Soft Drink and Juice Consumption and Renal Cell Carcinoma Incidence and Mortality in the European Prospective Investigation into Cancer and Nutrition

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ABSTRACT

Background: Renal cell carcinoma (RCC) accounts for more than 80% of kidney cancers in adults, and obesity is a known risk factor. Regular consumption of sweetened beverages has been linked to obesity and several chronic diseases, including some types of cancer. It is uncertain whether soft drink and juice consumption is associated with risk of RCC. We investigated the associations of soft drink and juice consumption with RCC incidence and mortality in the European Prospective Investigation into Cancer and Nutrition (EPIC).

Methods: A total of 389,220 EPIC participants with median age of 52 years at recruitment (1991–2000) were included. Cox regression yielded adjusted HRs and 95% confidence intervals (CI) for RCC incidence and mortality in relation to intakes of juices and total, sugar-sweetened, and artificially sweetened soft drinks.

Results: A total of 888 incident RCCs and 356 RCC deaths were identified. In models including adjustment for body mass index and energy intake, there was no higher risk of incident RCC associated with consumption of juices (HR per 100 g/day increment = 1.03; 95% CI, 0.97–1.09), total soft drinks (HR = 1.01; 95% CI, 0.98–1.05), sugar-sweetened soft drinks (HR = 0.99; 95% CI, 0.94–1.05), or artificially sweetened soft drinks (HR = 1.02; 95% CI, 0.96–1.08). In these fully adjusted models, none of the beverages was associated with RCC mortality (HR, 95% CI per 100 g/day increment 1.06, 0.97–1.16; 1.03, 0.98–1.09; 0.97, 0.89–1.07; and 1.06, 0.99–1.14, respectively).

Conclusions: Consumption of juices or soft drinks was not associated with RCC incidence or mortality after adjusting for obesity.

Impact: Soft drink and juice intakes are unlikely to play an independent role in RCC development or mortality.

Introduction

Consumption of sweet beverages such as soft drinks and juices has been rising worldwide (1). These beverages contribute to adiposity (1, 2) and contain additives and chemical contaminants from food packaging that might have carcinogenic properties (3). Sweetened beverage consumption has been suggested to be associated with the incidence of obesity-related cancers such as kidney cancer, but results from

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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epidemiological studies are inconclusive (4–6), and kidney cancer mortality remains unexplored.

We investigated soft drink and juice consumption in relation to renal cell carcinoma (RCC) incidence and mortality in the European Prospective Investigation into Cancer and Nutrition (EPIC).

Materials and Methods

Participants

EPIC is a prospective cohort study of >520,000 participants aged 30–70 years, recruited between 1991 and 2000 in 10 European countries. At recruitment, data on diet, lifestyle, medical history, anthropometric measurements, and blood samples were collected (7). All participants provided written informed consent and the study was approved by the ethics committees of the International Agency for Research on Cancer (IARC) and each participating center.

Soft drink and juice consumption

Baseline soft drink and juice consumption was mostly assessed by diet questionnaires covering the past year (7). Total soft drinks combined carbonated/soft/isotonic drinks and diluted syrups, and was subdivided into sugar-sweetened and artificially sweetened soft drinks. Types of soft drinks were unmeasured in Italy, Spain, and Umeå (Sweden), and these centers were excluded from this part of the analyses. Juices comprised fruit and vegetable juices and nectars.

Ascertainment of cases

Cancer cases and deaths were ascertained through linkage to population registries or active follow-up, depending on the study center. RCC was defined as ICD-10 C64. Participants were followed from recruitment until date of first invasive cancer diagnosis (for RCC incidence analyses), death, emigration, or end of follow-up, whichever occurred first.

Statistical analysis

Multivariable Cox regression models with age as the timescale were used to estimate HRs and 95% confidence intervals (CI) for RCC incidence and mortality in relation to intakes of juices and total, sugar-sweetened, and artificially sweetened soft drinks modeled continuously (per 100 g/day increment) and as 3-knot restricted cubic splines. Models were stratified by sex and country and adjusted for age at recruitment, education, smoking status, alcohol consumption, physical activity, juice intake (for soft drink analyses), and total soft drink intake (for juice analyses). Models for sugar-sweetened and artificially sweetened soft drinks were mutually adjusted. Separate models additionally adjusted for body mass index (BMI) and total energy intake. Interactions with sex were evaluated with likelihood ratio tests. Sensitivity analyses were performed additionally adjusting for fruit and vegetable intake, excluding the first 2 years of follow-up, and excluding participants with self-reported diabetes at baseline. All analyses were conducted using Stata 13.1 (StataCorp).

