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**Systematic review: the association between obesity and hepatocellular carcinoma – epidemiologic evidence**

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## Systematic review: the association between obesity and hepatocellular carcinoma – epidemiologic evidence

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## SUMMARY

**Background:** Evidence increasingly implicates obesity as an independent risk factor for different cancers. We examined such evidence for hepatocellular carcinoma.

**Aim:** To review the effect of increased levels of body mass index on hepatocellular carcinoma risk.

**Methods:** We systematically reviewed the literature examining the association between increasing body mass index and hepatocellular carcinoma risk. For each identified study, relevant data were extracted and appraised.

**Results:** Ten cohort studies (>90 million person-years), one nested case-control study (244 cases) and two case-control studies (494 cases) were identified. Of the cohort studies, 75% of person-years related to North Americans, 15% to East Asians, and 10% to Europeans. Three cohort studies adjusted for alcohol consumption, only one cohort study adjusted for hepatitis infection status. Seven cohort studies found a positive association between obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>) and hepatocellular carcinoma risk (relative risks ranging from 1.4-4.1); two reported no association; and one reported a significant inverse association for a population subgroup (relative risk = 0.7, 95% confidence interval: 0.5-0.9).

**Conclusion:** Although most studies did not adjust for confounders and most data relate to a single world region, the overall evidence is suggestive of an increased hepatocellular carcinoma risk in obese and overweight individuals.

## BACKGROUND

An increasing body of epidemiological evidence suggests that obesity is an independent risk factor for cancers of the breast, endometrium, kidney, colon, pancreas, gallbladder and oesophagus.<sup>1</sup> Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer; if diagnosed at an early stage, the 5-year survival could be greater than 50%.<sup>2</sup> However most HCC patients are diagnosed at a symptomatic stage and have a much poorer prognosis (5-year survival of less than 10%).<sup>3</sup> Both HCC incidence and obesity prevalence have been rising in recent years. For example, in England, between 1993 and 2006, the incidence of liver cancer has increased from 3.2 to 5.4 per 100,000 in men, and from 1.4 to 2.4 per 100,000 in women,<sup>4,5</sup> while, between 1993 and 2007, the adult prevalence of obesity (defined as a body mass index (BMI) equal to or greater than 30 kg/m<sup>2</sup>) has increased from 15% to 24%.<sup>6</sup> Known risk factors for HCC include chronic viral hepatitis (B or C), high alcohol intake and diabetes.<sup>7,8,9</sup>

It has been suggested that increasing population exposure to known risk factors such as infection with hepatitis B or C virus (HBV, HCV) and high alcohol intake is unlikely to fully account for the observed rise in HCC incidence,<sup>8,10</sup> and that this may at least in part be associated with the increasing prevalence of obesity. Such an association is biologically plausible (Box). Diabetes mellitus is an independent risk factor for HCC, both in the general population as well as in patients with HCV and HBV cirrhosis.<sup>11,12</sup> Obesity and diabetes mellitus form part of the metabolic syndrome, which has been linked to HCC.<sup>13</sup> Given the proposed mechanism for the link between obesity and HCC being that of insulin resistance,<sup>14</sup> obesity and diabetes are correlated.

Obesity is a potentially avoidable or modifiable condition, and establishing whether it is associated with different disease outcomes could help motivate population-based

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2  
3 prevention efforts. We aimed to identify and appraise the available epidemiological  
4 evidence to address the question whether obesity is an independent risk factor for  
5 HCC. We intended to update and enhance the literature by more specifically  
6 considering both cohort and case-control studies; by using a structured approach in  
7 determining the relevance and validity of the evidence, particularly in relation to  
8 adjustment for important confounders such as chronic hepatitis infection status,  
9 alcohol intake and diabetes status; and by specifically considering the generalisability  
10 of the evidence in relation to different geographical regions and populations.  
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**Box. Obesity and Hepatocellular Carcinoma: Why an association is biologically plausible**

*Mechanistic model and evidence from animal studies.* Fatty liver is associated with systemic insulin resistance.<sup>15</sup> Numerous animal models of insulin resistance and of fatty liver result in development of primary cancers in the livers of these animals.<sup>16, 17</sup> This outcome is thought to relate to the hepatocellular stress induced by the increased liver fat load, impairment of fatty acid oxidation and increased lipogenesis. This process can lead to dysregulation of cellular proliferative signals and oxidative DNA damage, which can promote carcinogenesis. Recent work has reinforced the importance of fatty acid metabolism on cancer evolution, with direct evidence that high-fat diet can direct evolution of a tumour towards a more aggressive phenotype.<sup>18</sup>

