Oral contraception and the risk of hepatocellular carcinoma
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CRD summary
This review concluded that there was no robust evidence to suggest an association between oral contraceptive use and risk of hepatocellular carcinoma. The sole reliance on case control studies, a limited search strategy and an absence of study quality assessment meant that the potential for biases could not be ruled out and the reliability of the authors’ conclusion is unclear.

Authors' objectives
To assess the association between oral contraceptive use and risk of hepatocellular carcinoma.

Searching
PubMed was searched to March 2006 for studies in any language. Search terms were reported. Reference lists were handsearched for further relevant studies.

Study selection
All controlled study designs that focused specifically on hepatocellular carcinoma and oral contraceptive were eligible for inclusion in the review. All included studies were case-control designs published between 1983 and 1997. Outcomes were primarily measured by questionnaires delivered by interview or mail, or by chart abstraction. The included cases were women aged from 18 to 74 years who had been diagnosed or died with hepatocellular carcinoma between 1975 and 1996 (numbers ranged from 9 to 317). The controls (numbers ranging from 22 to 1779) comprised women who were age-matched to cases. The average oral contraceptive use in hepatocellular carcinoma cases was 49.5% (range 19% to 90.9%); in controls, this was 34.1% (range 5.3% to 61%). Data were collected worldwide from hospital settings or population-based registries. It appeared that two independent reviewers performed the study selection and disagreements were resolved between them.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Odds ratios (and adjusted rates, where available) and 95% confidence intervals (CI) were abstracted or calculated from the included studies. Data were also extracted on testing for hepatitis B and C, alcohol use history, cirrhosis, duration of oral contraceptive use, time since last oral contraceptive use and hepatitis B endemicity. It appeared that two independent reviewers performed the data extraction.

Methods of synthesis
Where possible, odds ratios were pooled in a random-effects meta-analysis (DerSimonian and Laird) and the results presented in forest plots. Heterogeneity was assessed using the I^2 test (values over 50% indicating high heterogeneity) and was explained further in meta-regression analyses exploring the effects of age, geographic region, year of publication, study setting and hepatitis B status. Publication bias was assessed using Egger’s test and a modified version of Macaskill’s test.

Results of the review
Twelve case-control studies were included in the review (739 hepatocellular carcinoma cases and 5,223 controls).

The pooled analysis (adjusted only for age and sex) was non-significant (odds ratio 1.57, 95% CI: 0.96 to 2.54, p=0.07; 12 studies). The trend was towards high heterogeneity amongst the studies (I^2=39.9%). The exclusion of one study reduced heterogeneity to 16.9% and the pooled odds ratio increased to a significant 1.70 (95% CI: 1.12 to 2.59, p=0.01). Publication bias was significant in both tests (p=0.0001 and p=0.007).

The pooled analysis adjusted for variables in addition to age and sex was non-significant (odds ratio 1.45, 95% CI: 0.93
to 2.27, p=0.11; eight studies). Heterogeneity was slightly lower than the unadjusted result ($I^2=20.4$). The exclusion of any study from the analysis had little effect on heterogeneity, but increased the odds ratio to a significant level at 1.68 (95% CI: 1.05 to 2.67, $p=0.03$).

No significant effects were found in the meta-regression analysis.

Six studies revealed that durations of oral contraceptive use greater than five years were associated with significantly increased risks of hepatocellular carcinoma (odds ratio range: 2 to 20.1), although reporting was insufficient to allow meta-analysis. Two studies conducted in hepatitis B endemic areas revealed a non-significant association between any oral contraceptive use and hepatocellular carcinoma in terms of duration or recency of use.

Authors’ conclusions
There was no conclusive evidence to suggest an association between any duration of oral contraceptive use and risk of hepatocellular carcinoma.

CRD commentary
The review question was clear, but inclusion criteria were lacking on participants. The search strategy was based largely on one electronic database and there was no apparent attempt to retrieve unpublished studies, so relevant studies may have been missed. Publication bias was subsequently confirmed as a possible threat to the validity of the findings. The absence of validity assessment meant that the reliability of included studies and their synthesis was unclear. Other parts of the review process appeared to have been carried out with some efforts to minimise errors and biases. The choice of meta-analytic method appeared to be appropriate given the trend towards high heterogeneity between the included studies. The various methodological concerns and the inherent biases associated with sole reliance on case control studies suggested that the reliability of the authors’ conclusions is unclear.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that more research was needed to explore the impact of current oral contraceptive formulations on hepatocellular carcinoma risk in terms of duration and patterns of use.

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