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Concentrated sugars and incidence of prostate cancer in a prospective cohort

Fayth L. Miles[1,2]*, Marian L. Neuhouser[2] and Zuo-Feng Zhang[1,3,4]

[1]*Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, CA 90095-1772, USA*
[2]*Cancer Prevention Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA*
[3]*David Geffen School of Medicine, Center for Human Nutrition, UCLA, Los Angeles, CA 90095, USA*
[4]*Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, CA 90095-1781, USA*

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Abstract

The association between consumption of added or concentrated sugars and prostate cancer risk is unclear. We examined the association between concentrated sugars in beverages and desserts and prostate cancer risk among 22 720 men in the usual-care arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, enrolled during 1993–2001. After a median follow-up of 9 years, 1996 men were diagnosed with prostate cancer. Cox proportional hazards regression models were used to estimate hazard ratios (HR) for prostate cancer risk and 95 % CI, adjusting for potential confounding factors. Increased consumption of sugars from sugar-sweetened beverages was associated with increased risk of prostate cancer for men in the highest quartile of sugar consumption (HR: 1·21; 95 % CI 1·06, 1·39), and there was a linear trend ($P < 0·01$). There were no linear associations between prostate cancer risk and consumption of sugars from fruit juices or dessert foods. In conclusion, in this prospective substudy within the PLCO trial, consumption of sugars from sugar-sweetened beverages was associated with increased risk of prostate cancer among men receiving standard medical care. Our study suggests that limiting intake of sugars from beverages may be important in the prevention of prostate cancer.

Key words: Added sugars: Proportional hazards regression: Prostate cancer risk: Prospective cohorts

Consumption of added sugars in America has increased considerably over time[1]. Dietary intake of energetic sweeteners including sucrose and high-fructose maize syrup increased by nearly 40 % between 1950–59 and 2000[2]. Consumption of added sugars from beverages, particularly, has increased. Between 1977 and 2003 energy content from added sugars in beverages increased by 377 kJ/d (90 kcal/d) and from added sugars in foods by 96 kJ/d (23 kcal/d) in the USA[3]. In spite of a decline in consumption of absolute energy content of added sugars, percentage of total energy intake from added sugars has remained high[3]. In light of the growing body of evidence highlighting unfavourable health effects of added sugars, the 2015 Dietary Guidelines Advisory Committee recommended that Americans limit sugar to no more than 10 % of daily energy content[4]. Intake of high-fructose maize syrup or added sugars has been associated with the metabolic syndrome, characterised by elevated blood pressure, TAG, LDL-cholesterol, uric acid and inflammation[5–7]. Not surprisingly, there is some evidence that dietary added sugars are associated with cancer, although the evidence is limited. Case–control and prospective studies have shown an association of consumption of sugary foods[8,9], and particularly beverages[10,11], with increased risk of pancreatic cancer, which may be mediated in part through induction of transketolase[12]. In addition, sweet foods and beverages were shown to increase breast cancer risk by 27 %[13]. Recently, we reported an association between sugary beverages (fruit juices and sugar-sweetened) and reduced survival among head and neck cancer patients[14].

Little is known about the associations of dietary added and concentrated sugars with the development of prostate cancer, although it is understood that lifestyle plays an important role in prostate cancer prevention[15]. Because of the putative link between chronic inflammation and prostate cancer, dietary items that are potentially pro-inflammatory deserve particular attention. It has been shown, for example that heterocyclic amines promote the development of cancer and induce accumulation of inflammatory cells (lymphocytes and macrophages) in the prostate[16], that processed meat or dietary fat from meat is associated with increased prostate cancer risk[17,18] and there is some evidence that dairy consumption may be associated with increased prostate cancer risk[19]. It is possible that the increased fructose and consequently TAG in items with concentrated sugars promotes an inflammatory response that supports DNA damage and genetic changes leading to neoplastic lesions of the prostate[6,20–22]. We hypothesised that consumption of sugar-dense items, or items with concentrated

Abbreviations: DHQ, diet history questionnaire; HR, hazard ratio; PLCO, Prostate, Lung, Colorectal and Ovarian; PSA, prostate-specific antigen.

