Diabetes mellitus and increased risk of cholangiocarcinoma: a meta-analysis

Wei Jing, Gang Jin, Xuyu Zhou, Yingqi Zhou, Yijie Zhang, Chenghao Shao, Rui Liu and Xiangui Hu

Diabetes mellitus (DM) has been reported to be associated with an increased risk of several types of cancers. However, its relationship with cholangiocarcinoma (CC), which includes intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC), remains unclear. We conducted a meta-analysis to assess the association between diabetes and the risk of CC (including ICC and ECC). We identified studies by a literature search of Medline (from 1 January 1966) and Embase (from 1 January 1974), through 30 November 2010, and by searching the reference lists of pertinent articles. Summary relative risks (RRs) with corresponding 95% confidence intervals (CIs) were calculated with a random-effects model. A total of 15 articles (10 case–control and five cohort studies) were included in this study. The number of reports on DM and risk of specific cancer were as follows: CC ($n=5$), ECC ($n=9$), and ICC ($n=9$). Compared with those without diabetes, individuals with diabetes had an increased risk of CC (summary RRs, 1.60; 95% CI, 1.38–1.87; $P=0.992$ for heterogeneity), ECC (summary RRs, 1.63; 95% CIs, 1.29–2.05; $P=0.005$ for heterogeneity), and ICC (summary RRs, 1.97; 95% CIs, 1.57–2.46; $P=0.025$ for heterogeneity). The funnel plot revealed no evidence for publication bias concerning diabetes and the risk of CC (including ICC and ECC). These findings strongly support the positive link between DM and the increased risk of CC (including ICC and ECC). *European Journal of Cancer Prevention* **21:24–31 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

European Journal of Cancer Prevention 2012, **21**:24–31

Keywords: cholangiocarcinoma, diabetes mellitus, extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma, meta-analysis

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Received 16 February 2011 **Accepted** 20 April 2011

Introduction

Cholangiocarcinoma (CC), a malignant tumor arising from the epithelial cells (cholangiocytes) lining the biliary tree, is characterized by a highly fatal cancer and by scarce response to current therapies. Anatomically, CC is classified as intrahepatic CC (ICC) and extrahepatic CC (ECC) according to their location with respect to the liver (Khan *et al.*, 2005). Annually, approximately 5000 new cases of CC are diagnosed in the USA, accounting for almost 3% of all tumors of the gastrointestinal tract (Vauthey and Blumgart, 1994). Data from the Surveillance Epidemiology and End Results database have shown that the incidence of ICC tripled between 1975 and 1999, and the increase in incidence has affected men and women of all racial groups (Patel, 2001; Shaib *et al.*, 2004). In contrast, the rates of ECC have been reported to be steady or have even decreased (Shaib *et al.*, 2004; Welzel *et al.*, 2006a, 2006b). These opposing trends are puzzling, and to our knowledge, no plausible explanation has been proposed.

The most commonly reported risk factors for ICC development include primary sclerosing cholangitis (PSC) and inflammatory bowel diseases (IBD) (Claessen *et al.*, 2009; Erichsen *et al.*, 2009). In addition, alcohol consumption, cirrhosis, and hepatitis C virus (HCV) have also been suggested as the risk factors for ICC development (Shaib *et al.*, 2005; Lee *et al.*, 2008). With respect to ECC, several risk factors, such as obesity, history of gallstones or cholecystitis, and lifestyle-related factors, have also been suggested for ECC development (Larsson and Wolk, 2007; Shaib *et al.*, 2007; Welzel *et al.*, 2006a, 2006b, 2007). Nevertheless, only approximately 10% of CC (including ICC and ECC) cases are associated with a recognized risk factor, because of its rarity (Lazaridis and Gores, 2005).

Over the past two decades, the prevalence of diabetes mellitus (DM) elevated markedly in both industrialized and developing countries (Zimmet *et al.*, 2001; Chen *et al.*, 2008). The relationship between DM and malignancies has been investigated extensively; and DM is highly suspected to be one of the risk factors for several malignancies, including cancers of the breast (Heidemann *et al.*, 2009), endometrium (Saltzman *et al.*, 2008), non-Hodgkin's lymphoma (Lin *et al.*, 2007), pancreas (Ben *et al.*, 2011), and the liver (El-Serag *et al.*, 2006). Several biological mechanisms have been indicated to explain the potentially causal relationship between DM and the risk

