. Additionally, regression was performed after separation according to the median consumption of sugars from soft drinks or fruit juices (separately) among cases—soft drinks: 4.0, fruit juices: 0.71. For analysis of cancer incidence or 5-year survival, logistic regression was used to obtain adjusted odds ratios (aOR) and 95 % confidence intervals (CIs). For survival analysis, Cox proportional hazards regression was used to obtain adjusted hazard ratios (aHR) and corresponding 95 % CIs. Time to death was calculated as the interval between the date of diagnosis and the date of death or last follow-up, 10 October 2013. The median follow-up time was 12.1 years for all cancer cases. Models included potential confounding factors such as age, gender (male or female), ethnicity (non-Hispanic White, Hispanic, African American, Asian/Pacific Islander, and other), education (continuous), smoking (pack-years), alcohol drinking (drinks per day), caloric intake (continuous), pathology type (squamous, adenocarcinoma or other), and tumor differentiation grade (well differentiated, poorly differentiated, undetermined). Additional variables such as body mass index, and fruit and vegetable intake were examined but found to be non-influential on results and therefore not included. Missing caloric intake data were imputed using the SAS Proc MI procedure with the default Markov chain Monte Carlo (MCMC) algorithm to generate five imputed datasets and using SAS Proc MIANALYZE procedure to combine the results. The imputation included a total of eight covariates: saturated fat, total dietary fat, daily caloric intake, body mass index, education, gender, cancer diagnosis, and age.

Results

Demographic and clinical characteristics of UADT cancer cases and controls are shown in Table 1. The majority of cases and controls were male −75.5 and 59.9 %, respectively. More cases were smokers—an average of 22.5 pack-years compared to 9.3 pack-years among controls. Cases consumed an average of 2.54 alcoholic drinks per day, and controls consumed an average of one alcoholic beverage per day. Examination of intake of sugars from sugary beverages revealed soft drinks to be the prominent source of sugars, with a mean consumption of 23.9 g per day for cases and 17.2 g per day for controls. The majority of UADT cancers were squamous and well-differentiated. Out of 601 UADT cancer cases, there were 248 deaths (41 %) over the follow-up period.

Odds ratios for the association between intake of sugars from beverages and susceptibility to UADT cancers are shown in Table 2. No associations with UADT cancer were detected when considering either sugars from soft drinks and fruit juices (SB1), or soft drinks, fruit juices, and sugars added to tea, coffee or cereal (SB2). However, higher intake in grams of sugar from soft drinks and fruit juices was associated with poorer survival among UADT cancer cases in all upper quartiles (aHR, Q2 vs. Q1: 1.67, 95 % CI 1.13–2.45; aHR, Q3 vs. Q1: 1.83, 95 % CI 1.20–2.79; aHR, Q4 vs. Q1: 1.88, 95 % CI 1.29–2.72), and this was associated with a strong dose–response trend ($p = 0.002$) (Table 3). Higher intake of sugars from all sugary drinks, including sugar added to tea, coffee, or cereal, was weakly associated with poorer survival in the upper third and fourth quartiles, and this was associated with a

linear trend ($p = 0.02$). Interestingly, a dose–response correlation between sugary beverages (soft drinks and fruit juices) and mortality 5 years post-diagnosis was also observed ($p = 0.007$) (Table 1, Supplementary). Next, we examined the association between daily servings of sugary beverages and overall survival among UADT cancer cases (Table 4). Higher daily consumption of fruit juices and soft drinks was associated with poorer survival, (aHR, Q2 vs. Q1: 1.80, 95 % CI 1.23–2.65; aHR, Q3 vs. Q1: 1.74, 95 % CI 1.14–2.66; aHR, Q4 vs. Q1: 1.97, 95 % CI 1.32–2.93). A strong linear trend was noted again ($p = 0.003$). This association was not observed when considering all sugary beverages, including sugars added to tea, coffee, or cereal. The associations between consumption of sugary beverages and overall survival among UADT cancer cases persisted when a complete case analysis considering only cases with complete caloric intake data was performed (Table 2, Supplementary).

