Original research

Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women

Jinhee Hur ![ORCID],[1] Ebunoluwa Otegbeye ![ORCID],[2,3] Hee-Kyung Joh,[1,4] Katharina Nimptsch,[1,5] Kimmie Ng,[6] Shuji Ogino ![ORCID],[7,8,9] Jeffrey A Meyerhardt,[6] Andrew T Chan,[9,10,11,12,13] Walter C Willett,[1,8,12] Kana Wu,[1] Edward Giovannucci ![ORCID],[1,8,12] Yin Cao ![ORCID][3,14,15]

ABSTRACT

Objective Sugar-sweetened beverage (SSB) consumption had substantially increased across successive US birth cohorts until 2000, and adolescents and young adults under age 50 years have the highest consumption. However, the link between SSBs and early-onset colorectal cancer (EO-CRC) remains unexamined.

Design In the Nurses' Health Study II (1991–2015), we prospectively investigated the association of SSB intake in adulthood and adolescence with EO-CRC risk among 95 464 women who had reported adulthood beverage intake using validated food frequency questionnaires (FFQs) every 4 years. A subset of 41 272 participants reported beverage intake at age 13–18 years using a validated high school-FFQ in 1998. Cox proportional hazards models were used to estimate relative risks (RRs) with 95% CIs.

Results We documented 109 EO-CRC cases. Compared with individuals who consumed <1 serving/week of SSBs in adulthood, women who consumed ≥2 servings/day had a more than doubled risk of EO-CRC (RR 2.18; 95% CI 1.10 to 4.35; p_{trend}=0.02), with a 16% higher risk (RR 1.16; 95% CI 1.00 to 1.36) per serving/day increase. Each serving/day increment of SSB intake at age 13–18 years was associated with a 32% higher risk of EO-CRC (RR 1.32; 95% CI 1.00 to 1.75). Replacing each serving/day of adulthood SSB intake with that of artificially sweetened beverages, coffee, reduced fat milk or total milk was associated with a 17%–36% lower risk of EO-CRC.

Conclusion Higher SSB intake in adulthood and adolescence was associated with a higher risk of EO-CRC among women. Reduction of SSB consumption among adolescents and young adults may serve as a potential strategy to alleviate the growing burden of EO-CRC.

Significance of this study

What is already known on this subject?
► Incidence of early-onset colorectal cancer (EO-CRC, diagnosed under age 50 years) has been on the rise in many high-income countries over the past two decades.
► Sugar-sweetened beverages (SSBs) can exert adverse metabolic repercussions throughout the life course, including childhood and adulthood obesity and type 2 diabetes.
► Despite the highest level of SSB consumption being characterised among adolescents and young adults, the association between SSBs and EO-CRC has not been investigated.

What are the new findings?
► Compared with <1 serving/week of SSB consumption, higher intake (ie, ≥2 servings/day) in adulthood was associated with a 2.2-fold higher risk of EO-CRC.
► Each serving/day increment of SSB intake at age 13–18 years was associated with a 32% higher risk of EO-CRC.
► Replacing adulthood intake of SSBs with that of artificially sweetened beverages, coffee, reduced fat milk or total milk was associated with a lower risk of EO-CRC.

How might it impact on clinical practice in the foreseeable future?
► SSB consumption may contribute to the rising incidence of EO-CRC.
► Reducing SSB intake and/or replacing SSBs with other healthier beverages among adolescents and young adults may serve as a potential actionable strategy to alleviate the growing burden of EO-CRC.

INTRODUCTION

The incidence of early-onset colorectal cancer (EO-CRC, age <50 years at diagnosis) has been on the rise in many high-income countries over the past two decades.[1–3] In the US population born after 1950, the EO-CRC incidence has increased across subsequent birth cohorts.[4 5] Compared with adults born around 1950, those born around 1990 had two times the risk of colon cancer and four times the risk of rectal cancer.[4] This postulates that increasingly prevalent exposures across birth cohorts may be driving the incidence upward; yet, such aetiologic factors remain largely unidentified.

Sugar-sweetened beverages (SSBs, eg, soft drinks, fruit drinks, sports drinks and energy drinks) comprise the leading (39%) source of added sugar in US diets,[6] and 12% of the population consume more than three servings per day.[7] Coinciding

with the rising EO-CRC incidence that showed a birth cohort effect,[4 5] age- and birth cohort-specific SSB consumption considerably increased from 1977 to 2001.[8] For example, caloric contribution from SSBs more than doubled from 5.1% to 12.3% among individuals aged 19–39 years and from 4.8% to 10.3% among those aged 2–18 years.[8] SSBs can exert adverse metabolic repercussions throughout the life course.[9–11] In adulthood, each additional daily serving of SSBs was associated with a 12% higher risk of obesity[12] and a 18% higher risk of type 2 diabetes.[13] SSBs are also considered a major contributor to childhood obesity[14–16] and insulin resistance.[17] Interestingly, childhood obesity is known to exacerbate insulin resistance during puberty[18 19] and interrupt recovery of glucose homeostasis afterwards, which can leave lasting adverse metabolic consequences.[20]

As growing evidence supports a plausible link of metabolic conditions, including adulthood and adolescent obesity and early-onset type 2 diabetes with EO-CRC,[21–23] investigation of SSB intake throughout the life course with EO-CRC risk is a logical step and immediate need due to limited actionable strategies to reduce the growing burden of EO-CRC. Although existing epidemiologic evidence linking SSBs and CRC risk is inconclusive,[24–28] emerging experimental studies strongly support such a link.[29 30] Artificially sweetened beverages (ASBs) and 100% fruit juice have been considered alternatives to SSBs and increasingly consumed in adolescents and adults,[31–33] but much remains to be answered regarding their long-term health implications.

