Research Article

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Sugar-Sweetened Beverage Intake and the Risk of Type I and Type II Endometrial Cancer among Postmenopausal Women

Maki Inoue-Choi[1], Kim Robien[5], Andrea Mariani[3], James R. Cerhan[4], and Kristin E. Anderson[1,2]

Abstract

Background: Sugar-sweetened beverage (SSB) intake has been associated with an increased risk of obesity and type II diabetes. However, its association with endometrial cancer is unclear.

Methods: We evaluated dietary intake of SSB, fruit juice, sugar-free beverages, sweets/baked goods, starch, and sugars among 23,039 postmenopausal women in the Iowa Women's Health Study. Incident estrogen-dependent type I and estrogen-independent type II endometrial cancers were identified via linkage with the Surveillance Epidemiology and End Results Registry. Risks of type I and type II endometrial cancers were separately compared by energy-adjusted dietary intake in Cox proportional hazards regression models.

Results: From 1986 to 2010, 506 type I and 89 type II incident endometrial cancers were identified. An increased risk of type I endometrial cancer was observed with increasing SSB intake after adjustment for body mass index (BMI) and other cofounders ($P_{trend} = 0.0005$). Compared with nondrinkers of SSB, the risk was 78% higher [95% confidence intervals (CI), 1.32–2.40] among women in the highest quintile of SSB intake. The observed association was not modified by BMI, physical activity, history of diabetes, or cigarette smoking. Higher risk of type I endometrial cancer was also observed with higher intake of sugars. None of the dietary items included in the analysis was associated with type II endometrial cancer risk.

Conclusion: Higher intake of SSB and sugars was associated with an increased risk of type I, but not type II, endometrial cancer.

Impact: SSB intake may be a risk factor for type I endometrial cancer regardless of other lifestyle factors.
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Introduction

Endometrial cancer is the fourth most common cancer and eighth most common cause of cancer death among women in the United States (1). An estimated 49,560 women are expected to be diagnosed with incident endometrial cancer and 8,090 women are expected to die from endometrial cancer in 2013 (1). To date, convincing evidence exists to support that factors that increase estrogen exposure, such as greater body fatness, postmenopausal estrogen therapy, late menopause, and being nulliparous, increase the risk of endometrial cancer (1, 2). In contrast, cigarette smoking and physical activity are protective against endometrial cancer presumably through their antiestrogenic effects (2, 3). These classical risk factors have been associated mostly with type I estrogen-dependent endometrioid tumors whereas associations with the less common clinically aggressive estrogen-independent type II endometrial cancers remain controversial (4–7).

Insulin resistance and hyperglycemia are associated closely with obesity (2, 8). Consistent with a substantial amount of evidence supporting greater body fatness as a risk factor for endometrial cancer, there have been an increasing number of epidemiologic studies suggesting that diabetes may also influence endometrial carcinogenesis (9–15). Indeed, obese women tend to have higher levels of estrogens compared with normal weight women, which is considered a major reason for the excess risk of endometrial cancer related to obesity (16). Some of the previous studies reported the highest risk of endometrial cancer among women who were obese and diabetic (9–11).

Sugar-sweetened beverages (SSB) are the leading source of added sugars in the U.S. diet (17). Insulin and glucose concentrations in blood, both postprandial and average, are directly affected by the type, amount, and rate of digestion of dietary sugar. Sugars in beverages are metabolized and absorbed more quickly than sugars in

Authors' Affiliations: [1]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota; [2]Masonic Cancer Center, University of Minnesota, Minneapolis; [3]Department of Obstetrics and Gynecology, Mayo Clinic College of Medicine; [4]Division of Epidemiology, Mayo Clinic College of Medicine, Rochester, Minnesota; and [5]Department of Epidemiology and Biostatistics, School of Public Health and Health Services, George Washington University, Washington, District of Columbia

Corresponding Author: Maki Inoue-Choi, M.S. 1300 S. Second Street, Suite 300, Minneapolis, MN 55454. Phone: 612-625-4542; Fax: 612-624-0315; E-mail: inou0021@umn.edu

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whole foods, in which fibers may slow down sugar metabolism and absorption. In fact, plasma glucose levels rise higher and fall lower with the consumption of SSB compared with whole foods (18). Population-based studies have shown that higher SSB consumption is associated with higher risk of obesity and type 2 diabetes (19–21). The 2007 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) comprehensive literature review on food, nutrition, physical activity, and cancer prevention concluded a "probable" role of SSB intake in the risk of obesity, one of the established risk factors for endometrial cancer (2). Therefore, the link between SSB consumption and a higher risk of endometrial cancer is biologically plausible. However, negligible evidence exists for the association between SSB intake and the risk of endometrial cancer.

To our knowledge, an association between SSB intake and endometrial cancer risk has been evaluated in only one prospective cohort study (22). In that study, however, information on intake levels of SSB was not provided, and the risk of endometrial cancer did not differ between SSB drinkers and nondrinkers. Moreover, endometrial cancers were not classified into type I endometriod and type II nonendometrioid, the 2 major histological categories of these tumors. Here, we evaluated the association between dietary intake of SSB, other sugar-rich food groups, and sugars and the risk of type I and type II endometrial cancers separately among postmenopausal women. We hypothesized that high consumption of SSB may lead to obesity-related alteration in estrogen status, and thus increase the risk of estrogen-dependent type I endometrial cancer.

