Incidence of Colorectal Cancer After Liver Transplantation for Primary Sclerosing Cholangitis: A Systematic Review and Meta-Analysis

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Patients with primary sclerosing cholangitis (PSC) and associated inflammatory bowel disease (IBD) have an increased risk of colorectal cancer (CRC). We estimated the pooled incidence of CRC after liver transplantation (LT) in patients with PSC as well as in a subset of patients with associated IBD (PSC-IBD). Through a systematic review of major bibliographic databases up to April 1, 2013, we identified cohort studies reporting the incidence of de novo CRC after LT for PSC. The main outcome measure was CRC incidence rate (IR) per 1000 person-years after LT in all patients with PSC and in a subset of patients with PSC-IBD with an intact colon. According to a meta-analysis of 18 independent cohorts (69 cases of CRC among 1987 patients), the pooled IR of de novo CRC in patients with PSC after LT was 5.8 per 1000 person-years [95% confidence interval (CI) = 3.8-7.8]. According to a meta-analysis of 16 independent cohort studies (66 cases of CRC among 1017 patients), the IR of CRC in patients with PSC-IBD and an intact colon at the time of LT was 13.5 per 1000 person-years (95% CI = 8.7-18.2). A long duration of IBD and extensive colitis were identified as risk factors for CRC. Specific transplant-related factors that can increase the risk of CRC have not been identified. In conclusion, the risk of CRC remains high for patients who undergo LT for PSC, particularly in the subset of patients with associated IBD and an intact colon at the time of LT. Aggressive colonoscopic surveillance for CRC would be prudent for patients with PSC-IBD even after LT. Liver Transpl 19:1361-1369, 2013. © 2013 AASLD.
De novo malignancy is one of the leading causes of long-term mortality in patients after LT. In a recent systematic review, the relative risk of CRC was 2.8 times higher for all patients who underwent LT versus an age- and sex-matched general population; in patients who underwent LT for non-PSC indications, this risk was 1.8 times higher. Individual studies have reported varied incidence of CRC after LT for PSC, and the incidence has been high for patients with PSC-IBD with an intact colon. Risk factors for CRC after LT for PSC are variable, and it is unclear whether transplant-related immunosuppression modifies the CRC risk after LT.

Hence, in this systematic review and meta-analysis, we sought to estimate the pooled incidence of CRC after LT in patients with PSC and in a subset of patients with PSC-IBD with an intact colon at the time of LT.

PATIENTS AND METHODS

This systematic review was conducted according to guidance provided by the Cochrane Handbook for Systematic Reviews of Interventions, and it is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Search Strategy and Selection Criteria

A systematic literature search of the PubMed (1966 through April 1, 2013), Embase (1988 through April 1, 2013), and Web of Science databases (1993 through April 1, 2013) was conducted for all relevant articles on the incidence of de novo CRC after LT in patients with PSC. Studies considered in this meta-analysis were cohort studies that met the following inclusion criteria: (1) they identified patients with PSC (with or without associated IBD) who underwent LT for any indication, (2) they reported incident cases of de novo CRC after LT, and (3) they reported total person-years (mean or median follow-up of the cohort) to estimate the incidence rate (IR) of de novo CRC. Medical Subject Headings terms used in the search included a combination of colorectal neoplasms; cholangitis, sclerosing; ulcerative colitis; inflammatory bowel diseases; and liver transplantation. The results were exported to a common EndNote (reference manager) file. After this, duplicates were removed, and 185 unique studies were identified. Then, in accordance with the protocol-defined study inclusion and exclusion criteria, 2 authors (S.S. and J.E.V.) independently reviewed the titles and abstracts of studies identified in the search to exclude studies that did not investigate the incidence of de novo CRC after LT for PSC. The full texts of the remaining articles were examined to determine whether they contained relevant information. The κ coefficient of agreement between the reviewers for initial article selection was 0.89. Disagreements were resolved by consensus and in conjunction with a senior reviewer (J.A.T.). Next, bibliographies of the selected articles as well as review articles on the topics were manually searched for additional articles. We also searched conference proceedings of major gastroenterology, hepatology, and transplantation conferences (Digestive Diseases Week, the Liver Meeting (organized by the American Association for the Study of Liver Diseases), the International Liver Congress (organized by the European Association for the Study of the Liver), and the American Transplant Congress (organized by the American Society of Transplantation and the American Society of Transplant Surgeons) from 2008 to 2012 for studies that had been published only in abstract form. We included only studies with a cohort size of at least 10 patients; case reports and case series were excluded. Because the estimation of incidence was not possible for case-control studies, these too were excluded. Inclusion was not otherwise restricted by language or publication type. When there were multiple publications examining the same population, data were included only from the most comprehensive report; if, however, 1 study from the cohort provided data on the CRC risk for all patients with PSC and another study provided data on the CRC risk for patients with PSC-IBD, both studies were included in the respective analyses. A flow diagram summarizing the study’s identification and selection process is shown in Fig. 1.