To address these knowledge gaps, we investigated the association between intake of sweetened beverages in adulthood and adolescence, with a particular emphasis on SSBs, and risk of EO-CRC. We leveraged data from the Nurses' Health Study II (NHSII), a large, prospective US cohort of young women, which uses a validated assessment of both adulthood and adolescent beverage intake.

METHODS
Study population
The NHSII is an ongoing prospective cohort study of 116 429 US female registered nurses aged 25–42 years at enrolment in 1989. Biennially, participants self-reported detailed information on demographics, lifestyle and medical history. Dietary intake was assessed using validated, semi-quantitative food frequency questionnaires (FFQs) approximately every 4 years. Return of the completed questionnaire implied informed consent to study participation.

Ascertainment of colorectal cancer
The primary end point was the diagnosis of incident invasive EO-CRC. We requested permission to review medical records or pathology reports for CRC diagnoses reported on a biennial questionnaire or lethal CRC cases identified from the National Death Index, tumour registries or death certificates. Study physicians were masked to participant information, reviewed the records and confirmed diagnosis, date, anatomic location, histology and stage.

Assessment of adulthood and adolescent beverage intake
In 1991 and every 4 years thereafter, beverage intake was assessed via validated semi-quantitative FFQs,[34 35] where participants reported how often, on average, they consumed each of ~130 food or beverage items during the past 12 months. Nine response options were available, ranging from 'never or less than once per month (referred to never)' to '≥6 times per day'. SSBs were defined as carbonated or non-carbonated beverages

with sugar (eg, soft drinks, fruit drinks, sports drinks and sweetened tea beverages). ASBs were defined as low-calorie carbonated beverages. One standard serving size for SSBs and ASBs was equivalent to 12 ounces (oz). Fruit juice included apple juice, orange juice, grapefruit juice, prune juice and other fruit juices, with 4–6 oz as the standard portion size. We also assessed consumption of other beverages including tap or bottled water, tea, coffee, reduced fat milk and whole milk with the serving size of 8 oz. In the current analysis, we converted the portion size of any beverages into 8 oz for consistency. As a measure of validity, the Pearson's correlation coefficients between the FFQ and multiple dietary records were 0.84 for soft drinks and fruit juice, 0.93 for tea, 0.78 for coffee, 0.81 for reduced fat milk, and 0.62 for whole milk.[36]

In 1998, we additionally assessed dietary intake in adolescence among a subset of participants through a supplementary, high school (HS)-FFQ, comprising 124 food items typically consumed between 1960 and 1982 during which participants were at age 13–18 years. Adolescent beverage consumption was categorised into SSBs, ASBs and fruit juice, having 8 oz as one serving size. The validity and reproducibility of adolescent diet recalled in adulthood have been reported.[37 38] The Pearson's correlation coefficient was 0.58 for energy-adjusted nutrient intake among two FFQs that 80 young women completed in high school and the HS-FFQ administered 10 years later.[37] In randomly selected 333 NHSII participants who also completed a second HS-FFQ in 2002, the Spearman's rank correlation coefficient for adolescent beverage intake was 0.70 between the two HS-FFQs.[38]

Assessment of covariates
Detailed information on potential CRC risk factors was obtained at baseline with updates during follow-up. This included weight, menopausal status and menopausal hormone use, family history of CRC in one or more first-degree relatives at any age at first diagnosis, smoking habits, physical activity in metabolic equivalent of task (MET)-hours, regular use (≥2 times/week) of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) and current use of multivitamins. Using FFQs, intake of total calories, alcohol, red and processed meat, dietary fibre, total folate (from foods and supplements) and total calcium was updated every 4 years. Diet quality was assessed by the Alternative Healthy Eating Index (AHEI)-2010.[39] Biennially, participants reported history of colonoscopy/sigmoidoscopy during the previous 2 years with the corresponding indications.

In 1989, we asked participants to recall their health status and lifestyle in adolescence. Adolescent body mass index (BMI) was calculated using recalled weight at age 18 years and height. Pack-years of smoking before age 20 years were obtained using the duration and average number of cigarettes smoked per day. Alcohol intake at age 15–17 years was estimated from the usual number of alcoholic drinks consumed per week. Dietary intake and multivitamin use at age 13–18 years was assessed via a HS-FFQ. In 1997, physical activity in MET-hours/week at grade 9–12 was assessed using a questionnaire with reasonable reliability.[40]

Statistical analysis
We set the analytic baseline to 1991 when beverage intake was first reported. We excluded women who had died or had CRC or IBD prior to baseline, who reported implausible energy intake (<600 or >3500 kcal/day) and who had missing information on beverage intake. A total of 95 464 women were included in the final analysis.

