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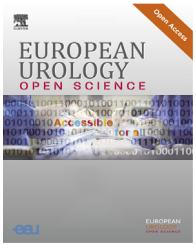

European Association of Urology

Kidney Cancer

Association of Artificially Sweetened Beverage Consumption and Urinary Tract Cancers in the Women's Health Initiative Observational Study

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Article info

Article history:
Accepted November 27, 2022

Associate Editor:
Guillaume Ploussard

Keywords:
Artificially sweetened beverages
Kidney cancer
Bladder cancer
Urinary tract cancer
Artificial sweetener

Abstract

Background: Insufficient data exist to conclude whether consumption of artificially sweetened beverages is associated with a higher risk of urinary tract cancers.
Objective: We sought to investigate whether urinary tract cancer incidence differed among women who consumed various amounts of artificially sweetened beverages.
Design, setting, and participants: This was a secondary analysis of data from the Women's Health Initiative Observational Study, a multicenter longitudinal prospective study of the health of 93 676 postmenopausal women with a mean follow-up time of 13.5 yr. Women were identified at 40 clinical centers across the USA and enrolled from 1993 to 1998. Women between the ages of 50 and 79 yr were enrolled. We included women who answered questions about artificially sweetened beverage consumption and reported no prior urinary tract cancer diagnoses. The frequency of artificially sweetened beverage consumption was categorized as follows: rare artificially sweetened beverage consumption (never to fewer than one serving per week), frequent consumption (one to six servings per week), and daily consumption (more than one servings per day).
Outcome measurements and statistical analysis: The incidence of urinary tract cancer reported during subsequent visits until February 28, 2020 was recorded. Demographic characteristics were compared between those with varying levels of artificially sweetened beverage consumption. Descriptive statistics were used to report the rates of urinary tract cancer diagnosis, and Cox regression models were constructed to determine hazard ratios and adjust for potential confounders.

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https://doi.org/10.1016/j.euros.2022.11.016

Results and limitations: We identified 80 388 participants who met the inclusion criteria. Most participants (64%) were infrequent consumers of artificially sweetened beverages, with 13% (n = 10 494) consuming more than one servings per day. The incidence of urinary tract cancers was low, with only 804 cases identified. Cox regression models showed that frequent artificially sweetened beverage consumption was associated with a higher risk of kidney cancer (adjusted hazard ratio 1.34, 95% confidence interval 1.03–1.75). There was no significant association between artificially sweetened beverage intake and bladder cancer.
Conclusions: Frequent consumption of artificially sweetened beverages may be associated with a higher risk of kidney cancer among postmenopausal women.
Patient summary: A secondary analysis of the Women's Health Initiative Observational Study showed that higher consumption of artificially sweetened beverages was associated with a higher risk of kidney cancer.

1. Introduction

The extent to which artificially sweetened beverage (ASB) intake is associated with urinary tract malignancies has been a topic of debate for years. Several studies conducted in the past showed an association between artificial sweeteners and urinary tract cancer (UTC) in rats [1–5], which led to increased investigation in other animal models. Through this research, it was found that long-term consumption of artificial sweeteners in monkeys demonstrated no increased cancer risk [6,7], and a more recent meta-analysis of rodent data showed no significant carcinogenic effect [8]. In humans, epidemiologic studies have had mixed results, with some older studies demonstrating an increased risk of bladder cancer with consumption of artificial sweeteners [9,10] and others showing no correlation [11–15]. More recently, a systematic review of the relationship between artificial sweetener consumption and cancer in humans showed a higher risk of UTC with long-term consumption of ASBs [16], but this was largely based on the results from a small case-control study [17]. Another epidemiologic study looking specifically at renal cell carcinoma found no increased risk of incident renal cell carcinoma diagnosis associated with artificially sweetened soft drinks [18], but other UTCs were not investigated. Therefore, insufficient data exist to conclude whether consumption of ASBs is associated with a higher risk of UTCs [19].

