Cancer Research

# Body Mass Index, Waist Circumference, Diabetes, and Risk of Liver Cancer for U.S. Adults

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## Abstract

Incidence rates for liver cancer have increased 3-fold since the mid-1970s in the United States in parallel with increasing trends for obesity and type II diabetes mellitus. We conducted an analysis of baseline body mass index (BMI), waist circumference (WC), and type II diabetes mellitus with risk of liver cancer. The Liver Cancer Pooling Project maintains harmonized data from 1.57 million adults enrolled in 14 U.S.-based prospective studies. Cox regression estimated HRs and 95% confidence intervals (CI) adjusted for age, sex, study center, alcohol, smoking, race, and BMI (for WC and type II diabetes mellitus). Stratified analyses assessed whether the BMI–liver cancer associations differed by hepatitis sera-positivity in nested analyses for a subset of cases ($n =$ 220) and controls ($n = 547$). After enrollment, 2,162 incident liver cancer diagnoses were identified. BMI, per 5 kg/m$^2$, was associated with higher risks of liver cancer, more so for men (HR = 1.38; 95% CI, 1.30–1.46) than women (HR = 1.25; 95% CI, 1.17–1.35; $P_{\text{interaction}} = 0.02$). WC, per 5 cm, was associated with higher risks of liver cancer, approximately equally by sex (overall, HR = 1.08; 95% CI, 1.04–1.13). Type II diabetes mellitus was associated with higher risk of liver cancer (HR = 2.61; 95% CI, 2.34–2.91). In stratified analyses, there was a null association between BMI and liver cancer risk for participants who were sera-positive for hepatitis. This study suggests that high BMI, high WC, and type II diabetes mellitus are associated with higher risks of liver cancer and that the association may differ by status of viral hepatitis infection. *Cancer Res; 76(20); 6076–83. ©2016 AACR.*

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## Introduction

Established risk factors for liver cancer include chronic infection with hepatitis B (HBV) or C (HCV) viruses and heavy alcohol use (1, 2). These factors likely increase risk through inducing chronic hepatic inflammation that may lead to fibrosis and cirrhosis. Worldwide, most liver cancers (principally, hepatocellular carcinomas) occur in developing countries due to the high prevalence of HBV infection in these areas (3). In some areas of Asia where widespread HBV vaccination has occurred, incidence rates for hepatocellular carcinoma are decreasing (3, 4). In contrast, rates for liver cancer have tripled since the mid-1970s in the United States (5), in parallel with increasing trends for obesity (6) and diabetes (principally, type II diabetes mellitus; ref. 7).

Several meta-analyses of primarily Asian- and European-based prospective cohort studies (8–10) have identified higher risks of liver cancer with increasing body mass index (BMI), an indicator of general adiposity. To date, U.S.-based prospective studies on this topic are especially rare: a 2-fold higher risk of hepatocellular carcinoma was reported when comparing obese ($\geq$30 kg/m$^2$) with normal BMI (18.5 < 25 kg/m$^2$) in a cohort study of 2,126 cirrhosis patients (11). The few prospective studies that examined the association between waist circumference (WC), an indicator of central adiposity, and liver cancer risk are somewhat conflicting, likely due to small sample sizes, but generally suggest higher risk with increasing WC (12–14). These observations are

supported by findings that general and central adiposity are associated with higher risks of nonalcoholic fatty liver disease and the more severe nonalcoholic steatohepatitis, both of which are major risk factors for liver cancer (15).

Several prospective studies and meta-analyses support a higher risk of liver cancer incidence and mortality among persons with diabetes (8, 12, 16–21), but many early studies were from administrative datasets that were unable to adjust for important confounders, including BMI, or had short follow-up times that may have been prone to biases. Prospectively collected data with sufficiently long follow-up time are important in this context because the clinical diagnosis of liver cancer and diabetes may coincide (i.e., reverse causation; ref. 22).

We conducted a pooled analysis of individual-level data from U.S. cohort studies to investigate the associations of BMI, WC, and type II diabetes mellitus with risk of primary liver cancer, overall and when stratified by sex and viral hepatitis status.

