Dose–Response Association between Adiposity and Liver Cancer Incidence: A Prospective Cohort Study among Non-Smoking and Non–Alcohol-Drinking Chinese Women

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ABSTRACT

Background: Based on a population with very low prevalence of smoking and alcohol drinking, we examined the associations between overall obesity and fat distribution in middle age, obesity in early adulthood, and adult weight gain with the risk of liver cancer incidence.

Methods: The associations between body mass index (BMI) at study enrollment and at age 20, waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), adult weight gain, and annual average weight gain with the risk of liver cancer were estimated using Cox regression models. Multivariable-adjusted HRs and 95% confidence intervals (CIs) were calculated.

Results: After a mean follow-up time of 17.5 years, 241 liver cancer cases were identified from 69,296 participants. The HRs for per 5-kg/m^2 increment of BMI, per 10-cm increment of WC and HC, and per 0.1-unit increment of WHtR in middle age were 1.29 (95% CI, 1.07–1.57), 1.23 (95% CI, 1.05–1.43), 1.30 (95% CI, 1.10–1.55), and 1.37 (95% CI, 1.07–1.75), respectively. The HRs for per 5-kg increment of absolute adult weight gain and per 0.5-kg/year increment of annual average weight gain were 1.15 (95% CI, 1.06–1.25) and 1.44 (95% CI, 1.08–1.92).

Conclusions: Overall and abdominal obesity in middle age and weight gain through adulthood were positively associated with liver cancer risk among non-smoking and non–alcohol-drinking women.

Impact: Based on a cohort of non-smoking and non–alcohol-drinking women, the current study confirmed the association between obesity in middle age and increased liver cancer risk and suggested weight gain through adulthood as a risk factor for liver cancer.

Introduction

Liver cancer is the sixth most common incidence of cancer and the third leading cause of cancer death worldwide, causing about 906,000 new cases and 830,000 deaths globally in 2020 (1). Except for established risk factors, such as hepatitis virus, aflatoxin, and aristolochic acid (2, 3), the association between body fatness and the risk of liver cancer has been extensively investigated (4–6). Overall obesity was widely known to be associated with an increased risk of liver cancer. The World Cancer Research Fund (WCRF) Continuous Update Project Expert Report 2018 concluded that there was strong evidence to establish body mass index (BMI), a measure of overall obesity, as a risk factor for liver cancer (4). Abdominal obesity, generally characterized by waist circumference (WC) and waist-to-hip ratio (WHR), was also reported to have extra effects on liver cancer risk beyond BMI (7–9). Few studies have examined the association between early-life adiposity and dynamic change of obesity throughout the life course with the risk of liver cancer, but the results were inconsistent (9–11).

Cigarette smoking and alcohol drinking are two important confounders in studies of obesity and health outcomes (12). Smokers tend to be leaner, and the exposure effect of obesity on health outcomes may be underestimated among a population with high smoking rate. Alcohol drinking is an established risk factor for liver cancer and has been identified to have a synergic effect with obesity (13). The existence of these confounders may distort the real association between adiposity and the risk of liver cancer. Multivariable adjustment is the most commonly used way to control for confounding, but it is impossible to remove all confounding through statistical control; there is room for residual confounding. An alternative way to address these confounding is to restrict the analyses to non-smoking and non–alcohol-drinking population. The Shanghai Women's Health Study (SWHS) is a large prospective and population-based cohort study conducted in urban Shanghai residents. Low consumption of tobacco (2.8%) and use of alcohol (2.2%) were noteworthy characteristics of this study (14), which afforded the opportunity to evaluate the effect of adiposity on liver cancer incidence where otherwise smoking and alcoholic drinking might be significant confounders.

Using the data of the SWHS, the aim of this study is to systematically examine the associations between overall obesity and fat distribution in middle age, obesity in early adulthood, and weight gain through adulthood with the risk of liver cancer among non-smoking and non–alcohol-drinking women.

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Materials and Methods

Study population

Detailed information on the SWHS has been described elsewhere (14). Briefly, 74,941 women ages 40 to 70 years from seven urban communities in Shanghai, China, were enrolled from 1997 to 2000, with a response rate of 92.7%. In-person interviews were conducted to collect information on demographic characteristics, anthropometric measurements, reproductive history, medical history, dietary habits, and other lifestyle factors by trained staff. All participants provided written informed consent at baseline and follow-up surveys. This study was approved by the Renji Hospital Ethics Committee of Shanghai Jiao Tong University School of Medicine (KY2019–197).

The current study further excluded participants (i) who reported a previous cancer diagnosis at baseline interviews ($N = 1{,}598$); (ii) loss to follow-up shortly after study enrollment ($N = 3$); (iii) without exact primary cancer site or diagnosis date ($N = 311$); (iv) diagnosed with cancer *in situ* during follow-up ($N = 135$); (v) with extreme total energy intake that <500 kcal/day or >3,500 kcal/day (ref. 15); $N = 125$); (vi) with incomplete information on the key covariates ($N = 105$); and (vii) who reported history of cigarette smoking or alcohol drinking (smoking was defined as ever smoked at least one cigarette per day for more than six months continuously; alcohol drinking was defined as ever consumed alcohol at least three times per week for more than six months continuously. $N = 3{,}371$), yielding 69,296 participants included in the analysis. The flow diagram for participant inclusion was attached in Supplementary Fig. S1.