Quality Assessment

The quality of cohort studies was assessed with a modified score derived from a previous systematic review of CRC risk for all LT recipients. This quality score consisted of 10 yes/no questions:

1. Was it a multicenter study?
2. Were consecutive, unselected patients with PSC included?
3. Was the cohort size > 50 patients?
4. Was a separate analysis of PSC patients with IBD and PSC patients without IBD reported?
5. Was clear information on the mean or median follow-up of the cohort reported?
6. Were patients diagnosed with CRC within 1 year of LT reported separately?
7. Were the baseline characteristics of age and sex reported?
8. Was information on immunosuppressant use reported?
9. Was routine CRC surveillance performed for the entire cohort?
10. Was incident CRC diagnosed on the basis of screening or symptoms?

From this, a study was considered to be high-, medium-, or low-quality if the cumulative score was ≥7, 4 to 6, or ≤3, respectively. Two reviewers (S.S. and J.E.V.) rated the quality of studies independently, and in cases of disagreement, consensus was achieved by a joint re-evaluation of the article.
Data Abstraction

Data were independently abstracted onto a standardized form by 2 reviewers (S.S. and J.E.V.). The following data were collected from each study: the time period of the study and the year of publication, the country of the studied population, the number of patients who underwent LT for PSC (the total number, the number of patients with PSC-IBD, and the number of patients with an intact colon at the time of LT), the number of incident cases of CRC after LT (with or without a preceding diagnosis of colorectal dysplasia before LT), the duration of follow-up (the reported total follow-up in person-years or the follow-up estimated from the mean or median duration of follow-up after LT), the mean age and sex, the transplant-related immunosuppression, the duration of associated IBD, and the use of routine CRC surveillance. When the study reported the incidence of CRC for all patients who underwent LT (for any indication), we specifically abstracted data on the CRC incidence for a subset of patients with PSC; when such data were not available, the study was excluded. Conflicts in data abstraction were resolved by consensus with referral back to the original article.

Assessed Outcomes

The primary analysis was focused on assessing the incidence of de novo CRC after LT for patients with PSC and for a subset of patients with PSC-IBD and an intact colon at the time of LT. A priori hypotheses explaining potential heterogeneity in the magnitude of the effect among the different observational studies included the study location (North America versus Europe) and the study setting (a single center versus multiple centers). A sensitivity analysis based on the study quality was also performed.