*Epidemiological evidence:* Fatty liver disease is the commonest cause of abnormal liver function in western societies.<sup>19, 20</sup> Fatty liver has two forms, steatosis and fatty liver with inflammation/scarring (steatohepatitis), both associated with a raised BMI.<sup>21</sup> Among obese individuals, the presence of diabetes (or impaired insulin tolerance) further increases the risk of liver fibrosis and cirrhosis.<sup>22, 23, 24, 25</sup> Furthermore, obesity in the context of cirrhosis (of different aetiologies, including chronic excess alcohol intake or HCV infection) is an independent risk factor for the development of HCC.<sup>9, 26</sup>

## METHODS

### *Literature search*

We have used the PRISMA statement checklist for suggested best-practice in the reporting of systematic reviews to inform the methods and the reporting of our study.<sup>27</sup> A review protocol was developed based on pre-determined aims and objectives. *PubMed* was searched for relevant peer-reviewed epidemiological evidence, published in English, using the keywords (and MeSH terms) *hepatocellular carcinoma, liver neoplasm, body mass index* and *obesity*. Studies were considered if they were published between 1980 and June 2009. We focused on primary studies, but the search was not otherwise restricted by study design. Studies were preliminarily selected based on their title and abstract. After full text examination studies were included if they met the following inclusion criteria: outcomes included HCC or liver cancer incidence or mortality (as a surrogate marker of incidence, given the HCC's poor prognosis); exposure variables considered were obesity and/or overweight categories; comparisons of risks in different overweight or obesity categories were made with members of the general population or individuals with normal range BMI values (as defined in different studies). Overweight individuals were defined as those with a BMI value between 25.0-29.9 kg/m<sup>2</sup> and obese as those with a BMI value  $\geq 30.0$  kg/m<sup>2</sup>. Data extraction was carried out as part of the full text examination. Risk of study bias was assessed by study type and on individual study characteristics. The reference lists of relevant studies and two reviews<sup>28, 29</sup> were also examined to help identify primary studies that may have been missed by the original search.

### *Study population stratification*

Population characteristics, such as lifestyle, environment and genetic background, vary around the world as does the incidence of HCC and the prevalence of related risk factors. Most HCC cases occur in Asia (the incidence in East Asian populations



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3 exceeds 20/100 000)<sup>30</sup> where the prevalence of both HBV and HCV infection is more  
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5 common than in European or North American populations.<sup>31, 32</sup> In contrast, in the  
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7 USA the prevalence of adult obesity has increased from 10% to 20% from 1986 to  
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9 2000,<sup>33</sup> which is higher than in Europe, and much higher than in East Asia.<sup>34, 35</sup> These  
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11 differences in population exposures to risk factors could have potentially significant  
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13 effects on the generalisability of the findings of studies conducted in different  
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15 populations. Therefore relevant extracted data from publications were further  
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17 stratified according to the region of the study population (i.e. North America, East  
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19 Asia and Europe).  
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## RESULTS

Of an initial yield of over 850 abstracts, eighteen studies of potential relevance were identified based on their title and abstract. After full-text examination, seven studies were excluded because they lacked an adequate control group,<sup>13, 36, 37, 38, 39, 40, 41</sup> one study<sup>42</sup> was excluded because it was part duplicate of another study,<sup>43</sup> and another study<sup>44</sup> was excluded because of its small sample size (n=210). Four further studies were identified by examining the reference lists of the included studies as well two previous meta-analyses.<sup>28, 29</sup> A total of thirteen primary studies met the inclusion criteria and were included in our review.

### *Study characteristics*

The study characteristics can be found in Tables 1 and 2. Of the thirteen studies, ten were cohort studies,<sup>1, 43, 45, 46, 47, 48, 49, 50, 51, 52</sup> one was a nested case-control study,<sup>53</sup> and two were case-control studies.<sup>9, 54</sup> Three were conducted in North American populations (two cohort and one case-control),<sup>1, 45, 54</sup> four in East Asian populations (three cohort and one nested case-control)<sup>43, 46, 47, 53</sup> and six in European populations (five cohort and one case-control).<sup>9, 48, 49, 50, 51, 52</sup>