## Materials and Methods

### Study population

All U.S.-based studies in the NCI Cohort Consortium (http://epi.grants.cancer.gov/Consortia/cohort.html) were invited to participate in the Liver Cancer Pooling Project (LCPP). For this analysis, 14 studies were included: Health Professionals Follow-up Study (HPFS); Physicians' Health Study (PHS); NIH-AARP Diet and Health Study (NIH-AARP); Agricultural Health Study (AHS); United States Radiologic Technologists Study (USRT); 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); Black Women's Health Study (BWHS); Women's Health Initiative (WHI); and the Nurses' Health Study (NHS). All studies were approved by the Institutional Review Boards of their host centers. All studies submitted deidentified, participant-level data from their entire study to the LCPP data coordinating center. Data were centrally harmonized and pooled for analyses as a single cohort. Some studies with BMI data (CPS-II, PLCO, WHS, PHS, NYUWHS, HPFS, NHS, and WHI) also provided prediagnostic sera samples from a subset of participants for HBV and HCV serologic testing: liver cancer cases ($n = 220$) and controls ($n = 547$) were frequency matched 1-to-2 or 1-to-3, depending on study, based on study, sex, month, and year of blood draw, and age (1-year). These data were used in nested case–control analyses to examine potential effect modification by viral hepatitis status for the association between BMI and liver cancer risk. Cases and controls with versus without available sera had similar mean BMI values and prevalence of type II diabetes mellitus (data not shown).

The following exclusions were applied: diabetes diagnosis prior to age 30 years (to avoid misclassification from type I diabetes mellitus), missing age at study entry, missing follow-up time, and missing all three of BMI, WC, and diabetes. Data for 1.57 million participants comprised the analytic cohort. Liver cancer diagnoses (International Classification of Diseases, 10th version: C22.0; ref. 23) were verified after enrollment by linking to state cancer registries, medical record abstraction, and/or linking to the National Death Index (NDI). In the harmonized LCPP dataset, after the above-mentioned exclusions, 2,543 liver cancer cases were initially identified. Participants who were diagnosed with intrahepatic cholangiocarcinoma ($n = 296$) or with another histology that was inconsistent with hepatocellular carcinoma ($n = 85$; generally, germ cell tumors, lymphomas, or mesenchymal tumors) were censored on their date of diagnosis. Data from 2,162 cases were included in this analysis ($n = 1,335$ verified from cancer registries and/or medical record abstraction; $n = 827$ verified as deaths from liver cancer according to NDI linkage).

### Exposures

Baseline BMI was calculated from self-reported (all cohort studies except for WHI) or directly measured (WHI only) weight (kg) divided by height squared ($m^2$) and categorized according to World Health Organization criteria (24): underweight (15 < 18.5 $kg/m^2$), normal weight (18.5 < 25 $kg/m^2$), overweight (25–29.9 $kg/m^2$), and obese ($\geq$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 ($\geq$40 $kg/m^2$).

WC was measured by trained staff (WHI and NYUWHS) or self-measured (NIH-AARP, PHS, CPS-II, WHS, BCDDP, HPFS, IWHS, and BWHS) by participants who were given tape measures and instructions on the protocol. Some cohort studies did not have WC data available (AHS, USRT, PLCO, and NHS); other studies evaluated WC after baseline enrollment (NIH-AARP, NYUWHS, PHS, CPS-II, WHS, and BCDDP). WC, in centimeters (cm), was categorized in four groups (women: <70, 70–<80, 80–<90, and 90+; men: <90, 90–<100, 100–<110, and 110+).

Diabetes was self-reported on the baseline questionnaires of all 14 cohort studies used in this analysis. Wording varied slightly by study but generally included phrasing such as, "Have you ever been diagnosed with diabetes by a physician, excluding when you were pregnant?" Some studies (e.g., CPS-II, WHI, NHS, HPFS) corroborated a portion of self-reported diabetes via review of medical records (25, 26).

