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

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 (WHR), 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 were harmonized and included in this analysis. Multivariable Cox proportional hazards regression estimated HRs 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/m², HR: 1.24; 95% CI, 1.13–1.35), young adult BMI (per 5 kg/m², 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), WHR (per 0.1 unit, HR: 1.24; 95% CI, 1.13–1.35), and WHR (per 0.1 unit, HR: 1.12), waist circumference (WC), waist–height ratio (WHR), 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 were harmonized and included in this analysis. Multivariable Cox proportional hazards regression estimated HRs and 95% confidence intervals (CI).

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.

Introduction

Gallbladder cancer etiology is poorly understood with only a few, mostly nonmodifiable, established risk factors, including older age, female sex, abnormal prostatic-biliary 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 cancer.
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 cholecystec-
tomy 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/m² 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, an indicator of central adiposity
that might be more etiologically relevant to cancers of the diges-
tive system, has been evaluated by only one relatively small study
(76 cases) that reported higher risks with increasing waist circum-
ference (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 circum-
ference, and waist–hip ratio with gallbladder cancer risk.

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/m² or greater than 60 kg/m² (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 Classification
of Diseases, 10th version (ICD-10): C23.9; ref. 19] were veri-
fied 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, SIS-
TER): BMI was calculated as weight (kg) divided by height-
squared (m²) and categorized according to World Health
Organization criteria (20): overweight (15 < 18.5 kg/m²),
normal weight (18.5 < 25 kg/m²), overweight (25 < 30 kg/m²),
and obese (≥30 kg/m²). Obesity was additionally strati-
fied as classes I (30–34.9 kg/m²), II (35–39.9 kg/m²), and III (≥40 kg/
m²). Young-adult BMI was available from 10 of the cohort
studies (NIH-AARP, AHS, COSM, CPS-II, IWS, MCCS, PLCO,
SMC, VITAL, and WHL), 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 subtract-
ing 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, IWS, CPS-II (waist
circumference only), WHL, 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, IWS, MCCS, SISTER, SMC,
SMHS, SWHS, and WHL, 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, respec-
tively). 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 pre-defined groups
(women: 50–<90, 90–<100, 100–<110, and 110–<191; men:
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

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 (IWS); California
Teachers’ Study (CTS); European Prospective Investigation into
Cancer and Nutrition (EPIC); Melbourne Collaborative Cohort
Study (MCCS); Cohort of Swedish Men (COSM): Swedish Mam-
mography Cohort (SMC): The Sister Study (SISTER); Shanghai
Men’s Health Study (SMHS): Shanghai Women’s Health Study
(SWHS); Vitamins and Lifestyle Study (VITAL); and Women’s
Lifestyle and Health Study (WLH). 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.
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 non-drinker 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 HRs 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 (i.e., COSM, EPIC, SMCG, and WHL, Asia (i.e., SMHS and SWHS), and Australia (i.e., 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/m², 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/m²), 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
### Table 1. Summary of cohort studies included in the Rare Cancer Collaboration (gallbladder cancer)

<table>
<thead>
<tr>
<th>Study name (acronym)</th>
<th>Gender</th>
<th>N</th>
<th>Baseline cohort sample size</th>
<th>Baseline cohort sample size</th>
<th>Baseline age (mean SD)</th>
<th>Baseline BMI (mean SD)</th>
<th>Baseline BMI &gt; 30 kg/m² %</th>
<th>Baseline WC (cm)</th>
<th>Baseline WC man: &lt;100 cm women: &lt;90 cm %</th>
<th>Current cigarette smoker %</th>
<th>Alcohol intake (g/day) among drinkers %</th>
<th>Any alcohol intake %</th>
<th>History of gallstones %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH-AARP Diet and Health Study</td>
<td>Women</td>
<td>191,306</td>
<td>57</td>
<td>61.3 (5.4)</td>
<td>26.9 (5.6)</td>
<td>23.1</td>
<td>84.6 (13.4)</td>
<td>30.7</td>
<td>14.5</td>
<td>8.5 (20.9)</td>
<td>10.6</td>
<td>11.7</td>
<td>6.5</td>
</tr>
<tr>
<td>NIH-AARP Diet and Health Study</td>
<td>Men</td>
<td>296,183</td>
<td>53</td>
<td>61.5 (5.4)</td>
<td>27.3 (4.2)</td>
<td>21.4</td>
<td>97.9 (10.0)</td>
<td>53.0</td>
<td>10.0</td>
<td>22.9 (51.1)</td>
<td>76.9</td>
<td>6.5</td>
<td></td>
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<tr>
<td>Agricultural Health Study</td>
<td>Women</td>
<td>21643</td>
<td>4</td>
<td>46.7 (2.0)</td>
<td>25.9 (4.9)</td>
<td>18.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10.1</td>
<td>2.9 (6.1)</td>
<td>55.6</td>
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<tr>
<td>Agricultural Health Study</td>
<td>Men</td>
<td>20,464</td>
<td>4</td>
<td>47.4 (3.0)</td>
<td>27.5 (4.1)</td>
<td>23.4</td>
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<td>14.3</td>
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<td>67.5</td>
<td>-</td>
</tr>
<tr>
<td>The Breast Cancer Detection Demonstration Project (BCDDP)</td>
<td>Women</td>
<td>21,643</td>
<td>4</td>
<td>46.7 (12.0)</td>
<td>25.9 (4.9)</td>
<td>18.6</td>
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<td>14.3</td>
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<td>67.5</td>
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</tr>
</tbody>
</table>

*Among nonmissing responders.*
Table 2. Associations of BMI, adult weight gain, and height with gallbladder cancer

