Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies
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CRD summary
A sustained virological response after treatment of hepatitis C virus-infected patients at all stages of fibrosis and with advanced liver disease was associated with a protective effect against the development of liver cancer. Despite limitations associated with the design of the included observational studies, the large, precise and consistent estimates suggest that the conclusions are likely to be reliable.

Authors' objectives
To examine the association between achieving a sustained virological response to hepatitis C virus therapy and development of hepatocellular carcinoma (liver cancer) in adults at any stage of fibrosis and adults with advanced liver disease.

Searching
DARE, MEDLINE, EMBASE, CINAHL, Web of Science and The Cochrane Library were searched from inception up to February 2012 for studies in English. Search terms were reported in an appendix.

Study selection
Observational studies that compared therapy-derived sustained virological response with no response to therapy among hepatitis C virus-infected adults were eligible for inclusion. Studies that compared hepatocellular carcinoma diagnoses by sustained virological response and non-response were included. Eligible studies were required to have an average follow-up of at least two years. The definition of sustained virological response was reported in the paper. Studies had to report that participants were screened and confirmed to be negative for hepatocellular carcinoma and hepatitis B virus co-infection at study initiation, or report adjusted analyses accounting for hepatitis B virus presence at baseline. The primary outcome was the relative effect of developing hepatocellular carcinoma after achieving a sustained virological response versus non-response in patients treated with any antiviral regimen capable of viral eradication.

Studies with less than 20 participants, or with patients that received ongoing therapy, or with patients who had previously received a liver transplant, or studies with a primary population of patients co-infected with HIV were excluded.

In included studies, the mean patient age ranged from 37 to 61 years. Most studies reported on patients at all stages of disease progression. About half of the studies included a population or a subgroup of patients with advanced liver disease.

Two reviewers independently selected the studies, with disagreements resolved via discussion or by a third reviewer.

Assessment of study quality
Risk of bias was assessed using the Newcastle-Ottawa Scale. The GRADE framework was used to evaluate the quality of the evidence. Quality of evidence could be classed as very low, low, moderate or high.

Two reviewers independently assessed study quality.

Data extraction
Outcomes data were extracted to calculate hazard ratios and 95% confidence intervals. Study authors were contacted in case of missing data.

Two reviewers independently extracted the data, with disagreements resolved by discussion.

Methods of synthesis
Pooled hazard ratios and 95% confidence intervals were calculated using a random-effects meta-analysis. Pooled
estimates were obtained separately for hepatitis C virus infected patients at any stage of fibrosis and for those with advanced fibrosis. Only studies that adjusted for potential confounders were included in the analyses. Heterogeneity was assessed using Q and I² tests.

Pooled estimates were stratified by geographic region (Asia versus Europe and North America); the authors stated that they explored the extent to which these changed when the number and types of confounders adjusted for in the studies were varied.

A sensitivity analysis was used to assess whether including adjusted versus unadjusted study results affected the final effect estimate.

Publication bias was assessed by visual inspection of funnel plots.

**Results of the review**
Thirty studies (31,528 participants) were included in the review. The average length of follow-up after treatment ranged from 2.5 to 14.4 years. The overall quality of evidence was classed as moderate. Nearly all the studies were retrospective observational studies, so the risk of selection bias was high and loss to follow-up was rarely reported.

For patients at all stages of liver disease, achieving a sustained virological response was associated with a reduction in the chance of developing hepatocellular carcinoma (HR 0.24, 95% CI 0.18 to 0.31; 12 studies; 25,497 patients). A similar association was observed in patients with advanced liver disease (HR 0.23; 95% CI 0.16 to 0.35; eight studies; 2,649 patients). There was no evidence of significant heterogeneity.

Subgroup and sensitivity analyses found no significant effect of confounders and adjustment for confounders on the pooled estimates.

There was some evidence of publication bias based on the funnel plots.

**Authors’ conclusions**
A sustained virologic response after treatment for hepatitis C virus was associated with a protective effect against the development of hepatocellular carcinoma in infected patients at all stages of fibrosis and with advanced liver disease.

**CRD commentary**
The review question and selection criteria were clearly stated. Although language restrictions were applied to the searches, several sources were consulted to identify published and unpublished studies. Steps were taken to minimise reviewer bias and error at all stages of the review.

Quality assessment of included studies was conducted using appropriate tools; the quality of the evidence was considered moderate. A relatively large number of patients were included in the analyses. The results of a large number of small non-adjusted studies were not included in the main pooled analyses and were not reported. However, various subgroup and sensitivity analyses were conducted to explore the impact of excluding non-adjusted studies and the risk of confounding; the authors indicated that their results confirmed the robustness of the main analyses.

Despite the risk of bias associated with the design of the included studies, the large, precise and consistent effects suggest that the conclusions are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that the association between sustained virological response and hepatocellular carcinoma should be considered when weighing the benefits and harms of identifying and treating hepatitis C virus-infected patients.

**Research:** The authors did not state any implications for research.

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