The studies reported HCC risks for different categories of raised BMI levels, however studies varied in how many such categories were used (Table 3). Eight studies reported HCC risks associated with both overweight (BMI 25.0-29.9 kg/m<sup>2</sup>) and obesity (BMI ≥30.0 kg/m<sup>2</sup>) categories.<sup>1, 9, 43, 46, 48, 49, 50, 54</sup> Three studies reported HCC risks only for individuals in the obese category;<sup>45, 51, 52</sup> and two studies reported HCC risks for individuals in the overweight category.<sup>47, 53</sup> Obesity diagnosis was based on height and weight measurements, by trained interviewers in six studies,<sup>43, 46, 48, 49, 50, 53</sup> diagnosis of obesity on International Classification of Disease discharge data, following hospitalisation for any reason in three studies;<sup>45, 51, 52</sup> and self-reports in four studies.<sup>1, 9, 47, 54</sup>

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6 As for the cohort studies, follow-up ranged from one year<sup>50, 51, 52</sup> to as long as thirty-  
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8 five years,<sup>49</sup> with sample sizes also varying considerably (from 17,000<sup>49</sup> up to 4.5  
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10 million).<sup>45</sup> The total number of participants from all the cohort studies combined was  
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12 over 7 million, of which over 5.25 million are from North America, over 1.25 million  
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14 from East Asia and over 0.5 million from Europe. The total number of person-years of  
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16 follow-up exceeds 90 million, of which over 68 million relate to North American  
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18 populations, over 13 million to East Asian populations and over 9 million to European  
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20 populations. Six cohort studies reported findings separately by gender,<sup>1, 43, 46, 47, 51, 52</sup>  
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22 and only one study for different ethnic groups (white and black USA veterans).<sup>45</sup>  
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28 The outcome was reported as 'liver cancer' in nine studies (eight cohort and one  
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30 case-control)<sup>1, 43, 45, 47, 49, 50, 51, 52, 54</sup> and as HCC in four studies (two cohort and two  
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32 case-control studies).<sup>9, 46, 48, 53</sup> Of the ten cohort studies, eight used HCC or liver  
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34 cancer incidence as the outcome of interest and two used mortality (as a surrogate  
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36 for HCC or liver cancer incidence).<sup>1, 49</sup> In two studies,<sup>51, 52</sup> the reference population (to  
37  
38 which obese or overweight individuals were compared) was the national population  
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40 as a whole. One study<sup>45</sup> used non-obese study cohort individuals as the reference  
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42 group, while the rest used specific BMI ranges (with varying upper and lower limits)  
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44 as the reference group.  
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50 The ten cohort studies all identified incident cases of HCC or liver cancer via national  
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52 registries. Ohishi *et al.*<sup>53</sup> also used a cancer registry for HCC identification. In this  
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54 study, three controls were selected from the Adult Health Study longitudinal cohort  
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56 for each of the 224 cases, and they were selected at random among those who  
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58 matched for gender, age, city, and radiation exposure history. Pan *et al.*,<sup>54</sup> a  
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60 population based case-control study, identified cases and controls from the National  
Enhanced Cancer Surveillance System (NECSS) in Canada. Polesel *et al.*,<sup>9</sup> a case-

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3 control study, identified controls from acute hospital admission patients from the  
4 same hospitals from which HCC cases were selected. In this study the controls were  
5 more likely to be female and younger than the HCC cases, and patients who were  
6 admitted to hospital with diseases related to alcohol and tobacco were specifically  
7 excluded.  
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16 The risk of bias is generally lower among cohort studies than case-control studies.  
17 This is due to the use of incident cancers, removing any case-status bias, and  
18 identification of incident cases through national registries, reducing potential  
19 ascertainment bias. The study by Ohishi *et al.*<sup>53</sup> used a nested case-control design  
20 which minimized selection bias. Pan *et al.*<sup>54</sup> used a study population based on a large  
21 geographical region to reduce selection bias. The potential for bias in the Polesel *et*  
22 *al.*<sup>9</sup> study was reduced by employing the same interviewers for both cases and  
23 controls and achieving a high participation rate (cases: 71%, controls: 87%).  
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36 Six studies (three cohort and three case-control studies)<sup>1, 9, 46, 47, 53, 54</sup> adjusted for  
37 alcohol consumption, and three studies (one cohort and two case-control studies)<sup>9, 46,</sup>  
38 <sup>53</sup> adjusted for hepatitis infection status. None of the remaining studies considered  
39 these potential confounders.  
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47 The association between diabetes and HCC risk was examined by three studies (one  
48 cohort and two case-controls).<sup>9, 46, 53</sup>  
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### 53 54 55 **Effect sizes**