As our primary analysis, we investigated the associations of adulthood and adolescent beverage intake with risk of EO-CRC. Person-years of follow-up accrued from the date of the 1991 questionnaire return to the diagnosis of EO-CRC, 50th birthday, death or the end of follow-up (June 2015), whichever came first. To deal with the time-varying nature of adulthood beverage intake over the long duration of follow-up, we calculated the cumulative average of beverage intake collected across all available FFQs from the study baseline up to each questionnaire cycle to better represent long-term beverage intake reflecting true changes and minimising the extent of measurement error and within-person variation. Intake of SSBs, ASBs and fruit juice was categorised a priori according to a modification of the categories used in the prior studies (<1 serving/week, 1 serving/week to <1 serving/day, 1 to <2 servings/day, ≥2 servings/day).[27 41] Cox proportional hazards models were used to compute HRs, as estimates of relative risks (RRs) and 95% CIs. Models were stratified by age in months and biennial questionnaire cycle and adjusted for total caloric intake. We adjusted for the following putative CRC risk factors: race, height, BMI, menopausal status and menopausal hormone use, family history of CRC, pack-years of smoking, physical activity, regular use of aspirin or NSAIDs, current use of multivitamins, intake of alcohol, red and processed meat, dietary fibre, total folate and total calcium,

AHEI-2010 score without SSBs and alcohol and lower endoscopy due to screening or for other indications within the past 10 years. In additional analyses, we mutually adjusted for consumption of SSBs, ASBs and fruit juice. Test for trend was performed using the median of each category of beverage intake as a continuous variable.

For adolescent SSBs (<1 serving/week, 1 serving/week to <2 servings/day, ≥2 servings/day), we restricted the analyses to 41 272 participants who completed and returned the HS-FFQ in 1998. In addition to age- and energy-adjusted models, we adjusted for the following putative CRC risk factors in adolescence: race, height, BMI at age 18 years, pack-years of smoking before age 20 years, intake of alcohol at age 15–17 years, red and processed meat, dietary fibre, total folate and total calcium at age 13–18 years, multivitamin use at age 13–18 years and physical activity at grade 9–12.

We estimated risk of EO-CRC associated with substitution of other beverages including ASBs, fruit juice, water, tea, coffee, reduced fat milk or total milk for SSB intake in adulthood, by adding SSBs and the alternative beverage in the same multivariable model. RR was calculated using the difference in the two β-coefficients, with 95% CI using the corresponding variances and covariance.[42] Furthermore, we performed stratified analyses for the association of SSB intake (per each serving/day

Table 1 Age-standardised participant characteristics of person-years according to average beverage intake in adulthood among women younger than age 50 years in the NHSII, 1991–2015*

Characteristic	Sugar-sweetened beverages		Artificially sweetened beverages		Fruit juice	
	<1 serving/week	≥2 servings/day	<1 serving/week	≥2 servings/day	<1 serving/week	≥2 servings/day
Person-years, no.	536 446	138 469	424 283	353 780	450 890	14 825
Age, years	42.0 (5.2)	41.5 (5.5)	41.8 (5.3)	42.0 (5.2)	41.9 (5.2)	40.1 (5.6)
Race, white, %	94	90	91	95	93	85
Height, cm	165 (6.6)	165 (6.7)	165 (6.7)	165 (6.6)	165 (6.6)	165 (6.8)
BMI, kg/m²	25.2 (5.3)	25.5 (6.2)	23.7 (4.8)	26.7 (5.9)	25.5 (5.6)	23.6 (4.8)
Postmenopausal, %	8.8	11	8.9	9.8	9.9	8.1
Current menopausal hormone use among postmenopausal women, %	66	63	62	65	66	63
Family history of colorectal cancer, %	5.8	5.6	5.7	6.0	5.8	4.8
Screening lower endoscopy within the past 10 years, %	3.3	3.1	3.2	3.1	3.2	3.5
Lower endoscopy due to other indications within the past 10 years, %	6.5	8.3	6.8	7.5	6.9	6.6
Ever smokers, %	36	33	32	36	38	29
Pack-years among ever smokers	12.3 (9.4)	15.5 (11.3)	13.7 (10.5)	13.1 (9.8)	13.9 (10.3)	11.6 (9.4)
Physical activity, MET-hour/week	24.5 (26.4)	19.9 (24.6)	21.3 (24.8)	23.2 (25.4)	20.9 (24.1)	29.8 (33.1)
Regular use of aspirin, %	11	12	10	12	11	10
Regular use of non-aspirin NSAIDs, %	26	31	22	33	28	22
Current use of multivitamins, %	47	42	47	45	41	52
Dietary intake						
Alcohol, g/day	3.7 (6.3)	2.3 (5.2)	2.8 (5.6)	3.6 (6.3)	3.2 (6.1)	3.1 (6.4)
Red and processed meat, servings/week	5.5 (3.7)	8.1 (4.5)	6.3 (4.1)	6.8 (4.1)	6.1 (3.9)	6.1 (4.1)
Dietary fibre, g/day	20.1 (5.6)	14.6 (3.9)	17.9 (5.6)	18.4 (4.9)	18.2 (5.7)	18.7 (5.7)
Total folate, µg/day	523 (267)	410 (213)	497 (267)	478 (234)	455 (258)	597 (252)
Total calcium, mg/day	1119 (438)	837 (329)	1018 (417)	1042 (395)	1022 (439)	1039 (377)
Alternative Healthy Eating Index-2010 score†‡	42.4 (8.9)	35.3 (7.5)	40.3 (9.4)	38.9 (8.1)	39.2 (8.9)	43.2 (9.5)

*Data are presented as mean (SD) of person-years unless otherwise indicated. All values other than age were directly standardised to the age distribution (in 5-year intervals) of all participants.
†Without sugar-sweetened beverages and alcohol.
‡According to the predefined intake criteria for 11 dietary components (eg, fruits, vegetables, whole grains, nuts and legumes, red and processed meat, sugar-sweetened beverages, sodium, alcohol, polyunsaturated fatty acids, omega-3 fatty acids and trans fatty acids), a score ranging from 0 to 10 was given to each component, yielding a total score ranging from 0 to 110. A higher score reflects better diet quality.
BMI, body mass index; MET, metabolic equivalent of task; NHSII, Nurses' Health Study II; NSAID, non-steroidal anti-inflammatory drug.

