Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Wang Y. et al. (2012) Body mass index and risk of primary liver cancer: a meta-analysis of prospective studies. *Oncologist*, 17(11):1461-1468
Date of Review:	April 7, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** **hepatitis B, primary liver cancer, body mass index (BMI)** **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **patients with HCV** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **China** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	meta-analysis; to further analyze the relationship between excess weight and primary liver cancer risks
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Data/information was not used for decision-making. Authors suggested future research with randomized trials to examine the effect of weight reduction in obese population to decrease the risk of primary liver cancer.
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	Results of this study is true in both men and women, true in North American, European, and Asian studies, and is

				independent of confounders.
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	Results can be extended to various populations worldwide.
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	
The research study/tool/data dictionary is easily accessed/available electronically	☒	☐	☐	Free PDF available for download from http://theoncologist.alphamedpress.org/
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☐	☒	☐	
How is the research study/tool funded? ***Please got to Comments section***	☐	☒	☐	No funding stated
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	- 5 unit increase in BMI associated with 39% increased risk of primary liver cancer - HCV or cirrhotic patients with excess weight had higher risk of PLC development than general population - Results show nonlinear positive association between increase BMI and PLC risks - Summary relative risks of PLC with increased BMI in non-Asian studies was stronger than those in Asian studies
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				

Are these data regularly collected?	☐	☒	☐	Literature search of electronic database from the beginning of indexing for each database to November 30, 2011
Are these data regularly collected at and/or below a national level?	☐	☒	☐	
Are these data collected manually or electronically?	☐	☐	☐	Electronically: search in Medline and Embase
RESEARCH REPORTS				
Has this research been published in a juried journal?	☒	☐	☐	*Oncologist*
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	Existing data: 21 articles included

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Hepatobiliary

Body Mass Index and Risk of Primary Liver Cancer: A Meta-Analysis of Prospective Studies

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Key Words. Primary liver cancer • Body mass index • Meta-analysis • Relative risk

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ABSTRACT

Background. **Questions remain about the dose-response relationship between body mass index (BMI) and primary liver cancer (PLC) risk, possible confounding by hepatitis virus infection, and differences by gender or geographic location. We performed a meta-analysis of prospective studies to explore these issues.**

Methods. **We searched PubMed and Embase for studies of BMI and risk of PLC through November 30, 2011. Summary relative risks with their corresponding 95% confidence intervals (CIs) were calculated using a random effects model.**

Results. **A total of 21 prospective studies (including 17,624 PLC cases) were included in our analysis. The summary relative risk for a 5-unit increment in BMI (in kg/m^2) was 1.39 (95% CI: 1.25–1.55), with high heterogeneity. These positive results were robust when stratified by sex, geographic location, ascertainment of exposure and outcome, the number of cases, duration of follow-up, sample source, and cofounders. There was evidence of a nonlinear association between BMI and PLC risk, with the most pronounced increase in risk among persons with a BMI >32 kg/m^2. Patients with hepatitis C virus or cirrhosis (but not patients with hepatitis B virus) with excess weight had a higher risk of PLC development than general populations with excess weight.**

Conclusion. **Excess weight increases PLC risk. For people with HCV infection or cirrhosis, risk increases are greater than for general population.** ***The Oncologist*** 2012;17: 1461–1468

INTRODUCTION

Primary liver cancer (PLC) is the sixth most common cancer and the third most common cause of cancer death globally [1]. It is estimated to cause approximately 500,000 new cases worldwide annually [2], and a nearly equivalent number of persons die from this disease [3]. Hepatocellular carcinoma (HCC) is the major histological subtype, representing up to 85% of PLCs. Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) has been recognized as the most important risk factor for HCC development [4]. In addition, excessive alcohol consumption, cigarette smoking, a history of diabetes mellitus (DM), and environmental exposure to aflatoxin B1 are also potential risk factors for HCC [5].

Interestingly, the incidence of PLC in several developed countries, including Japan, Europe, and the United States, has been increasing over the last 20 years, whereas the incidence of PLC in some developing countries has decreased [6]. It is suggested that infection with HCV may account for about half of this increase in HCC incidence in those developed countries; however, the etiology in 15%–50% of new HCC cases remains unclear [7].

