

RESEARCH ARTICLE

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

Jia-Ping Huai^{1&}, Jin Ding^{2&}, Xiao-Hua Ye^{2*}, 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

Asian Pac J Cancer Prev, **15** (8), 3477-3482

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; Sripta 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; Sripta 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; Sripta 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

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Table 1. Characteristics of 6 Studies of Inflammatory Bowel Disease and the Risk of Cholangiocarcinoma

Author/Year	Region	CC	ICC	ECC	Controls	Design	Source	IBD assessment	CC ascertainment	Risk estimates for CC (95% CIs)	Risk estimates for ICC (95% CIs)	Risk estimates for ECC (95% CIs)	Adjustments
Shaib et al. 2005	US	-	625	-	90,834	Case-control	Population records	Medical	Cancer Registry	-	IBD: 2.3 (1.4-3.8)	-	Age, gender, race, geographic location, and medicare/medicaid dual enrollment
Welzel et al. 2006	Denmark	-	764	-	3,065	Case-control	Population	ICD-code	Cancer Registry	IBD: 4.67 (1.57-13.89)	IBD: 2.1 (1.1-4.0)	-	Age at ICC diagnosis, sex and year of birth
Welzel et al. 2007 ¹	US	1,084	535	549	102,782	Case-control	Population records	Medical	Cancer Registry	CD: 2.61 (1.44-4.73) UC: 3.07 (1.92-4.91)	CD: 2.4 (1.0-5.9) UC: 4.5 (2.6-7.9)	CD: 2.8 (1.3-6.4) UC: 1.7 (0.7-4.0)	Age, sex, race, geographic location, state buy-in status
Erichsen et al. 2009	Denmark	96	-	-	-	Cohort	-	Registry	Cancer Registry	IBD: 4.0 (2.5-6.4) CD: 3.0 (0.9-8.6) UC: 4.1 (2.4-6.8)	-	-	Age, sex
El-Serag et al. 2009	US	112	37	75	-	Cohort	-	Registry	Cancer Registry	IBD: 2.54 (1.31-4.93)	IBD: 1.05 (0.60-1.85)	-	Age, sex, baseline visit date, type of visit, a preceding visit
Chang et al. 2013 ¹	Taiwan	5,157	2,978	2,179	20,628	Case-control	Population	Registry	Cancer Registry	IBD: 1.63 (1.37-1.94)	IBD: 1.7 (1.4-2.1)	IBD: 1.5 (1.1-1.9)	Age, sex, and the time of diagnosis

CC, cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; CI, confidence interval; ¹The Summary relative risks and 95% CIs for CC were derived by pooling site- or IBD subtype-specific risks

studies where distinction of CC or IBD type was used, there seemed to be differential effect on the cancer incidence.

The aim of this study was to conduct a meta-analysis of risk of CC in patients with IBD. As previously mentioned, we decided to summarize the data with respect to ICC and ECC separately, because of the possibly different epidemiological feature. Otherwise, CC would be used when studies did not specify cancer type.

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

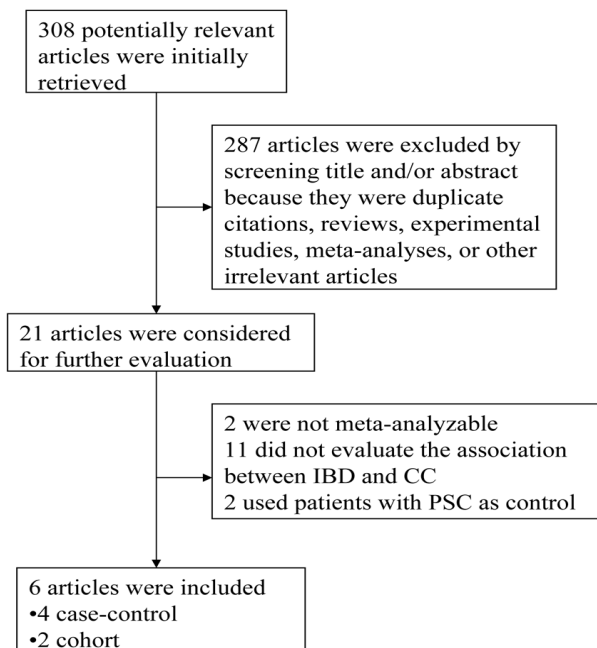
Different measures of risk estimates were included in this meta-analysis: odds ratio, incidence rate ratio, standardized incidence ratio, and hazard ratio. In practice, these measures of effect yielded similar risk estimates because of the low absolute incidence of cholangiocarcinoma.