* **Corresponding author:** F. L. Miles, fax +1 206 667 7850, email fmiles@fredhutch.org

sugars lacking the phytonutrients and fibre found in plant-based foods is particularly problematic, with a more detrimental impact on blood sugar, and ultimately promoting inflammation and prostate cancer growth.

The goal of the present study was to examine the association of concentrated sugars with prostate cancer risk. The term concentrated sugars was defined as sugars (in grams) from sugar-sweetened beverages and fruit juices as well sugars in refined and processed desserts, constituting at least 30 % of total energy content. Thus, this included added sugars in beverages and dessert foods, as well as natural sugars in fruit juices, which are naturally present in high amounts. These associations were evaluated in men receiving usual medical care in the prospective, population-based Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Methods

Study population

This study utilised data from the PLCO Cancer Screening Trial, a large, prospective, randomised, multi-site study (Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St Louis, MO and Washington, DC) designed initially to examine the effects of cancer screening on cancer mortality[23]. In brief, ten screening centres across the USA enrolled men ages 55–74 years to an intervention (screening) or control arm between 1993 and 2001. These men were recruited from the general population in the geographic area of the screening centres. A total of 38 343 men were randomised to the control arm, where they received usual medical care from their health care providers, unlike men in the screening arm who received digital rectal exams and annual blood draws for prostate-specific antigen (PSA). The follow-up rate was 99·5 % (Fig. 1).

Annual study update questionnaires were used to ascertain prostate cancer incidence and were sent to all study participants. For men reporting a prostate cancer diagnosis, or men with abnormal test results from screening, medical records were obtained and used to confirm the diagnosis, clinical stage and grade. In the present study, cancers of Gleason <7 were defined as low grade, and cancers of Gleason ≥7 were defined as high grade.

Of the 38 343 men in the usual-care arm, 26 927 completed the baseline and diet history questionnaires (DHQ). After excluding participants who were diagnosed with any cancer before the questionnaires (1867), skipped eight or more food frequency questions (1728), or were in the first or last percentile of energetic intake (<2314 kJ/d (<553 kcal/d) and >23 510 kJ/d (>5619 kcal/d)) (1148), there were 23 839 men in the eligible DHQ cohort. Additional exclusion of men with missing data for smoking status, pack-years of smoking, education, family history and diabetes history, which was found to be related to prostate cancer risk in this cohort[24], resulted in an eligible cohort containing 22 720 men. Median follow-up for these men was 9 years (183 430 person-years) (Fig. 1).

The study was reviewed and approved by the National Cancer Institute (NCI) institutional review board and screening centres (Clinicaltrials.gov identifier: NCT00002540).

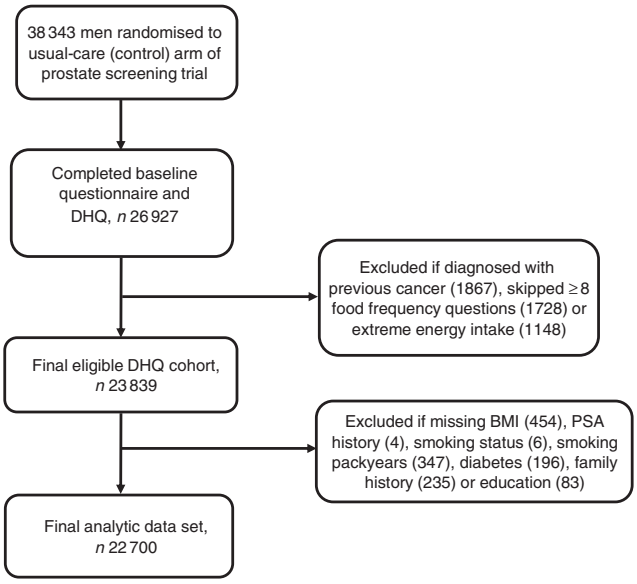

Fig. 1. Study design and flowchart of participant selection. DHQ, diet history questionnaire; PSA, prostate-specific antigen.