Coinciding with the increased HCC incidence and mortality in developed countries, the prevalence of obesity, as measured by body mass index (BMI) ≥30 kg/m^2, has also grown markedly over the past two decades. Epidemiological studies have suggested that excess weight is associated with increased several cancer risks, particularly PLC risk. A recent meta-analysis of 11 cohort studies showed increased PLC risks of 17% for overweight people (BMI 25–30 kg/m^2) and 90% for obese (≥30 kg/m^2) people compared to those in normal weight

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[8]. The authors, however, recognized the lack of allowance for potential confounders—in particular, chronic HBV and HCV infections and alcohol abuse—as potential limitations [8]. According to the World Cancer Research Fund/American Institute for Cancer Research, there is limited and inconsistent evidence suggesting that excess body weight may increase PLC risk [9]. In addition, the exact shape of the dose-risk relationship between BMI and PLC has not been clearly defined. Since this meta-analysis was published, other relevant studies on this association have been published with inconsistent results [10–21]. In the present study, we aimed to further analyze this relationship by conducting an updated meta-analysis of prospective studies following the meta-analysis of observational studies in epidemiology guidelines [22].

Methods

A comprehensive, computerized literature search was conducted in Medline and Embase from the beginning of indexing for each database to November 30, 2011, by two independent investigators (W.Y.Q. and W.B.C.). Research papers were selected using the following text words or medical subject heading terms: "body mass index,", "BMI," or "obesity"; "liver cancer," "hepatocellular carcinoma," or "HCC." We also reviewed the reference lists of selected research papers to identify additional relevant studies. No language restrictions were imposed.

Inclusion and Exclusion Criteria

Three authors (C.H.X., W.Y.Q. and W.B.C.) independently evaluated all of the studies retrieved based on the prespecified selection criteria. To be included, the study had to meet the following criteria: (a) published as an original article; (b) used a prospective cohort or nested case-control design; (c) reported relative risk (RR) estimates with corresponding 95% confidence intervals (CIs) for more than three categories of BMI and the risk of PLC (or HCC) or provided an RR per unit (in kg/m^2) increase in BMI; (d) adjusted the RR and corresponding 95% CIs at least for age. If more than one study used the same cohort and objectives, the one with the most comprehensive population or most adjusted estimate of risk associated with BMI were included. We excluded studies that reported populations with human immunodeficiency virus (HIV) infection. Studies that did not provide risk estimates, duplicate publications, or reports from non-peer-reviewed sources were also excluded. Discrepancies between the three reviewers were solved by discussion.

Data Extraction

Two investigators (C.H.X. and W.Y.Q.) independently extracted the following information from each included study using a standardized data-collection protocol: the first author's last name, publication year, country of origin, sample size, sex, age, number of cases, ascertainment of exposure and outcome, duration of follow-up, and covariates adjusted for in the analysis. For studies that reported several multivariable-adjusted RRs, we extracted the risk estimates that reflected the greatest degree of control for potential confounders. We did not assess study quality using a quality score, but investigated whether specific study characteristics—such as duration of follow-up, number of cases, and adjustment for confounders, which are indicators of study quality—influenced the results in subgroup analyses.

Statistical Analysis

Summary RR estimates with their corresponding 95% CIs for a 5-unit increment in BMI were derived using the method of DerSimonian and Laird with the assumptions of a random effects model, which incorporates between-study variability [23]. A two-tailed p value $<.05$ was considered statistically significant. If a study reported results specific for men and women, respectively, we combined the sex-specific RR estimates using a fixed-effects model to generate an estimate for both sexes combined. Due to its high fatality, we conducted combining analyses for the incidence and mortality of PLC.

We computed linear trends from the correlated natural logarithm of the RR across categories of BMI according to the methods described by Greenland and Longnecker [24]. We performed dose-response meta-analysis of the relationship of per 5-unit increase in the BMI and PLC risk by using generalized least-squares trend estimation analysis or by using variance-weighted least-squares regression analysis [24, 25]. Both analyses require that the medians for each category of BMI level are known. If they were not reported, we estimated the midpoint of the upper and lower boundaries in each category as the average BMI level. For open-ended categories (e.g., >30 kg/m^2), we estimated the median values using data from the Calcium Polyp Prevention Study cohort in Europe for non-Asians [26, 27] or obtained the values from studies in Japanese for Asians [28]. A potential nonlinear dose-response relationship was examined by using fractional polynomial models [29]. We determined the best-fitting second-order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity [29]. We also defined body mass categories using the following BMI categories: normal (BMI 18.5–<25 kg/m^2), overweight (BMI 25–<30 kg/m^2), and obese (BMI ≥ 30 kg/m^2).

