

Research Article

Sucrose, High-Sugar Foods, and Risk of Endometrial Cancer—a Population-Based Cohort Study

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Abstract

Background: Consumption of high-sugar foods stimulates insulin production, which has been associated with endometrial cancer. Although a relationship between sucrose, high-sugar food consumption, and endometrial cancer risk is biologically plausible, this hypothesis has previously been explored in very few studies.

Methods: We used data from the Swedish Mammography Cohort, including 61,226 women aged 40 to 74 years. We examined the association between consumption of total sucrose, high-sugar foods (at baseline 1987–1990 and 1997) and endometrial cancer risk by using Cox proportional hazards models to estimate incidence rate ratios (RR) with 95% CI.

Results: During 18.4 years of follow-up, 729 participants were diagnosed with incident endometrial cancer. Total sucrose intake and consumption of sweet buns and cookies was associated with increased risk of endometrial cancer. RRs (with 95% CIs) for consuming more than 35 grams of sucrose per day and consuming sweet buns and cookies more than 3 times per week were 1.36 (1.04–1.77) and 1.42 (1.15–1.75) as compared with less than 15 grams of sucrose per day and consuming sweet buns and cookies less than 0.5 times per week, respectively. RRs for consuming more than 15 grams of sucrose per day as compared with 15 grams or less were 1.97 (1.27–3.04) among obese women and 1.56 (1.20–2.04) among women with low fat intake.

Conclusions: These data indicate that sucrose intake and consumption of sweet buns and cookies may be associated with increased risk of endometrial cancer.

Impact: Given the high intake of sweetened foods, these results have public health implications in terms of prevention of endometrial cancer. *Cancer Epidemiol Biomarkers Prev*; 20(9); 1831–7. ©2011 AACR.

Introduction

Endometrial cancer risk has been directly associated with obesity, insulin resistance, and the resultant hyperinsulinemia (1–5). Frequent consumption of sucrose and high-sugar foods may induce frequent hyperglycemia, increased insulin demand, and decreasing insulin sensitivity. Therefore, an association between sugar consumption and endometrial cancer risk, possibly modified by body weight and physical activity, also related to insulin sensitivity/resistance, is biologically plausible. Only 3 cohorts (6–8) have examined a possible relation between sugar and endometrial cancer risk, showing nonsignificant risk increases. None of those examined the relation-

ship between high-sugar foods and endometrial cancer risk, and only one specifically examined sucrose (table sugar). Case-control studies have examined intake of sugars (9–12) and/or selected high-sugar foods, that is, candy, sweets, and desserts (10, 13–17), with only one showing a positive association with intake of sugars (10). None of the previous studies have examined the possible effect modification by insulin-related factors such as body mass index (BMI) or physical activity.

We used data from the Swedish Mammography Cohort, a population-based prospective cohort study of more than 60,000 women. The objective of the study was to prospectively examine the association of consumption of total sucrose (capturing contribution from a wide range of products and recipes as opposed to only table sugar added to coffee, tea, cereals etc.) and high-sugar foods (such as sweet buns and cookies, sweets, soft drinks, jam, marmalade, sweetened fruit soups, and stewed fruit) with the risk of endometrial cancer.

Methods

From 1987 to 1990, questionnaires and invitations to participate in a free mammography screening program were mailed to all women born during 1914 to 1948 and

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living in the Uppsala County of central Sweden ($n = 48,517$), and to all women that were born 1917 to 1948 and were living in the adjacent Västmanland County ($n = 41,786$). A total of 66,651 women (74%) returned a completed questionnaire on diet, as well as information about weight, height, parity, and education.

In 1997, a second more extensive questionnaire was sent to all 56,030 cohort members who were still living in the study area; the second questionnaire also included information about diabetes and hypertension, age at menarche, history of oral contraceptive use, age at menopause, postmenopausal hormone use, and lifestyle factors such as history of cigarette smoking, physical activity and use of dietary supplements; 39,227 (70%) women returned a completed questionnaire.

