

#### JOURNAL ARTICLE CRITIQUE: Sugar-containing Beverages and Their Association with Risk of Breast, Endometrial, Ovarian and Colorectal Cancers Among Canadian Women



## **ARTICLE SELECTION**

- HOW: ScienceDirect.com, 2021 Research Articles, search "cancer epidemiology"
- WHY: This is an epidemiologic research article was recently published in a reputable journal, is in an area I am interested in, and focuses on women in a culture similar to my own.
  - In middle school, I stopped drinking basically anything except water and (rarely) some fruit juices, so I considered myself to be pretty healthy in this regard. But, I hadn't considered the amount of sugar in "fruit" juices and really wanted to know more about the impact they may be having on my body.
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- **FUNDING:** Breast Cancer Research Foundation
- **CONFLICTS OF INTEREST:** None



## **INTRODUCTION**

- "The association of sugar containing beverages (SCBs) with risk of breast, endometrial, ovarian and colorectal cancers is unclear."
  - Other research studies have provided **sparse and/or inconclusive results**.
- Besides the sugar content, these SCBs may also contain **carcinogenic** substances of varying types and amounts.
- This study also examined fruit juice intake, which is often considered a healthier option, but frequently has a sugar content similar to that of SSBs.
  - In this study, fruit juice intake was significantly higher than intake of SSBs.
  - Fruit juices may also contain **anti-carcinogenic** compounds of varying types and amounts.
- **STUDY AIM:** "Examine the associations between SCBs and risk of breast, endometrial, ovarian and/or colorectal cancers among females in the Canadian Study of Diet Lifestyle and Health (CSDLH)."

## **STUDY OUTLINE**

- **STUDY DESIGN:** Prospective Cohort with a Case-Cohort substudy
- **TIMEFRAME:** 1992 to 2010
- TARGET POPULATION: Canadian women
- **SAMPLING FRAME:** Females who completed the Canadian Study of Diet Lifestyle and Health (CSDLH)
  - Primarily recruited from alumni of the Universities of Alberta, Toronto and Western Ontario
- **EXPOSURE VARIABLE:** Sugar containing beverages (SCBs)
  - Includes sugar-sweetened beverages (SSBs) and 100% fruit juices
- **OUTCOME VARIABLE:** Cancer (breast, endometrial, ovarian, and/or colorectal)
- **SAMPLE SIZE:** 3,185 female participants
- **DATA COLLECTION:** 2 self-administered questionnaires and 1 self-administered body measurement
- **ANALYTIC METHOD:** Cox proportional hazards regression models
- MAIN FINDINGS:
  - "Relatively high SCB intake was associated with higher risk of endometrial and ovarian cancers."
  - Also, "relatively high SSB and fruit juice intake are associated with higher risk of Type 1 endometrial cancer."

## **METHODS**

#### • EXPOSURE ASSESSMENT: (1992 - 1998)

- "At enrollment, a 166-item **self-administered** food frequency **questionnaire** (FFQ) was used to estimate usual dietary intake of the participants over the last 12 months."
- "Information on sociodemographic characteristics, personal medical history, history of cigarette smoking, physical activity, height and weight, menstrual and reproductive history, and use of oral contraceptives and hormone replacement therapy (HRT) was collected from the participants at enrollment using a self-administered questionnaire."
- "Participants were also provided with tape measures and instructions on how to measure their waist and hip circumferences." Researchers calculated BMI.
  OUTCOME ASCERTAINMENT: (2005 2010)
  - "Incident [breast, endometrial, ovarian, and colorectal] cancer cases were ascertained via record linkage to the **Canadian Cancer Registry (CCR) and to the Ontario Cancer Registry.**"

## **METHODS**

#### • CASE-COHORT DESIGN:

- "The subcohort comprised an age-stratified random sample of 3,185 participants [8%] selected from the total female cohort (N = 39,618) at baseline, with each 5-year age group having a different sampling fraction that increased with age (ranging from 0.003 for the <25 age group to 0.600 for the 90+ age group), in order to estimate the expected distribution of age at diagnosis for all incident cancers."
  - Breast cancer: 848 women
  - **Endometrial cancer: 161 women**
  - Ovarian cancer: 91 women
  - Colorectal cancer: 243 women

#### • EXCLUSION CRITERIA:

- Unusual energy intake (i.e. < 500 kcal or > 3500 kcal/day)
- > Previous history of cancer, hysterectomy, or bilateral oophorectomy
- **ANALYSIS:** The researchers "used **Cox proportional hazards regression models** modified for the case-cohort design to assess the associations of SCBs with risk of the aforementioned cancers."
  - Results were **stratified** by age at entry.
  - Results were adjusted for education, smoking, alcohol intake, physical activity, age at menarche, parity, age at menopause, hormone replacement therapy use, oral contraceptive use, family history of breast cancer, history of benign breast disease.