Potential sources of heterogeneity were investigated in heterogeneity tests, subgrouped analyses, and meta-regression. Heterogeneity among studies was assessed using Q and I2 statistics [30]. The role of several potential sources of heterogeneity were examined by subgrouped analyses and restricted maximum likelihood (REML)-based random-effects meta-regression analysis according to geographic locations, ascertainment of exposure and outcome, the number of cases, duration of follow-up, sample source, and adjustments for confounding variables. Sensitivity analysis was also conducted to evaluate the stability of the results.

We carried out formal testing using the Begg's test [31] and Egger's to test publication bias [32]. All statistical analyses were performed using STATA version 11.0 (STATA, College Station, TX) and R-package statistical software (Version 2.11.0 beta).

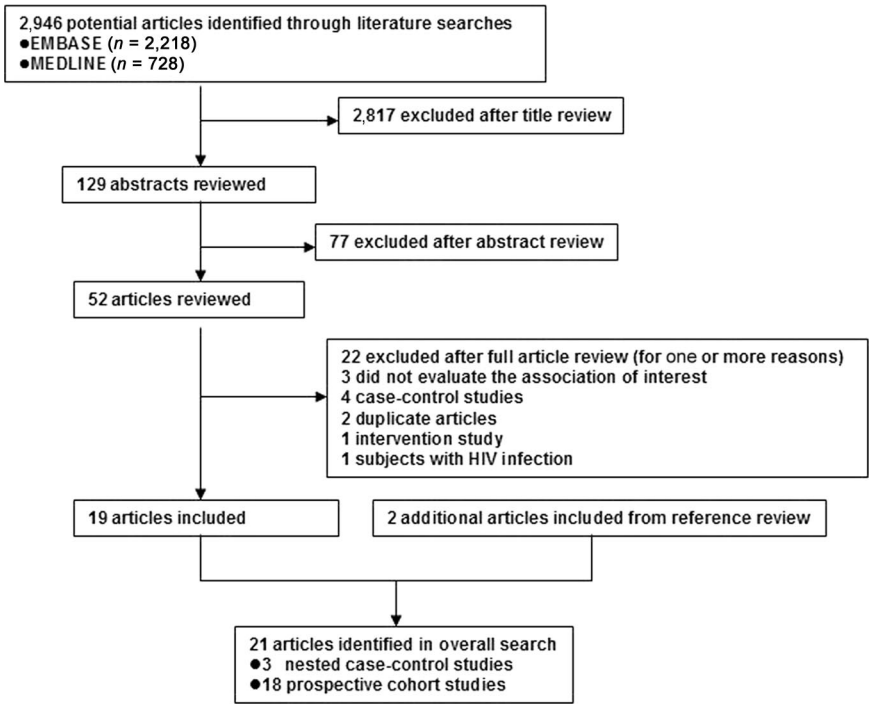

Figure 1. Flow diagram of study selection.
Abbreviation: HIV, human immunodeficiency virus.

RESULTS

The search strategy generated 2,946 citations, of which 52 were considered of potential value and being retrieved for detailed evaluation (Fig. 1). Of these 52 articles, 33 were subsequently excluded from the meta-analysis for various reasons. An additional two articles were included from reference review. Thus, a total of 21 articles were used in this meta-analysis (Table 1). The number of participants ranged from 248 to 1,213,829, and a total of 17,624 PLC cases were identified in this meta-analysis.

Meta-analysis

The summary relative risks (SRRs) of PLC per 5-unit increase in BMI for each study are shown in Figure 2. The meta-analysis of all 21 studies in a random-effects model found that a 5-unit increase in BMI was associated with a 39% increased risk of PLC, with significant heterogeneity among studies (SRR: 1.39, 95% CI: 1.25–1.55; $p < .001$, $I^2 = 79.8\%$). We conducted subgroup meta-analyses by sex, geographic locations, ascertainment of exposure and outcome, case size, duration of follow-up, sample source, and confounders (Table 2). The SRRs of the association between a 5-unit increase in BMI and risk of PLC were positive in all strata.