0959-8278 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CEJ.0b013e3283481d89

of cancers. It is suggested that insulin resistance and subsequent hyperinsulinemia may upregulate the production of insulin-like growth factor-1 (IGF-1). IGF-1 and insulin were found to be involved in the development and progression of malignancies (Calle and Kaaks, 2004; Frasca *et al.*, 2008). Furthermore, abnormal metabolic, immunologic, and hormonal characteristics of DM are also suggested to promote cancer development. With respect to the association of DM and risk of CC (including ICC and ECC), most studies report a positive association between these two diseases (Adami *et al.*, 1996; Shaib *et al.*, 2005; Welzel *et al.*, 2007; Lee *et al.*, 2008; Grainge *et al.*, 2009; Jamal *et al.*, 2009; Hemminki *et al.*, 2010), whereas other reports found no association (Khan *et al.*, 2006; Shebl *et al.*, 2010; Tao *et al.*, 2010). It is still unknown whether these disparate results are due to true differences between the study populations or due to methodologic differences in exposure definitions, outcome definitions, or other aspects.

Data synthesis by the method of meta-analysis can not only help to evaluate the effect of different study populations, study designs, etc. on the exposure–disease association but also help to explore associations that individual studies may lack the power to investigate, such as the influence of sex or the presence of confounding factors. To provide a quantitative assessment of the relationship between DM and risk of CC, we thus conducted a meta-analysis of the current epidemiological literature to better characterize the associations between the two diseases.

Materials and methods

Data sources and searches

A computerized literature search was performed in Medline (from 1 January 1966) and Embase (from 1 January 1974), through 30 November 2010, by two independent investigators (W.J. and G.J.). We searched the relevant studies with the following text words and/or Medical Subject Headings: 'diabetes mellitus', 'diabetes', 'cholangiocarcinoma', 'intrahepatic', 'extrahepatic', 'bile duct cancer', and 'epidemiologic studies'. We also reviewed citations from retrieved articles to search for more studies. No language restrictions were imposed.

Inclusion and exclusion criteria

In this meta-analysis, we included studies that fulfilled the following criteria: (i) case–control or cohort design; (ii) diabetes as one of the exposure of interests; (iii) ICC, ECC, or CC as one of the outcome of interests; and (iv) reported relative risk (RR) in cohort studies (rate ratio) or in case–control studies [odds ratio, (OR)] with their 95% confidence intervals (CIs), or provided sufficient information to calculate them. We did not consider studies in which the exposure of interest was type 1 diabetes, which was defined as early-onset (age ≤ 30 years) of diabetes. If data were duplicated in more than one study, the estimate effects controlled for the most appropriate confounders were included. This resulted in the exclusion of three articles from our study (Adami *et al.*, 1991; Hou *et al.*, 2006; Hsing *et al.*, 2008). Articles or reports from nonpeer-reviewed sources were also not considered for this analysis.

Data extraction

For each study, the following information was extracted when applicable: the first researcher's last name, year of publication, country where the study was performed, type of study design (cohort and case–control studies), type of controls for case–control studies (hospital-based or population-based controls), sample size, methods of ascertainment of DM and outcome, adjusted factors, and the RR estimates with corresponding 95% CIs for DM. We extracted the risk estimates that reflected the greatest degree of control for potential confounders (if applicable). When studies provided more than one RR according to the duration of diabetes before CC was diagnosed, we extracted and combined the RRs for individuals diagnosed with diabetes more than 1 year before the diagnosis of CC. On account of the dismal prognosis, mortality often serves as a marker for incidence. If studies reported both incidence and mortality rate, we extracted the incidence rate, as mortality rate could be confounded by survival-related factors. Two researchers (W.J. and G.J.) independently performed data extraction. Discrepancies were resolved by consensus.

Statistical analysis

Studies that reported different measures of RR were included in this meta-analysis: case–control studies (OR), cohort studies (rate ratio), and cohort studies of patients with diabetes using external population comparisons (standardized incidence ratio). In practice, these three measures of effect yield similar estimates of RR on the basis that the absolute number of CC or cancer of its subsites is low.