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.

Data collection

PLCO study participants completed a baseline questionnaire with information on demographics, medical history and smoking history. Height and weight were measured at the randomisation clinic visit and BMI was computed as weight (kg)/height (m^2). The DHQ, a FFQ developed by the Risk Factor Monitoring and Methods Branch of the NCI, was introduced in December of 1998, 5 years into the trial. It included 156 questions on frequencies of consumption of various foods and beverages from which daily nutrient intake data were estimated. The food list and nutrient database used with the DHQ are based on national dietary data (US Department of Agriculture's 1994–1996 Continuing Survey of Food Intakes by Individuals). The DHQ has been validated and found to be as good as or superior to two widely used FFQ at the time the PLCO study was conducted[25]. Participants in the usual-care arm randomised before 1998 were offered the DHQ in 1999 or 2000, around the anniversary of randomisation, and individuals randomised after December 1998 were offered the DHQ at baseline. The FFQ was self-administered and asked about frequency of consumption of desserts, sweetened beverages, fruit drinks, fruit juices, fruit, vegetables and other items. For the purposes of this analysis, sugars from soft drinks and sodas, milkshakes, punch, and fruit drinks, and sugar or honey added to tea or coffee were summed to generate a composite variable for sugar-sweetened beverages. Sugars from fruit juices included sugars from orange, grapefruit, tomato, and 'other' fruit or vegetable juices. In addition, we considered common desserts

determined to have concentrated sugars (comprising at least 30 % of total energy content per item), to generate a composite variable including sugars from cakes, cookies, pies, pastries, chocolate, candy, pudding, syrups, ice cream, and added sugar or sweet creams. In addition, the sum of all added sugars was calculated, including sugar added to processed foods or used in baked goods or sodas and other beverages, in addition to sugar added 'at the table'. The total amount of sugars in grams was calculated from the sum of fructose, galactose, glucose, lactose, maltose and sucrose using DietCalc Software developed by the NCI. The sugar variables were generated based on the Nutrition Data Systems for Research – Nutritional Analysis Software developed at the University of Minnesota.

Statistical analysis

The main categories of added sugar considered for analyses were sugar-sweetened beverages, fruit juices and desserts. In addition, composite variables representing the sum of these three variables, as well as intake of all added sugars from the diet were generated. The association of daily consumption of concentrated sugars with prostate cancer risk was analysed using the quartile distribution for sugar consumption for the final eligible DHQ cohort. Cox proportional hazards regression was used to calculate hazard ratios (HR) and 95 % CI. Sugar consumption was additionally modelled linearly, as a continuous variable, representing a ten-unit increment in dietary intakes. Follow-up time was calculated as the interval between days from completion of the DHQ to prostate cancer diagnosis, death, or 30 September 2009, depending on which came first. Models were adjusted for study centre, age, race (White *v.* non-White), education (less than high school, high school graduate, post-high school/some college, college graduate or more), cigarette status (never, current, former), pack-years of smoking, current BMI (at baseline), previous history of diabetes (yes/no), family history of prostate cancer (yes/no), number of PSA screens over the previous 3 years (none, once, more than once, unknown), and energy (kJ/d (kcal/d)). These variables were included as they possibly confound the relationship between sugar consumption and prostate cancer risk, or were previously found to be associated with prostate cancer risk. Other variables considered were red and processed meat (g/d), fruit (servings/d), and vegetables (servings/d), but were not included in final models as they were found to be non-influential on results. *P* value for trend was calculated treating the exposure of interest as a continuous variable, based on the Wald statistic.