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57 Out of the ten cohort studies, seven<sup>1, 43, 46, 48, 49, 51, 52</sup> reported statistically significant  
58 positive associations between higher BMI levels and greater HCC risk, although the  
59 association differed in magnitude (Table 3). For obese populations (BMI  $\geq 30$  kg/m<sup>2</sup>)  
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3 the effect sizes in these studies ranged from 1.4 (HR for women)<sup>43</sup> to 4.1 (RR for  
4 both genders who were HCV positive).<sup>46</sup> On the other hand, two cohort studies  
5 reported no statistically significant associations.<sup>47, 50</sup> One USA cohort study<sup>45</sup> reported  
6 a significantly greater HCC risk in obese white male veterans (RR = 1.44, 95% CI:  
7 1.28-1.61) and a significant lower HCC risk in obese black male veterans (RR = 0.68,  
8 95% CI: 0.49-0.94). Overall, increased levels of BMI appeared to confer a greater  
9 risk of HCC in men than in women. Increasing risks across levels was evident in six  
10 out of seven cohort studies which categorised population by increasing BMI levels.<sup>1,</sup>  
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21 43, 46, 48, 49, 50

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25 A case-control study<sup>53</sup> reported the highest statistically significant positive association  
26 of 4.6 (RR for both genders with a BMI of >25 kg/m<sup>2</sup>). No significant association was  
27 reported by two case-control studies.<sup>9, 54</sup>  
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34 One out of two North American cohort studies,<sup>1</sup> two out of three East Asian cohort  
35 studies<sup>43, 46</sup> and four out of five European cohort studies<sup>48, 49, 51, 52</sup> reported a positive  
36 association between increasing BMI levels and HCC risk. As alluded above, one  
37 study found a negative association in US black men.<sup>45</sup> The only case-control study  
38 reporting a significant positive association was based on an East Asian population.<sup>53</sup>  
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47 Ten studies (nine cohort and one case-control study) included in this review  
48 assessed associations of obesity with several cancers.<sup>1, 43, 45, 47, 48, 49, 50, 51, 52, 54</sup> In  
49 these studies adjustment for risk factors associated with each individual cancer was  
50 not practical. Only three studies, one cohort<sup>46</sup> and two case-control studies,<sup>9, 53</sup>  
51 adjusted for both hepatitis infection status and alcohol intake. These studies reported  
52 varying associations: Chen *et al.*<sup>46</sup> obtained a statistically significant independent  
53 association between higher obesity levels and HCC risk but only in HCV patients (RR  
54 = 4.1, 95% CI: 1.4-12.4); Ohishi *et al.*<sup>53</sup> reported the highest observed RR for the  
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3 association between higher BMI levels and greater HCC risk (see above), in spite of  
4 the adjustment; whereas Polesel *et al.*<sup>9</sup> found no statistically significant independent  
5 association between obesity and HCC risk.  
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11 One case-control study<sup>53</sup> adjusted for diabetes status reporting a statistically  
12 significant positive association between increasing BMI levels and HCC risk (see  
13 above). Three studies (one cohort and two case-control studies)<sup>9, 46, 53</sup> also stratified  
14 results depending on diabetes status. Ohishi *et al.*<sup>53</sup> stratified results by diabetes  
15 status 10 years before HCC diagnosis, and found no statistically significant  
16 association (RR = 2.0, 95% CI: 0.6-6.3) with increasing BMI levels. Polesel *et al.*<sup>9</sup>  
17 reported a statistically significant association between patients with diabetes and  
18 HCC risk compared to normal patients (OR = 3.7, 95% CI: 1.7-8.4). Chen *et al.*<sup>46</sup>  
19 stratified results by HBV and HCV infection status and history of diabetes. A  
20 statistically significant association between history of diabetes and HCC risk was  
21 found in HBV individuals (RR = 2.2, 95% CI: 1.1-4.4) as well as HCV individuals (RR  
22 = 3.5, 95% CI: 1.4-8.8) but not in those without viral hepatitis (RR = 2.9, 95% CI: 0.9-  
23 9.3).  
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42 There was also evidence of synergy ('effect modification') between obesity and  
43 diabetes. Polesel *et al.*<sup>9</sup> found that obese patients with diabetes had an OR of 5.2  
44 (95% CI: 1.2-22.0), which was higher than that for obese patients without diabetes  
45 (OR = 1.9, 95% CI: 0.9-3.9) and normal weight patients with diabetes (see above).  
46 Significant effect modification between hepatitis infection, obesity and diabetes status  
47 is also reported in Chen *et al.*<sup>46</sup>, where the HBV positive obese diabetic population  
48 reportedly had a RR of HCC of 264.7 (95% CI: 35.2-1993) compared to non-obese,  
49 non-diabetic individuals without hepatitis infection.  
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## DISCUSSION