Smoking was defined according to baseline cigarette smoking status and categorized as never, former, or current. Alcohol consumption was queried for consumption in the 3 months to one year prior to enrollment and defined as nondrinker and, among persons who consumed alcohol, in categories of grams per day (grams/day: $\leq$1.08, 1.09–3.58, 3.59–13.54, and >13.54). Race was self-identified and categorized in this study as white, black/African American, and all other races, including those who did not report race. All main exposures and covariables were abstracted and harmonized from baseline study data only. Missing data were treated with an indicator variable.

### Laboratory methods

Serum samples in a subset of participants were analyzed for markers of HBV and HCV infection. For HBV, hepatitis B surface antigen (HBsAg) was detected with the Bio-Rad GS HBsAg 3.0 enzyme immunoassay (Bio-Rad Laboratories) and antibody to the hepatitis B core antigen (anti-HBc) was detected using the Ortho HBc ELISA test system (Ortho-Clinical Diagnostics, Inc.). For HCV, antibody to the hepatitis C virus (anti-HCV) was detected using the Ortho HCV Version 3.0 ELISA test system (Ortho-Clinical Diagnostics, Inc.), and positive results were confirmed using the Chiron RIBA HCV 3.0 SIA (Ortho-Clinical Diagnostics, Inc.). All assays were conducted in the Protein Expression Laboratory at the Frederick National Laboratory for Cancer Research (Frederick, MD).

**Statistical analysis**

Cox proportional hazards models estimated HR and 95% confidence intervals (CI) for the associations of BMI, WC, and type II diabetes mellitus with liver cancer risk. Follow-up time for WC analyses began on the date of WC evaluation; cases that were diagnosed between baseline and WC assessment were excluded from the WC analyses. All statistical models were analyzed from a pooled cohort of the combined studies. Initially, Cox models included only age, study, and sex. Subsequently, more comprehensive models included age, study, sex, alcohol consumption, race, and smoking status. Because education and NSAID use made no meaningful differences to the HRs of the main exposures, they were not included in the fully adjusted models. Results for WC and type II diabetes mellitus are presented with and without adjustment for BMI. BMI results are presented with and without adjustment for type II diabetes mellitus. Linear models estimated associations of BMI (per 5 kg/m$^2$; and per 1 SD and WC (per 5 cm; and per 1 SD) with liver cancer risk. Wald tests assessed linear trends.

Unconditional logistic regression assessed the association (OR) of BMI and liver cancer risk stratified by viral hepatitis status (i.e., sera-positive for HBV or HCV vs. sera-negative for both HBV and HCV) in the nested series of cases and controls with available sera. The unconditional logistic regression models included the frequency-matching factors (i.e., age, sex, and study). When we examined whether the associations between BMI and liver cancer risk differed by hepatitis infection status, we tested multiplicative interaction terms and likelihood ratio tests.

Sensitivity analyses excluded liver cancers that were diagnosed in the first 2 and 5 years after baseline and were also restricted to cases with a confirmed hepatocellular carcinoma histology ($n =$ 996; histology codes: 8170–8175). We also conducted two-stage individual participant meta-analyses to explore potential heterogeneity of HRs across studies. Sensitivity analyses also evaluated if censoring at the time of diagnosis of stomach, colorectal, breast, lung, and pancreatic cancers had any material effect on the study results in 9 of the 14 cohorts where those additional data were available.

Interaction terms with the main exposures (continuous terms for WC and BMI, and type II diabetes mellitus status defined categorically) and time tested the proportional hazards assumption of the Cox models. No violations were observed except for BMI overall ($P = 0.002$); from visual inspection of the log–log survival curve, it seems the interaction with time occurs during the first 3 years of follow-up, wherein the survival curves generally overlap.

All $P$ values were two-sided; $P < 0.05$ was considered statistically significant. SAS software was used for all statistical analyses (SAS Institute, Inc., version 9.4).

## Results

In this analysis of 1.57 million U.S. adults, 2,162 liver cancers occurred during 19 million person-years of observation. Supplementary Table S1 shows baseline characteristics of participants: mean age was 58.2 years, mean BMI was 26.6 kg/m$^2$, mean WC was 89.8 cm, and the prevalence of type II diabetes mellitus was 6.5%.