Statistical Analysis

For each study, we estimated the IR of CRC from the number of patients diagnosed with de novo CRC after LT and the total duration of follow-up (either reported in the study in person-years or estimated from the mean or median follow-up for the entire cohort). For studies in which no cases of CRC were reported, a correction of 0.05 was added to all columns to allow the estimation of the incidence for study, as previously reported. Subsequently, we used the random effects model described by DerSimonian and Laird to calculate the pooled IR of de novo CRC per 1000 person-years and the 95% confidence intervals (CI). We assessed heterogeneity between study-specific estimates with 2 methods. First, Cochran’s Q statistic was measured to assess the presence of heterogeneity. Because tests for heterogeneity lacked power, a P value < 0.10 was considered suggestive of significant heterogeneity. Second, to estimate what proportion of the total variation across studies was due to heterogeneity rather than chance, the inconsistency index (I²) was calculated. Values of <30%, 30% to 59%, 60% to 75%, and >75% were considered suggestive of low, moderate, substantial, and considerable heterogeneity, respectively. Between-study sources

Figure 1. Flow diagram summarizing the study’s identification and selection process.
of heterogeneity were investigated with subgroup analyses through the stratification of the original estimates according to study characteristics (as described previously). In this analysis also, a \( P \) value for differences between subgroups < 0.10 was considered statistically significant (ie, a \( P_{\text{interaction}} \) value < 0.10 suggested that stratification based on a particular study characteristic partly explained the heterogeneity observed in the analysis). We assessed publication bias quantitatively with Egger’s regression test\(^17\) and qualitatively with a visual inspection of funnel plots of the logarithmic odds ratios versus their standard errors.\(^18\) All calculations and graphs were performed with Comprehensive Meta-Analysis 2 (Biostat, Englewood, NJ).

RESULTS

From a total of 185 unique studies, 18 independent cohort studies met the inclusion criteria and provided sufficient data to estimate the IR of de novo CRC after LT for PSC.\(^8,9,19-34\) These studies cumulatively reported 69 cases of CRC among 1987 patients with PSC. Sixteen cohort studies reported 66 cases of de novo CRC among 1017 patients with PSC-IBD with an intact colon at the time of LT, and their results were pooled to estimate the IR of CRC after LT for a subset of patients with PSC-IBD with an intact colon at the time of LT.\(^8,10,19-24,26,27,30,32,34-36\) Three studies were excluded because of overlapping populations.\(^37-39\) Two separate studies of overlapping populations reported the CRC risk for patients with PSC and patients with PSC-IBD, so both studies were included in the respective analyses.\(^10,33\)

Characteristics of the Included Studies

Table 1 and Supporting Table 1 report the baseline characteristics of the included studies as well as the number of cases, timing, and location of incident CRC after LT. The earliest study started to recruit patients in 1981, and the last study ended in 2009. Three studies were multicenter, although none of the studies were truly population-based.\(^8,20,34\) The mean age of the patients at the time of LT ranged from 41 to 52 years, and the majority were male. The mean/median duration of follow-up after LT in the included studies varied from 3.0 to 11.1 years, and the average time to the diagnosis of de novo CRC varied from 1 to 4 years. The largest published study came from the Nordic LT registry\(^5\): it included 439 patients who underwent LT for PSC and identified 8 cases of CRC among 244 patients with PSC-IBD and an intact colon at the time of LT. An early study by Goss et al.\(^23\) reported the highest incidence of de novo CRC (IR = 31.5 per 1000 person-years for all patients with PSC, IR = 43.5 per 1000 person-years in patients with PSC-IBD and an intact colon) with 12 cases of CRC (including 6 cases of carcinoma in situ) among 127 patients with PSC (92 with associated IBD and an intact colon) over a median follow-up of 3.0 years.\(^23\) In 4 small studies (20-78 patients with PSC), no cases of CRC were observed, with the largest series from the Cleveland Clinic identifying 11 cases of colorectal dysplasia among 78 patients with PSC over a median follow-up of 4.6 years.\(^19,24,25,28\)

Quality of the Included Studies

The overall quality of the included studies was moderate (Supporting Table 2). In most studies, the total duration of follow-up was estimated from the mean or median reported follow-up for the entire cohort. Studies variably reported analyses of patients with PSC and IBD separately (14 of 18 studies), and they usually did not report the CRC incidence for PSC patients without IBD. Most studies did not present data on patients diagnosed with CRC within the first year after LT (reported in 4 of 18 studies). Although screening and/or surveillance colonoscopy was performed for most patients before LT, studies inadequately reported whether routine colonoscopic surveillance for dysplasia was performed (and, if so, what the compliance was) after LT for PSC (reported in 9 of 18 studies).