Anthropometric measurements and categorization

Anthropometrics including height, weight, WC, and hip circumference (HC) were recorded according to a standardized protocol at the end of the baseline interview. Two measurements were taken, with a tolerance for differences of less than 1.0 cm for height, WC, and HC, and 1.0 kg for weight. A third measurement should be taken if the difference between the first two measurements was larger than the defined tolerances. The average value of the two closest measurements was used for further analysis. Height and weight at 20 years old were obtained by a self-administrated questionnaire. BMI at baseline and at 20 years old was calculated as weight divided by height squared (kg/m^2). Adult weight gain was calculated by subtracting the recalled weight at 20 years old from measured weight at study enrollment. Annual average weight gain was further calculated as the weight gain divided by years between 20 years old and study enrollment. WHR and waist-to-height ratio (WHtR) were calculated by division from relevant measurements.

In our analysis, BMI at baseline was categorized by three different ways: (i) the Chinese classification (16): underweight (<18.50 kg/m^2), normal weight (18.50–23.99 kg/m^2), overweight (24.00–27.99 kg/m^2), and obese (≥28.00 kg/m^2); (ii) the World Health Organization (WHO) classification (17): underweight (<18.50 kg/m^2), normal weight (18.50–24.99 kg/m^2), overweight (25.00–29.99 kg/m^2), and obese (≥30.00 kg/m^2); and (iii) four groups based on quartile distributions. Considering the small number of underweight participants (7 cases only), we combined the underweight group with the normal weight group in two predefined BMI categories. The BMI at 20 years old of our cohort members was generally low, and very few individuals were overweight/obese at their age of 20 according to the Chinese/WHO classification. Therefore, this variable was categorized only by the quartile distributions. Adult weight gain was categorized into five groups: (i) ≤5.00 kg (including any level of weight loss), (ii) 5.01–10.00 kg, (iii) 10.01–15.00 kg, (iv) 15.01–20.00 kg, and (v) >20.00 kg. Annual average weight gain, WC, HC, WHR, and WHtR were categorized into four groups based on corresponding quartile distributions. WC was also dichotomized into two groups: <85 cm and ≥85 cm (18).

Outcome ascertainment

The method of follow-up used in the SWHS was routinely active follow-ups, coupled with annual record linkage to the Shanghai Cancer Registry and Shanghai Vital Statistics Registry (19). In-person follow-up surveys were conducted every 3 to 4 years, with response rates of 99.7% (2000–2002), 98.7% (2002–2004), 94.9% (2004–2006), 92.3% (2007–2010), and 91.1% (2012–2017) for the first to the fifth interviews. Cancer cases were coded using the International Classification of Diseases, the Ninth Revision (ICD-9; ref. 20). Liver cancer was defined as a primary tumor with an ICD-9 code of 155. All possible cancer diagnoses were verified through medical records review by a panel of clinical and pathologic experts. In the current analysis, follow-up information was censored on December 31, 2016.

Statistical analyses

Baseline characteristics were described as frequencies for categorical variables and means with SDs for continuous variables. The differences between participants with and without liver cancer were compared using χ^2 tests for categorical variables and Wilcoxon–Mann–Whitney tests for continuous variables.

The association between anthropometric measurements and the risk of liver cancer was analyzed using Cox proportional hazard models (21), with follow-up time as the time metric. The proportional hazard assumption was examined by calculating the correlation between the Schoenfeld residuals of each covariate and the follow-up time (22). No evidence of a violation of the assumption was detected. The follow-up time was calculated from the date of study enrollment to the date of liver cancer diagnosis, or to the date of censoring due to death, loss to follow-up, or December 31, 2016, whichever came first. HRs and 95% confidence intervals (CI) were calculated in two following models: age-adjusted model (model 1) and multivariable-adjusted model (model 2). Model 1 adjusted for age at study enrollment (year, continuous) only. Model 2 further adjusted for following potential confounders: education (elementary school or less, middle school, high school, college or above), family income (low, lower middle, upper middle, high), postmenopausal at baseline (yes, no), age at menarche (year, continuous), history of chronic hepatitis (yes, no), history of cholelithiasis (yes, no), family history of liver cancer (yes, no), total energy intake (kcal/day, tertiles), and total physical activity (MET-h/week, tertiles). The multivariable-adjusted models for adult weight gain and annual average weight gain were further adjusted for weight at 20 years old (continuous). Other potential confounders including occupation, oral contraceptive, hormone replacement therapy, red meat intake, vegetable intake, and fruit intake were also considered. However, the results did not change appreciably (<10%) with inclusion of these variables, so we excluded them in the final model.

The anthropometric measurements were considered in both categorical and continuous manners. For the categorical manner, exposure variables were categorized by corresponding quartiles or predefined categories as mentioned above. Trends across categories were evaluated by entering the median of each category into the model as a continuous variable. For the continuous manner, each exposure variable was symmetrically trimmed at the 0.5% level (excluded observations with values of top 0.5% and bottom 0.5%) before the

analyses to minimize the influence of outliers. Following the WCRF Continuous Update Project Expert Report 2018 (4), the HRs for per 5-kg/m^2 increment of BMI at baseline and BMI at 20 years old, per 5-kg increment of adult weight gain, per 0.5-kg/year increment of annual average weight gain, per 10-cm increment of WC and HC, and 0.1-unit increment of WHR and WHtR were calculated. Restricted cubic spline function was used to investigate potential non-linear relationship and to characterize dose–response curves flexibly (23, 24). Exposure variables fitted with three knots (5th, 50th, and 95th percentiles), four knots (5th, 35th, 65th, and 95th percentiles), and five knots (5th, 25th, 50th, 75th, and 95th percentiles) were included in the abovementioned multivariable-adjusted models. Nonlinearity was evaluated by a Wald χ^2 test. No significant nonlinearity between any anthropometrics and the risk of liver cancer was found. For a detailed description of the dose–response relationship, we focused on BMI, adult weight gain, WC, and HC. Dose–response curves were characterized based on the best-fitted models selected by the Akaike information criterion (25).

