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

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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

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 infection 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

| Author/Year | Region | CC          | ICC       | ECC   | Controls | Design              | Source         | ... estimates                | Risk estimates                | Risk estimates                                        | Adjustments |
|-------------|--------|-------------|-----------|-------|----------|----------------------|----------------|-----------------------------|-----------------------------|--------------------------------------------------------|-------------|
| Shaib et al. 2005 | US     | _ 625 _ 90,834 | Case-control | Population Medical records | Cancer Registry | IBD: 2.3 (1.4-3.8) | Age, gender, race, geographic location, and medicare/medicaid dual enrollment |                        |                                            | Age, sex, age at diagnosis, sex and year of birth     |                         |
| Welzel et al. 2006 | Denmark | _ 764 _ | Case-control | Population Medical records | Cancer Registry | IBD: 4.67 (1.57-13.89) | Age at ICC diagnosis, sex and year of birth |                        |                                            | Age, sex, location, state buy-in status               |                         |
| Erichsen et al. 2009 | Denmark | _ 96 _ | Cohort | Cancer Registry | Cancer Registry | IBD: 4.0 (2.5-6.4) | Age, sex |                        |                                            | Age, sex, and the time of diagnosis                   |                         |
| El-Serag et al. 2009 | US     | _ 112 _ | Cohort | Cancer Registry | Cancer Registry | IBD: 2.54 (1.3-4.9) | Age, sex, baseline visit date, type of visit, a preceding visit |                        |                                            | Age, sex, IBD type                                      |                         |
| Taiwan 5,157 | 2,978 | 2,179 | Cohort | Cancer Registry | Cancer Registry | IBD: 4.0 (2.5-6.4) | Age, sex, and the time of diagnosis |                        |                                            | Age, sex, IBD type                                      |                         |

CC, cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; IBD, inflammatory bowel disease/IBD, Crohn’s disease/CD, ulcerative colitis/UC. The references of all relevant articles were reviewed manually to identify additional studies.

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**Materials and Methods**

**Literature collection**

A computerized search of PUBMED, EMBASE, and Web of Science Databases up to December 2013 was performed to identify potentially relevant articles using the following text words and/or Medical Subject Headings: cholangiocarcinoma, intrahepatic, extrahepatic, bile duct cancer, combined with inflammatory bowel disease/IBD, Crohn’s disease/CD, ulcerative colitis/UC. The references of all relevant articles were reviewed manually to identify additional studies.

**Criteria for inclusion and exclusion**

Studies were eligible for inclusion if they fulfilled the following criteria: (1) case-control or cohort design and published in manuscript form; (2) IBD included as an exposure of interest; (3) CC, ICC or ECC included as an outcome of interest; and (4) risk estimates with 95% confidence intervals (CI) (or sufficient data to calculate them) reported. If data on the same population were reported in multiple papers, the most informative report was selected. Studies were excluded if: (1) cancer types were not specified; (2) those with reported data for another type of cancer; (3) those with incomplete or repetitive data.

**Data extraction**

The following data from all included studies were extracted: (1) first author’s last name, date of publication, geographic location of the study population, (2) study design (case-control or cohort), assessment for IBD and CC, sample size (cases and controls or cohort size), adjustment, and risk estimates with corresponding 95% CIs. For each study, the risk estimates that indicated the greatest degree of control for potential confounders were extracted, and discrepancies were resolved by discussion.

**Evaluation of study quality**

The quality of the included studies was assessed using the Newcastle-Ottawa (NOS) scale (Wells et al., 2000). The scale comprising nine items includes three dimensions: (1) patient selection; (2) comparability between two study arms; and (3) outcome assessment. The total NOS score ranges from zero to nine, with higher scores indicating higher quality. Studies that scored seven or more points were considered to be of high quality. The NOS score was assessed independently by two reviewers (Huai JP and Ye XH). Discrepancies in the score were resolved by consensus.

**Statistical analysis**

Different measures of risk estimates were included in this meta-analysis: odds ratio, incidence rate ratio, standardized incidence ratio, and hazard ratio. In practice, these measures of effect yielded similar risk estimates because of the low absolute incidence of cholangiocarcinoma.

Summary risk estimates with their corresponding 95% CIs were calculated 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
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Table 2. Assessment of Study Quality

| Study             | Quality variables of NOS | Score |
|-------------------|--------------------------|-------|
|                   | Selection | Comparability | Exposure/outcome |
|                   | Ia  | Ib  | Ic  | Id  | IIa | IIb | IIIa | IIIb | IIIc |
| Shaib et al. 2005 | No     | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No  | 7   |
| Welzel et al. 2006| No     | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No  | 7   |
| Welzel et al. 2007| No     | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No  | 7   |
| Erichsen et al. 2009| Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8   |
| El-Serag et al. 2009| Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8   |
| Chang et al. 2013 | No     | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No  | 7   |

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; (IIlb) 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; (IIlb) follow-up long enough for ECC to occur; and (IIIc) complete follow-up.

Figure 1. Flow Chart of the Study Selection

identify potential heterogeneity, we conducted subgroup analyses according to prespecified criteria. Publication bias was assessed using Begg’s funnel plot and Egger’s test (Begg et al., 1994; Egger et al., 1997). All statistical analyses were carried out using STATA software (Version 12.0; College Station, Texas, United States).

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 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, I² = 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 = 18.41, P = 0.277 for heterogeneity, I² = 22.0%).

**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, I² = 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 generalization 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 from regions in Asia are warranted. Thirdly, both CD and UC patients were found to be associated with the increased risk of CC, whereas CD patients seemed to have a lower risk of CC than UC patients. Reason for this may be that CD patients were younger at diagnosis than UC patients, hence receiving earlier treatment (Jacobson et al., 2006; Erichsen et al., 2009). Clinical use of acetylsalicylic acid and Five-aminosalicylic acid (5-ASA) in IBD patients could prevent the occurrence of colon cancer, as well as CC (Luciani et al., 2007; Erichsen et al., 2009). On the other hand, PSC is found more rarely in CD (O’Toole et al., 2012). These may partly explain the lower risk of CC in CD patients.

Although the incidence of CC remained low, even decreased in ICC, our results carry substantial clinical and public health implications due to the increasing prevalence of IBDs in recent years and younger age when first diagnosed (Shivananda et al., 1996; Vind et al., 2006). The extra-intestinal cancer risk of IBD patients has been studied elsewhere (Pedersen et al., 2010). However, the risk of CC was not specified and the mechanism remained obscure. In analogy to that of colonic cancer, the mechanism was hypothesized that the continuous inflammation might lead to the development of upper gastrointestinal cancer (Jess et al., 2005). Therefore, it is necessary to carry out studies specifically assessing the association between localization of IBD and upper gastrointestinal cancer occurrence with large sample size.

As with all meta-analyses of observational studies, our results have several potential limitations. First, only a few studies reporting on CC risk in IBD, CD or UC were identified, limiting the interpretation of the overall risk estimates. In addition, data stratified by sex, age, IBD subtype and duration of IBD were not accessible in most of included studies, precluding further analysis. 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.

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