JNCI J Natl Cancer Inst (2016) 108(10): djw125

doi: 10.1093/jnci/djw125
First published online June 8, 2016
Article

OXFORD

ARTICLE

Sweetened Beverage Consumption and Risk of Biliary Tract and Gallbladder Cancer in a Prospective Study

Susanna C. Larsson, Edward L. Giovannucci, Alicja Wolk

Affiliations of authors: Unit of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (SCL, AW); Departments of Nutrition and Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA (ELG); Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (ELG)

Correspondence to: Susanna C. Larsson, PhD, Unit of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Box 210, SE-17177 Stockholm, Sweden (e-mail: susanna.larsson@ki.se).

Abstract

Background: Sugar-sweetened beverage consumption raises blood glucose concentration and has been positively associated with weight gain and type 2 diabetes, all of which have been implicated in the development of biliary tract cancer (BTC). This study examined the hypothesis that sweetened beverage consumption is positively associated with risk of BTC in a prospective study.
Methods: The study population comprised 70 832 Swedish adults (55.9% men, age 45-83 years) from the Swedish Mammography Cohort and Cohort of Swedish Men who were free of cancer and diabetes and completed a food frequency questionnaire at baseline. Incident BTC case patients were ascertained through linkage with the Swedish Cancer Register. Cox proportional hazards regression model was used to analyze the data. All statistical tests were two-sided.
Results: During a mean follow-up of 13.4 years, 127 extrahepatic BTC case patients (including 71 gallbladder cancers) and 21 intrahepatic BTC case patients were ascertained. After adjustment for other risk factors, women and men in the highest category of combined sugar-sweetened and artificially sweetened beverage consumption had a statistically significantly increased risk of extrahepatic BTC and gallbladder cancer. The multivariable hazard ratios for two or more servings per day (200 mL/serving) of sweetened beverages compared with no consumption were 1.79 (95% confidence interval [CI] = 1.02 to 3.13) for extrahepatic BTC and 2.24 (95% CI = 1.02 to 4.89) for gallbladder cancer. The corresponding hazard ratio for intrahepatic BTC was 1.69 (95% CI = 0.41 to 7.03).
Conclusions: These findings support the hypothesis that high consumption of sweetened beverages may increase the risk of BTC, particularly gallbladder cancer.

Biliary tract cancers (BTCs) include tumors of the bile ducts within and outside the liver, as well as gallbladder cancer. Little is known about the causes of BTC, but emerging evidence indicates that excess body weight (1–3) and type 2 diabetes (4) may increase the risk of BTC. Moreover, prospective studies have found a strong positive association between fasting blood glucose concentration and risk of BTC and gallbladder cancer (5–7). Consumption of sugar-sweetened beverages, such as soft drinks, raises blood glucose concentration (8,9) and has been associated with weight gain (10) and with increased risk of the metabolic syndrome (11) and type 2 diabetes (11,12) in most but not all studies. Thus, high consumption of sweetened beverages may increase the risk of BTC. To date, only one previous prospective study has examined this hypothesis (13).

The aim of this study was to evaluate the hypothesis that sweetened beverage consumption is positively associated with risk of BTC by using data from two population-based prospective cohorts of Swedish adults. Because sweetened beverages are usually rich in sugar, a secondary aim was to investigate the association between sucrose intake and BTC risk.

Methods

Study Population

The study population comprised women from the Swedish Mammography Cohort (SMC) and men from the Cohort of

Received: December 12, 2015; **Revised:** March 16, 2016; **Accepted:** April 1, 2016

© The Author 2016. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

Downloaded from http://jnci.oxfordjournals.org/ at Oxford University Press USA on July 19, 2016

ARTICLE

Swedish Men (COSM). The SMC began in 1987 to 1990, when a dietary questionnaire was mailed to all women who were born between 1914 and 1948 and who resided in Västmanland and Uppsala counties, central Sweden; 74% of the eligible women answered the questionnaire and gave informed consent to participate in the study. In the autumn of 1997, the 56 030 surviving participants received a new questionnaire that was expanded to include about 350 items concerning diet, lifestyle, and other risk factors for cancer; 39 227 women (70%) answered the questionnaire. Because data on diabetes and smoking were only available in the 1997 questionnaire, only women who completed that questionnaire were included in the present study. Concomitantly in the autumn of 1997, all 100 303 men who were born between 1918 and 1952 and who resided in Västmanland and Örebro counties, central Sweden, were mailed the same diet and lifestyle questionnaire; 48 850 men (49%) completed the questionnaire and provided informed consent to participate. The two cohorts are representative of the Swedish population in 1997 in terms of distribution of age, occurrence of overweight, and educational level (14).