Table 2 Sweetened beverage intake in adulthood and risk of early-onset colorectal cancer

Exposure	<1 serving/week	1 serving/week to <1 serving/day	1 serving/day to <2 servings/day	≥2 servings/day	P_{trend}*	Each serving/day increase
Sugar-sweetened beverages						
Person-years	536 446	504 341	178 886	138 469		
No. of cases	45	34	14	16		
Age- and energy-adjusted RR (95% CI)	1 (reference)	0.89 (0.56 to 1.41)	1.03 (0.55 to 1.92)	1.72 (0.93 to 3.20)	0.06	1.11 (0.96 to 1.29)
Multivariable RR (95% CI)†	1 (reference)	0.97 (0.61 to 1.55)	1.24 (0.65 to 2.39)	2.18 (1.10 to 4.35)	0.02	1.16 (1.00 to 1.36)
Artificially sweetened beverages						
Person-years	424 283	321 864	258 215	353 780		
No. of cases	32	33	19	25		
Age- and energy-adjusted RR (95% CI)	1 (reference)	1.25 (0.76 to 2.04)	0.95 (0.54 to 1.68)	0.86 (0.50 to 1.46)	0.32	0.96 (0.86 to 1.07)
Multivariable RR (95% CI)†	1 (reference)	1.20 (0.73 to 1.98)	0.86 (0.48 to 1.54)	0.73 (0.42 to 1.27)	0.11	0.93 (0.83 to 1.04)
Fruit juice						
Person-years	450 890	799 663	92 765	14 825		
No. of cases	44	59	5	1		
Age- and energy-adjusted RR (95% CI)	1 (reference)	0.81 (0.53 to 1.22)	0.66 (0.25 to 1.71)	0.90 (0.12 to 6.76)	0.41	1.04 (0.64 to 1.67)
Multivariable RR (95% CI)†	1 (reference)	0.86 (0.56 to 1.31)	0.77 (0.29 to 2.05)	1.20 (0.16 to 9.11)	0.69	1.20 (0.74 to 1.94)

One beverage serving is 8 oz.
*Calculated using the median of each category of beverage intake as a continuous variable.
†Additionally adjusted for race (white, non-white), height (continuous), body mass index (continuous), menopausal status and menopausal hormone use (premenopausal, postmenopausal never user, postmenopausal ever user, unknown menopausal status or hormone use), family history of colorectal cancer (yes, no), pack-years of smoking (continuous), physical activity (continuous), regular use of aspirin (yes, no), regular use of non-steroidal anti-inflammatory drugs (yes, no), current use of multivitamins (yes, no), intake of alcohol, red and processed meat, dietary fibre, total folate (from foods and supplements) and total calcium (all continuous), Alternative Healthy Eating Index-2010 score without sugar-sweetened beverages and alcohol (continuous) and lower endoscopy due to screening (yes, no) or for other indications within the past 10 years (yes, no).
RR, relative risk.

increment) with risk of EO-CRC, according to family history of CRC (yes, no), BMI (<25, ≥25 kg/m²), alcohol use (never, ever), cigarette use (never, ever) and adolescent SSB intake (<1, ≥1 serving/day). Test for interaction was performed using the Wald test with a cross-product term of SSB intake, modelled as a continuous variable and each potential effect modifier. All statistical analyses were performed using SAS 9.4 (SAS Institute), with a two-sided α=0.05.

Patient and public involvement
No patients and the public were involved in the design, conduct, reporting, and dissemination plans of this research.

RESULTS
Among 95 464 women studied, we documented a total of 109 incident EO-CRC cases over up to 24 years of follow-up (1 358 142 person-years). Participant characteristics of person-years according to beverage intake are presented in table 1. Individuals with higher SSB intakes in adulthood tended to be less physically active and more likely to have a lower endoscopy history due to indications, use NSAIDs and consume red and

processed meat. Also, they were less likely to take multivitamins and had lower intake of alcohol, fibre, folate and calcium, along with poorer diet quality. Individuals with higher ASB intakes were more likely to be overweight, and those with higher fruit juice intakes were less likely to be overweight. Similarly, women with greater SSB consumption at age 13–18 years were more likely to engage in unhealthy diet and lifestyle in adolescence (online supplemental table 1). Baseline characteristics of the study population according to beverage intake in adulthood is shown in online supplemental table 2).

Higher SSB intake in adulthood was associated with a higher risk of EO-CRC after adjusting for a list of putative CRC risk factors. Compared with individuals who consumed <1 serving/week, women who consumed ≥2 servings/day had a 2.2-fold higher risk of EO-CRC (RR 2.18; 95% CI 1.10 to 4.35; p_{trend}=0.02), with a 16% higher risk per each additional serving/day of SSB intake (RR 1.16; 95% CI 1.00 to 1.36) (table 2). Additional adjustment for adulthood intake of ASBs and fruit juice slightly attenuated the magnitude of this association (online supplemental table 3). In contrast, each serving/day increase in ASBs or fruit juice consumption in adulthood was not associated

Table 3 Sugar-sweetened beverage intake at age 13–18 years and risk of early-onset colorectal cancer