Materials and Methods

Study population and data collection

The detailed study design of the Iowa Women's Health Study (IWHS) has been described previously (23). In 1986, a questionnaire was mailed to women aged 55 to 69 years randomly selected from the State of Iowa driver's license list. A total of 41,836 women (42%) completed the self-administered questionnaire assessing demographics, anthropometry, reproductive and lifestyle factors, family history of cancer, medical history, and dietary intake. Compared with nonresponders to the baseline questionnaire, responders were on average 3 months younger and had a lower body mass index (BMI) by 0.38 kg/m^2 but were otherwise comparable in other demographic and lifestyle factors (24). The design and protocol of the IWHS were approved for human subject research by the Institutional Review Board of the University of Minnesota. Return of the completed questionnaire was considered as a subject's consent to study participation.

Dietary intake was assessed using the Harvard Food Frequency Questionnaire (FFQ) at study baseline. The validity and reproducibility of the Harvard FFQ have been shown in the IWHS population (25). Study participants were asked to report usual intake frequency of 127 food items during the past 12 months using the nine frequency levels ranging from "never or less than once per month" to "six or more per day." A typical portion size for each food item was provided to enable study participants to have a sense of scale. The FFQ included 4 questions asking usual intake frequency of SSB, including (i) Coke, Pepsi, or other cola with sugar; (ii) caffeine-free Coke, Pepsi, or other cola with sugar; (iii) other carbonated beverage with sugar (e.g., 7-Up); and (iv) Hawaiian Punch, lemonade, or other noncarbonated fruit drinks. "Sugar-free soft drinks" included low-calorie caffeinated and caffeine-free cola (e.g., Pepsi-Free) and other low-calorie carbonated beverages (e.g., Fresca, Diet 7-Up, and Diet Ginger Ale). "Sweets and baked goods" included 13 items in the FFQ, including chocolate, candy bars, candy without chocolate, cookies (home baked and ready-made), brownies, doughnuts, cake (home baked and ready-made), sweet roll, coffeecake or other pastry (home baked and ready-made), and pie (home baked and ready-made). Usual intake of food groups, including SSB, was computed based on a serving size for each food item. Dietary nutrient intake was calculated by multiplying intake frequency of the specified portion of each food item by the nutrient content in the unit of the food item.

BMI was calculated (kg/m^2) using self-reported current height and weight. A paper tape measure and instructions to have a friend measure circumferences of the waist and hip were enclosed with the questionnaire. Using these measurements, the waist–hip ratio (WHR) was computed. The baseline questionnaire included 2 questions about whether or not a subject participated in moderate- or vigorous-intensity physical activities. The subjects were categorized into 3 physical activity levels; "high" if they reported $\geq$2 times/week vigorous (e.g., jogging, racket sports, swimming, aerobics, strenuous sports) or $\geq$5 times/week moderate activities (e.g., bowling, golf, light sports, or physical exercise, gardening, taking long walks), "moderate" if they reported 2 to 4 times/week moderate or once/week vigorous and moderate activities, or otherwise "low" (26).

Incident cancer ascertainment

The cohort has been followed for vital status and cancer incidence annually. Incident cancers are identified via annual linkage with the State Health Registry of Iowa, part of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program. Information on each incident cancer such as the date of diagnosis, morphology, and a stage of cancer was collected. Vital status is updated annually through matching with the State Health Registry of Iowa, and supplemented with data from the National Death Index.

Incident endometrial cancers [International Classification of Diseases (ICD)-10 codes: c.54–c.55] were identified from the cohort baseline through December 31, 2010, and morphology codes were used to classify these cancers into type I (morphology codes: 8000, 8010, 8041, 8071, 8140, 8210, 8262, 8263, 8380, 8382, 8480, 8560, and 8570) and type

II (morphology codes: 8050, 8260, 8310, 8323, 8441, 8460, 8461, 8950, 8951, and 8980; ref. 27). Carcinosarcoma (morphology code: 8980) was classified as type II cancer because it has been considered as a special type of endometrial cancer (28).

Statistical analysis

At cohort baseline, we excluded women with a history of cancer except nonmelanoma skin cancer ($n = 3{,}830$), a history of hysterectomy ($n = 14{,}721$), incomplete FFQ (more than 30 blank food items) or extreme dietary intake (<600 or >5,000 kcal/day; $n = 3{,}102$), and who were not postmenopausal ($n = 569$). We also excluded women diagnosed with endometrial cancer *in situ* ($n = 21$) and sarcoma ($n = 10$) during the follow-up, yielding a total of 23,039 women in the analytic cohort. Person-years of follow-up were assigned for each study participant from the date of return of the baseline questionnaire to the date of endometrial cancer diagnosis, hysterectomy, emigration from Iowa, death, or administrative censoring on December 31, 2010, whichever occurred first.

We assessed pairwise correlations among intakes of beverages (SSB, fruit juice, sugar-free beverages, and coffee), sweets/baked goods, starch, sucrose (a.k.a., table sugar), and compounds of sucrose (glucose and fructose) using Spearman correlation coefficients (r). Dietary intake of SSB, sugars, and other food groups and nutrients were adjusted using nutrient residual methods to control for confounding by total energy intake (29). Study participants were grouped into quintiles of energy-adjusted intake levels of each food item or nutrient. We used Cox proportional hazards regression to estimate HR and their 95% confidence intervals (CI) for the association of each food group or nutrient intake with endometrial cancer risk, with the lowest intake level as a reference group. To determine covariates in the final analytic model, we performed univariate analyses to evaluate associations between demographic, lifestyle, medical, and reproductive characteristics, and the risk of endometrial cancer.