Table 5 presents hazard ratios for the association between high sugar consumption and survival according to UADT cancer subtypes. High intake of sugars from soft drinks was associated with poorer survival among all UADT cancer cases (aHR: 1.79, 95 % CI 1.37–2.34), oropharyngeal cancers (aHR: 1.65, 95 % CI 1.13–2.39), esophageal cancers (aHR: 2.29, 95 % CI 1.32–3.93), and squamous cancers excluding esophageal cases (aHR: 1.65, 95 % CI 1.20–2.26). When considering all squamous cancers including esophageal, associations of sugary beverages with survival were more pronounced (data not shown). We found sugars from fruit juices to be weakly associated with poorer survival among UADT cancer cases, but inversely associated with reduced survival among oropharyngeal cancer cases (aHR: 0.70, 5 % CI 0.48–1.01). The composite exposures, SB1 and SB2, revealed positive associations with poorer survival for UADT cancer cases overall (aHR: 1.44, 95 % CI 1.10–1.88, and aHR: 1.40, 95 % CI 1.07–1.82, respectively). Specifically, there was an observed association with poorer survival among esophageal cancer cases (SB1, aHR: 2.58, 95 % CI 1.45–4.60; SB2, aHR: 1.94, 95 % CI 1.06–3.53), driven largely by squamous cases, wherein a statistical association was noted when analyzed separately (data not shown). Lastly, we examined the association of consumption of sugars from beverages with overall survival among UADT cancer cases after stratification according to gender (Table 6). The associations of sugary beverages with survival were more pronounced in males (SB1, aHR: 1.26, 95 % CI 0.94–1.70 and SB2, aHR: 1.38, 95 % CI 1.03–1.87), but there was no statistical interaction.

Discussion

Although there is some evidence of the detrimental role of dietary added sugar in chronic disease, such an association has not been well studied in cancer. We sought to analyze the role of sugars from beverages including soft drinks and fruit juices in susceptibility to UADT cancers and overall survival among cancer cases to help elucidate dietary exposures associated with etiology or prognosis. Recently, we reported an association between consumption of red and processed meat and poorer survival among UADT cancer patients [3]. In the current study, we report that high intake of sugars from beverages is associated with poorer survival among UADT cancer cases, notably those with oropharyngeal and esophageal cancers. This association of sugary beverages with survival among such patients has not been reported previously.

In our study, soft drinks represented the main source of sugar from beverages as expected, and consumption of sugars from soft drinks was associated most strongly with survival. Although juices derived solely from fruit may be more beneficial than artificially sweetened beverages or soft drinks, they may contain a high concentration of sugar in the absence of buffering by fiber and phytonutrients that are present in whole fruit. However, in the present study, sugars from fruit juices showed only a weak association with poorer survival among UADT cancer cases overall, and a weak inverse association with poorer survival among oropharyngeal cancer cases, contrary to soft drinks. This highlights soft drinks as potentially the most potent source of sugars from beverages. Estimates generated from comparisons based on the median split were greatest when considering sugary beverages including soft drinks and fruit juices as compared to sugars from all beverages including sugar added to tea, coffee, or cereal. It is unclear why the inclusion of these added sugars in general did not contribute to increased risk. It could be due to the potentially beneficial effect of polyphenols and other bioactive components in these beverages [23, 24]. Associations with poorer survival were noted among esophageal cancer cases for each exposure of sugary beverages examined. However, esophageal cancers are not exclusively responsible for the observed association with survival among UADT cancer cases, as squamous cancers not including esophageal cases also revealed an association with survival, particularly for soft drinks. In our analyses, we did not observe an association of sugary beverages with cancer susceptibility. Such an association has been reported in previous studies of pancreatic cancer risk [12, 14]. Additionally, consumption of sweets including dessert foods, sweet beverages, and added sugars, but particularly desserts, was found to be positively associated with breast cancer risk [10].

Fruit and vegetables have been reported to lower the risk of UADT cancers. In fact, each portion consumed may reduce risk of oral cancer by 50 % [25, 26]. When included in models (servings per day) examining the association between sugary beverages and survival, there was no appreciable change in estimates (not shown). However, in our study, fruit consumption was very low among participants, with a median of only one serving per day. It may be relevant to consider servings of fruit and vegetables in additional studies of larger sample size with a broader range of consumption.

The mechanism whereby sugar promotes disease progression could be predominantly through increased inflammation. Although not completely clear, this is potentially induced by oxidative stress, which ultimately induces DNA damage and upregulation of interleukin cytokines and other pro-inflammatory molecules. Uric acid may be an important player in sugar-mediated inflammation, which is increased upon depletion of ATP during metabolization of fructose, leading to elevated levels of interleukin and other inflammatory cytokines [7, 27].

Our study is limited by small numbers of deaths, consequently limiting the ability to detect interactions with potential confounding factors, and stronger associations among cancer subtypes. Additionally, the possibility of misclassification of sugary beverages or added sugars cannot be ignored and could introduce bias in estimates, along with residual bias due to unmeasured or mismeasured confounders, such as information on human papilloma virus status among other factors, which could partially explain the absence of an observed

association of sugary beverages with UADT cancer susceptibility. Furthermore, the dietary history and reported consumption of sugary beverages reflected by the questionnaire does not necessarily reflect actual diet during follow-up, and our findings must be interpreted in light of this fact. Lastly, the possibility of selection bias due to loss of eligible UADT cancers in the initial study [20] as a result of early death, sickness or hospitalization precluding interviewing, or refusal to participate for other reasons cannot be disregarded.

