Risk of colorectal carcinoma in post-liver transplant patients: a systematic review and meta-analysis

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CRD summary
The review assessed the risk of colorectal cancer in patients who underwent liver transplantation (including liver transplant patients with non-primary sclerosing cholangitis). The authors concluded that these patient groups have an increased colorectal cancer risk compared with the general population. These conclusions appear appropriate, but limitations in the review process mean that the overall reliability is unclear.

Authors' objectives
To determine whether colorectal cancer risk and incidence were increased after liver transplantation, specifically in patients with non-primary sclerosing cholangitis, compared with the general population.

Searching
MEDLINE (from 1986 to November 2008) and the Cochrane Library (November 2008) were searched; search terms were reported. The related article function on PubMed was used to identify additional relevant studies. Reference lists of retrieved studies were handsearched.

Study selection
Eligible studies were randomised controlled trials (RCTs) or cohort studies. Eligible studies were required to have sufficient data on the incidence or risk of colorectal cancer and size of cohort. Only studies that reported data from transplantation patients in general, without reporting separately observed cases of colorectal cancer after transplant, were included in the review. Studies that did not specify cancers by anatomical sites, studies that investigated colorectal cancer incidence in transplantation patients and/or ulcerated colitis, and studies that involved only paediatric patients, were excluded.

In the included studies, the mean age at liver transplantation ranged from 42 to 56 years. Two studies had pre-transplantation screening protocols; another two studies had post transplantation screening colonoscopies.

The authors did not state how the papers were selected for the review.

Assessment of study quality
Data quality scores (DQS) were created to assess the quality of the included studies. The scale included 14 yes or no questions. Each study could achieve a maximum score of 16 points based on study design and conduct. On the basis of this score, studies were then classified as high (10.5 points or more), medium (6.5 to 10 points), or low quality (6 points or less).

Two reviewers independently undertook the quality assessment, with consensus reached by discussion with a third reviewer.

Data extraction
Added highlighted to specify the basic data extracted to calculate colorectal cancer incidence rate and relative risks (RRs).

Data on the number of colorectal cancer cases for the overall post liver transplant cohort, and the non-primary sclerosing cholangitis patients, were extracted to calculate colorectal cancer incidence rates per 100,000 person years of follow-up and relative risks (RR) for colorectal cancer with 95% confidence intervals (CI). Where the counts were zero, a correction factor of 0.5 was added to the number of cases and total follow up time in person years.

Where studies had insufficient data, attempts were made to contact the authors of the studies to obtain the missing
information.

The authors did not state how the data extraction was performed or how many reviewers performed data extraction.

**Methods of synthesis**

Colorectal cancer incidence rates per 100,000 person years and relative risks, with 95% confidence intervals, were pooled in a meta-analysis for all post liver transplant indications using a random-effects model; this included the subgroup of non-primary sclerosing cholangitis patients after liver transplantation. The comparison for the pooled incidence rate was an age-matched control incidence rate for colorectal cancer, which was based on data from the SEER database (USA National Cancer Institute cancer statistics and surveillance methods). Liver transplant patients were compared with the general population for the pooled estimate of the relative risk for colorectal cancer, where data were available. When no formal relative risk meta-analyses could be performed, an extracted relative risk was calculated using the weighted age-matched control incidence rate based on SEER and used for comparison with the general population.

Heterogeneity between studies was assessed by $I^2$ test.

Sensitivity analysis was undertaken to determine the impact of each study.

Publication bias was tested using Egger's test and, if this test was significant, a scatter plot was performed for inspection.

**Results of the review**

Twenty-nine studies (n=18,640 patients) were included in the review. Six studies (n=3,276 patients) were categorised as high quality, 15 studies were categorised as medium quality (n=11,089 patients) and eight studies were categorised as low quality (n=4,275 patients). The mean follow up ranged from three to 11 years.

Colorectal cancer incidence rate: The overall colorectal cancer incidence rate after liver transplantation was 119 (95% CI 88 to 161) cases per 100,000 person years (15 studies). The overall weighted age-matched control incidence rate for colorectal cancer was 77.9 (95% CI 77.6 to 78.3) cases per 100,000 person years (13 studies). The incidence rate of colorectal cancer in the subgroup of non-primary sclerosing cholangitis post liver transplant patients was 129 (95% CI 81 to 207) cases per 100,000 person years (10 studies). The non-primary sclerosing cholangitis weighted age-matched control incidence rate for colorectal cancer was 71.2 (95% CI 70.6 to 71.8) cases per 100,000 years. There was no evidence of heterogeneity between the studies for the overall or subgroup analysis using the $I^2$ test; Egger's test indicated potential evidence of publication bias for both analyses. Sensitivity analyses for the overall incidence rate suggested that estimates were not changed markedly when studies were omitted from the analyses. Sensitivity analysis for the non-primary sclerosing cholangitis patients indicated that one study was predictive for the high colorectal cancer incidence rate.

Colorectal cancer relative risk: The overall pooled relative risk for colorectal cancer in patients after liver transplantation was 2.59 (95% CI 1.65 to 4.05) compared with the general population. There was moderate heterogeneity ($I^2=42.7\%$). There was no evidence of publication bias. The relative risk for colorectal cancer in the subgroup of non-primary sclerosing cholangitis patients after liver transplantation was 1.8 (95% CI 1.1 to 2.9) compared with the weighted age-matched control group (based on the SEER).

**Authors' conclusions**

After liver transplantation, patients had an increased risk for colorectal cancer, along with the subgroup of patients with non-primary sclerosing cholangitis, when compared with the general population.

**CRD commentary**

The review question was clearly defined and inclusion criteria were appropriate. Two electronic databases were searched and attempts were made to find additional studies. The authors did not report if attempts were made to find unpublished studies. There was a suggestion of possible publication bias for two of the analyses. It was unclear whether
steps were taken to reduce language bias. Although validity assessment was conducted in duplicate, the authors did not report methods using methods designed to reduce reviewer bias and error for selection of studies or data extraction.

Validity assessment was appropriate, with studies categorised as high, medium or low quality. Analyses were almost exclusively based on the high and medium quality studies; the authors noted that there was no relationship between quality of the studies and the observed summary estimates. Where comparison with the general population was missing, methods to calculate control group estimates were appropriate, although the estimates were based exclusively on the USA population. Screening protocols before liver transplantation varied between studies; variation in the use of colonoscopy could have affected the estimates. Synthesis of the studies in meta-analyses was appropriate.

The authors’ conclusions were appropriate and reflected the evidence base, but some shortcomings in the review process and potential biases suggest that the reliability of the conclusions is unclear.

**Implications of the review for practice and research**

**Practice:** The authors stated that the calculated risk of colorectal cancer may be too small to justify an intensified surveillance strategy in liver transplant patients with non-primary sclerosing cholangitis.

**Research:** The authors stated that a large prospective cohort study is required to evaluate the yield of a colonoscopy after liver transplantation; further research is required to clarify recommendations for non-primary sclerosing cholangitis patients who have a liver transplant.

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