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Authors
Florio, Andrea A
Campbell, Peter T
Zhang, Xuehong
et al.

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Abdominal and Gluteofemoral Size and Risk of Liver Cancer: The Liver Cancer Pooling Project

Andrea A. Florio[1], **Peter T. Campbell**[2], **Xuehong Zhang**[3], **Anne Zeleniuch-Jacquotte**[4], **Jean Wactawski-Wende**[5], **Stephanie A. Smith-Warner**[6,7], **Rashmi Sinha**[1], **Tracey G. Simon**[8], **Howard D. Sesso**[7,9], **Catherine Schairer**[1], **Lynn Rosenberg**[10], **Thomas E. Rohan**[11], **Kim Robien**[12], **Andrew G. Renehan**[13], **Mark P. Purdue**[1], **Jenny N. Poynter**[14], **Julie R. Palmer**[10], **Christina C. Newton**[2], **Yunxia Lu**[15], **Martha S. Linet**[1], **Linda M. Liao**[1], **I-Min Lee**[7,9], **Jill Koshiol**[1], **Cari M. Kitahara**[1], **Victoria A. Kirsh**[16], **Jonathan N. Hofmann**[1], **Barry I. Graubard**[1], **Edward Giovannucci**[7], **J. Michael Gaziano**[9,17], **Susan M. Gapstur**[2], **Neal D. Freedman**[1], **Jane Demuth**[18], **Dawn Q. Chong**[19], **Andrew T. Chan**[3,20,8], **Julie E. Buring**[7,9], **Patrick T. Bradshaw**[21], **Laura E. Beane Freeman**[1], **Katherine A. McGlynn**[1], **Jessica L. Petrick**[1,10]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD

[2]Behavioral and Epidemiology Research Group, American Cancer Society, Atlanta, GA

[3]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA

[4]Department of Population Health, New York University School of Medicine, New York, NY

[5]Department of Epidemiology and Environmental Health, University at Buffalo, Buffalo, NY

[6]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

[7]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[8]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA

[9]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA

[10]Slone Epidemiology Center, Boston University, Boston, MA

Corresponding author: Jessica L. Petrick, PhD, MPH, 72 East Concord Street, L-7, Boston, MA 02118 phone: 617-206-6179 jpetrick@bu.edu.

Authors' contributions
Study concept and design: All authors
Acquisition of data: PTC, HZ, AZ, JW, RS, TGS, HDS, CS, LR, TER, KR, MPP, JNP, JRP, CCN, YL, MSL, LML, IL, CMK, VAK, JNH, EG, JMG, SMG, NDF, DQC, ATC, JEB, LEBF, KAM, JLP
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Revised the manuscript: AAF, JLP
Approved manuscript: All authors

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[11]Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY

[12]Department of Exercise and Nutrition Sciences, Milken Institute School of Public Health, George Washington University, Washington, DC

[13]Faculty Institute of Cancer Sciences, University of Manchester, Manchester, United Kingdom

[14]Division of Pediatric Epidemiology and Clinical Research and Masonic Cancer Center, University of Minnesota, Minneapolis, MN

[15]Department of Population Health and Disease Prevention, Program in Public Health, University of California Irvine, Irvine, CA

[16]Epidemiology Division, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

[17]VA Boston Healthcare System, Boston, MA

[18]Information Management Services Inc., Silver Spring, MD

[19]Division of Medical Oncology, National Cancer Centre Singapore, Singapore

[20]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Boston, MA

[21]Division of Epidemiology and Biostatistics, School of Public Health, University of California, Berkeley, CA

Abstract

Obesity is known to be associated with primary liver cancer (PLC), but the separate effects of excess abdominal and gluteofemoral size are unclear. Thus, we examined the association between waist and hip circumference with risk of PLC overall and by histologic type – hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). The Liver Cancer Pooling Project is a consortium of prospective cohort studies that includes data from 1,167,244 individuals (PLC n=2,208, HCC n=1,154, ICC n=335). Multivariable-adjusted hazards ratios (HRs) and 95% confidence intervals (CI) were estimated using proportional hazards regression. Waist circumference, per 5 cm increase, was associated with an 11% increased PLC risk (HR=1.11, 95%CI: 1.09–1.14), including when adjusted for hip circumference (HR=1.12, 95%CI: 1.08–1.17) and also when restricted to individuals in a normal body mass index (BMI) range (18.5-<25 kg/m^2; HR=1.14, 95%CI: 1.07–1.21). Hip circumference, per 5 cm increase, was associated with a 9% increased PLC risk (HR=1.09, 95%CI: 1.06–1.12), but no association remained after adjustment for waist circumference (HR=0.99, 95%CI: 0.94–1.03). HCC and ICC results were similar. These findings suggest that excess abdominal size is associated with an increased risk of liver cancer, even among individuals considered to have a normal BMI. However, excess gluteofemoral size alone confers no increased risk. Our findings extend prior analyses, which found an association between excess adiposity and risk of liver cancer, by disentangling the separate effects of excess abdominal and gluteofemoral size through utilization of both waist and hip circumference measurements.

Keywords

hepatocellular carcinoma; intrahepatic cholangiocarcinoma; abdominal obesity; gluteofemoral obesity; epidemiology

Introduction

Obesity, most commonly characterized as having a body mass index (BMI, kg/m^2) greater than 30, is an established risk factor for primary liver cancer (PLC),[1] including the predominant type of liver cancer, hepatocellular carcinoma (HCC),[2] and the second most common type, intrahepatic cholangiocarcinoma (ICC).[3] Liver cancer is typically predated by oxidative stress and inflammation in the liver, which can result from hepatitis B or C virus (HBV or HCV) infection, aflatoxin consumption, smoking, excess alcohol consumption, diabetes, fatty liver, or obesity.[2, 4] To examine obesity, many studies have utilized BMI as a proxy. However, the location of excess body size is critically important, as abdominal and gluteofemoral fat deposits have distinct physiologic properties. Abdominal visceral adipose tissue is hypothesized to predispose individuals to metabolic disorders based on its venous drainage directly into liver portal circulation, potentially leading to lipolysis, insulin resistance, and systematic inflammation.[5–7] In contrast, gluteofemoral adiposity, which is subcutaneous fat deposited in the hip and thigh region, has venous drainage into the systemic circulation and is associated with a reduced risk of diabetes and dyslipidemia.[8, 9] The reduced risk of metabolic complications arising as a result of gluteofemoral adiposity may be due to the delayed release of fatty acids and long-term protection to visceral organs compared to abdominal adiposity.[8]