For the present study, 70 832 participants (31 258 women age 49 – 83 years and 39 574 men age 45 – 79 years) were included after the following exclusions: 540 with erroneous or missing personal identification numbers; 81 who died before baseline; 4403 with a prior cancer diagnosis in the Swedish Cancer Register; 6084 with a cholecystectomy before baseline (data from the National Swedish Patient Register) because participants with a gallbladder removal operation were not at risk of developing gallbladder cancer; 5301 with a history of diabetes (defined as a diagnosis in the Swedish National Patient or Diabetes Registers or self-reported) because diabetes patients may have changed their consumption of sweetened beverages after the diagnosis; and 836 with implausible energy intake (ie, 3 SDs from the $\log_e$-transformed mean total energy intake). The Regional Ethical Review Board at Karolinska Institutet (Stockholm, Sweden) approved this study.

Trial registration: The Swedish Mammography Cohort and the Cohort of Swedish Men are registered at clinicaltrials.gov as NCT01127698 and NCT01127711, respectively.

Baseline Data Collection

Information on education, smoking, weight, height, physical activity, alcohol consumption, and diet was obtained through a self-administered questionnaire. Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in m). Total physical activity was assessed with six activities (work/occupation, home/housework, walking/bicycling, exercise, watching TV/reading, and sitting/lying down or sleeping) that were assigned a metabolic equivalent task score for energy expenditure, and reported time was multiplied by these scores and summed over all activities to create a metabolic equivalent hours-per-day (24 hours) score (15).

Assessment of Sweetened Beverage Consumption

Consumption of sweetened beverages and other foods was assessed at baseline (in 1997) with a 96-item semiquantitative food frequency questionnaire (FFQ). The FFQ had one question about sweetened beverages: How many soft drinks or "juice" drinks do you consume per day or per week? Participants were asked to indicate their usual consumption, during the past year, of a standard glass (200 mL) of sweetened beverages. No distinction was made between sugar-sweetened and artificially sweetened (low-calorie) beverages. According to Swedish national consumption data, low-calorie soft drinks and "juice" drinks accounted for 9.9% (in men) to 19.2% (in women) of total soft drink and "juice" drink consumption in 1997 (16). Sweetened beverages did not include fruit juices, energy and sports drinks, or sweetened coffee, tea, or milk. Intake of sucrose and other nutrients was calculated using composition values from the Swedish Food Administration Database (17) and was adjusted for total energy intake by using the residual method (18). All sucrose-containing foods in the FFQ were used in the calculation of sucrose intake, and the calculation was made under the assumption that all sweetened beverages were sweetened with sugar (sucrose).

The FFQ has been validated for nutrient intake in a subsample of men from the study area; the correlation coefficient between estimates from the FFQ and the mean of fourteen 24-hour diet recall interviews was 0.70 for sucrose (19). An FFQ similar to the one used in the present study has been validated in a subsample of 129 women from the SMC; the correlation coefficient between the FFQ and four 1-week diet records was 0.6 for sweetened beverage consumption (A. Wolk, unpublished data).

Case Ascertainment

Incident cases of BTC were ascertained by record linkage with the Swedish Cancer Register, which is at least 96% complete (20). The register contains data on location, histological type, and diagnosis date of all malignant tumors in Sweden. BTC cases were classified according to the 10th Revision of the International Classification of Diseases. Extrahepatic BTC was defined as cancers of the gallbladder (C23.9), ampulla of Vater (C24.1), and extrahepatic bile ducts (C24.0, C24.8, and C24.9). Intrahepatic BTC was defined by the code C22.1.

