©2012
Melony G. King
ALL RIGHTS RESERVED

CONSUMPTION OF SUGARY FOODS AND DRINKS AND RISK OF ENDOMETRIAL AND OVARIAN CANCERS

by MELONY G. KING

A Dissertation submitted to the

School of Public Health

University of Medicine and Dentistry of New Jersey

and the

Graduate School-New Brunswick

Rutgers, The State University of New Jersey

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

Graduate Program in Epidemiology

UMDNJ-School of Public Health

Awarded jointly by these institutions and

written under the direction of

Dr. Elisa V. Bandera

and approved by

_____

_____

_____

_____

New Brunswick, New Jersey

OCTOBER, 2012

ABSTRACT OF THE DISSERTATION

Consumption of Sugary Foods and Drinks and Risk of Endometrial and Ovarian Cancers

By MELONY G. KING

Dissertation Director:

Dr. Elisa V. Bandera

Endometrial and ovarian cancers are among the top ten cancers that occur in women in the US. The consumption of refined sugars has increased dramatically over the past few decades, accounting for almost 15% of total energy intake. Yet, there is limited evidence on how sugar consumption affects risk of these cancers. Our review of the published literature on sugar consumption and endometrial and ovarian cancers yielded inconsistent results. Furthermore, we found that few studies considered effect modification by insulin-related risk factors [i.e. body mass index, waist-to-hip ratio (WHR), physical activity]. Using data from two related New Jersey population-based case-control studies, we evaluated endometrial and ovarian cancer risk in relation to sugary foods and beverages, and total and added sugar intakes, while considering effect modification by insulin-related factors.

In our first study, women in the highest quartile of added sugar intake had significantly higher endometrial cancer risk (OR=1.84, 95% CI:1.16-2.92). Sugary drink intake moderately increased endometrial cancer risk with each unit increase (OR=1.61, 95% CI:1.09-2.40 per serving/1000 kcal). Among women with WHR $\geq$0.85, risk was significantly higher for the highest vs. lowest tertile of added sugar intakes (OR=2.50, 95% CI:1.38-4.52). The association with added sugar also became stronger when analyses were restricted to never users of hormone replacement therapy (OR: 2.03; 95% CI: 1.27-3.26 for highest vs. lowest tertile). For ovarian

cancer, we did not find evidence of an association between consumption of sugary foods and beverages and risk.

In conclusion, we performed a comprehensive assessment of sugar intake and endometrial and ovarian cancer risk, with consideration of insulin-modifiers. Endometrial cancer risk was adversely related to sugary drink and added sugar intakes, after adjusting for several major risk factors. Also, there was evidence that insulin-related risk factors, mainly central obesity, modified these relationships. However, there was little indication that sugar intake influenced ovarian cancer risk. Our study is the first to evaluate endometrial and ovarian cancer risk in relation to added sugar consumption from all food sources, while considering effect modification by several insulin-related factors. Given the high prevalence of intake of sugary foods and drinks in Western populations, additional research is warranted to confirm our findings on endometrial cancer and to further elucidate the role of sugar intake on ovarian cancer risk.

Acknowledgements

I would like to thank Dr. Elisa Bandera for her unrelenting help and support throughout my academic career. I would also like to thank my committee members, Drs. Olson, Demissie, and Lu for their valuable assistance during this process. Also, this research could not have been performed without the help of several interviewers and students who were involved in this study, personnel from the New Jersey Department of Health and Senior Services, as well as all the participants who generously contributed their time to our study. Lastly, I would like to thank my family and friends for encouraging me throughout the frustrations and successes of doctoral research.

The studies in which this dissertation is based were funded by the National Cancer Institute (R01CA83918, NIH-K07 CA095666, and K22CA138563) and The Cancer Institute of New Jersey.

Table of contents

Abstract ii

Acknowledgements iv

List of Tables vii

Introduction 1

Chapter 1: Sugar consumption and endometrial cancer risk: A review of the literature 3

Methods 6

Sugary Foods and Beverages 6

Sugars 10

Conclusions 13

Chapter 2: Sugary Foods and Drinks and Endometrial Cancer Risk 20

Introduction 20

Materials and Methods 22

Study Population 22

Data Collection 23

Processing of Dietary Data 25

Statistical Analyses 26

Results 27

Discussion 35

Chapter 3: Sugar consumption and ovarian cancer risk: A review of the literature 41

Possible Underlying Mechanisms 42

Methods 43

Sugary Foods and Beverages 43

Sugars 45

Conclusions 47

Chapter 4: Sugary foods and drinks and ovarian cancer risk 53

Introduction 53

Materials and Methods 55

Study Population 55

Data Collection 56

Processing of Dietary Data 57

Statistical Analyses 58

Results 59

Discussion 67

Summary and Conclusions 72

Appendix 74

Bibliography 76

List of Tables

Chapter 1: Sugar consumption and endometrial cancer risk: A review of the literature

Table 1. Characteristics of prospective cohort studies evaluating sugar consumption and endometrial cancer risk. 15

Table 2. Characteristics of case-control studies evaluating sugar consumption and endometrial cancer risk. 17

Table 3. List of exposure variables and effect modifiers evaluated in studies on sugar consumption and endometrial cancer risk. 19

Chapter 2: Sugary Foods and Drinks and Endometrial Cancer Risk

Table 1. Selected characteristics of women participating in The EDGE Study. 28

Table 2. Age-adjusted means (± SE) for sources of sugars among women in The EDGE Study. 29

Table 3. Sources of sugar and endometrial cancer risk in The EDGE Study. 30

Table 4. Sources of sugar and endometrial cancer risk by selected characteristics in The EDGE Study..... 33

Chapter 3: Sugar consumption and ovarian cancer risk: A review of the literature

Table 1. Characteristics of prospective cohort studies evaluating sugar consumption and ovarian cancer risk. 49

Table 2. Characteristics of case-control studies evaluating sugar consumption and ovarian cancer risk. 50

Table 3. List of exposure variables and effect modifiers evaluated in studies on sugar consumption and ovarian cancer risk. 52

Chapter 4: Sugary foods and drinks and ovarian cancer risk

Table 1. Selected characteristics of women participating in The NJ Ovarian Cancer Study. 60

Table 2. Age-adjusted means (± SE) for sugary foods and drinks and added sugar among women in The NJ Ovarian Cancer Study. 61

Table 3. Sources of sugar and ovarian cancer risk in The NJ Ovarian Cancer Study. 62

Table 4. Sugary foods and drinks and added sugar and ovarian cancer risk by selected characteristics in The NJ Ovarian Cancer Study. 65

Introduction

The consumption of caloric sweeteners has increased rapidly in the United States over the past three decades. This is likely due to the fact that sweetening foods with sugar has desirable sensory effects and promotes enjoyment of meals and snacks(1). Although there has been a recent drop in the amount of added sugars consumed by Americans older than 2 years, it still accounts for almost 15% of total energy intake(2). This amount exceeds the 2010 Dietary Guidelines for Americans that recommend limiting calories from solid fats and added sugars to 5 to 15% of total energy intake(2, 3). Together, sugary foods and beverages contributed to two-thirds of added sugar intake in 2007-2008. Regular soft drinks, in particular, were the largest source of added sugars in the United States(2). High-fructose corn syrup (HFCS) is the predominant sweetener in soft drinks in the US and a major source of dietary sugars, representing 75% of corn sweeteners and 40% of total caloric sweeteners that are consumed in America(4, 5). Corn-based sweeteners are sweeter than sucrose and are inexpensive to create, making it more profitable to replace sucrose and simple sugars in foods and beverages(4, 6). By and large, sugar seems to be the number one food additive and even appears in savory (non-dessert) foods such as pizza, bread, spaghetti sauce, salad dressing and much more(5).

Total sugars are the sum of both natural and added sugars in the diet(1). Natural sugars, such as fructose or lactose, are found in whole fruit, vegetables, or milk products, which also have nutrients and phytochemicals that are beneficial to one's health(7). On the other hand, added sugars are all caloric sweeteners that have been added to foods or beverages during processing, preparation, and also consumed separately or at the table. Foods with added sugars tend to be high in calories and lacking essential nutrients(7). Examples of added sugars are sucrose (i.e. table sugar), HFCS, honey, molasses, and syrups(1, 2, 7). Sucrose and high-fructose corn syrup are both made up of approximately equal amounts of glucose and fructose(2, 4).

Sugary foods and beverages are foods that have been processed, prepared, or consumed with caloric sweeteners(7).

National and international expert panels(3, 8) have recommended that individuals limit their consumption of added sugars for good reason. Overconsumption of added sugars has been associated with multiple adverse health outcomes in adults, including obesity (4, 9, 10), insulin resistance and type II diabetes(7, 10-12), cardiovascular disease, high cholesterol and hypertension(7). Yet, few studies have tested the relevance of public health recommendations to reduce added sugar intake in relation to women's health. In particular, there is limited epidemiologic research evaluating the impact of sugar consumption on endometrial and ovarian cancer risk and the findings have been inconsistent. Furthermore, much of the research has focused either on specific sugary foods or beverages or sugar as a nutrient without considering the effects of factors that influence insulin sensitivity (e.g. central obesity or physical activity).

The overall aims of this dissertation are to evaluate the relationship between sugary foods and beverages and total and added sugars in relation to endometrial and ovarian cancers. To our knowledge, this is the first study to conduct a comprehensive assessment of sugary foods and drinks, total and added sugar consumption, and potential effect modification by insulin-related risk factors, (i.e. central adiposity) in relation to endometrial and ovarian cancer risk.

Chapter 1: Sugar consumption and endometrial cancer risk: A review of the literature

The consumption of refined sugars has increased dramatically over the past few decades and these sweeteners represent a substantial portion of caloric intake among Americans(4, 5).The amount of added sugars consumed by Americans ≥2 years accounts for approximately 15% of total energy intake and international and national expert panels recommend that individuals limit their consumption of energy-dense foods and avoid sugary drinks (2, 8). Even so, there are few studies that have tested the relevance of this public health recommendation in relation to endometrial cancer risk.

Endometrial cancer is the most common cancer of the female genital system and ranks fourth among all cancers in women in the United States(13). Endometrial cancer risk is primarily associated with reproductive characteristics that impact a woman's hormone balance. Particularly, high cumulative exposure of unopposed estrogens to the endometrium is a well-established risk factor for endometrial cancer(13, 14). Overconsumption of high-sugar, low-nutrient foods can lead to obesity(4, 9, 10, 15), a significant risk factor for insulin resistance and hyperinsulinemia(16-19). Obesity, insulin resistance, chronic hyperinsulinemia, and diabetes are hypothesized increase risk of endometrial cancer(20, 21).

The relationship between body weight and endometrial cancer risk is well established and apparent in both pre- and postmenopausal women, and can be explained by changes in endogenous hormone metabolism(14, 20). In premenopausal women, obesity may increase the frequency of anovulatory cycles and consequently decrease progesterone. Progesterone stimulates gene expression and synthesis of endometrial IGFBP-1, the most plentiful IGF-binding protein in the endometrium and an inhibitor of IGF-I activity(20). After menopause, there is a cessation in ovarian production of estrogen and the chief source of endogenous estrogens comes from the aromatization of plasma androstenedione, a steroid hormone, into estrone, and

later estradiol, in adipose tissue(22). Thus, increased bioavailability of estrogen, offset by insufficient progesterone, induces insulin-like growth factor 1 (IGF-1) production, increasing cell proliferation within the endometrium(14, 20).

The role of excess weight in endometrial carcinogenesis is well-known and several studies have reported a direct association between obesity and endometrial cancer risk(8, 23, 24). Excess weight and chronically elevated insulin levels have been linked to changes in sex steroid levels by inhibiting the production of sex hormone-binding globulin (SHBG) in the liver, enhancing androgen synthesis by the gonads and adrenal glands, as well as, increasing estrogen production through the aromatization of androgens to estrone in adipose tissue(20). Consequently, these mechanisms can result in lower SHBG levels, increased estrone levels, and increases in testosterone unbound to SHBG. Body mass index (BMI) and plasma insulin have been shown to be inversely related with SHBG, regardless of menopausal status(20, 22, 25). Although *in vitro* research have provided evidence that insulin stimulates ovarian steroid production, BMI and plasma insulin concentrations have not been linked to androstenedione in postmenopausal women and only weakly correlated with plasma testosterone levels(20, 26-29). All in all, insulin may influence cancer risk directly and indirectly. First, insulin promotes cellular proliferation and tumor growth by acting directly on endometrial tissue as a mitogenic and antiapoptotic growth factor (20, 30, 31). Also, insulin may directly improve tumor development via insulin receptors in the endometrium(20). Indirectly, there is indication that chronic hyperinsulinemia plays a significant part in the onset of ovarian hyperandrogenism, which is linked to anovulation and decreased progesterone levels(20).

The impact of sugar intake on endometrial cancer may be modified by several factors. A small number of studies have focused on fat distribution and the relationship between sugar intake and endometrial cancer risk. More often, BMI, which is based on weight and height, is

used to measure body fat. However, BMI is limited in that it may overestimate body fat among muscular persons and underestimate body fat in older persons or those who have lost muscle(32). It also does not reliably measure the extent of central obesity, a strong correlate of insulin resistance(33). In the Quebec Health Survey(34), Pouliot et al. found that lean subjects and obese subjects with low central adiposity had similar blood glucose and insulin levels during an oral glucose tolerance test compared to subjects with greater central adiposity and poorer glucose tolerance(35). In this case, waist circumference, rather than BMI, better explained of the relationship between obesity, insulin resistance, and hypertension.

Furthermore, since being overweight or physically inactive is associated with decreased insulin sensitivity and higher insulin levels, it may be possible that overweight or inactive women have greater insulin response to foods with refined sugars(19, 36). To the contrary, a healthful diet, physical activity, weight loss, or the use of insulin-lowering drugs may reduce endometrial cancer risk by improving insulin sensitivity(20, 30, 37) and normalizing plasma androgen levels(20). Folsom et al. suggests that women with diabetes may have lower risk of endometrial cancer if they are more health conscious and have controlled their diabetes(38). Moderate alcohol consumption (1-2 drinks/day) is also shown to lower fasting insulin levels, enhance insulin sensitivity, and decrease risk of type 2 diabetes(39-42), independent of body mass index(42). Also, individuals with high fat intake vs. low fat intake have been shown to have impaired glucose tolerance or type 2 diabetes. Saturated fat, compared to unsaturated fats, can have a more harmful effect on insulin-sensitivity(43). However, the lack of epidemiologic evidence to support these relationships with respect to sugar consumption and endometrial cancer risk further emphasizes the need for a more in depth investigation. Specifically, the relationship between sugar consumption and endometrial cancer should be evaluated while taking into consideration several factors related to insulin resistance or chronic

hyperinsulinemia. The aim of this review is to provide a general overview of the published literature on sugary foods and drinks, and total and added sugar consumption, in relation to endometrial cancer risk.

Methods

We used PubMed to search for articles related to sugar consumption and risk of endometrial cancer and that were published up to July 15, 2012. Examples of search terms used include: sugar*[tiab] OR food and beverages[MeSH] OR diet[tiab] OR diets[tiab] OR dietary[tiab] AND endometrial cancer[tiab]. Additional search terms included: “sugary food”, “sugary beverage”, “sugary drinks”, or “added sugar”. We also manually searched bibliographies of published papers. We included only cohort and case-controls studies in our review. To our knowledge, there were no intervention or cross-sectional studies. We excluded one ecological study(44). **Tables 1 and 2** describe characteristics of the studies that were included in this review. **Table 3** provides a concise list of exposure variables and effect modifiers for included studies.

Sugary Foods and Beverages

Few studies have performed a comprehensive assessment of total sugary food (i.e. desserts, snacks, candies) and beverage (i.e. juice, soda, tea) intake and endometrial cancer risk. A dozen studies(30, 45-55) have evaluated sugary foods, however, only half of these studies (30, 46, 47, 49, 52, 55) examined sugary drinks, most often soft drinks. Even fewer have evaluated sugary foods and beverage intake and endometrial cancer risk while considering factors the modify insulin sensitivity such as diabetes(30, 46), body mass index (BMI)(30, 45-47), waist-to-hip ratio (WHR)(30), or physical activity(30, 46).

A review of the three cohort(30, 46, 48), four population-based case-control studies(47, 50, 53, 54), and five hospital case-control studies(45, 49, 51, 52, 55) revealed

generally null findings. Only two studies(46, 49) found a significant relationship between the consumption of sugary foods and/or beverages and risk of endometrial cancer. In the first study, using dietary data of over 60,000 women in the Swedish Mammography Cohort, Friberg et al. (46) reported significant increased risk for those who consumed >3 servings/ week of "sweet buns and cookies" vs. <0.5 servings/ week, for both baseline (1987) and follow-up (1997) [Rate Ratio(RR)=1.42, 95% Confidence Intervals(CI):1.14-1.75 and RR=1.72, 95% CI:1.06-2.78, respectively]. Excluding women with diabetes from the analyses or further adjustment for fat intake did not substantially alter results(46). The authors did not detect a relationship between soft drinks (yes vs. no) and endometrial cancer risk. However, they noted that in Sweden soft drinks are sweetened with sucrose as opposed to high-fructose corn syrup, the predominant caloric sweetener used in soft drinks in the US. Furthermore, compared to Americans who participated in the Third National Health and Nutrition Examination Survey (NHANES III) 1988-1944, their study population had lower sucrose consumption (46). On the contrary, two other prospective studies did not find an adverse relationship between sugary foods and/or beverages and endometrial cancer risk. In the European Prospective Investigation into Cancer and Nutrition Cohort (EPIC) Study(30), a study of more than 288,000 women, investigators detected a borderline inverse association between cancer risk and "cakes, pastries, biscuits" and null association with carbonated beverages and confectionery sugar and endometrial cancer risk. Lastly, in another large cohort study, Kasum et al.(48) did not find greater risk of endometrial cancer associated with the category "refined grains," which included pancakes or waffles, in addition to other foods such as white bread, pita bread, cold breakfast cereals, English muffins, bagels or rolls, white rice, pasta and pizza. However, these results must be interpreted carefully, as the food group, "refined grains", included some foods that would not be considered sugary foods. Friberg et al. and Kasum et al. did not evaluated if insulin-related factors modified the

relationships between sugary foods and drinks and cancer risk. It was not clear if investigators tested for effect modification in the EPIC study.

In a population-based case-control study in Western New York, McCann et al. reported that the highest intake of snacks and sweets did not significantly increase risk [Odds Ratio (OR)=1.2, 95% CI:0.7-2.0], although it was not specified how foods were selected in the group "Snacks and sweets"(50). Therefore, we are unable to separate the effects of sugary foods from other snack foods on endometrial cancer risk. However, a high monthly frequency of consuming canned or frozen fruit increased cancer risk (> 33 times/month: OR=2.0, 95% CI:1.1-3.4), while fresh fruit, citrus fruit, and total fruit did not seem to affect risk. Although the authors adjusted for diabetes in their multivariable models, they did not account for total energy intake. Levi and colleagues(49) carried out a case-control study that was both population-based (in Switzerland) and hospital-based (in Italy) and reported a significant moderate increase in risk for the highest tertile of pastry consumption (OR=1.60, $p_{trend}<0.05$). It is noteworthy that the authors did not adjust for other major confounding factors (i.e. BMI, ERT, education, and physical activity) that did not substantially modify their odds ratios. The authors presented results that adjusted for study center and age, only. Potischman et al. evaluated intake of high-fat snacks and desserts among women in five areas of the US and reported non-significant decreases in risk (Quartile 4, OR=0.7, 95% CI:0.4-1.2)(53). Adjustment for waist-to-thigh ratio and diabetes did not materially alter their findings for nutrients, however, it was not specified if the same tests were performed for food groups like high-fat snacks and desserts. Because the investigators combined high-fat snacks with desserts, we are unable to tease apart the impact of high-fat non-sugary foods (i.e. French fries, chips or popcorn) and sugary foods (i.e. ice cream, pie, doughnuts, cakes) on endometrial cancer risk in this study population. Similarly, Shu et al.(54) were unable to detect a relationship between sweets and endometrial cancer among Chinese women, after adjusting for

age, parity, BMI, and total calories. The authors did not state which foods were included in the category, sweets. Lastly, a study by Goodman and colleagues(47) is the only population-based case-control study examining both sugary foods and drinks and endometrial cancer risk. They found that desserts and candy did not affect risk among their Hawaiian study population. Also, regular cola beverages did not significantly increase risk, although the OR for Quartile 3 (13.6 g/day) was 1.5 (CI not provided, but included 1.0). The multivariate models did adjust for diabetes, but did not adjust for smoking status or pack-years. Smoking has anti-estrogenic effects and therefore reduces endometrial cancer risk. Potischman et al.(53), Shu et al.(54), McCann et al.(50) did not explore waist-to-hip ratio or BMI as potential effect modifiers of the relationship between sugary foods and cancer risk. None of these population-based studies assessed possible effect modification by physical activity.