We reviewed evidence from thirteen different studies on the effect of obesity on HCC risk. Of the ten cohort studies, seven reported a statistically significant increased risk of HCC with increasing BMI levels, two reported no association, and one reported significantly greater risk in one ethnic population subgroup (white USA veterans) and significantly lower risk in another (black veterans). Six studies suggested a positive dose response pattern indicating greater HCC risk with higher BMI exposure. Cohort study evidence, which help to establish a temporal relationship between the onset of obesity and the development of HCC, relates to over seven million people who were followed up for a maximum of 35 years, and appears consistent along a wide range of different populations. Although major risk factors for HCC include chronic viral hepatitis infection, high alcohol intake and diabetes only three studies adjusted for hepatitis infection (one cohort and two case-control studies),<sup>9, 46, 53</sup> only six adjusted for alcohol intake (three cohort and three case-control studies),<sup>1, 9, 46, 47, 53, 54</sup> and only one included result adjusted for diabetes (case-control study).<sup>53</sup> Only three studies considered both alcohol intake and hepatitis infection status, the two most potent risk factors.<sup>9, 46, 53</sup>

Current evidence strongly indicates a positive association; however some doubt about causality still exists, given imperfections in the evidence, mainly because of the above alluded limited adjustment for major confounders. Lack of adjustment for important risk factors also limits the generalisability of the evidence, as it impedes comparisons between populations with varied prevalence of risk factors. The predominance in the evidence base of study populations from North America also means generalisations to other populations (with different population exposure to either obesity of known important HCC risk factors, such as hepatitis infection status) ought to be cautious. Only one study considered ethnic background,<sup>45</sup> with contrasting findings in relation to the direction of the association. This finding

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3 indicates the need for further research in (either genetic or environmental)  
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6 determinants of ethnic group differences in HCC risk among obese individuals in the  
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8 future. Effect modification (i.e. a synergistic increase in HCC risk) has been observed  
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10 for obesity and diabetes<sup>9</sup> consistent with the hypothesis that the oncogenic effect of  
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12 obesity on the liver is mediated primarily through insulin resistance and resultant  
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14 lipotoxicity.  
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18 Renehan *et al.*<sup>29</sup> used evidence from four cohort studies<sup>42, 47, 48, 50</sup> in a meta-analysis  
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20 of the effects of increasing BMI on risk of different cancers. They reported a positive  
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22 association between each 5 kg/m<sup>2</sup> increase and liver cancer for men (RR = 1.24,  
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24 95% CI: 0.95-1.62), and no association for women (RR = 1.07, 95% CI: 0.55-2.08).  
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26 This study did not assess qualitative aspects of evidence nor did they discuss the  
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28 use of adjustments for the major risk factors of HCC, nor did they consider case-  
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30 control studies. Larsson & Wolk<sup>28</sup> compiled a meta-analysis of eleven cohort studies  
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32 comparing the effect of increasing BMI levels and liver cancer risk. Eight of the  
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34 studies<sup>1, 45, 47, 48, 49, 50, 51, 52</sup> formed part of the present study, however we have also  
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36 considered two further cohort studies,<sup>43, 46</sup> one nested case-control study,<sup>53</sup> and two  
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38 case-control studies.<sup>9, 54</sup> This study found that persons who were overweight (BMI  
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40 25.0-29.9 kg/m<sup>2</sup>) and obese (BMI ≥30.0 kg/m<sup>2</sup>) had a 17% and 89% increased HCC  
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42 risk compared to those of normal weight, respectively. There was no consideration of  
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44 stratification by follow-up length or by study region. No study that adjusted for HBV or  
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46 HCV infection status was included in their meta-analysis either.  
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53 Although we excluded Oh *et al.*<sup>42</sup> from formal data extraction because it was a part  
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55 duplicate of Jee *et al.*,<sup>43</sup> that study also reported a positive association between BMI  
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57 ≥30 kg/m<sup>2</sup> and HCC risk (RR = 1.6, 95% CI: 1.3-2.1) compared to a BMI of 18.5-22.9  
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59 kg/m<sup>2</sup>.  
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3 All ten cohort studies<sup>1, 43, 45, 46, 47, 48, 49, 50, 51, 52</sup> used administrative data from nation-  
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5 wide statistics systems greatly helping in optimising the ascertainment of follow-up  
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7 events. However, use of administrative ('routine') datasets relies on assumptions  
8  
9 about accurate diagnosis and classification of disease. Participation rates in the  
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11 case-control studies considered in this review were all acceptable. The nested case-  
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13 control design of Ohishi *et al.*<sup>53</sup> reported a participation rate of 62% due to non-  
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15 availability of stored serum. Pan *et al.*<sup>54</sup> reported a 69% participation rate of cases  
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17 due to failure of consent and incomplete questionnaires. Polesel *et al.*<sup>9</sup> had a 71%  
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19 participation rate among eligible cases due to failure to give a blood sample and  
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21 inadequate anthropometric measurements at cancer diagnosis.  
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27 The incidence of HCC varies with age, gender, race and geographic region.<sup>26</sup> Three  
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29 of the studies included in this review (one cohort and two case-control studies)<sup>9, 46, 53</sup>  
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31 did not categorise their study population, nine studies (eight cohort and one case-  
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33 control study)<sup>1, 43, 47, 48, 49, 50, 51, 52, 54</sup> categorised participants by gender, and only one  
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35 cohort study<sup>45</sup> categorised study population by gender and ethnic group. Variance in  
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37 association between obesity and HCC risk in different subpopulations could be  
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39 masked by studying the population as a whole. Such considerations are important  
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41 when considering the potential for preventive efforts (e.g. through screening) that  
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43 could be better targeted to population subgroups at highest risk.  
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49 Measuring obesity using BMI may not be the best way for assessing obesity-related  
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51 health risk. Waist circumference (WC) has been suggested to be a better predictor of  
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53 adverse health outcomes than BMI.<sup>55, 56</sup> The use of waist circumference, or other  
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55 anthropometric markers, may provide more pertinent results. This is a matter that  
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57 should be better addressed by future research.  
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3 In conclusion, epidemiological evidence from a range of different populations and  
4 study designs indicates that, consistent with biological plausibility studies, a causal  
5 link between increasing levels of obesity and greater HCC risk is very likely. This  
6 realisation could help inform and motivate healthcare planning efforts to prevent  
7 obesity and improve its management. Conversely, currently increasing obesity trends  
8 are likely to lead to higher HCC disease burden in the future. Given the known  
9 survival benefit of early detection of this form of cancer, and the poor prognosis of  
10 symptomatic presentation, this may also enable research about the potential  
11 usefulness of HCC screening in patients judged to be at high HCC risk because of  
12 obesity or other known risk factors. More importantly, and from the point of view of  
13 public health, this evidence can help underpin both research and policies about  
14 population-based obesity prevention and control efforts.  
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For Peer Review

