Research Article

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Body Size Indicators and Risk of Gallbladder Cancer: Pooled Analysis of Individual-Level Data from 19 Prospective Cohort Studies

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Abstract

Background: There are few established risk factors for gallbladder cancer beyond gallstones. Recent studies suggest a higher risk with high body mass index (BMI), an indicator of general heaviness, but evidence from other body size measures is lacking.

Methods: Associations of adult BMI, young adult BMI, height, adult weight gain, waist circumference (WC), waist–height ratio (WHtR), hip circumference (HC), and waist–hip ratio (WHR) with gallbladder cancer risk were evaluated. Individual-level data from 1,878,801 participants in 19 prospective cohort studies (14 studies had circumference measures) were harmonized and included in this analysis. Multivariable Cox proportional hazards regression estimated hazard ratios (HR) and 95% confidence intervals (CI).

Results: After enrollment, 567 gallbladder cancer cases were identified during 20.1 million person-years of observation, including 361 cases with WC measures. Higher adult BMI (per 5 kg/m^2, HR: 1.24; 95% CI, 1.13–1.35), young adult BMI (per 5 kg/m^2, HR: 1.12; 95% CI, 1.00–1.26), adult weight gain (per 5 kg, HR: 1.07; 95% CI, 1.02–1.12), height (per 5 cm, HR: 1.10; 95% CI, 1.03–1.17), WC (per 5 cm, HR: 1.09; 95% CI, 1.02–1.17), WHtR (per 0.1 unit, HR: 1.24; 95% CI, 1.00–1.54), and HC (per 5 cm, HR: 1.13; 95% CI, 1.04–1.22), but not WHR (per 0.1 unit, HR: 1.03; 95% CI, 0.87–1.22), were associated with higher risks of gallbladder cancer, and results did not differ meaningfully by sex or other demographic/lifestyle factors.

Conclusions: These findings indicate that measures of overall and central excess body weight are associated with higher gallbladder cancer risks.

Impact: Excess body weight is an important, and potentially preventable, gallbladder cancer risk factor. *Cancer Epidemiol Biomarkers Prev; 26(4); 597–606. ©2017 AACR.*

Introduction

Gallbladder cancer etiology is poorly understood, with only a few, mostly nonmodifiable, established risk factors, including older age, female sex, abnormal pancreaticobiliary junction, and history of cholesterol gallstones (1). Identifying modifiable risk factors for gallbladder cancer is hindered by its rarity and poor prognosis. In more-developed areas, such as the United States, Australia, and Western Europe, incidence rates are 1 to 2 cases per 100,000 persons each year, whereas in certain high-risk populations, such as Mapuche Indians in South America, incidence rates exceed 20 per 100,000 (2). Overall 5-year relative survival is approximately 18% for U.S. adults diagnosed with gallbladder

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cancer, and the overall median survival time is 3 to 7 months (3). The poor prognosis is due, in part, to the lack of specific symptoms for the disease. Early-staged gallbladder cancers are uncommon and are typically only detected incidentally during cholecystectomy for gallstones, but only 1% to 3% of patients with gallstones will ever develop gallbladder cancer (4).

Because excess body weight is a risk factor for gallstones and several other digestive system cancers (e.g., colorectum, liver, and pancreas; refs. 5–9), it is a plausible risk factor for gallbladder cancer. The 2015 World Cancer Research Fund's Continuous Update Project (CUP) on gallbladder cancer concluded that body fatness, as defined by high body mass index (BMI), is a "probable" risk factor for gallbladder cancer (10). The CUP identified eight prospective cohort studies (11–18) that contributed to dose–response meta-analyses and reported that each 5 kg/m^2 increase in BMI was associated with a 25% higher risk of gallbladder cancer. Of those eight studies, four provided relative risks (RR) for BMI that were not statistically significant (11, 12, 14, 15), and two included biliary system cancer mortality as the main outcome (14, 18). Waist circumference (WC), an indicator of central adiposity that might be more etiologically relevant to cancers of the digestive system, has been evaluated by only one relatively small study (76 cases) that reported higher risks with increasing waist circumference (11).

Because the evidence base for overall body fatness (based on BMI) and gallbladder cancer risk is considered probable and not convincing, and because risk estimates for indicators of central adiposity and other non-BMI measures of body size are especially rare, we conducted a pooled analysis of data from 19 prospective cohort studies based in the United States, Europe, Australia, and Asia to investigate associations of BMI (at enrollment during adulthood and recalled from young-adulthood), height, adult weight gain, waist circumference, waist–height ratio, hip circumference, and waist–hip ratio with gallbladder cancer risk.

Materials and Methods

Study population

All member studies of the NCI Cohort Consortium (http://epi.grants.cancer.gov/Consortia/cohort.html) with body size data were invited to participate, and 19 prospective cohort studies were included in this analysis: Physicians' Health Study (PHS); NIH-AARP Diet and Health Study (NIH-AARP); Agricultural Health Study (AHS); Breast Cancer Detection Demonstration Project Follow-Up Study (BCDDP); Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO); Women's Health Study (WHS); New York University Women's Health Study (NYUWHS); Cancer Prevention Study-II Nutrition Cohort (CPS-II); Iowa Women's Health Study (IWHS); California Teachers Study (CTS); European Prospective Investigation into Cancer and Nutrition (EPIC); Melbourne Collaborative Cohort Study (MCCS); Cohort of Swedish Men (COSM); Swedish Mammography Cohort (SMC); The Sister Study (SISTER); Shanghai Men's Health Study (SMHS); Shanghai Women's Health Study (SWHS); VITamins And Lifestyle (VITAL) Study; and Women's Lifestyle and Health Study (WLHS). Participants gave written informed consent at enrollment, or consent was implied from the return of questionnaires. All studies were approved by the institutional review boards of their host centers.

All studies submitted de-identified, participant-level data from their entire cohort study to the data coordinating center. Data were centrally harmonized and pooled for analyses. Prior to exclusions, participant-level data were provided for 2,213,174 men and women. The following exclusions were applied: missing age at study entry, or baseline age less than 18 years, or older than 85 years ($n = 5{,}501$); less than 1 year of follow-up time ($n = 51{,}399$); missing BMI ($n = 147, 552$); BMI less than 15 kg/m^2 or greater than 60 kg/m^2 ($n = 2{,}110$); missing height ($n = 26{,}698$); height less than 122 cm or greater than 244 cm ($n = 137$); and prevalent cancer at baseline ($n = 100{,}976$). Data from 1,878,801 participants comprised the analytic cohort.

Gallbladder cancer diagnoses International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10: C23.9; ref. 19) were verified after enrollment by linking to state/provincial/federal cancer or death registries and/or medical record abstraction.