Given the recent finding that ASB consumption is associated with higher risks of stroke, coronary heart disease, and morbidity/mortality [20], as well as the nearly two-fold rise in kidney cancer incidence in the USA (from four to seven per 100 000 among women) in recent decades [21], it is important to investigate the potential associations between ASB consumption and UTCs to better understand the risks of ASB consumption on the urinary tract. As behavior change is often difficult to achieve, establishing a strong scientific association between ASB consumption and UTCs could significantly aid in counseling efforts to help patients plan their diet and avoid potentially harmful links to UTCs, as well as possibly inform screening guidelines.

The objective of this study was to evaluate the association between intake of ASBs and incident UTCs among postmenopausal women in the Women's Health Initiative (WHI) Observational Study (WHI-OS). We hypothesized that a higher intake of ASBs would be directly associated with a higher risk of incident UTCs after adjusting for confounders.

2. Patients and methods

The WHI-OS is a prospective, multicenter cohort study of 93 676 postmenopausal women. The detailed methods have previously been published elsewhere [22]. Briefly, women between the ages of 50 and 79 yr were identified at 40 clinical centers across the USA and enrolled from 1993 to 1998. Women completed several self-administered questionnaires, and the WHI staff collected anthropometric measures at enrollment and throughout follow-up. In a follow-up visit 3 yr after enrollment, participants completed a questionnaire that asked them to estimate their consumption of ASBs. Women also completed self-administered questionnaires at baseline and throughout follow-up asking about a diagnosis of cancer. The overall WHI protocol was approved by the institutional review boards of participating institutions, and all participants provided written informed consent for their study activities.

2.1. Ascertainment of ASB consumption

The question regarding ASBs was as follows: "During the past 3 mo, how often did you drink these beverages?" (Beverages refer to "diet drinks such as Diet Coke or diet fruit drinks," with a 12 fl. oz. can as a reference serving size.) The frequency of ASB consumption was described in nine categories: never or fewer than one serving per month (reference), one to three servings per month, one serving per week, two to four servings per week, five to six servings per week, one serving per day, two to three servings per day, four to five servings per day, and six or more servings per day. These categories were collapsed for our analysis into three categories: never or fewer than one serving per week (reference), one to six servings per week, and one or more servings per day, as the authors felt that these categories adequately represented rare, frequent, and daily consumption, respectively, while balancing sample sizes in each group.

2.2. Ascertainment of incident UTC diagnosis

Participants completed questionnaires regarding their past medical history at enrollment and annually throughout the study. Women who self-reported a prior bladder cancer diagnosis at enrollment were excluded. No data were collected on other UTC diagnoses at baseline, but annual outcome assessments were used to exclude newly diagnosed UTCs in

the first 3 yr of the study, prior to when the ASB questionnaire was administered. From year 3, an incident diagnosis of UTC was defined as answering "yes" to the question "Since the date on the front of this form, has a doctor told you for the first time that you have a new cancer or a malignant tumor?", where a UTC was then reported. Cancers reported during follow-up were confirmed by physician adjudicators.

We collected data on demographic variables of participants, including age, race, ethnicity, body mass index (BMI), diabetes, and hypertension, that were reported either during the participant's initial screening visit or at her year 3 follow-up visit. We also recorded data on additional self-reported dietary and activity variables that could possibly relate to UTCs, including smoking history, alcohol intake, recreational physical activity, diet quality or Healthy Eating Index (HEI), and water consumption. Diet quality was assessed using the HEI, which is a measure of diet quality that assesses conformity to US Dietary Guidelines 2015 [23]. Recreational physical activity was assessed using information about the duration, frequency, and intensity of activity, as described previously [24]. Neighborhood socioeconomic status (nSES) was based on US census tracts from the 2000 census, with index ranges from 0 to 100 where higher scores indicate more affluent tracts [25].