Results

Baseline characteristics of the eligible study cohort according to intake of concentrated sugars from foods and beverages are shown in Table 1. Differences were noted for previous history of diabetes, with the most individuals with a previous history (47·8 %) falling in the lowest quartile of sugar intake. Notable differences were also observed for race, with an increased percentage of Black participants in the highest quartile of intake of concentrated sugars (40·9 %), and more Asians in the lowest quartile (40 %) relative to the other quartiles. An increased proportion of men with high school or less education (approximately 29 %), as well as current smokers (approximately 32 %) were in the highest quartile of concentrated sugar consumption. A lower proportion of men in the highest quartile had multiple PSA screens (21·3 %). Participants in the highest quartile of concentrated sugar consumption consumed the greatest amounts of sugar from sugar-sweetened beverages (which were the major source of concentrated sugars), fruit juices and desserts, as well as added sugars overall. Energetic intake was notably higher for men in the highest quartile (10 669 kJ/d (2550 kcal/d)).

Multivariable-adjusted associations of consumption of concentrated sugars with prostate cancer risk are shown in Table 2. Consumption of sugars from sugar-sweetened beverages was associated with increased overall prostate cancer risk, with 21 % increased risk for men in the top quartile of consumption (HR: 1·21; 95 % CI 1·06, 1·39; $P_{\text{for trend}} < 0{\cdot}01$). In addition, an association of sugar-sweetened beverages with increased risk of low grade prostate cancer was observed for individuals in the highest quartile ($P = 0{\cdot}02$). However, there was no statistical difference between sugar consumption and risk of low and high grade prostate cancer. Consumption of sugars from fruit juices was associated with increased overall prostate cancer risk in the upper second and third quartiles, but the association diminished thereafter. There were no significant associations between consumption of sugars from desserts and prostate cancer risk. There was additionally no association between consumption of concentrated sugars and prostate cancer risk when sugar consumption was analysed as a continuous variable (not shown).

There were no associations between servings of sugar-sweetened beverages and prostate cancer risk. There was also no discernable pattern between servings of fruit juices and prostate cancer risk (data not shown).

We sought to determine if the associations between sugars from sugar-sweetened beverages and prostate cancer risk were modified by race (White *v.* non-White) or number of PSA screens (none *v.* at least one) (Table 3). Number of PSA screens had no effect on the association between sugar consumption and prostate cancer risk, and there was no statistical interaction (Q4 *v.* Q1, $P_{\text{interaction}} = 0{\cdot}92$). Similarly, race did not significantly modify the association between consumption of sugars from sugar-sweetened beverages and prostate cancer risk (Q4 *v.* Q1, $P_{\text{interaction}} = 0{\cdot}94$), and positive associations with sugar consumption were noted for White men only, in the third and fourth quartiles. As diabetes history has previously been inversely associated with prostate cancer risk, and is likely associated with sugar consumption, we also examined the association between sugar-sweetened beverages and prostate cancer risk in individuals without previous history of diabetes. The trend was similar to that seen in the full analytic cohort (Q2, HR: 1·11; 95 % CI 0·97, 1·26; Q3, HR: 1·16; 95 % CI 1·02, 1·33; Q4, HR: 1·20; 95 % CI 1·05, 1·37) (not shown).

We additionally examined multivariable-adjusted associations between consumption of all concentrated sugars (sugar-sweetened beverages, fruit juices and desserts) or all dietary added sugars and prostate cancer risk (Table 4). No significant associations were found.