Availability of data and materials

For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

Results

A total of 389,220 participants with complete data were included, in whom 888 incident RCCs and 356 RCC deaths occurred during a mean follow-up of 15 years for incidence and 16 years for mortality (range, 0–22.8 years). **Table 1** displays characteristics of participants.

Intakes of juices and total, sugar-sweetened, or artificially sweetened soft drinks were not associated with RCC incidence (**Table 2**). Total and artificially-sweetened soft drinks were positively associated with RCC mortality in models unadjusted for BMI and energy intake, but not after adjustment. Juice consumption was positively associated with RCC mortality in women, even after adjustment for BMI and energy intake (HR per 100 g/day increment = 1.17; 95% CI, 1.05–1.29; $P_{\text{interaction}}$ by sex = 0.02). There was no strong evidence of nonlinearity of associations (Supplementary Figs. S1 and S2), and in fully adjusted models HRs (95% CIs) for 400 g/day compared with no intake of juices, total soft drinks, sugar-sweetened soft drinks, and artificially sweetened soft drinks were 1.06 (0.85–1.34), 1.13 (0.93–1.38), 1.00 (0.77–1.29), and 1.21 (0.91–1.61), respectively, for RCC incidence, and 1.25 (0.87–1.79), 1.01 (0.75–1.37), 0.86 (0.59–1.27), and 1.38 (0.93–2.05) for RCC mortality (Supplementary Table S1). Results were similar in sensitivity analyses (Supplementary Tables S2–S4).

Discussion

In this prospective European study, intakes of juices or soft drinks were not associated with RCC incidence or mortality independent of obesity.

The absence of clear associations between consumption of juices and RCC risk in EPIC is consistent with other prospective studies (4, 8). The higher RCC mortality associated with higher juice intake in women is not interpretable and could be a chance finding.

The lack of association between soft drink consumption and RCC mortality aligns with previous EPIC findings showing no association between soft drink consumption and overall cancer mortality, despite a strong association with all-cause mortality (9). A meta-analysis did not identify associations between soft drink consumption and several cancer types, including kidney cancer (5), and other prospective studies investigating RCC/kidney cancer similarly have not found clear associations (4, 6).

Strengths of this study include its prospective design in European populations with different food and beverage habits, long follow-up time, many RCC cases, and detailed personal and lifestyle information which enabled control for multiple covariates. Limitations include the single assessment of diet at baseline, incomplete data on soft drink types in some countries, and inability to distinguish between juice types (fruit/vegetable/nectars/added sugars). Because few participants had very high intakes of these beverages, we cannot rule out the possibility that higher consumption levels might be associated with RCC.

In conclusion, in this large European prospective cohort study, consumption of soft drinks or juices was not associated with RCC incidence or mortality independent of obesity.

Table 1. Characteristics of EPIC participants included in analyses of soft drink and juice consumption and risk of renal cell carcinoma.