A review of five hospital-based case-control studies generally reported null findings. Biel and colleagues(45) did not find risk to be influenced by consumption of less healthy sweets and additionally reported no effect modification by BMI. Two other hospital-based case-control studies in Mexico(52) and Greece(51) presented null findings for sugary foods, although their studies likely had limited statistical power due to a small number of cases: 85 and 84, respectively. Among the hospital-based case-control studies that evaluated sugary drinks, there were no reported significant associations with endometrial cancer risk. Levi et al.(49) found a non-significant moderate increase in risk associated with cola-containing beverages (OR=1.71, χ^2_{trend}=1.76) after adjusting for age and study center. We speculate that this study may have had limited statistical power to assess the association between soft drinks and endometrial cancer risk as 93% of cases and 94% of controls had the lowest level (referent group) of consumption of cola-containing beverages. Salazar-Martinez et al. (52) reported null findings for “soda, coffee and tea” and endometrial cancer risk in their study within Mexico (Tertile 2: OR=1.30, 95%

CI:0.70-2.44; Tertile 3: OR=0.99, 95% CI:0.48-2.03). However, this category incorporates beverages that may be consumed with or without added sugars (e.g. regular or diet sodas, tea or coffee). Also, while the authors did adjust for total energy intake, BMI, physical activity, and diabetes, they did not adjust for smoking status or pack-years. Similarly, Tzonou et al. did not find a relationship between non-alcoholic beverages (defined as bottled fruit juice, various sodas, various colas, other carbonated beverages) and endometrial cancer risk in the Greek study population(55). Besides Biel et al., no other hospital-based case-control studies tested for effect modification BMI, WHR, or physical activity in relation to consumption of sugary foods and/or beverages and endometrial cancer risk(45).

Sugars

Taken together, studies have reported mixed findings on the relationship between sugar consumption (i.e. total sugars, sugar, added sugar, sucrose or fructose) and endometrial cancer risk. To our knowledge, four cohort studies(30, 36, 46, 56), two population-based case-control studies(57, 58), and seven hospital- and prison-based case-control studies(49, 51, 52, 55, 59-61) have evaluated this relationship.

Overall, prospective studies(30, 36, 46, 56) that evaluated sugar consumption suggest a detrimental effect on endometrial cancer risk. In the EPIC study, Cust et al.(30) found a non-significant increase in endometrial cancer risk associated with the highest intake of total sugars (RR=1.20, 95% CI:0.97-1.48). However, after correcting their models for measurement error using 24-hour recall values, they detected significant increased risk of developing endometrial cancer associated with total sugars on a continuous scale (per 50 g/day) [RR(95% CI): 1.36(1.05-1.76)]. The adverse effect of total sugars on endometrial cancer risk was more evident among women who were normal weight, postmenopausal, or postmenopausal and never used HRT. The authors suggest that HRT use (e.g. exogenous hormones) may override the influence of

endogenous hormone levels to a point where diet no longer has additional impact on cancer risk(30). Cust et al. also reported that physical activity, oral contraceptive use, or having diabetes did not seem to modify risk estimates(30). However, women with WHR below the median vs. above the median had elevated cancer risk(30). Likewise, in the Swedish Mammography Cohort, Friberg et al.(46) reported significant moderate increases in risk across all levels of sucrose intake (g/day) in their baseline (1987) dietary data (RRs for Quartiles 1-4, respectively: 1.00, 1.50, 1.41, 1.36). Their follow-up after 10 years showed a great magnitude of increased risk for the highest category of intake (RR=1.73, 95% CI:1.04-2.97). Interestingly, when comparing women who consumed >15 vs. $\leq$ 15 grams of sucrose per day, there was a stronger adverse effect among women who were overweight, obese, or had low fat intake (RRs=1.59; 1.97; and 1.56, respectively). Similarly, in the Canadian National Breast Screening Study, Silvera and colleagues(36) found a borderline positive relationship between total sugar (g/day) and endometrial cancer risk (Quartile 4: OR=1.26, 95% CI:0.94-1.68). However, they did not collect information on diabetes or test for effect modification by any factors.

The National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, a prospective study of over 400,000 men and women, is the only study that has separately examined the relationship between total added sugar intake and endometrial cancer risk and did not find a relationship(56). They detected both borderline and significantly elevated endometrial cancer risk associated with total sugars, total fructose, and sucrose. The investigators looked for potential effect modification by BMI and reported no effect. However, they did not adjust for diabetes in their analyses and did not assess for effect modification by insulin-related risk factors such as diabetes, physical activity, or WHR(56).

Using data from the EDGE Study, a population-based case-control study in NJ, Chandran et al.(58) evaluated endometrial cancer risk in relation to calories from solid fat, alcohol, and

added sugars (SoFAAS). SoFAAS is one of the components of the Healthy Eating Index- a tool that quantifies adherence to Dietary Guidelines for Americans(58). The authors found a suggestion of increased risk associated with the highest intake of SoFAAS, but the confidence interval included the null value (OR=1.57, 95% CI:0.87-2.84)(58). We also examined the relationship between sugar added to coffee and tea and endometrial cancer risk in the EDGE Study(57). We found that endometrial cancer risk more than doubled among women who usually added $\geq$ 2 teaspoons of sugar or honey per cup of tea compared to women who added none (OR=2.66, 95% CI:1.42-4.98). There was also some suggestion of an adverse effect for women who consumed, daily, $\geq$ 3 teaspoons of sugar or honey added to coffee or tea vs. women who did not add sugar (OR=1.58, 95% CI:0.92-2.71)(57). Neither of these studies evaluated potential effect modification by insulin-related risk factors.

Six hospital-based case-control studies(49, 51, 52, 55, 59, 60) and one prison-based case-control study(61) have assessed the relationship between sugar intake and endometrial cancer and have reported inconsistent findings. Levi et al. reported a significant increase in endometrial cancer risk associated with sugar intake (OR for tertiles 2 and 3: 1.72 and 2.49, respectively; $p_{trend}<0.01$)(49). This association remained after adjusting for total energy intake (OR for tertiles 2 and 3:1.55 and 2.07, respectively; $p_{trend}<0.01$)(49). In a hospital-based case-control study in Poland, Zemla et la.(60) reported significantly higher endometrial cancer risk associated with consuming more sugar added to tea or coffee vs. the same amount of sugar consumed by other members of the household (RR=4.50, χ^2=46.12) (60). Similarly, Zemla and colleagues(61) also found that prisoners who consumed sugar more often than fellow inmates had significantly higher uterine cancer risk in a prison-based case-control study in Poland (Natives: RR=5.01, χ^2=35.648 and Immigrants: RR=2.17, χ^2=4.612). It is important to note that the investigators did not perform age-adjusted or multivariable analyses in either of these

studies (60, 61). In contrast, the remaining case-control studies reported null findings. Lucenteforte et al.(59) reported no association between sugar intake (g/day) and risk of endometrial cancer among patients admitted to a network of hospitals in Italy. Likewise, studies by Tzonou et al.(55) and Petridou et al.(51) did not find a relationship between "sugars or syrups" and endometrial cancer risk among Greek patients. However, these authors did not separately evaluate sugary foods and sugar in relation to endometrial cancer risk. Salazar-Martinez et al.(52) found sucrose intake to be unrelated to endometrial cancer risk among patients admitted to an Obstetrics and Gynecology hospital in Mexico City. The latter three studies had a small number of cases (145, 84, and 85 cases, respectively) and may have had limited statistical power to evaluate sugar consumption and cancer risk. None of these case-control studies have tested for possible effect modification by insulin-related factors.

Conclusions

In summary, a review of twenty articles on sugar consumption and endometrial cancer yielded inconsistent results and suggested no associations. A number of studies[24,39-49] have evaluated endometrial cancer risk in relation to sugary food and/or beverage intake, yet only two of these studies[40,43] reported a significant inverse association, while the remaining studies did not detect a relationship. With more than a dozen studies investigating sugar intake and endometrial cancer risk, prospective studies[24,30,40,50] suggested a hazardous relationship exists, while case-control studies(49, 51, 52, 55, 57-61) reported conflicting results. In addition, very few studies tested for effect modification by BMI(30, 46, 56), physical activity(30, 46), WHR(30) or diabetes(30, 46).

After carefully reviewing the published literature on this topic, some limitations are apparent. Among the five cohort studies and 15 case-controls studies included, there were no studies that have taken a comprehensive approach by evaluating risk associated with several

forms of sugar consumption, including sugary food and beverage intake, as well total and added sugar intakes from all food sources. Although several studies have evaluated sugary food consumption and cancer risk, few have evaluated the effects of sugary drink intake. Furthermore, these studies typically evaluated select food and beverage items, such as, sweets, syrups, or caffeinated beverages. There were no studies that reported on the impact of consuming a variety foods, both sweet and savory, with added sugars. In addition, to our knowledge, there is only one study that directly examined intake of total sugars and added sugars from all food sources and endometrial cancer risk, reporting null findings(56).

From a public health point of view, it may be more informative to evaluate the effects of total sugary foods and drinks, in addition to added sugars, as the incremental exposure to added sugars from all foods could impact endometrial cancer risk. Furthermore, waist circumference and other factors that affect insulin sensitivity, have rarely been explored as effect modifiers of the relationship between sugar intake and endometrial cancer risk. Thus, it is important to perform a more thorough investigation into the relationship between the consumption of sugar, particularly, added sugar, and endometrial cancer risk, especially while considering effect modification by factors related to insulin. Lastly, although a few studies have evaluated the impact of dietary sugars on endometrial cancer, the results have generally been inconsistent. The limited epidemiologic research with contradictory findings highlights the need for further investigation of these issues, preferably using data from large prospective cohort studies.

Table 1. Characteristics of prospective cohort studies evaluating sugar consumption and endometrial cancer risk.

Reference	Location	Cases/ cohort (n)	Dietary assessment	Time Frame of Dietary Assessment	Sugar variables	Effect modifiers	Results
(30)	10 countries in Europe (DK, FR, DE, GR, IT, NO, ES, SZ, NL, UK)	710 / 288,428	FFQ, food records or 7-day menu book, 24-hour dietary recall among subset	1 year prior to index date	Total sugars, breakfast cereals, "cakes, pastries, biscuits", confectionery sugar, carbonated drinks	BMI, menopausal status at baseline, HRT use, OC use, physical activity, diabetes, WHR	*+ association:* total sugars, and total sugars among women with BMI <25, women with WHR below the median, postmenopausal women, never users of HRT *Borderline + association:* total sugars among women with BMI $\geq$ 30 *No association:* individual foods, no effect modification by OC use, physical activity or diabetes
(46)	Sweden	729 / 61,226	Baseline assessment FFQ: 67 items; 2nd assessment FFQ: 96 items	Baseline: Diet during last 6 mo; 2nd assessment: previous year	Total sucrose, high sugar foods: "sweet buns and cookies", sweets, soft drinks, "jam, marmalade, sweetened fruit soups and stewed fruit"	BMI, diabetes, physical activity, fat and alcohol intake	*+ association:* total sucrose, "sweet buns and cookies" in total population at baseline & 2nd assessment. *no association:* sweets, soft drinks, or jam, marmalade, sweetened fruit soups and stewed fruit Effect modification: Increased risk associated with sucrose intake among overweight and obese women and women with low fat intake. No modification by diabetes or physical activity
(48)	Iowa, USA	382 / 23,014	FFQ (127 items)	Current intake at baseline	"Refined grains" [1]	HRT use	*No association:* Refined grains No effect modification by HRT use
(36)	Canada	426 / 34,391	FFQ (86 items)	Current intake at baseline	Total sugar	None	*No association:* total sugar

(56)	8 States in USA (CA, FL, LA, NJ, NC, MI, GA, PA)	924 / 179,990	FFQ, DHQ (124 items)	1 year prior to index date	Total sugars, added sugar, sucrose, total fructose, added sucrose, added fructose	BMI, HRT use	*+ association:* total sugars *No association:* added sugars, total fructose, sucrose, added sucrose, added fructose; no effect modification by BMI, HRT

Abbreviations: FFQ- food frequency questionnaire, DHQ- diet history questionnaire, BMI- body mass index, HRT- hormone replacement therapy, ERT- unopposed estrogen replacement therapy, OC- oral contraceptives, WHR- waist-to-hip ratio, "+ association" - positive association, "- association"- negative association

[1]Refined grains" category included: white bread, pita bread, cold breakfast cereals <25% whole grain or bran content by weight, English muffins, bagels or rolls, pancakes or waffles, white rice, pasta, and pizza

Table 2. Characteristics of case-control studies evaluating sugar consumption and endometrial cancer risk.

Reference	Location	Cases/ controls (n)	Dietary assessment	Time Frame of Dietary Assessment	Sugar variables	Effect modifiers	Results
Population-based							
(57)	New Jersey	417/395	FFQ (131 items)	6 months prior to index date	Sugar/honey added to coffee and/or tea	None	*+ association:* ≥2 tsp of sugar per cup of tea vs. no added sugar *No association:* sugar/honey (tsp/day) added to coffee or tea, tsp of sugar per cup of coffee
(58)	New Jersey	424/398	FFQ (110 items)	6 months prior to index date	SoFAAS: total calories from solid fat, alcoholic beverages, and added sugar	None	Strong suggestions of *+ association:* SoFAAS
(47)	Hawaii	332/511	Interviewer-administered diet questionnaire (250 items)	1 year prior to index date	"desserts and candy", regular cola	BMI, ERT use	*No association:* desserts and candy, regular cola No effect modification by BMI or ERT use.
(50)	New York	232/639	Interviewer-administered diet questionnaire (172 items)	12 month period 2yr before interview	"Canned or frozen fruit", "snacks and sweets"	None	*+ association:* canned or frozen fruit *No association:* Snacks and sweets
(53)	IL, PA, CA, MN, NC	399/296	FFQ (60 items)	Past few years, ignoring recent changes	"High-fat snacks and desserts:	None	*No association:* high-fat snacks and desserts
(54)	Shanghai, China	268/268	FFQ (63 items)	10-year period prior to interview, ignoring recent changes	Sweets	None	*No association:* sweets

Hospital-based							
(45)	Canada	506/981	FFQ	1 year prior to index date	Sweets	BMI	*No association*: sweets No effect modification by BMI
(62)							
(49)	Switzerland and Italy	274/572	Questionnaire of weekly frequencies of 50 food items	Intake before symptoms of disease	Pastry, sugar, cola-containing beverages	None	*+ association:* sugar, pastry *No association:* cola-containing beverages
(59)	Italy	454/908	FFQ	2 years (78 items)	Sugars	None	*No association:* sugars
(51)	Greece	84/84	FFQ (~110 items)	1 year prior to index date	"Sugars and syrups"	None	*No association:* sugar and syrups
(52)	Mexico	85/629	FFQ (116 items)	1 year prior to index date	Sucrose, fructose, glucose, maltose, "sweets and desserts", "soda, coffee and tea"	None	*No association:* sucrose, fructose, glucose, maltose, sweets and desserts, soda, coffee and tea
(55)	Greece	145/298	FFQ (115 items)	1 year prior to index date	"Sugars or syrups", Non-alcoholic beverages	None	*No association:* Sugars or syrups, non-alcoholic beverages
(60)	Poland	173/346	Not stated	Not stated	Sugars added to tea or coffee [2]	None	*+ association:* sugar added to tea or coffee
Prison-based							
(61)	Poland	200/400	Not stated	Not stated	Consumption of sugar (as foods): less than, the same, or more than other inmates	Native vs. Immigrant	*+ association:* increased risk for inmates who consumed sugar more often than other inmates vs. the same

Abbreviations: FFQ- food frequency questionnaire, DHQ- diet history questionnaire, BMI- body mass index, HRT- hormone replacement therapy, ERT- unopposed estrogen replacement therapy, OC- oral contraceptives, WHR- waist-to-hip ratio, "+ association" - positive association, "- association"- negative association

[1] Zemla 1986 and 1991 were from the same study

[2] In comparison to members of the household

Table 3. List of exposure variables and effect modifiers evaluated in studies on sugar consumption and endometrial cancer risk.

Reference	Sugary Foods	Sugary Drinks	Total Sugars, Sugar or Sucrose	Added Sugar	Effect Modifiers					
					BMI	HRT use	Menopausal Status	Physical Activity	WHR	Diabetes
Cohort studies										
(30)	✓	✓	✓	✓[a]	✓	✓	✓	✓	✓	✓
(46)	✓	✓	✓		✓			✓		✓
(48)	✓					✓				
(36)			✓							
(56)			✓	✓	✓					
Case-control studies: population-based										
(57)				✓[b]						
(58)				✓						
(47)	✓	✓								
(50)	✓									
(53)	✓									
(54)	✓									
Case-control studies: hospital-based										
(45)	✓				✓					
(62)	✓		✓							
(49)	✓	✓	✓							
(59)			✓							
(51)	✓		✓							
(52)	✓	✓	✓							
(55)	✓	✓	✓							
(60)			✓	✓[b]						
Case-control studies: prison-based										
(61)			✓							

Abbreviations: BMI- body mass index, HRT- hormone replacement therapy, WHR- waist-to-hip ratio, ?-Unable to translate article

[a] Confectionery sugar [b] Sugar or honey added to tea and coffee

Chapter 2: Sugary Foods and Drinks and Endometrial Cancer Risk

Introduction

Endometrial cancer is the most common gynecologic cancer in the United States and it is estimated that 47,130 new cases of uterine cancers will be diagnosed in 2012 and about 8,010 of these women will die from the disease(13). Risk is mainly related to reproductive characteristics that affect hormone levels. In particular, high levels of endogenous estrogen unopposed by progesterone, increases the stimulation of endometrial epithelial cells providing opportunity for carcinogenesis(14). Unopposed estrogen hormone replacement therapy, early onset of menses, nulliparity, and obesity increase endometrial cancer risk by prolonging or increasing estrogen exposure to the endometrium. Factors such as having multiple pregnancies, oral contraceptive use, and current cigarette smoking are known to lower risk of endometrial cancer by decreasing the endometrium's exposure to estrogen(13, 63). Hyperinsulinemia and diabetes have also been independently associated with endometrial cancer(20, 64, 65).

Consuming foods with high sugar content promotes insulin production and when consumed in great amounts can lead to obesity and ultimately hyperinsulinemia. In premenopausal women, obesity may increase the frequency of anovulatory cycles and consequently decrease progesterone. Progesterone stimulates gene expression and synthesis of endometrial IGFBP-1, the most plentiful IGF-binding protein in the endometrium and an inhibitor of IGF-I activity(20). After menopause, there is a cessation of ovarian production of estrogen and the chief source of endogenous estrogens comes from the aromatization of plasma androstenedione into estrone, and later estradiol, in adipose tissue(22). Thus, increased bioavailability of estrogen, offset by insufficient progesterone, induces IGF-1 production, increasing cell proliferation within the endometrium(14, 20). Additionally, obesity is also a major risk factor for insulin resistance(17, 20). Insulin may influence cancer risk directly and indirectly.

First, insulin promotes cellular proliferation and tumor growth by acting directly on endometrial tissue as a mitogenic and antiapoptotic growth factor (20, 30, 31). Insulin may also directly improve tumor development via insulin receptors in the endometrium(20). There is evidence that chronic hyperinsulinemia may play a significant role in the onset of ovarian hyperandrogenism, through anovulation and decreased progesterone levels(20).

While the impact of obesity on invasive endometrial cancer risk is well established, the evidence for the role of individual dietary factors is generally inconsistent(66). Even though there has been a substantial increase in endometrial cancer research over the past decade, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) 2nd expert report on endometrial cancer emphasized the need to further evaluate the role of food and nutrition in endometrial cancer etiology (66). In particular, there is limited epidemiologic research evaluating the impact of sugar consumption on endometrial cancer risk and the findings have been inconsistent. Furthermore, much of the research has focused either on specific sugary foods or beverages or sugar as a nutrient without considering the effects of insulin-related factors (e.g. central obesity or physical activity). Studying the effects of insulin-modifiers such as body mass index (BMI), waist-to-hip ratio (WHR), and physical activity, may provide a greater insight into the underlying mechanisms between dietary intake of sugary foods and beverages and endometrial cancer.