There was no evidence that the estimated RRs differed significantly by sex (SRR: 1.26, 95% CI: 1.11–1.44 for men vs. SRR: 1.18, 95% CI: 1.08–1.29 for women; $p = .414$). Similarly, there was no difference in the association between increased BMI and PLC risk between strata in ascertainment of exposure and outcome, the number of cases, duration of follow-up, and confounders (alcohol consumption, smoking, infection with HBV and/or HCV, history of DM). However, geographic location and sample source were found to significantly modify the association between increased BMI and PLC risk. The SRRs were significantly higher in non-Asian studies than in Asian studies (SRR: 1.60, 95% CI: 1.34–1.91 for non-Asians vs. SRR: 1.21, 95% CI: 1.09–1.34 for Asians; $p = .048$).

When combining results on studies of population with known liver disease (with HBV and/or HCV infection, cirrhosis), the SRRs were significantly stronger in people with known liver disease and excess weight than in the general population with excess weight (SRR: 1.67, 95% CI: 1.37–2.04, $p = .012$, $I^2 = 60.9\%$ for patients with known liver disease; SRR: 1.24, 95% CI: 1.13–1.37, $p < .001$, $I^2 = 70.8\%$; $p_{difference} = .016$). Further analysis found that HCV-positive patients with excess weight had a higher risk of PLC development than general population (SRR: 1.59, 95% CI: 1.22–2.07; $p = .086$). Cirrhotic individuals with excess weight had a pooled RR of 1.98 (95% CI: 1.59–2.48), which was significant higher than general population with excess weight ($p < .001$). However, HBV-positive patients with excess weight had a similar risk of PLC development as the general population with excess weight ($p = .731$, Table 2).

There was evidence of a nonlinear association between increased BMI and PLC risk ($p < .001$), with the most pronounced increase in risk among persons with a BMI >32 kg/m^2. Higher BMIs were associated with a further, stronger increase in PLC risk (Fig. 3).

We also conducted a sensitivity analysis and found that there were no changes in the direction of effect when any one study was excluded. When combining analyses of studies of PLC incidence and mortality, respectively, we found similar

Table 1. Characteristics of prospective studies of body mass index per 5 kg/m^2 increase and primary liver cancer risk