Statistical Analysis

Participants contributed follow-up time from January 1, 1998, until the date of BTC diagnosis, date of cholecystectomy, death (data acquired from the Swedish Cause of Death Register), or December 31, 2012, whichever came first. In the categorical analysis of sweetened beverage consumption, nonconsumers (referent group) were compared with approximate quartiles of consumption among consumers (0.1–0.4, 0.5–1.9, and ≥2 servings/day). Sweetened beverage consumption was also analyzed as a continuous variable (per 1 serving per day [1 SD]; containing about 20 g sucrose). Sucrose intake was categorized into sex-specific quartiles. Baseline characteristics of the study population by categories of sweetened beverage consumption were age-standardized to the age distribution of the entire study population at baseline. Hazard ratios (HRs) with 95% confidence intervals (CIs) of BTC were estimated using Cox proportional hazards regression models with age as the time scale. All analyses were adjusted for sex by stratification on sex in the Cox model. The multivariable models were further adjusted for education (less than high school, high school, university); smoking (never, past, current) and BMI (<25, 25–29.9, ≥30 kg/m^2) because smoking and high BMI have been associated with an increased risk of gallbladder cancer in previous studies (1–3,21); and total energy intake (kcal/day, continuous) to reduce measurement error because of general over- or under-reporting of food items (18). Other variables considered for inclusion in the multivariable model were intake of protein, total fat, and carbohydrates

ARTICLE

Downloaded from http://jnci.oxfordjournals.org/ at Oxford University Press USA on July 19, 2016

Table 1. Baseline characteristics of the study population (n = 70 832) by categories of sweetened beverage consumption

	Sweetened beverage consumption, servings/d†			
Characteristics*	0 (0)‡	0.1–0.4 (0.3)	0.5–1.9 (1.0)	≥2 (2.1)
No. of participants	37 405	13 383	12 716	7328
Age, mean ± SD, y	60.8 ± 9.4	58.5 ± 8.9	60.3 ± 9.7	61.1 ± 9.9
Men, %	52.0	50.8	64.4	71.1
Postsecondary education, %	20.4	19.9	15.3	11.8
Current smokers, %	25.2	20.2	22.7	26.4
Overweight, %	46.1	48.7	52.5	55.8
Body mass index, mean ± SD, kg/m^2	25 ± 3.5	25 ± 3.5	26 ± 3.5	26 ± 3.7
Total energy intake, mean ± SD, kcal/d	2100 ± 790	2200 ± 760	2500 ± 850	2900 ± 980
Protein intake, mean ± SD, g/d	84 ± 13	81 ± 11	78 ± 11	71 ± 12
Total fat intake, mean ± SD, g/d	70 ± 12	70 ± 11	68 ± 11	63 ± 11
Saturated fat intake, mean ± SD, g/d	32 ± 7.8	32 ± 6.7	31 ± 6.6	28 ± 6.9
Carbohydrate intake, mean ± SD, g/d	240 ± 30	250 ± 27	250 ± 27	270 ± 31
Sucrose intake, mean ± SD, g/d	33 ± 15	40 ± 14	48 ± 16	69 ± 25

*All variables except age are age-standardized.
†One serving corresponds to 200 mL (containing about 20 g sucrose).
‡The value in parentheses is the median consumption.

(all in g/day, sex-specific quartiles); fruit juice, coffee, tea, and milk consumption (in approximate quartiles); alcohol consumption (drinking status and drinks per week); and physical activity (either total physical activity or walking/bicycling and exercise). Only adjustment for protein intake changed the hazard ratios by more than 5% and was included in the multivariable model. The proportional hazards assumption was tested using Schoenfeld residuals and was found to be satisfied.

Tests for trend across categories of sweetened beverage consumption and sucrose intake were performed by assigning the median value to each category and modeling this variable as a continuous variable. To examine whether the results may have been influenced by reverse causality, a sensitivity analysis excluding cases of BTC diagnosed within the first two years of follow-up was performed. In an additional sensitivity analysis, participants with a history of diabetes were included in the analysis. Potential effect modification by sex and BMI (<25 kg/m^2 or ≥ 25 kg/m^2) was tested by introducing an interaction term into the multivariable model that also included sweetened beverage consumption (as a continuous variable) and the modifying variable. The statistical significance of the interactions was tested by using the likelihood ratio test that compared models with and without the interaction term.

SAS version 9.4 (SAS Institute Inc, Cary, NC) was used for the statistical analyses. All statistical tests were two-tailed, and a *P* value of less than .05 was interpreted as statistically significant.