The consumption of refined sugars has increased dramatically over the past few decades and these sweeteners represent a substantial portion of the American diet (4, 5). Even with a recent drop in added sugar consumption by Americans older than 2 years, it still accounts for almost 15% of total energy intake(2). This exceeds the 2010 Dietary Guidelines for Americans that recommend limiting calories from solid fats and added sugars to 5 to 15% of total energy intake(2, 3). Furthermore, in the WCRF/AICR 2nd expert report, *Food, Nutrition, Physical Activity,*

and the Prevention of Cancer: a Global Perspective (2007) it is recommended that individuals limit their consumption of energy-dense foods and avoid sugary drinks, and that populations reduce their consumption of sugary drinks by half every 10 years(8). From a public health point of view, it may be more informative to evaluate the effects of total sugary foods and drinks, in addition to added sugars, as the incremental exposure to added sugars from all foods could impact endometrial cancer risk. Evaluating sugar consumption, specifically added sugar intake, will not only help us better understand its health effects; it will also test the relevance of this public health recommendation to endometrial cancer. To our knowledge, this is the first study to conduct a comprehensive assessment of sugary foods and drinks, total and added sugar consumption, and potential effect modification by factors that impact insulin sensitivity, (i.e. waist-to-hip ratio) in relation to endometrial cancer risk.

Materials and Methods

Study Population

We evaluated the association between sugary foods and beverages on endometrial cancer risk among participants in the EDGE (Estrogens, Diet, Genetics, and Endometrial Cancer) Study, which has been described in detail elsewhere(67-69). Briefly, the EDGE Study is a population-based case-control study among women older than 21 years, who were able to speak English and/or Spanish, and residents of six contiguous counties in New Jersey (Essex, Union, Morris, Middlesex, Bergen, and Hudson). Women with newly diagnosed, histologically confirmed epithelial endometrial cancer were eligible as cases. Cases were identified between July 1, 2001 and June 30, 2005, through rapid case ascertainment by the New Jersey Cancer Registry and interviewed between January 2002 and April 2006. During this period, 1104 women out of the 1559 eligible women identified were contacted within one year of their diagnosis.

Pathology reports and slide were obtained for cases who participated in the study and were reviewed by the study pathologist.

Controls had to meet the same eligibility criteria as cases and were not eligible if they have had a hysterectomy. A commercial research service identified 355 eligible women under 65 years of age via random digit dialing (RDD, stratified by age) of whom 175 completed the interview. Women who were 65 years and older were randomly selected from lists purchased from the Centers for Medicare and Medicaid Services (CMS) and contacted by letter, followed by telephone calls when able to locate their phone numbers. Sixty-eight (22%) of the 316 women identified completed the interview. Forty percent of those who declined had unknown eligibility. Starting in August 2003, we employed area sampling for controls in randomly selected areas within the six counties. A letter was mailed to households to introduce the study, followed by home visits by interviewers to ascertain eligibility and interest in participating. We initially sought women ages 65 years and over and later included women ages 55 years and over. Of the 524 eligible women identified, 224 (43%) completed the interview. Controls were interviewed between January 2002 and December 2005.

Informed consent was obtained from all participants and this study has been approved by the New Jersey Department of Health and Senior Services, Memorial Sloan-Kettering Cancer Center and University of Medicine and Dentistry of New Jersey (UMDNJ) Robert Wood Johnson Medical School Institutional Review Boards (IRBs).

Data Collection

Once passive approval was obtained from physicians, informed consent was obtained before the phone interview by mail, facsimile, or during the home interviews for women choosing this option. The main questionnaire was administered to obtain information on several factors, including demographic characteristics, risk factors for endometrial cancer, and other

exposures up to a year prior to their diagnosis (or reference date for controls). Factors ascertained included: menstrual history, pregnancy history, a detailed history of exogenous estrogen use (hormone replacement therapy and oral contraceptive use), self-reported height and weight, medical history (diabetes, hypertension, and other conditions), a detailed family history of cancer, and other related exposures. Physical activity, smoking history, and exposure to passive smoking were also assessed. A food frequency questionnaire and mouthwash sample for DNA extraction and analysis were also collected from participants. We also obtained self-recorded waist and hip measurements with a measuring tape (sent to them with instructions before the interview).

This study used the Block 98.2 Food Frequency Questionnaire (FFQ) to assess usual dietary intake 6 months prior to the case's diagnosis date or the control's date of interview. It is based on the NHANES (National Health and Nutrition Examination Survey) III dietary recall data and includes 110 food items and questions on frequency of intake and amount consumed for each food. Pictures were provided to help participants estimate the usual amount of food consumed. Nutrient calculations based on the USDA Nutrient Database for Standard Reference were provided by Berkeley Nutrition Services.

In total, 469 cases and 467 controls participated in the study. Of these, 424 cases (90.4%) and 398 controls (85.2%) completed both the main interview and FFQ. Participants were excluded from the analysis if they did not complete the FFQ or their menopausal status was unknown or if they were missing other major covariates. Those who were postmenopausal but did not know their age at menopause were included in the analysis. There were no significant differences in age, education, BMI and HRT use between women who returned the FFQ and those who did not.

Processing of Dietary Data

Participants' responses on frequency and portion sizes for sugary foods and beverages were converted to number of servings per day. For most foods, frequency was measured as 'never', 'a few times per year', 'once per month', '2-3 times per month', 'once per week', '2 time per week', '3-4 times per week', '5-6 times per week', and 'everyday'. For a few foods, 'never' and 'a few times per year' were combined into one choice: 'never or a few times per year' and the choice of '2+ times per day' was added. For drinks, portion size was measured as number of cups, glasses, cans or bottles consumed. For food items, portion sizes were measured in teaspoons, tablespoons, ounces, pounds, cups, pieces, patties, bowls or slices.
Serving sizes were based on the Reference Amounts Customarily Consumed (RACC) Per Eating Occasion: General Food Supply by the Food and Drug Administration(70). This document provides the amount of food that is usually consumed per eating occasion, and is based on the 1977-1978 and 1987-1988 Nationwide Food Consumption Surveys. We used the FDA's assigned RACC values to guide our assumptions about participants' portion sizes consumed. For example, we assumed that one cookie (RACC=30 grams) is equivalent to one serving. Therefore, participants who reported usually eating one cookie per occasion were assigned as eating one serving for this food item.

Select foods and drinks were converted to number of servings per day to calculate each individual's number of servings of dessert foods, non-dessert foods, sugary drinks and total sugary foods and drinks. Foods items included in the calculation of these food groups are listed in the Appendix. Total and added sugar intakes (g/day) were calculated separately by multiplying the frequency of consumption of each food by its total/added sugar content per 100 grams of food. Total and added sugar values for all food and drink items were assigned using the USDA Database for the Added Sugars Content of Selected Foods, Release 1(71).

Statistical Analyses

Descriptive statistics were conducted first. For all analyses, statistical significance was considered a p-value less than 0.05. Mean, median, standard errors, and range for nutrient and food groups under consideration were derived and inspected. We computed frequencies to characterize the study population, including age, race, education, oral contraceptive (OC) use, unopposed estrogen hormone replacement therapy (ERT) use, age at onset of menses, parity, body mass index (BMI; weight in kg / height in m^2), diabetes, smoking status, menopausal status. Age-adjusted OR and 95% CI were also estimated.

Using ANCOVA, age-adjusted means were calculated to compare mean intake between cases and controls for each of the following food and drink groups: dessert foods, non-dessert foods, and sugary drinks. Age-adjusted means were also calculated for a fourth group called total sugary foods and drinks, as well as total and added sugar intakes.

Based on the controls, quartiles were created for each of the food and drink groups and total and added sugar intakes and frequencies were calculated across the quartiles. Multiple unconditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for age and other potential confounders to compare endometrial cancer risk with each unit increase in servings, as well as, across the quartiles for each of the food and drink groups and total and added sugars.

Covariates for the multiple logistic regression model included age (continuous), years of education (<12, 13-16, >16 years), race (White, Black, Other, Hispanic-any race), age at menarche (>13, 12-13, <11), menopausal status (pre- or postmenopausal) and age at menopause for postmenopausal women (<40, 41-54, >55), parity (0-1, 2, >3), OC use (ever vs. never), hormone replacement therapy (HRT) use (never, unopposed estrogen only, any combined HRT), BMI (weight in kg / height in m^2; continuous), smoking status (never, past,

current) and pack-years for ever smokers, physical activity measured in METs (continuous), and diabetes (yes vs. no). To adjust for total energy intake we used the multivariate nutrient density method(72). Specifically, we calculated density measures for servings of sugary foods and/or drinks per 1,000 kcal of intake, as well as, grams of total or added sugars per 1,000 kcal of intake and daily caloric intake was included as a continuous variable in the multivariable models. Tests for trends were derived by assigning to each quartile, the median number of servings of sugary foods and/or beverages or total and added sugar (g/day) intakes among controls. Additionally, quartiles were created based on the controls, for percent of calories from sweets (i.e. dessert foods group) per day and frequencies calculated across these quartiles. Multiple logistic regression models calculated ORs and 95% CIs to assess endometrial cancer risk across these quartiles.

We also explored if women who have risk factors of hyperinsulinemia have higher odds of developing endometrial cancer associated with sugar consumption. We calculated ORs and 95% CIs and used the Wald test to obtain p-values to evaluate if factors like BMI (normal vs. overweight or obese), waist-to-hip ratio (WHR; <0.85 vs. >0.85), and physical activity (<median vs. > median, determined by controls) modified endometrial cancer risk across tertiles for total sugary foods and drinks and total and added sugars. Since, the number of women with diabetes is small, we repeated the analyses evaluating sugary foods and drinks and total and added sugars, excluding cases and controls diagnosed with diabetes.

Results

Controls were slightly older than cases (mean age was 63.4 vs. 61.6 years, respectively, $p<0.01$). Demographic characteristics for the study population and the distribution of major risk factors for cases and controls are shown in **Table 1**. Our study population was composed of predominantly white, postmenopausal women. As expected, obesity was strongly associated

with endometrial cancer risk, while having more children, use of oral contraceptives or any combined HRT, late onset of menses, and current smoking was associated with reduced risk.

Table 1. Selected characteristics of women participating in The EDGE Study.

Characteristic	Cases (n=417) n (%)	Controls (n=395) n (%)	Age-Adjusted OR (95% CI)
Education			
High school or less	154 (36.9)	134 (33.9)	1.00
College	183 (43.9)	158 (40.0)	0.92 (0.66-1.27)
Graduate school	80 (19.2)	103 (26.1)	0.60 (0.41-0.88)
Race/Ethnicity*			
White	355 (85.3)	349 (88.8)	1.00
Black	36 (8.7)	17 (4.3)	1.96 (1.08-3.57)
Other	10 (2.4)	16 (4.1)	0.54 (0.24-1.21)
Hispanic (any race)	15 (3.6)	11 (2.8)	1.14 (0.51-2.54)
Parity**			
0-1	147 (35.3)	92 (23.3)	1.00
2	142 (34.1)	140 (35.4)	0.64 (0.45-0.90)
≥3	128 (30.7)	163 (41.3)	0.53 (0.37-0.76)
Oral Contraceptive Use			
Never	224 (53.7)	199 (50.4)	1.00
Ever	193 (46.3)	196 (49.6)	0.69 (0.51-0.93)
HRT Use*			
Never	335 (80.3)	291 (73.7)	1.00
Unopposed E only	34 (8.2)	31 (7.9)	0.97 (0.58-1.63)
Any combined HRT	48 (11.5)	73 (18.5)	0.54 (0.36-0.81)
Age at Menarche*			
>13	74 (17.8)	102 (25.9)	0.66 (0.46-0.95)
12-13	233 (56.0)	198 (50.3)	1.00
≤11	109 (26.2)	94 (23.9)	0.93 (0.66-1.31)
Menopause			
Premenopausal	59 (14.2)	48 (12.2)	
Postmenopausal	358 (85.9)	347 (87.9)	
Age at menopause			
<40	13 (3.1)	12 (3.0)	0.97 (0.43-2.21)
41-54	254 (60.9)	243 (61.5)	1.00
≥55	41 (9.8)	39 (9.9)	1.11 (0.68-1.80)
Unknown	50 (12.0)	53 (13.4)	0.91 (0.59-1.40)
BMI**			
Normal (<25)	105 (25.2)	189 (47.9)	1.00
Overweight (25-29.9)	121 (29.0)	119 (30.1)	1.93 (1.36-2.75)
Obese (30-34.9)	68 (16.3)	62 (15.7)	2.02 (1.32-3.08)
Very obese (≥35)	123 (29.5)	25 (6.3)	8.47 (5.16-13.89)

Smoking status			
Never	231 (55.4)	207 (52.7)	1.00
Past	159 (38.1)	148 (37.7)	0.97 (0.72-1.30)
Current	27 (6.5)	38 (9.7)	0.58 (0.34-0.98)

OR: Odds Ratio, CI: Confidence Interval
*p<0.05 for frequencies
** p<0.01 for frequencies

Age-adjusted mean values for sources of sugars are shown in **Table 2**. Compared to controls, cases had significantly higher total and added sugar intakes, which may be attributed to their greater consumption of dessert foods, such as cookies and candies, as well as, soft drinks or bottle drinks. Cases were also more likely to consume breads and condiments with added sugars.

Table 2. Age-adjusted means (± SE) for sources of sugars among women in The EDGE Study.

Sources of Sugars	Cases (n=417)	Controls (n=395)	*p*
Total Sugary Foods & Drinks[a]	4.79 (0.07)	4.61 (0.07)	0.02
Dessert Foods[a]	0.93 (0.04)	0.83 (0.05)	0.12
Doughnuts, Danish pastry	0.05 (0.00)	0.04 (0.00)	0.05
Cakes, sweet rolls, coffee cakes	0.03 (0.00)	0.03 (0.00)	0.19
Cookies	0.42 (0.03)	0.39 (0.03)	<0.01
Ice cream	0.06 (0.00)	0.05 (0.00)	0.16
Pumpkin pie, sweet potato pie	0.01 (0.00)	0.01 (0.00)	0.72
Other pies or cobbler	0.02 (0.00)	0.02 (0.00)	0.03
Chocolate candy, candy bars	0.08 (0.01)	0.07 (0.01)	0.18
Other candy, not chocolate	0.29 (0.03)	0.24 (0.03)	0.85
Non-Dessert Foods[a]	3.86 (0.06)	3.78 (0.06)	0.10
Canned fruit, dried fruits	0.04 (0.00)	0.05 (0.00)	0.02
Pancakes, waffles, French toast, Pop Tarts	0.07 (0.01)	0.07 (0.01)	0.95
Breakfast bars, granola bars, Power bars	0.02 (0.01)	0.03 (0.01)	<0.01
Cooked cereals	0.10 (0.01)	0.11 (0.01)	<0.01
Cold cereals	0.17 (0.01)	0.18 (0.01)	0.33
Yogurt/Frozen Yogurt	0.07 (0.01)	0.08 (0.01)	0.33
Breads	0.84 (0.03)	0.80 (0.03)	<0.01
Soups	0.13 (0.01)	0.11 (0.01)	0.01
Jelly, jam, or syrup	0.16 (0.01)	0.15 (0.01)	<0.01
Other condiments	1.56 (0.04)	1.50 (0.04)	0.04
Sugary Drinks[a]	0.33 (0.02)	0.25 (0.02)	0.05

Drinks with added vitamin C	0.01 (0.00)	0.01 (0.01)	0.38
Drinks with some fruit juices	0.02 (0.01)	0.01 (0.01)	0.43
Regular soft drinks or bottled drinks	0.11 (0.01)	0.09 (0.01)	0.04
Total Sugars[b]	65.95 (1.18)	62.78 (1.21)	<0.01
Added Sugars[b]	30.58 (0.80)	27.28 (0.82)	<0.01

SE: Standard Error
[a] Density measure calculated as servings per 1,000 kcal
[b] Density measure calculated as grams per 1,000 kcal

Likewise, in multivariate analyses (**Table 3**) higher consumption of sugary foods and drinks tended to be associated with increased endometrial cancer risk after adjusting for age and energy intake. Further adjustments for known risk factors for endometrial cancer resulted in attenuation of risk estimates with confidence intervals including one for total sugary foods and drinks, dessert food, non-dessert foods, total sugars, and % kcal from sweets. However, a strong association with added sugars persisted. Women in the highest vs. the lowest quartile of total sugary foods and drinks had an OR of 1.84 (95% CI: 1.16-2.92). There was also a suggestion of an association with sugary drinks consumption, with an estimated 61% increase per serving/1000 kcal. Further adjustment for diabetes (yes vs. no), fiber intake (g), or date of interview did not significantly influence results.

Table 3. Sources of sugar and endometrial cancer risk in The EDGE Study.

Sources of Sugar	Cases (n=417)	Controls (n=395)	OR1	95% CI	OR2	95% CI
Total Sugary Foods & Drinks[a]						
Continuous			1.14	(1.03-1.27)	1.07	(0.95-1.20)
(<3.90)	73 (17.5)	99 (25.1)	1.00		1.00	
(3.90-4.74)	96 (23.0)	99 (25.1)	1.32	(0.87-2.00)	1.38	(0.86-2.19)
(4.75-5.76)	135 (32.4)	98 (24.8)	1.88	(1.26-2.82)	1.46	(0.93-2.29)
(>5.76)	113 (27.1)	99 (25.1)	1.66	(1.10-2.51)	1.38	(0.87-2.20)
p trend				<0.01		0.22
Dessert Foods[a]						
Continuous			1.13	(0.96-1.33)	1.11	(0.93-1.32)
(<0.25)	94 (22.5)	100 (25.3)	1.00		1.00	
(0.25-0.52)	77 (18.5)	97 (24.6)	0.85	(0.56-1.29)	0.77	(0.49-1.23)

(0.53-1.08)	112 (26.9)	100 (25.3)	1.19	(0.80-1.76)	1.10	(0.70-1.72)
(>1.08)	134 (32.1)	98 (24.8)	1.48	(0.99-2.20)	1.29	(0.83-2.01)
p trend				0.01		0.07
Non-Dessert Foods[a]						
Continuous			1.07	(0.94-1.21)	0.98	(0.85-1.12)
(<2.92)	80 (19.2)	99 (25.1)	1.00		1.00	
(2.92-3.69)	122 (29.3)	98 (24.8)	1.61	(1.08-2.41)	1.45	(0.93-2.27)
(3.70-4.46)	102 (24.5)	99 (25.1)	1.31	(0.87-1.97)	1.21	(0.77-1.91)
(>4.46)	113 (27.1)	99 (25.1)	1.52	(1.01-2.29)	1.17	(0.74-1.84)
p trend				0.37		0.80
Sugary Drinks[a]						
Continuous			1.57	(1.11-2.23)	1.61	(1.09-2.40)
(<0.02)	88 (21.1)	98 (24.8)	1.00		1.00	
(0.02-0.09)	109 (26.1)	99 (25.1)	1.22	(0.82-1.83)	1.29	(0.83-2.00)
(0.10-0.33)	94 (22.5)	100 (25.3)	1.01	(0.67-1.52)	1.07	(0.67-1.69)
(>0.33)	126 (30.2)	98 (24.8)	1.42	(0.96-2.11)	1.48	(0.94-2.33)
p trend				0.11		0.14
Total Sugars[b]						
Continuous			1.01	(1.00-1.01)	1.01	(1.00-1.01)
(<46.54)	95 (22.8)	98 (24.8)	1.00		1.00	
(46.54-60.68)	99 (23.7)	100 (25.3)	1.05	(0.70-1.56)	1.25	(0.80-1.97)
(60.69-78.55)	108 (25.9)	99 (25.1)	1.21	(0.82-1.81)	1.28	(0.82-1.99)
(>78.55)	115 (27.6)	98 (24.8)	1.36	(0.91-2.04)	1.43	(0.91-2.27)
p trend				0.09		0.15
Added Sugars[b]						
Continuous			1.01	(1.00-1.02)	1.01	(1.00-1.02)
(<16.27)	73 (17.5)	99 (25.1)	1.00		1.00	
(16.27-24.06)	108 (25.9)	98 (24.8)	1.61	(1.06-2.44)	1.47	(0.92-2.33)
(24.07-34.16)	99 (23.7)	100 (25.3)	1.35	(0.89-2.05)	1.27	(0.80-2.02)
(>34.16)	137 (32.9)	98 (24.8)	1.94	(1.29-2.92)	1.84	(1.16-2.92)
p trend				<0.01		0.02
% Kcal from sweets						
Continuous			1.02	(1.00-1.03)	1.02	(1.00-1.03)
(<6.50)	79 (18.9)	95 (24.1)	1.00		1.00	
(6.50-11.50)	91 (21.8)	100 (25.3)	1.09	(0.72-1.65)	1.16	(0.73-1.85)
(11.51-17.90)	109 (26.1)	100 (25.3)	1.27	(0.84-1.92)	1.22	(0.78-1.92)
(>17.90)	138 (33.1)	100 (25.3)	1.62	(1.08-2.43)	1.49	(0.94-2.35)
p trend				0.01		0.08

OR: Odds Ratio, CI: Confidence Interval

OR1: adjusted for age (continuous), energy intake (continuous)

OR2: additionally adjusted for education (high school or less, college, graduate school), race (White, Black, Other, Hispanic), age at menarche (continuous), menopausal status (premenopausal, postmenopausal) and age at menopause for postmenopausal women (<40, 42-54, $\geq$ 55, unknown), parity (0-1, 2, 3-4), oral contraceptive use (ever, never), HRT use (never, unopposed estrogen only, any combined HRT), BMI (continuous), smoking status (never, past, current) and pack-years for ever smokers (continuous), physical activity (METs for reported average hours per week of moderate or strenuous recreational activities). Further adjustment for diabetes (no, yes), fiber intake (g), or date of interview did not

significantly change results.
[a] Density measure calculated as servings per 1,000 kcal
[b] Density measure calculated as grams per 1,000 kcal

We also evaluated possible effect modification of the association between sugary foods and drinks and endometrial cancer by several factors. Risk of endometrial cancer in relation to sugary foods, sugary drinks, and total and added sugars did not change after repeating multivariate analyses excluding cases and controls diagnosed with diabetes (data not shown). Oral contraceptive use did not appear to influence results either (data not shown). We attempted to evaluated results by HRT use. However, the number of women who ever used unopposed estrogen replacement therapy or combined HRT was too small to evaluate, separately. We compared results for the overall population to those in never HRT users (**Table 4**). The magnitude of the association was similar for all variables under evaluation, except for added sugars. When compared to the total population, risk was much stronger for never users of HRT (OR= 1.62, 95% CI: 1.09-2.42 and OR=2.03, 95% CI: 1.27-3.26 for the second and third tertiles of added sugar intake, respectively).