Exposures

Height and weight were self-reported in most cohorts and directly measured in others (MCCS, SMHS, SWHS, EPIC, SISTER); BMI was calculated as weight (kg) divided by height squared (m^2) and categorized according to World Health Organization criteria (20): underweight (15 < 18.5 kg/m^2), normal weight (18.5 < 25 kg/m^2), overweight (25 < 30 kg/m^2), and obese (≥30 kg/m^2). Obesity was additionally stratified as classes I (30–34.9 kg/m^2), II (35–39.9 kg/m^2), and III (≥40 kg/m^2). Young adult BMI was available from 10 of the cohort studies (NIH-AARP, AHS, COSM, CPS-II, IWHS, MCCS, PLCO, SMC, VITAL, and WLHS), derived from recalled weight at ages 18 to 21 years, and categorized as above for adult BMI. Height, in cm, was categorized into four groups for women (<160, 160 < 165, 165 < 170, and ≥170) and men (<170, 170 < 175, 175 < 180, and ≥180). Adult weight gain was estimated by subtracting young adult weight from baseline weight, both in kg, and categorized as: any weight loss, weight stable (0 kg change) or weight gain of ≤5, weight gain of 6 to 10, weight gain of 11 to 15, weight gain of 16 to 20, and weight gain of ≥21.

Waist circumference and hip circumference were measured by trained staff (EPIC, MCCS, NYUWHS, SISTER, SMHS, SWHS) or self-measured by participants who were given instructions on the protocol [NIH-AARP, BCDDP, COSM, CTS, IWHS, CPS-II (waist circumference only), WLHS, and SMC]. The remaining five cohort studies did not collect waist circumference or hip circumference data. Waist circumference and hip circumference were available at baseline enrollment for COSM, IWHS, MCCS, SISTER, SMC, SMHS, SWHS, and WLHS, whereas NIH-AARP, BCDDP, CPS-II (waist circumference only), CTS, EPIC, and NYUWHS collected these data 1 to 8 years after baseline. Participants with waist or hip circumference measures below 50 cm or above 190 cm were excluded from the relevant analysis ($n = 1{,}329$ and $n = 345$ were excluded from waist and hip circumference analyses, respectively). Waist circumference, in cm, was categorized in four predefined groups (women: 50–<70, 70–<80, 80–<90, and 90–<191; men: 50–<90, 90–<100, 100–<110, and 110–<191). Hip circumference, in cm, was also categorized in four predefined groups (women: 50–<90, 90–<100, 100–<110, and 110–<191; men: 50–<95, 95–<105, 105–<115, and 115–<191). Waist–height ratio was calculated by dividing waist by height, both in cm, and categorized as <0.45, 0.45–<0.50, 0.50–<0.55, and ≥0.55 for women and <0.50, 0.50–<0.55, 0.55–<0.60, and ≥0.60 for men. Waist–hip ratio was calculated by dividing waist circumference by hip circumference, both in cm, and categorized into four groups

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for women (<0.75, 0.75–<0.80, 0.80–<0.85, and ≥0.85) and men (<0.90, 0.90–<0.95, 0.95–<1.00, and ≥1.00).

Smoking was defined according to baseline cigarette smoking status and categorized as never, former, current, or missing. Alcohol consumption was defined as nondrinker and, among persons who consumed alcohol, in categories of grams per day (grams/day: <10, 10–<20, 20–<30, and 30+), or missing. Race was self-identified and categorized as white, black/African American, and all other races including those who did not report race. Physical activity was categorized into study-specific quintiles or missing. Education was categorized as less than high school, high school graduate, some college, college graduate or more, or missing. Sex (men, women) and history of gallstones (yes, no) were defined as binary variables. Missing data were treated with an indicator variable.

Statistical analysis

Cox proportional hazards regression models estimated hazard ratios (HR) and 95% confidence intervals (CI) for the associations of body size variables with gallbladder cancer risk. Follow-up time for both BMI measures and height began on the date of enrollment when height and weight were first reported, whereas follow-up time for waist circumference, hip circumference, waist–height circumference, and waist–hip ratio analyses began on the date waist/hip circumference was evaluated. Cases that were diagnosed after baseline but before the time of waist/hip circumference assessment were excluded from those analyses. Studies that did not collect waist/hip circumference data were omitted from the respective analyses. All statistical models were analyzed from a pooled cohort of the combined studies with individual-level data. Initially, Cox models included only baseline age, study, and sex as covariates. Subsequently, more comprehensive models included age, study, sex, alcohol consumption, race, education, physical activity, and smoking status. An additional, more comprehensively adjusted model also included personal history of gallstones. Waist circumference, waist–height ratio, hip circumference, and waist–hip ratio are presented with and without adjustment for BMI. Adult weight gain statistical models included young adult BMI. Linear models estimated associations of continuous body size measures (per unit increase and per 1 SD) with gallbladder cancer risk. Wald tests assessed linear trends.

Sensitivity analyses excluded gallbladder cancers that were diagnosed in the first 2 and 5 years after baseline to evaluate potential bias from prediagnosis weight loss due to disease progression. Sensitivity analyses also evaluated the impact of excluding participants who were diagnosed with gallstones at baseline. Two-stage individual participant meta-analyses explored potential heterogeneity of HRs across studies for continuous body size measures. Meta-analysis methods also evaluated potential heterogeneity according to region of study origin [i.e., North America (NIH-AARP, AHS, BCDDP, CPS-II, CTS, NYUWHS, PHS, PLCO, SISTER, VITAL, and WHS), Europe (COSM, EPIC, SMC, and WLHS), Asia (SMHS and SWHS), and Australia (MCCS)] and BMI assessment method (i.e., self-reported vs. directly measured weight and height) for the association between adult BMI and gallbladder cancer risk.

Interaction terms with the main exposures (continuous terms) and time tested the proportional hazards assumption of the Cox models. No interactions were observed. Restricted cubic splines evaluated potential nonlinearity of the associations for body size measures with gallbladder cancer risk. All *P* values were two sided; *P* values less than 0.05 were considered statistically significant. SAS software was used for all statistical analyses (SAS Institute Inc., version 9.4).

Results

In this analysis of 1.88 million adults enrolled in 19 prospective cohort studies, 567 gallbladder cancers occurred during 20.1 million person-years of observation. For analyses of waist circumference/waist–height ratio and hip circumference, 361 and 318 cases were identified, respectively. Table 1 shows baseline characteristics of participants: mean age was 56.7 years, mean BMI at baseline was 26.1 kg/m^2, mean waist circumference was 86.5 cm, 71% reported any alcohol intake, and 15.6% were current smokers.

The overall and sex-specific associations between adult BMI and gallbladder cancer risk are shown in Table 2. Compared with a normal adult BMI at baseline, overweight, class I obesity, class II obesity, and class III obesity were associated with 27%, 53%, 86%, and 131% higher risks of gallbladder cancer, respectively, after adjusting for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones. There was no indication that risks differed meaningfully by sex (*P* interaction, 0.89). There was no statistically significant evidence of between-study heterogeneity for adult BMI (I^2: 0%; *P* value, 0.49; Supplementary Fig. S1). HRs for continuous adult BMI from both the pooled cohort approach (Table 2) and from the two-stage individual participant meta-analysis (Supplementary Fig. S1) yielded similar results. Restricted cubic spline analyses supported a linear association (Fig. 1; *P* value for linearity: <0.0001; *P* value for nonlinearity: 0.95).