Summary RR estimates with their corresponding 95% CIs were calculated with a random-effects model of DerSimonian and Laird (1986), which considers both within-study and between-study variations. Statistical heterogeneity among studies was evaluated using the Q and I^2 statistics (Higgins and Thompson, 2002). For the Q statistic, a P value of less than 0.10 was used as an indication of the presence of heterogeneity. I^2 is the proportion of total variation contributed by between-study variation. To explore the potential heterogeneity between studies, we conducted analyses stratified by study design, geographic area, and the adjustment for infection with hepatitis B virus (HBV)/HCV. Publication bias was assessed by both Begg's funnel plot and the Egger's test. The Begg's funnel plot is based on adjusted rank correlation and the Egger's test is based on a regression model ($P < 0.10$ as an indication for publication bias) (Begg and Mazumdar, 1994; Egger *et al.*, 1997). Typically, the Egger's test is more sensitive than the

Begg's funnel plot. All statistical analyses were performed with STATA, version 11.0 (STATA, College Station, Lakeway Drive, Texas, USA).

Results

Study characteristics

A total of 15 articles, which met the inclusion and exclusion criteria, were used in this meta-analysis (Tables 1 and 2). The countries or continents in which the studies were conducted were as follows: Asia ($n = 6$), the USA ($n = 5$), and Europe ($n = 4$).

The 10 case–control studies were published between 2004 and 2010, and reported a total of 1032 cases with ECC and 3115 cases with ICC. The report from Grainge *et al.* (2009) did not present results specific for ICC and ECC, but presented results for 372 cases with CC. Among these 4519 cases, 755 cases with diabetes were reported (Table 1), whereas, among 329 417 controls, a total of 37 658 patients had diabetes. Control individuals included originated from a population-based (Shaib *et al.*, 2005; Welzel *et al.*, 2006a, 2006b, 2007; Lee *et al.*, 2008; Grainge *et al.*, 2009; Shebl *et al.*, 2010) or hospital-based setting (Yamamoto *et al.*, 2004; Shaib *et al.*, 2007; Zhou *et al.*, 2008; Tao *et al.*, 2010). DM status was ascertained by a self-reported history of DM (Shaib *et al.*, 2005) or hospital records (Yamamoto *et al.*, 2004; Welzel *et al.*, 2006a, 2006b, 2007; Zhou *et al.*, 2008; Shebl *et al.*, 2010; Tao *et al.*, 2010), with the exception of three studies in which the methods of DM ascertainment were not available (Shaib *et al.*, 2007; Lee *et al.*, 2008; Grainge *et al.*, 2009). Ascertainment of ECC or ICC was based on histologic methods or a review of medical records in seven studies, and the remaining three studies were based on diagnostic codes (Shaib *et al.*, 2005; Welzel *et al.*, 2006a, 2006b, 2007). Adjustments were made for potential confounders of one or more factors in seven of eight studies, with the exception of one study in which only the univariate OR was available (Shaib *et al.*, 2007).

Five cohort studies that reported an association between DM and the risk of ICC or ECC were identified (Table 2). Among these five studies, two were diabetic cohorts, using standardized incidence ratio as the measure of RR (Adami *et al.*, 1996; Hemminki *et al.*, 2010), and the other three studies used rate ratio as the measure of RR. These five cohort studies comprised between 56 881 and 836 283 persons with a median follow-up period of 6.7 years (range: 2.3–20 years), reporting a total of 878 incident cases of ICC or ECC. The methods of DM ascertainment were based on medical records in three studies, except for two studies in which the ascertainment of DM was based on self-reported history or registry of disease (Khan *et al.*, 2006; El-Serag *et al.*, 2009). The ascertainment of outcome was based on cancer registry in all studies. Potential confounders (at least for age) were controlled in all studies.

Diabetes mellitus and risk of cholangiocarcinoma

Four case–control studies and one cohort study reported results on DM and risk of CC (or risk of ICC and ECC, respectively) (Fig. 1a). Of these, two studies found statistically significant positive relationships (Welzel *et al.*, 2007; Grainge *et al.*, 2009), and the other three studies did not find a significantly increased risk of CC in patients with diabetes (Shaib *et al.*, 2007; El-Serag *et al.*, 2009; Tao *et al.*, 2010). In the analysis of all five studies that reported RR of DM and CC, the summary RRs and corresponding 95% CIs were 1.60 (95% CI, 1.38–1.87) in a random-effects model for those with diabetes compared with those without diabetes. There was no statistically significant heterogeneity among studies ($Q = 0.27$; $P = 0.992$; $I^2 = 0\%$).