IR of CRC in All Patients With PSC

According to a meta-analysis of 18 independent cohort studies (69 cases of CRC among 1987 patients with PSC), the pooled IR of de novo CRC after LT was 5.8 cases per 1000 person-years (95% CI = 3.8-7.8), with the rates from individual studies varying from 0 to 31.5 (Fig. 2).\(^8,9,19-34\) This risk remained stable when the analysis was restricted to high-quality studies (n = 7, IR = 6.0 per 1000 person-years, 95% CI = 2.2-9.9).\(^8,9,20,23,24,31,34\) Moderate heterogeneity was observed in the overall analysis [\( P = 0.03 \) (Cochran’s \( Q \), \( I^2 = 41\% \)]. The estimated IR was consistent across North American studies (n = 12, IR = 6.9, 95% CI = 3.7-10.0) and European studies (n = 6, IR = 4.6, 95% CI = 2.7-6.6, \( P_{\text{interaction}} = 0.23 \)); no significant heterogeneity was observed across the North American studies [\( P = 0.52 \) (Cochran’s \( Q \), \( I^2 = 0\% \)]. The results were similar in multicenter studies (n = 3, IR = 4.9, 95% CI = 1.5-8.3) and single-center studies (n = 15, IR = 6.2 per 1000, 95% CI = 3.7-8.6, \( P_{\text{interaction}} = 0.53 \)). After the exclusion of the outlier study by Goss et al.,\(^23\) the IR was 5.2 per 1000 person-years (95% CI = 3.5-6.8), and the previously observed moderate heterogeneity was resolved [\( P = 0.20 \) (Cochran’s \( Q \), \( I^2 = 21\% \)]. According to a sensitivity analysis after the exclusion of 1 study at a time, the IR remained stable (range = 5.2-6.3 per 1000 person-years).