Separate multivariable-adjusted analyses were carried out for risks of type I and type II endometrial cancers. Because body weight is potentially on our *a priori* causal pathway between SSB intake and endometrial cancer, and diabetes has been associated with both SSB intake and endometrial cancer, we performed 3 statistical models for each analysis. Covariates in Model 1 included factors associated with endometrial cancer risk such as age (continuous), smoking status (never, past, current), physical activity (low, medium, or high), alcohol intake (none, <4 g/day, or $\geq$4 g/day), estrogen use (never, ever), age at menarche ($\leq$ or >12 years), age at menopause (< or $\geq$50 years), number of live births (continuous), and a history of diabetes. Coffee intake was also included as a covariate because it has been associated with a decreased risk of endometrial cancer in our study population (30) and others (31–33). In addition to these covariates, Model 2 included BMI (continuous). Model 3 was used as a sensitivity analysis and excluded women who reported a history of diabetes at baseline. Trends across dietary intake quintiles were tested using the median in each quintile to create a continuous variable.

To test whether the association between SSB intake and the risk of type I endometrial cancer would be modified by factors that may affect estrogen exposure, we further stratified the analysis by BMI, physical activity levels, a history of diabetes, and cigarette smoking status. Statistical significance was defined as $P < 0.05$.

Results

The mean age at baseline of the 23,039 women included in the analysis was 61.6 years (range, 52–71 years; SD, 4.2 years). During the follow-up, we identified 592 incident invasive endometrial cancers (506 type I and 89 type II). The mean ages at diagnosis were 72.6 and 74.4 years for type I and type II endometrial cancers, respectively. Approximately 93% and 21% of type I and type II endometrial cancers, respectively, were local or regional at diagnosis. Women with older age, higher BMI, higher WHR, and a history of diabetes, and women who experienced early menarche, delayed menopause, and ever estrogen use were at higher risk of endometrial cancer (data not shown). In contrast, women who ever smoked or experienced a greater number of live births were at lower risk of endometrial cancer. Physical activity level was not associated with endometrial cancer risk in our study population.

Table 1 shows pairwise correlations among dietary intake included in the analysis. SSB intake was positively weakly correlated with fruit juice intake and inversely weakly correlated with sugar-free beverage intake, but had virtually no correlation with coffee intake. Intakes of sweets/baked goods and starch were moderately correlated with SSB intake. As expected, intakes of sucrose, glucose, and fructose were reasonably correlated with SSB intake.

Selected demographic, lifestyle, reproductive, and medical characteristics, and dietary intake are shown by SSB intake levels in Table 2. Low physical activity level and ever estrogen use were associated with higher intake of SSB. More women with a history of diabetes reported no SSB intake, suggesting that these women might have been refraining from drinking SSB because of their diabetic condition. Other characteristics including BMI and cigarette smoking were not different across SSB intake levels. Women drinking more SSB reported higher total energy intake. Similarly, women who drank higher amount of SSB reported higher intake levels of other nutrients and food groups including carbohydrate, protein, total fat, vegetables, fruits, and total meat.

Table 3 shows the risk of type I endometrial cancer by energy-adjusted dietary intake of SSB and other food groups/nutrients. Without adjustment for BMI, women who reported higher intake of SSB were at higher risk of type I endometrial cancer in a dose-dependent manner ($P_{trend} = 0.001$, Model 1). Compared with nonconsumers

Table 1. Spearman correlation coefficients (*r*) among intakes of food items and nutrients

	Sugar-sweetened drinks	Fruit juice	Sugar-free drinks	Coffee	Sweets/baked goods	Starch	Sucrose	Glucose	Fructose
Sugar-sweetened drinks	1								
Fruit juice	0.12	1							
Sugar-free drinks	−0.14	0.01	1						
Coffee	−0.01	−0.07	−0.07	1					
Sweets/baked goods	0.26	0.06	−0.05	0.08	1				
Starch	0.24	0.12	−0.03	0.06	0.45	1			
Sucrose	0.41	0.20	−0.07	0.02	0.69	0.56	1		
Glucose	0.42	0.58	−0.02	−0.06	0.22	0.37	0.63	1	
Fructose	0.38	0.55	−0.00	−0.08	0.16	0.33	0.59	0.93	1

of SSB (the lowest quintile), the risk of type I endometrial cancer was 72% higher (95% CI = 1.28–2.32) among women in the highest quintile of SSB intake. Fruit juice intake was not associated with the risk of type I endometrial cancer. When fruit juice intake was added to SSB intake, the risk of type I endometrial cancer was 38% higher (95% CI = 1.03–1.87) among women in the highest quintile than the risk in the lowest quintile of intake. These associations became stronger by adjusting for BMI (Model 2). The risk among women in the highest versus lowest quintile was 78% (95% CI, 1.32–2.40) and 48% (95% CI, 1.09–2.00) higher for SSB and for SSB and fruit juice combined (P_{trend} = 0.0005 and 0.02), respectively. In contrast, there was no association between sugar-free beverage intake and the risk of type I endometrial cancer regardless of BMI adjustment. Similarly, neither sweet/baked good nor starch intake was associated with type I endometrial cancer risk. Before adjusting for BMI, there were no associations between intake of glucose, fructose, and sucrose and the risk of type I endometrial cancer. After adjusting for BMI, there were marginally insignificantly higher risk with higher intake of sucrose ($P_{trend} = 0.09$) and glucose ($P_{trend} = 0.08$). In the sensitivity analysis excluding women with diabetes, most observed associations remained unchanged or slightly stronger (Model 3). The risks of type I endometrial cancer among the highest versus

Table 2. Distributions of baseline demographic, lifestyle, and dietary factors by level of SSB intake