Diabetes mellitus and risk of extrahepatic cholangiocarcinoma

We identified nine studies (four case–control and five cohort studies) that presented results on diabetes and risk of ECC (Fig. 1b). Of these, five studies found an increased risk of ECC in patients with diabetes (Adami *et al.*, 1996; Welzel *et al.*, 2007; Jamal *et al.*, 2009; Hemminki *et al.*, 2010; Tao *et al.*, 2010), and in another four studies positive relationships were not found (Khan *et al.*, 2006; Shaib *et al.*, 2007; El-Serag *et al.*, 2009; Shebl *et al.*, 2010). In the analysis of all nine studies, the summary RRs and corresponding 95% CIs were 1.63 (95% CI, 1.29–2.05) in a random-effects model for those with diabetes compared with those without diabetes, with evidence of significant heterogeneity among studies ($Q = 22.12$, $P = 0.005$, $I^2 = 63.8\%$).

We then conducted subgroup meta-analyses by geographic area and study design (Table 3). The summary RRs of the associations between diabetes and ECC risk were similar for cohort studies and case–control studies [summary RRs (95% CIs), 1.61 (1.14–2.29) in cohort studies and 1.62 (1.05–2.49) in case–control studies, respectively]. A positive association between DM and ECC risk was found in studies conducted in non-Asian regions (the USA and Europe) (summary RRs, 1.64; 95% CI, 1.31–2.06) and a positive, but non-significant association was found in Asia (summary RR, 1.32; 95% CI, 0.58–2.99).

DM and ICC risk

We identified eight case–control and one cohort study that presented results for the association of diabetes and ICC risk (Fig. 1c). Three of these nine studies found a statistically significant positive association (range of individual RRs, 0.53–3.2; summary RRs for all nine studies, 1.97; 95% CIs, 1.57–2.46). There was significant heterogeneity among studies ($P = 0.025$, $I^2 = 54.3\%$). Research by Tao *et al.* (2010) reported an inverse, but not significant, correlation of diabetes and risk of ICC. Excluding this research, a stronger association and less heterogeneity were found among the remaining studies (summary RRs, 2.00; 95% CIs, 1.65–2.44; $P = 0.093$ for heterogeneity).

Table 1 Characteristics of 10 case–control studies of diabetes and intrahepatic and extrahepatic cholangiocarcinoma

Author/year/country	CC	ECC	ICC	Source	Controls (DM, *n*)	Diabetes assessment	Outcome ascertainment	AOR (95% CI)	Adjustments
Yamamoto *et al.* (2004) Japan			50 (11)	Hospital	205 (24)	Hospital records	Pathological diagnosis	ICC: 1.95 (0.65–5.85)	HCV, hypertension, transfusion, TBi, Alb, Plt count, ALT.
Shaib *et al.* (2005) USA			625 (165)	Population	90 834 (14 201)	Self-report	Cancer registry	ICC: 2.0 (1.6–2.4)	Age, sex, race, geographic location, medicare/medical enrollment
Welzel *et al.* (2006a, 2006b) Denmark			764 (15)	Population	3056 (43)	Hospital records	Cancer registry	ICC: 1.43 (0.78–2.63)	NA
Welzel *et al.* (2007) USA		549 (165)	535 (177)	Population	102 782 (22 764)	Hospital records	Cancer registry	CC: 1.64 (1.37–1.96)[a] ICC: 1.8 (1.5–2.1) ECC: 1.5 (1.3–1.8)	Age, sex, race, geographic region
Shaib *et al.* (2007) USA		163 (19)	83 (12)	Hospital	236 (20)	NA	Histologic diagnosis	CC: 1.55 (0.89–2.69)[a] ICC: 1.8 (0.7–4.1) ECC: 1.4 (0.7–2.9)	NA
Lee *et al.* (2008) Korea			685 (96)	Population	124 763 (139)	NA	Pathological diagnosis	ICC: 3.2 (2.3–4.3)	Age, sex
Zhou *et al.* (2008) China			312 (13)	Hospital	438 (11)	Hospital records	Pathological diagnosis	ICC: 1.50 (0.60–3.80)	Age, sex, HCV/HBV markers, heavy drinking
Grainge *et al.* (2009) UK	372 (35)			Population	5760 (342)	NA	Hospital records	CC: 1.48 (1.00–2.17)	Smoking, alcohol use, BMI, NSAID use, gallstone
Shebl *et al.* (2010) China		191 (20)		Population	959 (78)	Hospital records	Hospital records	ECC: 0.79 (0.30–2.07)	Age, sex, education, aspirin use, BMI, DM duration, waist-to-hip ratio
Tao *et al.* (2010) China		129 (24)	61 (3)	Hospital	384 (36)	Hospital records	Pathological diagnosis	CC: 1.39 (0.24–8.06)[a] ICC: 0.53 (0.17–1.65)[a] ECC: 3.2 (1.7–5.9)	Age, sex, HBV markers, history of cholecystectomy

Alb, albumin; ALT, alanine aminotransferase; AORs, adjusted odds ratios; CC, cholangiocarcinoma; CI, confidence interval; DM, diabetes mellitus; ECC, extrahepatic cholangiocarcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; ICC, intrahepatic cholangiocarcinoma; NA, not available; NSAID, nonsteroidal anti-inflammatory drug; Plt, platelet; Tbi, total bilirubin.
[a]The AOR and 95% confidence intervals were derived by pooling the site-specific AORs.