Previous studies have found inverse associations of excess gluteofemoral size, as measured by hip circumference, with adverse outcomes, including cardiovascular disease[10, 11] and total mortality.[12–14] However, the association between excess gluteofemoral size and liver cancer is understudied. A recent meta-analysis of European prospective cohort studies examined BMI, waist circumference, hip circumference, and waist-to-hip ratio and reported that waist circumference was associated with an increased risk of all obesity-related cancers; however, the study did not examine excess body size in relation to liver cancer, specifically.[15] Additionally, another study based in the Liver Cancer Pooling Project found that BMI and waist circumference were associated with increased risk of liver cancer but did not examine hip circumference, waist-to-hip ratio, or other classifications of body size.[2] Thus, the current study aimed to determine the association between excess abdominal and gluteofemoral body size and risk of liver cancer overall and by histologic type.

Methods

Study Population

As described previously,[16] 15 North American-based cohort studies that are members of the National Cancer Institute's Cohort Consortium agreed to participate in the Liver Cancer Pooling Project. Of these, 12 studies contributed individual participant level data on waist and/or hip circumference: NIH-AARP Diet and Health Study (AARP),[17] The Breast Cancer

Detection Demonstration Project (BCDDP),[18] Women's Health Study (WHS),[19] Physicians' Health Study (PHS),[20] Health Professionals Follow-Up Study (HPFS),[21] New York University Women's Health Study (NYUWHS),[22] Cancer Prevention Study–II Nutrition Cohort (CPS-II),[23] Iowa Women's Health Study (IWHS),[24] Black Women's Health Study (BWHS),[25] Women's Health Initiative (WHI),[26] Nurses' Health Study (NHS),[27] and the Canadian Study of Diet, Lifestyle, and Health (CSDLH)[28] (Supporting Table S1). All studies had complete information available on the entire cohort, with the exception of the CSDLH, which employed a case-cohort design. In the CSDLH, a sub-cohort of 6,127 participants was created by randomly selecting an age-stratified sample of participants from the total cohort at baseline (n=73,909).[28] There were 1,590,648 study participants that were eligible to be included in the current study. We excluded participants with missing age (n=9,813), no follow-up time (n=69,736), no waist or hip measurements (n=311,626), BMI <15 kg/m^2 (n=32,156), and prior diagnosis of stomach, colorectal, lung, pancreas, or breast cancer within 5 years preceding PLC diagnosis (i.e., potential primary cancer of another site that metastasized to the liver, n=73). Our final study population included 1,167,244 individuals (707,281 women and 457,755 men). The individual cohorts were approved by the institutional review boards of the participating institutions; LCPP was approved by the NIH Office of Human Subjects Research.

Outcomes

Linkage to state or national cancer registries or medical/pathology record review was used to ascertain incident PLC (defined as International Classification of Diseases, 10th edition [ICD-10] diagnostic code C22). Cases were further classified as HCC (International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] histology codes of 8170–8175) or ICC (ICD-O-3 histology codes of 8032–8033, 8041, 8050, 8070–8071, 8140–8141, 8160, 8260, 8480, 8481, 8490, and 8560). The current study included 2,208 PLC cases, 1,154 HCC cases, 335 ICC cases, and 1,165,036 non-cases.

Exposure

Waist and hip circumference were available from all studies, with the exception of CPSII which only collected waist circumference. Measurements were taken by trained staff (BCDDP, NYUWHS, WHI) or self-measured by participants (AARP, WHS, PHS, HPFS, CPSII, IWHS, BWHS, NHS, CSDLH). Participants who self-measured were provided specific instructions, which usually included a measuring tape and an illustration demonstrating exactly where on the body to measure. Prior studies have reported self-measured waist and hip circumference to be accurate and reproducible.[29–32] To examine possible effect modification by measurement method in the current analysis, results were stratified by method. Results were similar (data not shown). Waist circumference, in centimeters (cm), was categorized according to previously published literature (women: <70, 70–<80, 80–<90, and ≥90; men: <90, 90–<100, 100–<110, and ≥110),[2] World Health Organization categories (women: <80, 80–<88, and ≥90; men: <94, 94–<102, and ≥102),[33] and using sex- and study-specific quartiles. Similarly, waist-to-hip ratio (WHR) was classified according to previously published literature (women: <0.80, 0.80–<0.85, 0.85–<0.90, and ≥0.90; men: <0.85, 0.85–<0.90, 0.90–<0.95, and ≥0.95),[34] World Health Organization categories (women: <0.85 and ≥0.85; men: <0.90 and ≥0.90),[33] and using sex-

and study-specific quartiles. Hip circumference was categorized using sex- and study-specific quartiles. In addition, we created a cross-classification of sex- and study-specific categories based on waist and hip circumference quartiles (Category 1: Both hip and waist circumference below the 75th percentile; Category 2: Hip circumference above the 75th percentile and waist circumference below the 75th percentile; Category 3: Hip circumference below the 75th percentile and waist circumference above the 75th percentile; Category 4: Both hip and waist circumference above the 75th percentile).