In conclusion, consumption of sugar-rich beverages may have an unfavorable effect on survival among individuals with UADT cancers. To our knowledge, this study is the first to report an association between dietary added sugar and prognosis of UADT cancers. These associations should be examined further in studies of larger sample size. Additional studies shedding light on the role of sugar and other potential pro-inflammatory dietary factors in the etiology and prognosis of cancers of the UADT are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline demographic, health, and lifestyle characteristics among UADT cancer cases and controls

Characteristic	UADT cases (*n* = 601)	Controls (*n* = 1,040)
Gender, no. (%)		
Male	454 (75.5)	623 (59.9)
Female	147 (24.5)	417 (40.1)
Age, mean (SD)	50.38 (7.6)	49.9 (7.3)
Ethnicity, no. (%)		
White/Caucasian	341 (56.1)	634 (61.0)
Mexican/Latino	109 (17.9)	204 (19.6)
Black/African American	69 (11.4)	102 (9.8)
Asian/Pacific Islander	64 (10.5)	62 (6.0)
Native American	16 (2.6)	37 (3.6)
Education, mean (SD)	13.14 (3.7)	14.4 (3.6)
Education, no. (%)		
0–12	273 (45.4)	300 (28.9)
13–16	259 (43.1)	481 (46.3)
>16	69 (11.5)	258 (24.8)
Smoking		
Pack-years, mean (SD)	22.5 (24.4)	9.3 (15.7)
0	182 (30.2)	491 (47.3)
<20	145 (24.1)	353 (34.0)
20–40	146 (24.3)	132 (12.7)
≥40	128 (21.3)	63 (6.1)
BMI (kg/m^2), no. (%)		
<25	242 (40.4)	386 (37.2)
≥25	357 (59.6)	652 (62.8)
Alcoholic drinks/day, mean (SD)	2.54 (4.6)	1.0 (2.0)
Alcohol drinking, no. (%)		
Yes	482 (79.3)	776 (74.6)
No	117 (19.2)	264 (25.4)
Sugar from beverages (g/day)		
Soft drinks, mean (SD)	23.9 (43.6)	17.2 (34.5)
Fruit juice, mean (SD)	6.1 (13.2)	5.6 (9.0)
Sugar added to tea/coffee, mean (SD)	6.1 (17.6)	4.1 (9.3)
Total calories/day, mean (SD)	1,784.0 (1,011.1)	1,478.7 (628.4)
Histology		
Squamous	497 (82.7)	N/A
Adenocarcinoma	74 (12.3)	N/A
Other	30 (5.0)	N/A
Tumor grade		
Well differentiated	399 (65.6)	N/A

Characteristic	UADT cases (*n* = 601)	Controls (*n* = 1,040)
Poorly differentiated	121 (19.9)	N/A
Undetermined[a]	81 (13.3)	N/A
Deaths, no. (%)	248 (41.3)	N/A

[a] Not graded because of prior hormone therapy

Table 2

Odds ratios for UADT cancers according to intake of sugars from beverages

	SB1[a]			SB2[b]		
	Cases/controls	**aOR (95 % CI)**	***p*[c]**	**Cases/controls**	**aOR (95 % CI)**	***p*[c]**
Q1	155/273	1.0		136/263	1.0	
Q2	109/227	0.97(0.79–1.20)		123/253	0.99 (0.81–1.21)	
Q3	128/279	0.94 (0.77–1.14)		130/257	0.98 (0.80–1.19)	
Q4	198/251	1.01 (0.83–1.23)	0.67	201/257	0.96 (0.78–1.17)	0.54

[a] SB1, Sugars from soft drinks and fruit juices (g/day)

[b] SB2, Sugars from soft drinks, fruit juices, and sugar added to tea, coffee or cereal (g/day)

[c] *p* value for trend

Table 3

Hazard ratios for survival among UADT cancer cases according to grams of sugar consumed from beverages

	SB1[a]			SB2[b]		
	Dead/all	**aHR (95 % CI)**	***p*[c]**	**Dead/all**	**aHR (95 % CI)**	***p*[c]**
Q1	48/155	1.0		50/139	1.0	
Q2	60/141	1.67 (1.13–2.45)		52/157	0.93 (0.62–1.39)	
Q3	47/122	1.83 (1.20–2.79)		66/148	1.37 (0.94–2.01)	
Q4	85/171	1.88 (1.29–2.72)	0.002	72/145	1.41 (0.96–2.08)	0.02

[a] SB1, Sugars from soft drinks and fruit juices (g/day)