	SSB intake (servings/wk)				
	0	0.5	1.0–1.5	2.0–<4.0	≥4.0
Number of subjects	10,055	4,206	4,101	2,315	2,362
Age, mean (SD), y	61.7 (4.2)	61.8 (4.2)	61.6 (4.2)	61.5 (4.2)	61.1 (4.2)
BMI, mean (SD), kg/m^2	26.9 (5.3)	26.8 (5.0)	26.6 (4.6)	26.7 (4.9)	27.2 (5.4)
WHR, mean (SD)	0.83 (0.09)	0.83 (0.08)	0.83 (0.08)	0.83 (0.08)	0.84 (0.08)
Current smoking (%)	17.6	13.6	12.3	12.9	18.2
Low physical activity (%)	44.1	45.3	49.1	51.5	56.1
Alcohol use (%)	45.1	45.7	47.1	48.6	45.4
Diabetes (%)	9.8	4.3	2.8	2.6	3.0
Ever estrogen use (%)	71.0	74.0	74.2	75.0	75.3
Dietary intake, mean (SD)					
Total energy intake, kcal	1,644 (538)	1,799 (575)	1,888 (581)	2,021 (631)	2,227 (711)
Carbohydrate, g/day	194.7 (69.7)	217.6 (74.6)	229.6 (74.4)	248.2 (80.7)	284.1 (94.5)
Protein, g/day	77.0 (29.1)	81.3 (29.5)	83.1 (29.7)	86.8 (31.8)	88.8 (33.9)
Total fat, g/day	62.6 (25.6)	68.9 (26.6)	73.0 (27.1)	77.2 (29.1)	82.2 (32.2)
Vegetables, servings/wk	25.3 (14.9)	25.7 (14.7)	25.6 (14.2)	25.9 (14.2)	26.1 (14.7)
Fruits, servings/wk	18.0 (10.9)	18.4 (11.0)	18.5 (10.5)	19.1 (12.2)	18.8 (12.0)
Total meat[a], servings/wk	12.8 (6.7)	13.5 (6.7)	13.9 (6.7)	14.9 (7.1)	15.5 (7.9)

Abbreviation: SD, standard deviation.

[a]Total meat includes chicken, turkey, beef, pork, lamb, hamburger, liver, and processed meat products (bacon, hot dogs, sausage, salami, bologna, and other products).

Table 3. SSB, other high-sugar food/drink, and sugar intake and type I endometrial cancer

	Intake level[a] (quintile)			HR (95% CI)		
Food groups	**Range**	**Median**	**Cases**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**
SSB (servings/wk)	0	0	76	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	>0–0.01	0.007	101	1.34 (0.99–1.82)	1.42 (1.05–1.93)	1.34 (0.96–1.86)
	0.02–0.6	0.4	105	1.42 (1.04–1.86)	1.48 (1.09–2.02)	1.36 (0.98–1.89)
	0.7–1.6	1.0	101	1.37 (1.00–1.86)	1.49 (1.09–2.03)	1.40 (1.01–1.94)
	1.7–60.5	3.3	123	1.72 (1.28–2.32)	1.78 (1.32–2.40)	1.74 (1.27–2.38)
P_{trend}				0.001	0.0005	0.001
Fruit juice (servings/wk)	0–0.6	0.006	86	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	0.7–2.4	1.4	93	1.04 (0.77–1.40)	1.05 (0.78–1.41)	0.96 (0.70–1.31)
	2.5–5.0	3.7	111	1.24 (0.93–1.65)	1.25 (0.94–1.67)	1.19 (0.88–1.61)
	5.1–8.3	6.6	111	1.20 (0.90–1.60)	1.27 (0.95–1.70)	1.23 (0.91–1.67)
	8.4–63.0	10.8	105	1.10 (0.82–1.47)	1.16 (0.87–1.56)	1.18 (0.87–1.61)
P_{trend}				0.34	0.14	0.09
SSB + fruit juice (servings/wk)	0–1.3	0.5	76	1.00 (ref.)	1.0	1.00 (ref.)
	1.4–3.6	2.4	104	1.35 (1.00–1.83)	1.40 (1.03–1.90)	1.36 (0.99–1.88)
	3.7–6.2	5.0	106	1.38 (1.02–1.87)	1.46 (1.08–1.98)	1.45 (1.05–2.00)
	6.3–9.8	7.9	108	1.37 (1.01–1.85)	1.47 (1.09–1.99)	1.52 (1.10–2.09)
	9.9–72.3	13.0	112	1.38 (1.03–1.87)	1.48 (1.09–2.00)	1.54 (1.12–2.12)
P_{trend}				0.06	0.02	0.008
Sugar-free beverages (servings/wk)	0	0	152	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	>0–0.0002	0.0001	36	0.72 (0.49–1.04)	0.69 (0.48–1.00)	0.73 (0.50–1.06)
	0.0003–0.4	0.0008	93	0.93 (0.71–1.21)	0.85 (0.65–1.11)	0.86 (0.65–1.13)
	0.5–2.8	1.0	125	1.17 (0.92–1.50)	1.03 (0.80–1.32)	0.99 (0.76–1.28)
	2.8–64.1	5.6	100	0.96 (0.74–1.26)	0.77 (0.59–1.01)	0.80 (0.60–1.06)
P_{trend}				0.49	0.31	0.35
Sweets/baked goods (servings/wk)	0–2.7	1.5	94	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	2.8–5.0	4.0	94	1.01 (0.75–1.36)	1.00 (0.75–1.35)	0.93 (0.68–1.29)
	5.1–7.6	6.3	117	1.18 (0.88–1.57)	1.20 (0.90–1.60)	1.16 (0.86–1.58)
	7.7–11.8	9.4	100	1.06 (0.79–1.43)	1.08 (0.81–1.45)	1.07 (0.79–1.47)
	11.9–91.8	15.9	101	1.03 (0.77–1.39)	1.11 (0.83–1.49)	1.08 (0.79–1.48)
P_{trend}				0.77	0.41	0.40
Starch (g/d)	2.8–47.2	40.0	105	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	47.3–56.6	52.4	95	0.80 (0.60–1.07)	0.83 (0.63–1.11)	0.79 (0.59–1.08)
	56.7–64.9	60.8	104	0.90 (0.69–1.19)	0.95 (0.72–1.26)	0.92 (0.69–1.23)
	65.0–75.0	69.6	106	0.96 (0.73–1.26)	1.00 (0.76–1.32)	0.94 (0.70–1.26)
	75.1–233.2	83.6	96	0.84 (0.63–1.11)	0.92 (0.69–1.22)	0.94 (0.70–1.27)
P_{trend}				0.57	0.97	0.89
Sucrose (g/d)	1.3–28.4	23.5	95	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	28.5–35.3	32.2	88	0.83 (0.62–1.13)	0.83 (0.62–1.12)	0.93 (0.67–1.29)
	35.4–41.2	38.3	98	0.92 (0.68–1.23)	0.98 (0.73–1.31)	1.04 (0.75–1.43)
	41.3–49.2	44.8	108	1.00 (0.75–1.33)	1.08 (0.81–1.44)	1.15 (0.84–1.58)
	49.3–165.3	55.8	117	1.05 (0.79–1.40)	1.16 (0.87–1.54)	1.23 (0.90–1.69)
P_{trend}				0.37	0.09	0.06
Glucose (g/d)	1.0–12.9	10.3	71	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	13.0–16.8	15.0	110	1.42 (1.05–1.93)	1.47 (1.09–2.00)	1.47 (1.06–2.04)
	16.9–20.5	18.7	105	1.33 (0.98–1.81)	1.38 (1.02–1.89)	1.40 (1.01–1.95)
	20.6–25.3	22.6	110	1.40 (1.03–1.90)	1.47 (1.08–2.00)	1.47 (1.06–2.04)
	25.4–118.7	29.5	110	1.31 (0.96–1.78)	1.41 (1.03–1.92)	1.50 (1.08–2.08)
P_{trend}[c]				0.20	0.08	0.04
Fructose (g/d)	0.9–14.8	11.6	84	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	14.9–19.5	17.3	101	1.14 (0.84–1.53)	1.17 (0.87–1.57)	1.24 (0.02–1.70)