Descriptive statistics were used to report the frequency of ASB consumption, and comparisons were made between ASB consumption groups using chi-square tests for categorical variables and analysis of variance for continuous variables. Cox proportional hazard models were used to examine the relationship between ASB intake and risk of UTC. Models were adjusted for variables that have been associated with the development of these cancers in the literature. The primary model adjusted for age, race, ethnicity, nSES, and smoking was assessed via a baseline questionnaire, as these variables are associated with a higher risk of developing any UTC (with nSES used as a proxy for the likelihood of environmental exposures) [21,26]. The model for bladder cancer was additionally adjusted for water consumption [26], as water consumption has been correlated with bladder cancer but not kidney cancer, and the model for kidney cancer was additionally adjusted for BMI, history of hypertension, and diet quality [21], as these variables have been associated with the risk of developing the kidney cancers but not bladder cancer. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) and all statistical testing with a significance level of 0.05.

3. Results

We included 80 388 women after excluding those who did not complete form F143 at year 3 (n = 11 108), those with missing data on urinary incontinence (n = 909), those with missing data on ASB consumption (n = 850), those diagnosed with UTC prior to year 3 (n = 270), and those with

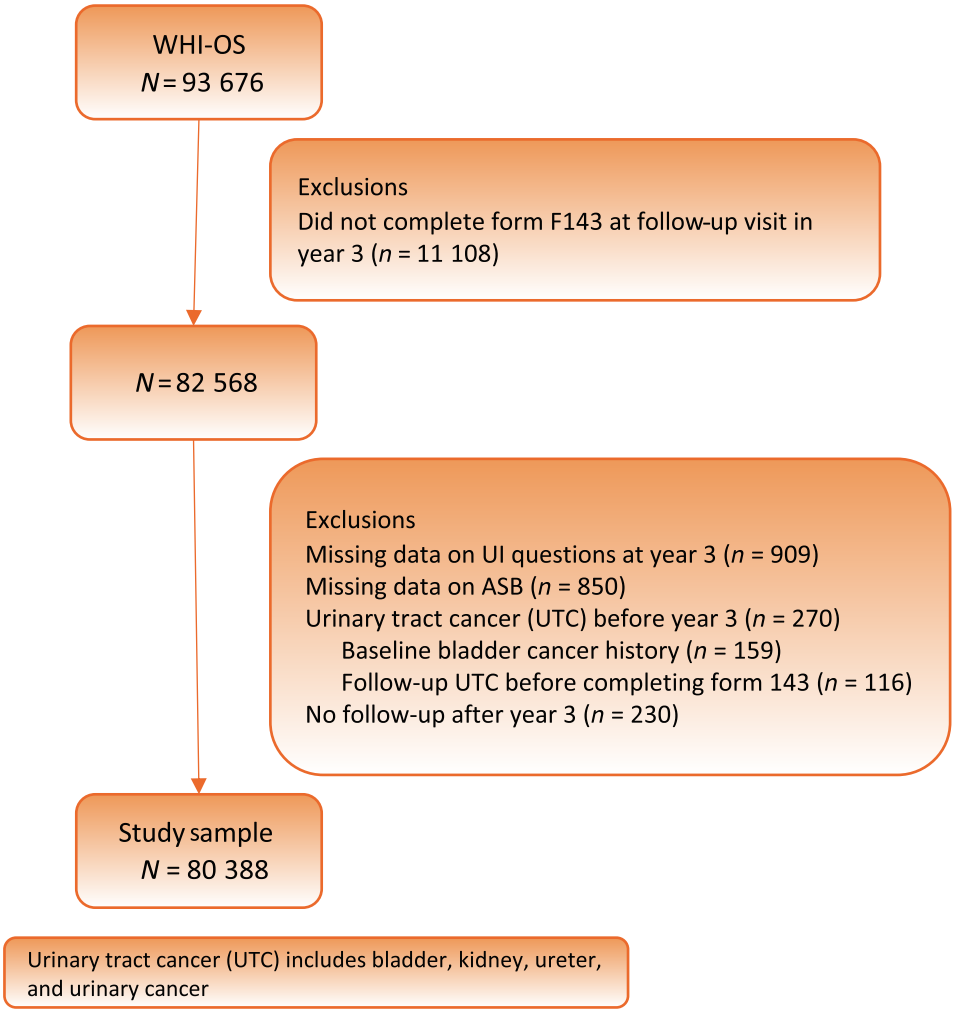

Fig. 1 – Study sample flow diagram. ASB = artificially sweetened beverage; UI = urinary incontinence; WHI-OS = Women's Health Initiative Observational Study.