Results

During a mean follow-up of 13.4 years (951 523 person-years) of 70 832 women and men (55.9% men), 127 incident extrahepatic BTC case patients (83 in women and 44 in men), including 71 gallbladder cancer case patients (54 in women and 17 in men) and 21 intrahepatic BTC case patients (11 in women and 10 in men), were ascertained. The mean (± SD) consumption of sweetened beverages was 0.5 (± 1.1) servings per day in the whole study population and 1.1 (± 1.3) servings per day among consumers. Compared with nonconsumers of sweetened beverages, participants with high consumption (≥2 servings/day) were less likely to have a postsecondary education, were more likely to be overweight, and had, on average, higher intakes of total energy, carbohydrates, and sucrose and lower intakes of protein and fat (Table 1).

High consumption of sweetened beverages was associated with a statistically significantly increased risk of extrahepatic BTC and gallbladder cancer (Table 2). The multivariable hazard ratios for women and men who consumed two or more servings per day of sweetened beverages compared with nonconsumers were 1.79 (95% CI = 1.02 to 3.13) for extrahepatic BTC and 2.24 (95% CI = 1.02 to 4.89) for gallbladder cancer. The age- and sex-adjusted incidence rates of gallbladder cancer for participants who had the highest (≥2 servings/day) and lowest (0 servings/day) consumption of sweetened beverages were, respectively, 12 and six per 100 000 person-years. Sweetened beverage consumption was not associated with risk of nongallbladder extrahepatic BTC (n = 56 case patients; multivariable RR for the highest vs the lowest category = 1.40, 95% CI = 0.62 to 3.13) (data not shown) or intrahepatic BTC (1.69; 95% CI = 0.41 to 7.03) (Table 2).

The multivariable HR of gallbladder cancer per one-serving-per-day increment of sweetened beverage consumption was 1.24 (95% CI = 1.05 to 1.47) (Table 2). In sensitivity analyses, the results persisted after exclusion of BTC case patients diagnosed within the first two years of follow-up (HR of gallbladder cancer per 1 serving per day = 1.26, 95% CI = 1.06 to 1.49) and when participants with diabetes were included in the analysis (corresponding HR [also adjusted for diabetes] = 1.22, 95% CI = 1.03 to 1.43). When other beverages (fruit juice, coffee, tea, and milk) were included in the multivariable model, the hazard ratio of gallbladder cancer for each one-serving-per-day increment of sweetened beverage consumption was 1.23 (95% CI = 1.04 to 1.46). The association between sweetened beverage consumption and gallbladder cancer was not modified by sex ($P_{\text{interaction}}$ = .82) or BMI ($P_{\text{interaction}}$ = .55). For example, the multivariable hazard ratios of gallbladder cancer for each one-serving-per-day increment of sweetened beverage consumption were 1.25 (95% CI = 1.00 to 1.56) in individuals with BMIs of less than 25 kg/m^2 and 1.26 (95% CI = 0.97 to 1.64) in those with BMIs of 25 kg/m^2 or more (data not shown).

Sucrose intake was statistically significantly positively associated with risk of gallbladder cancer but not with extrahepatic or intrahepatic BTC. Compared with the lowest quartile of sucrose intake (referent group; mean intake = 20.2 g/day), the multivariable hazard ratios of gallbladder cancer were 2.05 (95%

Downloaded from http://jnci.oxfordjournals.org/ at Oxford University Press USA on January 19, 2016

ARTICLE

Table 2. Adjusted hazard ratios (and 95% CIs) of biliary tract cancer according to sweetened beverage consumption in 70 832 Swedish women and men free of cancer and without a history of diabetes and cholecystectomy at baseline (follow-up 1998-2012)

	Extrahepatic biliary tract cancer (n = 127)				Gallbladder cancer (n = 71)			Intrahepatic biliary tract cancer (n = 21)		
Servings of sweetened beverages*	No. cases	Person-years	Age & sex-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)†	No. cases	Age & sex-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)†	No. cases	Age & sex-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)†
0	61	501 535	1.00 (referent)	1.00 (referent)	32	1.00 (referent)	1.00 (referent)	10	1.00 (referent)	1.00 (referent)
0.1–0.4/d	23	184 679	1.16 (0.72 to 1.88)	1.15 (0.71 to 1.87)	13	1.28 (0.67 to 2.44)	1.28 (0.67 to 2.46)	3	0.90 (0.25 to 3.26)	0.86 (0.23 to 3.15)
0.5–1.9/d	23	170 239	1.26 (0.78 to 2.04)	1.20 (0.72 to 1.97)	16	1.76 (0.96 to 3.21)	1.78 (0.96 to 3.32)	5	1.58 (0.54 to 4.64)	1.48 (0.49 to 4.50)
≥2/d	20	95 070	1.96 (1.18 to 3.27)	1.79 (1.02 to 3.13)	10	2.01 (0.98 to 4.10)	2.24 (1.02 to 4.89)	3	1.68 (0.46 to 6.16)	1.69 (0.41 to 7.03)
P_{trend}‡			.01	.05		.02	.02		.31	.37
Per serving			1.16 (1.03 to 1.31)	1.14 (0.99 to 1.30)		1.20 (1.03 to 1.39)	1.24 (1.05 to 1.47)		1.10 (0.79 to 1.53)	1.10 (0.75 to 1.61)