To examine the extra effect of fat distribution, models with additional adjustment for BMI were conducted in WC, HC, WHR, and WHtR. Because anthropometric measurements were highly correlated (the correlation matrix was shown in Supplementary Table S1), we utilized the residual method as a complement to the conventional method (include terms of BMI in the same model). The residual method is commonly used in nutritional epidemiologic studies to provide a measure of nutrient intake uncorrelated with total energy intake (26). In the current study, for instance, the BMI-adjusted WC represents the difference between the actual WC and the WC predicted by one's BMI. We also put BMI and each of the residual in the same model to compare the effect of overall obesity and fat distribution. Log-likelihood ratio tests were conducted to examine whether the model with both BMI and the fat distribution measurements provides better fit than the model with BMI only.

Exploratory analyses were conducted to examine the consistency of our main findings. First, we examined the impact of type 2 diabetes (T2DM) by repeating the analyses with the exclusion of prevalent T2DM subjects. Because T2DM has been reported to increase the risk of liver cancer and may be a mediator for the adiposity–liver cancer association. Second, we calculated the multivariable-adjusted HRs for postmenopausal women because estrogen was suggested to play a protective role against the development of hepatocellular carcinoma (HCC; ref. 27). Third, the main analyses were repeated among participants without a history of chronic hepatitis, cholelithiasis, or family history of liver cancer, to eliminate possible modifying effects of these factors. In addition, we excluded the first two-years' cohort observations (i.e., the follow-up time was calculated from two years after the date of study enrollment) to rule out possible reverse causation.

A two-sided *P* value of less than 0.05 was considered statistically significant. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Results

During a mean follow-up time of 17.5 years (SD: 2.8 years), 241 incident liver cancer cases were identified among 69,296 participants. Compared with participants without liver cancer, those who developed liver cancer during follow-up were approximately 6 years older at study enrollment and were more likely to report a family history of liver cancer and history of chronic hepatitis, cholelithiasis, and T2DM. The distributions of education, income, age at menarche, and menopausal status at study enrollment were also significantly different between the participants with and without liver cancer (**Table 1**). For anthropometric measurements, participants who developed liver cancer had significantly higher height, weight, BMI, adult weight gain, WC, HC, WHR, and WHtR than those without liver cancer (**Table 1**).

BMI in middle age was significantly associated with an increased risk of liver cancer, with a multivariable-adjusted HR of 1.54 (95% CI, 1.08–2.20) for obese participants based on the Chinese classification (**Table 2**). Similar results were found in WHO categories and quartile categories (**Table 2**). The dose–response curve suggested significantly increased risks at higher BMI levels (24 kg/m^2 and above; **Fig. 1**). The multivariable-adjusted HR for per 5-kg/m^2 increment of BMI was 1.29 (95% CI, 1.07–1.57; **Table 2**).

Both adult weight gain and annual average weight gain were found to be associated with an increased risk of liver cancer. Participants who gained more than 20 kg from 20 years old to study enrollment had a 69% higher risk of liver cancer compared with those who gained less than 5 kg (**Table 2**). Women who gained more than 0.52 kg/year from 20 years old to study enrollment had about a twice higher risk of liver cancer than those who gained less than 0.13 kg/year (**Table 2**). Linear dose–response analyses suggested a 15% and 44% increase of liver cancer risk for per 5-kg increment of adult weight gain and per 0.5-kg/year increment of annual average weight gain (**Table 2**). The dose–response curve showed that the risk increased with adult weight gain throughout the range observed and the slope steepened gradually (**Fig. 1**).

For fat distribution measurements, WC, HC, and WHtR were found to be positively associated with the risk of liver cancer. The multivariable-adjusted HRs for the highest quartile versus the lowest quartile for three measurements were 1.52 (95% CI, 1.03–2.25), 1.58 (95% CI, 1.05–2.38), and 1.53 (95% CI, 0.99–2.37), respectively (**Table 2**). The HRs for per 10-cm increments of WC and HC and per 0.1-unit of WHtR were 1.23 (95% CI, 1.05–1.43), 1.30 (95% CI, 1.10–1.55), and 1.37 (95% CI, 1.07–1.75), respectively. Dose–response curves showed increased risks with greater levels of WC and HC, which became steeper after about 80 and 95 cm, respectively (**Fig. 1**). No significant association was found between BMI at 20 years old and WHR with the risk of liver cancer in neither categorical nor continuous manner in our study.

After additionally adjusted for BMI (continuous), the positive associations between WC, HC, and WHtR with the risk of liver cancer disappeared, the insignificant results of WHR were unchanged (Supplementary Table S2). The results were similar when BMI were adjusted through the residual method. Results of mutual adjustment models showed that the HRs for BMI in all the four models were quite close to the main analyses, while the HRs for WC, HC, WHR, and WHtR residuals were insignificant. The log-likelihood ratio test showed that the models with BMI and the fat distribution measurements did not provide better fit compared with models with BMI only. Above results suggested that the effect of overall obesity was stronger than fat distribution on the risk of liver cancer. Overall obesity was independently associated with the risk of liver cancer despite the distribution of adipose tissue.

The results of exploratory analyses substantially supported the main findings (Supplementary Table S3). Multivariable-adjusted HRs for the highest quartile versus the lowest quartile among the subgroups were all very close to our main analyses. In addition, the results were consistent after excluding the first two-years' cohort observations.

Discussion

The current study comprehensively examined the association between different types of anthropometrics and the risk of liver cancer in non-smoking and non–alcohol-drinking Chinese women. Overall

Table 1. Baseline demographics, selected risk factors, and anthropometric measurements for liver cancer cases and non-cases among non-smoking and non–alcohol-drinking women (1997–2016).