There was evidence supporting a positive association between young adult BMI (modeled as a continuous measure) and gallbladder cancer risk (HR, 1.12, per 5 kg/m^2), although the prevalence of obesity was lower than at baseline enrollment, as expected, and the sex-specific obese categories contained few cases (Table 2). Adult weight gain also was positively associated with risk (HR, 1.07, per 5 kg). The continuous model for height showed a 10% increased risk with each 5 cm increase. There was no evidence of statistically significant interactions for sex and young adult BMI, height or adult weight gain (all *P* values for interaction ≥0.23) or of between-study heterogeneity for young adult BMI (I^2: 0%; *P* value: 0.72; Supplementary Fig. S2), height (I^2: 28%; *P* value: 0.13; Supplementary Fig. S3), or adult weight gain (I^2: 6%; *P* value: 0.39; Supplementary Fig. S4). Restricted cubic spline analyses confirmed linear associations of young adult BMI, adult weight gain, and height with gallbladder cancer risk and demonstrated no evidence of nonlinearity (all *P* values for linearity: <0.0001; all *P* values for nonlinearity: ≥0.30).

Associations of waist circumference, waist–height ratio, hip circumference, and waist–hip ratio overall and by sex with gallbladder cancer risk are shown in Table 3. Although sample sizes were smaller for the waist and hip circumference–related measures than for the weight- and height-related measures, statistically significant positive associations were identified for continuous measures of waist circumference (HR, 1.09, per 5 cm), waist–height ratio (HR, 1.24, per 0.1), and hip circumference (HR, 1.13, per 5 cm). Waist–hip ratio was not statistically significantly associated with risk. Associations were similar when stratified by sex (all *P* values for interaction: ≥0.34). There was no statistically significant evidence of between-study heterogeneity for waist

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Table 1. Summary of cohort studies included in the Rare Cancer Collaboration (gallbladder cancer)

Study name (acronym)	Gender	Baseline cohort sample size *N*	Gallbladder cancer case *N*	Baseline age Mean (SD)	Baseline BMI (kg/m^2) Mean (SD)	Baseline BMI $\geq$30 kg/m^2 %	WC (cm)[a] Mean (SD)	Baseline WC Men: $\geq$110 cm Women: $\geq$90 cm[a] %	Current cigarette smoker[a] %	Alcohol intake (g/day) among drinkers[a] Mean (SD)	Any alcohol intake[a] %	History of gallstones[a] %
NIH-AARP Diet and Health Study	Women	191,306	57	61.3 (5.4)	26.9 (5.6)	23.3	84.6 (13.4)	30.7	14.5	8.5 (20.9)	70.6	13.7
(NIH-AARP)	Men	296,183	53	61.5 (5.4)	27.3 (4.2)	21.4	97.9 (11.0)	13.0	11.0	22.9 (51.1)	78.9	6.5
Agricultural Health Study (AHS)	Women	21,643	4	46.7 (12.0)	25.9 (4.9)	18.6	–	–	10.1	2.9 (6.1)	55.6	–
	Men	20,464	4	47.4 (13.0)	27.5 (4.1)	23.4	–	–	14.3	8.3 (14.6)	67.5	–
The Breast Cancer Detection Demonstration Project (BCDDP)	Women	37,793	8	61.2 (8.0)	25.1 (4.6)	13.2	81.9 (11.8)	21.2	12.8	8.0 (14.2)	48.9	12.4
Cohort of Swedish Men (COSM)	Men	42,790	9	60.0 (9.6)	25.8 (3.4)	10.1	96.0 (10.1)	9.0	24.7	15.4 (23.5)	91.3	11.3
Cancer Prevention Study-II (CPS-II)	Women	80,354	43	62.1 (6.6)	25.6 (4.7)	15.7	86.3 (13.0)	35.1	8.6	9.0 (13.1)	52.4	17.1
	Men	71,304	21	63.9 (6.1)	26.4 (3.7)	14.4	98.8 (10.1)	12.7	9.1	17.1 (21.6)	65.7	9.0
California Teachers Study (CTS)	Women	103,811	21	51.4 (13.5)	24.8 (5.0)	13.9	81.7 (13.0)	23.6	5.0	11.3 (9.7)	66.7	6.4
European Prospective	Women	254,169	61	50.4 (10.7)	25.5 (4.6)	15.2	81.2 (11.5)	21.4	20.2	9.6 (12.0)	83.6	9.2
Investigation into Cancer and Cancer and Nutrition (EPIC)	Men	143,357	24	51.7 (10.1)	26.5 (3.7)	15.5	95.1 (10.3)	8.1	29.9	21.8 (23.7)	93.4	4.2
Iowa Women's Health Study (IWHS)	Women	37,506	54	61.5 (4.2)	26.1 (4.9)	18.5	69.4 (10.9)	4.9	14.7	8.9 (13.1)	43.6	–
Melbourne Collaborative Cohort	Women	22,197	17	54.3 (8.6)	26.8 (4.9)	22.3	80.1 (11.8)	20.0	9.0	12.4 (14.2)	57.6	12.2
Study (MCCS)	Men	15,537	4	54.9 (8.8)	27.2 (3.6)	19.1	93.5 (10.0)	6.2	14.8	24.7 (25.3)	81.3	4.7
New York University Women's Health Study (NYUWHS)	Women	13,211	4	50.2 (8.7)	24.9 (4.6)	12.7	75.1 (11.7)	10.8	18.0	13.3 (14.4)	42.0	5.0
Physicians' Health Study (PHS)	Men	28,108	7	54.7 (9.7)	25.1 (3.0)	6.2	–	–	9.2	–	–	3.7
Prostate, Lung, Colorectal and	Women	68,905	22	62.5 (5.4)	27.1 (5.5)	24.9	–	–	9.5	5.6 (14.0)	99.9	16.7
Ovarian Cancer Screening Trial (PLCO)	Men	68,964	15	62.7 (5.3)	27.6 (4.2)	23.4	–	–	11.5	16.5 (33.1)	99.9	7.5
The Sister Study (SISTER)	Women	47,551	3	55.0 (9.0)	27.8 (6.2)	29.6	86.3 (14.7)	36.0	8.3	6.8 (10.0)	95.4	14.5
Swedish Mammography Cohort (SMC)	Women	33,718	32	61.3 (9.1)	25.0 (4.0)	10.6	83.6 (10.7)	26.4	23.6	6.9 (10.2)	83.5	19.7
Shanghai Men's Health Study (SMHS)	Men	60,885	19	54.8 (9.7)	23.7 (3.1)	2.6	85.1 (8.7)	0.5	58.7	35.4 (32.3)	33.4	7.5
Shanghai Women's Health Study (SWHS)	Women	74,460	57	52.1 (9.1)	24.0 (3.4)	5.2	77.9 (8.8)	10.4	2.4	10.4 (13.9)	1.9	11.3
Vitamins and Lifestyle Study	Women	30,842	7	60.7 (7.4)	27.2 (5.8)	25.3	–	–	7.6	9.4 (13.1)	57.9	–
(VITAL)	Men	30,866	4	60.6 (7.3)	27.6 (4.4)	23.9	–	–	8.9	17.4 (21.8)	70.1	–
Women's Health Study (WHS)	Women	38,686	10	54.2 (7.0)	26.0 (5.1)	18.2	–	–	13.1	8.6 (11.1)	56.6	9.9
Women's Lifestyle and Health Study (WLHS)	Women	44,191	7	40.2 (5.8)	23.5 (3.6)	5.8	77.0 (9.3)	9.6	20.9	4.1 (4.5)	86.2	–
All women	Women	1,100,343	407	55.4 (10.7)	25.8 (5.0)	17.1	81.3 (12.5)	22.3	13.2	8.6 (14.0)	66.5	12.1
N (%) missing		–	–	–	–	–	36.2	36.2	1.6	5.9	5.9	20.4
All men	Men	778,458	160	58.6 (9.0)	26.7 (4.0)	17.3	95.1 (11.2)	9.2	19.0	21.3 (38.6)	77.7	6.7
N (%) missing		–	–	–	–	–	44.8	44.8	2.1	10.0	10.0	14.0
All combined	All	1,878,801	567	56.7 (10.1)	26.1 (4.7)	17.2	86.5 (13.8)	17.4	15.6	14.2 (28.4)	71.0	9.8
N (%) missing		–	–	–	–	–	39.7	39.7	1.8	7.6	7.6	17.8

[a]Among nonmissing responders.