*One serving of sweetened beverages corresponds to 200 mL. CI = confidence interval; HR = hazard ratio.

†The hazard ratios were adjusted for age, sex education (less than high school, high school, university), smoking (never, past, current), body mass index (<25, 25–29.9, ≥30 kg/m^2), dietary protein intake (g/day, sex-specific quartiles), and total energy intake (kcal/day, continuous).

‡Calculated by treating median consumption in each category as a continuous variable. All statistical tests are two-sided.

CI = 0.88 to 4.79) for the second quartile (mean intake = 31.9 g/day), 2.22 (95% CI = 0.95 to 5.15) for the third quartile (mean intake = 42.6 g/day), and 2.55 (95% CI = 1.08 to 6.00) for the highest quartile (mean intake = 67.2 g/day) (P_{trend} = .05) (data not shown).

Discussion

In this prospective study of Swedish adults, sweetened beverage consumption was positively associated with risk of BTC, in particular gallbladder cancer. Compared with no consumption, daily consumption of two or more servings of sweetened beverages was associated with a 2.2-fold increased risk of gallbladder cancer. Results were robust in sensitivity analyses and were not modified by sex or BMI. Sweetened beverages often contain high levels of sucrose, which was also positively associated with risk of gallbladder cancer.

Sweetened beverage consumption may increase gallbladder cancer risk directly through blood glucose and insulin concentrations and indirectly through associated gallbladder cancer risk factors such as obesity and diabetes. Consumption of sugar-sweetened beverages acutely raises fasting blood glucose (8,9) and insulin concentrations (8). Findings from prospective studies have shown that fasting blood glucose concentration is positively associated with risk of gallbladder and bile duct cancer, with over a three-fold to five-fold increased risk observed in individuals with a fasting blood glucose concentration above 6 mmol/L (5–7). The biological mechanisms that may link elevated blood glucose concentration to gallbladder cancer risk are unclear, but growth-promoting effects of insulin and insulin-like growth factors are possible mechanisms. The insulin-like growth factor-I receptor is frequently expressed in carcinomas of the gallbladder and biliary tract and is associated with poor prognosis (22,23).

Sugar-sweetened beverage consumption has been positively associated with weight gain (24) and risk of developing type 2 diabetes (11) and the metabolic syndrome (11). Available data indicate that obesity (1–3) and type 2 diabetes (4) may increase the risk of gallbladder cancer by approximately 40% to 65%. Thus, obesity and type 2 diabetes are not as strongly associated with gallbladder cancer risk as blood glucose concentration. This may suggest that the observed association between sweetened beverage consumption and gallbladder cancer likely is mediated to a large extent via elevated blood glucose and circulating insulin more so perhaps than indirectly via obesity and type 2 diabetes.

Another potential mechanism whereby high intakes of sweetened beverages and sucrose might increase the risk of gallbladder cancer is through gallstone disease, which is strongly positively associated with risk of gallbladder cancer (25). A large prospective study observed that a high sucrose intake was associated with a statistically significantly increased risk of symptomatic gallstone disease (26). Furthermore, prospective studies have reported a positive association between diets with high glycemic load, a measure of the glycemic responses of foods, and risk of symptomatic gallstone disease (26,27).