Data on sucrose and high-sugar food consumption were collected at baseline 1987 to 1990 by use of a self-administered food-frequency questionnaire that included 67 food items commonly consumed in the study population. Women were asked to report how often on average they consumed different foods during the last 6 months; they could choose 1 from 8 prespecified frequencies ranging from "never or seldom" to "4 times per day or more." The second questionnaire of 1997 included 96 food items and participants were asked how often on average they consumed each food during the previous year. Eight predefined response categories were provided ranging from "never" to "3 times a day or more." The questionnaire also included open-ended questions about some specific foods and beverages, including coffee and soft drinks (both carbonated and noncarbonated drinks, and not discriminating artificially sweetened drinks). We used age-specific (<53, 53–65, >65 years) serving sizes that were based on mean values obtained from 129 randomly chosen women from the Swedish Mammography Cohort who weighed and recorded food and beverage intake during four 1-week periods (completed 3–4 months apart). Sucrose intake was calculated by multiplying the frequency of consumption by the sucrose content of age-specific portion sizes by using composition values from the Swedish Food Administration Database (18). We adjusted for total energy intake by using the residual method (19). Among the studied high-sugar food groups, the contribution to total sucrose intake was 10.2% from sweet buns and cookies, 6.3% from sweets, 4.2% from soft drinks, 3.3% from jam or marmalade and 1.3% from sweetened fruit soups or stewed fruit. The Pearson correlation coefficients between the food-frequency questionnaire based self-reports and dietary records were as follows: 0.5 for sweet buns and cookies, 0.4 for sweets, 0.6 for soft drinks, 0.5 for jam or marmalade and 0.5 for sweetened fruit soups or stewed fruit (A. Wolk, unpublished data).

BMI was calculated as weight in kg divided by the square of the height in meters (BMI, kg/m^2). The validity of self-reported weight and height as compared with measurements in Swedish women, assessed by Pearson correlation coefficient, was $r = 0.9$ and 1.0 , respectively

(20). Information on physical activity was based on 6 questions about physical activity/inactivity during the previous year; work/occupation, household work, walking/bicycling, leisure time activity, inactive leisure time, and hours of sleep. We asked for duration of specific activities and we assigned mean MET-values [multiples of the metabolic equivalent (MET, $\text{kcal}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$)] to each activity. The total physical activity was estimated by summing the products of duration by intensity of specific activities. Education was assessed with 6 questions ranging from 6 years of basic education to university studies. Diabetes history was obtained through linkage of the cohort to the Swedish In-patient Register, to the recent National Diabetes Register, or self-reported on the second questionnaire.

Follow-up of the cohort

We carried out linkage of the cohort to the Swedish Cancer Register through December 31, 2008, which has been estimated to be almost 100% complete (21). Furthermore, by linkage to the nationwide Swedish In-patient Register, we identified women who had a hysterectomy for reasons other than endometrial cancer. Dates of death or migration from the study area were ascertained by linkage to the Swedish Death Register and the Swedish Population Register, respectively. Of the 66,651 women who responded to the first questionnaire in 1987–1990, we excluded those with a missing identification number, with a cancer diagnosis (other than nonmelanoma skin cancer) before the study baseline, with a history of hysterectomy before entry to the cohort, and with extreme values of reported energy intake. After these exclusions, 61,226 women aged 40 to 76 years at baseline remained for the baseline analysis, including 729 incident endometrial cancer (endometrioid adenocarcinoma) cases.

This study was approved by the Ethics Committees at the Uppsala University Hospital (Uppsala, Sweden) and the Karolinska Institutet (Stockholm, Sweden). Completion of the self-administered questionnaire was considered to imply informed consent to participate in this study.