Characteristics[a]	All subjects ($N = 69,296$)	Liver cancer ($N = 241$)	Non-liver cancer ($N = 69,055$)	P value[b]
Age (year)	52.31 ± 8.97	58.40 ± 8.37	52.29 ± 8.96	<0.001
Education				<0.001
Elementary school or less	14,005 (20.21)	99 (41.08)	13,906 (20.14)	
Middle school	26,031 (37.56)	60 (24.90)	25,971 (37.61)	
High school	19,658 (28.37)	60 (24.90)	19,598 (28.38)	
College or above	9,602 (13.86)	22 (9.13)	9,580 (13.87)	
Income[c]				0.001
Low	10,840 (15.64)	56 (23.24)	10,784 (15.62)	
Lower middle	26,455 (38.18)	88 (36.51)	26,367 (38.18)	
Upper middle	19,691 (28.42)	71 (29.46)	19,620 (28.41)	
High	12,310 (17.76)	26 (10.79)	12,284 (17.79)	
Occupation				0.134
Professional	20,162 (29.10)	56 (23.24)	20,106 (29.12)	
Clerical	14,300 (20.64)	53 (21.99)	14,247 (20.63)	
Manual workers	34,600 (49.93)	130 (53.94)	34,470 (49.92)	
Housewife	234 (0.34)	2 (0.83)	232 (0.34)	
Ever had chronic hepatitis	1,784 (2.57)	35 (14.52)	1,749 (2.53)	<0.001
Ever had cholelithiasis	7,600 (10.97)	49 (20.33)	7,551 (10.93)	<0.001
Ever had diabetes	2,916 (4.21)	24 (9.96)	2,892 (4.19)	<0.001
Family history of liver cancer	2,275 (3.28)	25 (10.37)	2,250 (3.26)	<0.001
Postmenopausal	33,331 (48.10)	184 (76.35)	33,147 (48.00)	<0.001
Ever had oral contraceptive	14,196 (20.49)	56 (23.24)	14,140 (20.48)	0.289
Ever had hormone replacement therapy	2,506 (3.62)	7 (2.90)	2,499 (3.62)	0.553
Age at menarche (year)	14.91 ± 1.73	15.26 ± 1.72	14.91 ± 1.73	0.002
Total physical activity (MET-h/week)	106.59 ± 44.98	107.10 ± 48.47	106.59 ± 44.97	0.953
Total energy intake (kcal/day)	1,675.38 ± 390.82	1,630.95 ± 390.26	1,675.54 ± 390.82	0.101
Height (cm)	157.57 ± 5.54	156.46 ± 4.97	157.57 ± 5.54	<0.001
Weight (kg)	59.56 ± 8.86	61.28 ± 9.52	59.55 ± 8.86	0.007
Body mass index (kg/m^2)	23.99 ± 3.40	25.04 ± 3.75	23.99 ± 3.40	<0.001
Height at 20 years old (cm)[d]	159.04 ± 4.89	158.58 ± 4.47	159.04 ± 4.89	0.065
Weight at 20 years old (kg)[d]	49.53 ± 6.56	49.38 ± 6.35	49.53 ± 6.56	0.714
Body mass index at 20 years old (kg/m^2)[d]	19.58 ± 2.44	19.78 ± 2.46	19.58 ± 2.44	0.268
Adult weight gain (kg)[d]	9.97 ± 9.09	12.06 ± 9.66	9.97 ± 9.09	<0.001
Annual average weight gain (kg/year)[d]	0.34 ± 0.32	0.33 ± 0.27	0.34 ± 0.32	0.797
Waist circumference (cm)	77.76 ± 8.73	81.26 ± 9.13	77.75 ± 8.73	<0.001
Hip circumference (cm)	95.89 ± 7.59	98.66 ± 8.2	95.88 ± 7.58	<0.001
Waist-to-hip ratio (cm/cm)	0.81 ± 0.05	0.82 ± 0.05	0.81 ± 0.05	<0.001
Waist-to-height ratio (cm/cm)	0.49 ± 0.06	0.52 ± 0.06	0.49 ± 0.06	<0.001

[a]Continuous variables were presented as means ± SDs; categorical variables were presented as numbers (percentages).
[b]Continuous variables were compared using Wilcoxon–Mann–Whitney tests, and categorical variables were compared using χ^2 tests.
[c]Defined as low: < ¥10,000 per family per year. Lower middle: ¥10,000–19,999 per family per year. Upper middle: ¥20,000–29,999 per family per year. High: ≥ ¥30,000 per family per year.
[d]Self-reported data on height and weight at 20 years old were unavailable for a minority of participants, resulting in slightly decreased sample size for related variables.

and abdominal obesity in middle age and weight gain though adulthood were found to be positively associated with the risk of liver cancer. To the best of our knowledge, this is the first prospective cohort study that systematically estimated different measures of adiposity and the risk of liver cancer among a non-smoking and non–alcohol-drinking population, with a considerable number of cases and fairly long follow-up time.

Similar to previous studies, we found a significantly positive association between BMI in middle age and the risk of liver cancer. Our estimates were close to the WCRF Continuous Update Project Expert Report 2018 (relative risk = 1.21; 95% CI, 1.10–1.33 for per 5-kg/m^2 increment of BMI among women; ref. 4) and the Liver Cancer Pooling Project (LCPP; HR = 1.25; 95% CI, 1.17–1.35 for per 5-kg/m^2 increment of BMI among women; ref. 28); slightly higher than a study held in 2.9 million UK women (HR = 1.14; 95% CI, 1.04–1.26 for per 5-kg/m^2 increment of BMI; ref. 29) and a study held in Korean women (HR = 1.39; 95% CI, 1.00–1.94 for BMI > 30 kg/m^2 compared with 23–24 kg/m^2; ref. 30). A previous study held in Shanghai women also estimated the linear dose–response association between BMI and the risk of liver cancer, but the result was insignificant because of a smaller number of cases (31).