Table 4 also shows the results of multivariate analyses, stratified by BMI, waist-to-hip ratio (WHR), and level of physical activity adjusted for major risk factors. There was no heterogeneity of effects for any of these factors, with the exception of added sugar by WHR. Specifically, the association between added sugar and endometrial cancer risk appeared to be much stronger among women with central obesity (WHR$\geq$0.85), with an OR of 2.50 (95% CI: 1.38-4.52) for women in the highest tertile of consumption compared to the lowest. There was also some suggestion that women in the highest level of physical activity had a stronger association with total sugar and added sugars. However, *p* for heterogeneity was not significant for any of these analyses.

Table 4. Sources of sugar and endometrial cancer risk by selected characteristics in The EDGE Study.

Sources of Sugar	Cases/Controls	Tertile 1	Tertile 2 OR* (95% CI)	Tertile 3 OR* (95% CI)1	*p* for heterogeneity
Total sugary foods[a]	(Tertile Cutpoints)	(<4.06)	(4.06-5.19)	(>5.19)	
Total population	417/395	1.00	1.13 (0.76-1.67)	1.03 (0.70-1.52)	
BMI (kg/m^2)					
<25	105/189	1.00	1.06 (0.57-2.01)	1.07 (0.55-2.08)	0.85
≥ 25	312/206	1.00	1.31 (0.77-2.24)	1.06 (0.63-1.78)	
WHR (cm)					
<0.85	174/208	1.00	0.82 (0.47-1.44)	0.96 (0.54-1.72)	0.10
≥0.85	232/181	1.00	2.02 (1.10-3.70)	1.35 (0.76-2.42)	
Physically activity (METs)					
<12,2872.5	261/196	1.00	1.21 (0.69-2.12)	0.76 (0.44-1.32)	0.20
≥12,2872.5	154/197	1.00	1.04 (0.57-1.89)	1.32 (0.71-2.42)	
No HRT use	335/291	1.00	1.03 (0.65-1.63)	1.09 (0.69-1.73)	
Total sugary drinks[a]	(Tertile Cutpoints)	(<0.04)	(0.04-0.27)	(>0.27)	
Total population	417/395	1.00	0.99 (0.68-1.44)	1.35 (0.91-1.99)	
BMI (kg/m^2)					
<25	105/189	1.00	0.80 (0.42-1.54)	1.38 (0.71-2.69)	0.67
≥ 25	312/206	1.00	1.08 (0.66-1.76)	1.33 (0.80-2.19)	
WHR (cm)					
<0.85	174/208	1.00	0.89 (0.52-1.54)	1.42 (0.81-2.52)	0.81
≥0.85	232/181	1.00	0.97 (0.56-1.70)	1.20 (0.67-2.13)	
Physically activity (METs)					
<12,2872.5	261/196	1.00	1.03 (0.60-1.74)	1.34 (0.77-2.32)	0.99
≥12,2872.5	154/197	1.00	1.00 (0.55-1.81)	1.35 (0.74-2.46)	
No HRT use	335/291	1.00	1.51 (0.74-1.79)	1.45 (0.91-2.30)	
Total sugars[b]	(Tertile Cutpoints)	(<51.90)	(51.90-72.82)	(>72.82)	
Total population	417/395	1.00	1.23 (0.84-1.81)	1.34 (0.91-1.99)	
BMI (kg/m^2)					
<25	105/189	1.00	0.95 (0.49-1.85)	1.33 (0.69-2.57)	0.36

≥ 25	312/206	1.00	1.66 (1.00-2.74)	1.42 (0.86-2.37)	
WHR (cm)					
<0.85	174/208	1.00	1.63 (0.93-2.86)	1.60 (0.88-2.90)	0.46
≥0.85	232/181	1.00	0.99 (0.56-1.74)	1.32 (0.74-2.35)	
Physically activity (METs)					
<12,2872.5	261/196	1.00	1.18 (0.70-1.99)	0.99 (0.57-1.70)	0.29
≥12,2872.5	154/197	1.00	1.41 (0.76-2.62)	1.87 (1.00-3.47)	
No HRT use	335/291	1.00	1.27 (0.80-2.00)	1.34 (0.84-2.14)	
Added sugars[b,c]	(Tertile Cutpoints)	(<19.92)	(19.92-32.24)	(>32.24)	
Total population	417/395	1.00	1.17 (0.80-1.72)	1.62 (1.09-2.42)	
BMI (kg/m^2)					
<25	105/189	1.00	0.98 (0.49-1.96)	1.79 (0.90-3.58)	0.71
≥ 25	312/206	1.00	1.32 (0.81-2.14)	1.75 (1.04-2.95)	
WHR (cm)					
<0.85	174/208	1.00	0.91 (0.52-1.59)	1.29 (0.70-2.36)	0.18
≥0.85	232/181	1.00	1.83 (1.01-3.30)	2.50 (1.38-4.52)	
Physically activity (METs)					
<12,2872.5	261/196	1.00	1.08 (0.63-1.88)	1.48 (0.86-2.55)	0.86
≥12,2872.5	154/197	1.00	1.36 (0.76-2.45)	1.64 (0.87-3.08)	
No HRT use	335/291	1.00	1.58 (1.00-2.50)	2.03 (1.27-3.26)	

OR: Odds Ratio, CI: Confidence Interval, WHR: waist-to-hip ratio

OR*: adjusted for age (continuous), energy intake (continuous), education (high school or less, college, graduate school), race (White, Black, Other, Hispanic), age at menarche (continuous), menopausal status (premenopausal, postmenopausal) and age at menopause for postmenopausal women (<40, 42-54, ≥ 55, unknown), parity (0-1, 2, 3-4), oral contraceptive use (ever, never), HRT use (never, unopposed estrogen only, any combined HRT), BMI (continuous), smoking status (never, past, current) and pack-years for ever smokers (continuous), physical activity (METs for reported average hours per week of moderate or strenuous recreational activities). Further adjustment for diabetes (no, yes) and date of interview did not significantly change results (except for added sugars results).

[a] Density measure calculated as servings per 1,000 kcal

[b] Density measure calculated as grams per 1,000 kcal

[c] Further adjusted for diabetes

Discussion

In this population-based case-control study we conducted a comprehensive assessment of the relationship between endometrial cancer and sugary foods and drinks, total and added sugar consumption. We found that the consumption of added sugars had a significant harmful effect on endometrial cancer risk after adjusting for several major risk factors. Specifically, those who were in the highest category of added sugar intake were approximately 84% more likely to have endometrial cancer. In addition, consuming sugary beverages moderately increased the risk of endometrial cancer, posing a 61% increase in risk with each unit increase in servings per 1,000 kcal. There was also some suggestion of increased risk associated with the consumption of dessert foods, non-dessert foods, total sugars and percent of calories from sweets, although risk estimates were not significant after adjusting for other covariates.

There have been a handful of population-based case-control studies(47, 50, 53, 54) evaluating the effects of sugary foods and beverages on endometrial cancer risk and most have reported null findings. To our knowledge, our study is the first population-based case-control study to examine the independent effects of total and added sugars consumption on cancer risk, and to evaluate the influence of insulin on these relationships. In a previously published study, also using data from the EDGE Study, we examined the relationship between sugar added to coffee/tea and endometrial cancer risk in the EDGE Study(57). We found endometrial cancer risk more than doubled among women who usually added $\geq$ 2 teaspoons of sugar/honey per cup of tea compared to women who added none (OR=2.66, 95% CI: 1.42-4.98). There was a suggestion of an adverse effect for women who consumed, daily, $\geq$ 3 teaspoons of sugar/honey added to coffee or tea vs. women who did not add sugar (OR=1.58, 95% CI: 0.92-2.71).

Consistent with our findings, several large prospective cohort studies found increased risk associated with sugar consumption. In the Swedish Mammography Cohort, Friberg et al.(46)

reported significantly higher endometrial cancer risk for those who consumed >3 servings/week of “sweet buns and cookies” vs. <0.5 servings/week, at both baseline (1987) and follow-up (1997) (Quartile 4: Rate Ratio (RR)=1.42, 95% CI:1.14-1.75 and RR=1.72, 95 % CI:1.06-2.78, respectively). Although they did not find an association between soft drinks (yes vs. no) and cancer risk, the authors noted that in Sweden soft drinks are sweetened with sucrose as opposed to high-fructose corn syrup, the predominant caloric sweetener used in soft drinks in the US. To add, their study population has lower levels of sucrose intake in comparison to American’s surveyed by the Third National Health and Nutrition Examination Survey (NHANES III) 1988-1944(46). Friberg et al. also reported significant higher risk associated with increasing sucrose intake (g/day) in both their baseline and follow-up dietary data. Similarly, in the Canadian National Breast Screening Study (NBSS), Silvera and colleagues(36) found a borderline positive relationship between total sugar (g/day) and endometrial cancer risk. In the NIH-AARP Diet and Health Study, a prospective cohort study of over 400,000 men and women, Tasevska et al. found greater risk of endometrial cancer associated with the consumption of total sugars, and evidence of increased risk associated with total fructose and sucrose. Though, they did not find a relationship between added sugar intake and endometrial cancer risk(56).

Conversely, in the European Prospective Investigation into Cancer and Nutrition Cohort (EPIC) Study(30), Cust et al. did not find an association between “cakes, pastries, biscuits”, carbonated beverages, and confectionery sugar and endometrial cancer risk, although there was a suggestion of moderate increased risk with total sugar consumption. Like to our study, the investigators found a non-significant increase in endometrial cancer risk associated with high level of total sugars intake (g/day) (Quartile 4: RR=1.20, 95% CI: 0.97-1.48). After calibrating their model using 24-hour recall values, they detected significantly higher risk associated with total sugars intake on a continuous scale (per 50 g/day) [RR(95% CI): 1.36(1.05-1.76)].

Since being overweight or physically inactive is associated with decreased insulin sensitivity and higher insulin levels, it may be possible that overweight or inactive women have greater insulin response to foods with refined sugars(19, 36). To the contrary, a healthful diet, physical activity, weight loss, or the use of insulin-lowering drugs may reduce endometrial cancer risk by improving insulin sensitivity(20, 30, 37) and normalizing plasma androgen levels(20). Folsom et al. suggests that women with diabetes may have lower risk of endometrial cancer if they are more health conscious and keep their diabetes in control(38). Therefore, we further explored the effects of insulin-modifiers such as diabetes, physical activity, excess body weight and central obesity on the relationship between sugar consumption and endometrial cancer risk. In our study, there were very few women with diabetes (64 cases, 34 controls) and excluding them did not have a major impact on the relationship between cancer risk and any of the exposure variables. Then again, Friberg et al.(46) found that excluding women with diabetes from the analyses or further adjustment for fat intake did not substantially alter results in their cohort of over 60,000 women. On the other hand, in our study greater consumption of total sugars was associated with a borderline increase in risk of endometrial cancer among subjects with physical activity above the median. Those who were less physically active did not appear to have increased risk, regardless of the amount of total sugars consumed. In the EPIC study, physical activity or having diabetes did not seem to modify risk estimates(30). The NIH-AARP Diet and Health Study did not assess for effect modification by diabetes, physical activity, or WHR(56). Similarly, the NBSS study did not test for potential effect modification by any insulin-related factors.

Interestingly, WHR, a marker of central obesity, influenced several of our results, suggesting insulin-sensitivity may modify cancer risk. In particular, we found a strong association between added sugar intakes for women with a WHR $\geq$0.85. Unexpectedly, the

relationship between total sugar intake and cancer risk displayed an opposite pattern, with higher total sugar intake associated with a nonsignificant increase in cancer risk for women with WHR <0.85, and risk was not signficantly affected by total sugar intake among women with WHR ≥ 0.85. Similar to our findings, Cust et al.(30) found that women with WHR below the median vs. above the median had elevated cancer risk associated with consumption of total sugars. Nevertheless, this may have been a sporadic finding and caution must be used when interpreting our results.

Similar to Tasevska et al. (56), we found little evidence of an effect modification by BMI. In contrast, when comparing women who consumed >15 vs. ≤ 15 grams of sucrose per day, Friberg et al. found a stronger significant adverse effect among women who were overweight, obese, or had low fat intake(46), while Cust et al. reported that the adverse effect of total sugars on endometrial cancer risk was more evident among lean women in their study population(30). Clearly, more research is required to further understand potential effect modification by insulin-related factors.

Some limitations of our study must be noted. First, our exposure assessment may have been influenced by recall bias. For example, cases may have systematically over reported or underreported consuming unhealthy foods, such as sugary foods and beverages compared to controls. However, this type of bias is less likely to have occurred in our study as cases reported higher mean intakes of dessert foods and sugary beverages compared to controls. Furthermore, sugary food and beverage consumption is not broadly known as a risk factor for endometrial cancer and thus, cases may not have purposely underreported those foods. We should also be careful when applying our findings to the general population. As with most population-based case-control studies, our study's response rates were low and willingness to participate in our study may have been related to subjects' lifestyle characteristics. For example, our study

participants may live healthier lifestyles and be more enthusiastic about participating in a study on women's health compared to those who refused to participate. However, we were unable to compare controls with women who did not participate, as we could not collect information on those who could not be reached or declined to participate in our study. Also, when examining if selection bias occurred in our study, we found our cases were more likely to be younger and be diagnosed with an earlier stage of disease compared to all women diagnosed with endometrial cancer in the same NJ counties. Hopefully, minimal selection bias has occurred in our study as the distribution of major risk factors, apart from estrogen replacement therapy (ERT), is similar to that of previous reports. However, only a small proportion of cases and controls (less than 10%) used ERT, and excluding them from our analyses did not alter results.

To our knowledge, we are the first study to have reported on the relationship between endometrial cancer and several forms of sugar consumption: sweet and savory foods with added sugars, beverages with added sugars, total sugars and total added sugars; while also considering insulin-related factors. Over a dozen of studies(30, 45-55, 62, 73) have evaluated sugary foods and/or beverages, but less than half (30, 46, 47, 49, 52, 55) have examined sugary drinks (most often soft drinks). Only one study has evaluated added sugars from all food sources and cancer risk(56). Furthermore, only four have considered possible effect modification by insulin-related factors such as diabetes(30, 46), BMI(30, 45-47), WHR(30), or physical activity(30, 46). Our study emphasizes the need for future research, ideally large prospective studies, to further investigate the role of added sugar consumption and endometrial cancer risk in relation to insulin-modifiers.

In summary, we conducted a comprehensive assessment of the relationship between endometrial cancer and sugar consumption, with consideration of insulin modifiers. We found that endometrial cancer risk was significantly adversely related to the consumption of sugary

beverages, and particularly to added sugars after adjusting for several major risk factors. Furthermore, there was evidence to support that insulin-related risk factors, particularly central obesity, may modify the relationship between sugar consumption and endometrial cancer risk. Our results support the WCRF/AICR 2007 Export Report recommendations to avoid sugary drinks and the 2010 Dietary Guidelines for Americans that recommend reducing added sugar intake. Our research should be replicated in large cohort studies to further elucidate the role of sugar intake and insulin-modifiers in the etiology of endometrial cancer.

Chapter 3: Sugar consumption and ovarian cancer risk: A review of the literature

Ovarian cancer ranks fifth in overall cancer deaths in women with more women dying from this cancer than from all gynecological cancers combined(13, 74). One reason for this is the difficulties in early detection and poor survival. Even with its considerable public health impact, the etiology of ovarian cancer is still not well understood. Although family history of ovarian cancer is an important determinant, only 10% of cases, have a family history of this disease(74). Risk of developing the disease increases with age and mostly occurs in perimenopausal and postmenopausal women(13, 74). Obesity, infertility, prior history of pelvic inflammatory disease, polycystic ovarian syndrome, endometriosis, having a mutation in the BRCA genes, Lynch II syndrome, and a variety of environmental factors including tobacco smoke, radiation exposure, and dietary factors amongst others, may also increase risk of developing the disease(13, 74). It has been suggested that nulliparity also increases risk due to incessant ovulation, which involves the continual injury and repair of the ovarian epithelium(75, 76). On the other hand, the relationship between diet and ovarian cancer has been extensively evaluated with generally inconclusive results(77-79).

The consumption of added sugars has dramatically increased over the past several years. Caloric sweeteners continue to remain a substantial part of the American diet, representing about 15% of total energy intake(2). The overconsumption of added sugars has been linked to several adverse health outcomes such as obesity (4, 9, 10), insulin resistance and type II diabetes(7, 10-12). So it is with good reason that expert panels have recommended that individuals limit consumption of refined sugars, to reduce their chance of developing cancer (2, 8). Even so, there is still much to learn on how consuming foods and beverages with added sugars affect ovarian cancer risk. Thus, our objective is to summarize the published research on

ovarian cancer risk and consumption of sugary foods and beverages, as well as, total and added sugar intake.

Possible Underlying Mechanisms

Overconsumption of sugary foods and drinks could lead to obesity(4, 9, 10, 15), a risk factor for ovarian cancer(13, 74). A systematic review by Olsen et al. reported a modest adverse relationship between adult obesity and ovarian cancer risk(80). More specifically, overweight and obesity is related to several factors that affect ovarian cancer risk, including hormone levels, ovulatory function, and polycystic ovarian syndrome(81). Furthermore, approximately 10% of ovarian tumors have endometrioid histology(74, 82), which has a similar histology to endometrial cancer, a cancer strongly impacted by high cumulative exposure of unopposed estrogens to the endometrium(14). Thus, obesity may be an important risk factor for endometrioid ovarian tumors, because it increases estrogen production via the aromatization of androgens to estrone in adipose tissue(20).