Table 1. Baseline, demographic and lifestyle characteristics of participants in the control arm of the Prostate, Lung, Colorectal and Ovarian study according to intake of concentrated sugars*† (Numbers and percentages; mean values and standard deviations)

			Quartiles (g/d)							
	Total		<23·47 (*n* 5680)		23·47–40·20 (*n* 5680)		40·21–65·93 (*n* 5678)		≥65·94 (*n* 5682)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Family history	1625	7·2	359	22·1	386	23·8	443	27·3	437	26·9
History of diabetes	1842	8·1	880	47·8	473	25·7	282	15·3	207	11·2
Ethnicity										
White	20 633	90·8	5040	24·4	5190	25·2	5251	25·5	5152	25·0
Black	589	2·6	103	17·5	114	19·4	131	22·2	241	40·9
Hispanic	357	1·6	90	25·2	76	21·3	93	26·1	98	27·5
Asian/Pacific Islander	1089	4·8	436	40·0	286	26·3	192	17·6	175	16·1
Other	52	0·2	11	21·2	14	26·9	11	21·2	16	30·8
Education										
<12 years	1542	6·8	394	25·6	319	20·7	384	24·9	445	28·9
High school	4187	25·3	1005	24·0	988	23·6	990	23·6	1204	28·8
Post-high school	7392	57·9	1885	25·5	1786	24·2	1807	24·5	1914	25·9
College graduate	9557	42·1	2383	24·9	2577	27·0	2484	26·0	2113	22·1
Smoking										
Never	8588	37·7	1881	22·0	2090	24·4	2232	26·1	2355	27·5
Current	2301	10·1	520	22·6	499	21·7	551	24·0	731	31·8
Former	11861	52·2	3279	27·7	3091	26·1	2895	24·4	2596	21·9
Number of PSA screens‡										
None	9956	43·4	2430	24·4	2401	24·1	2444	24·6	2681	26·9
Once	8518	37·5	2135	25·1	2167	25·4	2187	25·7	2029	23·8
More than once	2314	10·2	586	25·3	637	27·5	598	25·8	493	21·3
Unknown	1932	8·5	529	27·4	475	24·6	449	23·2	479	24·8
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	65·6	5·9	65·5	5·8	65·9	5·9	65·9	6·0	65·0	6·0
Pack-years	24·4	30·8	26·6	30·9	24·1	30·3	23·0	20·1	23·6	31·7
BMI (kg/m^2)	27·5	4·1	27·9	4·3	27·5	3·9	27·3	4·0	27·5	4·1
Sugar-sweetened beverages (g/d)	16·0	29·7	2·0	3·2	5·8	6·8	12·5	12·4	43·7	47·2
Fruit juices (g/d)	13·7	19·6	4·6	4·5	10·4	7·9	14·9	11·9	24·8	33·0
Desserts (g/d)	21·5	20·1	7·7	5·1	15·4	8·5	24·2	13·3	38·9	28·2
All added sugars (teaspoons/d)	14·3	10·3	6·4	3·1	10·0	3·6	14·4	4·5	26·4	12·6
Energy content (kJ/d)	8322	3414	6581	2883	7464	2753	8577	2916	10 669	3586
Energy content (kcal/d)	1989	816	1573	689	1784	658	2050	697	2550	857

* Quartiles represent total sugars consumed from sugar-sweetened beverages, fruit juices and desserts.
† *P* value family history = 0·01; *P* value for all other variables <0·0001.
‡ Screening over previous 3 years.

Table 2. Multivariable associations of consumption of concentrated sugars (g) from beverages with prostate cancer risk†‡ (Hazard ratios (HR) and 95 % confidence intervals)