Nested Case-Control Study of HBV/HCV

HBV and HCV are known risk factors for PLC but none of the participating cohorts had previously ascertained HBV/HCV status. Thus, a nested case-control study was conducted within LCPP to determine HBV/HCV status among a subset of participants. Serum was selected from all LCPP participants with samples available for determination of HBV and HCV status, which included 185 PLC cases and 419 controls. To determine HBV status, hepatitis B surface antigen (HBsAg) was assayed using the Bio-Rad GS HBsAg 3.0 enzyme immunoassay (Bio-Rad Laboratories, Redmond, WA, USA). To determine HCV status, antibody to hepatitis C virus (anti-HCV) was assessed using the Ortho HCV Version 3.0 ELISA test system (Ortho-Clinical Diagnostics, Inc.). For the current analysis, we examined whether HBV/HCV was a potential confounder for the association between hip or waist circumference and PLC.

Statistical Analysis

Data were harmonized and pooled for analysis. Between-study heterogeneity was assessed by individual participant data (IPD) random-effects meta-analysis using a chi-square test based on the Q statistic and the I^2 statistic (where 0% indicates no heterogeneity and larger values indicate increasing heterogeneity between studies).[35] Cox proportional hazard regression analysis, with follow-up time as the underlying time metric, was used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of excess body size measurements with PLC, HCC, and ICC, with modification for the case-cohort design of CSDLH.[36] In CSDLH, all cases were weighted as one, and non-cases were weighted according to the inverse of their stratum-specific sampling fractions. All participants in the remaining cohorts were weighted as one. Follow-up of the analytic cohort was from time of waist or hip circumference measurement until the occurrence of an event (i.e., incident liver cancer) or right-censoring (i.e., death, other cancer diagnosis, loss to follow-up, or last date of follow-up), whichever occurred first. A cause-specific analysis was utilized, rather than a competing risk analyses, as it does not require independence of the outcome and competing events to estimate relative risk.[37] The proportional hazards assumption was tested using an interaction between waist circumference, hip circumference, or waist-to-hip ratio with log(time), as a continuous variable, in models that included confounders. No interactions were observed ($p \geq 0.05$). BMI-adjusted (15–<18.5 kg/m^2, 18.5–<25 kg/m^2, 25–<30 kg/m^2, and ≥30 kg/m^2) models are presented for all body fat distribution measurements. Additionally, results for waist circumference were adjusted for hip circumference, while results for hip circumference were adjusted for waist circumference.

Based on existing literature, potential confounders[38] included age, race, sex, alcohol consumption, smoking, and history of diabetes diagnosis. Variables remained in the adjusted model if they were associated with the exposure and outcome and not a mediator between excess body size and liver cancer.[39] Final models included age (continuous), race (white, black, other), sex, alcohol consumption (nondrinker and ≤1.08, 1.09–3.58, 3.59–13.54, >13.54 g/day), and cigarette smoking (never, former, current). Parent study was also adjusted for in all models (AARP, BCDDP, WHS, PHS, HPFS, NYUWHS, CPS-II, IWHS, BWHS, WHI, NHS, and CSDLH). Diabetes is a potential mediator of the association between excess body size and liver cancer and was therefore not included as a potential confounder.

Effect measure modification by sex and menopausal hormone therapy (MHT) use was assessed. We also stratified by BMI category (18.5–<25 kg/m^2, 25–<30 kg/m^2, and ≥30 kg/m^2). Departures from the null were assessed using likelihood ratio tests to compare regression models with and without a multiplicative term.[38] Tests of linear trend were conducted using continuous variables, per 5 cm increase for waist and hip circumference and per 0.05 unit increase for waist-to-hip ratio. All p-values are two-sided. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Data availability

The authors confirm that some access restrictions apply to the data underlying the findings. Data are stored at NCI and initial requests for data may be directed to Katherine McGlynn (mcglynnk@mail.nih.gov).

Ethics approval and consent to participate

The individual cohorts were approved by the institutional review boards of the participating institutions; LCPP was approved by the NIH Office of Human Subjects Research.

Results

Table 1 summarizes participant characteristics. Compared with non-cases, individuals who developed PLC were more likely to be older (median baseline age of cases vs. non-cases: 64 years vs. 60 years), male (68% vs. 39%), heavy alcohol drinkers (quartile 4 of alcohol consumption: 24% vs. 18%), and current/former smokers (67% vs. 55%).

Waist circumference, per 5 cm increase, was associated with an 11% increased risk of PLC (HR=1.11, 95% CI: 1.09–1.14); results were similar by histologic type, HCC (HR=1.14, 95% CI: 1.10–1.17) and ICC (HR=1.11, 95% CI: 1.06–1.16; Table 2). Waist circumference remained associated with an increased risk of PLC after adjustment for BMI (HR=1.08, 95% CI: 1.04–1.12) and hip circumference (HR=1.12, 95% CI: 1.08–1.17), although the association was attenuated in the BMI-adjusted models. The highest sex- and study-specific quartile of waist circumference was associated with a 90% increased risk of PLC compared to the first quartile (HR=1.90, 95% CI: 1.61–2.23); results were similar when examined by *a priori* categories.

Hip circumference, per 5 cm increase, was associated with a 9% increased risk of PLC (HR=1.09, 95% CI: 1.06–1.12), but no association remained after adjustment for BMI (HR=1.01, 95% CI: 0.97–1.05) or waist circumference (HR=0.99, 95%CI: 0.94–1.03; Table 3).

The associations between WHR and liver cancer are shown in Table 4. Participants with roughly equivalent waist and hip circumference (≥0.95 in men and ≥0.90 in women) had a 61% increased risk of PLC (HR=1.61, 95% CI: 1.31–1.98). When adjusted for BMI, results were attenuated but remained significant. Estimates for HCC and ICC were similar.

To examine the separate effects of excess abdominal and gluteofemoral size, quartiles of waist and hip circumference were cross-classified (Table 4). Compared to individuals below the 75th percentile for both waist and hip circumference (Category 1), individuals that had an elevated hip circumference (above the 75th percentile) and low waist circumference (below the 75th percentile) had no increased risk of PLC (Category 2 HR=1.04, 95% CI: 0.82–1.32). However, the highest category of waist circumference was associated with an increased risk of PLC for individuals in the lower (Category 3 HR=1.46, 95% CI: 1.20–1.77) or the higher (Category 4 HR=1.67, 95% CI: 1.45–1.92) category of hip circumference.