Study and location	Participants	Sex and age (mean or range)	Follow-up (years)	Ascertainment of BMI	BMI range (kg/m^2)	Case ascertainment	*n* of cases	Adjustments
Yu et al. [33], Taiwan	4,841 HBsAg carriers for health examinations	Men, >30 yrs	12	Self-reported	16.7–32	Histologic finding or AFP ≥400 ng/mL plus positive image	119	Age, the time of blood draw, ethnicity, education, smoking, alcohol, and history of chronic liver disease
Calle et al. [34], USA	900,053 participants in the Cancer Prevention Study II	Men and women, 57 yrs	16	Self-reported	18.5–39.9	Death certificates	965	Age, education, smoking, physical activity, alcohol use, marital status, race, aspirin use, estrogen-replacement therapy, fat consumption, and vegetable consumption
Batty et al. [35], United Kingdom	18,403 nonindustrial London-based government employees	Men, 40–64 yrs	35	Measured	18.5–30+	Death certificates	51	Age, employment grade, marital status, physical activity, smoking, other
Kuriyama et al. [36], Japan	27,539 population subjects	Men, 56.1 yrs; women, 56.7 yrs	7.6	Self-reported	18.5–29.9	Cancer registry	31	Age, type of health insurance, smoking; intakes of alcohol, meat, fish, fruits, vegetables, bean-paste soup
Oh et al. [37], Korea	781,283 civil servants and private school workers and their dependants	Men, >20 yrs	9.9	Measured	18.5–30+	Histologic finding	2,410	Age, area of residence; family history of cancer, smoking, exercise, alcohol
Rapp et al. [38], Australia	67,447 adult Vorarlberg residents	Men, 42 yrs	10	Measured	18.5–35+	Histologic finding	57	Age, occupational group, smoking
N'Kontchou et al. [39], France	771 patients with compensated alcoholic/viral cirrhosis	Men and women, 61 yrs	4.2	Self-reported	<25–30+	Histologic finding or AFP ≥400 ng/mL plus positive image	220	Age, gender, diabetes mellitus
Samanic et al. [40], Sweden	362,552 workers in the construction industry	Men, 34.3 yrs	19	Measured	18.5–30+	Cancer registry	194	Age, smoking
Ioannou et al. [41], USA	2,120 veterans with cirrhosis	Men and women, 52 yrs	3.6	Measured	18.5–30+	Cancer registry	100	Age, smoking, alcohol use, HBV/HCV
Chen et al. [10], Taiwan	23,567 residents of seven townships	Men and women, 47 yrs	14	Measured	<23–30+	Histologic finding or AFP ≥400 ng/mL plus positive image	291	Age, gender, smoking, alcohol use, BMI, educational level, HBV/HCV
Jee et al. [11], Korea	1,213,829 from the National Health Insurance Corporation	Men and women, 30–95 yrs	10.8	Measured	<20–30+	Cancer registry or hospital admission diagnosis	10,520	Age, smoking
Ohishi et al. [13], Japan	20,000 from the Adult Health Study longitudinal cohort in Hiroshima	Men and women, 66.4 yrs	NA	Measured	21.3–25+	Cancer registry or histologic finding	224	Age, hepatitis virus infection, alcohol, smoking, coffee, diabetes mellitus, and radiation dose
Joshi et al. [12], Korea	548,530 Korean civil service workers	Men, 30–59 yrs	6	Measured	18.5–30+	Death registry	998	Age, fasting serum glucose, HBsAg, alcohol intake, and tobacco smoking
Ohki et al. [14], Japan	1,431 patients positive for HCV-RNA	Men and women, 60 yrs	6.1	Measured	18.5–30+	Histologic finding or AFP ≥400 ng/mL plus positive image	341	Age, gender, alcohol, serum albumin, ALT, AFP, bilirubin, platelet count
Veldt et al. [15], Europe and Canada	541 patients with advanced fibrosis or cirrhosis	Men and women, 50 yrs	4	Measured	23–29[a]	Histologic finding or AFP ≥400 ng/mL plus positive image	38	Age, fibrosis stage, genotype, gender, anti-HBc, bilirubin, albumin, platelet count.
Batty et al. [16], Asia Pacific Cohort Studies Collaboration	405,799 residents of Australia/New Zealand	Men and women, 48 yrs	4	Measured	18.5–25+	Death registries	445	Age, sex, study, alcohol, blood pressure, smoking, serum cholesterol, and diabetes mellitus
Inoue et al. [17], Japan	17,590 subjects participating in a health checkup	Men and women, 40–69 yrs	12.7	Measured	<25–27+	Death registry	102	Age, sex, smoking, alcohol, HBV, HCV, coffee intake
Hart et al. [18], United Kingdom	27,121 from the general population	Men and women, 50 yrs	26	Measured	18.5–30+	Cancer registry	69	Age, social class, smoking, systolic blood pressure, bronchitis, angina, and diabetes mellitus
N'Kontchou et al. [19], France	248 patients with compensated HCV-positive cirrhosis	Men and women, 58.4 yrs	6	Measured		Histologically proven in 22 patients and noninvasive criteria in 39 patients	61	Age, diabetes mellitus, alcohol, platelet count
Arano et al. [20], Japan	325 patients with CHC	Men and women, 58 yrs	9	Measured	20.4–24.6[a]	Histologic finding	122	Age, sex, AFP, diabetes mellitus, platelet count
Borena et al. [21], Norway, Austria, and Sweden	578,700 participants	Men and women, 44 yrs	Men, 12.8; women, 11.3	Measured	<25–30+	Histologic finding	266	Age, sex, smoking, alcohol, birth year, metabolic equivalent task score

[a]Expressed as 25th–75th percentiles.

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BMI, body mass index; CHC, chronic hepatitis C; HBsAG, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