	Sugar-sweetened beverages			Fruit juices			Desserts		
	Cases (*n*)/ total person-years	HR	95 % CI	Cases (*n*)/ total person-years	HR	95 % CI	Cases (*n*)/ total person-years	HR	95 % CI
Prostate cancer (*n* 1996)									
Q1	398/41 955	1·00	–	433/45 505	1·00	–	481/45 662	1·00	–
Q2	544/48 923	1·11	0·97, 1·26	524/46 618	1·14	1·01, 1·30	488/45 975	0·97	0·85, 1·10
Q3	519/45 944	1·14	1·00, 1·31	514/44 009	1·15	1·01, 1·31	527/45 746	1·03	0·91, 1·18
Q4	535/46 608	1·21**	1·06, 1·39	525/47 298	1·07	0·94, 1·22	500/46 047	0·95	0·83, 1·10
Low grade (*n* 1014)									
Q1	202/41 032	1·00	–	218/44 466	1·00	–	262/44 596	1·00	–
Q2	274/47 668	1·09	0·91, 1·31	271/45 336	1·17	0·97, 1·39	241/44 751	0·86	0·72, 1·03
Q3	251/44 693	1·14	0·94, 1·37	262/42 822	1·20	0·95, 1·37	257/44 436	0·90	0·76, 1·08
Q4	277/45 305	1·25*	1·03, 1·51	263/46 074	1·05	0·87, 1·26	254/44 915	0·87	0·71, 1·05
High grade (*n* 960)									
Q1	193/41 020	1·00	–	212/44 534	1·00	–	217/44 493	1·00	–
Q2	264/47 746	1·12	0·93, 1·36	248/45 378	1·13	0·94, 1·36	244/44 973	1·10	0·91, 1·33
Q3	251/44 850	1·14	0·94, 1·39	243/42 915	1·13	0·94, 1·36	262/44 563	1·18	0·98, 1·43
Q4	252/45 333	1·19	0·97, 1·45	257/46 122	1·09	0·90, 1·31	237/44 920	1·05	0·85, 1·29

Q, quartile; PSA, prostate-specific antigen.
* $P_{for\ trend} < 0{\cdot}05$, ** $P_{for\ trend} < 0{\cdot}01$.
† Adjusted for age, race, study centre, BMI, education, smoking, family history of prostate cancer, history of diabetes, PSA screening and energy intake.
‡ Quartile cutpoints (g/d): sugar-sweetened beverages – 0·63, 4·83, 19·21; fruit juices – 2·55, 9·24, 20·01; desserts – 7·85, 16·18, 28·87.

Table 3. Multivariable associations of consumption of concentrated sugars (g) from sugar-sweetened beverages with prostate cancer risk according to prostate-specific antigen (PSA) screens and race*† (Hazard ratios (HR) and 95 % confidence intervals)

	No PSA screens			≥ 1 PSA screen			
	Cases (*n*)/total person-years	HR	95 % CI	Cases (*n*)/total person-years	HR	95 % CI	*P*‡
Q1	180/20 059	1·00	–	216/24 553	1·00	–	
Q2	225/20 123	1·16	0·95, 1·41	253/23 447	1·04	0·86, 1·24	0·40
Q3	219/20 209	1·15	0·94, 1·40	271/21 526	1·15	0·97, 1·38	0·95
Q4	218/20 511	1·18	0·97, 1·44	271/17 630	1·17	0·97, 1·40	0·92
	White			Non-white			
Q1	368/39 120	1·00	–	38/2835	1·00	–	
Q2	448/40 082	1·22	0·98, 1·29	46/3365	1·07	0·70, 1·63	0·83
Q3	488/41 140	1·20	1·04, 1·37	34/4566	0·78	0·49, 1·22	0·07
Q4	513/46 084	1·19	1·03, 1·36	61/6238	1·21	0·80, 1·82	0·94

Q, quartile.
* Adjusted for age, race, study centre, BMI, education, smoking, family history of prostate cancer, history of diabetes, PSA screening and energy intake.
† Quartile cutpoints (g/d): no PSA screens – 0·89, 5·95, 21·17; ≥1 PSA screen – 0·63, 4·13, 17·23; white – 0·63, 3·92, 16·42; non-white – 1·19, 7·74, 22·67.
‡ *P* value from heterogeneity test.

Discussion

In this prospective study of men within the usual-care arm of the PLCO screening trial, we found that consumption of sugars from sugar-sweetened beverages was associated with increased prostate cancer risk for men in the upper third and fourth quartiles of sugar intake.