**Table 1.** Eligible cohort studies identified by the literature search (n=10)

First author, country, year	Population, sample (n)	Recruitment period / Age range at recruitment (years) / % male	Ascertainment of exposure	Min-max follow-Up (years)	HCC Incident cases (n)		Ascertainment of outcome
					Overall	Obese subjects	
Samanic <i>et al.</i> , <sup>45</sup> USA, 2004	Inpatient visit to the Veterans Affairs hospitals. U.S. white men: 3,668,486 black men: 832,214	1969-1996 / 18-100 / 100% M	Discharge diagnosis of obesity at recruitment	From 2 to 27 (mean: 12)	White men: 3,934 Black men: 1,206	White men: 322 Black men: 38	Discharge records of Veterans Affairs hospitals
Calle <i>et al.</i> , <sup>1</sup> USA, 2003	The Cancer Prevention Study II. U.S. men: 404,576 women: 495,477	1982 / >30 / 45% M	Self-reported at recruitment	Up to 16	Men: 620* Women: 345*	–	National Death Index and personal inquiries
Chen <i>et al.</i> , <sup>46</sup> Taiwan, 2008	Taiwanese men: 11,973 women: 11,847	1991-1992 / n/a / 50% M	Measured at recruitment	Up to 14	Men: 222 Women: 69	–	Taiwan National Cancer Registry
Jee <i>et al.</i> , <sup>43</sup> Korea, 2008	Korean National Health Insurance Corporation. Korean men: 770,556 women: 443,273	1992-1995 / 30-95 / 63% M	Measured at recruitment	From 2 to 14 (mean: 10.8)	Men: 8759 Women: 1,761	Men: 112 Women: 63	Korean National Cancer Registry
Kuriyama <i>et al.</i> , <sup>47</sup> Japan, 2005	Japanese men: 12,485 women: 15,054	1984 / ≥40 / 45% M	Self-reported at recruitment	Up to 9	Men: 69 Women: 31	–	Miyagi Prefectural Cancer Registry
Samanic <i>et al.</i> , <sup>48</sup> Sweden, 2006	The Swedish Foundation for Occupational Safety and Health of the Construction Industry.	1971-1992 / 18-67 / 100% M	Measured at recruitment	Up to 28 (mean: 19)	Men: 194	Men: 31	National Swedish Cancer Registry