Additionally, being overweight or obese is associated with insulin resistance and hyperinsulinemia(16-18, 30, 83). Abdominal obesity(84) and high waist-to-hip ratio (WHR)(85), both markers of insulin resistance(33), have been shown to significantly increase ovarian cancer risk. Insulin encourages ovarian production of androgens (direct precursors of oestrogen synthesis)(86-89) and controls metabolism and transport of androgens in peripheral tissue(89). This results in lower levels of insulin-like growth factor binding protein and promotes ovarian carcinogenesis(85, 90). Furthermore, as central obesity is a risk factor for insulin resistance, it may modify the relationship between sugar intake and cancer risk. For example, Nagle and colleagues(91) found sugar intake to have a beneficial effect on ovarian cancer risk among normal weight women and an adverse effect among overweight and obese women. Thus, a high-sugar diet could possibly have a stronger deleterious effect on ovarian cancer risk among

women who are obese compared to normal weight women, as obesity adversely affects metabolic responses to sugar intake(91). However, this is the only study to investigate effect modification by body mass index (BMI) and there should be further investigation of the relationship between sugar intake and ovarian cancer risk while considering insulin-related risk factors such as waist-to-hip ratio (WHR), BMI, or physical activity.

Methods

Using PubMed, we searched for articles related on the consumption of sugar and ovarian cancer risk that were published up to July 15, 2012. Search terms included: sugar*[tiab] OR food and beverages[MeSH] OR diet[tiab] OR diets[tiab] OR dietary[tiab] AND ovarian cancer[tiab]. We also used terms such as, “sugary food”, “sugary beverage”, “sugary drinks”, or “added sugar”. In addition, we manually searched bibliographies of published papers. One paper was excluded because we were unable to fully translate the text into English(73). In this review, we included only cohort and case-controls studies and excluded four ecological studies(44, 92-94). We are unaware of any clinical trials or cross-sectional studies addressing this topic. **Tables 1 and 2** describe characteristics of all studies included in our review. **Table 3** summarizes the exposure variables and effect modifiers of included studies.

Sugary Foods and Beverages

There is limited epidemiological research on the relationship between sugary foods and beverages and ovarian cancer. In fact, one cohort study(95) and five case-control studies(96-100) have investigated the role of sugary food consumption and ovarian cancer risk. Even fewer studies(97, 100, 101) have evaluated consumption of sugary drinks and ovarian cancer risk. The only prospective cohort study(95) to investigate this relationship found a strong adverse association between sweets and ovarian cancer risk using data from over 29,000 postmenopausal women[Odds Ratios (OR) from lowest to highest category: 1.00, 2.32, 2.49, and

1.61; p_{trend}=0.17](95). Although the authors adjusted for total energy intake, WHR and level of physical activity, they did not adjust for BMI or diabetes status, nor did they test for potential effect modification by insulin-related factors.

Among the case-control studies that evaluated sugary foods and beverages and ovarian cancer risk were four population-based case-control studies(97-99, 101) with inconsistent results. Using data from the Canadian National Enhanced Cancer Surveillance System (NECSS), Pan et al.(99) did not find an association between baked desserts (servings/week) and ovarian cancer after adjusting for multiple factors including BMI, total caloric intake, and recreational physical activity (99). Similarly, Kolahdooz et al.(97) evaluated the effect of "meat and fat" consumption on ovarian cancer risk among women in Australia. The "meat and fat" dietary pattern was described as consuming large amounts of red and processed meat, eggs, fat spreads, and sweetened foods. Although the authors found that consuming large amounts of "meat and fat" significantly increased risk, this relationship was not explained by sweetened food, sugar intake, or high-energy drinks(97). This suggests that sugary foods and beverages did not have an impact on ovarian cancer risk in this study population. McCann et al.(98) reported non-significant increases in cancer risk for the highest two categories of snack consumption (ORs from lowest to highest category: 1.00, 0.80, 0.90, 1.37, and 1.28). This study sample may have been too small with limited statistical power to evaluate snack consumption and ovarian cancer risk, as there were only 124 cases. The authors did not specify the foods included in the "snacks" group, therefore we are unable to confirm whether the group included sugary foods. To the contrary, Kuper et al.(101) found that women who consumed the highest level of caffeinated cola beverages had elevated risk of ovarian cancer in their population-based case-control study in Massachusetts and New Hampshire (data was not shown)(101). None of these studies looked for potential effect modification by BMI, WHR, physical activity, or diabetes.

Only two hospital-based case-control studies(96, 100) have evaluated sugary food intake and risk of ovarian cancer and both suggested an adverse relationship exists. In a multi-center case-case-control study in Italy, Bosetti et al.(96) reported non-significant increases in risk associated with dessert consumption (ORs for quintiles 1-5: 1.00, 1.16, 1.19, 1.31, 1.33; p_{trend}=0.05). Similarly, Salazar-Martinez et al.(100) performed a study in Mexico City and found a non-significant increase in risk associated with the highest intake of sweets and desserts [OR=1.36; 95% Confidence Interval (CI):0.64-2.92]. However, they did not find an association with soda, coffee and tea combined. It is worth noting that this category incorporates beverages that may be consumed with or without added sugar (e.g. tea or coffee) and thus measurement error might have occurred. Also, while the authors did adjust for total energy intake, recent changes in weight, physical activity, and diabetes, they did not adjust for smoking status or pack-years, BMI or WHR. Furthermore, this study had a small number of cases (84 cases) and may have had limited statistical power to evaluate sugary food consumption and ovarian cancer risk.

Sugars

In general, studies have produced inconsistent findings on the relationship between dietary sugars (i.e. total sugars, sugar, added sugar sucrose or fructose) and ovarian cancer risk. Only two prospective studies(56, 90) have evaluated the relationship between sugar intake and ovarian cancer with contradicting results. Interestingly, using data from over 400,000 men and women in the NIH-AARP Diet and Health Study, Tasevska et al.(56) found the risk of developing ovarian cancer to be significantly inversely associated with the highest intake of total sugars, total fructose, and sucrose [HR(95% CI) for the highest vs. lowest quartile: 0.70(0.51-0.97); 0.68(0.49-0.95); and 0.65(0.47-0.89), respectively]. They also observed significant protection against ovarian cancer among women who consumed the greatest amount of added sugars, after adjusting for multiple factors (HR=0.72, 95% CI:0.51-1.00; p_{trend}=0.02). To the contrary,

Silvera et al.(90) identified a hazardous effect of total sugar intake on ovarian cancer risk among postmenopausal women (HRs from lowest to highest category: 1.00, 1.67, 2.35, and 1.79; p_{trend}=0.08). They did not detect a relationship among premenopausal women and found no heterogeneity of effects among pre- or postmenopausal women by smoking status, parity, age at menarche, HRT use, or alcohol intake. Neither of these studies tested for effect modification by BMI, WHR, physical activity, or diabetes status. Ninety-seven percent of the ovarian cancer cases in the NIH-AARP study were postmenopausal, which may explain the discrepancy in findings between these two studies.

Using data from the Australian Ovarian Cancer Study, Nagle and colleagues(91) are the only population-based case-control study to directly assess sugar intake and ovarian cancer risk. They did not find a relationship between total sugar (g) intake and ovarian cancer in their overall study population. However, among women with BMI $\geq$ 25 (kg/m^2), there was greater risk associated with total sugar intake for the highest vs. lowest quartile [OR=1.61, 95% CI:1.20-2.16; p_{trend}=0.008]. Remarkably, there was evidence for a protective effect against ovarian cancer among normal weight women across all levels of total sugar intake (ORs from lowest to highest quartile: 1.0, 0.65, 0.70, 0.73; p_{trend}=0.11). In a population-based case-control study in New Jersey, (102) we did not find an association between ovarian cancer risk and the category SoFAAS, which is defined as calories from solid fat, alcohol, and added sugars. However, SoFAAS included calories from solid fat, alcoholic beverages, and added sugar, and we did not separately evaluate the effects of added sugar on cancer risk in this study population. Neither of these studies accounted for possible effect modification by insulin-related factors (e.g. BMI, WHR, physical activity, etc.).

Lastly, among the four hospital-based case-control studies(96, 100, 103, 104) that have evaluated sugar consumption and ovarian cancer risk, only one study, by Bosetti et al.(96),

reported a modest increase in risk (ORs for Q1 to Q5: 1.16, 1.19, 1.31, 1.33; p_{trend}=0.05) in their Italian population. The remaining hospital-based case-control studies based in Italy(103), Greece(104), and Mexico(100) did not detect a relationship between sugar(103) or sucrose(100, 104) intake and ovarian cancer. It is worth noting that none of the studies adjusted for confounding by BMI and none have tested for effect modification by insulin-related factors.

Conclusions

In summary, a small number of studies (95-100) have evaluated the association between sugary food consumption and ovarian cancer risk, reporting mixed results. Only three of these studies(97, 100, 101) have studied the effects of sugary beverage intake. Similarly, results were also inconsistent among studies that evaluated consumption of dietary sugars and ovarian cancer risk.

Some limitations were apparent after reviewing thirteen manuscripts on this subject. First, most of these studies evaluated specific food and beverage items, such as, sweets, syrups, or caffeinated beverages and there were no studies that reported on the effects of all foods and beverages, both sweet and savory, with added sugars. Only one study, a prospective cohort study evaluating multiple cancers, has directly assessed the association between added sugar intake and ovarian cancer risk(56). Additionally, a population-based case-control study examined ovarian cancer risk in relation to calories from added sugars, combined with calories from solid fat and alcoholic beverages(102). However, neither of these studies reported on sugary food and beverage consumption, and thus, we are unable to discern which foods and beverages were major sources of added sugars in their diet. It would be worthwhile to evaluate the effects of total sugary foods and drinks, in addition to added sugars, since the incremental exposure to added sugars from all food sources could impact cancer risk. Lastly, among the three cohort and ten case-control studies, none explored the relationship between sugar and

ovarian cancer risk while considering effect modification by WHR, physical activity, or diabetes status. Only one study(91) has tested for effect modification by BMI, but unfortunately, unlike waist circumference, BMI does not reliably indicate body fat distribution, specifically central adiposity(33). Ideally, a comprehensive assessment should evaluate sugar consumption and ovarian cancer risk, while considering potential effect modification by insulin-related risk factors. These gaps in literature emphasize the need for future research, preferably using large prospective datasets, to thoroughly the relationship between food and beverages with added sugars and ovarian cancer risk, while taking into consideration insulin-modifiers(105).

Table 1. Characteristics of prospective cohort studies evaluating sugar consumption and ovarian cancer risk.

Reference	Location	Cases/ cohort size (n)	Dietary assessment	Time Frame of Dietary Assessment	Sugar variables	Effect modifiers	Results
(95)	IA	139 / 29,083	FFQ (126 items), 24-hour dietary recall among a subset	Current intake at baseline	"Breads, cereals, starches", sweets	None	- *association:* breads, cereals, starches *+ association:* sweets
(90)	Canada	264 / 48776	FFQ (86 items)	Current intake at baseline	Total sugar	Menopausal status, smoking history, age at menarche, HRT use, alcohol intake, parity	*No association:* total sugar *+association:* strong, suggested association with sugar among postmenopausal women No effect modification by smoking history, age at menarche, HRT use, alcohol intake, parity
(56)	8 States in USA (CA, FL, LA, NJ, NC, MI, GA, PA)	457 / 179,990	FFQ, DHQ (124 items)	1 year prior to index date	Total sugars, added sugar, sucrose, total fructose, added sucrose, added fructose	HRT	- *association:* total sugars, added sugars, total fructose, sucrose, added sucrose, added fructose; no modification by HRT

Abbreviations: FFQ- food frequency questionnaire, DHQ- diet history questionnaire, BMI- body mass index, HRT- hormone replacement therapy, ERT- unopposed estrogen replacement therapy, OC- oral contraceptives, WHR- waist-to-hip ratio, "+ association" - positive association, "- association"- negative association

Table 2. Characteristics of case-control studies evaluating sugar consumption and ovarian cancer risk.

Reference	Location	Cases/ controls (n)	Dietary assessment	Time Frame of Dietary Assessment	Sugar variables	Effect modifiers	Results
Case-control studies: population-based							
(102)	NJ	205/390	FFQ (110 items)	6 months prior to index date	SoFAAS: total calories from solid fat, alcoholic beverages, and added sugar	None	*No association*: SoFAAS
(97)	Australia	717 / 806	FFQ (123 items)	1 year prior to index date	"Meat and fat"[1] category: High-energy drinks and sweetened food and sugar	Tumor stage	*No association*: high-energy drinks and sweetened food and sugar did not explain the relationship between "meat and fat" and ovarian cancer
(106)	MA, NH	549/516	FFQ plus open ended section for unlisted foods	1 year prior to index date	Caffeinated cola	Menopausal status, tumor histologic type	*+ association:* highest level of consumption of caffeinated cola No evidence of effect modification
(98)	NY	124 / 696	Interviewer-administered diet questionnaire (172 items)	12 month period 2yr before interview	Snacks	None	*No association:* Snacks
(91)	Australia	1,366 / 1,414	FFQ (136 items)	1 year or if diet changed in last 6-12 mo, their usual diet	Total sugar	BMI, HRT use, menopausal status	*No association:* total sugar *+ association:* total sugars among overweight/obese women. No effect modification by HRT use and menopausal status
(99)	Canada	442 / 2,135	FFQ (69 items)	2 years prior to index date	Baked desserts	None	*No association:* baked desserts

Case-control studies: hospital-based							
(103) [2]	Italy	1,031 / 2,411	FFQ (78 items, plus range of courses and dishes)	2 year prior to index date	Sugar	Parity, menopausal status, energy intake, age, education, OC use	*No association:* sugar No evidence of effect modification
(96) [2]	Italy	1,031 / 2,411	FFQ (78 items, plus range of courses and dishes)	2 year prior to index date	Desserts, Sugar	None	*+ association:* sugar, *Borderline + association:* desserts
(100)	Mexico	84/629	FFQ (116 items)	1 year prior to index date	Sucrose, fructose, glucose, maltose, "bread and cereal", "sweets and desserts", "soda, coffee, and tea", tortilla	None	*No association:* sucrose, fructose, glucose, maltose, bread and cereal, sweets and desserts, soda, coffee and tea, tortilla
(104)	Greece	189 / 200	FFQ (110 items)	1 year prior to index date	Sucrose	None	*No association:* sucrose

Abbreviations: FFQ- food frequency questionnaire, DHQ- diet history questionnaire, BMI- body mass index, HRT- hormone replacement therapy, ERT- unopposed estrogen replacement therapy, OC- oral contraceptives, WHR- waist-to-hip ratio, "+ association" - positive association, "- association"- negative association

[1] "Meat and fat" category included processed and red meat, poultry, liver, high-energy drinks (Cola drinks, other soft drinks, and cordials) and sweetened foods (cake, tart or pie, pastry, pavlova (meringue dessert), cheesecake, sweet roll, bun, plain sweet biscuits, fancy biscuits (e.g. chocolate coated), chocolate, lollies (candies), jam, peanut butter, and sugar) [2] Bidoli (2002) and Bosetti (2001) were from the same study

Table 3. List of exposure variables and effect modifiers evaluated in studies on sugar consumption and ovarian cancer risk.

Reference	Sugary Foods	Sugary Drinks	Total Sugars, Sugar, or Sucrose	Added Sugar	Effect Modifiers					
					BMI	HRT use	Menopausal Status	Physical Activity	WHR	Diabetes
Cohort studies										
(95)	✓									
(90)			✓			✓	✓			
(56)			✓	✓						
Case-control studies: population-based										
(102)				✓						
(97)	✓	✓								
(106)		✓					✓			
(98)	✓									
(91)			✓		✓	✓	✓			
(99)	✓									
Case-control studies: hospital-based										
(103)			✓				✓			
(96)	✓		✓							
(100)	✓	✓	✓							
(104)			✓							

Abbreviations: BMI- body mass index, HRT- hormone replacement therapy, WHR- waist-to-hip ratio

Chapter 4: Sugary foods and drinks and ovarian cancer risk

Introduction

Ovarian cancer is the ninth most common cancer among women and ranks fifth in overall cancer deaths in women(13). It is estimated that about 22,280 women will be diagnosed with ovarian cancer and approximately 15,500 will die from this cancer in 2012(13). The 5-year survival rate is approximately 90% if the cancer is found at an early stage. However, this cancer is largely asymptomatic until it has metastasized and unfortunately, less than 20% of ovarian cancers are found before the cancer has spread(13, 74).

Not much is known about the etiology of ovarian cancer, which is compounded by difficulties in early detection and poor survival. Family history of ovarian cancer is an important risk factor, however less than 10% of cases have a family history of this disease(74). A woman's chance of developing ovarian cancers increases with age and this cancer more often occurs in perimenopausal and postmenopausal women(13, 74). There are several factors that increase ovarian cancer risk, including obesity, infertility, prior history of pelvic inflammatory disease, polycystic ovarian syndrome, endometriosis, having a mutation in the BRCA genes, as well as various environmental and dietary factors(13, 74). A woman's ovulatory age is a strong predictor of ovarian cancer risk, perhaps due to incessant ovulation, which involves the continual injury and repair of the ovarian epithelium (75, 76, 78, 107). Protective factors include oral contraceptive use, particularly with increasing duration, having multiple births, lactation, hysterectomy, and the use of certain analgesics(13, 74). Overall, ovarian carcinogenesis is multifactorial and genetic, environmental, and hormonal factors are implicated to play a part(74).

The role of dietary factors in the risk of developing this disease is poorly understood(79). It is well-known that most cancers are preventable and a balanced diet plays a crucial role in

improving an individual's overall health(8). The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) 2nd expert report suggests that people make better decisions, such as limiting consumption of refined sugars, to reduce their chance of developing cancer(8). Nevertheless, the consumption of caloric sweeteners has increased rapidly in the United States over the past three decades(1). Even with a recent drop in added sugar consumption by Americans older than 2 years, it still accounts for almost 15% of total energy intake(2). This exceeds the 2010 Dietary Guidelines for Americans that recommend limiting calories from solid fats and added sugars to 5 to 15% of total energy intake(2, 3).

Unhealthy eating habits, including the overconsumption of sugar may be one cause of obesity(4, 9, 10, 15), and has been shown to increase ovarian cancer risk (13, 74, 80). In fact, overweight and obesity is related to several factors that can have an impact in the development of the disease, including hormone levels, ovulatory function, and polycystic ovarian syndrome(81). Furthermore, approximately 10% of ovarian tumors have similar histology as endometrial cancer(74, 82), a cancer strongly influenced by high cumulative exposure of unopposed estrogens to the endometrium(14). Thus, obesity may be an important risk factor for endometrioid ovarian tumors, because it increases estrogen production via the aromatization of androgens to estrone in adipose tissue(20). Additionally, being overweight or obese is associated with insulin resistance and hyperinsulinemia, also risk factors for this disease(16-18, 30, 83).

Although, the relationship between diet and ovarian cancer has been extensively evaluated, results are generally inconclusive(77, 78). Furthermore, few of studies(95-101) have examined the relationship between sugary foods and beverages and risk of ovarian cancer and most did not detect a relationship. Only one study has independently investigated the effects of added sugars on ovarian cancer risk, finding an inverse association(56). No studies have

explored the relationship between sugar consumption and ovarian cancer risk while considering effect modification by insulin-related factors, except for one study(91) that tested for effect modification by BMI. We intend to test the relevance of the WCRF/AICR's recommendation to reduce sugar consumption in relation to ovarian cancer prevention. Our study will the first of its kind to evaluate ovarian cancer risk in relation to the consumption of sugary foods and beverages, total and added sugar intakes, as well as potential effect modification by insulin-related factors. Understanding how the consumption of sugar affects ovarian cancer risk may further elucidate the role of diet in ovarian cancer etiology, as well as provide some strategies for prevention of this deadly disease

Materials and Methods

Study Population

The New Jersey Ovarian Cancer (NJOC) Study(102, 108, 109) is a population-based case-control study which used the same controls as in the EDGE (Estrogens, Diet, Genetics, and Endometrial Cancer) Study(67, 68). Like the EDGE Study, eligible women were older than 21 years, able to speak English and/or Spanish, and residents of six contiguous counties in New Jersey (Essex, Union, Morris, Middlesex, Bergen, and Hudson). Women with newly diagnosed, histologically confirmed invasive epithelial ovarian cancer identified by rapid case ascertainment by the New Jersey Cancer Registry between January 2004 and May 2008 were eligible as cases. EDGE controls were identified via random digit dialing (RDD, stratified by age) if under 65 years of age and Centers for Medicare and Medicaid Services (CMS) and area sampling if age 65+ years and 55+ years, respectively. Women who had a hysterectomy and/or had a bilateral oophorectomy were not eligible as controls in the NJ Ovarian Cancer Study. Consent was obtained from all participants. This study has been approved by the Institutional Review Boards of the New Jersey Department of Health and Senior Services, Memorial Sloan-Kettering Cancer

Center and University of Medicine and Dentistry of New Jersey (UMDNJ) Robert Wood Johnson Medical School.