The overall and sex-specific associations between BMI and liver cancer risk are shown in Table 1. Overall, compared with a normal BMI, overweight, class I obesity, class II obesity, and class III obesity were associated with 21%, 87%, 142%, and 116% higher risks of liver cancer, respectively. HRs were higher for men than women; for both sexes, however, statistically significant higher risks were observed. There was evidence of between-study heterogeneity for this association ($I^2 = 55.82$; $P = 0.006$; Supplementary Fig. S1).

Overall, continuous WC (per 5 cm) was associated with higher risks of liver cancer (HR, 1.08), even after adjustment for BMI and other factors (Table 2). There was no clear evidence that the association differed by sex. Categorical models for WC and risk of liver cancer were generally consistent with the continuous models. There was evidence of between-study heterogeneity ($I^2 = 51.52$; $P = 0.03$; Supplementary Fig. S2).

The overall and sex-specific associations between type II diabetes mellitus and liver cancer are shown in Table 3. Overall, type II diabetes mellitus was associated with a greater than 3-fold increased risk of liver cancer in the minimally adjusted statistical model. Inclusion of alcohol, smoking, race, and BMI into the Cox model attenuated the HR to 2.61. There was no strong evidence that this association differed by sex. There was evidence of between-study heterogeneity ($I^2 = 67.33$; $P < 0.001$; Supplementary Fig. S3).

The joint effect of BMI and type II diabetes mellitus with liver cancer risk is shown in Supplementary Table S2. Compared with participants with a normal BMI and no type II diabetes mellitus at baseline, type II diabetes mellitus was associated with higher risks of liver cancer at each level of BMI.

In the nested case–control analysis of participants with measured viral hepatitis status, there was a null association between BMI and liver cancer risk for participants who were sera-positive for hepatitis (OR per 5 kg/m$^2$, 0.86; 95% CI, 0.53–1.37), whereas a higher risk of liver cancer was observed with high BMI for participants who were sera-negative for hepatitis (OR per 5 kg/m$^2$, 1.69; 95% CI, 1.36–2.09; $P_{\text{interaction}} = 0.04$).

When analyses were restricted to participants that had both WC and BMI data available, liver cancer risks were similarly increased for each 1 SD unit increase in WC (HR = 1.35; 95% CI, 1.25–1.45) and BMI (HR = 1.31; 95% CI, 1.22–1.41). When BMI was added to the WC model (HR = 1.20; 95% CI, 1.05–1.36), and when WC was added to the BMI model (HR = 1.15; 95% CI, 1.02–1.29), both results were attenuated toward the null but still remained statistically significant.

In sensitivity analyses, the main study findings for BMI, WC, and type II diabetes mellitus were not materially different after excluding liver cancers that occurred in the first 2 and 5 years after baseline (Supplementary Table S3). The main study findings for BMI, WC, and type II diabetes mellitus were also consistent when the outcome was restricted to cases with histologically confirmed hepatocellular carcinoma (Supplementary Tables S4–S6) and when censoring participants at the time of diagnosis of stomach, colorectal, pancreatic, breast, and lung cancers (data not shown).

## Discussion

BMI, WC, and type II diabetes mellitus were associated with higher risks of liver cancer in this prospective analysis of 1.57 million participants enrolled in 14 U.S.-based cohort studies. Higher BMI was associated with liver cancer in a dose–response manner, and associations were robust after controlling for smoking, alcohol intake, and other risk factors. High WC was associated with higher risks of liver cancer, and these associations were