Table 1 – Characteristics of participants by frequency of artificially sweetened beverage consumption

	Overall	Frequency of artificially sweetened beverage consumption			
		Never or <1 serving/wk	1–6 serving/wk	1+ serving/d	*p* value
	80 388	51 480	18 414	10 494	
	N (%)	*N* (%)	*N* (%)	*N* (%)	
Age, mean (SD)	66.6 (7.3)	67.3 (7.3)	66.0 (7.1)	64.4 (7.0)	<0.001
nSES, mean (SD)	76.3 (8.3)	76.4 (8.2)	76.2 (8.3)	76.0 (8.2)	<0.001
Missing	8345	5298	1927	1120	
Race/ethnicity					
American Indian or Alaskan Native	314 (0.4)	195 (0.4)	63 (0.3)	56 (0.5)	<0.001
Asian or Pacific Islander	2293 (2.9)	1727 (3.4)	387 (2.1)	179 (1.7)	
Black or African American	5552 (6.9)	3610 (7.0)	1267 (6.9)	675 (6.4)	
Hispanic/Latino	2557 (3.2)	1661 (3.2)	572 (3.1)	324 (3.1)	
White (not of Hispanic origin)	68 590 (85.3)	43 542 (84.6)	15 908 (86.4)	9140 (87.1)	
Other	1082 (1.3)	745 (1.4)	217 (1.2)	120 (1.1)	
BMI (kg/m^2)					
<25	29 425 (39.7)	21 636 (45.4)	5353 (31.6)	2436 (25.5)	<0.001
25–<30	25 747 (34.7)	16 041 (33.6)	6313 (37.3)	3393 (35.5)	
≥30	18 984 (25.6)	9996 (21.0)	5271 (31.1)	3717 (38.9)	
Missing	6232	3807	1477	948	
Treated diabetes	4390 (5.5)	1804 (3.5)	1450 (7.9)	1136 (10.8)	<0.001
Missing	75	51	11	13	
Treated hypertension	28 655 (36.0)	17 611 (34.6)	6975 (38.3)	4069 (39.1)	<0.001
Missing	786	516	184	86	
Smoking status					
Never smoked	40 817 (51.4)	26 872 (52.8)	9168 (50.4)	4777 (46.0)	<0.001
Past smoker	34 902 (43.9)	21 554 (42.4)	8347 (45.9)	5001 (48.1)	
Current smoker	3737 (4.7)	2438 (4.8)	690 (3.8)	609 (5.9)	
Missing	932	616	209	107	
HEI 2015, mean (SD)	67.8 (10.3)	68.5 (10.3)	67.5 (9.6)	64.8 (10.4)	<0.001
Missing	561	363	122	76	
Water consumption (8 oz serving)					
<1/d	8597 (10.7)	5042 (9.8)	2154 (11.7)	1401 (13.4)	<0.001
1–5/d	53 292 (66.3)	33 867 (65.8)	12 231 (66.5)	7194 (68.6)	
6+/d	18 457 (23.0)	12 552 (24.4)	4017 (21.8)	1888 (18.0)	

Data are expressed as *N* (%) unless otherwise indicated. The *p* value is chi-square for categorical variables and ANOVA for continuous variables. Measures were collected or updated to year 3 except race/ethnicity.
ANOVA = analysis of variance; BMI = body mass index; HEI = Healthy Eating Index; nSES = neighborhood socioeconomic status; SD = standard deviation.