There was no evidence of effect measure modification by sex (Tables 2–4 and Supplemental Table S2). Although the p-value for interaction by MHT was not statistically significant, the association between excess body size and PLC appeared stronger among women who used MHT (Supplemental Table S3). For example, the highest study-specific quartile of waist circumference was associated with a 3-fold increased risk of PLC among MHT users (HR=2.87, 95% CI: 1.86–4.42), while MHT non-users only had a 35% increased risk (HR=1.35, 95% CI: 0.89–2.03, p-interaction=0.09).

When stratified by BMI categories (Supplemental Table S4), waist circumference was associated with an increased risk of PLC in all BMI categories (18.5–<25 kg/m^2 HR=1.14, 95% CI: 1.07–1.21, 25–<30 kg/m^2 HR=1.06, 95% CI: 1.00–1.12, and ≥30 kg/m^2 HR=1.07, 95% CI: 1.02–1.12).

Low-to-moderate heterogeneity was observed between studies (waist circumference overall I^2=38.8%, p=0.08, hip circumference overall I^2=59.2%, p=0.006; Supplemental Figures 1–4).

We tested a subset of both PLC cases (n=185) and matched controls (n=419) for hepatitis B surface antigen (HBsAg) and antibody to HCV (anti-HCV). For HBV, 9 PLC cases (4.9%) and 7 controls (1.7%) were positive for HBsAg. For HCV, 32 PLC cases (17.3%) and 6 controls (1.4%) were positive for anti-HCV. There was no association between HCV or HBV status and waist or hip circumference (data not shown).

Discussion

In our pooled analysis of 12 North American-based prospective cohort studies, comprising over 1.16 million adults, excess abdominal size was associated with a significantly increased risk of PLC. Each 5 cm increase in waist circumference was associated with an 11%

increased risk of PLC. Waist circumference remained associated with an increased risk of PLC, even after adjustment for BMI or hip circumference. Further, when we examined the cross-classification of waist and hip circumference, the highest category of waist circumference was associated with a 46–67% increased risk of PLC, regardless of hip circumference. However, individuals in the highest category of hip, but not waist, circumference had no increased risk of PLC. Results were similar by sex, BMI, MHT use, and for the two main histologic types of PLC, HCC and ICC. Existing heterogeneity reported between studies may be explained by methodological variability in cohort study design (e.g., measurement method), though the estimated HRs were similar across stratifications (i.e., waist circumference per 5 cm increase: self-reported HR=1.10, 95% CI 1.07–1.12; direct measurement HR=1.13, 95% CI 1.07–1.20). Additionally, when we examined the influence of individual studies, whereby we excluded one study at a time and the summary effect estimates were re-estimated, results were similar.

Our findings extend prior analyses, that have found an association between excess adiposity (i.e., BMI ≥30 or increased waist circumference) and risk of liver cancer,[1–3] by disentangling the separate effects of excess abdominal and gluteofemoral size through utilization of both waist and hip circumference measurements. This approach enabled us to identify the region of excess body size associated with liver cancer risk, specifically excess abdominal size. One previous study, utilizing data from seven European cohort studies, reported that one standard deviation (~11 cm) increase in waist circumference was associated with a 13% increased risk of *all* obesity-associated cancers, which included liver cancer.[15] However, this study did not have a sufficient sample size to examine liver cancer as a distinct outcome.

Obesity is a heterogeneous condition, with abdominal and gluteofemoral fat deposits having distinct properties. Though waist circumference and the other anthropometric measurements used here are not exact measurements of body fat, excess abdominal or gluteofemoral size can be indicative of fat in those regions and may be good proxies for risk associated with these specific body fat distributions in both men and women.[40–42] As reported in the current study, excess abdominal size conferred an increased risk of liver cancer, which was independent of excess generalized or gluteofemoral size. Conversely, we found that excess gluteofemoral size, as measured by hip circumference, conferred no increased risk after accounting for excess abdominal size. Specifically, among those in the group with high hip and low waist circumference, representing excess gluteofemoral size, there was no increased liver cancer risk. While among individuals with a low hip circumference and high waist circumference, representing excess abdominal size, we saw a significantly increased risk of liver cancer, which remained significant after BMI adjustment. Those with high hip and high waist circumference, representing the greatest general excess size, also had a significantly increased risk of liver cancer. This suggests that the obesity-liver cancer association is primarily driven by excess abdominal size. Moreover, excess abdominal size, indicative of abdominal adiposity, is often considered a marker of metabolic dysregulation in overweight or obese individuals. However, we report herein that increased waist circumference conferred an increased risk of liver cancer even among “normal” weight individuals (18.5–<25 kg/m^2), which suggests that it could be important to target waist circumference for prevention strategies, even among individuals with a normal BMI.

Why excess abdominal and gluteofemoral size would have different effects on the risk of PLC is not certain, but several plausible mechanisms are hypothesized, presuming that excess size is indicative of adiposity. Visceral, or intraperitoneal, fat accounts for approximately 1/3 of abdominal fat,[43] which also includes intraabdominal retroperitoneal fat and subcutaneous fat.[7] Visceral fat is metabolically active and releases substantial amounts of growth factors, inflammatory markers, free fatty acids (which contribute to insulin resistance), locally produced estrogen, and adipokines, which might contribute to cancer development.[44, 45] Only visceral, and not subcutaneous, adipose tissue has venous drainage into the portal vein and therefore has a direct connection with the liver. Due to the higher lipolytic activity of visceral versus subcutaneous adipocytes, free fatty acids are more rapidly mobilized from visceral fat cells. Chronic exposure to free fatty acids contributes to β-cell failure and type 2 diabetes.[44] Additionally, as more fat is accumulated in the midsection, adipose tissue undergoes tissue remodeling to accommodate excess energy storage, resulting in chronic inflammation that can lead to severe hepatic injury.[46]

In contrast to visceral fat, gluteofemoral fat, which is subcutaneous fat deposited in the hip and thigh region, is thought to act as a ‘metabolic sink’, entrapping fatty acids and preventing lipid overflow in tissues surrounding abdominal organs.[8, 47] The primary function of subcutaneous adipose tissue is fatty acid storage, which are reintroduced into the circulation in the form of non-esterified fatty acids during periods of fasting, exercise, or starvation.[8] Additionally, excess hip size is associated with lower risk of various metabolic dysfunctions, including diabetes.[48–50] In persons with a greater hip circumference compared to waist circumference, excess hip size may offer long-term protection from inflammation and elevated lipid levels.