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

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	Yes	No	7
Welzel et al. 2006	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Welzel et al. 2007	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Erichsen et al. 2009	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	8
El-Serag et al. 2009	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	8
Chang et al. 2013	No	Yes	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; (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

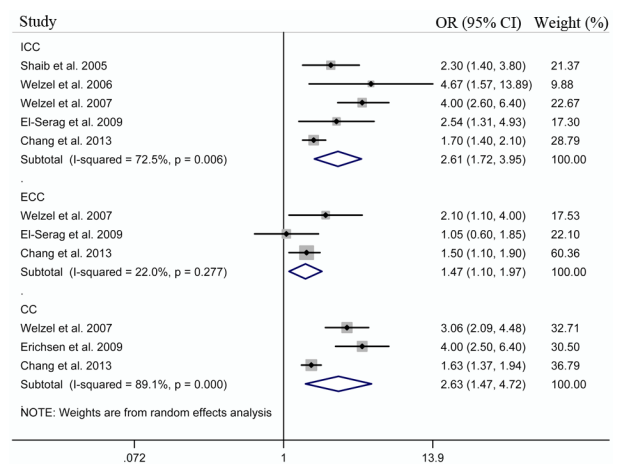
**Figure 1. Flow Chart of the Study Selection**

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 present results specific for ICC and ECC, but included 96 cases for CC (Erichsen et al., 2009). Of those, most

**Figure 2. Risks of ICC, ECC, CC and IBD. OR: odds ratio; CI: confidence interval; ICC: intrahepatic cholangiocarcinoma; ECC: extrahepatic cholangiocarcinoma; CC: cholangiocarcinoma**

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

Table 3. Subgroup Analyses for the Association between IBD and Cholangiocarcinoma

Subgroups	Number of studies	Relative risk (95% CIs)	Tests for heterogeneity		
			Q	P	I ² (%)
ICC					
Geographical region					
Non-Asia	4	3.08 (2.24-4.23)	3.49	0.322	14.1
Asia	1	1.70 (1.39-2.08)	-	-	-
Study design					
Case-control	4	2.66 (1.61-4.39)	14.13	0.003	78.8
Cohort	1	2.54 (1.31-4.93)	-	-	-
ECC					
Geographical region					
Non-Asia	2	1.46 (0.74-2.87)	2.52	0.113	60.3
Asia	1	1.50 (1.14-1.97)	-	-	-
Study design					
Case-control	2	1.58 (1.23-2.03)	0.89	0.347	0.0
Cohort	1	1.05 (0.60-1.84)	-	-	-
CC					
Geographical region					
Non-Asia	2	3.40 (2.53-4.58)	0.75	0.386	0.0
Asia	1	1.63 (1.37-1.94)	-	-	-
Study design					
Case-control	2	2.18 (1.18-4.04)	8.68	0.003	88.5
Cohort	1	4.0 (2.5-6.4)	-	-	-

ICC, intrahepatic cholangiocarcinoma; ECC: extrahepatic cholangiocarcinoma; CC, cholangiocarcinoma; CIs: confidence intervals

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 ($Q = 2.57, P = 0.277$ for heterogeneity, $I^2 = 22.0\%$).

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, $I^2 = 89.1\%$).

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

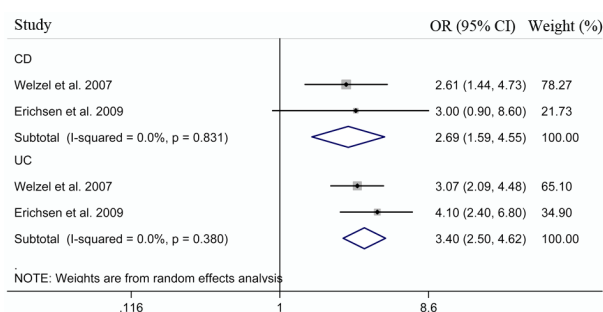


Figure 3. CD, UC and the Risk of CC. OR: odds ratio; CI: confidence interval; CD: Crohn’s Disease; UC: Ulcerative Colitis