Table 2 – Number and rate per 1000 person-years for urinary tract cancer outcomes through February 28, 2020 from year 3

	Frequency of artificially sweetened beverage consumption			
	Overall	Never or <1/wk	1–6/wk	≥1/d
	80 388	51 480	18 414	10 494
Urinary tract cancers (overall)	804 (0.74)	505 (0.73)	204 (0.82)	95 (0.67)
Bladder cancer	448 (0.41)	295 (0.43)	106 (0.42)	47 (0.33)
Kidney cancer	327 (0.30)	188 (0.27)	91 (0.36)	48 (0.34)
Ureteral cancer	31 (0.03)	21 (0.03)	8 (0.03)	2 (0.01)
Other urinary tract cancer	15 (0.01)	7 (0.01)	8 (0.03)	0 (0.00)

no follow-up after year 3 (n = 230; see Fig. 1). Most participants (64%) rarely consumed ASBs and 13% (n = 10 494) consume more than one servings per day (Table 1). Women who consumed a higher number of ASBs were younger, had lower nSES, were more likely to be White and not of Hispanic origin, and had higher BMIs. They were also more likely to have diabetes and hypertension. Women with higher ASB consumption were more commonly smokers, had poorer-quality diets, and drank less water than women with lower ASB consumption.

Throughout the follow-up period, there were 804 new diagnoses of UTCs (Table 2). The most common UTC diagnosis was bladder cancer (n = 448), followed by kidney cancer (n = 327), ureter cancer (n = 31), and other urinary organ cancer (n = 15).

In the adjusted models, the risk of developing a UTC did not differ between ASB groups (Table 3 and Fig. 2A). ASB intake was not significantly associated with the risk of bladder cancer (Table 3 and Fig. 2B). ASB consumption of one to six servings of ASBs per week was, however, associated with a higher risk of kidney cancer (Table 3 and Fig. 2C) relative to rare consumption, and this risk persisted after adjustments (adjusted hazard ratio [aHR] 1.34, 95% confidence interval [CI] 1.03–1.75). A similar increased risk was seen with ASB consumption of one or more servings per day (Fig. 2C), but this association was not statistically significant (aHR 1.14, 95% CI 0.80–1.62). The association between ASB consumption and incidence of ureter and other urinary organ cancers was not assessed due to small numbers of participants in each group.

Table 3 – Hazard ratios and 95% CIs for artificially sweetened beverage consumption and urinary tract cancers

	Artificially sweetened beverage		
	Never or <1/wk	1–6/wk	≥1/d
Urinary tract cancers (*n* = 804)			
N events	505	204	95
Crude	Ref	1.12 (0.95–1.32)	0.91 (0.73–1.14)
Age adjusted	Ref	1.19 (1.01–1.40)	1.05 (0.84–1.31)
Model 1	Ref	1.16 (0.97–1.38)	0.94 (0.74–1.20)
Bladder cancer (*n* = 448)			
N events	295	106	47
Crude	Ref	0.99 (0.80–1.24)	0.77 (0.57–1.05)
Age adjusted	Ref	1.07 (0.86–1.34	0.92 (0.68–1.26)
Model 1	Ref	1.00 (0.78–1.27)	0.76 (0.54–1.07)
Model 2	Ref	0.99 (0.78–1.26)	0.75 (0.53–1.06)
Kidney cancer (*n* = 327)			
N events	188	91	48
Crude	Ref	1.35 (1.05–1.73)	1.24 (0.90–1.71)
Age adjusted	Ref	1.40 (1.09–1.79)	1.36 (0.98–1.87)
Model 1	Ref	1.47 (1.13–1.92)	1.36 (0.96–1.92)
Model 3	Ref	1.34 (1.03–1.75)	1.14 (0.80–1.62)

BMI = body mass index; CI = confidence interval; HEI = Healthy Eating Index; nSES = neighborhood socioeconomic status.
Model 1—adjusted for age, race and ethnicity, nSES, and smoking (*N* = 71 132).
Model 2—model 1 plus water consumption (*N* = 71 100).
Model 3—model 1 plus BMI, history of hypertension, and HEI (*N* = 69 896).