Liver cancer incidence has notable sex differences, with rates among males being two to three-fold higher than rates among females.[4] However, sex differences in liver cancer rates are most pronounced around the menopause transition (45–60 years of age), with males having four-fold higher rates than females during this period.[51] While estrone and estradiol production in visceral adipose tissue increases with increasing waist circumference, estradiol is produced more efficiently in subcutaneous fat.[52] Men and post-menopausal women have more visceral fat deposits than pre-menopausal women,[53] but post-menopausal women still have a lower proportion of abdominal fat compared to men.[54] In the current study, we did not find effect measure modification by sex, which may be in part due to the female study population predominately including post-menopausal women. Additionally, MHT use did not modify the associations among post-menopausal women. However, the associations between excess abdominal size and liver cancer were slightly more pronounced among MHT users compared to non-users. While post-menopausal women are using MHT, they typically do not have adiposity gains seen in post-menopausal women not using MHT. However, we were only able to examine ever use of MHT. Thus, the women classified as using MHT may not have been currently using MHT when they had their waist and hip circumference measurements taken.

The current study has several strengths, including long follow-up time and wide geographic representation of North America. The large sample size of our study provided the statistical power to stratify by BMI, sex, and histologic type within each adiposity measure. Due to the

low incidence of liver cancer in North America and other western countries,[55] other studies conducted in these geographic locations have been underpowered to examine the association between excess body size distribution and liver cancer risk by BMI, sex, and histologic type. Additionally, we were able to identify HCC and ICC cases through cancer registries or medical record review, minimizing misclassification of metastatic tumors. Most importantly, we were able to mutually adjust our analyses for each body size measure when examining waist and hip circumference. The inclusion of this adjustment allowed us to isolate the effect of each body size distribution profile; without it, all three measures could simply be indicative of general adiposity, which does not offer insight to the potential biological mechanisms involved.

Our study was not without limitations. Waist circumference, hip circumference, and waist-to-hip ratio are proxies for fat deposition, and thus are imperfect measures of abdominal and gluteofemoral adiposity. However, studies have shown that anthropometric measures tend to reliably measure total fat and adiposity risk when compared to gold standard measurements.[40–42] Several cohorts pooled for this analysis collect only self-measured data on waist and hip circumference, which could result in exposure misclassification. However, this potential limitation was lessened by the detailed instructions given to participants to take these measurements. Additionally, individuals with higher BMI or larger waist circumference tend to underestimate self-measured waist circumference,[56, 57] which would bias our results towards the null. Another limitation was the lack of information on potential confounders such as physical activity, diet, and HBV and HCV infection status. Data on physical activity and diet either were not ascertained by the parent cohort or could not be harmonized in a meaningful way to examine as potential confounders. For individuals with HBV or HCV status available, there was no association between these potential covariates and the exposures of excess body size. While this suggests that HBV and HCV are not confounders of the association between excess body size and PLC, our sample size was limited to examine this. Lastly, further research is needed to determine whether our results are generalizable to individuals of non-European descent, due to the characteristics of the current study population.

In conclusion, these results suggest that excess abdominal size is associated with an increased risk of liver cancer, independent of excess generalized or gluteofemoral size, and that excess gluteofemoral size does not confer an increased risk of liver cancer independent of waist circumference. Further studies should investigate whether these associations exist in other populations, including groups at high risk for liver cancer. Additionally, in a study population with repeated measures data, it would be valuable to examine risk of liver cancer among those with changing excess adiposity over time (i.e., reduced or increased waist or hip circumference over time). Future studies should also utilize imaging techniques, rather than anthropometric measurements, to further disentangle the association between visceral versus subcutaneous fat and liver cancer. Overall, these results suggest that targeted prevention efforts, focused on reducing abdominal obesity, even among normal weight individuals, could potentially be an important intervention opportunity for liver cancer, and potentially other obesity-related cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HCC	hepatocellular carcinoma
ICC	intrahepatic cholangiocarcinoma
HBV	hepatitis B virus
HCV	hepatitis C infection
BMI	body mass index
AARP	NIH-AARP Diet and Health Study
BCDDP	The Breast Cancer Detection Demonstration Project
WHS	Women's Health Study
PHS	Physicians' Health Study
HPFS	Health Professionals Follow-Up Study
NYUWHS	New York University Women's Health Study
CPS-II	Cancer Prevention Study—II Nutrition Cohort

IWHS	Iowa Women's Health Study
BWHS	Black Women's Health Study
WHI	Women's Health Initiative
NHS	Nurses' Health Study
CSDLH	Canadian Study of Diet, Lifestyle, and Health
WHR	waist-to-hip ratio
ICD-10	International Classification of Diseases, 10th edition
ICD-O-3	International Classification of Diseases for Oncology, 3rd edition
NAFLD	non-alcoholic fatty liver disease
HBsAg	hepatitis B surface antigen
anti-HCV	antibody to hepatitis C virus

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Novelty and Impact

Utilizing data from 12 North American-based, prospective studies with over 2,200 liver cancer cases within the Liver Cancer Pooling Project, we report that excess abdominal size is associated with an increased risk of liver cancer, even among individuals considered to have a normal body mass index. However, excess gluteofemoral size alone confers no increased risk.

Table 1.

Characteristics of participants in the Liver Cancer Pooling Project.