Up to now, few studies have examined the association between obesity at young adulthood and the risk of liver cancer. The present study did not support the association between obesity at early adulthood and the risk of liver cancer, which was consistent with previous report of the European Prospective Investigation into Cancer and Nutrition (EPIC) study (9) and the Japan Collaborative Cohort (JACC) study (death from liver cancer as outcome; ref. 32). However,

Table 2. Associations between anthropometric measurements and liver cancer risk among non-smoking and non–alcohol-drinking women (1997–2016).

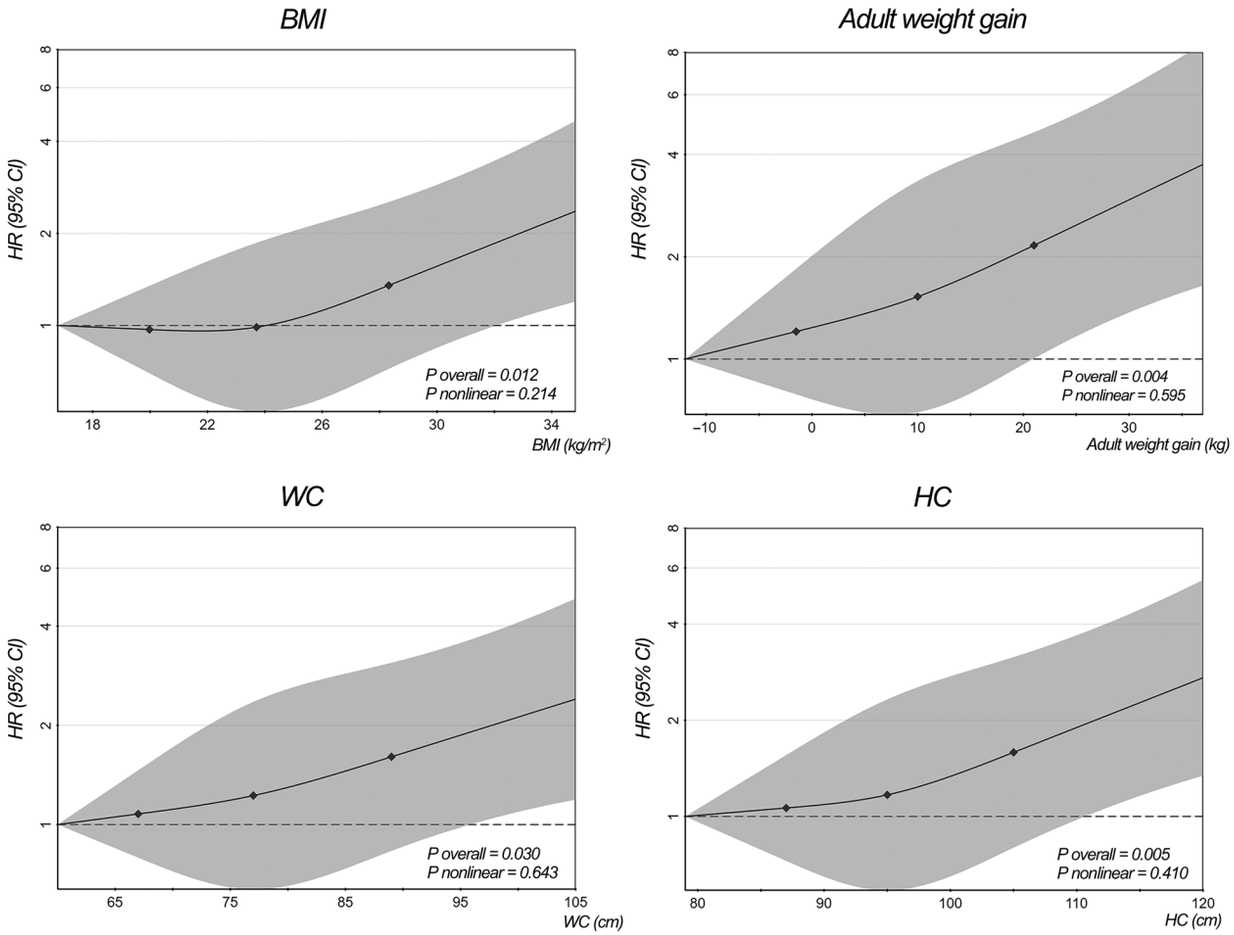
Overall adiposity	Cases	Person year	HR[a] (95% CI)	HR[b] (95% CI)	Fat distribution	Cases	Person year	HR[a] (95% CI)	HR[b] (95% CI)
BMI, Chinese classification (kg/m^2)					WC (cm)				
<24.00	100	654,125	1.00 (Reference)	1.00 (Reference)	<85	149	966,609	1.00 (Reference)	1.00 (Reference)
<28.00	92	416,807	1.15 (0.87–1.54)	1.17 (0.88–1.56)	≥85	92	244,630	1.63 (1.24–2.13)	1.61 (1.22–2.12)
≥28.00	49	140,306	1.54 (1.09–2.19)	1.54 (1.08–2.20)	WC[c] (cm)				
BMI, WHO classification (kg/m^2)					<71.50	38	303,756	1.00 (Reference)	1.00 (Reference)
<25.00	130	796,778	1.00 (Reference)	1.00 (Reference)	<76.75	42	279,482	1.03 (0.67–1.61)	1.05 (0.68–1.63)
<30.00	84	357,222	1.11 (0.84–1.47)	1.11 (0.84–1.47)	<82.75	51	301,996	0.97 (0.63–1.48)	0.98 (0.64–1.51)
≥30.00	27	57,238	1.95 (1.28–2.96)	1.90 (1.24–2.91)	≥82.75	110	326,004	1.51 (1.03–2.23)	1.52 (1.03–2.25)
BMI[c] (kg/m^2)					*P trend*			0.010	0.012
<21.63	42	304,809	1.00 (Reference)	1.00 (Reference)	Per 10 cm	239	1,201,545	1.24 (1.06–1.44)	1.23 (1.05–1.43)
<23.71	50	306,401	1.08 (0.72–1.63)	1.08 (0.72–1.64)	HIP[c] (cm)				
<26.03	58	303,424	1.11 (0.74–1.65)	1.12 (0.75–1.67)	<89.75	31	232,386	1.00 (Reference)	1.00 (Reference)
≥26.03	91	296,605	1.50 (1.04–2.18)	1.51 (1.03–2.20)	<94.75	47	327,647	0.99 (0.63–1.56)	1.00 (0.63–1.57)
P trend			0.018	0.019	<99.90	53	297,426	1.09 (0.70–1.70)	1.10 (0.70–1.71)
Per 5 kg/m^2	238	1,200,025	1.30 (1.07–1.57)	1.29 (1.07–1.57)	≥99.90	110	353,779	1.55 (1.03–2.32)	1.58 (1.05–2.38)
BMI at 20 years old[c] (kg/m^2)					*P trend*			0.005	0.004
<17.79	41	262,739	1.00 (Reference)	1.00 (Reference)	Per 10 cm	239	1,202,268	1.30 (1.10–1.54)	1.30 (1.10–1.55)
<19.29	42	264,937	0.95 (0.62–1.47)	0.96 (0.63–1.48)	WHR[c]				
<21.09	42	263,317	0.92 (0.59–1.41)	0.93 (0.60–1.43)	<0.77	41	311,102	1.00 (Reference)	1.00 (Reference)
≥21.09	53	259,690	1.14 (0.76–1.71)	1.14 (0.75–1.72)	<0.81	56	298,384	1.25 (0.83–1.87)	1.23 (0.82–1.85)
P trend			0.493	0.500	<0.84	55	307,526	1.04 (0.69–1.57)	1.03 (0.69–1.55)
Per 5 kg/m^2	176	1,040,596	1.08 (0.79–1.48)	1.08 (0.78–1.47)	≥0.84	89	294,227	1.38 (0.94–2.02)	1.32 (0.90–1.94)
Adult weight gain (kg)					*P trend*			0.139	0.227
≤5	50	326,271	1.00 (Reference)	1.00 (Reference)	Per 0.1 unit	240	1,199,707	1.18 (0.92–1.52)	1.14 (0.88–1.47)
≤10	29	250,026	0.80 (0.50–1.26)	0.85 (0.53–1.37)	WHtR[c]				
≤15	46	238,376	1.31 (0.88–1.96)	1.44 (0.94–2.20)	<0.45	32	307,116	1.00 (Reference)	1.00 (Reference)
≤20	38	156,267	1.53 (1.01–2.34)	1.67 (1.06–2.61)	<0.49	44	309,744	1.10 (0.70–1.74)	1.11 (0.70–1.76)
>20	35	128,846	1.58 (1.03–2.43)	1.69 (1.06–2.69)	<0.53	66	303,389	1.33 (0.86–2.06)	1.33 (0.86–2.05)
P trend			0.005	0.003	≥0.53	99	290,989	1.55 (1.01–2.38)	1.53 (0.99–2.37)
Per 5 kg	196	1,089,964	1.13 (1.04–1.22)	1.15 (1.06–1.25)	*P trend*			0.021	0.030
Annual average weight gain[c] (kg/year)					Per 0.1 unit	239	1,200,594	1.40 (1.11–1.78)	1.37 (1.07–1.75)
<0.13	44	272,145	1.00 (Reference)	1.00 (Reference)					
<0.32	50	274,038	1.09 (0.72–1.63)	1.19 (0.78–1.82)					
<0.52	56	276,019	1.44 (0.97–2.14)	1.60 (1.05–2.45)					
≥0.52	48	277,583	1.80 (1.18–2.75)	1.99 (1.25–3.16)					
P trend			0.003	0.002					
Per 0.5 kg/year	198	1,088,690	1.37 (1.05–1.79)	1.44 (1.08–1.92)					