Data Collection

To ensure similar data collection methods between cases and controls, the same study procedures from the EDGE Study were implemented in the NJOC Study. Interviewers for the NJ Ovarian Cancer Study were trained in the same manner as interviewers for the EDGE Study to ensure a standard method of data collection. Once passive approval was obtained from physicians, informed consent was obtained before the phone interview by mail, facsimile, or in person. Cases and controls completed a phone interview during which a questionnaire was administered ascertaining demographic characteristics and major risk factors for the disease such as hormone use, family history of cancer, reproductive history, medical history, and lifestyle factors up to a year prior to diagnosis (or date of interview for controls). A food frequency questionnaire (FFQ), the Block 98.2 FFQ, was self-administered and returned by mail, along with waist and hip measurements (a tape measure and instructions were provided), and a mouthwash sample for DNA extraction.

In total, 233 cases and 467 controls participated in the study. Two hundred and five cases (88%) and 398 controls (85%) completed both the interview and FFQ. Eight of these controls were excluded from these analyses because both of their ovaries had been removed. Participants were also excluded from the analysis if their menopausal status was unknown or if they were missing other major covariates. Those who were postmenopausal but did not know their age at menopause were included in the analysis. There were no significant differences in major characteristics between those who did and did not complete the food frequency questionnaire.

Processing of Dietary Data

Participants' responses were converted to number of servings per day based on their reported frequency and portion sizes for sugary foods and beverages. Frequency was measured as 'never', 'a few times per year', 'once per month', '2-3 times per month', 'once per week', '2 time per week', '3-4 times per week', '5-6 times per week', and 'everyday' for most food items. For a few foods, 'never' and 'a few times per year' were combined into one choice: 'never or a few times per year' and the choice of '2+ times per day' was added. Portion size for food items was measured in teaspoons, tablespoons, ounces, pounds, cups, pieces, patties, bowls or slices. Portion size for beverages was measured as number of cups, glasses, cans or bottles consumed.

Serving sizes were based on the guidelines listed in Reference Amounts Customarily Consumed (RACC) Per Eating Occasion: General Food Supply by the Food and Drug Administration(70). This document provides the amount of food typically consumed per eating occasion, and is based on the 1977-1978 and 1987-1988 Nationwide Food Consumption Surveys. When making assumptions about participants' portion sizes consumed, we used the FDA's assigned RACC values as a guideline. For example, we assumed that one doughnut (RACC=55 grams) is equivalent to one serving. Therefore, participants who reported usually eating one doughnut per occasion were assigned as eating one serving for this food item.

Number of servings per day was calculated for select foods and beverages. Next, we computed the number of servings of dessert foods, non-dessert foods, sugary drinks and total sugary foods and drinks for each participant. The Appendix lists foods that were included in the calculation of these food groups. Total and added sugar intakes (g/day) were calculated for each food items by multiplying the frequency of intake by the total/added sugar content per 100 grams of food. Total and added sugar content values were based on the USDA Database for Added Sugars Content of Selected Foods(71).

Statistical Analyses

Descriptive statistics were estimated for selected nutrients and food and drink groups. For all analyses, statistical significance was considered a p-value less than 0.05. To describe our study population, frequencies were calculated between cases and controls for major determinants such as race, education, oral contraceptive use, unopposed estrogen hormone replacement therapy (ERT) use, body mass index (BMI; weight in kg / height in m^2), smoking status, age at menarche, parity, tubal ligation, menopausal status, family history of ovarian cancer, and polycystic ovarian syndrome.

Two sample t tests were used to compare cases and controls across continuous variables and chi square tests were used for evaluating differences in the distribution of categorical variables between cases and controls. Age-adjusted logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CI) to compare ovarian cancer risk across major risk factors (except for age).

ANCOVA was used to calculate age-adjusted means to compare mean intake between cases and controls for each food and drink group: dessert foods, non-dessert foods, sugary drinks, total sugary foods and drinks, as well as total and added sugar intakes. Based on the distribution in controls, tertiles for the food and drink groups and total and added sugars intake were created and frequencies calculated across the tertiles. Age-adjusted and multiple unconditional logistic regression models were used to estimate ORs and 95% CIs for the food and drink groups and total and added sugar intakes.

Covariates used in the multiple logistic regression model include age (continuous), years of education ($\leq$12, 13-16, >16), race (White, Black, Other, Hispanic-any race), age at menarche (>13, 12-13, $\leq$11), menopausal status (pre- or postmenopausal) and age at menopause for postmenopausal women (<40, 41-54, $\geq$55), parity (0-1, 2, $\geq$3), OC use (ever vs. never), hormone

replacement therapy (HRT) use (never, unopposed estrogen only, any combined HRT), BMI (weight in kg / height in m^2; continuous), smoking status (never, past, current) and pack-years for ever smokers, physical activity measured in METs (continuous), tubal ligation (yes vs. no), and diabetes (yes vs. no). We adjusted for total energy intake using the multivariate nutrient density method(72). Specifically, we computed density measures for servings of sugary foods and/or drinks per 1,000 kcal of intake, as well as, grams of total or added sugars per 1,000 kcal of intake and included daily caloric intake as continuous variable in the multivariable models. We derived tests for trends by assigning to each tertile, the median number of servings of sugary foods and/or drinks or total or added sugar intakes (g/day) among controls. In addition, tertiles for percent of calories from sweets (i.e. dessert foods group) per day were created based on the controls, and frequencies calculated across these tertiles. Multivariate ORs and 95% CIs assessed ovarian cancer risk across these tertiles.

Lastly, we explored if women at risk of hyperinsulinemia have greater odds of developing ovarian cancer associated with sugar consumption. Multivariate ORs and 95% CIs were estimated for ovarian cancer risk across tertiles for total sugary foods and drinks and total and added sugars, stratified by factors related to hyperinsulinemia such as BMI (normal weight: <25 kg/m^2 vs. overweight or obese: $\geq$25 kg/m^2), waist-to-hip ratio (WHR; $\leq$0.85 vs. >0.85), or physical activity (< median vs. $\geq$median). Because the number of women with diabetes is small, we also repeated analyses excluding women diagnosed with diabetes. The Wald test was used to calculate p values.

Results

Selected demographic characteristics and risk factors are presented in **Table 1**. In our study population, participants were mainly white and most had at least college education. Compared to controls, cases were younger (64.6 vs. 57.0 years, respectively; p<0.01), more

likely to be either nulliparous or uniparous and premenopausal at time of diagnosis. Combined HRT use and having tubal ligation were protective against ovarian cancer.

Table 1. Selected characteristics of women participating in The NJ Ovarian Cancer Study.

	Cases (*n*=205) n (%)		Controls (*n*=390) n (%)		Age-Adjusted OR (95% CI)
Education					
High school or less	61	(29.8)	132	(33.9)	1.00 (Ref)
College	93	(45.4)	159	(40.8)	0.90 (0.59-1.38)
Graduate school	51	(24.9)	99	(25.4)	0.76 (0.47-1.24)
Race/ethnicity					
White	179	(87.3)	343	(88.4)	1.00 (Ref)
Black	9	(4.4)	17	(4.4)	1.02 (0.42-2.44)
Other	8	(3.9)	17	(4.4)	0.82 (0.33-1.99)
Hispanic (any race)	9	(4.4)	11	(2.8)	1.13 (0.44-2.92)
Parity*					
0 – 1	97	(47.3)	92	(23.6)	1.00 (Ref)
2	60	(29.3)	136	(34.9)	0.45 (0.29-0.69)
≥3	48	(23.4)	162	(41.5)	0.42 (0.26-0.66)
Oral contraceptive use					
Never	85	(41.5)	192	(49.2)	1.00 (Ref)
Ever	120	(58.5)	198	(50.8)	0.88 (0.61-1.28)
Use of HRT					
Never	159	(77.6)	284	(72.8)	1.00 (Ref)
Unopposed E only	22	(10.7)	34	(8.7)	1.56 (0.86-2.83)
Any combined HRT	24	(11.7)	72	(18.5)	0.63 (0.38-1.06)
Age at menarche					
>13	41	(20.1)	98	(25.2)	0.81 (0.51-1.28)
12-13	117	(57.4)	200	(51.4)	1.00 (Ref)
≤11	46	(22.6)	91	(23.4)	0.75 (0.48-1.17)
Menopause status*					
Premenopausal	71	(34.6)	49	(12.6)	
Postmenopausal	134	(65.4)	341	(87.4)	
Age at menopause					
<40	5	(2.4)	14	(3.6)	0.77 (0.26-2.31)
41-54	86	(42.0)	239	(61.3)	1.00 (Ref)
≥55	12	(5.9)	36	(9.3)	0.99 (0.48-2.02)
Unknown	31	(15.1)	52	(13.3)	1.52 (0.91-2.56)
BMI					
Normal (<25)	91	(44.4)	180	(46.5)	1.00 (Ref)
Overweight (25-29.9)	54	(26.3)	122	(31.5)	1.07 (0.69-1.65)
Obese (30-34.9)	36	(17.6)	59	(15.3)	1.39 (0.83-2.32)
Very obese (≥35)	24	(11.7)	26	(6.7)	1.54 (0.82-2.89)
Smoking status					
Never	108	(52.7)	203	(52.1)	1.00 (Ref)

Past	78	(38.1)	149	(38.2)	1.12 (0.76-1.64)
Current	19	(9.3)	38	(9.7)	0.87 (0.46-1.62)
Tubal Ligation					
No	175	(85.4)	314	(80.5)	1.00 (Ref)
Yes	30	(14.6)	76	(19.5)	0.59 (0.36-0.94)
First relative with ovarian cancer					
No	195	(95.1)	376	(96.4)	1.00 (Ref)
Yes	10	(4.9)	14	(3.6)	1.32 (0.55-3.17)

OR: Odds Ratio, CI: Confidence Interval
* $p<0.01$ for frequencies

Table 2 shows age-adjusted means for the consumption of sugary foods and drinks, as well as, total and added sugars. Cases were more likely than controls to consume dessert foods, non-dessert foods and sugary drinks, although these differences were not significant. However, cases had significantly greater mean total sugar intake (64.7 vs. 60.2 grams/1,000 kcal, respectively), as well as, higher added sugar intake (29.5 vs. 26.3 g/1,000 kcal, respectively) compared to controls, although the latter did not reach statistical significance.

Table 2. Age-adjusted means (± SE) for sugary foods and drinks and added sugar among women in The NJ Ovarian Cancer Study.

Sources of Added Sugar	Cases (n=205)	Controls (n=390)	*p*
Total Sugary Foods & Drinks[a]	5.12 (0.10)	4.83 (0.07)	0.39
Dessert Foods[a]	0.87 (0.07)	0.83 (0.05)	0.64
Doughnuts, Danish pastry	0.04 (0.01)	0.04 (0.00)	0.85
Cakes, sweet rolls, coffee cake	0.03 (0.00)	0.03 (0.00)	0.40
Cookies	0.37 (0.04)	0.39 (0.03)	0.25
Ice cream	0.06 (0.01)	0.05 (0.00)	0.03
Pumpkin pie, sweet potato pie	0.01 (0.00)	0.01 (0.00)	0.72
Other pies or cobbler	0.02 (0.00)	0.02 (0.00)	0.11
Chocolate candy, candy bars	0.08 (0.01)	0.07 (0.01)	0.11
Other candy, not chocolate	0.28 (0.04)	0.24 (0.03)	0.81
Non-Dessert Foods[a]	3.94 (0.08)	3.80 (0.06)	0.39
Entrees	0.70 (0.03)	0.59 (0.02)	<0.001
Canned fruit, dried fruits	0.04 (0.01)	0.04 (0.00)	<0.01
Pancakes, waffles, French toast, Pop Tarts	0.06 (0.01)	0.07 (0.01)	0.89

Breakfast bars, granola bars, Power bars	0.03 (0.01)	0.03 (0.01)	0.08
Cooked cereals	0.07 (0.01)	0.11 (0.01)	<0.001
Cold cereals	0.15 (0.02)	0.17 (0.01)	0.36
Yogurt/Frozen Yogurt	0.08 (0.01)	0.08 (0.01)	0.72
Biscuits or muffins	0.79 (0.04)	0.80 (0.03)	<0.01
Jelly, jam, or syrup	0.15 (0.01)	0.15 (0.02)	<0.01
Other condiments	1.61 (0.06)	1.53 (0.05)	<0.01
Sugary Drinks[a]	0.30 (0.03)	0.24 (0.02)	0.17
Drinks with added vitamin C	0.01 (0.00)	0.01 (0.00)	0.35
Drinks with some fruit juices	0.01 (0.00)	0.01 (0.00)	0.97
Regular soft drinks or bottled drinks	0.12 (0.02)	0.09 (0.01)	0.18
Total Sugars[b]	64.66 (1.72)	60.15 (1.22)	<0.01
Added Sugars[b]	29.46 (1.12)	26.25 (0.80)	0.07

SE: Standard Error
[a] Density measure calculated as servings per 1,000 kcal
[b] Density measure calculated as grams per 1,000 kcal

Multivariable analyses revealed an increased ovarian cancer risk associated with higher consumption of total sugary foods and drinks and sugary non-dessert foods after adjusting for age and energy intake (**Table 3**). However, these associations did not remain significant after further adjustment for additional risk factors. There was a suggestion of a 63% increase in risk associated with each additional serving of sugary drinks per 1,000 kcal after adjusting for all risk factors, but the confidence interval included the null value (OR=1.63, 95% CI: 0.94-2.83). Overall, there was little evidence that sugary foods and drinks had a major impact on ovarian cancer risk.

Table 3. Sources of sugar and ovarian cancer risk in The NJ Ovarian Cancer Study.

Sources of Sugar	Cases (n=205)	Controls (n=390)	OR1	95% CI	OR2	95% CI
Total Sugary Foods & Drinks[a]						
Continuous			1.15	(1.02-1.31)	1.05	(0.90-1.22)
<4.14	50 (24.4)	130 (33.3)	1.00		1.00	
4.14-5.37	74 (36.1)	130 (33.3)	1.45	(0.91-2.29)	1.25	(0.73-2.16)
>5.37	81 (39.5)	130 (33.3)	1.74	(1.10-2.74)	1.25	(0.73-2.17)
p trend				0.02		0.46

Dessert Foods[a]						
Continuous			1.05	(0.87-1.27)	0.94	(0.75-1.17)
<0.35	68 (33.2)	132 (33.9)	1.00		1.00	
0.35-0.80	66 (32.2)	128 (32.8)	0.99	(0.64-1.54)	0.92	(0.55-1.56)
>0.80	71 (34.6)	130 (33.3)	1.24	(0.79-1.94)	1.04	(0.61-1.76)
p trend				0.29		0.81
Non-Dessert Foods[a]						
Continuous			1.10	(0.95-1.29)	1.02	(0.85-1.23)
<3.21	52 (25.4)	132 (33.9)	1.00		1.00	
3.21-4.20	73 (35.6)	128 (32.8)	1.47	(0.93-2.31)	1.30	(0.76-2.22)
>4.20	80 (39.0)	130 (33.3)	1.58	(1.01-2.48)	1.31	(0.77-2.24)
p trend				0.05		0.35
Sugary Drinks[a]						
Continuous			1.53	(0.96-2.44)	1.63	(0.94-2.83)
<0.03	62 (30.2)	130 (33.3)	1.00		1.00	
0.03-0.21	64 (31.2)	129 (33.1)	0.91	(0.59-1.44)	0.83	(0.48-1.41)
>0.21	79 (38.5)	131 (33.6)	1.17	(0.76-1.82)	1.09	(0.65-1.84)
p trend				0.30		0.47
Total Sugars[b]						
Continuous			1.01	(1.00-1.02)	1.01	(1.00-1.02)
<49.33	68 (33.2)	129 (33.1)	1.00		1.00	
49.33-69.61	70 (34.2)	130 (33.3)	1.19	(0.77-1.84)	1.32	(0.78-2.25)
>69.61	67 (32.7)	131 (33.6)	1.31	(0.84-2.04)	1.13	(0.66-1.94)
p trend				0.24		0.69
Added Sugars[b]						
Continuous			1.01	(1.00-1.03)	1.01	(0.99-1.02)
<18.63	61 (31.2)	129 (33.1)	1.00		1.00	
18.63-29.59	65 (33.2)	131 (33.6)	1.01	(0.64-1.59)	1.03	(0.59-1.77)
>29.59	79 (35.6)	130 (33.3)	1.35	(0.87-2.09)	1.05	(0.61-1.79)
p trend				0.16		0.87
% Kcal from sweets						
Continuous			1.02	(1.00-1.04)	1.01	(0.99-1.03)
<8.10	58 (28.3)	127 (32.6)	1.00		1.00	
8.10-15.10	63 (30.7)	127 (32.6)	1.11	(0.70-1.76)	0.84	(0.49-1.46)
>15.10	84 (41.0)	136 (34.9)	1.40	(0.89-2.19)	1.10	(0.63-1.92)
p trend				0.13		0.57

OR: Odds Ratio, CI: Confidence Interval

OR1: adjusted for age (continuous), energy intake (continuous)

OR2: additionally adjusted for education (high school or less, college, graduate school), race (White, Black, Other, Hispanic), age at menarche (continuous), menopausal status (premenopausal, postmenopausal) and age at menopause for postmenopausal women (<40, 42-54, $\geq$ 55, unknown), parity (0-1, 2, 3-4), oral contraceptive use (ever, never), HRT use (never, unopposed estrogen only, any combined HRT), tubal ligation (no, yes), BMI (continuous), smoking status (never, past, current) and pack-years for ever smokers (continuous), physical activity (METs for reported average hours per week of moderate or strenuous recreational activities),

Further adjustment for diabetes (yes, no) or fiber intake (g) did significantly change results.
[a] Density measure calculated as servings per 1,000 kcal
[b] Density measure calculated as grams per 1,000 kcal

We further evaluated possible effect modification by several factors, including BMI, WHR, physical activity, oral contraceptive use, and HRT use. Because the numbers of HRT users were too small to conduct separate analyses on them, we repeated analyses restricted to HRT users and results were similar (data not shown). Stratified analyses by BMI, WHR, and physical activity did not provide clear evidence of effect modification (**Table 4**). Lastly, excluding those diagnosed with diabetes did not affect multivariate analyses results (data not shown). History of oral contraceptive use or menopausal status also did not appear to influence any of the risk estimates evaluated (data not shown).

Table 4. Sugary foods and drinks and added sugar and ovarian cancer risk by selected characteristics in The NJ Ovarian Cancer Study.

