Inflammatory Bowel Disease and Risk of Cholangiocarcinoma: Evidence from a Meta-analysis of Population-based Studies

Jia-Ping Huai1&, Jin Ding2&, Xiao-Hua Ye2*, Yan-Ping Chen2

Abstract

Objective: Patients with inflammatory bowel disease (IBD) have an increased risk of extra-intestinal cancer, whereas its impact on cholangiocarcinoma (CC) remains unknown. The aim of this study was to obtain a reliable estimate of the risk of CC in IBD patients through a meta-analysis of clinical observational studies.

Methods: Relevant studies were retrieved by searching PUBMED, EMBASE and Web of Science Databases up to Dec 2013. Four population-based case-control and two cohort studies with IBD were identified. Summary relative risk (RR) and its corresponding 95% confidence interval (CI) were calculated using a random-effects model. Potential sources of heterogeneity were detected using subgroup analyses.

Results: The pooled risk estimate indicated IBD patients were at increased risk of CC (RR = 2.63, 95% CI = 1.47-4.72). Moreover, the increased risk of CC was also associated with Crohn’s disease (RR = 2.69, 95% CI = 1.59-4.55) and ulcerative colitis (RR = 3.40, 95% CI = 2.50-4.62). In addition, site-specific analyses revealed that IBD patients had an increased risk of intrahepatic CC (ICC) (RR = 2.61, 95% CI = 1.72-3.95) and extrahepatic CC (ECC) (RR = 1.47, 95% CI = 1.10-1.97).

Conclusions: This study suggests the risk of CC is significantly increased among IBD patients, especially in ICC cases. Further studies are warranted to enable definite conclusions to be drawn.

Keywords: Inflammatory bowel disease - cholangiocarcinoma - meta-analysis - relative risk

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Introduction

Cholangiocarcinoma (CC), a malignant tumor arising from the epithelial cells (cholangiocytes) lining the biliary tree, is characterized by a diagnostically and therapeutically challenging cancer (Patel, 2011). It is the second most common primary hepatic malignancy after hepatocellular cancer, contributing to approximately 10–25% of all hepatobiliary malignancies (Blechacz et al., 2008; Sripa et al., 2008; Gatto et al., 2010). The incidence of CC varies enormously by geographic region and demographic diversity, with the highest incidence in Southeast Asia and the lowest in Australia (Shaib et al., 2004; Sripa et al., 2008; Barusrux et al., 2012). Differing exposure to risk factors is considered to account for the variation of geographic incidences (Shaib et al., 2004; Sripa et al., 2008; Songserm et al., 2012). Anatomically, CC can be categorized as intrahepatic CC (ICC) and extrahepatic CC (ECC) on the basis of its location (Patel, 2011). Klatskin tumor, i.e Hilar CC, is typically classified as extrahepatic (Tyson et al., 2011). The clinical distinction between ICC and ECC has become significantly crucial due to their possibly different epidemiological characteristics (Patel., 2006; Gatto et al., 2010).

Although little is known about the etiology of CC, several predisposing factors have been well validated. Epidemiological studies have found that primary sclerosing cholangitis (PSC), liver flukes infestation and cholecystitis are well-established (Tyson et al., 2011; Songserm et al., 2012; Hussain et al., 2013; Manwong et al., 2013). Also, hepatitis virus infection may also play a role in the development of CC (Srivatanakul et al., 2010). However, the occurrence of most CC cases is not associated with any recognized risk factor, because of its rarity (Lazaridis et al., 2005). Knowledge of the risk factors for CC would allow early identification of patients with a high risk of developing CC and would be helpful for positive prevention and developing intervention strategies for vulnerability factors.