Table 2 Characteristics of five cohort studies of diabetes and intrahepatic and extrahepatic cholangiocarcinomas

Author/year/country	Number of patients	Demographics of all patients (age in years)	Diabetes assessment	Cancer ascertainment	Follow-up (years)	ICC/ECC in DM	Adjusted RR (95% CI)	Adjustments
Adami *et al.* (1996) Sweden	153 852	74 male: 64%	Hospital discharge diagnosis	Cancer registry	6.7	272	ECC: 1.4 (1.1–1.8)	Alcohol use, hepatitis, cirrhosis, jaundice, etc.
Khan *et al.* (2006) Japan	56 881	40–70	NA	Cancer registry	18–20	40	ECC: 0.30 (0.04–2.22)	Age, BMI, smoking, alcohol use
El-Serag *et al.* (2009) USA	718 687	52 male: 97%	Registry	Cancer registry	2.3	NA	CC: 1.60 (0.67–3.83)[a] ICC: 2.54 (1.31–4.94) ECC: 1.04 (0.59–1.83)	Age, sex, baseline visit date, type of visit
Jamal *et al.* (2009) USA	836 283	65 male: 98%	Hospital discharge diagnosis	Cancer registry	NA	NA	ECC: 2.1 (1.6–2.5)	Age
Hemminki *et al.* (2010) Sweden	125 126	>39 male: NA	Medical records	Cancer registry	15	566	ECC: 2.53 (1.44–4.11)	Age

AORs, adjusted odds ratios; CC, cholangiocarcinoma; CI, confidence interval; DM, diabetes mellitus; ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; NA, not available; RR, relative risk.
[a]The AOR and 95% confidence intervals were derived by pooling the site-specific RRs.

Subgroup meta-analyses by study design indicated that the positive association was significant not only among case–control studies (summary RRs, 1.91; 95% CIs, 1.50–2.43; $P = 0.016$ for heterogeneity) but also among cohort studies (summary RRs, 2.54; 95% CIs, 1.31–4.94) (Table 3). In case–control studies, the source of control individuals significantly affected the magnitude of the association of DM and ICC risk; the summary RRs and corresponding 95% CIs were 2.07 (95% CI, 1.59–2.69) for population-based studies and 1.36 (95% CI, 0.80–2.33) for hospital-based studies, respectively. In addition, we also conducted subgroup analysis by geographic area. The association between diabetes and ICC risk was significantly positive in studies conducted in both Asia (summary RRs, 1.94; 95% CI, 1.26–2.97; $P = 0.011$ for heterogeneity) and in non-Asian regions (summary RRs, 1.80; 95% CI, 1.54–2.01; $P = 0.63$ for heterogeneity).

When we limited the meta-analysis to studies that controlled for infection with HCV/HBV (Yamamoto *et al.*, 2004; Zhou *et al.*, 2008; El-Serag *et al.*, 2009; Tao *et al.*, 2010), a positive, but not significant, association between diabetes and ICC risk was found (summary RRs, 1.54; 95% CIs, 0.82–2.91; $P = 0.134$ for heterogeneity).

Publication bias

The funnel plot revealed no evidence for publication bias concerning diabetes and the risk of ICC and ECC. *P* values for Begg's adjusted rank correlation test and Egger's regression asymmetry test were 0.529 and 0376, respectively, both suggesting that publication bias probably has little effect on summary estimates (Fig. 2).