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Table 2. Associations of BMI, adult weight gain, and height with gallbladder cancer

	All				Women				Men			
BMI (kg/m^2)	Case[a]	Minimally adjusted RR (95% CI)[b]	Multivariable-adjusted RR1 (95% CI)[c]	Multivariable-adjusted RR2 (95% CI)[d]	Case[a]	Minimally adjusted RR (95% CI)[b]	Multivariable-adjusted RR1 (95% CI)[c]	Multivariable-adjusted RR2 (95% CI)[d]	Case[a]	Minimally adjusted RR (95% CI)[b]	Multivariable-adjusted RR1 (95% CI)[c]	Multivariable-adjusted RR2 (95% CI)[d]
Baseline BMI												
<18.5	8	1.20 (0.59–2.43)	1.19 (0.59–2.43)	1.21 (0.60–2.47)	6	1.04 (0.46–2.36)	1.06 (0.47–2.39)	1.07 (0.47–2.43)	2	2.13 (0.51–8.89)	2.00 (0.48–8.36)	2.03 (0.49–8.50)
18.5–<25	200	1.00 (ref)	1.00 (ref)	1.00 (ref)	159	1.00 (ref)	1.00 (ref)	1.00 (ref)	41	1.00 (ref)	1.00 (ref)	1.00 (ref)
25–<30	226	1.36 (1.12–1.64)	1.29 (1.07–1.57)	1.27 (1.04–1.54)	147	1.31 (1.05–1.65)	1.24 (0.99–1.56)	1.21 (0.97–1.52)	79	1.53 (1.04–2.24)	1.49 (1.01–2.19)	1.46 (0.99–2.16)
30–<35	91	1.76 (1.37–2.26)	1.60 (1.24–2.06)	1.53 (1.18–1.98)	59	1.56 (1.16–2.12)	1.41 (1.04–1.92)	1.35 (0.99–1.83)	32	2.37 (1.47–3.83)	2.16 (1.33–3.52)	2.11 (1.30–3.44)
35-<40	29	2.26 (1.52–3.35)	1.99 (1.33–2.96)	1.86 (1.25–2.78)	25	2.38 (1.56–3.65)	2.11 (1.37–3.26)	1.97 (1.28–3.05)	4	1.68 (0.60–4.75)	1.45 (0.51–4.11)	1.39 (0.49–3.96)
≥40	13	2.94 (1.67–5.18)	2.50 (1.41–4.43)	2.31 (1.30–4.09)	11	2.84 (1.53–5.25)	2.47 (1.32–4.62)	2.28 (1.22–4.26)	2	3.48 (0.83–14.5)	2.74 (0.65–11.6)	2.61 (0.62–11.0)
<18.5	8	1.20 (0.59–2.43)	1.19 (0.59–2.43)	1.21 (0.60–2.47)	6	1.05 (0.46–2.36)	1.06 (0.47–2.40)	1.08 (0.48–2.43)	2	2.13 (0.51–8.89)	2.00 (0.48–8.36)	2.03 (0.49–8.50)
18.5–<25	200	1.00 (ref)	1.00 (ref)	1.00 (ref)	159	1.00 (ref)	1.00 (ref)	1.00 (ref)	41	1.00 (ref)	1.00 (ref)	1.00 (ref)
25–<30	226	1.36 (1.12–1.65)	1.29 (1.07–1.57)	1.27 (1.04–1.54)	147	1.31 (1.05–1.65)	1.24 (0.99–1.56)	1.21 (0.96–1.52)	79	1.53 (1.04–2.24)	1.49 (1.01–2.19)	1.46 (0.99–2.16)
≥30	133	1.92 (1.54–2.41)	1.72 (1.37–2.17)	1.64 (1.30–2.07)	95	1.82 (1.40–2.36)	1.62 (1.24–2.12)	1.54 (1.17–2.01)	38	2.31 (1.46–3.66)	2.08 (1.30–3.33)	2.02 (1.26–3.24)
Per 5 kg/m^2[e]		1.31 (1.21–1.43)	1.26 (1.16–1.37)	1.24 (1.13–1.35)		1.31 (1.20–1.44)	1.27 (1.15–1.40)	1.24 (1.13–1.37)		1.31 (1.09–1.59)	1.24 (1.02–1.50)	1.22 (1.01–1.49)
P value for trend		<0.0001	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001		0.005	0.0312	0.0431
P interaction with sex		0.99	0.98	0.89								
Per Std Dev[e]		1.28 (1.19–1.39)	1.24 (1.14–1.34)	1.21 (1.12–1.31)		1.29 (1.18–1.40)	1.24 (1.14–1.36)	1.22 (1.12–1.34)		1.28 (1.08–1.53)	1.22 (1.02–1.45)	1.20 (1.01–1.44)
Young adult BMI												
<18.5	38	0.85 (0.60–1.19)	0.83 (0.59–1.17)	0.83 (0.59–1.18)	28	0.75 (0.50–1.13)	0.74 (0.49–1.10)	0.74 (0.49–1.11)	10	1.24 (0.63–2.44)	1.20 (0.61–2.35)	1.20 (0.61–2.36)
18.5–<25	222	1.00 (ref)	1.00 (ref)	1.00 (ref)	163	1.00 (ref)	1.00 (ref)	1.00 (ref)	59	1.00 (ref)	1.00 (ref)	1.00 (ref)
25–<30	29	1.29 (0.87–1.90)	1.25 (0.84–1.84)	1.24 (0.84–1.83)	15	1.24 (0.73–2.11)	1.18 (0.70–2.02)	1.18 (0.69–2.00)	14	1.36 (0.76–2.45)	1.35 (0.75–2.43)	1.34 (0.75–2.42)
≥30	7	1.92 (0.90–4.08)	1.77 (0.83–3.77)	1.75 (0.82–3.73)	4	1.59 (0.59–4.29)	1.45 (0.54–3.93)	1.44 (0.53–3.90)	3	2.74 (0.86–8.79)	2.60 (0.81–8.36)	2.57 (0.80–8.26)
Per 5 kg/m^2[e]		1.13 (1.02–1.25)	1.12 (1.00–1.26)	1.12 (1.00–1.26)		1.18 (0.95–1.47)	1.15 (0.91–1.45)	1.15 (0.91–1.45)		1.12 (0.97–1.29)	1.12 (0.97–1.30)	1.12 (0.96–1.30)
P value for trend		0.0175	0.0445	0.0531		0.1385	0.2349	0.2502		0.1375	0.1285	0.1399
P interaction with sex		0.67	0.85	0.86								
Per Std Dev[e]		1.07 (1.01–1.14)	1.07 (1.00–1.14)	1.07 (1.00–1.14)		1.10 (0.97–1.25)	1.08 (0.95–1.24)	1.08 (0.95–1.23)		1.06 (0.98–1.16)	1.07 (0.98–1.16)	1.07 (0.98–1.16)
Adult weight change (kg)[f]												
Lost weight	26	1.12 (0.66–1.91)	1.11 (0.65–1.90)	1.12 (0.66–1.90)	17	0.81 (0.44–1.49)	0.82 (0.44–1.53)	0.82 (0.44–1.53)	9	3.44 (1.05–11.3)	3.18 (0.95–10.6)	3.18 (0.95–10.6)
Gained 0 to 5	31	1.00 (ref)	1.00 (ref)	1.00 (ref)	27	1.00 (ref)	1.00 (ref)	1.00 (ref)	4	1.00 (ref)	1.00 (ref)	1.00 (ref)
Gained 6 to 10	50	1.23 (0.78–1.92)	1.19 (0.76–1.87)	1.19 (0.76–1.87)	37	1.06 (0.65–1.74)	1.03 (0.63–1.70)	1.03 (0.63–1.70)	13	2.38 (0.78–7.30)	2.33 (0.76–7.17)	2.33 (0.76–7.17)
Gained 10 to 15	43	1.09 (0.69–1.73)	1.04 (0.65–1.65)	1.03 (0.65–1.65)	32	0.98 (0.58–1.63)	0.93 (0.56–1.56)	0.93 (0.55–1.56)	11	1.92 (0.61–6.06)	1.84 (0.58–5.82)	1.83 (0.58–5.78)
Gained 16 to 20	44	1.29 (0.82–2.06)	1.20 (0.76–1.91)	1.19 (0.75–1.90)	32	1.16 (0.70–1.95)	1.09 (0.65–1.82)	1.08 (0.64–1.82)	12	2.28 (0.73–7.11)	2.08 (0.67–6.51)	2.06 (0.66–6.45)
Gained ≥21	96	1.68 (1.12–2.54)	1.50 (0.99–2.27)	1.48 (0.97–2.25)	61	1.35 (0.86–2.14)	1.22 (0.76–1.95)	1.20 (0.75–1.93)	35	3.76 (1.32–10.7)	3.17 (1.10–9.14)	3.13 (1.08–9.03)
Per 5 kg		1.07 (1.02–1.12)	1.07 (1.02–1.12)	1.07 (1.02–1.12)		1.07 (1.02–1.13)	1.07 (1.01–1.13)	1.07 (1.01–1.13)		1.06 (0.98–1.15)	1.05 (0.97–1.15)	1.05 (0.96–1.14)
P value for trend		0.0032	0.0054	0.0072		0.009	0.0149	0.0182		0.1675	0.2454	0.2667
P interaction with sex		0.96	0.94	0.93								
Per Std Dev[e]		1.19 (1.06–1.34)	1.18 (1.05–1.33)	1.18 (1.05–1.33)		1.20 (1.05–1.38)	1.19 (1.03–1.37)	1.19 (1.03–1.37)		1.16 (0.94–1.44)	1.14 (0.91–1.43)	1.13 (0.91–1.42)
Height (cm)												
M <170, W <160	167	1.00 (ref)	1.00 (ref)	1.00 (ref)	137	1.00 (ref)	1.00 (ref)	1.00 (ref)	30	1.00 (ref)	1.00 (ref)	1.00 (ref)
M 170–<175, W 160–<165	137	1.00 (0.79–1.27)	1.06 (0.83–1.34)	1.06 (0.83–1.34)	110	1.04 (0.80–1.35)	1.11 (0.86–1.45)	1.12 (0.86–1.45)	27	0.84 (0.49–1.45)	0.87 (0.51–1.49)	0.86 (0.50–1.48)
M 175–<180, W 165–<170	143	1.21 (0.95–1.54)	1.31 (1.03–1.68)	1.31 (1.03–1.68)	102	1.24 (0.94–1.64)	1.37 (1.04–1.82)	1.38 (1.04–1.82)	41	1.09 (0.65–1.83)	1.15 (0.68–1.95)	1.14 (0.67–1.93)
M 180+, W 170+	120	1.23 (0.94–1.61)	1.37 (1.05–1.80)	1.37 (1.05–1.79)	58	1.16 (0.83–1.61)	1.32 (0.94–1.83)	1.32 (0.94–1.84)	62	1.27 (0.76–2.10)	1.36 (0.81–2.27)	1.34 (0.80–2.24)
Per 5 cm		1.07 (1.00–1.13)	1.10 (1.03–1.17)	1.10 (1.03–1.17)		1.04 (0.96–1.12)	1.07 (0.99–1.16)	1.07 (0.99–1.16)		1.13 (1.01–1.25)	1.14 (1.03–1.27)	1.14 (1.02–1.27)
P value for trend		0.049	0.0043	0.0046		0.3755	0.0718	0.0701		0.0318	0.0155	0.0179
P interaction with sex		0.24	0.23	0.23								
Per Std Dev[e]		1.13 (1.00–1.28)	1.20 (1.06–1.36)	1.20 (1.06–1.36)		1.07 (0.92–1.25)	1.15 (0.99–1.34)	1.15 (0.99–1.35)		1.26 (1.02–1.56)	1.30 (1.05–1.61)	1.30 (1.05–1.61)