Inflammatory bowel diseases (IBD), i.e., Crohn’s Disease (CD) or ulcerative colitis (UC) are autoimmune disorders of unknown etiology with poor disease progress, involvement of other organs, and an increased risk of intestinal and extra-intestinal cancers at least in subsets of patients (Jess et al., 2005; Pedersen et al., 2010; Jess et al., 2012). The association between IBD and the risk of CC was also investigated in several studies (Shaib et al., 2005; Welzel et al., 2006; Welzel et al., 2007; El-Serag et al., 2009; Erichsen et al., 2009; Chang et al., 2013). However, the reported correlations are inconsistent. Moreover, in
Table 1. Characteristics of 6 Studies of Inflammatory Bowel Disease and the Risk of Cholangiocarcinoma

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Region</th>
<th>CC</th>
<th>ICC</th>
<th>ECC</th>
<th>Controls</th>
<th>Design</th>
<th>Source</th>
<th>Risk estimates for CC (95%CIs)</th>
<th>Risk estimates for ICC (95%CIs)</th>
<th>Risk estimates for ECC (95%CIs)</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaib et al. 2005</td>
<td>US</td>
<td>625</td>
<td>90,834</td>
<td>Case-control</td>
<td>Population Medical Cancer Registry</td>
<td>IBD: 2.3 (1.4-3.8)</td>
<td>Age, gender, race, geographic location, and smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Denmark</td>
<td>764</td>
<td>3,065</td>
<td>Case-control</td>
<td>Population</td>
<td>ICD-code Cancer Registry</td>
<td>IBD: 4.67 (1.57-13.89)</td>
<td>Age at ICC diagnosis, sex and year of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Welzel et al. 2007</td>
<td>US</td>
<td>1,084</td>
<td>535</td>
<td>549</td>
<td>102,782</td>
<td>Case-control</td>
<td>Population Medical Cancer Registry</td>
<td>IBD: 3.06 (2.09-4.48)</td>
<td>IBD: 3.06 (2.09-4.48)</td>
<td>IBD: 3.06 (2.09-4.48)</td>
<td>Age, sex, race, geographic location, state buy-in status</td>
</tr>
<tr>
<td></td>
<td>Denmark</td>
<td>96</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Cancer Registry</td>
<td>IBD: 2.61 (1.44-4.73)</td>
<td>IBD: 2.61 (1.44-4.73)</td>
<td>IBD: 2.61 (1.44-4.73)</td>
<td></td>
</tr>
<tr>
<td>Erichsen et al. 2009</td>
<td>Denmark</td>
<td>56</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Cohort</td>
<td>Cancer Registry</td>
<td>IBD: 2.4 (1.2-4.6)</td>
<td>IBD: 2.4 (1.2-4.6)</td>
<td>IBD: 2.4 (1.2-4.6)</td>
<td></td>
</tr>
<tr>
<td>El-Serag et al. 2009</td>
<td>US</td>
<td>112</td>
<td>37</td>
<td>75</td>
<td>-</td>
<td>Cohort</td>
<td>Cancer Registry</td>
<td>IBD: 1.05 (0.60-1.85)</td>
<td>IBD: 1.05 (0.60-1.85)</td>
<td>IBD: 1.05 (0.60-1.85)</td>
<td></td>
</tr>
<tr>
<td>Chang et al. 2013</td>
<td>Taiwan</td>
<td>5,157</td>
<td>2,978</td>
<td>2,179</td>
<td>20,628</td>
<td>Case-control</td>
<td>Population Registry</td>
<td>IBD: 1.63 (1.31-1.94)</td>
<td>IBD: 1.63 (1.31-1.94)</td>
<td>IBD: 1.63 (1.31-1.94)</td>
<td></td>
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</tbody>
</table>

CC, cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; IBD, inflammatory bowel disease; CD, Crohn’s disease; UC, ulcerative colitis; CI, confidence interval; RR, relative risk; OR, odds ratio; HR, hazard ratio. The Summary relative risks and 95%CIs for CC were calculated using the method by Hamling et al (Hamling et al., 2008). Heterogeneity for CC subsites (ICC and ECC), we combined the corresponding risk estimates with a random-effects model, which considers both within- and between-study variations (DerSimonian et al., 1986). When the same set of controls was used for CC subsites (ICC and ECC), we combined the corresponding risk estimates using the method by Hamling et al (Hamling et al., 2008). Heterogeneity was evaluated using the Q and I² statistic (Higgins et al., 2002). For the Q test, P > 0.10 was considered of no statistically significant heterogeneity. To
Inflammatory Bowel Disease and Risk of Cholangiocarcinoma: Evidence from a Meta-analysis