[a]Adjusted for age.
[b]Adjusted for age, education, income, menopausal status, age at menarche, history of chronic hepatitis, history of cholelithiasis, family history of liver cancer, total energy intake and total physical activity. Analyses of adult weight gain and annual average weight gain were further adjusted for weight at 20 years old.
[c]Categorized by quartiles.

results from the NIH–American Association of Retired Persons (NIH-AARP) cohort have shown that obesity at age 18 (BMI≥30 kg/m^2, results for both genders) was associated with an 86% higher risk of HCC (10). Another study also reported a positive association between BMI at 17 years old and increased risk of liver cancer in Israeli women (11). The effect of early adulthood obesity in the development of liver cancer still warranted further investigation.

Both the absolute growth and the annual average increment of weight from 20 years old to middle age were found to be strongly associated with increased risk of liver cancer. Compared with two existing studies, our estimates were lower than those of the EPIC study (HR = 3.51; 95% CI, 1.93–6.41 for per 1-kg/year increment of weight from 20 years old to baseline, results for both genders; ref. 9) and the NIH-AARP study, which concluded that BMI trajectories that resulted in obesity were associated with ∼80% higher HCC incidence (results for both genders; ref. 10). Besides, the JACC study found an insignificant association between weight change from age 20 to baseline and mortality from liver cancer (32). Given the limited evidence so far, further studies are warranted to better understand the role of weight trajectory throughout the life course in the development of liver cancer.