4. Discussion

We found that frequent ASB consumption was associated with a higher risk of kidney cancer among postmenopausal women. There was no significant association between ASB consumption and the risk of bladder cancer or UTC overall.

While the daily ASB consumption group did not show a statistically significantly increased risk of incident kidney cancer, the sample size in this group was small. In the cumulative hazard plot, a substantial overlap can be seen between the frequent and daily ASB consumption groups with divergence from the never/rare ASB consumption group (Fig. 2C), implying that different risk profiles exist for rare consumers compared with both frequent and daily consumers. The risk of incident bladder cancer does not appear to be associated with any amount of ASB consumption (Fig. 2B).

While many prior studies have demonstrated associations between artificial sweetener consumption and cancer in animal models [1–5], studies in humans reported mixed findings, particularly in population-based studies [9–19]. Associations between artificial sweeteners and bladder cancer have hotly been debated, but few studies have investigated any potential link between artificial sweeteners and other UTCs. Prior assessment from a large network of case-control studies showed no relationship between several artificial sweeteners and diagnosis of kidney cancer in Italy [27], although cases and matched controls were admitted hospital patients and might not have reflected the general population. Our study brings novel data to the discussion, as this higher risk of incident kidney cancer observed with frequent ASB consumption has not been reported previously.

It is possible that the observed higher incidence of kidney cancer was due to the generally poorer health of the more frequent ASB consumption cohorts (higher rates of medical comorbidities, being less physically active, and poorer diet quality); however, we demonstrated an effect independent of these factors. The WHI-OS did not have available data on genetic predispositions to or family history of UTC, and none of the cases that developed UTC had a history of kidney disease requiring dialysis, so these variables could not be included in our models and may contribute to confounding in our findings.

While these findings are noteworthy, the magnitude of the effect that we observed was small and is of uncertain clinical significance, and this should be taken into account when considering the potential risks of ASB consumption.

Strengths of this study include the use of a large sample of postmenopausal women with detailed information on numerous demographic and behavioral variables, which allowed for the ability to adjust for multiple potential confounders. The use of data from a prospective cohort study with many years of follow-up data allowed us to assess the incidence of cancers over time and thus capture more incident cancer diagnoses. This study is also generalizable to a US population of postmenopausal women given the diverse geographic, racial, and ethnic representation.

There are also several limitations to this study. While the WHI-OS has detailed information on a large number of variables and behaviors, additional variables that were not measured may have influenced our findings. Specifically, some data on known risk factors for developing bladder cancer and kidney cancer were unavailable, including genetic predispositions to cancer and a family history of UTC. There were also some variables, such as physical activity, that may influence the risk of developing urothelial cancers that were not included in the models. Additionally, while nSES was used to approximate the risk for environmental exposures, specific information on occupation, exposure to industrial chemicals, and history of exposure to arsenic in drinking water was unavailable.