Only one previous prospective study has, to the best of our knowledge, investigated the association between sweetened beverage consumption and BTC risk (13). In that prospective study of 477 206 adults (including 236 case patients of extrahepatic BTC, of which 87 case patients were gallbladder cancers) from 10 European countries, combined sugar-sweetened and artificially sweetened beverage (carbonated/soft/isotonic drinks

Downloaded from http://jnci.oxfordjournals.org/ at Oxford University Press USA on July 19, 2016

and diluted syrups) consumption was not associated with risk of BTC (13). A potential explanation for the disparate findings might be related to a higher proportion of artificially sweetened beverage consumption in the European cohort than in the Swedish cohort. In Sweden in 1997 (baseline for this study), low-calorie sweetened beverages accounted for about 10% in men and 19% in women of total sweetened beverage consumption (16). Among participants in the European cohort who daily consumed sweetened beverages, the proportion of artificially sweetened beverage consumption was 36% in nondiabetics and 74% in diabetics. In the present study, a statistically significantly increased risk of gallbladder cancer was observed only at a daily consumption of two or more servings of sweetened beverages. It is possible that the current study was able to detect a relation between sweetened beverage consumption and gallbladder cancer because a relatively large proportion (22%) of participants daily consumed sweetened beverages and 10% consumed two or more servings per day. Among nondiabetics in the European cohort, only 2.8% daily consumed sugar-sweetened beverages and 1.6% daily consumed artificially sweetened beverages (13).

Strengths of this study are the prospective design and the almost complete and objective ascertainment of BTC case patients by linkage with the Swedish Cancer Register. A shortcoming is the observational design. Thus, the possibility that residual confounding may have influenced the results cannot be ruled out. Another limitation is that sweetened beverage consumption was measured at baseline only and with the use of a self-administered questionnaire that did not distinguish between sugar-sweetened and artificially sweetened beverages. Therefore, some misclassification of consumption of sweetened beverages, in particular sugar-sweetened beverages, was inevitable, and this may have attenuated the associations observed. A further limitation is that dietary sucrose intake was calculated under the assumption that sweetened beverages were sugar-sweetened, thus resulting in an overestimation of sucrose intake and subsequently an underestimation of per-unit risk increase. Despite the large sample size and relatively long follow-up, the number of BTC case patients was limited and contributed to wide confidence intervals. Finally, participants were middle-aged and older Swedish adults, potentially limiting the generalizability of these results to other populations.

The association of sweetened beverage consumption with risk of other cancers associated with obesity and type 2 diabetes, such as pancreatic, colon, and endometrial cancer, has been investigated previously in these Swedish cohorts (28–30). Sweetened beverage consumption was positively associated with risk of pancreatic cancer (28) but not colon (29) or endometrial cancer (30). Thus, it does not appear to be a general, nonspecific relation between sweetened beverage consumption and other cancers.

In conclusion, findings from this prospective study support the hypothesis that high consumption of sweetened beverages is associated with an increased risk of BTC, particularly gallbladder cancer. Further studies of the relation between sweetened beverage consumption, preferably separately for sugar-sweetened and artificially sweetened drinks, and risk of BTC and gallbladder cancer specifically are warranted.

Funding

This work was supported by the Swedish Research Council/Council for Research Infrastructures, a Young Scholars Award from the Strategic Research Area in Epidemiology at Karolinska Institutet, and the Swedish Cancer Foundation.

Notes

The study sponsor had no role in the design of the study; the data collection, analysis, or interpretation; the writing of the article; or the decision to submit for publication.