Abbreviation: RR, relative risk; Per Std Dev, per standard deviation.
[a]Some counts do not add to totals because of missing data.
[b]Adjusted for age, sex, and study.
[c]Adjusted for age, sex, study, race, physical activity, education, smoking, and alcohol.
[d]Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones.
[e]Continuous BMI models exclude those <18.5 kg/m^2.
[f]All adult weight change models additionally adjust for young adult BMI.

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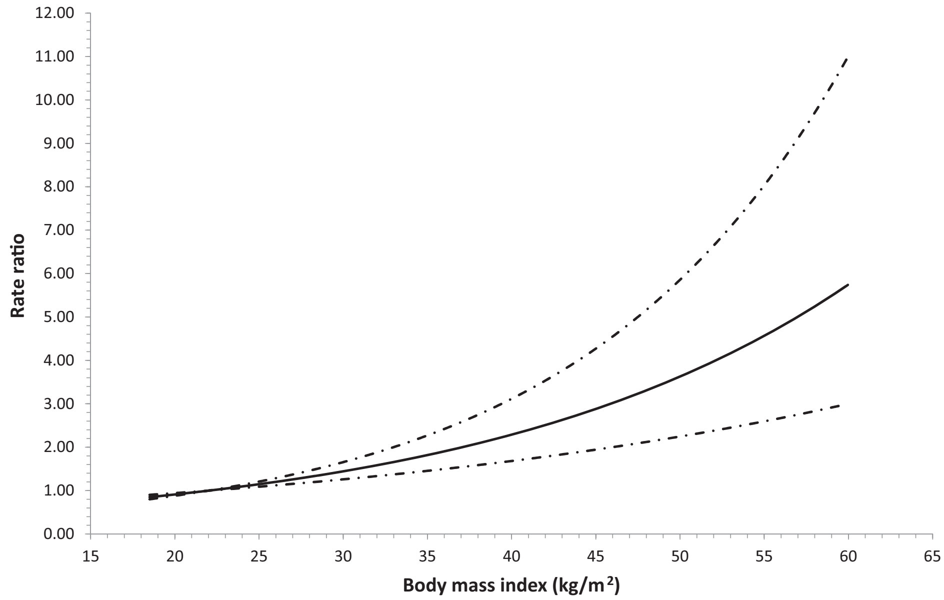