- **ANALYTIC METHOD:** Cox proportional hazards regression models
- "Compared to SCB intake in the lowest tertile, SCB intake in the highest tertile was positively associated with endometrial cancer risk (HR<sub>T3 vs T1</sub> = 1.58, 95 % Cl = 1.08-2.33 and 1.78, 95 % Cl = 1.12-2.81 for overall and Type 1 endometrial cancer, respectively) and ovarian cancer (HR<sub>T3 vs T1</sub> = 1.76, 95 % Cl: 1.09-2.83)."
  "Fruit juice intake was also positively associated with risk of Type 1 endometrial
- "Fruit juice intake was also positively associated with risk of Type 1 endometrial (HR<sub>T3 vs T1</sub> = 1.63, 95 % CI = 1.03- 2.60)."
  "After excluding women with diabetes or cardiovascular diseases, we also observed
- "After excluding women with diabetes or cardiovascular diseases, we also observed sugar-sweetened beverages (SSBs) intake in the highest tertile was associated with higher risk of Type 1 endometrial cancer (HR<sub>T3 vs T1</sub> = 1.65; 95 % CI: 1.03- 2.64)."
- "None of the beverages was associated with risk of breast or colorectal cancer."

# Table 4: HRs and 95 % CI for the associations of tertiles of sugar-containing<br/>beverages with risk of endometrial cancer among women from the<br/>Canadian Study of Diet, Lifestyle, and Health.

	Overall					Type 1 endometrial cancer					
		Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 3 <sup>c</sup>	Excluding persons with a known history of diabetes or heart disease <sup>d</sup>		Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 3 <sup>c</sup>	Excluding persons with a known history of diabetes or heart disease <sup>d</sup>	
	Number	HR (95 %	HR (95 %	HR (95 %		Number	HR (95 % CI)	HR (95 %	HR (95 %	18.	
	of cases	CI)	CI)	CI)		of cases		CI)	CI)		
(cups/ wk)											
≤4.4	52	1.00	1.00	1.00	1.00	35	1.00	1.00	1.00	1.00	
>4.4-7.6	45	0.88	0.88	0.96	0.93	34	0.96	0.97	1.08	1.05	
Statistical Control		(0.58 - 1.30)	(0.59 - 1.32)	(0.64 - 1.46)	(0.61 - 1.41)		(0.60 - 1.54)	(0.60 - 1.56)	(0.66 - 1.75)	(0.65 - 1.72)	
>7.6	72	1.50	1.56	1.58	1.60	56	1.67	1.73	1.78	1.82	
		(1.03 - 2.17)	(1.06 - 2.28)	(1.08-2.33)	(1.08 - 2.38)		(1.08 - 2.59)	(1.10-2.70)	(1.12-2.81)	(1.15-2.88)	
Ptrend		0.032	0.023	0.020	0.021		0.021	0.018	0.015	0.015	

Stratified by age at entry and adjusted for education, smoking, alcohol intake, physical activity, age at menarche, parity, age at menopause, HRT use, oral contraceptive use.

# Table 5: HRs and 95 % CI for the associations of tertiles of sugar-containing<br/>beverages with risk of ovarian cancer among women from the<br/>Canadian Study of Diet, Lifestyle, and Health.

	Overall	72	HR (95 % CI) Model 2 <sup>b</sup>	HR (95 % CI) Model 3 <sup>c</sup>	HR (95 % CI) Excluding persons with a history of diabetes or heart disease <sup>d</sup>	Epithelial ovarian cancer HR (95 % CI)		HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
	Number of cases	HR (95 % CI) Model 1 <sup>a</sup>								
						Number of cases	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 3 <sup>c</sup>	Excluding persons with a history of diabetes or heart disease <sup>d</sup>
SCBs (cups/ wk)										
≤4.3	29	1.00	1.00	1.00	1.00	24	1.00	1.00	1.00	1.00
>4.3-7.6	29	1.07 (0.63-1.80)	1.10 (0.65–1.87)	1.10 (0.65-1.88)	1.20 (0.70-2.08)	18	0.92 (0.49-1.71)	0.94 (0.50-1.77)	0.95 (0.50-1.77)	0.97 (0.51-1.84)
>7.6	40	1.63 (1.02-2.60)	1.76 (1.09–2.83)	1.76 (1.09–2.83)	1.90 (1.16-3.09)	30	1.51 (0.88–2.59)	1.64 (0.95–2.81)	1.63 (0.95–2.80)	1.65 (0.95–2.85)
Ptrend		0.043	0.021	0.022	0.010		0.138	0.081	0.084	0.080

Stratified by age at entry and adjusted for education, smoking, alcohol intake, physical activity, age at menarche, parity, menopausal status, HRT use, oral contraceptive use.