Sources of Sugar	Cases/Controls	Tertile 1	Tertile 2 OR (95% CI)	Tertile 3 OR (95% CI)	*p* for heterogeneity
Total sugary foods[a]		(<3.96)	(3.96-5.16)	(>5.96)	
Total population	205/390	1.00	0.99 (0.57-1.71)	0.92 (0.54-1.56)	
BMI (kg/m^2)					
<25	91/180	1.00	1.13 (0.51-2.50)	0.99 (0.44-2.26)	0.86
≥ 25	114/207	1.00	0.83 (0.36-1.92)	0.79 (0.36-1.73)	
WHR (cm)					
<0.85	114/206	1.00	0.71 (0.33-1.50)	0.93 (0.45-1.95)	0.36
≥0.85	87/178	1.00	1.57 (0.57-4.31)	0.97 (0.39-2.43)	
Physically activity (METs)					
<15,4917.2	181/192	1.00	1.13 (0.60-2.11)	0.87 (0.48-1.59)	0.72
≥15,4917.2	19/193	1.00	0.90 (0.18-4.45)	1.37 (0.28-6.67)	
Total sugary drinks[a]		(<0.03)	(0.03-0.21)	(>0.21)	
Total population	205/390	1.00	0.83 (0.48-1.41)	1.09 (0.65-1.84)	
BMI (kg/m^2)					
<25	91/180	1.00	0.58 (0.25-1.35)	0.82 (0.37-1.79)	0.62
≥ 25	114/207	1.00	0.97 (0.46-2.08)	1.28 (0.59-2.75)	
WHR (cm)					
<0.85	114/206	1.00	0.76 (0.36-1.57)	1.25 (0.61-2.57)	0.77
≥0.85	87/178	1.00	0.86 (0.35-2.13)	0.95 (0.39-2.32)	
Physically activity (METs)					
<15,4917.2	181/192	1.00	0.90 (0.49-1.67)	1.50 (0.82-2.75)	0.06
≥15,4917.2	19/193	1.00	0.62 (0.14-2.66)	0.17 (0.03-0.94)	
Total sugars[b]		(<49.33)	(49.33-69.61)	(>69.61)	
Total population	205/390	1.00	1.32 (0.78-2.25)	1.13 (0.66-1.94)	
BMI (kg/m^2)					
<25	91/180	1.00	0.76 (0.34-1.68)	0.89 (0.40-1.99)	0.14

≥ 25	114/207	1.00	2.36 (1.06-5.27)	1.39 (0.63-3.08)	
WHR (cm)					
<0.85	114/206	1.00	1.25 (0.61-2.58)	1.23 (0.58-2.61)	0.94
≥0.85	87/178	1.00	1.20 (0.46-3.11)	1.01 (0.39-2.62)	
Physically activity (METs)					
<15,4917.2	181/192	1.00	1.04 (0.57-1.89)	1.15 (0.62-2.12)	0.03
≥15,4917.2	19/193	1.00	7.77 (1.33-45.50)	0.85 (0.15-4.89)	
Added sugars[b]		(<18.63)	(18.63-29.59)	(>29.59)	
Total population	205/390	1.00	1.03 (0.60-1.77)	1.05 (0.61-1.79)	
BMI (kg/m^2)					
<25	91/180	1.00	0.82 (0.37-1.81)	0.55 (0.24-1.24)	0.08
≥ 25	114/207	1.00	1.30 (0.56-3.01)	1.97 (0.86-4.52)	
WHR (cm)					
<0.85	114/206	1.00	0.93 (0.43-1.99)	0.93 (0.44-1.96)	0.75
≥0.85	87/178	1.00	1.08 (0.42-2.80)	1.46 (0.56-3.77)	
Physically activity (METs)					
<15,4917.2	181/192	1.00	1.14 (0.61-2.12)	1.14 (0.62-2.09)	0.70
≥15,4917.2	19/193	1.00	1.15 (0.24-5.41)	0.57 (0.11-2.94)	

OR: Odds Ratio, CI: Confidence Interval, WHR: waist-to-hip ratio

OR: adjusted for age (continuous), energy intake (continuous), education (high school or less, college, graduate school), race (White, Black, Other, Hispanic), age at menarche (continuous), menopausal status (premenopausal, postmenopausal) and age at menopause for postmenopausal women (<40, 42-54, ≥ 55, unknown), parity (0-1, 2, 3-4), oral contraceptive use (ever, never), HRT use (never, unopposed estrogen only, any combined HRT), tubal ligation (no, yes), BMI (continuous), smoking status (never, past, current) and pack-years for ever smokers (continuous), physical activity (METs for reported average hours per week of moderate or strenuous recreational activities)

Further adjustment for diabetes (yes, no) did not significantly change results.

[a] Density measure calculated as servings per 1,000 kcal

[b] Density measure calculated as grams per 1,000 kcal

Discussion

Our population-based case-control study performed a comprehensive assessment on how consuming foods and beverages with added sugars can influence ovarian cancer risk. Our findings did not provide evidence of a relationship between ovarian cancer risk and sugary foods and beverage consumption or total and added sugars. There was a suggestion of a moderately increased cancer risk associated with each additional serving of sugary drinks per 1,000 kcal, however, this association was borderline significant.

Similar to our results, Pan et al.(99) used data from the Canadian National Enhanced Cancer Surveillance System (NECSS), a population-based case-control study in pre- and postmenopausal women, and did not find an association between baked desserts (servings/week) and ovarian cancer after adjusting for multiple factors including BMI, total caloric intake, and recreational physical activity (99). Salazar-Martinez et al.(100) also did not find an association with soda, coffee and tea combined (OR=0.96; 95% CI: 0.40-2.29) in their hospital-based case-control study in Mexico. It is worth noting, while the authors did adjust for total energy intake, recent changes in weight, physical activity (METs), and diabetes, they did not adjust for smoking status or pack-years, BMI or WHR. Unlike our findings, Kushi et al.(95) found a strong adverse association between sweets and ovarian cancer risk in the Iowa Women's Health Study, a prospective study of almost 30,000 postmenopausal women and 139 cases (ORs from lowest to highest category: 1.00, 2.32, 2.49, and 1.61; p_{trend}=0.17]. Almost 35% of our cases were premenopausal at the time of their diagnosis, which may explain why our findings are similar to Pan et al.(99) and inconsistent with Kushi et al.(95). In addition, although Kushi et al. adjusted for total energy intake, WHR and level of physical activity and they did not adjust for BMI or diabetes status. Similarly, two hospital-based case-control studies(96, 100) that have evaluated sugary food intake and risk of ovarian cancer reported non-significant

increases in risk associated with dessert consumption. Among the studies(97, 100, 101) that examined sugary beverage intake and ovarian cancer risk, a study by Kuper et al.(101) was the only study to report a positive association. Women who consumed the highest level of caffeinated cola beverages had elevated risk of ovarian cancer in their population-based case-control study in Massachusetts and New Hampshire (101).

Overall, studies have produced inconsistent findings on the relationship between dietary sugars (i.e. total sugars, sugar, added sugar sucrose or fructose) and ovarian cancer risk. Only two prospective studies(56, 90) have evaluated the relationship between sugar intake and ovarian cancer with conflicting results. Interestingly, using data from the NIH-AARP Diet and Health Study, Tasevska et al.(56) found the risk of developing ovarian cancer to be significantly inversely associated with total sugars, total fructose, and sucrose [HR (95% CI) for Q5, respectively: 0.70 (0.51-0.97); 0.68(0.49-0.95); and 0.65(0.47-0.89)]. Unlike our study, 97% of their 457 ovarian cancer cases were postmenopausal and the authors state that their results could be confounded by unknown factors. On the other hand, Silvera et al.(90) did not detect a relationship between total sugar intake and ovarian cancer risk among premenopausal women in a prospective cohort in Canada. However, they did detect a hazardous effect of total sugar intake (g/day) on ovarian cancer risk among postmenopausal women (HRs from lowest to highest category: 1.00, 1.67, 2.35, and 1.79; p_{trend}=0.08). They also found no heterogeneity of effects among pre- or postmenopausal women by smoking status, parity, age at menarche, HRT use, or alcohol intake(90). We did not find any differences in risk by menopausal status and the number of women who use HRT was too small to analyze. Finally, among the studies(44, 56, 90-94, 96, 100, 102-104) that have evaluated sugar intake, only one study(56, 102) independently evaluated the effects added sugar on risk of developing ovarian cancer. Tasevska et al.(56) detected significant protection against ovarian cancer among women in the highest quintile of

added sugars intake, after adjusting for multiple factors [Hazard Ratio=0.72, 95% CI:(0.51-1.00); p_{trend}=0.02].

We also considered potential effect modification by several insulin-related factors and did not identify any significant heterogeneity of effects estimates. Abdominal obesity(84) and high waist-to-hip ratio (WHR)(85), both markers of insulin resistance(33), have been shown to significantly increase ovarian cancer risk. Furthermore, insulin encourages ovarian production of androgens (direct precursors of estrogen synthesis)(86-89) and controls metabolism and transport of androgens in peripheral tissue(89). This results in lower levels of IGFBP and consequently increases IGF-1, promoting ovarian carcinogenesis(85, 90). Insulin-related factors, like WHR, might also modify the relationship between sugar intake and cancer risk. Nagle and colleagues(91) found sugar intake to have a beneficial effect on ovarian cancer risk among normal weight women and an adverse effect among overweight and obese women. They hypothesized that among heavier women, insulin resistance would exaggerate the harmful metabolic responses with carbohydrate consumption. Thus, a high-sugar diet could possibly have a more deleterious effect on ovarian cancer risk among women who are obese(91). However, we did not find consistent evidence that sugar consumption and ovarian cancer risk was negatively impacted by central adiposity or excess weight. However, Nagle et al. and our study are the only studies to evaluate possible effect modification by BMI and therefore additional studies are needed.

Lastly, recent studies have reported significant differences across histologic subtypes in the associations of epithelial ovarian cancer with reproductive and nonreproductive risk factors, perhaps due to variations in etiology, morphology, and genetic expression of ovarian tumors(110, 111). Using data from the Nurses' Health Study and Nurses' Health Study II, Gates et al. observed that determinants such as age, duration of estrogen use, BMI, duration of

breastfeeding, age at menopause, and smoking significantly differed by histologic subtype(110). It is possible that our inability to detect a relationship between sugar intake, ovarian cancer, and insulin modifiers may be a result of variations in risk across histologic subtypes. However, we were unable to evaluate these relationships by tumor histology due to our small number of cases. To our knowledge, no other studies have reported on sugar intake and ovarian cancer risk by histology.

Some limitations of our study must be noted. Recall and selection biases are a particular concern in case-control studies. Because ovarian cancer is often detected after the disease has metastasized, women often present at an advanced stage and may be too ill to accurately remember their dietary habits prior to diagnosis. We also assessed whether selection bias might have occurred by comparing characteristics of our ovarian cancer cases with all women diagnosed with epithelial ovarian cancer in the same NJ counties(112). Our study participants were slightly younger than the general population of cases (median age at diagnosis: 56 years vs. 61 years, respectively). On the other hand, our cases were similar with respect to race and ethnic distribution, as well as, histology, stage, and grade of cancer. Our study suffered from low response rates, which is comparable to other published population-based case-control studies(113). One concern is that participation may be related to subjects' lifestyle habits. For example, those who chose to participate in our study may make healthier choices and be more enthusiastic about participating in a healthy study than those who refused. Unfortunately, we were unable to compare controls with women who did not participate as we did not collect information on those who could not be reached or declined to participate in our study. However, we can be reassured that minimal selection bias may have occurred as the distribution of major risk factors in our study is comparable to those reported in the literature.

In conclusion, there is a paucity of epidemiologic research evaluating the role of sugary food(95-100) and beverage(97, 100, 101) intake and risk of ovarian cancer and the findings have been inconclusive. To our knowledge this is the first study to evaluate ovarian cancer risk in relation to total and individual consumption of sugary foods and beverages, total and added sugar intake, as well as potential effect modification by several insulin-related risk factors. Although in our study there was a suggestion of a moderately increased cancer risk associated with sugary beverage consumption, overall, we did not detect significant relationships between ovarian cancer and any of the sugar variables evaluated. These apparent gaps in literature emphasize the need for future research, preferably large prospective studies, to evaluate the role of added sugars in the etiology of ovarian cancer, while taking into consideration various insulin-modifiers such as anthropometric measures or physical activity.

Summary and Conclusions

A thorough review of the literature revealed that although a few studies have evaluated the impact of dietary sugars on endometrial and ovarian cancers, many have evaluated sugar as a nutrient or have evaluated specific sugary foods or beverages. Generally, the results of these studies have either been inconsistent or inconclusive. There is only one study that has directly examined intake of total and added sugars from all food sources and endometrial and ovarian cancer risk(56). There are no studies that have taken a comprehensive approach by incorporating the total consumption of sugary foods and beverages, as well as total and added sugars from all food sources, while accounting for effect modification by several insulin-related factors (e.g. BMI, WHR, physical activity). From a public health perspective, it may be more informative to evaluate the effects of total sugary foods and drinks, in addition to added sugars, as the incremental exposure to added sugars from all foods could impact cancer risk. Furthermore, waist circumference and other insulin-related factors, have been rarely explored as effect modifiers of the relationship between sugar intake and cancers of the endometrium and ovary. The limited epidemiologic research coupled with inconsistent findings emphasizes the importance of a thorough investigation on risk of endometrial and ovarian cancers and sugar consumption, and potential effect modification by insulin-related risk factors.

To our knowledge, we are the first study to have reported on the relationship between endometrial and ovarian cancers and several forms of sugar consumption: sweet and savory foods with added sugars, beverages with added sugars, total sugars and total added sugars, with consideration for insulin-related factors. To summarize, we found the consumption of sugary beverages and added sugars to have significant deleterious effects on endometrial cancer risk, after adjusting for several major risk factors. In addition, factors related to insulin sensitivity, notably central obesity, modified the relationship between sugar consumption and endometrial

cancer risk. Specifically, among women with central obesity, there was significantly higher endometrial cancer risk associated with sugary food consumption and added sugar intake. Additionally, overweight and obese women had increased endometrial cancer risk associated with total and added sugar intakes, compared to little evidence of increased risk among leaner women. On the other hand, we did not detect a significant association between ovarian cancer risk and sugary foods and beverage consumption or total and added sugars. Though, there was a suggestion of a borderline inverse relationship between risk of ovarian cancer and sugary drinks intake. We also looked at potential effect modification by insulin-modifiers, but did not observe any consistent patterns in ovarian cancer risk estimates.

Our results support the 2010 Dietary Guidelines for Americans that recommend reducing added sugar intake and the WCRF/AICR 2007 Export Report recommendations to avoid sugary drinks to prevent cancer. Still, further research is necessary to confirm our findings on endometrial cancer and future research, ideally large prospective studies, should further investigate the role of added sugar consumption and ovarian cancer risk, while accounting for factors related to insulin sensitivity.

Appendix. Foods and beverages included in sugary foods and drinks and added sugar analyses.

Selected Foods and Beverages	Frequency of Consumption									Portion Size Consumed*				
	Never	A few times/year	Once/month	2-3 times/mont	Once/week	2 times/week	3-4 times/week	5-6 times/week	Everyday					
Kool-Aid, Hi-C, or other drinks with added vitamin C										How many glasses?	1	2	3	4
Drinks with some juice in them, like Sunny Delight, Juice Squeeze										How many glasses?	1	2	3	4
Regular soft drinks, or bottled drinks like Snapple (not diet drinks)										How many bottles?	1	2	3-4	5+
Tea or Iced Tea (not herb teas)										How many cups?	1	2	3-4	5+
Sugar (honey) added to tea										If yes, how many Tsp. each cup?	1	2	3-4	5+
Sugar (honey) added to coffee										If yes, how many Tsp. each cup?	1	2	3-4	5+
Canned fruit like applesauce, fruit cocktail, or dried fruit like raisins										How much?*	A	B	C	D
Pancakes, waffles, French toast, Pop Tarts										How many pieces?	1	2	3	4
Breakfast bars, granola bars, Power bars										How many?	1	2	3	4
Cooked cereals like oatmeal, cream of wheat or grits										Which Bowl?		B	C	D
High-fiber cereals like All Bran, Raisin Bran, Fruit-n-Fiber										Which Bowl?		B	C	D
Product 19, Just Right or Total cereal										Which Bowl?		B	C	D
Any other cold cereal, like Corn Flakes, Cheerios, Special K										Which Bowl?		B	C	D
Yogurt or frozen yogurt										How much?	A	B	C	D
Salad dressing										How many Tbsp.?	1	2	3	4
Doughnuts, Danish pastry										How many?	1	2	3	4

Cakes, sweet rolls, coffee cake										How much?	A	B	C	D
Cookies										How many?	1-2	3-5	6-7	8+
Ice cream, ice milk, ice cream bars										How much?	A	B	C	D
Pumpkin pie, sweet potato pie										How many slices?	1/2	1	2	3
Any other pies or cobbler										How many slices?	1/2	1	2	3
Chocolate candy, candy bars										How many bars?	1 small	1 medium	1 large	2 large
Other candy, not chocolate, like hard candy, caramel, jelly beans										How many pieces?	1-2	3-5	6-7	8+
	Never or a few times/year		**Once/month**	**2-3 times/month**	**Once/week**	**2 times/week**	**3-4 times/week**	**5-6 times/week**	**Everyday**	**2+ times/day**					
Biscuits or muffins										How many each time?	1	2	3	5
Jelly, jam, or syrup										How many Tbsp.?	1	2	3	4
Catsup, salsa or chile peppers										How many Tbsp.?	1	2	3	4
Mustard, soy sauce, steak sauce, barbeque sauce, other sauces										How many Tbsp.?	1	2	3	4

*For portion sizes denoted by letter, please see the portion size form for further description.

Bibliography

1. Johnson RK, Appel LJ, Brands M, Howard BV, Lefevre M, Lustig RH, Sacks F, Steffen LM, Wylie-Rosett J, American Heart Association Nutrition Committee of the Council on Nutrition PA, Metabolism, the Council on E, Prevention. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. Circulation 2009;120(11):1011-20.

2. Welsh JA, Sharma AJ, Grellinger L, Vos MB. Consumption of added sugars is decreasing in the United States. The American journal of clinical nutrition 2011;94(3):726-34.

3. US Department of Agriculture and US Department of Health and Human Services. Dietary Guidelines for Americans, 2010. 7th Edition. In. Washington, DC: US Government Printing Office, December 2010.

4. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. American Journal of Clinical Nutrition 2004;79(4):537-43.

5. United States Department of Agriculture. Chapter 2: Profiling Food Consumption in America. In: Agriculture Fact Book. Washington, DC: US Government Printing Office; 2001-2002. p. 12-21.

6. Hanover LM, White JS. Manufacturing, composition, and applications of fructose. American Journal of Clinical Nutrition 1993;58(5 Suppl):724S-732S.

7. Welsh JA, Cunningham SA. The role of added sugars in pediatric obesity. Pediatric clinics of North America 2011;58(6):1455-66.

8. World Cancer Research Fund, American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: American Cancer Institute for Cancer Research; 2007.

9. Berkey CS, Rockett HRH, Field AE, Gillman MW, Colditz GA. Sugar-added beverages and adolescent weight change. Obesity Research 2004;12(5):778-88.

10. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, Hu FB. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA 2004;292(8):927-34.

11. Montonen J, Jarvinen R, Knekt P, Heliovaara M, Reunanen A. Consumption of sweetened beverages and intakes of fructose and glucose predict type 2 diabetes occurrence. Journal of Nutrition 2007;137(6):1447-54.

12. Palmer JR, Boggs DA, Krishnan S, Hu FB, Singer M, Rosenberg L. Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women. Archives of Internal Medicine 2008;168(14):1487-92.

13. American Cancer Society. Cancer Facts and Figures. In. Atlanta: American Cancer Society, 2011; 2012.

14. Key TJ, Pike MC. The dose-effect relationship between 'unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. British Journal of Cancer 1988;57(2):205-12.

15. Popkin BM, Nielsen SJ. The sweetening of the world's diet. Obesity Research 2003;11(11):1325-32.

16. Bradshaw PT, Sagiv SK, Kabat GC, Satia JA, Britton JA, Teitelbaum SL, Neugut AI, Gammon MD. Consumption of sweet foods and breast cancer risk: a case-control study of women on Long Island, New York. Cancer Causes & Control 2009;20(8):1509-15.

17. Giovannucci E. Insulin and colon cancer. Cancer Causes & Control 1995;6(2):164-79.

18. Kaaks R, Lukanova A. Effects of weight control and physical activity in cancer prevention: role of endogenous hormone metabolism. Annals of the New York Academy of Sciences 2002;963:268-81.

19. Larsson SC, Friberg E, Wolk A. Carbohydrate intake, glycemic index and glycemic load in relation to risk of endometrial cancer: A prospective study of Swedish women. International Journal of Cancer 2007;120(5):1103-7.

20. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiology, Biomarkers & Prevention 2002;11(12):1531-43.

21. Cust AE, Kaaks R, Friedenreich C, Bonnet F, Laville M, Tjonneland A, Olsen A, Overvad K, Jakobsen MU, Chajes V, Clavel-Chapelon F, Boutron-Ruault M-C, Linseisen J, Lukanova A, Boeing H, Pischon T, Trichopoulou A, Christina B, Trichopoulos D, Palli D, Berrino F, Panico S, Tumino R, Sacerdote C, Gram IT, Lund E, Quiros JR, Travier N, Martinez-Garcia C, Larranaga N, Chirlaque M-D, Ardanaz E, Berglund G, Lundin E, Bueno-de-Mesquita HB, van Duijnhoven FJB, Peeters PHM, Bingham S, Khaw K-T, Allen N, Key T, Ferrari P, Rinaldi S, Slimani N, Riboli E. Metabolic syndrome, plasma lipid, lipoprotein and glucose levels, and endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocrine-Related Cancer 2007;14(3):755-67.

22. MacDonald PC, Siiteri PK. The relationship between the extraglandular production of estrone and the occurrence of endometrial neoplasia. Gynecologic Oncology 1974;2(2-3):259-63.

23. Crosbie EJ, Zwahlen M, Kitchener HC, al. e. Body Mass Index, Hormone Replacement Therapy, and Endometrial Cancer Risk: A Meta-Analysis. Cancer Epidemiology, Biomarkers & Prevention 2010;19:3119-3130.

24. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371(9612):569-78.