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Table 3. SSB, other high-sugar food/drink, and sugar intake and type I endometrial cancer (Cont'd)

	Intake level[a] (quintile)			HR (95% CI)		
Food groups	**Range**	**Median**	**Cases**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**
	19.6–23.7	21.7	102	1.14 (0.84–1.53)	1.18 (0.87–1.59)	1.23 (0.90–1.70)
	23.8–29.3	28.2	105	1.13 (0.84–1.53)	1.18 (0.87–1.59)	1.28 (0.93–1.76)
	29.4–129.5	34.9	114	1.16 (0.86–1.56)	1.23 (0.92–1.66)	1.32 (0.96–1.82)
P_{trend}				0.42	0.22	0.11

[a]Adjusted for total energy intake using nutrient residual methods.

[b]Adjusted for age, smoking (never, past, and current), physical activity (low, medium, or high), alcohol use (none, <4 g/day, or ≥4 g/day), estrogen use (never, ever), age at menarche (≤12 or >12 years), age at menopause (<50 or ≥50 years), number of live births, history of diabetes, and coffee intake.

[c]Model 1 plus adjustment for BMI.

[d]Analysis excluding women who reported history of diabetes at baseline; adjusted for covariates included in Model 2 (except history of diabetes).

lowest quintile were 74%, 23%, 50%, and 32% higher for SSB, sucrose, glucose, and fructose, respectively.

Although not statistically significant, the risk of type II endometrial cancer seemed higher among women with higher intake of SSB (Table 4). The risk among women in the highest intake quintile was 47% higher than the risk in the lowest quintile (95% CI, 0.69–3.12). None of the other selected food groups and nutrients examined was associated with type II endometrial cancer risk.

In the stratified analysis, we did not find strong evidence indicating modifying effects of BMI, physical activity levels, a history of diabetes, or cigarette smoking on the association between SSB intake and the risk of type I endometrial cancer (Table 5).

Discussion

In this prospective cohort study among postmenopausal women, we found that higher consumption of SSB was associated with higher risk of type I endometrial cancer, regardless of BMI, physical activity, a history of diabetes, and cigarette smoking. Similarly, higher risk of type I endometrial cancer was observed in relation to higher intake of sugars. The risk of type II endometrial cancer was not associated with intake levels of SSB and sugars.