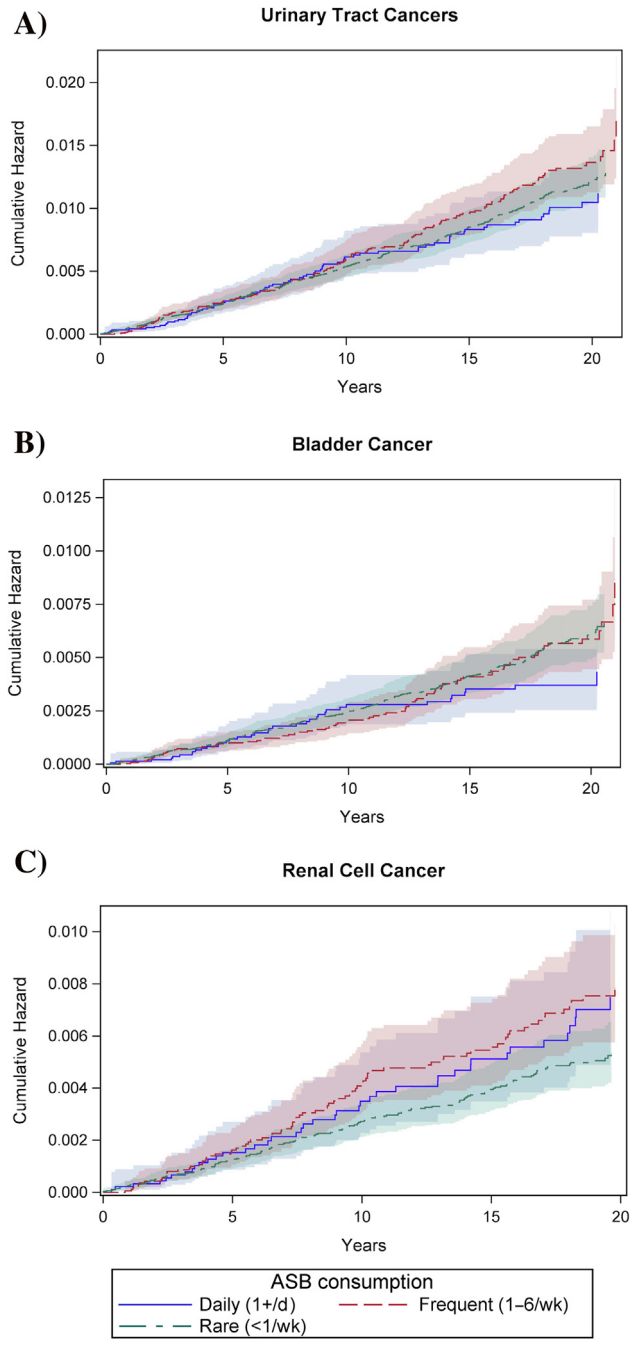

Fig. 2 – Association between time to urinary tract cancer diagnosis and ASB categories. Cox regression models/cumulative hazards with 95% confidence limits were used. (A) Urinary tract cancer. (B) Bladder cancer. (C) Kidney cancer. Graphs depict cumulative hazard (negative log survival) stratified by ASB categories and adjusted for model covariates. ASB = artificially sweetened beverage.

ASB consumption was also self-reported and not measured over time, and thus these data may contain inaccuracies from a recall bias. Furthermore, while 13.5 yr of follow-up is fairly long, it is possible that this time frame did not adequately capture the time required for these cancers to develop. This study was also observational rather than a clinical trial, and observed associations do not necessarily indicate causation.

Further research should investigate the possible association between ASB consumption and development of kidney cancer in a broader population, particularly one that includes men since kidney cancer is more common in men. Research elucidating any potential biological mechanisms for this association would also be beneficial, including studies that determine whether specific types of artificial sweeteners may be riskier. Similar population-based studies could also investigate links between ASB consumption and other types of cancer outside the urinary tract.

5. Conclusions

In this study of postmenopausal women in the USA, higher consumption of ASBs was associated with a higher risk of incident kidney cancer, but not with the risk of incident bladder cancer. A further study is needed in order to better understand the role that ASB consumption may play in the development of kidney cancer.

Author contributions: Nancy E. Ringel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ringel, Iglesia, Howard, Mossavar-Rahmani.
Acquisition of data: Hovey.
Analysis and interpretation of data: Hovey, Andrews, Ringel.
Drafting of the manuscript: Ringel.
Critical revision of the manuscript for important intellectual content: Hovey, Andrews, Mossavar-Rahmani, Shadyab, Snetselaar, Howard, Iglesia.
Statistical analysis: Hovey, Andrews.
Obtaining funding: None.
Administrative, technical, or material support: Ringel.
Supervision: Iglesia, Howard.
Other: Methodology: Ringel, Hovey, Andrews, Mossavar-Rahmani, Shadyab, Snetselaar, Howard, Iglesia.

Financial disclosures: Nancy E. Ringel certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: The Women's Health Initiative (WHI) program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. Dr. Nancy E. Ringel received support for this study through the Georgetown Howard Universities Center for Clinical and Translational Science (GHUCCTS).

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