	<1 serving/week	1 serving/week to <2 servings/day	≥2 servings/day	P_{trend}*	Each serving/day increase
Person-years	113 475	218 172	25 788		
No. of cases	12	17	6		
Age- and energy-adjusted RR (95% CI)	1 (reference)	0.73 (0.34 to 1.58)	2.43 (0.83 to 7.05)	0.05	1.19 (0.92 to 1.54)
Multivariable RR (95% CI)†	1 (reference)	0.78 (0.36 to 1.73)	3.41 (1.08 to 10.8)	0.01	1.32 (1.00 to 1.75)

One beverage serving is 8 oz.
*Calculated using the median of each category of beverage intake as a continuous variable.
†Additionally adjusted for race (white, non-white), height (continuous), body mass index at age 18 years (continuous), pack-years of smoking before age 20 years (continuous), intake of alcohol at age 15–17 years, red and processed meat, dietary fibre, total folate (from foods and supplements) and total calcium at age 13–18 years (all continuous), multivitamin use at age 13–18 years (yes, no) and physical activity at grade 9–12 (continuous).
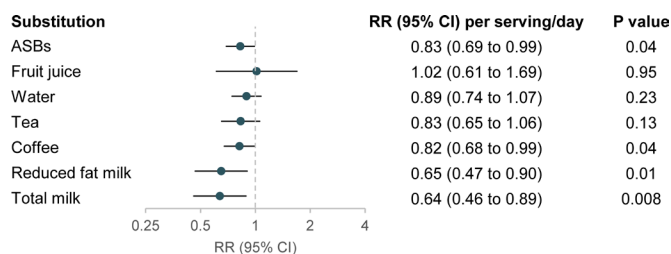RR, relative risk.

Substitution		RR (95% CI) per serving/day	P value
ASBs		0.83 (0.69 to 0.99)	0.04
Fruit juice		1.02 (0.61 to 1.69)	0.95
Water		0.89 (0.74 to 1.07)	0.23
Tea		0.83 (0.65 to 1.06)	0.13
Coffee		0.82 (0.68 to 0.99)	0.04
Reduced fat milk		0.65 (0.47 to 0.90)	0.01
Total milk		0.64 (0.46 to 0.89)	0.008

Figure 1 Substitution of other beverages for sugar-sweetened beverages with risk of early-onset colorectal cancer. ASB, artificially sweetened beverage; RR, relative risk. One beverage serving is 8 oz. The models were adjusted for covariates listed in the footnote of table 2.

with risk of EO-CRC (ASBs: RR 0.93; 95% CI 0.83 to 1.04; fruit juice: RR 1.20; 95% CI 0.74 to 1.94) (table 2).

Among a subset of participants, adolescent SSB consumption was also associated with a higher risk of EO-CRC after adjusting for potential confounding factors in adolescence (table 3). Each serving/day increment of SSB intake at age 13–18 years was associated with a 32% higher risk of subsequently developing EO-CRC (RR, 1.32; 95% CI 1.00 to 1.75). Further adjustment for adulthood intake of SSBs and total calories slightly attenuated the effect estimates (data not shown).

For adulthood SSB intake, we further evaluated the association of replacing 1 serving/day of SSBs with an equivalent amount of other beverages. This was associated with a 17%–36% lower risk of EO-CRC (ASBs: RR 0.83; 95% CI 0.69 to 0.99; coffee: RR 0.82; 95% CI 0.68 to 0.99; reduced fat milk: RR 0.65; 95% CI 0.47 to 0.90 and total milk: RR 0.64; 95% CI 0.46 to 0.89) (figure 1). Substituting water or tea for SSBs appeared to be associated with a lower EO-CRC risk but did not reach statistical significance. Fruit juice substitution did not appear to reduce risk of EO-CRC. In a stratified analysis for adulthood SSB intake and risk of EO-CRC, the positive association did not substantially vary by family history of CRC, BMI, alcohol use, cigarette use and adolescent SSB intake (all $p_{interaction} \geq 0.23$) (online supplemental figure 1).

DISCUSSION

In this large prospective US cohort study of younger women, higher SSB consumption in adulthood and adolescence was associated with a substantially higher risk of EO-CRC; no associations were observed for ASBs or fruit juice consumption in adulthood. Replacing SSB intake in adulthood with ASBs, coffee, reduced fat milk or total milk was associated with a lower risk of EO-CRC. Our findings add unique epidemiologic evidence that SSB intake may partly contribute to the rapid increase of CRC in younger adults.

Although US adults aged 20–34 years have had the highest level of SSB consumption (1.7 servings/day on average) across all age groups over the past several decades,[43 44] epidemiologic evidence on the role of SSBs in colorectal carcinogenesis remains inconclusive. In a pooled analysis of 13 prospective cohort studies, soft drink consumption was not associated with colon cancer.[24] Recent cohort studies from France and the USA reported no association between total SSBs and CRC;[25–27] however, these studies were subject to a limited number of cases consuming >1 serving/day of SSBs, and some used baseline SSB intake only.[25 27] In contrast, a recent Australian cohort study with 112 cases consuming ≥1 time/day of soft drinks showed a 28% (HR 1.28; 95% CI 1.04 to 1.57) higher CRC risk among these individuals, compared with those who consumed <1 time/

month.[28] During the second half of the 20th century, average US per capita soft drink consumption has dramatically increased by ~500%.[45] More importantly, compared with older generations, those born after the 1950s started to drink SSBs earlier in life and had higher intake across successive cohorts.[8] This age- and birth cohort-specific SSB consumption coinciding with the rising incidence of EO-CRC[4 5] lends support to the link between SSBs and risk of EO-CRC and may help explain the discrepancy between prior studies and ours. As accumulating evidence supports early- versus late-onset CRC may have different proportions of genetic, pathological and molecular characteristics,[46] established or putative CRC risk factors need to be examined in the context of EO-CRC, as strengths of the association for the same risk factor may differ. Our study thus addressed these knowledge gaps by leveraging long-term SSB intake assessed repeatedly via validated FFQs and demonstrated a positive association of SSB intake in adulthood with risk of EO-CRC. This association was independent of a list of confounding factors and did not appreciably vary by CRC family history, obesity and alcohol intake. We also reported a 32% higher risk of EO-CRC per serving/day increment of SSBs in adolescence. While our sample size was limited and this finding requires further validation, it is important to note that 30% of US children and adolescents consume >1.5 servings of SSBs daily.[7] Taken together, our study provides preliminary evidence linking SSB intake across different life stages with risk of EO-CRC. Further studies with larger sample sizes in more diverse populations are needed to validate these findings.