To date, SSB intake has been evaluated in relation to endometrial cancer risk in only one prospective study, a Swedish cohort, showing the risk of endometrial cancer did not differ between SSB drinkers and nondrinkers (22). In our study population, a statistically significant 47% higher risk of endometrial cancer was observed among women who reported at least some SSB consumption compared with nonconsumers (95% CI, 1.10–1.97, data not shown). SSB intake in our U.S. study population was considerably higher compared with that in the Swedish study population. The percentage of nonconsumers of SSBs was almost 60% in the Swedish study compared with 44% in our cohort, and the median intake among SSB drinkers was 0.57 servings/week in the Swedish study and 1.0 serving/week in our study population. The greater variability in SSB intake in our study than in the Swedish study may, in part, account for the different associations between SSB intake and endometrial cancer risk found in the 2 studies. It also should be noted that sucrose is the major sweetener added to soft drinks in Sweden, whereas high-fructose corn syrup (HFCS) has replaced sucrose as the major sweetener added to SSB since 1980s in the United States. Although sucrose has a 50–50 fructose–glucose ratio, the most common form of HFCS used in SSB is at 55% fructose and 45% glucose. Studies have reported that the HFCS in the vast majority of major SSB contained greater than the 55% fructose (34). However, higher fructose intake was not associated with a higher risk of endometrial cancer in our study. This lack of association may have been partly because of potential misclassification of sugar intake from HFCS-containing products such as SSB and sweets and baked goods assessed using an FFQ. In addition, fructose intake is derived in large part from fruits as well as SSB. Fructose in SSB is simply a large amount of fructose whereas fructose as part of fruits is consumed with fibers, which may slow down fructose metabolism and absorption.

SSB consumption has been increasing in parallel with increasing prevalence of obesity in the United States (19, 21). During 4 years of follow-up of more than 90,000 women in a prospective cohort study, greatest weight gain was observed among women who increased SSB intake from less than one serving per week to at least one serving per week (19). Obesity has been estimated to cause almost 50% of endometrial cancer in affluent societies (35). The risk of endometrial cancer increases linearly with increasing BMI. A meta-analysis of cohort studies showed the risk increased 59% with an increment of 5 kg/m^2 (36). Although the mechanisms are not completely understood, endogenous hormones seem to play a role in the development of endometrial cancer. Excess body weight increases circulating concentrations of bioavailable estrogens from extraglandular conversion of

Table 4. SSB, other high-sugar food/drink, and sugar intake and type II endometrial cancer

	Intake level[a] (quintile)			HR (95% CI)		
Food groups	**Range**	**Median**	**Cases**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**
SSB (servings/wk)	0	0	13	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	>0–0.01	0.007	23	1.65 (0.83–3.27)	1.69 (0.85–3.35)	1.88 (0.91–3.91)
	0.02–0.6	0.4	13	0.88 (0.40–1.93)	0.89 (0.40–1.95)	0.92 (0.40–2.12)
	0.7–1.6	1.0	19	1.26 (0.61–2.59)	1.31 (0.64–2.69)	1.46 (0.69–3.10)
	1.7–60.5	3.3	18	1.31 (0.63–2.69)	1.31 (0.63–2.69)	1.47 (0.69–3.12)
P_{trend}				0.81	0.80	0.63
Fruit juice (servings/wk)	0–0.6	0.006	19	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	0.7–2.4	1.4	13	0.68 (0.33–1.39)	0.69 (0.34–1.42)	0.68 (0.32–1.42)
	2.5–5.0	3.7	21	1.01 (0.53–1.93)	1.02 (0.54–1.94)	0.76 (0.50–1.90)
	5.1–8.3	6.6	14	0.72 (0.36–1.46)	0.75 (0.37–1.51)	0.80 (0.39–1.64)
	8.4–63.0	10.8	19	0.93 (0.48–1.79)	0.97 (0.50–1.88)	1.06 (0.54–2.07)
P_{trend}				0.89	0.99	0.73
SSB + fruit juice (servings/wk)	0–1.3	0.5	17	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	1.4–3.6	2.4	17	1.00 (0.50–1.98)	1.01 (0.51–2.00)	0.93 (0.46–1.91)
	3.7–6.2	5.0	17	0.92 (0.46–1.84)	0.94 (0.47–1.88)	0.93 (0.45–1.90)
	6.3–9.8	7.9	16	0.91 (0.45–1.82)	0.94 (0.47–1.88)	1.00 (0.49–2.03)
	9.9–72.3	13.0	19	1.05 (0.53–2.06)	1.09 (0.55–2.15)	1.17 (0.59–2.34)
P_{trend}				0.99	0.89	0.62
Sugar-free beverages (servings/wk)	0	0	27	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	>0–0.0002	0.0001	8	0.79 (0.34–1.83)	0.78 (0.34–1.79)	0.81 (0.35–1.86)
	0.0003–0.4	0.0008	13	0.69 (0.35–1.37)	0.66 (0.33–1.30)	0.63 (0.31–1.28)
	0.5–2.8	1.0	21	1.21 (0.68–2.17)	1.09 (0.61–1.95)	1.16 (0.64–2.09)
	2.8–64.1	5.6	17	1.05 (0.56–1.96)	0.89 (0.48–1.68)	0.87 (0.45–1.69)
P_{trend}				0.65	0.95	0.97
Sweets/baked goods (servings/wk)	0–2.7	1.5	22	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	2.8–5.0	4.0	10	0.42 (0.20–0.89)	0.42 (0.20–0.89)	0.31 (0.14–0.70)
	5.1–7.6	6.3	27	1.05 (0.58–1.90)	1.07 (0.59–1.94)	0.97 (0.54–1.75)
	7.7–11.8	9.4	11	0.44 (0.21–0.92)	0.46 (0.22–0.96)	0.38 (0.18–0.81)
	11.9–91.8	15.9	16	0.64 (0.33–1.25)	0.68 (0.35–1.33)	0.58 (0.29–1.13)
P_{trend}				0.26	0.35	0.19
Starch (g/day)	2.8–47.2	40.0	16	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	47.3–56.6	52.4	13	0.75 (0.35–1.60)	0.76 (0.56–1.62)	0.75 (0.35–1.61)
	56.7–64.9	60.8	21	1.32 (0.68–2.57)	1.35 (0.69–2.62)	1.16 (0.58–2.31)
	65.0–75.0	69.6	20	1.26 (0.64–2.48)	1.29 (0.66–2.52)	1.21 (0.62–2.40)
	75.1–233.2	83.6	16	0.96 (0.47–1.97)	1.01 (0.49–2.08)	1.02 (0.49–2.09)
P_{trend}				0.60	0.51	0.53
Sucrose (g/day)	1.3–28.4	23.5	18	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	28.5–35.3	32.2	22	1.15 (0.60–2.21)	1.17 (0.61–2.24)	1.28 (0.65–2.50)
	35.4–41.2	38.3	16	0.85 (0.42–1.71)	0.89 (0.44–1.79)	0.89 (0.43–1.84)
	41.3–49.2	44.8	12	0.57 (0.26–1.24)	0.60 (0.28–1.31)	0.64 (0.29–1.41)
	49.3–165.3	55.8	18	0.93 (0.47–1.86)	1.00 (0.50–1.99)	1.00 (0.49–2.05)
P_{trend}				0.33	0.45	0.41
Glucose (g/day)	1.0–12.9	10.3	23	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	13.0–16.8	15.0	16	0.68 (0.36–1.31)	0.69 (0.36–1.32)	0.72 (0.37–1.42)
	16.9–20.5	18.7	11	0.41 (0.19–0.87)	0.41 (0.20–0.88)	0.46 (0.22–0.99)
	20.6–25.3	22.6	15	0.62 (0.32–1.21)	0.63 (0.33–1.23)	0.66 (0.33–1.32)
	25.4–118.7	29.5	21	0.85 (0.46–1.57)	0.86 (0.47–1.63)	0.99 (0.53–1.88)
P_{trend}[c]				0.56	0.63	0.92
Fructose (g/day)	0.9–14.8	11.6	22	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	14.9–19.5	17.3	20	0.88 (0.48–1.63)	0.88 (0.48–1.63)	0.80 (0.42–1.54)