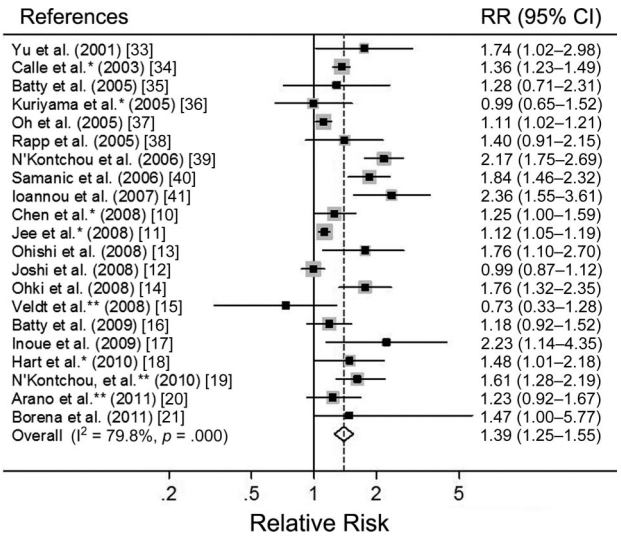

Figure 2. Forest plots of risk of primary liver cancer associated with each 5-unit increase in BMI (in kg/m^2). *Derived by pooling the sex-specific relative risks. **Derived from each 1-unit increment of body mass index.

Abbreviations: CI, confidence interval; RR, relative risk.

SRRs for PLC incidence and mortality (SRR: 1.38, 95% CI: 1.22–1.57, $p < .001$ for incidence; SRR: 1.27, 95% CI: 1.05–1.53, $p = .001$ for mortality).

We also performed a meta-analysis based on BMI categories and found that obese patients had a significantly higher risk of PLC than overweight patients did (SRR: 1.96, 95% CI: 1.66–2.32, $p = .003$, $I^2 = 56.7\%$ for obese patients; SRR: 1.17, 95% CI: 1.07–1.27, $p = .005$, $I^2 = 53.5\%$ for overweight patients; data not shown). We then conducted a REML-based random effects meta-regression analysis to investigate the source of the significant heterogeneity among studies. In univariate and multivariate meta-regression analyses, two variables (geographic locations and sample source) were statistically significant. The between-study variance was reduced from 0.0357 to 0.01035 based on the REML estimate, and the heterogeneity explained by these two variables was 71%. We found no statistical evidence of publication bias in this analysis ($p = .928$ using Begg's test; $p = .143$ using Egger's test).

Discussion

The comprehensive meta-analysis of observational studies on BMI and PLC risk suggests that a 5-unit increase in BMI was associated with a 39% increased risk of PLC when pooling across 21 prospective studies. This significantly positive relationship is independent of sex, geographic locations, case size, ascertainment of exposure and outcome, duration of follow-up, and confounders. Furthermore, HCV-positive or cirrhotic patients with excess weight had a higher risk of PLC development than general populations with excess weight. To our knowledge, for the first time in a meta-analysis of BMI and PLC based on linear and nonlinear analysis, we found the most pronounced increase in PLC risk was observed at a BMI >32 kg/m^2.

Strengths of the present study included the quantitative analysis based on prospective studies, which might minimize the possibility that our findings were due to selection or recall bias, which might be of concern in retrospective case-control studies. All the studies included in the meta-analysis evaluated multiple potential confounders, and the relationships between BMI and PLC risk in each study were derived from regression after adjustment several potential risk factors for PLC. The large number of studies that addressed the same research question and the subsequent possibility of stratified analyses permitted us to better explore the effect of excess weight on various subgroups (especially subgroups with known liver diseases).

However, our meta-analysis has several limitations that may affect the interpretation of the results. First, great heterogeneity was observed across studies. By conducting meta-regression analysis, we found that significant heterogeneity may exist in terms of geographic locations and sample source, both of which may account for 71% of heterogeneity across studies. Second, inadequate control for confounders may bias the results toward exaggeration or underestimation of risk estimates. Although most studies adjusted for other known risk factors for PLC, residual or unknown confounding cannot be excluded. Obese persons may have unhealthy lifestyles that include smoking, heavy alcohol consumption, and a history of DM. However, adjustment for a wide range of potential confounders only marginally altered the relationship between BMI and PLC risk. Third, as in any meta-analysis, the possibility of publication bias is of concern because small studies with null results tend not to be published. However, the results obtained from formal statistical tests did not provide evidence for such bias.