In line with prior studies among older adults,[25 26 28] we found that intake of ASBs or fruit juice in adulthood was not associated with risk of EO-CRC. However, considering the emerging link between these beverages and diabetes,[13] as well as overall and obesity-related cancers,[25 26] future research is warranted. Of note, substitution of reduced fat milk or total milk for SSBs appeared to be especially beneficial in lowering EO-CRC risk, which may point to the protective role of milk and calcium against EO-CRC, as with that in CRC among older adults.[47] From 1989 to 2008, along with a 63% increase in SSB consumption among US school-aged children, there was a 22% reduction in milk consumption,[48] which may have exacerbated EO-CRC risk among younger adults.

Various biological mechanisms support the plausibility of our findings on SSBs and EO-CRC. Compared with intake of isocaloric solid foods, energy-containing beverages that lack dietary compensation suppress feeling satiety and promote excess energy intake, which can ultimately result in weight gain.[9 49] As indicated by their high glycaemic index,[50] SSBs initiate rapid blood glucose response and insulin secretion, which in the long-term can induce insulin resistance, inflammation, obesity and type 2 diabetes,[51] all of which are metabolic conditions tied to increased CRC risk.[52] Specifically, fructose, a major component of sucrose and high fructose corn syrup (HFCS), which are primary sweeteners of SSBs, has been postulated to exert these adverse metabolic effects.[9 53] In addition to this classic, obesity-related pathway, emerging data have uncovered some novel mechanisms. Excess fructose surpassing the small intestinal absorption capacity reaches the colon.[29 54] By causing dysbiosis and endotoxaemia,[55] fructose can impair gut barrier function and increase gut permeability,[56] which could promote colorectal carcinogenesis. A recent experimental study demonstrated that HFCS-treated mice had substantial colon tumour growth with aggressive tumour grade, independent of obesity and metabolic syndrome,[30] which lends additional support to the link between SSBs and CRC risk.

Strengths of our study include a long-term follow-up and rigorous dietary data spanning various life stages from adolescence, which have been considered important aspects in studying the aetiology of EO-CRC.[46] Specifically, our analyses included 95 464 young women followed for up to 24 years. Prospective and repeated assessment of SSB intake via validated FFQs allowed the capture of long-term intake, reflecting true changes and minimising the extent of measurement error and recall bias. Additional use of validated data on adolescent dietary intake enabled us to examine the association between SSBs and EO-CRC across different life stages. Several limitations need to be considered while interpreting our findings. First, as with every observational study, residual or unmeasured confounding cannot be ruled out completely. Nonetheless, we have collected an extensive list of putative CRC risk factors both in adulthood and adolescence and thus were able to account for a wide variety of potential confounding factors. Second, despite detailed SSB intake information collected across various life stages, we were not able to conclusively identify the aetiologically relevant time window of exposure due to the limited number of EO-CRC cases (n=109). Third, the low proportion (<2%) of individuals with diabetes in our study population, which was similar to the prevalence among US adults under age 45 years,[57] allowed limited power and feasibility to account for or stratify by a personal history of diabetes when testing our hypothesis. Fourth, we were not able to probe whether the similar association would be observed among individuals carrying pathogenic germline mutations, which have been identified among ~20% of EO-CRC cases.[58] Fifth, the vast majority of our study population comprised white female nurses. The generalisability of our findings to men or other racial/ethnic groups remains to be explored.

In conclusion, in this large prospective cohort study of US women, higher SSB intake in adulthood and adolescence was associated with a substantially higher risk of EO-CRC. Considering the well-established, adverse health consequences of SSBs and the highest consumption being characterised in adolescents and young adults under age 50 years, our findings reinforce the public health importance of limiting SSB intake for better health outcomes. With recent downward trends,[43 44] limiting SSB intake may serve as an effective and actionable strategy to curb the rising incidence of EO-CRC.

Author affiliations

[1]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[2]Department of Surgery, Washington University School of Medicine, St. Louis, MO, USA
[3]Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA
[4]Department of Medicine, Seoul National University College of Medicine, Seoul, South Korea
[5]Molecular Epidemiology Research Group, Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany
[6]Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA
[7]Program in Molecular Pathological Epidemiology, Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[8]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[9]Eli and Edythe L. Broad Institute of Massachusetts Institute of Technology and Harvard University, Cambridge, MA, USA
[10]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
[11]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
[12]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[13]Department of Immunology and Infectious Disease, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[14]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, MO, USA
[15]Division of Gastroenterology, Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA

Twitter Yin Cao @yincaoScD

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Supplementary Table 1. Age-standardized participant characteristics of person-years according to average sugar-sweetened beverage intake at age 13-18 among women younger than age 50 in the NHSII, 1998-2015[a]