Statistical analysis

To estimate the risk of endometrial cancer, we used the Cox proportional hazards models. We calculated person-years of follow-up for each woman from the date of mammography to the date of endometrial cancer diagnosis, the date of a hysterectomy, the date of death from any cause, or the end of follow-up on December 31, 2008, whichever came first. In the analysis from the second questionnaire, we calculated person-time from January 1, 1998, these analyses included 36,773 women, 379,760 person-years, and 304 cases. We computed rate ratios (RR) of endometrial cancer (with 95% CIs). The cut points for sucrose were chosen as approximate quartiles on the basis of distribution of the population in the 1987 dietary assessment. The data conformed to the proportional hazards assumption (22). We carried out age-adjusted

and multivariable analyses. In the main analysis, we included consumption of total sucrose or high-sugar foods from the baseline questionnaire or the second questionnaire, and factors influencing the risk of endometrial cancer and the intake of sugar; BMI (categories), diabetes (yes/no), total energy intake (kcal/day, continuous), smoking (never/ever/missing, only for the 1998–2008 follow-up) and coffee intake (ref. 23; g/d, continuous). We also carried out analysis further adjusting for fat intake (g/d, continuous), and for known risk factors and potential confounders such as years of education (<10, 10–12, >12, and other), age at menopause (<48, 48–49, 50–52, and ≥53), age at menarche (<12, 12, 13, and ≥14), oral contraceptive use (yes/no), postmenopausal hormone therapy (yes/no), parity (continuous), smoking (ever/never/missing), and tea intake (g/d, continuous). Missing values for any potential confounder were treated as a separate "missing category" in the model. We also carried out analysis excluding all individuals with diabetes because diabetics are advised to limit sugar intake and have an increased risk of endometrial cancer (5). In test for linear trend, we used the median value in each category as a continuous variable in the model.

Both BMI and physical activity are related to insulin resistance. Therefore, we conducted analyses stratified on BMI (at baseline, additionally adjusting for continuous BMI within the strata), and physical activity (1998–2008 follow-up only). Furthermore, we stratified the analysis on other postulated insulin-related factors, such as con-

sumption of fat (24) and alcohol (25). Statistical significance of interactions was tested by adding an interaction term (on the basis of continuous variables) to the Cox model, simultaneously containing the main variables (continuous) and age in months.

Analyses were done by using SAS software (version 9.2; SAS Institute). All *P* values are 2-sided.

Results

During a mean follow-up time of 18.4 years among 61,226 women in the cohort (1,123,934 person-years), 729 incident adenocarcinoma endometrial cancer cases were diagnosed. The mean age at diagnosis of endometrial cancer was 67.6 (± 9.1) years. Table 1 shows the distribution of known risk factors and potential confounders for endometrial cancer in the cohort by categories of total sucrose consumption (table sugar). Women with high intake of sucrose had on average a higher intake of coffee, protein, fat, and energy and were less likely to smoke or have diabetes. Other characteristics did not vary substantially with respect to total sucrose consumption.

Overall, both consumption of sucrose and sweet buns and cookies was associated with increased risk of endometrial cancer, both at baseline and at the second assessment in 1997. Other high-sugar foods such as sweets, soft drinks, jam, marmalade, fruit soups, and stewed fruit were not significantly associated with endometrial cancer risk (Table 2). Mutual adjustment for all high-sugar

Table 1. Age-standardized characteristics of 61,226 women aged 40 to 74 years in the Swedish Mammography Cohort according to sucrose consumption

Median	Sucrose (table sugar), g/d			
	≤15	16–25	26–35	≥36
	11.4	20.0	29.3	49.3
Characteristics				
Participants, <i>n</i>	11,345	18,589	12,911	18,381
Age, y	54.9	53.5	53.4	53.5
BMI, kg/m ²	25.2	24.8	24.5	24.6
History of smoking, %	32.7	29.8	27.5	26.4
Diagnosis of diabetes, %	9.2	4.1	2.9	3.0
Energy intake, kcal	1,210	1,466	1,654	1,886
Coffee, g/d	433	431	435	449
Alcohol, g/d	2.4	2.7	2.7	2.4
Total fat, g/d	39.0	46.4	52.8	60.5
Tea, g/d	107.6	131.3	141.1	143.4
Age at menarche, y	13.2	13.2	13.3	13.3
Number of children	2.1	2.1	2.1	2.2
Oral contraceptive use, %	41.0	43.5	43.5	41.9
Age at menopause, y	50.0	50.2	50.2	50.1
Postmenopausal hormone therapy, %	45.0	49.3	49.6	47.7
Education ≥12 y, %	11.8	13.3	13.7	12.2

NOTE: All values other than for age have been directly standardized according to the age distribution of the cohort.