Figure 1.
Restricted cubic spline analysis of BMI and risk of gallbladder cancer in the Rare Cancer Collaboration. The solid line indicates the HR, whereas the dashed lines indicate 95% CIs.

circumference (I^2: 9%; *P* value: 0.36; Supplementary Fig. S5), waist–height ratio (I^2: 35%; *P* value: 0.11; Supplementary Fig. S6), hip circumference (I^2: 16%; *P* value: 0.29; Supplementary Fig. S7), or waist–hip ratio (I^2: 0%; *P* value: 0.88; Supplementary Fig. S8). Restricted cubic spline analyses supported linear associations of waist circumference (Fig. 2; *P* value for linearity: <0.0001; *P* value for nonlinearity: 0.62), waist–height ratio (*P* value for linearity: <0.0001; *P* value for nonlinearity: 0.76), hip circumference (*P* value for linearity: <0.0001; *P* value for nonlinearity: 0.97), and waist–hip ratio (*P* value for linearity: <0.0001; *P* value for nonlinearity: 0.13) with gallbladder cancer risk.

When analyses were restricted to studies and participants that had both BMI and waist circumference in the individual-level data that included all participants, gallbladder cancer risks were similarly elevated for each 1 SD unit increase in waist circumference (HR, 1.28; 95% CI, 1.13–1.46) and BMI (HR, 1.21; 95% CI, 1.09–1.34) when modeled separately. When BMI and waist circumference were included in the same model, both HRs were attenuated and no longer statistically significant (waist circumference HR, 1.21; 95% CI, 0.99–1.50; BMI HR, 1.06; 95% CI, 0.89–1.27).

In sensitivity analyses, the main study findings were not materially different after excluding gallbladder cancers that occurred in the first 2 and 5 years after baseline and after excluding participants who reported a history of gallstones (data not shown). No strong evidence for geographic heterogeneity was detected for continuous adult BMI and gallbladder cancer risk (i.e., North America: HR, 1.25; 95% CI, 1.12–1.38; Europe: HR, 1.12; 95% CI, 0.91–1.37; Asia: HR, 1.18; 95% CI, 0.84–1.67; Australia: HR, 1.85; 95% CI, 1.32–2.59; *P* value for heterogeneity: 0.09). Studies with self-reported versus directly measured height and weight yielded relatively similar results (i.e., self-reported BMI, per 5 kg/m^2, HR, 1.22; 95% CI, 1.10–1.35; directly measured BMI, per 5 kg/m^2, HR, 1.30; 95% CI, 1.10–1.54; *P* value for heterogeneity: 0.53).

Discussion

In this large prospective analysis of 1.88 million adults enrolled in 19 cohort studies, greater BMI (both at middle age and during young adulthood), adult weight gain, height, waist circumference, waist–height ratio, and hip circumference were all consistently associated with higher risks of gallbladder cancer. Results for waist–hip ratio generally suggested an increased risk, consistent with the other anthropometric measures, but the results were not statistically significant. Restricted cubic spline analyses supported linear associations for all anthropometric measures with gallbladder cancer risk, indicating dose–response associations throughout the ranges of body size measures observed in this study. The main study results were consistent when stratified by sex, and they were not materially different in statistical models that included many confirmed and potential risk factors for gallbladder cancer, including sex, smoking, alcohol, race, education, and history of cholesterol gallstones. The main study results were robust after a series of sensitivity analyses, including individual participant meta-analyses and when excluding cases that occurred in the first 5 years of follow-up.

Studies regarding BMI and gallbladder cancer risk have been generally hampered by small numbers of outcomes and the related issues of limited statistical power and imprecise risk estimates: of the 12 prospective cohort studies on this topic in the literature (11–13, 15–17, 21–26), six identified fewer than 100 cases (11, 12, 17, 22, 23, 25), and while most studies reported HRs above 1, many studies were not statistically significant (11, 12, 15, 23, 25). With data from 567 gallbladder cancer cases, this study makes an important contribution toward confirming the association between high BMI and this rare and highly fatal cancer. The HR identified in this study for obese BMI and gallbladder cancer risk (HR, 1.64) is similar in magnitude to results from individual large prospective cohort studies (13, 16, 21, 26), and to results from a recent meta-analysis (HR, 1.62; ref. 27). In addition, this study identified similar HRs for linear BMI and gallbladder cancer risk when stratified by sex, similar to the conclusion reached by the recent CUP (10) but somewhat in contrast to earlier reports that suggested the association was higher for women than men (27–29). Because gallbladder cancer is more common in women than in men (by approximately 2-fold, typically), it is plausible that the earlier studies compared

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Table 3. Associations of waist circumference, waist-to-height ratio, hip circumference, and waist-to-hip ratio with gallbladder cancer