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Case (M): Women</th>
<th>Men</th>
<th>All</th>
<th>Adult weight change (kg)</th>
<th>Height (cm)</th>
</tr>
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<tr>
<td>&lt;18.5</td>
<td>8</td>
<td>120 (0.59-2.43)</td>
<td>1.19 (0.59-2.43)</td>
<td>1.01 (0.60-2.47)</td>
<td>1.00 (0.60-2.47)</td>
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<tr>
<td>18.5-25</td>
<td>200</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>25-30</td>
<td>226</td>
<td>1.36 (1.12-1.64)</td>
<td>1.29 (1.07-1.57)</td>
<td>1.27 (1.04-1.54)</td>
<td>1.21 (0.97-1.52)</td>
</tr>
<tr>
<td>30-35</td>
<td>91</td>
<td>1.76 (1.37-2.16)</td>
<td>1.60 (1.24-2.06)</td>
<td>1.53 (1.18-1.98)</td>
<td>1.35 (0.99-1.83)</td>
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<tr>
<td>35-40</td>
<td>29</td>
<td>2.36 (1.32-3.65)</td>
<td>1.99 (1.33-2.66)</td>
<td>1.85 (1.25-2.78)</td>
<td>1.57 (1.07-2.05)</td>
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<tr>
<td>&lt;40</td>
<td>11</td>
<td>2.94 (1.67-5.16)</td>
<td>2.50 (1.44-4.42)</td>
<td>2.31 (1.30-4.09)</td>
<td>2.28 (1.22-4.10)</td>
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<tr>
<td>40-45</td>
<td>6</td>
<td>1.05 (0.46-2.46)</td>
<td>1.06 (0.47-2.40)</td>
<td>1.08 (0.48-2.48)</td>
<td>1.35 (0.66-2.76)</td>
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<tr>
<td>&gt;45</td>
<td>2</td>
<td>1.19 (0.59-2.43)</td>
<td>1.19 (0.59-2.43)</td>
<td>1.19 (0.59-2.43)</td>
<td>1.19 (0.59-2.43)</td>
</tr>
</tbody>
</table>

**Adjusted for age, sex, study, race, physical activity, education, smoking, and alcohol.**

**Continuous BMI models exclude those <18.5 kg/m².**

**All adult weight change models additionally adjust for young adult BMI.**

**Abbreviation: RR, relative risk.**

| Adjusted for age, sex, study, race, physical activity, education, smoking, and alcohol.** | Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones.**

Some counts do not add to totals because of missing data.
Cancer Epidemiology, Biomarkers & Prevention

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 one, 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 RUC (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...
### Table 3: Associations of waist circumference, waist to height ratio, hip circumference, and waist to hip ratio with gallbladder cancer

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Women</th>
<th>Men</th>
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<tbody>
<tr>
<td></td>
<td>Minimally adjusted</td>
<td>Multivariable-adjusted</td>
<td>Minimally adjusted</td>
</tr>
<tr>
<td>Waist circumference cm</td>
<td>RR (95% CI)</td>
<td>Adjusted for age, sex, race, physical activity, education, smoking, alcohol, and gallstones</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Waist to height ratio</td>
<td>RR (95% CI)</td>
<td>Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Hip circumference cm</td>
<td>RR (95% CI)</td>
<td>Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>W / H ratio</td>
<td>RR (95% CI)</td>
<td>Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Per 5 cm</td>
<td>1.17 (1.12-1.22)</td>
<td>Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones</td>
<td>1.17 (1.12-1.22)</td>
</tr>
<tr>
<td>P value for trend</td>
<td>&lt;0.0001</td>
<td>Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P interaction with sex</td>
<td>0.25</td>
<td>Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones</td>
<td>0.25</td>
</tr>
<tr>
<td>P interaction with age</td>
<td>0.12</td>
<td>Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones</td>
<td>0.12</td>
</tr>
<tr>
<td>P interaction with BMI</td>
<td>0.08</td>
<td>Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones</td>
<td>0.08</td>
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</tbody>
</table>

**Abbreviation:** RR, relative risk.

*Some counts do not add to totals because of missing data.

1Adjusted for age, sex, and study.

2Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, and gallstones.

3Adjusted for age, sex, study, race, physical activity, education, smoking, alcohol, gallstones, and BMI.
with the more recent, larger studies lacked sufficient statistical
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) that 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, but
when history of gallstones at baseline was included in the statisti-
cal 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 harmoni-
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 sug-
gest that self-reported BMI is slightly lower than directly measured
BMI, especially at obese levels of BMI (32); under-reporting
of BMI may inflate associations for overweight BMI and gallblad-
der 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 gallblad-
ner cancer risk were similar for studies with directly measured
versus self-reported height and weight. Six studies in this study

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 line indicates 95% CIs.
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-to-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-to-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.

Authors’ Contributions

Conception and design: P.T. Campbell, C.C. Newton, C.M. Kitahara, P. Hartge, M. Jenab, R.L. Milne, E. Weiderpass, A. Wolk, S.M. Gapstur

Development of methodology: P.T. Campbell, E. Weiderpass


Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.T. Campbell, C.C. Newton, H.-O. Adami, H.D. Sesso, E. Weiderpass, A. Wolk, Y.-B. Xiang, A. Zelemen-Jacquette, S.M. Gapstur


Administrative, technical, or material support (i.e., reporting and organizing data, creating databases): P.T. Campbell, C.M. Kitahara, L. Bernstein, N.D. Freedman, Y.T. Gao, G.G. Giles, K. Robien, E. Weiderpass

Study supervision: P.T. Campbell, L. Bernstein, X.-O. Shu, E. Weiderpass

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