IR of CRC in Patients With PSC-IBD With an Intact Colon

According to a pooled analysis of 16 independent cohort studies (66 cases of CRC among 1017 patients with PSC-IBD with an intact colon at the time of LT), the IR was 13.5 cases per 1000 person-years (95% CI...
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Location</th>
<th>Time Period</th>
<th>LT for PSC (n)</th>
<th>Total Intact Colon</th>
<th>Follow-Up (Years)</th>
<th>De Novo CRC (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabia et al. 22 (1998)</td>
<td>Dallas, TX</td>
<td>1984–1995</td>
<td>108</td>
<td>73</td>
<td>5.5 (0.5–11)*</td>
<td>6†</td>
</tr>
<tr>
<td>Goss et al. 23 (1997)</td>
<td>Los Angeles, CA</td>
<td>1984–1996</td>
<td>127</td>
<td>92</td>
<td>3.0 (not reported)*</td>
<td>12</td>
</tr>
<tr>
<td>Ho et al. 35 (2005)</td>
<td>Scotland, United Kingdom</td>
<td>1992–2003</td>
<td>42</td>
<td>26</td>
<td>4.4 (1.8–7.2)*</td>
<td>1</td>
</tr>
<tr>
<td>Hanouneh et al. 24 (2012)</td>
<td>Cleveland, OH</td>
<td>1998–2005</td>
<td>78</td>
<td>70</td>
<td>4.6 (4.0)*</td>
<td>0¶</td>
</tr>
<tr>
<td>Jonas et al. 25 (1997)</td>
<td>Berlin, Germany</td>
<td>1988–1994</td>
<td>28</td>
<td>—</td>
<td>4.2 (0.2–8.1)*</td>
<td>0</td>
</tr>
<tr>
<td>Joshi et al. 26 (2013)</td>
<td>King's College, United Kingdom</td>
<td>1990–2009</td>
<td>110</td>
<td>74</td>
<td>6.6 ± 4.8‡</td>
<td>5</td>
</tr>
<tr>
<td>Kelly et al. 27 (1999)</td>
<td>New York</td>
<td>1988–1996</td>
<td>72</td>
<td>56</td>
<td>4.4 ± 1.8‡</td>
<td>1</td>
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<tr>
<td>Koorstra et al. 28 (2007)</td>
<td>Groningen, the Netherlands</td>
<td>1979–2001</td>
<td>20</td>
<td>—</td>
<td>11.1 (5–23.2)*</td>
<td>0</td>
</tr>
<tr>
<td>Moncrief et al. 32 (2010)</td>
<td>Alberta, Canada</td>
<td>1989–2006</td>
<td>59</td>
<td>42</td>
<td>6 (2.8–8.9)*</td>
<td>1</td>
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<tr>
<td>Narumi et al. 33 (1995)</td>
<td>San Francisco, CA</td>
<td>1988–1993</td>
<td>33</td>
<td>22</td>
<td>3 (0.5–6.1)*</td>
<td>1</td>
</tr>
<tr>
<td>Sint Nicolaas et al. 31 (2010)</td>
<td>Erasmus, the Netherlands</td>
<td>1986–2007</td>
<td>64</td>
<td>38</td>
<td>5.1 (0.2–20)*</td>
<td>2</td>
</tr>
<tr>
<td>Oo et al. 33 (2005)</td>
<td>Birmingham, United Kingdom</td>
<td>1982–2004</td>
<td>197</td>
<td>—</td>
<td>5.5 (2.7–4.2)*</td>
<td>10</td>
</tr>
<tr>
<td>Vera et al. 10 (2003)</td>
<td>Birmingham, United Kingdom</td>
<td>1986–2000</td>
<td>152</td>
<td>100</td>
<td>Not reported#</td>
<td>8</td>
</tr>
<tr>
<td>[overlapping with Oo et al. 33 (2005)]</td>
<td></td>
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<tr>
<td>Watt et al. 34 (2009)</td>
<td>Rochester, MN (+2 centers)</td>
<td>1990–1994</td>
<td>127</td>
<td>87</td>
<td>10 (0–12)*</td>
<td>8</td>
</tr>
</tbody>
</table>

*The data are presented as medians and ranges.
†The data are presented as means and standard deviations.
‡This number is based on the number of patients who underwent colectomy for CRC.
§Five patients with CRC had associated ulcerative colitis, and 1 patient did not have associated ulcerative colitis.
¶Eleven patients with PSC-IBD were diagnosed with dysplasia (flat in 7 and polypoid in 4) during surveillance colonoscopy, but none were diagnosed with CRC.
#The IR was estimated from the cumulative incidence.
**This represents the time to CRC from LT; for the entire cohort of all transplant patients at the center, the mean follow-up was 9.3 years.
Although considerable heterogeneity was observed in the analysis \((P = 0.001\) (Cochran's \(Q\), \(I^2 = 67\%\); Fig. 3) \(^8\)-\(^{10},^{19-26},^{27,30,32,34-36}\) When the analysis was restricted to 7 high-quality studies, the IR remained stable \((IR = 14.1\) per 1000 person-years, 95% CI = 6.4-21.8) \(^8\)-\(^{10},^{20,23,24,34}\) The IR of de novo CRC was also stable across the geographical locations of the studies (North American studies: \(n = 11\), IR = 13.8, 95% CI = 7.6-20.0; European studies: \(n = 5\), IR = 13.6, 95% CI = 4.1-23.1; \(F_{\text{interaction}} = 0.97\)) and across study designs (multicenter studies: \(n = 3\), IR = 10.0, 95% CI = 2.1-18.0; single-center studies: \(n = 13\), IR = 14.5, 95% CI = 8.4-20.6; \(F_{\text{interaction}} = 0.38\)). After the exclusion of the outlier study by Goss et al.\(^{23}\) the IR was 12.4 per 1000 person-years (95% CI = 7.9-16.9), and considerable heterogeneity was still observed in the analysis \((P < 0.01\) (Cochran's \(Q\), \(I^2 = 63\%\))]. According to a sensitivity analysis after the exclusion of 1 study at a time, the IR remained stable \(\text{range} = 11.4-14.6\), per 1000 person-years).