Table 2. RRs and 95% CIs of endometrial cancer by total sucrose intake and high-sugar food consumption among women in the Swedish Mammography Cohort

Food items	No of cases	Person-years	Age-adjusted RR (95% CI) ^a	Multivariable RR (95% CI) ^b
1987 diet (baseline)	729			
Total sucrose, g/d				
≤15	112	203,213	1.00 (ref)	1.00 (ref)
16–25	248	342,793	1.35 (1.08–1.69)	1.50 (1.19–1.89)
26–35	158	239,495	1.23 (0.96–1.57)	1.41 (1.09–1.83)
≥36	211	338,431	1.16 (0.92–1.46)	1.36 (1.04–1.77)
Sweet buns and cookies, servings/wk				
<0.5	158	306,079	1.00 (ref)	1.00 (ref)
1	101	161,977	1.22 (0.95–1.57)	1.26 (0.98–1.63)
2–3	158	237,623	1.26 (1.01–1.57)	1.33 (1.06–1.67)
>3	312	418,254	1.28 (1.06–1.56)	1.42 (1.15–1.75)
Sweets, serving/wk				
No	279	412,932	1.00 (ref)	1.00 (ref)
Yes (0.07) ^c	450	711,002	1.05 (0.90–1.22)	1.09 (0.93–1.27)
Soft drinks, servings/week				
No	449	686,964	1.00 (ref)	1.00 (ref)
Yes (0.07) ^c	280	436,970	1.06 (0.91–1.23)	1.02 (0.87–1.18)
Jam, marmalade, fruit soups, stewed fruit, servings/wk				
No	210	323,170	1.00 (ref)	1.00 (ref)
Yes (0.14) ^c	494	770,890	0.95 (0.81–1.12)	1.05 (0.89–1.24)
1997 diet^d	304			
Total sucrose, g/d				
≤15	25	38,301	1.00 (ref)	1.00 (ref)
16–25	62	89,511	1.13 (0.71–1.82)	1.51 (0.88–2.58)
26–35	83	96,353	1.44 (0.91–2.28)	1.76 (1.03–3.01)
≥36	134	155,595	1.39 (0.90–2.16)	1.73 (1.01–2.97)
Sweet buns and cookies, servings/wk				
<0.5	28	39,781	1.00 (ref)	1.00 (ref)
1	47	88,445	0.80 (0.50–1.28)	1.01 (0.59–1.72)
2–3	48	67,155	1.04 (0.65–1.67)	1.25 (0.73–2.15)
>3	181	184,378	1.35 (0.90–2.02)	1.72 (1.06–2.78)
Sweets, servings/wk				
No	117	140,595	1.00 (ref)	1.00 (ref)
Yes (0.067) ^c	187	239,165	1.09 (0.85–1.38)	1.13 (0.88–1.45)
Soft drinks, servings/wk				
No	163	221,878	1.00 (ref)	1.00 (ref)
Yes (0.57) ^c	141	157,881	1.22 (0.97–1.54)	1.15 (0.91–1.46)
Jam, marmalade, fruit soups, stewed fruit, servings/wk				
No	304	379,760	1.00 (ref)	1.00 (ref)
Yes (0.28) ^c	268	334,155	1.05 (0.74–1.49)	1.22 (0.82–1.81)

^aRate ratios from Cox proportional hazards models adjusted for age in months.

^bRate ratios from Cox proportional hazards models adjusted for age in months, BMI (<20, 20–25, 26–30, >30 kg/m²), coffee (g/d, continuous), energy (kcal/d, continuous), diabetes (yes/no)

^cMedian frequency per week in the "yes" category.