The pathophysiological mechanisms underlying the association between increased BMI and the risk of PLC have been suggested. Obesity is associated with nonalcoholic fatty liver disease (NAFLD), the most common form of chronic liver disease in developed countries [42]. About 30% of individuals with NAFLD based on ultrasound were identified as having its severe form, nonalcoholic steatohepatitis (NASH), and 8% to 26% of individuals with NASH progress to cirrhosis [43]. Of patients with NASH-related cirrhosis, 40%–62% develop complications, including HCC, after 5–7 years of follow-up [44]. NASH's carcinogenic potential has been attributed to insulin resistance, which may lead to elevated levels of the proinflammatory cytokine, such as tumor necrosis factor (TNF) and interleukin (IL)-6. Both TNF and IL-6 favor the development of hepatic steatosis and inflammation and subsequent cancer of the liver [45, 46]. In addition, elevated levels of insulin may upregulate the production of insulin-like growth factor-1 (IGF-1), which stimulates cellular proliferation and inhibits apoptosis within the liver [47]. The involvement of insulin and IGF-1 in carcinogenesis of liver has been supported by in vitro studies, animal models, and epidemiologic studies [48, 49].

A previous meta-analysis showed the SRR of PLC was statistically significantly higher for obese men (RR: 2.42, 95% CI: 1.83–3.20) than that for obese women (RR: 1.67, 95% CI: 1.37–2.03; $p = .03$) [8]. However, the present meta-analysis showed no significant difference in the PLC risk with in-

Table 2. Stratified meta-analyses of body mass index per 5 kg/m^2 and the risk of primary liver cancer

Characteristic	*n* of studies	SRR (95% CI)	$p_{heterogeneity}$	$p_{difference}$	I^2 (%)
All	22	1.39 (1.25–1.55)	<.001		79.8
Sex					
Male	11	1.26 (1.11–1.44)	<.001	Reference	79.1
Female	5	1.18 (1.08–1.29)	.843	.414	0
Geographic location[a]					
Asia	10	1.21 (1.09–1.34)	.003	Reference	64.2
Other	10	1.60 (1.34–1.90)	.001	<.048	67.4
Source					
General population	13	1.24 (1.13–1.37)	<.001	Reference	70.8
Persons with known liver disease	8	1.67 (1.37–2.04)	.012	.016	60.9
HBV infection	2	1.33 (0.90–1.95)	.182	.731	43.8
HCV infection	6	1.59 (1.22–2.07)	.022	.086	62.0
Cirrhosis	3	1.98 (1.59–2.48)	.162	<.001	45.0
BMI ascertainment					
Self-reported	3	1.47 (1.01–2.15)	<.001	Reference	72.6
Measured	18	1.36 (1.22–1.51)	<.001	.475	89.1
Outcome					
Incidence	13	1.38 (1.22–1.57)	<.001	Reference	76.1
Mortality	6	1.27 (1.05–1.53)	<.001	.452	74.5
Outcome ascertainment					
Cancer/death registry	12	1.39 (1.16–1.68)	<.001	Reference	80.0
Histological finding or noninvasive diagnosis	9	1.36 (1.19–1.56)	<.001	.963	79.0
Duration of follow-up					
≥10 yrs	10	1.40 (1.22–1.61)	<.001	Reference	70.5
<10 yrs	11	1.38 (1.15–1.66)	<.001	.665	85.3
Case size					
<120	9	1.48 (1.20–1.82)	.065	Reference	45.6
≥120	12	1.35 (1.19–1.53)	<.001	.546	85.4
Adjustment for confounders					
Alcohol use					
Yes	13	1.36 (1.20–1.55)	<.001	Reference	75.2
No	8	1.40 (1.09–1.80)	<.001	.871	86.1
Smoking					
Yes	18	1.33 (1.20–1.47)	<.001	Reference	74.1
No	3	1.65 (1.19–2.28)	<.001	.211	79.1
Diabetes					
Yes	7	1.54 (1.25–1.89)	.011	Reference	64.0
No	14	1.32 (1.17–1.48)	<.001	.293	78.8
HBV and/or HCV					
Yes	11	1.53 (1.22–1.92)	<.001	Reference	83.8
No	10	1.27 (1.14–1.41)	<.001	.189	70.0

[a]One study conducted in the Asia Pacific Cohort Studies Collaboration was excluded [16].
Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; SRR, summary relative risk.