**Table 1.** Associations of BMI with liver cancer risk in LCPP

| | All | | | | Women | | | | Men | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BMI (kg/m$^2$) | No. cases[a] | Minimally adjusted HR (95% CI)[b] | Multivariable adjusted HR (95% CI)[c] | Multivariable adjusted HR (95% CI)[d] | No. cases[a] | Minimally adjusted HR (95% CI)[b] | Multivariable adjusted HR (95% CI)[c] | Multivariable adjusted HR (95% CI)[d] | No. cases[a] | Minimally adjusted HR (95% CI)[b] | Multivariable adjusted HR (95% CI)[c] | Multivariable adjusted HR (95% CI)[d] |
| <18.5 | 19 | 1.51 (0.96–2.39) | 1.40 (0.89–2.21) | 1.41 (0.89–2.23) | 11 | 1.46 (0.80–2.67) | 1.34 (0.73–2.46) | 1.35 (0.74–2.48) | 8 | 1.53 (0.76–3.08) | 1.44 (0.71–2.91) | 1.47 (0.73–2.96) |
| 18.5–<25 | 586 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 254 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 332 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| 25–<30 | 861 | 1.20 (1.08–1.33) | 1.21 (1.09–1.35) | 1.17 (1.05–1.30) | 191 | 1.07 (0.88–1.29) | 1.06 (0.88–1.29) | 1.03 (0.85–1.25) | 670 | 1.27 (1.11–1.45) | 1.29 (1.13–1.48) | 1.24 (1.08–1.42) |
| 30–<35 | 439 | 1.86 (1.64–2.11) | 1.87 (1.65–2.13) | 1.68 (1.48–1.91) | 122 | 1.65 (1.33–2.06) | 1.63 (1.30–2.03) | 1.49 (1.19–1.86) | 317 | 1.98 (1.69–2.31) | 2.01 (1.72–2.36) | 1.80 (1.53–2.11) |
| 35–<40 | 140 | 2.41 (2.00–2.91) | 2.42 (2.01–2.92) | 2.05 (1.69–2.48) | 55 | 2.21 (1.64–2.96) | 2.16 (1.60–2.91) | 1.85 (1.36–2.51) | 85 | 2.51 (1.97–3.20) | 2.57 (2.01–3.28) | 2.19 (1.72–2.80) |
| ≥40 | 42 | 2.17 (1.58–2.98) | 2.16 (1.57–2.96) | 1.79 (1.30–2.45) | 18 | 1.70 (1.05–2.74) | 1.64 (1.01–2.66) | 1.37 (0.84–2.23) | 24 | 2.39 (1.56–3.68) | 2.46 (1.60–3.77) | 2.11 (1.38–3.22) |
| <18.5 | 19 | 1.51 (0.95–2.39) | 1.40 (0.88–2.21) | 1.41 (0.89–2.23) | 11 | 1.46 (0.80–2.67) | 1.34 (0.73–2.46) | 1.35 (0.74–2.48) | 8 | 1.53 (0.76–3.08) | 1.44 (0.71–2.91) | 1.47 (0.73–2.96) |
| 18.5–<25 | 586 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 254 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 332 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| 25–<30 | 861 | 1.20 (1.08–1.33) | 1.21 (1.09–1.35) | 1.17 (1.05–1.30) | 191 | 1.07 (0.88–1.29) | 1.06 (0.88–1.29) | 1.03 (0.85–1.24) | 670 | 1.27 (1.11–1.45) | 1.29 (1.13–1.48) | 1.24 (1.08–1.42) |
| ≥30 | 621 | 1.98 (1.76–2.22) | 1.99 (1.77–2.24) | 1.75 (1.56–1.98) | 195 | 1.78 (1.47–2.15) | 1.75 (1.44–2.12) | 1.56 (1.27–1.90) | 426 | 2.08 (1.80–2.41) | 2.12 (1.83–2.46) | 1.88 (1.61–2.18) |
| Per 5 kg/m$^2$[e] | | 1.33 (1.27–1.39) | 1.33 (1.27–1.39) | 1.26 (1.21–1.32) | | 1.26 (1.18–1.35) | 1.25 (1.17–1.35) | 1.20 (1.11–1.29) | | 1.37 (1.29–1.45) | 1.38 (1.30–1.46) | 1.31 (1.23–1.39) |
| $P_{trend}$[f] | | <0.001 | <0.001 | <0.001 | | <0.001 | <0.001 | <0.001 | | <0.001 | <0.001 | <0.001 |
| $P_{interaction}$ with sex[g] | | 0.04 | 0.02 | 0.02 | | | | | | | | |

[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, alcohol, cigarette smoking, and race.
[d]Adjusted for age, sex, study, alcohol, cigarette smoking, race, and diabetes.
[e]Continuous BMI models exclude all participants <18.5 kg/m$^2$.
[f]$P_{trend}$ from Wald tests.
[g]$P_{interaction}$ with sex from log-likelihood ratio tests.