25. Davidson BJ, Gambone JC, Lagasse LD, Castaldo TW, Hammond GL, Siiteri PK, Judd HL. Free estradiol in postmenopausal women with and without endometrial cancer. Journal of Clinical Endocrinology & Metabolism 1981;52(3):404-8.

26. Newcomb PA, Klein R, Klein BE, Haffner S, Mares-Perlman J, Cruickshanks KJ, Marcus PM. Association of dietary and life-style factors with sex hormones in postmenopausal women. Epidemiology 1995;6(3):318-21.

27. Cauley JA, Gutai JP, Kuller LH, LeDonne D, Powell JG. The epidemiology of serum sex hormones in postmenopausal women. American Journal of Epidemiology 1989;129(6):1120-31.

28. Kaye SA, Folsom AR, Soler JT, Prineas RJ, Potter JD. Associations of body mass and fat distribution with sex hormone concentrations in postmenopausal women. International Journal of Epidemiology 1991;20(1):151-6.

29. Turcato E, Zamboni M, De Pergola G, Armellini F, Zivelonghi A, Bergamo-Andreis IA, Giorgino R, Bosello O. Interrelationships between weight loss, body fat distribution and sex hormones in pre- and postmenopausal obese women. Journal of internal medicine 1997;241(5):363-72.

30. Cust AE, Slimani N, Kaaks R, van Bakel M, Biessy C, Ferrari P, Laville M, Tjonneland A, Olsen A, Overvad K, Lajous M, Clavel-Chapelon F, Boutron-Ruault M-C, Linseisen J, Rohrmann S, Nothlings U, Boeing H, Palli D, Sieri S, Panico S, Tumino R, Sacerdote C, Skeie G, Engeset D, Gram IT, Quiros JR, Jakszyn P, Sanchez MJ, Larranaga N, Navarro C, Ardanaz E, Wirfalt E, Berglund G, Lundin E, Hallmans G, Bueno-de-Mesquita HB, Du H, Peeters PHM, Bingham S, Khaw K-T, Allen NE, Key TJ, Jenab M, Riboli E. Dietary carbohydrates, glycemic index, glycemic load, and

endometrial cancer risk within the European Prospective Investigation into Cancer and Nutrition cohort. American Journal of Epidemiology 2007;166(8):912-23.

31. Calle EE, Thun MJ. Obesity and cancer. Oncogene 2004;23(38):6365-78.

32. NIH Heart, Lung and Blood Institute. Assessing your weight and health risk. In; 2011.

33. Despres JP. Abdominal obesity: the most prevalent cause of the metabolic syndrome and related cardionmetabolic risk. European Heart Journal Supplements 2006;8(Supplement B):B4-B12.

34. Poirier P, Lemieux I, Mauriege P, Dewailly E, Blanchet C, Bergeron J, Despres JP. Impact of waist circumference on the relationship between blood pressure and insulin: the Quebec Health Survey. Hypertension 2005;45(3):363-7.

35. Pouliot MC, Despres JP, Nadeau A, Moorjani S, Prud'Homme D, Lupien PJ, Tremblay A, Bouchard C. Visceral obesity in men. Associations with glucose tolerance, plasma insulin, and lipoprotein levels. Diabetes 1992;41(7):826-34.

36. Silvera SAN, Rohan TE, Jain M, Terry PD, Howe GR, Miller AB. Glycaemic index, glycaemic load and risk of endometrial cancer: a prospective cohort study. Public Health Nutrition 2005;8(7):912-9.

37. Cust AE, Armstrong BK, Friedenreich CM, Slimani N, Bauman A. Physical activity and endometrial cancer risk: a review of the current evidence, biologic mechanisms and the quality of physical activity assessment methods. Cancer Causes & Control 2007;18(3):243-58.

38. Folsom AR, Demissie Z, Harnack L, Iowa Women's Health S. Glycemic index, glycemic load, and incidence of endometrial cancer: the Iowa women's health study. Nutrition & Cancer 2003;46(2):119-24.

39. Flanagan DE, Moore VM, Godsland IF, Cockington RA, Robinson JS, Phillips DI. Alcohol consumption and insulin resistance in young adults. European journal of clinical investigation 2000;30(4):297-301.

40. Lazarus R, Sparrow D, Weiss ST. Alcohol intake and insulin levels. The Normative Aging Study. American Journal of Epidemiology 1997;145(10):909-16.

41. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Arky RA, Hennekens CH, Speizer FE. A prospective study of moderate alcohol drinking and risk of diabetes in women. American Journal of Epidemiology 1988;128(3):549-58.

42. Davies MJ, Baer DJ, Judd JT, Brown ED, Campbell WS, Taylor PR. Effects of moderate alcohol intake on fasting insulin and glucose concentrations and insulin sensitivity in postmenopausal women: a randomized controlled trial. JAMA : the journal of the American Medical Association 2002;287(19):2559-62.

43. Lichtenstein AH, Schwab US. Relationship of dietary fat to glucose metabolism. Atherosclerosis 2000;150(2):227-43.

44. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. International Journal of Cancer 1975;15(4):617-31.

45. Biel RK, Friedenreich CM, Csizmadi I, Robson PJ, McLaren L, Faris P, Courneya KS, Magliocco AM, Cook LS. Case-Control Study of Dietary Patterns and Endometrial Cancer Risk. Nutrition and cancer 2011;63(5):673-686.

46. Friberg E, Wallin A, Wolk A. Sucrose, high-sugar foods and risk of endometrial cancer - a population-based cohort study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2011.

47. Goodman MT, Hankin JH, Wilkens LR, Lyu LC, McDuffie K, Liu LQ, Kolonel LN. Diet, body size, physical activity, and the risk of endometrial cancer. Cancer Research 1997;57(22):5077-85.

48. Kasum CM, Nicodemus K, Harnack LJ, Jacobs DR, Jr., Folsom AR, Iowa Women's Health S. Whole grain intake and incident endometrial cancer: the Iowa Women's Health Study. Nutrition & Cancer 2001;39(2):180-6.

49. Levi F, Franceschi S, Negri E, La Vecchia C. Dietary factors and the risk of endometrial cancer. Cancer 1993;71(11):3575-81.

50. McCann SE, Freudenheim JL, Marshall JR, Brasure JR, Swanson MK, Graham S. Diet in the epidemiology of endometrial cancer in western New York (United States). Cancer causes & control : CCC 2000;11(10):965-74.

51. Petridou E, Kedikoglou S, Koukoulomatis P, Dessypris N, Trichopoulos D. Diet in relation to endometrial cancer risk: a case-control study in Greece. Nutrition & Cancer 2002;44(1):16-22.

52. Salazar-Martinez E, Lazcano-Ponce E, Sanchez-Zamorano LM, Gonzalez-Lira G, Escudero-De Los Rios P, Hernandez-Avila M. Dietary factors and endometrial cancer risk. Results of a case-control study in Mexico. International Journal of Gynecological Cancer 2005;15(5):938-45.

53. Potischman N, Swanson CA, Brinton LA, McAdams M, Barrett RJ, Berman ML, Mortel R, Twiggs LB, Wilbanks GD, Hoover RN. Dietary associations in a case-control study of endometrial cancer. Cancer Causes & Control 1993;4(3):239-50.

54. Shu XO, Zheng W, Potischman N, Brinton LA, Hatch MC, Gao YT, Fraumeni JF, Jr. A population-based case-control study of dietary factors and endometrial cancer in Shanghai, People's Republic of China. American Journal of Epidemiology 1993;137(2):155-65.

55. Tzonou A, Lipworth L, Kalandidi A, Trichopoulou A, Gamatsi I, Hsieh CC, Notara V, Trichopoulos D. Dietary factors and the risk of endometrial cancer: a case--control study in Greece. British Journal of Cancer 1996;73(10):1284-90.

56. Tasevska N, Jiao L, Cross AJ, Kipnis V, Subar AF, Hollenbeck A, Schatzkin A, Potischman N. Sugars in diet and risk of cancer in the NIH-AARP Diet and Health Study. International journal of cancer. Journal international du cancer 2011.

57. Bandera EV, Williams-King MG, Sima C, Bayuga-Miller S, Pulick K, Wilcox H, Zauber AG, Olson SH. Coffee and tea consumption and endometrial cancer risk in a population-based study in New Jersey. Cancer Causes & Control 2010;21(9):1467-73.

58. Chandran U, Bandera EV, Williams-King MG, Sima C, Bayuga-Miller S, Pulick K, Wilcox H, Zauber AG, Olson SH. Adherence to the dietary guidelines for Americans and endometrial cancer risk. Cancer Causes Control 2010;21(11):1895-904.

59. Lucenteforte E, Talamini R, Montella M, Dal Maso L, Tavani A, Deandrea S, Pelucchi C, Greggi S, Zucchetto A, Barbone F, Parpinel M, Franceschi S, La Vecchia C, Negri E. Macronutrients, fatty acids and cholesterol intake and endometrial cancer. Annals of Oncology 2008;19(1):168-72.

60. Zemla B, Guminski S, Banasik R. Study of risk factors in invasive cancer of the corpus uteri. Neoplasma 1986;33(5):621-9.

61. Zemla B, Guminski S, Franek K, Kolosza Z, Banasik R. Etiological factors in invasive corpus uteri carcinoma. Neoplasma 1991;38(2):157-63.

62. Bravi F, Scotti L, Bosetti C, Zucchetto A, Talamini R, Montella M, Greggi S, Pelucchi C, Negri E, Franceschi S, La Vecchia C. Food groups and endometrial cancer risk: a case-control study from Italy. American journal of obstetrics and gynecology 2009;200(3):293 e1-7.

63. Hill HA, Austin H. Nutrition and endometrial cancer. Cancer Causes & Control 1996;7(1):19-32.

64. DeVivo I, Persson I, Adami HO, Hunter D, Trichopoulos D, editors. Textbook of cancer epidemiology. 2nd ed. New York: Oxford University Press; 2008.

65. Mulholland HG, Murray LJ, Cardwell CR, Cantwell MM. Dietary glycaemic index, glycaemic load and endometrial and ovarian cancer risk: a systematic review and meta-analysis. British Journal of Cancer 2008;99(3):434-41.

66. Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough M. The Association between Food, Nutrition, and Physical Activity and the Risk of Endometrial Cancer and Underlying Mechanisms. Second Report on Food, Nutrition, Physical Activity and the Prevention of Cancer: World Cancer Research Fund International/American Institute for Cancer Research; 2007.

67. Bandera EV, Williams MG, Sima C, Bayuga S, Pulick K, Wilcox H, Soslow R, Zauber AG, Olson SH. Phytoestrogen consumption and endometrial cancer risk: a population-based case-control study in New Jersey. Cancer Causes & Control 2009;20(7):1117-27.

68. Fortuny J, Sima C, Bayuga S, Wilcox H, Pulick K, Faulkner S, Zauber AG, Olson SH. Risk of endometrial cancer in relation to medical conditions and medication use. Cancer Epidemiology, Biomarkers & Prevention 2009;18(5):1448-56.

69. Olson SH, Orlow I, Bayuga S, Sima C, Bandera EV, Pulick K, Faulkner S, Tommasi D, Egan D, Roy P, Wilcox H, Asya A, Modica I, Asad H, Soslow R, Zauber AG. Variants in hormone biosynthesis genes and risk of endometrial cancer. Cancer Causes & Control 2008;19(9):955-63.

70. US Food and Drug Administration. Title 21- Food and Drugs, Chapter 1- Food and Drug Administration, Department of Health and Human Services, Subchapter B- Food for Human Consumption, Part 101- Food Labeling, Section 101.12-Reference amounts customarily consumed per eating occasion. In: Food and Drug Administration Department of Health and Human Services., editor. Code of Federal Regulations Title 21. USA: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=101.12; Revised as of April 1, 2011.

71. United States Department of Agriculture. USDA database for the added sugar content of selected foods. In. Beltsville, MD: USDA Agricultural Research Service; 2006.

72. Willett W. Nutritional Epidemiology. 1st ed. England: Oxford University Press; 1990.

73. Miao Q, Kong BH. [A case-control study on etiology of epithelial ovarian cancer in Shandong Province]. Ai zheng = Aizheng = Chinese journal of cancer 2006;25(7):871-5.

74. Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. Seminars in Surgical Oncology 2000;19(1):3-10.

75. Fathalla MF. Incessant ovulation--a factor in ovarian neoplasia? Lancet 1971;2(7716):163.

76. Riman T, Persson I, Nilsson S. Hormonal aspects of epithelial ovarian cancer: review of epidemiological evidence. Clinical Endocrinology 1998;49(6):695-706.

77. Bandera EV. Nutritional factors in ovarian cancer prevention: what have we learned in the past 5 years? Nutrition & Cancer 2007;59(2):142-51.

78. Agnoli C, Berrino F, Canevari S, Casazza G, Colombo C, Fusconi E, Grioni S, Krogh V, Menard S, Mugno E, Pala V, Panzoni L, Pasanisi P, Sieri S, Curtosi P, Evangelista A, Gualdana I, Grazia Guerrini M, Pistotti V. The Associations between Food, Nutrition and Physical Activity and the Risk of Ovarian Cancer and Underlying Mechanisms. Second Report on Food, Nutrition, Physical Activity and the Prevention of Cancer: World Cancer Research Fund International/American Institute for Cancer Research; 2007.

79. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, Gapstur S, Patel AV, Andrews K, Gansler T. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA: a Cancer Journal for Clinicians 2012;62(1):30-67.

80. Olsen CM, Green AC, Whiteman DC, Sadeghi S, Kolahdooz F, Webb PM. Obesity and the risk of epithelial ovarian cancer: a systematic review and meta-analysis. European Journal of Cancer 2007;43(4):690-709.

81. Purdie DM, Bain CJ, Webb PM, Whiteman DC, Pirozzo S, Green AC. Body size and ovarian cancer: case-control study and systematic review (Australia). Cancer causes & control : CCC 2001;12(9):855-63.

82. Kosary CL. Cancer of the Ovary. In: Ries L, Young J, Keel G, Eisner M, Lin Y, Horner M-J, editors. SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. Bethesda, MD: National Cancer Institute, SEER Program, NIH Pub. No. 07-6215; 2007.

83. Larsson SC, Bergkvist L, Wolk A. Consumption of sugar and sugar-sweetened foods and the risk of pancreatic cancer in a prospective study. American Journal of Clinical Nutrition 2006;84(5):1171-6.

84. Canchola AJ, Chang ET, Bernstein L, Largent JA, Reynolds P, Deapen D, Henderson KD, Ursin G, Horn-Ross PL. Body size and the risk of ovarian cancer by hormone therapy use in the California Teachers Study cohort. Cancer causes & control : CCC 2010;21(12):2241-8.

85. Lukanova A, Kaaks R. Endogenous hormones and ovarian cancer: epidemiology and current hypotheses. Cancer Epidemiology, Biomarkers & Prevention 2005;14(1):98-107.

86. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. New England Journal of Medicine 1996;335(9):617-23.

87. Poretsky L, Kalin MF. The gonadotropic function of insulin. Endocrine Reviews 1987;8(2):132-41.

88. Whittemore AS, Wu ML, Paffenbarger RS, Jr., Sarles DL, Kampert JB, Grosser S, Jung DL, Ballon S, Hendrickson M. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. American Journal of Epidemiology 1988;128(6):1228-40.

89. Pasquali R, Vicennati V, Gambineri A. [Influence of weight and distribution of adipose tissue in functional hyperandrogenism]. Contraception, fertilite, sexualite 1998;26(5):372-5.

90. Silvera SAN, Jain M, Howe GR, Miller AB, Rohan TE. Glycaemic index, glycaemic load and ovarian cancer risk: a prospective cohort study. Public Health Nutrition 2007;10(10):1076-81.

91. Nagle CM, Kolahdooz F, Ibiebele TI, Olsen CM, Lahmann PH, Green AC, Webb PM. Carbohydrate intake, glycemic load, glycemic index, and risk of ovarian cancer. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2011;22(6):1332-8.

92. Decarli A, La Vecchia C. Environmental factors and cancer mortality in Italy: correlational exercise. Oncology 1986;43(2):116-26.

93. Grant WB. Ecologic studies of solar UV-B radiation and cancer mortality rates. Recent results in cancer research. Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer 2003;164:371-7.

94. Kato I, Tominaga S, Kuroishi T. Relationship between westernization of dietary habits and mortality from breast and ovarian cancers in Japan. Japanese journal of cancer research : Gann 1987;78(4):349-57.

95. Kushi LH, Mink PJ, Folsom AR, Anderson KE, Zheng W, Lazovich D, Sellers TA. Prospective study of diet and ovarian cancer. American Journal of Epidemiology 1999;149(1):21-31.

96. Bosetti C, Negri E, Franceschi S, Pelucchi C, Talamini R, Montella M, Conti E, La Vecchia C. Diet and ovarian cancer risk: a case-control study in Italy. International Journal of Cancer 2001;93(6):911-5.

97. Kolahdooz F, Ibiebele TI, van der Pols JC, Webb PM. Dietary patterns and ovarian cancer risk. The American journal of clinical nutrition 2009;89(1):297-304.

98. McCann SE, Freudenheim JL, Marshall JR, Graham S. Risk of human ovarian cancer is related to dietary intake of selected nutrients, phytochemicals and food groups. Journal of Nutrition 2003;133(6):1937-42.

99. Pan SY, Ugnat AM, Mao Y, et al. A case-control study of diet and the risk of ovarian cancer. Cancer Epidemiology, Biomarkers & Prevention 2004;13:1521-1527.

100. Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G, Escudero-De los Rios P, Hernandez-Avila M. Nutritional determinants of epithelial ovarian cancer risk: a case-control study in Mexico. Oncology 2002;63(2):151-7.

101. Kuper H, Titus-Ernstoff L, Harlow BL, Cramer DW. Population based study of coffee, alcohol and tobacco use and risk of ovarian cancer. International Journal of Cancer 2000;88(2):313-8.

102. Chandran U, Bandera EV, Williams-King MG, Paddock LE, Rodriguez-Rodriguez L, Lu SE, Faulkner S, Pulick K, Olson SH. Healthy eating index and ovarian cancer risk. Cancer Causes & Control 2011.

103. Bidoli E, La Vecchia C, Montella M, Maso LD, Conti E, Negri E, Scarabelli C, Carbone A, Decarli A, Franceschi S. Nutrient intake and ovarian cancer: an Italian case-control study. Cancer Causes & Control 2002;13(3):255-61.

104. Tzonou A, Hsieh CC, Polychronopoulou A, Kaprinis G, Toupadaki N, Trichopoulou A, Karakatsani A, Trichopoulos D. Diet and ovarian cancer: a case-control study in Greece. International Journal of Cancer 1993;55(3):411-4.

105. Adham SA, Coomber BL. Glucose is a key regulator of VEGFR2/KDR in human epithelial ovarian carcinoma cells. Biochemical and biophysical research communications 2009;390(1):130-5.

106. Kuper H, Titus-Ernstoff L, Harlow BL, Cramer DW. Population based study of coffee, alcohol and tobacco use and risk of ovarian cancer. International journal of cancer. Journal international du cancer 2000;88(2):313-8.

107. Bernal A, Mendez-Moran L, Fajardo-Gutierrez A, Gonzalez-Lira G, Escudero P, Ortiz H. Univariate and multivariate analysis of risk factors for ovarian cancer: case-control study, Mexico City. Archives of Medical Research 1995;26(3):245-9.

108. Bandera EV, King M, Chandran U, Paddock LE, Rodriguez-Rodriguez L, Olson SH. Phytoestrogen consumption from foods and supplements and epithelial ovarian cancer risk: a population-based case control study. BMC women's health 2011;11:40.

109. Gifkins D, Olson SH, Paddock L, King M, Demissie K, Lu SE, Kong AN, Rodriguez-Rodriguez L, Bandera EV. Total and individual antioxidant intake and risk of epithelial ovarian cancer. BMC Cancer 2012;12:211.

110. Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk factors for epithelial ovarian cancer by histologic subtype. American Journal of Epidemiology 2010;171(1):45-53.

111. Kurian AW, Balise RR, McGuire V, Whittemore AS. Histologic types of epithelial ovarian cancer: have they different risk factors? Gynecologic Oncology 2005;96(2):520-30.

112. New Jersey State Cancer Registry. Cancer Epidemiology Services.New Jersey Department of Health and Senior Services. Primary Epithelial Ovarian Cancer in 6 NJ Counties, age-specific incidence rates by race and age, 2003–2006. November 2008 file. In; 2008.

113. Hartge P. Participation in population studies. Epidemiology 2006;17(3):252-4.