Table 2. Assessment of Study Quality

<table>
<thead>
<tr>
<th>Study</th>
<th>Quality variables of NOS</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ia</td>
<td>Ib</td>
</tr>
<tr>
<td>Shaib et al. 2005</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Welzel et al. 2006</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Welzel et al. 2007</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Erichsen et al. 2009</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>El-Serag et al. 2009</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chang et al. 2013</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NOS, Newcastle-Ottawa quality assessment Scale. For case-control studies, (Ia) represents cases with independent validation; (Ib) cases are consecutive or representative; (Ic) controls are community; (Id) controls have no history of ICC/ECC/CC; (IIa) study controls are comparable for age and sex; (IIb) study controls for any additional factor(s); (IIIa) cases and controls have the same method of ascertainment; (IIib) assessment of exposure is from secure record; and (IIIC) same non-response rate for both groups. For cohort studies, (Ia) indicates the exposed cohort study representative of the population; (Ib) the non exposed cohort drawn from the same population; (Ic) the exposure ascertainment are from secure record or structured interview; (Id) ECC was not present at start of study; (IIa) cohorts are comparable for age and sex; (IIb) cohorts are comparable for any additional factor(s); (IIIa) assessment is from secure record; (IIib) follow-up long enough for ECC to occur; and (IIIC) complete follow-up.

Results

Study characteristics

A total of 4 population-based case-control (Shaib et al., 2005; Welzel et al., 2006; Welzel et al., 2007; Chang et al., 2013) and 2 cohort studies (El-Serag et al., 2009; Erichsen et al., 2009) were included in the meta-analysis (Figure 1). These 6 studies included were published between 2005 and 2013 and included a total of 7838 incident cases (4939 for ICC; 2808 for ECC). One study did not present results specific for ICC and ECC, but included 96 cases for CC (Erichsen et al., 2009). Of those, most studies were conducted in Non-Asian areas (3 in US and 2 in Denmark), whereas only one was performed in Asia (Taiwan) (Table 1). Adjustments were made for potential confounders of one or more factors in all studies. Two studies reported the risk of CC associated with CD and UC separately (Welzel et al., 2007; Erichsen et al., 2009). All studies included were of high quality (NOS score ≥ 7; Table 2).

IBD and the risk of ICC

Four case control and one cohort studies reported the results on IBD and the risk of ICC (Shaib et al., 2005; Welzel et al., 2006; Welzel et al., 2007; El-Serag et al., 2009; Chang et al., 2013). The meta-analysis of these studies showed the pooled relative risk (RR) for ICC was 2.61 (95%CI: 1.72-3.95) in a random-effects model for IBD patients versus patients without IBD (Figure 2). However, there was significant heterogeneity detected among studies (Q = 14.52, \( P = 0.006 \) for heterogeneity, \( I^2 = 72.5\% \)).

IBD and the risk of ECC

We identified two case-control and one cohort studies...
that investigated the association between IBD and the risk of ECC (Welzel et al., 2007; El-Serag et al., 2009; Chang et al., 2013). Results of these three studies were inconsistent. Of these, no positive relationships were found in one study (El-Serag et al., 2009), whereas the other two showed an increased risk of ECC in patients with IBD (Welzel et al., 2007; Chang et al., 2013). The summary RR for ECC was 1.47 (95%CI: 1.10–1.97) in a random-effects model (Figure 2). There was no heterogeneity across studies (Q = 0.0%; I^2 = 60.3%). For the risk of CC, significant relationship with the incidence of CC remained significant in subgroup analyses and ICC. ICC remained significant in subgroup analyses and the heterogeneity became unremarkable when studies conducted in non-Asian areas (n = 2; summary RR = 1.46; 95%CI: 0.74–2.87; Q = 2.52, P = 0.113 for heterogeneity, I^2 = 89.1%).