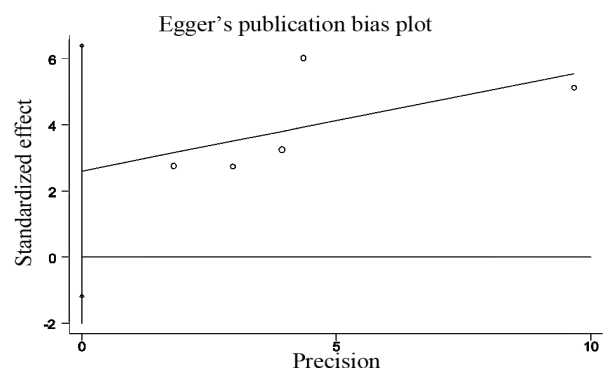


Figure 4. Egger’s Publication Bias Plot for Risk of ICC. The regression asymmetry graph plots the standardized effect estimates versus precision, along with the regression line and the confidence interval about the intercept. Failure of this confidence interval (arrows) to include 0 indicates asymmetry in the funnel plot and may give evidence of publication bias. Guide lines at $x = 0$ and $y = 0$ are plotted to assist in visually determining whether 0 is in the confidence interval. Circles represent individual studies

(CD: $Q = 0.05, P = 0.831$ for heterogeneity, $I^2 = 0.0\%$; UC: $Q = 0.77, P = 0.380$ for heterogeneity, $I^2 = 0.0\%$).

Subgroup analyses

In order to explore potential sources of heterogeneity, we performed subgroup analyses by geographic region and study design (Table 3). The summary RR for ICC remained significant in subgroup analyses and the heterogeneity became unremarkable when studies stratified by geographic region ($Q = 3.49, P = 0.322$ for heterogeneity, $I^2 = 14.1\%$). The association between IBD and risk of ECC was not statistically significant in 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, $I^2 = 60.3\%$). For the risk of CC, significant relationship between IBD and CC was found despite region or study design variations. The heterogeneity disappeared in studies carried out in non-Asian regions ($n = 2$; $Q = 0.75, P = 0.386$ for heterogeneity, $I^2 = 0.0\%$).

Publication bias

Egger’s publication bias plot is shown in Figure 4. P values for Begg’s adjusted rank correlation test and Egger’s regression asymmetry test were 0.327 and 0.116, respectively, both indicating that publication bias probably had little effect on summary estimates. Owing to the paucity of amount of studies, we did not perform a funnel plot analysis.

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 (Jacobsen 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.

References

- Barusru S, Nanok C, Puthisawas W, et al (2012). Viral hepatitis B, C infection and genotype distribution among cholangiocarcinoma patients in northeast Thailand. *Asian Pac J Cancer Prev*, **13**, 83-7.
- Begg CB, Mazumdar M (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, **50**, 1088-101.
- Blechacz BR, Gores GJ (2008). Cholangiocarcinoma. *Clin Liver Dis*, **12**, 131-50, ix.
- Chang JS, Tsai CR, Chen LT (2013). Medical risk factors associated with cholangiocarcinoma in taiwan: a population-based case-control study. *PLoS One*, **8**, e69981.
- DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Control Clin Trials*, **7**, 177-88.
- Egger M, Davey Smith G, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**, 629-34.
- El-Serag HB, Engels EA, Landgren O, et al (2009). Risk of hepatobiliary and pancreatic cancers after hepatitis C virus infection: A population-based study of U.S. veterans. *Hepatology*, **49**, 116-23.
- Erichsen R, Jepsen P, Vilstrup H, et al (2009). Incidence and prognosis of cholangiocarcinoma in Danish patients with and without inflammatory bowel disease: a national cohort study, 1978-2003. *Eur J Epidemiol*, **24**, 513-20.
- Gatto M, Bragazzi MC, Semeraro R, et al (2010). Cholangiocarcinoma: update and future perspectives. *Dig*