(Continued on the following page)

Table 4. SSB, other high-sugar food/drink, and sugar intake and type II endometrial cancer (Cont'd)

	Intake level[a] (quintile)			HR (95% CI)		
Food groups	**Range**	**Median**	**Cases**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**
	19.6–23.7	21.7	12	0.48 (0.23–1.00)	0.48 (0.23–1.01)	0.51 (0.25–1.08)
	23.8–29.3	28.2	14	0.56 (0.28–1.13)	0.56 (0.28–1.14)	0.61 (0.30–1.23)
	29.4–129.5	34.9	18	0.80 (0.42–1.53)	0.83 (0.43–1.57)	0.90 (0.47–1.73)
P_{trend}				0.24	0.27	0.53

[a]Adjusted for total energy intake using nutrient residual methods.

[b]Adjusted for age, smoking (never, past, and current), physical activity (low, medium, or high), alcohol use (none, <4 g/day, or ≥4 g/day), estrogen use (never, ever), age at menarche (≤12 or >12 years), age at menopause (<50 or ≥50 years), number of live births, history of diabetes, and coffee intake.

[c]Model 1 plus adjustment for BMI.

[d]Analysis excluding women who reported history of diabetes at baseline; adjusted for covariates included in Model 2 (except history of diabetes).

androgens in adipose tissues after menopause (16, 37). Increased estrogens stimulate the proliferation of endometrial cells, inhibit apoptosis, and promote angiogenesis, leading to the excess risk of endometrial cancer (38). Obesity also alters concentrations of insulin-like growth factor and its binding proteins (35).

Our data suggest that SSB consumption may increase the risk of type I endometrial cancer independent of its role in weight status, consistent with other studies examining insulin-raising potential of the diet and endometrial cancer risk. A recent meta-analysis of 5 prospective cohort studies reported the risk of endometrial cancer increased up to 21% among women who ate diets with a high glycemic load, an indicator of how quickly blood glucose levels rise after eating particular foods (39). Several studies, the majority of which were case–control studies, have evaluated the association between sugar intake (22, 40–43) or high-sugar foods (e.g., candy, sweets, and desserts;

Table 5. SSB intake and type I endometrial cancer risk, stratified by BMI, physical activity level, comorbid diabetes, and cigarette smoking

			SSB intake[a]			
			<1 serving/week (reference)	≥1 serving/week		
	Cases	**Person-years**	**Cases**	**Cases**	**HR (95% CI)[b]**	$P_{interaction}$
BMI (kg/m^2)						
<25	135	180,180	94	41	1.17 (0.80–1.70)	0.18
25–<30	139	159,835	93	46	1.09 (0.75–1.58)	
≥30	232	92,807	138	94	1.38 (1.05–1.82)	
Physical activity level						
Low	236	197,904	142	94	1.33 (1.01–1.74)	0.99
Medium	131	119,055	92	39	1.04 (0.71–1.53)	
High	131	109,344	88	43	1.44 (0.99–2.09)	
Diabetes						
No	458	411,368	285	173	1.29 (1.06–1.56)	0.77
Yes	47	21,160	40	7	1.14 (0.50–2.56)	
Cigarette smoking						
Never	371	59,058	233	138	1.21 (0.97–1.50)	0.79
Past	92	80,236	61	31	1.72 (1.10–2.68)	
Current	36	288,175	26	10	0.99 (0.47–2.07)	

[a]Adjusted for total energy intake using nutrient residual methods.