References

1. Larsson SC, Wolk A. Obesity and the risk of gallbladder cancer: a meta-analysis. *Br J Cancer*. 2007;96(9):1457–1461.
2. Park M, Song da Y, Je Y, Lee JE. Body mass index and biliary tract disease: a systematic review and meta-analysis of prospective studies. *Prev Med*. 2014;65:13–22.
3. Tan W, Gao M, Liu N, Zhang G, Xu T, Cui W. Body mass index and risk of gallbladder cancer: systematic review and meta-analysis of observational studies. *Nutrients*. 2015;7(10):8321–8334.
4. Gu J, Yan S, Wang B, et al. Type 2 diabetes mellitus and risk of gallbladder cancer: a systematic review and meta-analysis of observational studies. *Diabetes Metab Res Rev*. 2016;32(1):63–72.
5. Rapp K, Schroeder J, Klenk J, et al. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. *Diabetologia*. 2006;49(5):945–952.
6. Stocks T, Rapp K, Bjorge T, et al. Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts. *PLoS Med*. 2009;6(12):e1000201.
7. Borena W, Edlinger M, Bjorge T, et al. A prospective study on metabolic risk factors and gallbladder cancer in the metabolic syndrome and cancer (Me-Can) collaborative study. *PLoS One*. 2014;9(2):e89368.
8. Janssens JP, Shapira N, Debeuf P, et al. Effects of soft drink and table beer consumption on insulin response in normal teenagers and carbohydrate drink in youngsters. *Eur J Cancer Prev*. 1999;8(4):289–295.
9. Aeberli I, Gerber PA, Hochuli M, et al. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. *Am J Clin Nutr*. 2011;94(2):479–485.
10. Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. *Am J Clin Nutr*. 2013;98(4):1084–1102.
11. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care*. 2010;33(11):2477–2483.
12. Imamura F, O'Connor L, Ye Z, et al. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. *BMJ*. 2015;351:h3576.
13. Stepien M, Duarte-Salles T, Fedirko V, et al. Consumption of soft drinks and juices and risk of liver and biliary tract cancers in a European cohort. *Eur J Nutr*. 2014;55(1):7–20.
14. Stackelberg O, Bjorck M, Larsson SC, Orsini N, Wolk A. Sex differences in the association between smoking and abdominal aortic aneurysm. *Br J Surg*. 2014;101(10):1230–1237.
15. Norman A, Bellocco R, Bergstrom A, Wolk A. Validity and reproducibility of self-reported total physical activity-differences by relative weight. *Int J Obes Relat Metab Disord*. 2001;25(5):682–688.
16. Larsson SC, Akesson A, Wolk A. Sweetened beverage consumption is associated with increased risk of stroke in women and men. *J Nutr*. 2014;144(6):856–860.
17. Bergström L, Kylberg E, Hagman U, Erikson H, Bruce Å. The food composition database KOST: the National Administration's information system for nutritive values of food. *Vår Föda*. 1991;43:439–447.
18. Willett W, Stampfer M. *Implications of total energy intake for epidemiologic analyses in Nutritional epidemiology*, W. C. Willett, ed. Oxford, UK: Oxford University Press; 1998, 273–301.
19. Messerer M, Johansson SE, Wolk A. The validity of questionnaire-based micronutrient intake estimates is increased by including dietary supplement use in Swedish men. *J Nutr*. 2004;134(7):1800–1805.
20. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncol*. 2009;48(1):27–33.
21. Yagyu K, Kikuchi S, Obata Y, et al. Cigarette smoking, alcohol drinking and the risk of gallbladder cancer death: a prospective cohort study in Japan. *Int J Cancer*. 2008;122(4):924–929.
22. Kornprat P, Rehak P, Ruschoff J, Langner C. Expression of IGF-I, IGF-II, and IGF-IR in gallbladder carcinoma. A systematic analysis including primary and corresponding metastatic tumours. *J Clin Pathol*. 2006;59(2):202–206.
23. Suzuki H, Roa JC, Kawamoto T, et al. Expression of insulin-like growth factor I receptor as a biomarker for predicting prognosis in biliary tract cancer patients. *Mol Clin Oncol*. 2015;3(3):464–470.
24. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. *N Engl J Med*. 2011;364(25):2392–2404.

Downloaded from http://jnci.oxfordjournals.org/ at Oxford University Press USA on July 19, 2016

25. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. *Int J Cancer*. 2006;118(7): 1591–1602.
26. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Glycemic load, glycemic index, and carbohydrate intake in relation to risk of cholecystectomy in women. *Gastroenterology*. 2005;129(1):105–112.
27. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Dietary carbohydrates and glycaemic load and the incidence of symptomatic gall stone disease in men. *Gut*. 2005;54(6):823–828.
28. Larsson SC, Bergkvist L, Wolk A. Consumption of sugar and sugar-sweetened foods and the risk of pancreatic cancer in a prospective study. *Am J Clin Nutr*. 2006;84(5):1171–1176.
29. Zhang X, Albanes D, Beeson WL, et al. Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies. *J Natl Cancer Inst*. 2010;102(11):771–783.
30. Friberg E, Wallin A, Wolk A. Sucrose, high-sugar foods, and risk of endometrial cancer-a population-based cohort study. *Cancer Epidemiol Biomarkers Prev*. 2011;20(9):1831–1837.

Downloaded from http://jnci.oxfordjournals.org/ at Oxford University Press USA on July 19, 2016