**Table 2.** Associations of WC with liver cancer risk in LCPP

| | All | | | | Women | | | | Men | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WC (cm) | No. cases[a] | Minimally adjusted HR (95% CI)[b] | Multivariable adjusted HR (95% CI)[c] | Multivariable adjusted HR (95% CI)[d] | No. cases[a] | Minimally adjusted HR (95% CI)[b] | Multivariable adjusted HR (95% CI)[c] | Multivariable adjusted HR (95% CI)[d] | No. cases[a] | Minimally adjusted HR (95% CI)[b] | Multivariable adjusted HR (95% CI)[c] | Multivariable adjusted HR (95% CI)[d] |
| M < 90, F < 70 | 120 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 19 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 101 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| M: 90–100, F: 70–80 | 247 | 1.08 (0.87–1.35) | 1.15 (0.92–1.43) | 1.09 (0.86–1.37) | 55 | 1.08 (0.64–1.83) | 1.11 (0.66–1.87) | 1.11 (0.65–1.90) | 192 | 1.09 (0.85–1.39) | 1.14 (0.89–1.46) | 1.05 (0.80–1.37) |
| M: 100–110, F: 80–90 | 239 | 1.44 (1.15–1.80) | 1.55 (1.24–1.94) | 1.33 (1.02–1.72) | 76 | 1.36 (0.82–2.26) | 1.35 (0.82–2.25) | 1.27 (0.73–2.21) | 163 | 1.43 (1.11–1.84) | 1.54 (1.19–1.98) | 1.27 (0.93–1.73) |
| M ≥ 110, F ≥ 90 | 227 | 1.86 (1.48–2.35) | 1.93 (1.53–2.44) | 1.43 (1.05–1.94) | 110 | 1.80 (1.10–2.95) | 1.76 (1.07–2.89) | 1.43 (0.79–2.61) | 117 | 1.81 (1.38–2.39) | 1.88 (1.42–2.49) | 1.40 (0.97–2.03) |
| Per 5 cm | | 1.11 (1.08–1.14) | 1.11 (1.08–1.14) | 1.08 (1.04–1.13) | | 1.11 (1.07–1.16) | 1.11 (1.06–1.16) | 1.11 (1.04–1.18) | | 1.10 (1.06–1.14) | 1.10 (1.07–1.14) | 1.07 (1.01–1.13) |
| $P_{trend}$[e] | | <0.001 | <0.001 | 0.001 | | <0.001 | <0.001 | 0.001 | | <0.001 | <0.001 | 0.02 |
| $P_{interaction}$ with sex[f] | | 0.97 | 0.60 | 0.66 | | | | | | | | |

Abbreviations: F, females; M, males.

[a]Some counts do not add to totals because of missing data. Only 10 of the 14 cohorts in the LCPP contributed to WC analyses.

[b]Adjusted for age, sex, and study.

[c]Adjusted for age, sex, study, alcohol, cigarette smoking, and race.

[d]Adjusted for age, sex, study, alcohol, cigarette smoking, race, and BMI.

[e]$P_{trend}$ from Wald tests.

[f]$P_{interaction}$ with sex from log-likelihood ratio tests.