[b] SB2, Sugars from soft drinks, fruit juices, and sugar added to tea, coffee, or cereal (g/day)

[c] *p* value for trend

Table 4

Hazard ratios for survival among UADT cancer cases according to daily servings of sugary beverages

	SB1[a]			SB2[b]		
	Dead/all	**aHR (95 % CI)**	***p*[c]**	**Dead/all**	**aHR (95 % CI)**	***p*[c]**
Q1	43/141	1.0		54/137	1.0	
Q2	76/178	1.80 (1.23–2.65)		41/130	0.82 (0.54–1.23)	
Q3	50/124	1.74 (1.14–2.66)		68/170	1.04 (0.71–1.52)	
Q4	71/146	1.97 (1.32–2.93)	0.003	77/152	1.31 (0.90–1.90)	0.08

[a] SB1, Servings of soft drinks and fruit juices

[b] SB2, Servings of soft drinks, fruit juices, and sugar added to tea, coffee or cereal

[c] *p* value for trend

Table 5

Hazard ratios for survival according to intake of sugars from beverages stratified by cancer subtype and anatomic site

	Soft drinks		Fruit juices		SB1[a]		SB2[b]	
	Dead/all	**aHR (95 % CI)**	**Dead/all**	**aHR (95 % CI)**	**Dead/all**	**aHR (95 % CI)**	**Dead/all**	**aHR (95 % CI)**
UADT								
Lower median	94/293	1.0	119/292	1.0	108/296	1.0	107/303	1.0
Upper median	151/303	1.79 (1.37–2.34)	126/304	1.15 (0.89–1.49)	132/293	1.44 (1.10–1.88)	138/293	1.40 (1.07–1.82)
Oropharyngeal								
Lower median	50/166	1.0	69/161	1.0	62/168	1.0	57/170	1.0
Upper median	76/170	1.65 (1.13–2.39)	57/175	0.70 (0.48–1.01)	64/168	1.0 (0.69–1.44)	69/166	1.16 (0.81–1.66)
Laryngeal								
Lower median	13/45	1.0	16/50	1.0	15/46	1.0	12/45	1.0
Upper median	19/44	1.45 (0.65–3.25)	16/39	1.36 (0.58–3.17)	17/43	1.05 (0.47–2.36)	20/44	1.71 (0.71–4.10)
Esophageal								
Lower median	25/55	1.0	24/53	1.0	23/53	1.0	27/53	1.0
Upper median	38/53	2.29 (1.32–3.93)	39/55	2.39 (1.34–4.30)	40/55	2.58 (1.45–4.60)	36/55	1.94 (1.06–3.53)
Nasopharyngeal								
Lower median	4/22	1.0	7/21	1.0	3/23	1.0	4/24	1.0
Upper median	12/25	2.15 (0.47–9.83)	9/26	1.43 (0.32–6.35)	13/24	3.38 (0.79–14.47)	12/23	1.32 (0.31–5.67)
Squamous[c]								
Lower median	66/224	1.0	90/225	1.0	81/229	1.0	72/229	1.0
Upper median	107/237	1.65 (1.20–2.26)	83/236	0.93 (0.68–1.26)	92/232	1.12 (0.82–1.53)	101/232	1.36 (0.99–1.86)
Adenocarcinoma[d]								
Lower median	18/38	1.0	17/37	1.0	17/36	1.0	16/36	1.0
Upper median	24/36	1.84 (0.92–3.68)	25/37	1.60 (0.79–3.25)	25/38	1.51 (0.72–3.16)	23/38	1.44 (0.57–3.62)

[a] SB1, Sugars from soft drinks and fruit juices (g/day)

[b] SB2, Sugars from soft drinks, fruit juices, and sugar added to tea, coffee or cereal (g/day)

[c] Does not include esophageal cancers

[d] Esophageal cancers only

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Table 6

Hazard ratios for survival among UADT cancer cases according to consumption of sugars from beverages stratified by gender

	SB1[a]					SB2[b]				
	Lower median		Upper median			Lower median		Upper median		
	Dead/all	HR	Dead/all	aHR (95 % CI)	p^c	Dead/all	HR	Dead/all	aHR (95 % CI)	p^c
Gender										
Men	94/238	1.0	95/212	1.26 (0.94–1.70)	0.69	83/227	1.0	106/223	1.38 (1.03–1.87)	1.0
Women	25/71	1.0	31/75	1.17 (0.64–2.14)		24/74	1.0	32/72	1.43 (0.79–2.59)	

[a] SB1, Sugars from soft drinks and fruit juices (g/day)

[b] SB2, Sugars from soft drinks, fruit juices, and sugar added to tea, coffee, or cereal (g/day)

[c] *p* value for heterogeneity test