^dMultivariable rate ratios also adjusted for history of smoking (never/ever/missing).

foods in the model did not change the results (data not shown). Excluding women with diabetes did not change the results substantially; RRs (with 95% CI) for the second to fourth category of sucrose consumption as

compared with the lowest one were 1.59 (1.21–2.09); 1.48 (1.09–2.00); 1.48 (1.09–2.01). For consumption of sweet buns and cookies, the corresponding RRs were 1.28 (0.96–1.71), 1.42 (1.10–1.76), and 1.39 (1.10–1.76). Additional

Table 3. RRs and 95% CIs of sucrose consumption at baseline, stratified by BMI and fat intake, in relation to endometrial cancer for women in the Swedish Mammography Cohort

		No of cases	Person-years	Sucrose (table sugar), gram per day	
				≤15	>15
BMI, kg/m ^{2a}	20–24	263	581,515	1.00 (ref)	1.10 (0.76–1.60)
	25–29	236	324,369	1.00 (ref)	1.59 (1.07–2.37)
	≥30	177	102,703	1.00 (ref)	1.97 (1.27–3.04)
Fat intake, g/d ^b	Low ≤48	377	556,727	1.00 (ref)	1.56 (1.20–2.04)
	High >48	352	567,207	1.00 (ref)	1.18 (0.78–1.78)

^aRate ratios from Cox proportional hazards models adjusted for age in months, BMI (kg/m², continuous), coffee (g/d, continuous), energy (kcal/d, continuous), diabetes (yes/no).

^bRate ratios from Cox proportional hazards models adjusted for age in months, BMI (<20, 20–25, 26–30, >30 kg/m²), coffee (g/d, continuous), energy (kcal/d, continuous), diabetes (yes/no).

adjustment for total fat intake did not change the results, RRs (with 95% CI) for the second to fourth category of sucrose as compared with the lowest one were 1.49 (1.18–1.88), 1.40 (1.08–1.82), and 1.34 (1.02–1.75). For consumption of sweet buns and cookies, the corresponding RRs were 1.27 (0.98–1.63), 1.34 (1.07–1.69), and 1.45 (1.18–1.78). Further adjustment for potential confounders as education, age at menopause, age at menarche, oral contraceptive use, postmenopausal hormone therapy, parity, smoking, and tea intake did not change the result; RRs (with 95% CI) for the second to fourth category of sucrose and consumption of sweet buns and cookies as compared with the lowest ones were 1.45 (1.15–1.83), 1.36 (1.05–1.76), 1.30 (1.00–1.70), and 1.27 (0.98–1.63), 1.31 (1.05–1.65), and 1.39 (1.13–1.71), respectively.

Furthermore, we examined whether the observed association between total sucrose intake and endometrial cancer risk differed according to BMI by stratifying the cohort into groups (Table 3). The association between total sucrose intake and endometrial cancer seemed to be confined to overweight and obese women, already at higher risk for endometrial cancer, however, the interaction was not statistically significant ($P_{\text{interaction}} = 0.98$). We also carried out analyses stratified on fat intake because fat has been reported to modify the insulinemic response to foods. The associations with total sucrose were stronger among women with a low fat intake (below the median intake in the cohort, i.e., ≤48 g/d) than among those with a higher fat intake ($P_{\text{interaction}} = 0.07$). We also evaluated whether the associations differed depending on other insulin-related factors, physical activity (1998–2008 follow-up only) or alcohol intake but found no evidence of effect modification (data not shown).

Discussion

In this population-based prospective cohort study, we found that sucrose consumption (table sugar) and con-

sumption of sweet buns and cookies was associated with statistically significantly increased risk of endometrial cancer. The association seemed to be stronger among overweight and obese, as well as among those with low fat intake. There was no significant association with sweets, soft drinks, jam, marmalade, fruit soups, or stewed fruit.