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Swedish men: 362,552

Batty <i>et al.</i> , <sup>49</sup> UK, 2005	The Whitehall I study. London based government employees men: 17,102	1967-1970 / 40-64 / 100% M	Measured at recruitment	Up to 35 (median: 28.1)	Men: 51*	–	National Health Service central registry
Rapp <i>et al.</i> , <sup>50</sup> Austria, 2005	The Vorarlberg Health Monitoring and Promotion Program. Austrian men: 67,447	1985-2001 / 18-94 / 100% M	Measured at recruitment	From 1 to 17 (mean: 9.9)	Men: 57	Men: 10	Vorarlberg Cancer Registry
Wolk <i>et al.</i> , <sup>51</sup> Sweden, 2001	Swedish National Board of Health and Welfare. Swedish men: 8,165 women: 19,964	1965-1993 / >18 / 29% M	Discharge diagnosis of obesity at recruitment	From 1 to 29	Men: 15 Women: 13	Men: 15 Women: 13	National Swedish Cancer Registry
Moller <i>et al.</i> , <sup>52</sup> Denmark, 1994	The Danish Hospital Discharge Register. Danish men: 14,531 women: 29,434	1977-1987 / n/a / 33% M	Discharge diagnosis of obesity at recruitment	From 1 to 11 (mean: 4.8)	–	Men: 22 Women: 36	Danish Hospital Discharge Register, the Danish Cancer Registry and the Danish Register of Deaths

\*HCC incident cases ascertained as HCC-related deaths

**Table 2.** Eligible case-control studies identified by the literature search (n=3)

First author, country, year	Age range (years) / % Male	Ascertainment of exposure	Controls		HCC cases		Ascertainment of outcome
			Population	Number (n)	Population	Number (n)	
Pan <i>et al.</i> , <sup>54</sup> Canada, 2004*	20-76 / % M	Self-reported	Canadian participants in the National Enhanced Cancer Surveillance System	5039	Canadian participants in the National Enhanced Cancer Surveillance System	Men: 225 Women: 84	National Enhanced Cancer Surveillance System
Ohishi <i>et al.</i> , <sup>53</sup> Japan, 2008**	Mean: 66.4 / % M	Measured	Atomic bomb survivors	644	Atomic bomb survivors	244	Hiroshima Tumour and Tissue Registry and Nagasaki Cancer Registry
Polesel <i>et al.</i> , <sup>9</sup> Italy, 2009***	40-84 / % M	Self-reported	Italian hospitalised patients	404	Italian incident HCC cases who had not received any cancer treatment at study entry	185	Hospital diagnosis

\* Population based case-control study.

\*\* Nested case-control study.

\*\*\* Case-control study with acute hospital admission patients as controls.

**Table 3.** Effect sizes and 95% confidence intervals reported by the eligible studies (n = 13)

First author, year	BMI (kg/m <sup>2</sup> )	Effect size			Confounders adjusted for in analysis	
		Measure (95% CI)*			Alcohol intake, hepatitis infection status, diabetes status	Other confounders
		Men	Women	All		
Samanic <i>et al.</i> , <sup>45</sup> 2004	U.S. veterans	RR: 1.0				- Age, calendar year
	White men ICD obesity diagnosis	1.44 (1.28-1.61)	-	-	-	
	Black men ICD obesity diagnosis	0.68 (0.49-0.94)				
Calle <i>et al.</i> , <sup>1</sup> 2003	18.5-24.9	RR: 1.0	RR: 1.0		- Alcohol intake	- Age, race, education, marital status, smoking, physical activity, aspirin use, oestrogen replacement therapy (women), dietary factors (crude index of fat and vegetable consumption)
	25-29.9	1.13 (0.94-1.34)	1.02 (0.80-1.31)			
	30-34.9	1.90 (1.46-2.47)	1.40 (0.97-2.00)			
	35-39.9	4.52 (2.94-6.94)	1.68 (0.93-3.05)			
Chen <i>et al.</i> , <sup>46</sup> 2008	Hepatitis B and C negative				- Alcohol intake, hepatitis infection status	- Age, sex, smoking, education
	<23			RR: 1.0		
	23-24.9	-	-	0.88 (0.41-1.86)		
	25-29.9			0.86 (0.42-1.74)		
	≥30			2.36 (0.91-6.17)		