	Non-cases (N=1,165,036)		Primary Liver Cancer (N=2,208)		Hepatocellular Carcinoma (N=1,154)		Intrahepatic Cholangiocarcinoma (N=335)	
Age at entry, N (%)								
<50	151,234	(13.0)	55	(2.5)	25	(2.2)	7	(2.1)
50–59	395,084	(33.9)	572	(25.9)	311	(26.9)	87	(26.0)
60–69	531,168	(45.6)	1404	(63.6)	735	(63.7)	210	(62.7)
≥70	87,550	(7.5)	177	(8.0)	83	(7.2)	31	(9.3)
Sex, N (%)								
Male	457,755	(39.3)	1495	(67.7)	835	(72.4)	180	(53.7)
Female	707,281	(60.7)	713	(32.3)	319	(27.6)	155	(46.3)
Race, N (%)								
White	1,010,667	(86.7)	1913	(86.6)	974	(84.4)	298	(89.0)
Black	97,143	(8.3)	99	(4.5)	54	(4.7)	12	(3.6)
Asian/Pacific Islander	9,888	(0.8)	25	(1.1)	15	(1.3)	4	(1.2)
American Indian/Alaskan Native	2,626	(0.2)	8	(0.4)	4	(0.3)	2	(0.6)
Other	31,104	(2.7)	126	(5.7)	84	(7.3)	18	(5.4)
Missing	13,608	(1.2)	37	(1.7)	23	(2.0)	1	(0.3)
Alcohol, ever, N (%)								
No	299,308	(25.7)	623	(28.2)	345	(29.9)	75	(22.4)
Yes	851,745	(73.1)	1562	(70.7)	797	(69.1)	256	(76.4)
Unknown	13,983	(1.2)	23	(1.0)	12	(1.0)	4	(1.2)
Alcohol, grams/day, N (%)								
Non-drinker	299,308	(25.7)	623	(28.2)	345	(29.9)	75	(22.4)
Quartile 1: ≤1.08	200,161	(17.2)	343	(15.5)	179	(15.5)	66	(19.7)
Quartile 2: 1.09–3.58	205,391	(17.6)	357	(16.2)	173	(15.0)	55	(16.4)
Quartile 3: 3.59–13.54	216,550	(18.6)	320	(14.5)	150	(13.0)	51	(15.2)
Quartile 4: >13.54	214,283	(18.4)	533	(24.1)	288	(25.0)	83	(24.8)
Missing	29,343	(2.5)	32	(1.4)	19	(1.6)	5	(1.5)
Cigarette smoking, N (%)								
Never smoker	499,215	(42.8)	670	(30.3)	335	(29.0)	114	(34.0)
Former smoker	493,902	(42.4)	1162	(52.6)	627	(54.3)	175	(52.2)
Current smoker	143,883	(12.4)	308	(13.9)	153	(13.3)	38	(11.3)
Ever smoker	1,445	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Missing	26,591	(2.3)	68	(3.1)	39	(3.4)	8	(2.4)

Table 2.

Adjusted[a] hazard ratios (HR) and 95% confidence intervals (CI) for associations between waist Circumference and hepatocellular carcinoma and intrahepatic cholangiocarcinoma risk, Liver Cancer Pooling Project.

		Primary Liver Cancer						Hepatocellular Carcinoma					Intrahepatic Cholangiocarcinoma				
				BMI Adjusted	Hip Circumference Adjusted					BMI Adjusted	Hip Circumference Adjusted				BMI Adjusted	Hip Circumference Adjusted	
Waist Circumference	Non-case N	Case N	HR (95% CI)	HR (95% CI)	Non-case N	Case N	HR (95% CI)	Case N	HR (95% CI)	HR (95% CI)	Case N	HR (95% CI)	Case N	HR (95% CI)	HR (95% CI)	Case N	HR (95% CI)
Centimeters																	
M: <90, F: <70	122,764	149	1.00	1.00	103,707	130	1.00	75	1.00	1.00	60	1.00	19	1.00	1.00	17	1.00
M: 90-<100, F: 70-<80	257,505	337	1.16 (0.97–1.39)	1.08 (0.90–1.30)	212,187	286	1.10 (0.90–1.34)	174	1.15 (0.89–1.49)	1.03 (0.79–1.34)	139	1.11 (0.83–1.50)	58	1.50 (0.89–2.51)	1.41 (0.83–2.41)	50	1.37 (0.78–2.38)
M: 100-<110, F: 80-<90	208,677	341	1.62 (1.35–1.95)	1.39 (1.13–1.70)	170,882	313	1.60 (1.28–1.99)	171	1.64 (1.26–2.12)	1.26 (0.95–1.68)	153	1.66 (1.20–2.30)	59	2.01 (1.20–3.38)	1.78 (1.01–3.14)	54	1.83 (1.03–3.25)
M: ≥110, F: ≥90	192,688	320	2.06 (1.70–2.50)	1.53 (1.18–1.98)	161,050	284	1.88 (1.44–2.47)	177	2.25 (1.71–2.96)	1.35 (0.94–1.94)	151	2.04 (1.37–3.03)	61	2.58 (1.52–4.39)	2.02 (0.99–4.14)	55	2.08 (1.04–4.16)
$P_{interaction}$[c]			*0.5*						*0.8*					*1.0*			
WHO cutpoints, cm																	
M: <94, F: <80	324,570	365	1.00	1.00	275,332	321	1.00	177	1.00	1.00	146	1.00	60	1.00	1.00	54	1.00
M: 94-<102, F: 80-<88	197,508	300	1.24 (1.08–1.43)	1.12 (0.96–1.30)	159,991	265	1.18 (1.00–1.38)	158	1.31 (1.07–1.60)	1.12 (0.91–1.38)	133	1.24 (0.97–1.57)	55	1.42 (0.98–2.05)	1.27 (0.86–1.87)	49	1.28 (0.86–1.91)
M: ≥102, F: ≥88	259,556	482	1.66 (1.46–1.89)	1.26 (1.07–1.50)	212,503	427	1.47 (1.22–1.76)	262	1.84 (1.53–2.22)	1.22 (0.96–1.55)	224	1.61 (1.24–2.10)	82	1.72 (1.24–2.39)	1.29 (0.82–2.05)	73	1.32 (0.85–2.06)
$P_{interaction}$[c]			*0.9*						*0.5*					*0.6*			
Sex- and study-specific																	
Quartile 1	207,659	205	1.00	1.00	172,277	178	1.00	102	1.00	1.00	81	1.00	33	1.00	1.00	30	1.00