**Publication Bias**

For the overall analysis of PSC, there was evidence of publication bias from a visual inspection of the funnel plots and from a quantitative analysis using Egger's test \((P\text{ for the overall analysis} = 0.01)\). Because of the presence of considerable heterogeneity, a formal assessment of funnel plot asymmetry was not performed for the analysis of studies of patients with PSC-IBD and an intact colon at the time of LT.\(^{10}\)

**DISCUSSION**

In this systematic review and meta-analysis of 18 independent cohort studies, we estimated the pooled IR of CRC after LT for PSC to be 5.8 per 1000 person-years, with rates from individual studies varying from 0 to 31.5. The pooled incidence of CRC for a subset of patients with PSC-IBD with an intact colon at the time of LT was 13.5 per 1000 person-years. These results are similar to the CRC risk observed in the LT database of the National Institute of Diabetes and Digestive and Kidney Diseases. In a subgroup of 127 patients who underwent LT for PSC, Watt et al.\(^{34}\) estimated that the cumulative incidence of CRC 10 years after LT was 8.2% (versus 2.6% after LT for non-PSC conditions). This increased risk was seen only in patients with PSC-IBD (\(n = 60\)), who had 1-, 5-, and 10-year cumulative CRC incidences of 3.3%, 6.7%, and 11.8%, respectively. This estimated IR of CRC is significantly higher than the pooled IR estimated in a recent systematic review of 15 studies of 10,561 patients who underwent LT for any indication (with 61 reported cases of CRC).\(^{7}\) In their meta-analysis, Sint Nicolaas et al.\(^{7}\) estimated that the pooled IR of de

**Figure 2.** Incidence of de novo CRC after LT for PSC.
novo CRC after orthotopic liver transplantation (OLT) was 1.19 per 1000 person-years (95% CI = 0.88-1.61), and in a subset of patients who underwent LT for non-PSC indications, the IR was 1.29 per 1000 person-years (95% CI = 0.81-2.07). Hence, the risk of CRC appears to be almost 4-fold higher for patients with PSC undergoing LT versus the average patient undergoing LT and more than 10-fold higher for patients with PSC-IBD with an intact colon who undergo LT. Because the relative risk of de novo CRC after LT for non-PSC indications was estimated to be 1.8 times higher than the risk for the general population, it can be extrapolated that the risk of de novo CRC for a subset of patients with PSC-IBD with an intact colon may be up to 20-fold higher than the risk for the general population.

Similar to CRC in PSC-IBD patients who have not undergone LT, CRC after LT in these patients is usually right-sided in its location, and there is no difference in the distribution of CRC before and after LT. Several cases of CRC were diagnosed within the first 2 years after LT, even when colonoscopy had been recently performed as a part of the pre-OLT evaluation. This may possibly have been due to a sampling error and missed dysplasia, or perhaps it was related to accelerated malignant transformation due to immunosuppression or other conditions related to LT. Three studies compared the risk of CRC in patients with PSC before and after LT. In the Mayo Clinic cohort, the rate of CRC was 4.4-fold higher (95% CI = 0.9-12.8) after LT in comparison with a historical cohort of patients with PSC-IBD who did not undergo LT after an adjustment for the duration of IBD. Likewise, according to an analysis of 439 patients with PSC (353 with concomitant IBD) who underwent LT between 1984 and 2006 in the Nordic LT registry, the risk of CRC was higher after LT than it was before LT with a hazard ratio of 1.9 (95% CI = 1.3-2.9), and this risk was not entirely explained by the duration of IBD. In contrast, in a case-control analysis of patients with PSC-IBD who underwent LT (n = 43) and patients who did not undergo LT (n = 30), Hanouneh et al. reported comparable risks of CRC (25.6% and 30%, respectively). In a time-dependent analysis based on colectomy rates for CRC among 163 patients with PSC-IBD with an intact colon followed for a median of 5.9 years after OLT, only a long duration of IBD was a risk factor for CRC, and transplantation did not significantly influence the risk of CRC.