[b]Compared with type I endometrial cancer risk in women reporting <1 serving/week SSB intake as a reference group in each stratified category. Adjusted for age, BMI, smoking (never, past, and current), physical activity (low, medium, or high), alcohol use (none, <4 g/day, or ≥4 g/day), estrogen use (never, ever), age at menarche (≤12 or >12 years), age at menopause (<50 or ≥50 years), number of live births, history of diabetes, and coffee intake, except for the variable for stratification.

refs. 22, 44–46) and endometrial cancer risk, but most studies reported no association. One possible explanation for the lack of association in the previous studies is the failure to stratify endometrial cancers into type I endometrioid and type II nonendometrioid tumors (38, 47). Important differences exist between these 2 pathogenetic types including clinical characteristics and molecular abnormalities. Thus, the role of sugar and SSB intake in type I and type II endometrial carcinogenesis might be different.

High consumption of SSB was associated with higher risk of type I endometrial cancer, but not type II cancer in our study. Similar differences were observed for sucrose and glucose intakes. Type I endometrial cancers account for about 80% of endometrial cancers, whereas type II tumors are less common, accounting for about 10% of endometrial cancers. Because of the smaller numbers of type II tumors in our study, we might not have had enough statistical power to observe an association; however, the difference in risks is consistent with our *a priori* hypothesis. Type I tumors are estrogen driven, follow a clear development pathway, and are relatively well differentiated (38, 47). Type II endometrial tumors have not been associated with estrogen exposure and are more likely to be at an advanced-stage at diagnosis. In addition, type II tumors are more often metastatic, have a higher recurrence rate, and worse prognosis than type I tumors. In a recent pooled analysis of 10 cohort and 14 case–control studies, higher BMI was associated with both type I and II endometrial cancers, but the association was considerably stronger with type I cancer than type II cancer (5). The observed association with type I, but not type II, endometrial cancer risk is in line with our hypothesis that high consumption of SSB may lead to obesity-related alteration in estrogen status, and thus increase the risk of endometrial cancer. However, the association between higher SSB intake and higher risk of type I endometrial cancer risk became slightly stronger by adjusting for BMI. Thus, other factors than body weight may be involved in the link between SSB intake and type I endometrial cancer.

SSB drinking often coexists with other unhealthy lifestyle factors associated with endometrial cancer risk such as eating a poor-quality diet, being physically inactive, and being obese. However, despite its high sugar content, fruit juice consumption has been associated with eating a better quality diet as well as having lower BMI and biomarkers of better health (48, 49). In our study, SSB and juice intakes were only weakly correlated, and fruit juice intake was not associated with the risk of endometrial cancer. This behavior clustering makes it difficult to separate the effect of SSB consumption from these other risk factors. Therefore, high consumption of SSB may be a surrogate marker of an overall unhealthy lifestyle. However, in stratified analyses, we did not observe effect modification by major lifestyle-related risk factors including body weight, physical activity level, diabetes, and cigarette smoking.

Our study has several strengths. A prospective study design with a large sample size is a major strength. Incident cancers and their morphology information were ascertained by the State Health Registry of Iowa, a member of the SEER program. The annual loss to follow-up because of emigration from Iowa in the IWHS is minimal (<1%), meaning virtually complete follow-up of incident endometrial cancer cases (50). Data on potential confounders for the association between SSB intake and endometrial cancer risk, such as demographics, lifestyle, and reproductive and medical history, were collected at study baseline and therefore, were available to be included as covariates in the analyses.

Our study has limitations as well. Dietary intake of SSB and other food items were assessed through an FFQ. The FFQ used in our study has been shown to be valid and reliable in our cohort population (25); however, potential misclassification of dietary exposures is undeniable. Furthermore, we used dietary intake assessed at cohort baseline. It is likely that dietary intake changed during the follow-up. We reassessed dietary intake in the 2004 follow-up survey. Dietary intake assessed at cohort baseline and the 2004 follow-up were reasonably correlated: correlation coefficients were 0.23 for SSB, 0.25 for fruit juice, 0.34 for sweets/baked goods, and 0.35 for sucrose. Given the prolonged carcinogenic process, dietary intake assessed at baseline is likely more relevant to long-term dietary exposures than dietary intake assessed in 2004. Residual confounding by factors related to SSB and/or sugar intake and endometrial cancer risk, such as body weight, physical activity, diabetes, and cigarette smoking cannot be ruled out. We attempted to separate the effect of SSB and other sugar-related foods or nutrients from these factors by adjusting and stratifying the analyses and by conducting a sensitivity analysis excluding women with diabetes. We did not find strong evidence that the association between SSB consumption and type I endometrial cancer risk was dependent on body weight, physical activity, history of diabetes, or cigarette smoking.

In summary, our study is, to our knowledge, one of the first reports showing that higher intake of SSB may increase the risk of type I endometrial cancer among postmenopausal women, regardless of body weight, physical activity, history of diabetes, and cigarette smoking. Our findings did not support associations of higher intake of SSB and other high-sugar foods and nutrients with the risk of type II endometrial cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M. Inoue-Choi, A. Mariani, K.E. Anderson
Development of methodology: M. Inoue-Choi, J.R. Cerhan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Robien, J.R. Cerhan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Inoue-Choi, K. Robien, K.E. Anderson
Writing, review, and/or revision of the manuscript: M. Inoue-Choi, K. Robien, A. Mariani, J.R. Cerhan, K.E. Anderson

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Inoue-Choi, K. Robien
Study supervision: K. Robien, K.E. Anderson

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