	All				Women				Men			
	Case[a]	Minimally adjusted RR (95% CI)[b]	Multivariable-adjusted RR1 (95% CI)[c]	Multivariable-adjusted RR2 (95% CI)[d]	Case[a]	Minimally adjusted RR (95% CI)[b]	Multivariable-adjusted RR1 (95% CI)[c]	Multivariable-adjusted RR2 (95% CI)[d]	Case[a]	Minimally adjusted RR (95% CI)[b]	Multivariable-adjusted RR1 (95% CI)[c]	Multivariable-adjusted RR2 (95% CI)[d]
Waist circumference (cm)												
M <90, W <70	59	1.00 (ref)	1.00 (ref)	1.00 (ref)	36	1.00 (ref)	1.00 (ref)	1.00 (ref)	23	1.00 (ref)	1.00 (ref)	1.00 (ref)
M 90–<100, W 70–<80	99	1.30 (0.92–1.82)	1.26 (0.90–1.78)	1.25 (0.87–1.80)	73	1.42 (0.93–2.18)	1.37 (0.89–2.10)	1.38 (0.88–2.16)	26	1.07 (0.59–1.92)	1.04 (0.58–1.87)	0.78 (0.40–1.53)
M 100–<110, W 80–<90	110	1.87 (1.31–2.66)	1.72 (1.21–2.46)	1.68 (1.11–2.55)	87	1.93 (1.26–2.98)	1.73 (1.12–2.67)	1.77 (1.08–2.91)	23	1.80 (0.96–3.37)	1.69 (0.90–3.19)	1.17 (0.54–2.55)
M 110+, W 90+	93	2.45 (1.68–3.55)	2.08 (1.42–3.05)	2.03 (1.23–3.35)	79	2.46 (1.57–3.85)	2.02 (1.28–3.19)	2.09 (1.16–3.77)	14	2.79 (1.36–5.75)	2.46 (1.17–5.13)	1.83 (0.68–4.92)
Per 5 cm		1.12 (1.08–1.17)	1.10 (1.05–1.15)	1.09 (1.02–1.17)		1.12 (1.06–1.17)	1.09 (1.03–1.14)	1.09 (1.02–1.18)		1.15 (1.04–1.26)	1.12 (1.02–1.24)	1.08 (0.94–1.24)
P value for trend		<0.0001	0.0001	0.0076		<0.0001	0.0015	0.0157		0.0051	0.0191	0.2981
P interaction with sex		0.62	0.47	0.46								
Per Std Dev		1.38 (1.22–1.55)	1.29 (1.14–1.46)	1.27 (1.07–1.52)		1.36 (1.19–1.55)	1.26 (1.09–1.45)	1.28 (1.05–1.57)		1.46 (1.12–1.90)	1.38 (1.05–1.81)	1.23 (0.83–1.82)
Waist-to-height ratio												
M <0.50, W <0.45	71	1.00 (ref)	1.00 (ref)	1.00 (ref)	60	1.00 (ref)	1.00 (ref)	1.00 (ref)	11	1.00 (ref)	1.00 (ref)	1.00 (ref)
M 0.50–<0.55, W 0.45–<0.50	85	1.25 (0.90–1.74)	1.20 (0.86–1.67)	1.15 (0.81–1.63)	56	1.15 (0.78–1.69)	1.09 (0.74–1.60)	1.05 (0.70–1.57)	29	1.66 (0.82–3.36)	1.63 (0.81–3.30)	1.50 (0.67–3.36)
M 0.55–<0.60, W 0.50–<0.55	100	1.78 (1.28–2.48)	1.62 (1.16–2.26)	1.47 (1.00–2.17)	72	1.65 (1.13–2.41)	1.45 (0.99–2.13)	1.38 (0.89–2.13)	28	2.36 (1.16–4.82)	2.25 (1.10–4.61)	1.72 (0.70–4.26)
M 0.60+, W 0.55+	105	2.00 (1.43–2.81)	1.67 (1.18–2.37)	1.42 (0.90–2.27)	87	1.90 (1.30–2.76)	1.52 (1.03–2.25)	1.38 (0.82–2.32)	18	2.44 (1.12–5.31)	2.22 (1.01–4.90)	1.51 (0.52–4.37)
Per 0.1		1.42 (1.23–1.63)	1.30 (1.12–1.50)	1.24 (1.00–1.54)		1.41 (1.21–1.64)	1.27 (1.08–1.50)	1.29 (1.02–1.63)		1.46 (1.04–2.05)	1.37 (0.97–1.94)	1.06 (0.63–1.80)
P value for trend		<0.0001	0.0005	0.0497		<0.0001	0.0032	0.0371		0.0289	0.0751	0.8187
P interaction with sex		0.83	0.71	0.72								
Per Std Dev		1.30 (1.17–1.45)	1.22 (1.09–1.36)	1.18 (1.00–1.39)		1.30 (1.15–1.45)	1.20 (1.06–1.36)	1.21 (1.01–1.45)		1.33 (1.03–1.72)	1.27 (0.98–1.65)	1.05 (0.70–1.56)
Hip circumference (cm)												
M <95, W <90	55	1.00 (ref)	1.00 (ref)	1.00 (ref)	42	1.00 (ref)	1.00 (ref)	1.00 (ref)	13	1.00 (ref)	1.00 (ref)	1.00 (ref)
M 95–<105, W 90–<100	109	1.70 (1.14–2.54)	1.67 (1.12–2.49)	1.66 (1.09–2.53)	84	2.12 (1.31–3.43)	2.05 (1.26–3.32)	2.11 (1.25–3.55)	25	0.98 (0.49–1.96)	0.98 (0.49–1.96)	0.78 (0.35–1.70)
M 105–<115, W 100–<110	93	2.15 (1.39–3.32)	2.00 (1.29–3.09)	1.92 (1.17–3.17)	69	2.15 (1.28–3.63)	1.95 (1.15–3.30)	2.01 (1.09–3.69)	24	2.44 (1.17–5.07)	2.33 (1.11–4.88)	1.54 (0.63–3.78)
M 115+, W 110+	61	3.52 (2.20–5.64)	2.93 (1.82–4.73)	2.74 (1.48–5.08)	54	3.77 (2.18–6.52)	3.04 (1.74–5.32)	3.24 (1.55–6.75)	7	3.50 (1.31–9.35)	3.01 (1.11–8.17)	1.96 (0.58–6.68)
Per 5 cm		1.17 (1.11–1.23)	1.13 (1.07–1.20)	1.13 (1.04–1.22)		1.16 (1.09–1.22)	1.12 (1.05–1.19)	1.14 (1.05–1.24)		1.22 (1.07–1.38)	1.19 (1.04–1.35)	1.10 (0.92–1.30)
P value for trend		<0.0001	<0.0001	0.0021		<0.0001	0.0000	0.0028		0.0024	0.0095	0.3044
P interaction with sex		0.49	0.35	0.34								
Per Std Dev		1.37 (1.23–1.53)	1.30 (1.16–1.45)	1.28 (1.09–1.50)		1.35 (1.20–1.52)	1.27 (1.12–1.44)	1.31 (1.10–1.56)		1.50 (1.15–1.95)	1.42 (1.09–1.86)	1.21 (0.84–1.73)
Waist-to-hip ratio												
M <0.90, W <0.75	43	1.00 (ref)	1.00 (ref)	1.00 (ref)	27	1.00 (ref)	1.00 (ref)	1.00 (ref)	16	1.00 (ref)	1.00 (ref)	1.00 (ref)
M 0.90–<0.95, W 0.75–<0.80	94	1.48 (1.03–2.13)	1.42 (0.99–2.05)	1.35 (0.94–1.96)	70	1.56 (1.00–2.43)	1.47 (0.94–2.30)	1.43 (0.91–2.24)	24	1.35 (0.71–2.58)	1.31 (0.69–2.50)	1.13 (0.58–2.21)
M 0.95–<1.00, W 0.80–<0.85	81	1.34 (0.92–1.96)	1.23 (0.84–1.81)	1.11 (0.75–1.64)	66	1.40 (0.89–2.21)	1.26 (0.80–1.99)	1.17 (0.74–1.87)	15	1.23 (0.60–2.54)	1.14 (0.55–2.37)	0.83 (0.38–1.81)
M 1.00+, W 0.85+	99	1.65 (1.13–2.40)	1.43 (0.98–2.09)	1.19 (0.80–1.79)	85	1.69 (1.08–2.64)	1.43 (0.91–2.24)	1.27 (0.79–2.03)	14	1.69 (0.80–3.60)	1.49 (0.70–3.20)	0.96 (0.42–2.20)
Per 0.1		1.19 (1.03–1.37)	1.12 (0.96–1.31)	1.03 (0.87–1.22)		1.17 (0.99–1.38)	1.09 (0.92–1.30)	1.03 (0.85–1.25)		1.26 (0.97–1.66)	1.22 (0.89–1.66)	1.04 (0.70–1.53)
P value for trend		0.0197	0.1496	0.7076		0.0655	0.3229	0.7456		0.0876	0.2102	0.8482
P interaction with sex		0.63	0.45	0.42								
Per Std Dev		1.18 (1.03–1.36)	1.12 (0.96–1.30)	1.03 (0.88–1.22)		1.16 (0.99–1.37)	1.09 (0.92–1.29)	1.03 (0.86–1.24)		1.25 (0.97–1.63)	1.21 (0.90–1.64)	1.04 (0.71–1.51)

Abbreviation: RR, relative risk; Per Std Dev, per standard deviation.
[a]Some counts do not add to totals because of missing data.
[b]Adjusted for age, sex, and study.
[c]Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones.
[d]Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, gallstones, and BMI.