Our results are largely in line with previous studies on this issue, although previous results have not been statistically significant. The association between sucrose intake and endometrial cancer risk has only been studied in 1 prospective cohort study, showing a nonsignificant risk increase with higher consumption (8). Total sugar consumption (including sucrose, but not examining sucrose specifically) has been studied in 2 additional prospective studies, both observing nonsignificant risk increases (6, 7). Overall, this evidence suggests an association, albeit a modest one, between sucrose intake and risk of endometrial cancer.

Our results on soft drinks might not be directly applicable to other populations because sucrose is the sugar added as a caloric sweetener to soft drinks in Sweden, whereas high-fructose corn syrup is the major source of caloric sweeteners in soft drinks in the United States. According to the most recent dietary survey in Sweden, the average consumption of sweetened drinks, including soft drinks, was 135 mL per day among women, of which 19.2% were artificially sweetened (26). It should be noted that the study population on average had lower levels of sucrose intake as compared with the American National Health and Nutrition Examination Survey III (NHANES; ref. 27); the estimated mean energy percentage from sucrose at baseline was 7.5% as compared with 9.9% in the NHANES. Among the high-sugar foods, sweet buns and cookies were major contributors to total sucrose intake in the study population. Other high-sugar foods considered to be "empty calories" (i.e., not substantially contributing with other nutrients) were less commonly consumed.

There are several biological mechanisms through which high sucrose consumption might increase risk of endometrial cancer development. The main mechanism relates to the development of hyperglycemia, insulin resistance, hyperinsulinemia, obesity, and diabetes which in turn have been directly associated with risk of endometrial cancer (5, 28). Hyperinsulinemia has been shown to stimulate the growth of endometrial stromal cells by binding to insulin receptors in endometrium (29) and may also increase levels of free estrogens through decreasing concentrations of circulating sex hormone binding globulin (30, 31) and through decreasing levels of IGFBP-1 increase circulating free IGF-1. IGF-1 stimulates cell proliferation by binding and activating IGF-1 receptors in the endometrium (32–37). Estrogens in turn have been shown to increase endometrial cancer risk by stimulating proliferation of endometrial cells (38). Hyperinsulinemia is also associated with hypoadiponectinemia and low levels of adiponectin have been consistently related to higher risk of endometrial cancer (39–42). In our study, the strongest association with sucrose was observed among overweight and obese women, already at a higher risk for endometrial cancer; this observation is consistent with the notion that hypoadiponectinemia, insulin resistance, and hyperinsulinemia may be involved in the process (43–46). Dietary fat can modify the insulinemic response to foods by delaying the gastric emptying and enhancing the insulin response (24). Our results observing the strongest associations among women with a low intake of fat are consistent with this notion.

Major strengths of our study include its population-based design and the completeness of identification of endometrial cancer cases through the Swedish cancer registries. The prospective nature of the study makes it highly unlikely that the associations we observed were because of recall or selection biases that might lead to spurious associations in case-control studies. Furthermore, we had information on the known major potential

confounders. Although the possibility of uncontrolled or residual confounding cannot be entirely eliminated, we have adjusted for multiple potential confounders and observed little difference between the age-adjusted and multivariable models. However, our study also had limitations. First, because the exposure was assessed through self-administered food-frequency questionnaires, measurement errors are inevitable. However, results from comparisons of self-reported sucrose and high-sugar food intakes in the questionnaire with dietary records, suggest that we obtained a reasonable assessment of consumption. This kind of error would most likely tend to attenuate an association between intake and endometrial cancer risk. We were unable to do a longitudinal analysis combining the information from the 2 questionnaires because of the difference in questions asked about high-sugar foods. However, both time points rendered similar results. Point estimates from the second time point analysis were in general slightly higher, although CIs were wider because of less statistical power.

In conclusion, our results show that total sucrose intake and consumption of sweet buns and cookies is associated with an increased risk of endometrial cancer. If confirmed by other studies and in other populations, these data may prove to be of major public health significance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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