We did not find a similar trend with consumption of sugars from fruit juices. There was no linear association even after controlling for grams of tomato and vegetable juice consumed or exclusion of tomato and vegetable juices from the exposure variable. Type of fruit juice consumed might be particularly relevant, but this is not discernible from the present study. Additional investigation revealed <30 % overlap for consumption of sugars from fruit-juices and sugar-sweetened beverages comparing any one quartile, suggesting the association of consumption of fruit juices with prostate cancer risk was not confounded by sugar-sweetened beverages and vice versa.

Number of servings of sugar-sweetened beverages overall was low, and it was not possible to examine the quartile distribution of servings of these beverages without including servings of sugars added to tea and coffee, which included sugar and honey, which likely confounded results. Tea and coffee contain polyphenols and can potentially confound the association of sugar-rich beverages with prostate cancer risk. Moreover, it was not possible to separate sugars and honey added to tea or coffee. When analysing sugars in grams of soft drinks only, excluding sugars added to tea and coffee, the association was still present but not as strong, and the linear

Table 4. Multivariable associations of all concentrated or non-natural sugars with prostate cancer risk*
(Hazard ratios (HR) and 95 % confidence intervals)

Quartiles	Cases (*n*)/total person-years	HR	95 % CI
All concentrated†			
Q1	451/45 684	1·00	–
Q2	525/45 579	1·11	0·97, 1·26
Q3	507/46 021	1·04	0·91, 1·19
Q4	513/46 146	1·07	0·93, 1·23
All added‡			
Q1	457/45 316	1·00	–
Q2	535/45 766	1·12	0·99, 1·28
Q3	488/45 967	1·00	0·88, 1·15
Q4	516/46 381	1·08	0·93, 1·25

Q, quartile; PSA, prostate-specific antigen.
* Adjusted for age, race, treatment centre, BMI, education, smoking, family history of prostate cancer, history of diabetes, PSA screening and energy intake.
† Includes desserts, sugar-sweetened beverages and fruit juices; quartile cutpoints (g/d): 23·47, 40·20, 65·94.
‡ Quartile cutpoints (teaspoons/d): 7·43, 11·73, 18·15.

trend persisted. This might be expected as grams of sugars added to tea and coffee constituted approximately 25 % of sugars in the sugar-sweetened beverages category.

Other studies have examined the association between carbohydrate or added sugar intake and prostate cancer risk. In a prospective Swedish cohort study, it was found that some refined carbohydrates including cakes and biscuits, low-fibre cereals and rice and pasta were associated with low-grade or overall prostate cancer[26]. Increased consumption of sugar-sweetened beverages was associated with increased risk of symptomatic prostate cancer, characterised by malignancy-related symptoms (but not total or low-grade cancer). In a separate prospective study, an inverse association was reported between total fructose intake (fruit and non-fruit-derived) and prostate cancer risk[27]. Fructose, however, has been shown to promote growth of pancreatic cancer cells, and is believed to have an important role in inflammation[6,12]. We did not observe an association between fructose and prostate cancer risk in our study (not shown). Neither was an association observed when considering a composite variable representing all added sugars from the diet. These findings emphasise the potential significance of concentrated added sugars on prostate cancer risk. In our study, sugar-sweetened beverages, and particularly sodas, contributed the greatest amount of sugar relative to the other categories.

Other dietary and behavioural factors may affect prostate cancer risk. Fruit and vegetable consumption has been shown to affect cancer risk, although evidence on the relative role of fruit and vegetables in prostate cancer susceptibility is inconclusive. It was previously reported that high vegetable consumption may be associated with reduced risk of aggressive prostate cancer in the PLCO study[28]. In our models, the effect of daily servings of vegetables and fruits on associations between sugar intake and prostate cancer risk was negligible.