	<i>HBV positive only</i>					
	<23			RR: 1.0		
	23-24.9			1.40 (0.97-2.02)		
	25-29.9			1.17 (0.81-1.69)		
	≥30			1.36 (0.64-2.89)		
	<i>HCB positive only</i>					
	<23			RR: 1.0		
	23-24.9			1.05 (0.41-2.73)		
	25-29.9			3.02 (1.48-6.14)		
	≥30			4.13 (1.38-12.4)		
Jee <i>et al.</i> , <sup>43</sup> 2008	23-24.9	HR: 1.0	HR: 1.0			- Age, smoking
	25-29.9	1.04 (0.96-1.13)	1.14 (0.97-1.35)	-	-	
	≥30	1.63 (1.27-2.10)	1.39 (1.00-1.94)			
Kuriyama <i>et al.</i> , <sup>47</sup> 2005	18.5-24.9	RR: 1.0	RR: 1.0		- Alcohol intake	- Age, type of health insurance, smoking, dietary intake of meat, fish, fruits, vegetables, bean-paste soup, and for women age of menarche, age at end of first pregnancy and menopausal status
	25-27.4	0.80 (0.40-1.63)	1.30 (0.54-3.16)			
	27.5-29.9	1.14 (0.46-2.87)	0.91 (0.30-2.80)			
				-		
Samanic <i>et al.</i> , <sup>48</sup> 2006	18.5-24.9	RR: 1.0				- Age, smoking
	25-29.9	1.45 (1.06-1.98)		-	-	
	≥30	3.13 (2.04-4.79)				
Batty <i>et al.</i> , <sup>49</sup>	18.5-24.9	HR: 1.0		-	-	- Age *



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2005	25-29.9	0.91 (0.50-1.65)				
	≥30	3.55 (1.46-8.63)				
Rapp <i>et al.</i> , <sup>50</sup>	18.5-24.9	HR: 1.0				- Age, occupational group, smoking
2005	25-29.9	1.32 (0.73-2.37)	-	-	-	
	≥30	1.67 (0.75-3.72)				
Wolk <i>et al.</i> , <sup>51</sup>	Swedish population	SIR: 1.0	SIR: 1.0	SIR: 1.0		- Age, calendar year
2001	ICD obesity diagnosis	3.60 (2.0-6.0)	1.7 (0.9-2.9)	2.4 (1.6-3.4)		
Moller <i>et al.</i> , <sup>52</sup> 1994	Danish population	RR: 1.0	RR: 1.0	RR: 1.0		- Age
	ICD obesity diagnosis	1.9 (1.2-2.9)	1.9 (1.4-2.7)	1.9 (1.5-2.5)		
Pan <i>et al.</i> , <sup>54</sup>	<25	OR: 1.0	OR: 1.0	OR: 1.0	- Alcohol intake	- Age, geographical region, education level, smoking, physical activity, total calory intake, total vegetable consumption, dietary fibre intake, multivitamin intake, menopausal status, parity, age at menarche and age at end of first pregnancy
2004	25-<30	0.99 (0.72-1.38)	0.61 (0.35-1.07)	0.89 (0.68-1.17)		
	≥30	1.30 (0.85-1.97)	0.94 (0.48-1.84)	1.17 (0.83-1.66)		
Ohishi <i>et al.</i> , <sup>53</sup> 2008	21.3-22.9			RR: 1.0	- Alcohol intake, hepatitis infection status, diabetes status	- Age, gender, city, time of serum storage, method of serum storage, radiation exposure, smoking, coffee
	23-25			2.51 (0.99-6.37)		
	>25			4.57 (1.85-11.3)		

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Polesel <i>et al.</i> , <sup>9</sup> 2009	<25 25-<30 ≥30	-	-	OR: 1.0 1.0 (0.5-1.9) 1.9 (0.9-3.9)	- Alcohol intake, hepatitis infection status	- Age, gender, study centre, years of education, smoking
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Note: HR = hazard ratio, OR = odds ratio, RR = relative risk, and SIR = standardised incidence ratio.

\* Batty *et al.*<sup>49</sup> also calculated a multiply adjusted HR for liver cancer risk, however one of the adjustments made is for triceps skinfold thickness. As this variable is another marker of obesity, doing so may have resulted in over-adjustment of the model, reason for which we have opted not to report this multiply adjusted value here.

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