		Primary Liver Cancer						Hepatocellular Carcinoma					Intrahepatic Cholangiocarcinoma				
				BMI Adjusted	Hip Circumference Adjusted					BMI Adjusted	Hip Circumference Adjusted				BMI Adjusted	Hip Circumference Adjusted	
Waist Circumference	**Non-case N**	**Case N**	**HR (95% CI)**	**HR (95% CI)**	**Non-case N**	**Case N**	**HR (95% CI)**	**Case N**	**HR (95% CI)**	**HR (95% CI)**	**Case N**	**HR (95% CI)**	**Case N**	**HR (95% CI)**	**HR (95% CI)**	**Case N**	**HR (95% CI)**
Quartile 2	203,479	250	1.14 (0.95–1.36)	1.06 (0.89–1.27)	168,364	210	1.08 (0.89–1.31)	130	1.18 (0.92–1.51)	1.06 (0.82–1.36)	104	1.14 (0.86–1.51)	45	1.30 (0.83–2.05)	1.20 (0.76–1.92)	38	1.15 (0.70–1.88)
Quartile 3	185,588	294	1.48 (1.25–1.75)	1.30 (1.08–1.56)	154,737	272	1.48 (1.21–1.80)	147	1.48 (1.16–1.89)	1.19 (0.92–1.54)	134	1.53 (1.14–2.05)	58	1.87 (1.22–2.87)	1.62 (0.99–2.63)	51	1.62 (0.98–2.65)
Quartile 4	184,908	398	1.90 (1.61–2.23)	1.46 (1.18–1.80)	152,448	353	1.81 (1.45–2.26)	218	2.10 (1.67–2.64)	1.35 (1.00–1.82)	184	1.95 (1.41–2.71)	61	2.01 (1.32–3.06)	1.51 (0.84–2.71)	57	1.71 (0.96–3.04)
$P_{interaction}$ [c]			*0.3*						*0.3*					*0.4*			
Per 5 cm increase			1.11 (1.09–1.14)	1.08 (1.04–1.12)			1.12 (1.08–1.17)		1.14 (1.10–1.17)	1.07 (1.02–1.13)		1.15 (1.09–1.21)		1.11 (1.06–1.16)	1.08 (0.99–1.17)		1.10 (1.02–1.18)
P_{trend} [b]			*<0.001*	*<0.001*			*<0.001*		*<0.001*	*0.01*		*<0.001*		*<0.001*	*0.084*		*0.02*
$P_{interaction}$ [c]			*0.6*						*0.5*					*0.7*			

[a] Adjusted for age (continuous), race (white, black, other), sex, alcohol consumption (nondrinker and ≤1.08, 1.09–3.58, 3.59–13.54, >13.54 g/day), cigarette smoking (never, former, current), and study (AARP, BCDDP, WHS, PHS, HPFS, NYUWHS, CPS-II, IWHS, BWHS, WHI, NHS, and CSDLH).

[b] P_{trend} from Wald tests.

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

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Table 3.

Adjusted[a] hazard ratios (HR) and 95% confidence intervals (CI) for associations between waist Circumference and hepatocellular carcinoma and intrahepatic cholangiocarcinoma risk, Liver Cancer Pooling Project.

	Primary Liver Cancer							Hepatocellular Carcinoma					Intrahepatic Cholangiocarcinoma				
				BMI Adjusted	Waist Circumference Adjusted					BMI Adjusted	Waist Circumference Adjusted				BMI Adjusted	Waist Circumference Adjusted	
Hip Circumference	**Non-case N**	**Case N**	**HR (95% CI)**	**HR (95% CI)**	**Non-case N**	**Case N**	**HR (95% CI)**	**Case N**	**HR (95% CI)**	**HR (95% CI)**	**Case N**	**HR (95% CI)**	**Case N**	**HR (95% CI)**	**HR (95% CI)**	**Case N**	**HR (95% CI)**
Sex- and study-specific																	
Quartile 1	183,297	238	1.00	1.00	182,631	236	1.00	110	1.00	1.00	110	1.00	39	1.00	1.00	39	1.00
Quartile 2	155,733	198	1.00 (0.83–1.19)	0.92 (0.77–1.10)	155,346	198	0.88 (0.73–1.05)	107	1.14 (0.89–1.47)	1.03 (0.80–1.32)	107	0.99 (0.76–1.27)	28	0.82 (0.50–1.34)	0.78 (0.47–1.29)	28	0.73 (0.44–1.20)
Quartile 3	159,909	267	1.26 (1.07–1.48)	1.06 (0.89–1.26)	159,500	267	0.97 (0.81–1.16)	117	1.22 (0.95–1.56)	0.95 (0.73–1.23)	117	0.89 (0.67–1.17)	57	1.60 (1.06–2.42)	1.42 (0.89–2.26)	57	1.26 (0.80–1.98)
Quartile 4	150,757	313	1.53 (1.30–1.79)	1.06 (0.86–1.30)	150,349	312	0.92 (0.73–1.14)	169	1.76 (1.39–2.21)	1.03 (0.77–1.38)	169	0.97 (0.70–1.33)	52	1.58 (1.04–2.39)	1.21 (0.67–2.19)	52	0.99 (0.55–1.76)
$P_{interaction}$[c]			*0.5*						*0.2*					*0.1*			
Per 5 cm increase			1.09 (1.06–1.12)	1.01 (0.97–1.05)			0.99 (0.94–1.03)		1.12 (1.08–1.16)	0.99 (0.93–1.05)		0.99 (0.93–1.05)		1.11 (1.04–1.18)	1.07 (0.97–1.19)		1.02 (0.93–1.13)
P_{trend}[b]			*<0.001*	*0.7*			*0.5*		*<0.001*	*0.7*		*0.7*		*0.001*	*0.2*		*0.7*
$P_{interaction}$[c]			*0.8*						*0.5*					*0.5*			

[a] Adjusted for age (continuous), race (white, black, other), sex, alcohol consumption (nondrinker and ≤1.08, 1.09–3.58, 3.59–13.54, >13.54 g/day), cigarette smoking (never, former, current), and study (AARP, BCDDP, WHS, PHS, HPFS, NYUWHS, CPS-II, IWHS, BWHS, WHI, and CSDLH).