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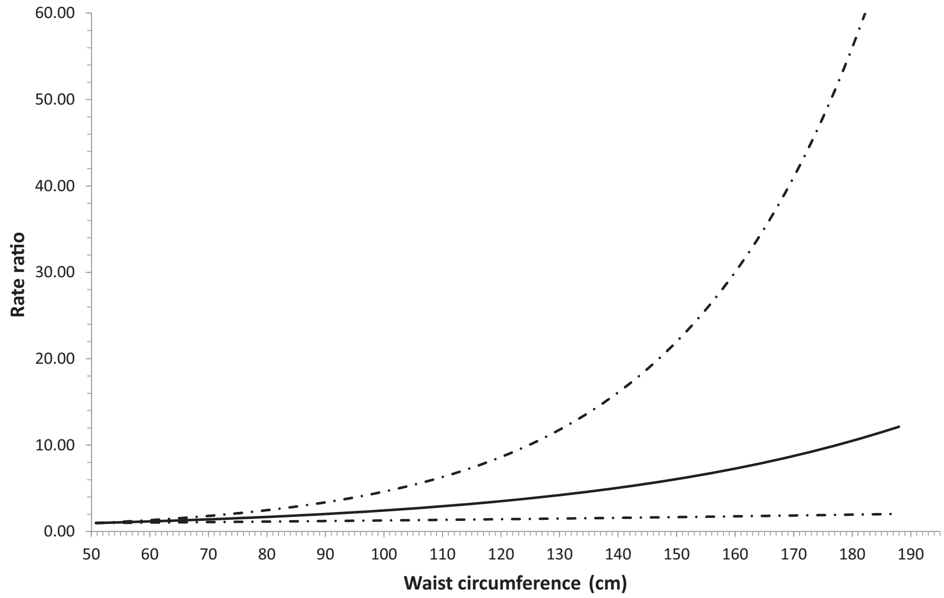

Figure 2.
Restricted cubic spline analysis of waist circumference and risk of gallbladder cancer in the Rare Cancer Collaboration. The solid line indicates the HR, whereas the dashed lines indicate 95% CIs.

with the more recent, larger studies lacked sufficient statistical power to detect a meaningful association for men.

We are not aware of any epidemiologic studies on young adult BMI as a risk factor for gallbladder cancer; therefore, our finding of higher risk with obese levels of BMI during young adulthood is novel but requires replication in other large prospective studies. This finding may highlight the importance of early-life energy excess with gallbladder cancer etiology. We identified a moderate association between adult weight gain and gallbladder cancer risk: Only one previous cohort study assessed adult weight gain with gallbladder cancer risk (11) and reported that average weight gain (in kg) per year from age 20 years onward was not statistically significantly associated with risk, although only 37 gallbladder cancer cases were identified in the cohort, so statistical power to detect an association was limited.

Taller height was associated with higher risk of gallbladder cancer in this study, whereas in one previous large prospective cohort study (16), height was not associated with gallbladder cancer risk. The Million Women Study collaboration reported an association between height and cancer risk overall (30), consistent with this study for gallbladder cancer, but that study did not report results specifically for gallbladder cancer, and it is unlikely that the overall result was materially affected from what would have been very few gallbladder cancer cases.

Prospective studies on waist and hip circumference–related measures and gallbladder cancer risk are especially rare, with only one published study to date (11), which reported each 5-cm increase in waist and hip circumferences was associated with 17% and 18% higher risks of gallbladder cancer risk, respectively, and the results were statistically significant despite a relatively small number of cases ($n = 76$). Likewise, a 0.1 increase in the waist–hip ratio was associated with a nonstatistically significant 33% higher risk of gallbladder cancer (11). With over 300 prospectively identified gallbladder cancer cases with reported waist and hip circumference–related measures, our study adds considerably to the sparse literature on central adiposity and gallbladder cancer risk, although further research from additional large prospective cohort studies is still warranted.

From the statistical models that included mutual adjustment of BMI and waist circumference, some of the risk imparted by these variables is likely shared since both of the main effect associations were attenuated to the null and were no longer statistically significant, although the HR for BMI decreased appreciably more than did the HR for waist circumference. Obesity increases risk of cholesterol gallstones and other gallbladder diseases (31), and gallstones, in turn, are a major risk factor for gallbladder cancer (4). Thus, gallstones might lie on the causal pathway between obesity and gallbladder cancer risk for some men and women; however, when history of gallstones at baseline was included in the statistical models, there was no appreciable change to the HRs for obesity. In addition, when persons with a history of gallstones at baseline were excluded, the results were not materially different (data not shown). More work is needed to define the mechanisms that connect general and central obesity to gallbladder cancer risk. Some plausible mechanisms to explain this link may include localized inflammation and the ensuing damage that occurs to gallbladder epithelial tissue over time, which for some men and women, may lead to gallbladder cancer.

The current study's strengths include its large sample size, prospective study design, inclusion of cohort studies from several regions of the world, long follow-up, and inclusion of harmonized data on many confirmed and plausible gallbladder cancer risk factors. Several limitations of this study should be also considered, particularly regarding the reliance by most studies on self-reported height and weight. Cross-sectional studies suggest that self-reported BMI is slightly lower than directly measured BMI, especially at obese levels of BMI (32); underreporting of BMI may inflate associations for overweight BMI and gallbladder cancer risk and simultaneously underestimate the association for obese BMI. Good-to-excellent agreement has been reported for self-reported and directly measured values of height and weight, however, in studies with participants who shared similar demographic characteristics to this study (33, 34), and it is reassuring that the main associations for adult BMI and gallbladder cancer risk were similar for studies with directly measured versus self-reported height and weight. Six studies in this study

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had interviewer-measured waist and hip circumference data, whereas eight studies had these data from participant measurements. The validity of self-measured versus interviewer-measured waist and hip circumferences is generally quite high, with correlations coefficients of 0.84 to 0.9 (35). Nonetheless, if circumference-related measures are more measurement-error prone than height and weight, then studies of body circumference measures and disease outcomes would tend to underestimate the true associations compared with studies that rely on height and weight. Further, waist–hip ratio tends to show weaker correlations between self-measured and interviewer-measured indices, suggesting that it is more prone to measurement error than other body size variables (35, 36). This potential measurement error may explain, at least in part, our null result for waist–hip ratio and gallbladder cancer risk. We did not have access to updated risk factor information in this pooling project study even though some individual cohort studies collected updated risk factor information during follow-up. For factors that change over time, including body weight and circumference-related measures, this limitation likely causes underestimation of the true associations. Another limitation in this study is the lack of data on cholecystectomy (i.e., gallbladder removal), although it is unclear what effect, if any, this omission would have on the HRs in this study. Five cohort studies did not collect circumference-related measures, and other studies only collected this information after their initial baseline enrollment; thus, we had fewer case numbers for these measures than for the height- and weight-related analyses.

In conclusion, this pooled cohort analysis of individual-level data from 19 prospective cohort studies identified higher risks of gallbladder cancer with indicators of general and central obesity and height. Because gallbladder cancer has such a poor prognosis with so few established risk factors, additional studies are required to identify further primary prevention opportunities for this disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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