### IBD and the risk of CC

One study did not report site-specific CC (Erichsen et al., 2009), and data of two studies that reported results on ICC and ECC were available to calculate risk estimates for CC (Welzel et al., 2007; Chang et al., 2013). Therefore, results on CC of the three studies were pooled and the summary RR with corresponding 95% CI for CC was 2.63 (1.47-4.72) (Figure 2). There was remarkable heterogeneity detected among these studies (Q = 18.41, P < 0.001 for heterogeneity, I^2 = 89.1%).

We further investigated associations between the risk of CC and CD/UC in two studies (Welzel et al., 2007; Erichsen et al., 2009). In CD patients, results of two individual studies were conflicting. One study did not find a significantly increased risk of CC in CD patients (Erichsen et al., 2009), while the other showed a statistically significant relationship with the incidence of CC (Welzel et al., 2007). Data on the association of UC and risk of CC were more consistent. All two studies showed an increased risk of CC in UC patients. The summary RRs with their 95% CIs of meta-analyses for CD and UC were 2.69 (1.59–4.55) and 3.40 (2.50–4.62), respectively (Figure 3). No heterogeneity was found among studies.
Discussion

To the best of our knowledge, this is the first meta-analysis that allowed us to provide more accurate estimates of the relationship between IBD and risk of CC or its subsets. Results from our analyses confirmed that IBD patients were at risk of CC (including ICC and ECC), especially a 2.61-fold increased risk of ICC. We further found that both CD and UC were associated with an increased risk of CC, respectively.

The primary strength of the present study was that the studies we included (case-control and cohort), were all population-based with large sample size, hence minimizing the risk of selection bias and thereby improving the generalizability of results. The reason we excluded two studies that focused on PSC patients concomitant with IBD was that the presence and magnitude of association between IBD and CC might be possibly affected by the existence of PSC and by the duration of observation in individual study. Also, PSC is frequently occurred in IBD patients, affecting up to 3.6 % of CD patients and 5% of UC patients (Loftus et al., 2005; Saich et al., 2008). Therefore, it is difficult to predict the onset point for each of PSC and IBD despite considering PSC as intermediate step in CC development (Erichsen et al., 2009). This perplexes the associations among PSC, IBD and CC.

Our results confirm that the risk of both ICC and ECC is increasing in IBD patients. However, our data suggest that IBD patients have lower risk of ECC than that of ICC, but the estimates were imprecise (RR: 2.61 versus 1.47 for ICC versus ECC). The differential effect on ICC and ECC implies different pathogenesis involved due to differing clinical presentation and natural history (Tyson et al., 2011; Palmer et al., 2012). Moreover, results of subgroup analyses raise the possibility of geographic variations in the risk of CC in IBD patients but are limited by the small number of studies and participants, thus additional studies are needed.

Second, confounding effects may also have influenced the results of this meta-analysis. As mentioned above, PSC is an established risk factor for CC, but PSC was not controlled for in the analysis of IBD in most studies except one from Taiwan (Chang et al., 2013). In this study, they found that PSC and cholelithiasis did not account for all of the CC predisposing effect of IBD, thereby suggesting the roles of additional factors. Thirdly, there was significant heterogeneity of some results. To address this issue, we performed subgroup analysis. The studies are heterogeneous partly due to study region and design. Finally, the possibility of publication bias is of concern. We only performed Egger’s test due to the small number of studies and no publication bias was detected.

In conclusion, the results from this meta-analysis suggest that IBD is associated with increased risk of CC, especially in ICC. However, the possibility that the association may be influenced by bias or confounding variables such as PSC cannot be fully excluded. Further well-designed, prospective studies, both epidemiological and mechanistic, are warranted to further clarify this association in the future.

References


Liver Dis, 42, 253-60.