Characteristic	Sugar-sweetened beverage intake at age 13-18		
	<1 serving/wk	1 serving/wk to <2 servings/d	≥2 servings/d
Person-years, No.	113 475	218 172	25 788
Age, y	44.5 (3.9)	44.6 (3.9)	44.1 (4.1)
Race, white, %	95	94	94
Height, cm	165 (6.7)	165 (6.6)	164 (6.6)
BMI at age 18, kg/m²	21.6 (3.3)	20.9 (3.1)	21.0 (3.5)
Ever smokers before age 20, %	20	22	33
Pack-years among ever smokers before age 20	2.9 (2.2)	2.8 (2.1)	3.4 (2.3)
Physical activity at grade 9-12, MET-h/wk	52.6 (36.6)	54.7 (36.2)	57.0 (38.4)
Use of multivitamins at age 13-18, %	17	17	12
Dietary intake in adolescence[b]			
Alcohol, g/d	1.3 (4.1)	1.3 (3.7)	2.1 (5.8)
Red and processed meat, servings/wk	1.3 (0.7)	1.5 (0.7)	1.7 (0.7)
Dietary fiber, g/d	22.6 (6.2)	20.8 (4.8)	18.3 (4.1)
Total folate, µg/d	369 (140)	334 (112)	283 (94.7)
Total calcium, mg/d	1160 (375)	1077 (328)	872 (255)

Abbreviations: BMI, body mass index; MET, metabolic equivalent of task; NHSII, Nurses' Health Study II.

[a] Data are presented as mean (standard deviation) of person-years unless otherwise indicated. All values other than age were directly standardized to the age distribution (in 5-year intervals) of all participants.

[b] At age 13-18 other than alcohol intake at age 15-17.

Supplementary Table 2. Age-standardized participant characteristics at baseline according to average beverage intake in adulthood among women younger than age 50 in the NHSII, 1991-2015[a]

Characteristic	Sugar-sweetened beverages		Artificially sweetened beverages		Fruit juice	
	<1 serving/wk	≥2 servings/d	<1 serving/wk	≥2 servings/d	<1 serving/wk	≥2 servings/d
N	44 769	8740	32 777	23 098	37 271	1431
Age, y	37.2 (4.5)	35.6 (4.8)	36.5 (4.6)	36.5 (4.7)	36.9 (4.6)	35.4 (4.8)
Race, white, %	94	90	91	95	93	88
Height, cm	165 (6.6)	165 (6.7)	165 (6.7)	165 (6.6)	165 (6.6)	165 (6.6)
BMI, kg/m²	24.6 (5.0)	24.6 (5.9)	23.2 (4.7)	25.8 (5.6)	24.7 (5.2)	23.0 (4.5)
Postmenopausal, %	3.0	3.9	3.0	3.5	3.5	3.8
Current menopausal hormone use among postmenopausal women, %	83	79	83	83	83	74
Family history of colorectal cancer, %	4.3	4.2	4.3	4.3	4.3	4.6
Screening lower endoscopy within the past 10 y, %	1.2	1.3	1.2	1.2	1.2	0.9
Lower endoscopy due to other indications within the past 10 y, %	1.8	2.2	1.8	2.0	1.8	2.0
Ever smokers, %	36	36	33	37	38	31
Pack-years among ever smokers	11.7 (8.4)	14.1 (9.9)	12.8 (9.1)	12.4 (8.8)	12.8 (9.0)	10.4 (8.0)
Physical activity, MET-h/wk	24.6 (28.5)	19.7 (26.3)	21.3 (26.4)	23.5 (27.6)	21.2 (26.2)	29.2 (34.1)
Regular use of aspirin, %	11	13	10	13	12	8.5
Regular use of non-aspirin NSAIDs, %	20	22	16	25	20	18
Current use of multivitamins, %	44	41	46	40	38	55
Dietary intake						
Beverage intake, servings/d	0.0 (0.0)	4.0 (1.7)	0.0 (0.0)	4.6 (2.2)	0.1 (0.0)	2.8 (0.9)
Alcohol, g/d	3.4 (6.3)	2.2 (5.2)	2.7 (5.8)	3.5 (6.6)	3.1 (6.2)	3.0 (6.0)
Red and processed meat, servings/wk	5.7 (4.3)	8.6 (5.1)	6.6 (4.8)	7.0 (4.8)	6.3 (4.6)	6.1 (4.6)
Dietary fiber, g/d	19.7 (5.9)	14.2 (4.0)	17.7 (5.8)	18.4 (5.4)	18.1 (6.1)	18.2 (5.8)
Total folate, µg/d	502 (302)	386 (240)	485 (312)	452 (266)	438 (291)	584 (285)
Total calcium, mg/d	1085 (464)	794 (346)	997 (451)	1016 (426)	1004 (467)	996 (378)
Alternative Healthy Eating Index-2010 score[b,c]	41.8 (9.4)	34.9 (8.2)	39.5 (9.8)	38.8 (8.9)	38.9 (9.5)	42.8 (9.8)

Abbreviations: BMI, body mass index; MET, metabolic equivalent of task; NHSII, Nurses' Health Study II; NSAID, nonsteroidal anti-inflammatory drug.

[a] Data are presented as mean (standard deviation) of person-years unless otherwise indicated. All values other than age were directly standardized to the age distribution (in 5-year intervals) of all participants.

[b] Without sugar-sweetened beverages and alcohol.