	Women		Men		Overall	
	Total	**Incident RCC cases**	**Total**	**Incident RCC cases**	**Total**	**Incident RCC cases**
N	264,652	373	124,568	515	389,220	888
Age (years), median (IQR)	51.4 (45.0–58.0)	57.1 (50.7–62.1)	52.7 (46.2–59.2)	56.0 (50.8–61.2)	51.8 (45.3–58.5)	56.5 (50.8–61.5)
Country[a], % (*n*)						
Denmark	10.8 (28,596)	16.6 (62)	21.0 (26,171)	24.1 (124)	14.1 (54,767)	21.0 (186)
France	23.1 (61,105)	1.1 (4)	0 (0)	0 (0)	15.7 (61,105)	0.5 (4)
Germany	10.3 (27,316)	14.5 (54)	17.0 (21,122)	20.8 (107)	12.4 (48,438)	18.1 (161)
Italy	11.5 (30,465)	18.5 (69)	11.1 (13,785)	11.3 (58)	11.4 (44,250)	14.3 (127)
The Netherlands	9.1 (24,087)	12.9 (48)	5.9 (7,388)	2.1 (11)	8.1 (31,475)	6.6 (59)
Spain	9.3 (24,645)	10.5 (39)	12.1 (15,051)	15.5 (80)	10.2 (39,696)	13.4 (119)
Sweden	9.9 (26,098)	14.5 (54)	17.6 (21,949)	16.1 (83)	12.3 (48,047)	15.4 (137)
United Kingdom	16.0 (42,340)	11.5 (43)	15.3 (19,102)	10.1 (52)	15.8 (61,442)	10.7 (95)
Education level, % (*n*)						
None/primary school	28.6 (75,751)	46.9 (175)	33.2 (41,410)	38.4 (198)	30.1 (117,161)	42.0 (373)
Technical/professional school	21.8 (57,741)	27.1 (101)	25.3 (31,495)	21.6 (111)	22.9 (89,236)	23.9 (212)
Secondary school	24.2 (63,992)	12.3 (46)	13.5 (16,864)	14.4 (74)	20.8 (80,856)	13.5 (120)
Longer education	25.4 (67,168)	13.7 (51)	27.9 (34,799)	25.6 (132)	26.2 (101,967)	20.6 (183)
Smoking status, % (*n*)						
Never	58.7 (155,273)	54.4 (203)	34.0 (42,410)	26.2 (135)	50.8 (197,683)	38.1 (338)
Former	22.7 (60,121)	20.1 (75)	37.0 (46,030)	37.7 (194)	27.3 (106,151)	30.3 (269)
Current	18.6 (49,258)	25.5 (95)	29.0 (36,128)	36.1 (186)	21.9 (85,386)	31.6 (281)
Physical activity, % (*n*)						
Inactive	22.3 (58,926)	26.5 (99)	17.6 (21,923)	20.6 (106)	20.8 (80,849)	23.1 (205)
Moderately inactive	36.3 (96,167)	37.5 (140)	31.8 (39,601)	37.9 (195)	34.9 (135,768)	37.7 (335)
Moderately active	24.7 (65,315)	17.4 (65)	24.8 (30,892)	22.7 (117)	24.7 (96,207)	20.5 (182)
Active	16.7 (44,244)	18.5 (69)	25.8 (32,152)	18.8 (97)	19.6 (76,396)	18.7 (166)
Hypertension[b], % (*n*)	17.8 (47,199)	29.8 (111)	20.2 (25,108)	30.5 (157)	18.6 (72,307)	30.2 (268)
Diabetes[b], % (*n*)	2.1 (5,577)	3.8 (14)	3.4 (4,176)	4.7 (24)	2.5 (9,753)	4.3 (38)
BMI (kg/m^2), median (IQR)	24.0 (21.8–27.1)	25.6 (23.2–28.9)	26.1 (24.0–28.5)	27.1 (24.8–29.7)	24.8 (22.4–27.7)	26.5 (24.2–29.5)
Alcohol intake (g/day), median (IQR)	4.2 (0.6–12.1)	1.8 (0.2–8.7)	12.9 (4.2–30.2)	13.6 (4.4–31.7)	6.4 (1.1–16.7)	7.5 (1.0–22.4)
Energy intake (kcal/day), median (IQR)	1,907.7 (1,580.6–2,293.2)	1,806.2 (1,496.6–2,207.5)	2,356.8 (1,953.3–2,818.4)	2,341.6 (1,986.0–2,791.0)	2,038.3 (1,669.2–2,478.1)	2,119.5 (1,724.6–2,578.0)
Fruit and vegetable juice intake (g/day), median (IQR)[c]	47.1 (10.7–120.0)	35.7 (8.3–120.0)	32.1 (8.3–101.9)	28.6 (8.2–103.4)	42.9 (9.0–120.0)	33.3 (8.3–120.0)
Total soft drink intake (g/day), median (IQR)[c]	41.9 (13.4–138.5)	56.0 (14.8–175.5)	62.6 (19.7–194.9)	71.4 (16.4–157.1)	48.6 (16.4–157.1)	63.4 (16.4–171.4)
Sugar-sweetened soft drink intake (g/day), median (IQR)[c,d]	28.6 (4.8–107.1)	31.5 (12.2–117.0)	45.5 (14.0–153.5)	46.3 (7.3–127.5)	32.1 (6.6–113.2)	35.4 (8.6–121.4)
Artificially sweetened soft drink intake (g/day), median (IQR)[c,d]	14.3 (2.0–85.7)	21.8 (6.6–103.8)	16.4 (3.3–85.7)	16.4 (3.3–89.0)	14.3 (2.0–85.7)	19.7 (6.5–92.3)

Abbreviations: BMI, body mass index; IQR, interquartile range; *n*, number of participants; RCC, renal cell carcinoma.

[a]Greece was excluded and Norway was not included in analyses because data on physical activity index were not available.

[b]Self-reported at recruitment.

[c]Median (IQR) among consumers. Overall ranges of intake were 0–4,000 g/day for juices, 0–4,202 g/day for total soft drinks, 0–4,202 g/day for sugar-sweetened soft drinks, and 0–3,389 g/day for artificially sweetened soft drinks.

[d]Information on types of soft drinks was not available in Umeå (Sweden) and centers in Italy and Spain.