For fat distribution measurements, WC, HC, and WHtR were associated with increased risk of liver cancer according to our study. Compared with existing studies, our results of WC were similar to those of the China Kadoorie Biobank (CKB) study (ref. 8; HR = 1.05; 95% CI, 1.01–1.09 for per 5-cm increment of WC) and the LCPP study (ref. 7; HR = 1.11; 95% CI, 1.09–1.14 for per 5-cm increment of WC), and lower than that of the EPIC study (HR = 1.25; 95% CI, 1.17–1.33 for per 5-cm increment of WC; ref. 9). The Kailuan male cohort study (33) suggested a significant U-shaped association between WC and the risk of liver cancer, and the lowest risk was found around



Note: all models were adjusted for age, education, income, menopausal status, age at menarche, history of chronic hepatitis, history of cholelithiasis, family history of liver cancer, total energy intake and total physical activity. Models for adult weight gain was further adjusted for weight at 20 years old. 0.5% symmatric trimming were applied before the analyses. Solid black line represents HR; Dark grey shading represents 95% CI. The lowest values were set as reference point. Diamonds square indicates knots (10th, 50th and 90th centiles).

Figure 1.

Dose–response curves for the associations between BMI, adult weight gain, WC, and HC with liver cancer risk among non-smoking and non–alcohol-drinking women (1997–2016).

85 cm, which was different from our study. Our study suggested a monotonic increase of risk throughout the observed range of WC. Unlike the EPIC study (9), the LCPP study (7), and the CKB study (8), no association was found between WHR and the risk of liver cancer in our study. Compared with WC, a well-accepted measure of abdominal fat, the biological meaning of HC and WHR were less clear. A large HC may reflect more accumulation of subcutaneous fat, greater gluteal muscle mass, or larger bone structure (pelvic width; ref. 15). As the ratio of two variables, the interpretation of WHR is quite complicated. Increased WHR can reflect both increased visceral fat mass and/or reduced gluteofemoral muscle mass (12). Unlike four studies mentioned above, the current study did not support the independent effect of fat distribution measurements beyond BMI. Strong intercorrelations among the anthropometrics made the mutual-adjusted models hard to interpret. It is hard to fully understand the complicated relationships and underlying mechanisms between fat distribution and liver cancer just through indirect anthropometric measurements. By means of newly developed approach of body composition measurement, such as dual-energy X-ray absorptiometry and computed tomography, the proportion and distribution of adiposity could be assessed at tissue and organ levels. More accurate and straightforward measurement of adiposity would possibly provide new insight into the association between adiposity and liver cancer risk.

The current study has several strengths. First, prospective design, large sample size, and long duration of follow-up provided convincing evidence. The low rates of cigarette smoking and alcohol drinking of the SWHS provided valuable opportunity to analyze the adiposity–liver cancer association without distortion by these two important confounders. Second, anthropometrics in middle age were measured by trained staff following standard protocols, resulted in more accurate estimates than self-reported information, and decreased the possibility of misclassification. Furthermore, detailed information on important risk factors for liver cancer such as chronic hepatitis, menopausal status, family history, etc., was available in our data sets, enabled comprehensive confounder control.

The main limitation of our study was the lack of information on hepatitis B/C virus infection status, which may be potential modifiers for adiposity–liver cancer association. As a complement, we collected self-reported history of chronic hepatitis and cholelithiasis and included them in the multivariable-adjusted models. Subgroup analyses were also conducted on participants without history of chronic hepatitis and cholelithiasis, the results were consistent with the main analyses. Still, results of the LCPP study have shown that the adiposity–liver cancer association might not hold in individuals infected with hepatitis B/C virus (albeit based on small sample size; refs. 7, 28), the role of hepatitis virus on the adiposity–liver cancer association still need further investigation. Besides, the definition of liver cancer cases was based on ICD-9 code 155, which captures both HCC and intrahepatic cholangiocarcinoma. The role of adiposity may differ between these two histologic types. Studies have found a similar increased risk for both histologic types (7, 9). But there is no hypothesized biological mechanism to link excess body fatness and intrahepatic cholangiocarcinoma as yet. Apart from this, height and weight at 20 years old of the current study were obtained by self-report at study enrollment. The accuracy of effect estimates may have been reduced on the analyses of BMI at 20 years old and adult weight gain. Nonetheless, previous studies have shown that self-reported BMI tends to underestimate the prevalence of obesity (12). Thus, the real effect was more likely to have been underestimated. Moreover, to fully address the confounding effect of tobacco smoking and alcohol drinking and enhance the internal validity, the current study was based on a homogeneous cohort of non-smoking and non–alcohol-drinking women. Accordingly, the generalizability was sacrificed. The interpretation of the results and extrapolation of the conclusion should be cautious.

In conclusion, based on a cohort study among non-smoking and non–alcohol-drinking women, the current study confirmed previous findings that overall obesity and abdominal obesity in middle age increased the risk of liver cancer and contributed additional evidence that suggested weight gain through adulthood as a strong predictor of liver cancer. Our findings highlighted the great significance of maintaining a healthy weight throughout adulthood for the primary prevention of liver cancer. Future studies are warranted to confirm current findings and further investigate the etiologic mechanisms underlying the association between adiposity and risk of liver cancer.

Authors' Disclosures

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Data Availability Statement

The data supporting the findings of this study are available at a reasonable request.