- Average intake of SCBs reported in this study was lower than typical Canadian, U.S., Europe, and Asia averages.
  - BIAS: Self-report? Recall?
    - This underreporting may mask the true effect of SCBs on cancer.
  - External validity issue?
  - To improve this, the study methods would have to be redesigned to more frequently and uniformly collect this information.
- Study population was comprised **mostly** of participants of **white** descent, most of whom had a relatively **high level of education**.
  - No data actually provided in the article regarding race distributions.
  - BIAS: Selection?
  - External validity issue?
  - To some degree, weighting the underrepresented race categories during analysis might help.
  - A better solution would be to more broadly administer the CSDLH instead of just at three university settings.

#### **STRENGTHS**

- "Very few studies have examined the associations of SCBs with risk of cancer," especially in cancers of the breast, endometrium, ovaries, and colon.
  - Also, fruit juices are not usually included in these studies.
  - Studies typically focus on SCBs and associations with outcomes such as obesity, diabetes, and cardiovascular disease
- "Incident cancer cases were ascertained via record linkage to the Canadian Cancer Registry (CCR) and to the Ontario Cancer Registry."
  - Mandated reporting from all provinces with 97% completeness
- As age increased, sampling fraction also increased.



#### **WEAKNESSES**

- X Not all subgroups within the cohort were followed over the same timeframe.
  - Data was not collected again at any time, and SCB consumption typically decreases with age.
- X Self-report questionnaire of "usual dietary intake of the participants over the last 12 months" and other personal characteristics (recall bias? nondifferential misclassification)
  - Randomized calibration sub-study found this data to be about 63% accurate.
- X "Participants were also provided with tape measures and instructions on how to measure their waist and hip circumferences." (measurement error? nondifferential misclassification)
  - Potential for a VERY wide range of results. Any instructional videos? Repeated measurements?
  - No information was provided regarding **how weight and height were obtained/determined. (recall?)**
- Sugar from other sources in the diet besides beverages did not seem to be considered in this study.
- X Cups per day defined as one cup equals 8 ounces. (measurement error? nondifferential misclassification)
  - How many people truly know what 8 ounces in a cup looks like?
- X All brands of SCBs likely do not contain the same carcinogenic or anti-carcinogenic components.
- **"Lacked information** on hormone-receptor status for breast cancer as well as **stage and grade of all cancers**."
- X None of the beverages was associated with risk of breast or colorectal cancer, and those groups had the highest sample sizes.
  - Is it possible that the small sample sizes of the other cancer groups caused inaccurate findings? (random chance?)
- X Other cohort studies on this topic arrived at different/opposite results. This may be due to inconsistencies in measurement methods and cutoff points across the different studies.

## **CONCLUSIONS AND IMPLICATIONS**

#### • CONCLUSIONS:

- "In this cohort, relatively high SCB intake was associated with higher risk of endometrial and ovarian cancers, but not of breast or colorectal cancers."
- "Findings also suggest that relatively high SSB and fruit juice intake are associated with higher risk of Type 1 endometrial cancer."
- While the methods of this study may cause concern regarding the degree of association these authors reached, it is still wise to consider further reducing fruit juice consumption in addition to SCB consumption.

#### • FUTURE RESEARCH:

- In particular, the role of relatively high intake of fruit juices in relation to risk of the cancers of interest warrants further investigation.
- Further studies with larger cohorts are needed to substantiate these findings.
- Studies that more clearly determine risk associations are also needed.

#### • IMPLICATIONS:

 "If further studies confirm these findings, this will provide a basis for the development of interventions aimed at lifestyle modification to ameliorate risk of these cancers."

#### RECOMMENDATIONS

- Overall, this topic was intriguing and potentially opened the door for additional research into these associations, but the methods in this particular study present several points of concern, which leads to issues with both internal and external validity.
- The authors seemed to utilize this particular study design because the data was already conveniently available, which is both time- and cost-efficient.
  - Due to the small sample size, some of the findings may have been completely the result of random chance, and the average consumption of SCBs was lower than the Canadian average as well as several other countries.
- A **prospective cohort with several follow-up appointments** (maybe once a week of daily recording dietary intake information per year) **and a larger sample size** would provide a lot more strength to these findings and improve the validity of the findings.
  - **Sugar intake** from sources other than just beverages should also be considered.
  - The **time and cost** of such a study, however, would be very high.



## **QUESTIONS?**

 Arthur, R. S., Kirsh, V. A., Mossavar-Rahmani, Y., Xue, X., & Rohan, T. E.
 (2021). Sugar-containing beverages and their association with risk of breast, endometrial, ovarian and colorectal cancers among Canadian women. *Cancer Epidemiology*, *70*, 101855.