It is plausible that body weight might interact with sugar to increase prostate cancer risk, but the relationship between obesity and prostate cancer is complex. There is evidence that obese men may have higher risk of high-grade cancers, although they may have lower PSA levels[29–31]. In addition, increased intake of sugar-sweetened beverages has been associated with increased weight gain[32,33], although an inverse association between BMI and sugar intake has also been reported for men, particularly[34]. For this reason BMI was included as a confounder when analysing the association between dietary sugar and prostate cancer risk, although its effect on estimates was negligible. Comparisons at baseline revealed markedly increased energy intake for men in the highest quartile of sugar consumption, although mean BMI was not higher for these men. Regular or vigorous exercise might also be associated with reduced risk of prostate cancer, particularly advanced cancer, based on some evidence from large, prospective cohort studies[35–37]. It is unclear how physical activity affected the association between sugar consumption and prostate cancer risk in the usual-care arm, as this information was not ascertainable from the DHQ.

Consumption of concentrated sugars may be related to prostate cancer risk through activation of inflammatory cytokines, such as interleukins, C-reactive protein, and TNF[38], among others, as a result of elevated uric acid in the serum or another mechanism. Increases in uric acid, particularly, may lead to increased production of IL-1β, and chronic inflammation[39]. Alternatively, elevated TAG or cholesterol could be related to prostate cancer risk[40] by inducing activation of signalling by NF-κB[21] or protein kinase B, and ultimately other inflammatory factors[41,42]. Furthermore, there is evidence that fructose, a common compound present at high concentrations in sugar-sweetened beverages and desserts, is converted to fat more rapidly than other sugars[43]. It is true that naturally occurring sugars and added sugars share the same chemical structure. However, the difference to be noted is perhaps in the broader range of physiological effects that ultimately regulate inflammatory processes. It is important to highlight that processed sugar-dense goods may not have the same effect on the blood glucose. Absorption of sugars in plant foods occurs more slowly and is more regulated due to buffering by vitamins and fibre, and phytonutrients, such that there is not a spike in blood sugar and consequently, a heightened inflammatory response[44]. Therefore, studies examining consumption of total sugars may not report positive associations with chronic disease. In addition to the potentially greater relevance of concentrated sugars over total sugars, our study highlights a more detrimental role of concentrated sugars from beverages than desserts in the context of prostate cancer risk. Physiological events associated with digestion and metabolism of these sugars, particularly, could lead to increases or alterations in pro-inflammatory cytokines, and ultimately chronic inflammation.

Strengths of the study include the large number of study participants and high follow-up rate, detailed information on sugar consumption obtained from the FFQ and subsequently thorough nutrient analysis, as well as complete information on demographic and clinical factors affecting prostate cancer risk. Limitations include possible measurement error in sugar intake due to misreporting or information bias, and limitations of the nutrient database in distinguishing natural from added sugars. Also, because dietary habits fluctuate, interpretation of findings of diet-related associations with cancer is more difficult in studies where the exposure assessed represents a single point in time. We were unable to accurately compare the role of sugar

consumption with prostate cancer risk between the screening and usual-care arms of the PLCO, as differences in the dietary assessment tools between study arms as well as the timing of administration of the DHQ precluded direct comparison. Furthermore, while risk of advanced stage prostate cancer or prostate cancer mortality are important clinically relevant endpoints, we were unable to examine the association of sugar consumption with these endpoints due to the very low number of men with advanced stage prostate cancer and limited number of prostate cancer-specific deaths. Therefore, conclusions of the present study are limited and consumption of concentrated sugars should be examined in other settings.

In conclusion, this study provides evidence for a positive association between sugars from sugar-sweetened beverages and increased risk of prostate cancer among men receiving usual medical care in the PLCO trial. Our findings highlight the potential significance of high consumption of added, concentrated sugars from beverages in prostate cancer aetiology. Additional studies examining this association are warranted.

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