Although it is probable that LT may be an independent risk factor for de novo CRC, this risk does not seem to be related to immunosuppressant therapy in several studies, although Jørgensen et al. observed only in a univariate analysis that cyclosporine use may be associated with a decreased risk of CRC. Likewise, higher rates of rejection, the use of high-dose steroids or OKT3 for the management of rejection, and the recurrence of PSC are not associated with an increased risk of CRC after LT. In the Cleveland Clinic cohort, cytomegalovirus was possibly associated with an increased risk of CRC after LT (hazard ratio = 4.5, 95% CI = 1.2-16.1), although in the Nordic LT registry, treatment for cytomegalovirus (a surrogate for the presence of cytomegalovirus) was
not associated with CRC risk. John Cunningham virus reactivation with expression of tumor antigens secondary to immunosuppressive therapy has been implicated in colorectal carcinogenesis after LT, but this has not been studied in the subset of patients with PSC.\textsuperscript{41}

It is well known that patients with long-duration IBD and pancolonic involvement have a higher risk of CRC, and this remains true for patients even after LT.\textsuperscript{5} Vera et al.\textsuperscript{10} observed that colitis for $>10$ years and pancolitis were associated with post-LT CRC. Bleday et al.\textsuperscript{20} also reported 3 cases of CRC among 27 patients with PSC-LT with a mean IBD duration of 19 years. In most studies, the age at the time of the diagnosis of IBD or LT has not been associated with the CRC risk after LT,\textsuperscript{20,21,24} although Vera et al. observed that an age $<45$ years at the time of LT was associated with a higher risk of CRC. IBD activity does not seem to influence the risk of post-LT CRC in patients with PSC-LT, although studies are limited in the endoscopic assessment of disease activity.\textsuperscript{8,10}

In one study, the use of 5-aminosalicylates and urso-deoxycholic acid was associated with a higher risk of CRC, whereas in another study, this association was not seen.\textsuperscript{8,20}

There are several limitations to our analysis that are related to the quality of the included studies. The included studies variably accounted for early mortality after LT when they estimated the CRC risk. This is particularly important for studies performed in the 1990s when early mortality after LT was considerable; early mortality after LT could potentially underestimate the true incidence of CRC because of the competing risk of mortality. Moreover, the included studies did not account for the competing risk of colectomy due to IBD disease activity after LT, so we may have underestimated the true CRC incidence after LT. The included studies did not provide sufficient information on whether surveillance colonoscopy was performed routinely. It was not clear whether colonoscopic surveillance was recommended (and what proportion actually underwent surveillance) in the individual studies. Because we included CRC as our primary endpoint, our analysis did not account for the incidence of colorectal dysplasia and resultant colectomy. Furthermore, there is considerable variation across centers in how colorectal dysplasia is managed, and colectomy rates for various degrees of dysplasia likely vary widely. There was insufficient information on the distribution of de novo CRC after LT. Moreover, the outcomes of patients who developed CRC were not adequately reported in the included studies. There was also limited information on the post-LT CRC risk in patients with PSC alone without IBD. In their multicenter analysis of the LT database of the National Institute of Diabetes and Digestive and Kidney Diseases, Watt et al.\textsuperscript{34} identified 39 patients with PSC without IBD; the 10-year cumulative CRC risk after LT was 2.8%, which was comparable to the risk for the general population.

In conclusion, it appears that patients with PSC-LT continue to have a high risk of de novo CRC after LT; this risk is approximately 10 times the risk for all other patients undergoing LT. Specific transplant-related factors that can increase the risk of CRC have not yet been identified. This high incidence of CRC suggests that aggressive colonoscopic surveillance would be prudent for patients with PSC-LT even after LT.

**REFERENCES**