Authors' Contributions

Z.-Y. Li: Resources, data curation, formal analysis, methodology, writing–original draft, writing–review and editing. **H.-L. Li:** Resources, data curation, validation, investigation, methodology, writing–review and editing. **X.-W. Ji:** Resources, data curation, writing–review and editing. **Q.-M. Shen:** Resources, data curation, writing–review and editing. **J. Wang:** Resources, data curation, investigation, writing–review and editing. **Y.-T. Tan:** Resources, data curation, investigation, writing–review and editing. **Y.-B. Xiang:** Conceptualization, resources, data curation, supervision, funding acquisition, investigation, methodology, project administration, writing–review and editing.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021. doi:10.3322/caac.21660.
2. Wogan GN. Impacts of chemicals on liver cancer risk. Semin Cancer Biol 2000; 10:201–10.
3. Aleksandrova K, Stelmach-Mardas M, Schlesinger S. Obesity and liver cancer. Recent Results Cancer Res 2016;208:177–98.
4. World Cancer Research Fund/American Institute for Cancer Research. Continuous update project expert report 2018. Body fatness and weight gain and the risk of cancer. Available from: dietandcancerreport.org.
5. Larsson SC, Wolk A. Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies. Br J Cancer 2007;97:1005–8.
6. Chen Y, Wang X, Wang J, Yan Z, Luo J. Excess body weight and the risk of primary liver cancer: an updated meta-analysis of prospective studies. Eur J Cancer 2012;48:2137–45.
7. Florio AA, Campbell PT, Zhang X, Zeleniuch-Jacquotte A, Wactawski-Wende J, Smith-Warner SA, et al. Abdominal and gluteofemoral size and risk of liver cancer: the liver cancer pooling project. Int J Cancer 2020;147:675–85.
8. Pang Y, Kartsonaki C, Guo Y, Chen Y, Yang L, Bian Z, et al. Central adiposity in relation to risk of liver cancer in Chinese adults: a prospective study of 0.5 million people. Int J Cancer 2019;145:1245–53.
9. Schlesinger S, Aleksandrova K, Pischon T, Fedirko V, Jenab M, Trepo E, et al. Abdominal obesity, weight gain during adulthood and risk of liver and biliary tract cancer in a European cohort. Int J Cancer 2013; 132:645–57.
10. Yang B, Petrick JL, Kelly SP, Graubard BI, Freedman ND, McGlynn KA. Adiposity across the adult life course and incidence of primary liver cancer: the NIH-AARP cohort. Int J Cancer 2017;141:271–8.
11. Furer A, Afek A, Sommer A, Keinan-Boker L, Derazne E, Levi Z, et al. Adolescent obesity and midlife cancer risk: a population-based cohort study of 2·3 million adolescents in Israel. Lancet Diabetes Endocrinol 2020;8:216–25.
12. Hu FB. Obesity epidemiology. New York: Oxford University Press; 2007.
13. Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok AS. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. J Hepatol 2005;42:218–24.
14. Zheng W, Chow WH, Yang G, Jin F, Rothman N, Blair A, et al. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. Am J Epidemiol 2005;162:1123–31.
15. Willett WC. Nutritional epidemiology. New York: Oxford University Press; 2013.
16. Zhou BF.; Cooperative Meta-Analysis Group of the Working Group on Obesity in China. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults–study on optimal cut-off

points of body mass index and waist circumference in Chinese adults. Biomed Environ Sci 2002;15:83–96.
17. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:i–253.
18. Gao M, Wei YX, Lyu J, Yu CQ, Guo Y, Bian Z, et al. [The cut-off points of body mass index and waist circumference for predicting metabolic risk factors in Chinese adults]. Zhonghua Liu Xing Bing Xue Za Zhi 2019;40: 1533–40. Chinese.
19. Rao C, Yang G, Hu J, Ma J, Xia W, Lopez AD. Validation of cause-of-death statistics in urban China. Int J Epidemiol 2007;36:642–51.
20. World Health Organization. International statistical classification of diseases, injuries, and causes of death. Vol 2. Geneva, Switzerland: World Health Organization; 1975.
21. Cox DR. Regression models and life-tables (with discussion). J R Stat Soc B 1972; 34:187–220.
22. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika 1982;69:239–41.
23. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989;8:551–61.
24. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med 2010;29:1037–57.
25. Harrell FE Jr. Regression modelling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer; 2001.
26. Willett WC. Nutritional epidemiology. 2nd ed. New York: Oxford University Press; 1998.
27. Ruggieri A, Barbati C, Malorni W. Cellular and molecular mechanisms involved in hepatocellular carcinoma gender disparity. Int J Cancer 2010;127:499–504.
28. Campbell PT, Newton CC, Freedman ND, Koshiol J, Alavanja MC, Beane Freeman LE, et al. Body mass index, waist circumference, diabetes, and risk of liver cancer for U.S. adults. Cancer Res 2016;76:6076–83.
29. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet 2014;384:755–65.
30. Yi SW, Choi JS, Yi JJ, Lee YH, Han KJ. Risk factors for hepatocellular carcinoma by age, sex, and liver disorder status: a prospective cohort study in Korea. Cancer 2018;124:2748–57.
31. Liu Y, Warren Andersen S, Wen W, Gao YT, Lan Q, Rothman N, et al. Prospective cohort study of general and central obesity, weight change trajectory and risk of major cancers among Chinese women. Int J Cancer 2016;139:1461–70.
32. Li Y, Yatsuya H, Yamagishi K, Wakai K, Tamakoshi A, Iso H, et al. Body mass index and weight change during adulthood are associated with increased mortality from liver cancer: the JACC study. J Epidemiol 2013;23:219–26.
33. Wei L, Li N, Wang G, Feng X, Lyu Z, Li X, et al. Waist circumference might be a predictor of primary liver cancer: a population-based cohort study. Front Oncol 2018;8:607.