[b] P_{trend} from Wald tests.

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

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Table 4.

Adjusted[a] Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Associations between Body Fat Distribution Metrics and Liver Cancer Risk, Liver Cancer Pooling Project.

		Primary Liver Cancer			Hepatocellular Carcinoma			Intrahepatic Cholangiocarcinoma		
				BMI Adjusted			BMI Adjusted			BMI Adjusted
Waist-to-Hip Ratio	**Non-case N**	**Case N**	**HR (95% CI)**	**HR (95% CI)**	**Case N**	**HR (95% CI)**	**HR (95% CI)**	**Case N**	**HR (95% CI)**	**HR (95% CI)**
WHR cutpoints										
M: <0.85, F: <0.80	230,387	164	1.00	1.00	74	1.00	1.00	40	1.00	1.00
M: 0.85-<0.90, F: 0.80-<0.85	136,303	181	1.31 (1.05–1.62)	1.19 (0.96–1.48)	88	1.36 (0.99–1.86)	1.20 (0.87–1.65)	36	1.23 (0.77–1.98)	1.13 (0.71–1.79)
M: 0.90-<0.95, F: 0.85-<0.90	135,443	275	1.42 (1.14–1.75)	1.24 (1.00–1.53)	134	1.46 (1.06–2.00)	1.20 (0.87–1.65)	46	1.41 (0.90–2.22)	1.23 (0.78–1.94)
M: ≥0.95, F: ≥0.90	145,693	393	1.61 (1.31–1.98)	1.29 (1.04–1.60)	207	1.73 (1.26–2.37)	1.26 (0.91–1.75)	54	1.47 (0.95–2.28)	1.19 (0.75–1.90)
WHO cutpoints										
M: <0.90, F: <0.85	366,690	345	1.00	1.00	162	1.00	1.00	76	1.00	1.00
M: ≥0.90, F: ≥0.85	281,136	668	1.29 (1.11–1.50)	1.13 (0.97–1.32)	341	1.33 (1.06–1.66)	1.10 (0.88–1.37)	100	1.29 (0.94–1.76)	1.13 (0.81–1.58)
Sex- and study-specific										
Quartile 1	163,980	190	1.00	1.00	87	1.00	1.00	30	1.00	1.00
Quartile 2	161,416	222	1.05 (0.87–1.27)	1.00 (0.83–1.21)	120	1.23 (0.95–1.61)	1.14 (0.88–1.50)	40	1.29 (0.81–2.08)	1.23 (0.76–2.00)
Quartile 3	162,073	245	1.17 (0.98–1.40)	1.06 (0.88–1.27)	110	1.14 (0.87–1.49)	0.99 (0.75–1.30)	53	1.70 (1.09–2.67)	1.55 (0.98–2.45)
Quartile 4	160,357	356	1.59 (1.34–1.89)	1.33 (1.12–1.60)	186	1.80 (1.40–2.32)	1.40 (1.08–1.82)	53	1.75 (1.11–2.73)	1.49 (0.90–2.45)
Per 0.05 unit increase			1.11 (1.08–1.14)	1.07 (1.04–1.11)		1.12 (1.08–1.16)	1.07 (1.02–1.13)		1.10 (1.04–1.16)	1.07 (0.99–1.15)
P_{trend}[b]			*<0.001*	*<0.001*		*<0.001*	*0.007*		*0.001*	*0.08*
$P_{interaction}$[c]			*0.7*			*0.3*			*0.1*	
Quartile Cross-Classification										
Sex- and study-specific										
Category 1: Hip and Waist <P75	448,999	595	1.00	1.00	281	1.00	1.00	107	1.00	1.00

		Primary Liver Cancer			Hepatocellular Carcinoma			Intrahepatic Cholangiocarcinoma		
				BMI Adjusted			BMI Adjusted			BMI Adjusted
Waist-to-Hip Ratio	**Non-case N**	**Case N**	**HR (95% CI)**	**HR (95% CI)**	**Case N**	**HR (95% CI)**	**HR (95% CI)**	**Case N**	**HR (95% CI)**	**HR (95% CI)**
Category 2: Hip >P75, Waist <P75	46,379	65	1.04 (0.82–1.32)	0.91 (0.71–1.17)	38	1.23 (0.90–1.68)	1.01 (0.74–1.40)	12	1.08 (0.59–1.98)	0.94 (0.50–1.77)
Category 3: Hip <P75, Waist >P75	48,478	106	1.46 (1.20–1.77)	1.25 (1.02–1.53)	53	1.57 (1.19–2.06)	1.22 (0.91–1.64)	17	1.47 (0.88–2.45)	1.27 (0.74–2.19)
Category 4: Hip and Waist >P75	103,970	247	1.67 (1.45–1.92)	1.24 (1.02–1.51)	131	1.87 (1.53–2.28)	1.18 (0.89–1.57)	40	1.60 (1.12–2.29)	1.19 (0.71–1.99)
$P_{interaction}$ [b]			*0.9*			*0.3*			*0.8*	

[a] Adjusted for age (continuous), race (white, black, other), sex, alcohol consumption (nondrinker and ≤1.08, 1.09–3.58, 3.59–13.54, >13.54 g/day), cigarette smoking (never, former, current), and study (AARP, BCDDP, WHS, PHS, HPFS, NYUWHS, CPS-II, IWHS, BWHS, WHI, and CSDLH).

[b] P_{trend} from Wald tests.

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