[c] According to the predefined intake criteria for 11 dietary components (e.g. fruits, vegetables, whole grains, nuts and legumes, red and processed meat, sugar-sweetened beverages, sodium, alcohol, polyunsaturated fatty acids, omega-3 fatty acids, and trans fatty acids), a score ranging from 0 to 10 was given to each component, yielding a total score ranging from 0 to 110. A higher score reflects better diet quality.

Supplemental material

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Supplementary Table 3. Sweetened beverage intake in adulthood and risk of early-onset colorectal cancer with mutual adjustment for beverages

Exposure	<1 serving/wk	1 serving/wk to <1 serving/d	1 serving/d to <2 servings/d	≥2 servings/d	P_{trend}[a]	Each serving/d increase
Sugar-sweetened beverages						
Person-years	536 446	504 341	178 886	138 469		
No. of cases	45	34	14	16		
Multivariable RR (95% CI)[b,c]	1 [Reference]	0.91 (0.57-1.48)	1.14 (0.58-2.23)	1.97 (0.96-4.03)	0.03	1.15 (0.97-1.35)
Artificially sweetened beverages						
Person-years	424 283	321 864	258 215	353 780		
No. of cases	32	33	19	25		
Multivariable RR (95% CI)[b,c]	1 [Reference]	1.29 (0.78-2.14)	0.96 (0.53-1.74)	0.83 (0.47-1.47)	0.24	0.95 (0.85-1.06)
Fruit juice						
Person-years	450 890	799 663	92 765	14 825		
No. of cases	44	59	5	1		
Multivariable RR (95% CI)[b,c]	1 [Reference]	0.84 (0.55-1.29)	0.74 (0.28-1.98)	1.13 (0.15-8.60)	0.63	1.17 (0.72-1.90)

Abbreviations: CI, confidence interval; RR, relative risk.

One beverage serving is 8 oz.

[a] Calculated using the median of each category of beverage intake as a continuous variable.

[b] Covariates listed in the footnote of Table 2 were included in the model: race (white, nonwhite), height (continuous), body mass index (continuous), menopausal status and menopausal hormone use (premenopausal, postmenopausal never user, postmenopausal ever user, unknown menopausal status or hormone use), family history of colorectal cancer (yes, no), pack-years of smoking (continuous), physical activity (continuous), regular use of aspirin (yes, no), regular use of nonsteroidal anti-inflammatory drugs (yes, no), current use of multivitamins (yes, no), intake of alcohol, red and processed meat, dietary fiber, total folate [from foods and supplements], and total calcium (all continuous), Alternative Healthy Eating Index-2010 score without sugar-sweetened beverages and alcohol (continuous), and lower endoscopy due to screening (yes, no) or for other indications within the past 10 years (yes, no).

[c] Additionally adjusted for consumption of the other two beverages, depending on the main exposure (continuous).
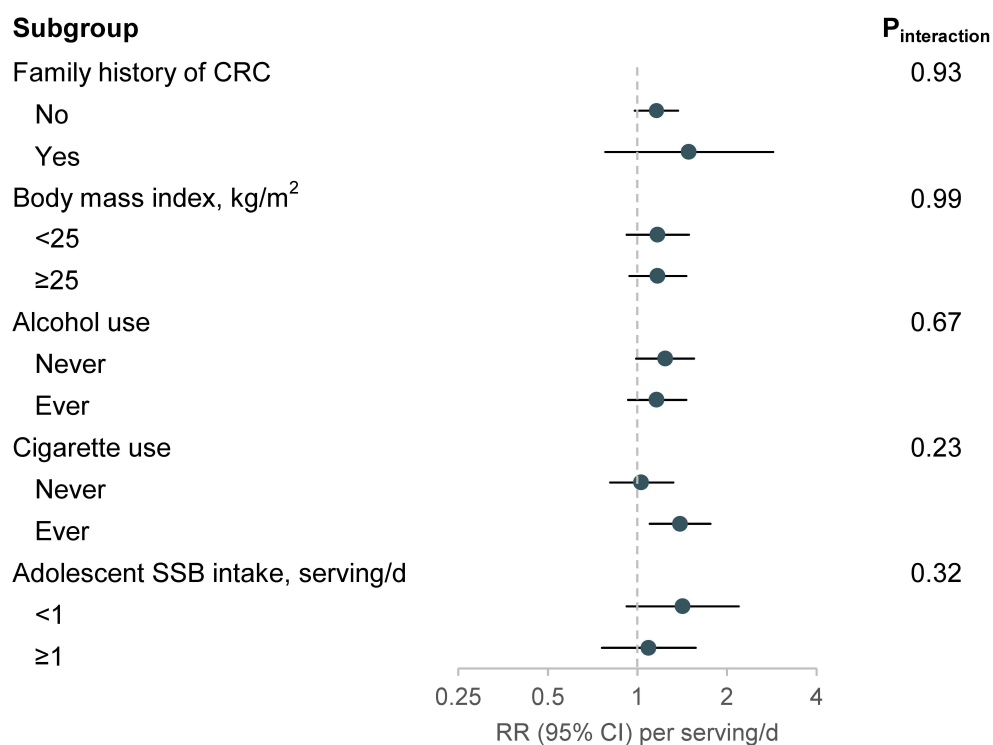
Supplementary Figure 1. Sugar-sweetened beverage intake in adulthood and risk of early-onset colorectal cancer according to participant characteristics

Abbreviations: CI, confidence interval; CRC, colorectal cancer; RR, relative risk; SSB, sugar-sweetened beverage.
One beverage serving is 8 oz. The models were adjusted for covariates listed in the footnote of Table 2, except family history of CRC in the corresponding stratified model, alcohol intake among never drinkers, and pack-years of smoking among never smokers.