**Table 3.** Associations of T2DM with liver cancer risk in the LCPP

| | All | | | | Women | | | | Men | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diabetes | No. cases[a] | Minimally adjusted HR (95% CI)[b] | Multivariable adjusted HR (95% CI)[c] | Multivariable adjusted HR (95% CI)[d] | No. cases[a] | Minimally adjusted HR (95% CI)[b] | Multivariable adjusted HR (95% CI)[c] | Multivariable adjusted HR (95% CI)[d] | No. cases[a] | Minimally adjusted HR (95% CI)[b] | Multivariable adjusted HR (95% CI)[c] | Multivariable adjusted HR (95% CI)[d] |
| No Diabetes | 1,697 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 573 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1,124 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Diabetes | 449 | 3.08 (2.77–3.43) | 2.85 (2.56–3.18) | 2.61 (2.34–2.91) | 99 | 2.89 (2.33–3.59) | 2.66 (2.13–3.32) | 2.39 (1.91–3.00) | 350 | 3.08 (2.73–3.49) | 2.88 (2.54–3.27) | 2.66 (2.34–3.02) |
| $P_{interaction}$ with sex[e] | | 0.67 | 0.54 | 0.20 | | | | | | | | |

Abbreviation: T2DM, type II diabetes mellitus.

[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, alcohol, cigarette smoking, and race.

[d]Adjusted for age, sex, study, alcohol, cigarette smoking, race, and BMI.

[e]$P_{interaction}$ with sex from log-likelihood ratio tests.

attenuated after including BMI in the statistical models, suggesting shared effects of both BMI and WC on liver cancer risk, perhaps owing to these phenotypes being correlated with visceral adiposity. Type II diabetes mellitus was a strong predictor of liver cancer risk, and these results were robust even at nonobese BMI levels and after controlling for their shared risk factors. Some evidence of heterogeneity was detected across studies when sensitivity analyses were conducted in individual participant meta-analyses, which seemed to be the result of our large study sample size and moderate differences in the magnitude of associations, not their direction.

Results from several prospective cohort studies (11, 13, 14, 27) and meta-analyses (9, 10, 28) have indicated an association between high BMI and higher risk of liver cancer, although many of the original studies had few liver cancer outcomes and were often not statistically significant. With data from 2,162 prospectively identified liver cancer cases, this study adds considerably to the evidence base regarding BMI and this highly fatal cancer. A recent meta-analysis of prospective cohort studies reported a summary HR (1.39 per 5 $kg/m^2$) that was similar to our findings (28); when stratified by geographic location of the original study, associations were higher for non-Asian (HR = 1.6; predominantly Europe) than Asian-based (HR = 1.21) prospective studies. Future work is warranted to explore potential geographic differences for this association in finer detail.

Few studies have examined the association between WC and risk of liver cancer (12–14), and the results are mixed. A large European cohort study identified 177 liver cancers and reported HRs for the associations of WC (per 5 cm) and liver cancer risk that were similar with (HR = 1.29) and without (HR = 1.25) control for BMI (14). In contrast, in our study of 833 liver cancer cases with WC data, controlling for BMI attenuated the WC association closer to the null. From our analyses per 1 SD unit increase in BMI and WC, it seems that both indicators of adiposity are similarly predictive of liver cancer risk.

Type II diabetes mellitus was associated with higher risk of liver cancer in this study, consistent with previous prospective studies (18, 19, 29, 30). Our pooled LCPP analysis included data from the NIH-AARP cohort study that previously reported a 2.11-fold higher risk of liver cancer among participants with versus without diabetes (19). Similar to the evidence base for BMI, the majority of studies on diabetes and liver cancer risk were drawn from non-U. S. populations, often in populations in which HBV infection is common. An important advantage of the current study was the long follow-up period and large sample size that allowed for the exclusion of cases diagnosed in the first 5 years after baseline enrollment. This exclusion allowed us to conclude that reverse causation (i.e., undiagnosed liver cancer causing insulin resistance and, ultimately, diabetes) was not playing a major role in our observed associations.

Excess adiposity and type II diabetes mellitus likely share common mechanistic pathways involved in hepatocarcinogenesis. As both general and central adiposity increase, so too does accumulation of adipocytes in the liver (31, 32). Excess adipose tissue in the liver, in turn, may lead to tissue remodeling (including the development of fibrosis and cirrhosis), increased localized inflammation, and insulin insensitivity/resistance (31, 32). Over many years, the constellation of these factors may lead to liver cancer for some patients.