- Liver Dis*, **42**, 253-60.
- Hamling J, Lee P, Weitkunat R, Ambuhl M (2008). Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med*, **27**, 954-70.
- Higgins JP, Thompson SG (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med*, **21**, 1539-58.
- Hussain SM, Al-Jashamy KA (2013). Determination of chemical composition of gallbladder stones and their association with induction of cholangiocarcinoma. *Asian Pac J Cancer Prev*, **14**, 6257-60.
- Jacobsen BA, Fallingborg J, Rasmussen HH, et al (2006). Increase in incidence and prevalence of inflammatory bowel disease in northern Denmark: a population-based study, 1978-2002. *Eur J Gastroenterol Hepatol*, **18**, 601-6.
- Jess T, Gamborg M, Matzen P, et al (2005). Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. *Am J Gastroenterol*, **100**, 2724-9.
- Jess T, Rungoe C, Peyrin-Biroulet L (2012). Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol*, **10**, 639-45.
- Lazaridis KN, Gores GJ (2005). Cholangiocarcinoma. *Gastroenterology*, **128**, 1655-67.
- Loftus EV, Jr., Harewood GC, Loftus CG, et al (2005). PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. *Gut*, **54**, 91-6.
- Luciani MG, Campregher C, Fortune JM, et al (2007). 5-ASA affects cell cycle progression in colorectal cells by reversibly activating a replication checkpoint. *Gastroenterology*, **132**, 221-35.
- Manwong M, Songserm N, Promthet S, et al (2013). Risk factors for cholangiocarcinoma in the lower part of northeast Thailand: a hospital-based case-control study. *Asian Pac J Cancer Prev*, **14**, 5953-6.
- O'Toole A, Alakkari A, Keegan D, et al (2012). Primary sclerosing cholangitis and disease distribution in inflammatory bowel disease. *Clin Gastroenterol Hepatol*, **10**, 439-41.
- Palmer WC, Patel T (2012). Are common factors involved in the pathogenesis of primary liver cancers? a meta-analysis of risk factors for intrahepatic cholangiocarcinoma. *J Hepatol*, **57**, 69-76.
- Patel T (2006). Cholangiocarcinoma. *Nat Clin Pract Gastroenterol Hepatol* **3**, 33-42.
- Patel T (2011). Cholangiocarcinoma--controversies and challenges. *Nat Rev Gastroenterol Hepatol*, **8**, 189-200.
- Pedersen N, Duricova D, Elkjaer M, et al (2010). Risk of extra-intestinal cancer in inflammatory bowel disease: meta-analysis of population-based cohort studies. *Am J Gastroenterol*, **105**, 1480-7.
- Saich R, Chapman R (2008). Primary sclerosing cholangitis, autoimmune hepatitis and overlap syndromes in inflammatory bowel disease. *World J Gastroenterol*, **14**, 331-7.
- Shaib Y, El-Serag HB (2004). The epidemiology of cholangiocarcinoma. *Semin Liver Dis*, **24**, 115-25.
- Shaib YH, El-Serag HB, Davila JA, et al (2005). Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. *Gastroenterology*, **128**, 620-6.
- Shivananda S, Lennard-Jones J, Logan R, et al (1996). Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut*, **39**, 690-7.
- Songserm N, Promthet S, Wiangnon S, et al (2012). Prevalence and co-infection of intestinal parasites among Thai rural residents at high-risk of developing cholangiocarcinoma: a cross-sectional study in a prospective cohort study. *Asian Pac J Cancer Prev*, **13**, 6175-9.
- Sripa B, Pairojkul C (2008). Cholangiocarcinoma: lessons from Thailand. *Curr Opin Gastroenterol*, **24**, 349-56.
- Srivatanakul P, Honjo S, Kittiwatanachot P, et al (2010). Hepatitis viruses and risk of cholangiocarcinoma in northeast Thailand. *Asian Pac J Cancer Prev*, **11**, 985-8.
- Tyson GL, El-Serag HB (2011). Risk factors for cholangiocarcinoma. *Hepatology*, **54**, 173-84.
- Vind I, Riis L, Jess T, et al (2006). Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003-2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol*, **101**, 1274-82.
- Wells G, Shea B, O'Connell D, et al (2000). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.
- Welzel TM, Graubard BI, El-Serag HB, et al (2006). Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. *Clin Gastroenterol Hepatol*, **5**, 1221-8.
- Welzel TM, Mellemejkjaer L, Gloria G, et al (2007). Risk factors for intrahepatic cholangiocarcinoma in a low-risk population: a nationwide case-control study. *Int J Cancer*, **120**, 638-41.