Table 2. RCC incidence and mortality in relation to a 100 g/day increment in the consumption of juices, total soft drinks, sugar-sweetened soft drinks, and artificially sweetened soft drinks in the EPIC study.

			RCC incidence[a]							RCC mortality[b]					
			Adjusted model[c]			Additionally adjusted for BMI and energy intake[d]				Adjusted model[c]			Additionally adjusted for BMI and energy intake[d]		
	Participants	Cases	HR (95% CI) per 100 g/day	*P*	$P_{interaction}$	HR (95% CI) per 100 g/day	*P*	$P_{interaction}$	Deaths	HR (95% CI) per 100 g/day	*P*	$P_{interaction}$	HR (95% CI) per 100 g/day	*P*	$P_{interaction}$
Juice intake															
Overall	389,220	888	1.03 (0.97–1.09)	0.31		1.03 (0.97–1.09)	0.39		356	1.08 (0.99–1.17)	0.11		1.06 (0.97–1.16)	0.20	
Women	264,652	373	1.02 (0.93–1.12)	0.71	0.78	1.02 (0.92–1.12)	0.74	0.82	158	1.18 (1.07–1.30)	0.001	0.02	1.17 (1.05–1.29)	0.003	0.02
Men	124,568	515	1.04 (0.97–1.11)	0.32		1.03 (0.96–1.10)	0.40		198	0.94 (0.80–1.11)	0.50		0.93 (0.79–1.09)	0.38	
Total soft drink intake															
Overall	389,220	888	1.02 (0.99–1.06)	0.21		1.01 (0.98–1.05)	0.46		356	1.05 (1.00–1.10)	0.06		1.03 (0.98–1.09)	0.28	
Women	264,652	373	1.05 (0.99–1.11)	0.08	0.25	1.04 (0.98–1.10)	0.19	0.32	158	1.09 (1.02–1.17)	0.01	0.16	1.07 (1.00–1.15)	0.07	0.19
Men	124,568	515	1.01 (0.96–1.06)	0.76		1.00 (0.95–1.05)	0.99		198	1.02 (0.95–1.09)	0.66		1.00 (0.93–1.08)	0.97	
Sugar-sweetened soft drink intake[e]															
Overall	281,483	589	1.00 (0.95–1.06)	0.95		0.99 (0.94–1.05)	0.84		265	0.99 (0.91–1.09)	0.90		0.97 (0.89–1.07)	0.56	
Women	197,502	242	1.04 (0.95–1.14)	0.42	0.38	1.03 (0.94–1.13)	0.53	0.38	123	1.07 (0.95–1.20)	0.27	0.16	1.05 (0.93–1.18)	0.44	0.15
Men	83,981	347	0.98 (0.92–1.06)	0.67		0.98 (0.91–1.05)	0.53		142	0.94 (0.83–1.07)	0.35		0.92 (0.81–1.05)	0.21	
Artificially sweetened soft drink intake[e]															
Overall	281,483	589	1.03 (0.97–1.09)	0.32		1.02 (0.96–1.08)	0.61		265	1.08 (1.01–1.16)	0.03		1.06 (0.99–1.14)	0.11	
Women	197,502	242	1.06 (0.98–1.15)	0.13	0.32	1.05 (0.96–1.14)	0.28	0.37	123	1.10 (1.01–1.21)	0.03	0.52	1.08 (0.98–1.19)	0.11	0.57
Men	83,981	347	1.00 (0.93–1.09)	0.93		0.99 (0.91–1.08)	0.85		142	1.06 (0.95–1.17)	0.30		1.04 (0.93–1.15)	0.49	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; RCC, renal cell carcinoma.

[a]Incident RCC was defined as histologically confirmed first invasive RCC diagnosis coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) C64.

[b]RCC deaths included all deaths in which the underlying cause of death was ICD-10 C64.

[c]Multivariable Cox regression models were stratified by sex and country and adjusted for age at recruitment (continuous, years), educational attainment (none/primary school, technical or professional school, secondary school, longer education including university), smoking status (never, former, current), alcohol consumption (continuous, g/day), physical activity (inactive, moderately inactive, moderately active, active), juice intake (continuous, g/day; for soft drink analyses), and total soft drink intake (continuous, g/day; for juice analyses). Sugar-sweetened and artificially sweetened soft drinks were mutually adjusted.

[d]Models were as described for the adjusted model[c] and additionally adjusted for body mass index (continuous, kg/m^2) and total energy intake (continuous, kcal/day).

[e]Umeå (Sweden) and centers in Italy and Spain were not included in these analyses as information on types of soft drinks was not available.

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