In the nested case–control analyses stratified by viral hepatitis status, there was a null association between BMI and liver cancer risk for participants who were sera-positive for hepatitis, whereas BMI was associated with higher risks of liver cancer for participants who were sera-negative. These results suggest that obesity is not an important risk factor for liver cancer in the presence of the established oncogenic viruses, HCV and HBV. Furthermore, these results may also help explain why the BMI–liver cancer association is often higher in predominantly European than in Asian populations.

This study has several strengths, including its large sample size, inclusion of harmonized data on many liver cancer risk factors, and prospective design with long follow-up times. Several limitations of this study should also be considered, particularly regarding the reliance by most studies on self-reported BMI, self-measured WC, and self-reported diabetes that are prone to misclassification. Cross-sectional data show that self-reported compared with directly measured BMI values are typically slightly lower (33); underreporting of self-reported BMI occurs more often at higher BMI values, and this trend may overestimate associations of overweight BMI with risk of liver cancer and concurrently underestimate the association for obese BMI. Good-to-excellent agreement was reported, however, in studies with similar demographic characteristics to this study for self-reported and directly measured values of height and weight (34, 35). Self-measured and interviewer-measured WCs are generally strongly correlated, with correlation coefficients reported in the ranges of 0.8 to 0.9, and more underreporting occurs at higher levels of WC (36, 37). These reporting errors, if present in this study, would likely cause an underestimation of the association between WC and liver cancer. In addition, we did not harmonize updated exposure information in this study; for diabetes, this is a particular limitation that would likely lead to an underestimation of the association. A further limitation related to diabetes was the absence of data on diabetes medications (e.g., insulin and metformin) or indicators of glucose control (e.g., HbA1c). Because we had hepatitis status for only a small series of cases and controls, we could not stratify by this important risk factor in our main statistical models. Further research is needed to investigate whether hepatitis status modifies the association between BMI and liver cancer risk.

The pooled analysis used for the primary analysis herein includes a fixed study effect to account for study-specific differences. Using a fixed study effect theoretically limits the generalizability of the results to the populations represented by the 14 cohort studies in our analysis; however, as there is close agreement between the selected meta-analysis results and the pooled analysis, the generalizability of the latter may be more extensive. The pooled approach was more appropriate for this analysis because liver cancer is a rare outcome and the pooled approach is better able to estimate by gender and exposure category, stable HRs, and more precise 95% CIs.

This study included data from more than 1.5 million U.S. adults who were, on average, older at baseline enrollment in the 1980s and 1990s, non-Hispanic white, non-current smokers, and drank alcohol at low-to-moderate levels. These results may not generalize to populations with different features, including those of Hispanic ethnicity and younger populations. NDI linkage was used as a source for liver cancer outcomes for some of the cases in this analysis; as liver cancer is rare, this approach would be expected to have good specificity in large studies compared with medical record–verified or registry-linked incidence data; however, it would only have moderate sensitivity because not all persons who are diagnosed with liver

cancer will necessarily die from the disease. Nonetheless, when our analyses were restricted to confirmed hepatocellular carcinoma incident cases, all of whom were identified from cancer registry linkage or medical record abstraction, the results were very similar to the results with the broader case definition that included NDI cases, suggesting that potential misclassification of liver cancer cases from NDI linkage did not have any material effect on the overall interpretation.

In conclusion, this pooled analysis of data from 14 prospective cohort studies identified robust associations of BMI, WC, and type II diabetes mellitus with risk of liver cancer. Because liver cancer has a poor prognosis, even when diagnosed at relatively early stages, additional efforts are needed to better understand opportunities for primary prevention of the disease.

## Disclosure of Potential Conflicts of Interest

A.G. Renehan has received speakers bureau honoraria from Janssen-Cilag Limited. No potential conflicts of interest were disclosed by the other authors.

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**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** P.T. Campbell, V.V. Sahasrabuddhe
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