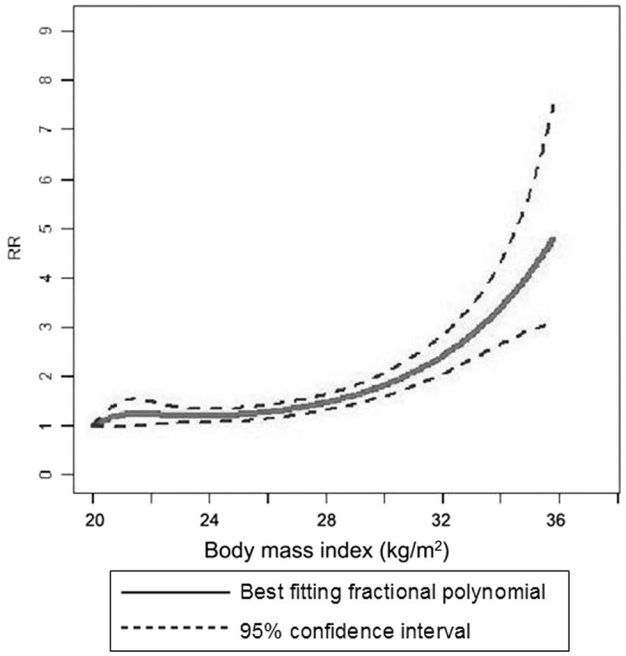

Figure 3. Body mass index and primary liver cancer risk, nonlinear dose-risk relationship.

Abbreviation: RR, relative risk.

creased BMI between men and women, although somewhat higher risk in males than that in females (SRR: 1.26 for men vs. 1.18 for women; $p = .414$). We assume that use of different statistical methods and the presence of nonlinear association may partially account for this discrepancy—that is, the linear model does not fit well with the data.

In the present meta-analysis, we found evidence of a nonlinear positive association between increased BMI and PLC risk, with the greatest risk increase when increasing from high levels of BMI (>32 kg/m^2). So, examining the shape of the dose-response curve seems to be important for clarifying this association. We also performed categorical meta-analysis based on included studies and found similar results with that from Larrson et al [8]—that is, obese men have a higher risk of HCC than do obese women (RR: 1.97, 95% CI: 1.50- 2.57 for men vs. RR: 1.43, 95% CI: 1.14–1.78 for women; $p = .072$). Thus, further studies will be necessary to dissect out the gender differences in the correlations between excess weight and the risk of PLC.

In the present meta-analysis, we found that the SRR of PLC with increased BMI in non-Asian studies was stronger than those in Asian studies. We do not know the exact mechanisms behind this phenomenon, but it may not be a chance finding because it was based on 10 prospective studies in both subgroups. It could be due to genetic factors or the prevalence of obesity. Another possibility is the difference in the prevalence of chronic liver disease between Asian and non-Asian studies. Further cohort studies of increased BMI and PLC risk in different geographic locations are needed.

Interestingly, findings from this meta-analysis indicate that the association between BMI and HCC risk is somewhat stronger for patients with HCV infection than for the general population ($p = .08$). We cannot completely rule out that this is a chance finding, because there were only six studies in this subgroup analysis. This phenomenon may suggest that the two risk factors, HCV and adiposity, could synergize to increase the risk of incident HCC. Adiposity is associated with hepatic steatosis and insulin resistance. Hepatic steatosis can cause hepatic inflammation and promote fibrosis through enhanced oxidative stress, increased susceptibility to apoptosis, and activation of subsinusoidal stellate cells [50]. Furthermore, HCV infection may induce insulin resistance by itself, which may also contribute to fibrosis progression [51]. More studies, including epidemiological and mechanism studies, are warranted to elucidate the exact contribution of excess weight on hepatocarcinogenesis in patients with HCV infection. In contrast to patients with HCV infection or cirrhosis, based on two studies, HBV-positive patients with excess weight were found to have a similar risk of PLC as the general population. However, because the sample size was small in these subgroups, we cannot exclude a type I error.

As obesity prevalence continues to be on an upward trajectory worldwide, the contribution of obesity to the development of PLC might constitute a significant proportion of the global burden of PLC. Obesity is an avoidable factor, as is smoking. The positive link between excessive weight and increased risk of PLC provides an excellent stimulus to intervene with individual and antiobesity treatment prior to malignant change.

In summary, this meta-analysis supports the hypothesis that excess body weight may significantly increase PLC risk. This positive association is true in both men and women; is true in North American, European, and Asian studies; and is independent of confounders. In future research, randomized trials are needed to further examine the effect of weight reduction in obese populations to decrease the risk of PLC.

Author Contributions

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Collection and/or assembly of data: Haixia Cao, Yuqin Wang, Jiangao Fan
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