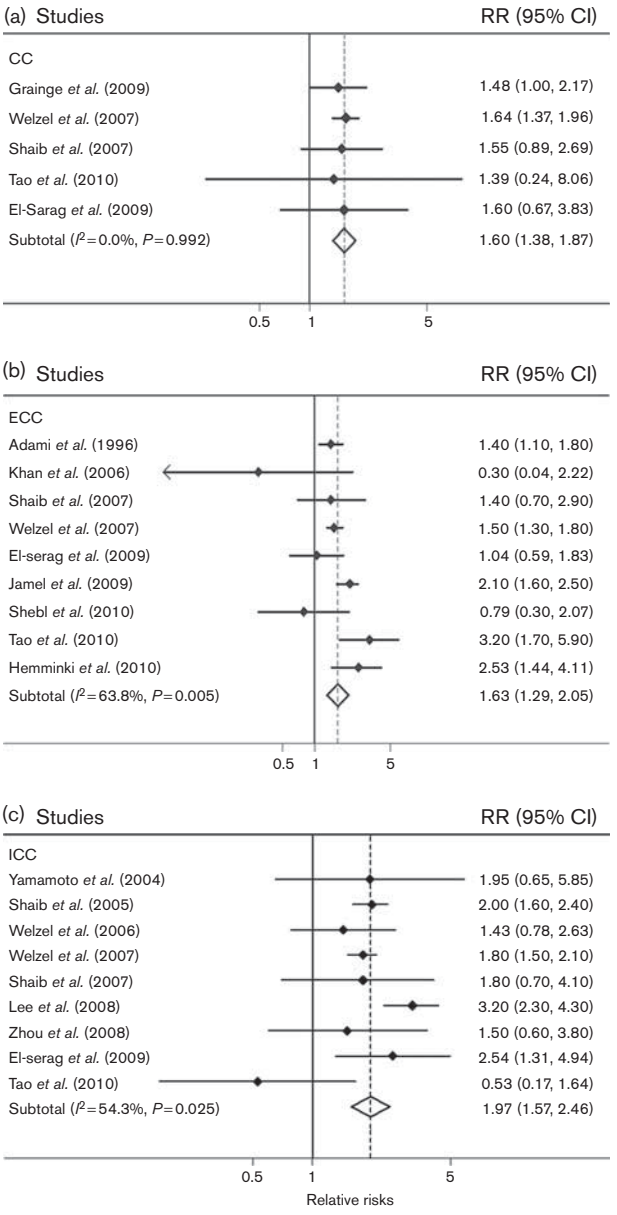
Discussion

In this meta-analysis, we find that compared with individuals without diabetes, individuals with diabetes have a more than 60% increased risk of CC (including ICC and ECC). The increased risk is independent of study design, geographic area, and HBV/HCV status. To date, this is the first meta-analysis to comprehensively evaluate the observational studies that report a link between DM (chiefly type 2 DM) and risk of CC or cancer of its subsites.

Although the absolute risks of CC (including ECC and ICC) are low among individuals with diabetes, our results have important clinical and public health significance because of the following reasons. First, DM is a very common disease; in the past two decades, the prevalence of DM has been elevated markedly both in developed countries and in developing countries (Zimmet *et al.*, 2001; Yang *et al.*, 2010). For example, Yang *et al.* (2010) found that in China, the age-standardized prevalence of total diabetes (including both previously diagnosed and undiagnosed diabetes) was 9.7%, which accounted for 92.4 million adults with diabetes (50.2 million men and 42.2 million women). In contrast, CC is a highly fatal tumor with a 5-year survival rate of only 20% (Nathan *et al.*, 2007). It has become more common in most areas in the recent years (Grainge *et al.*, 2009).

Our analysis must be interpreted in the context of the limitations of available data. First, case–control studies are susceptible to selection and recall biases; cohort studies may be affected by detection bias because patients with DM are under increased medical surveillance and thus may be more likely to be diagnosed with CC (including ECC and ICC). These biases may distort the true associations between these two variables. Second, most studies included in this study did not distinguish between type 1 and type 2 DM (although we excluded two studies that included all patients with young-onset diabetes). Therefore, some degree of misclassification of

Fig. 1



Forest plot of the relationships between diabetes and cholangiocarcinoma (CC) risk. (a) Summary risk of CC associated with diabetes. Test for heterogeneity: $P=0.992$, $I^2=0\%$. (b) Summary risk of extrahepatic CC associated with diabetes. Test for heterogeneity: $P=0.005$, $I^2=63.8\%$. (c) Summary risk of intrahepatic CC associated with diabetes. Test for heterogeneity: $P=0.025$, $I^2=54.3\%$. Diamonds represent the pooled relative risk estimates. The horizontal line represents the 95% confidence intervals for the observed effect in the pooled estimates. CI, confidence interval; ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; RR, relative risk.

DM is likely to have occurred. This nondifferential misclassification would tend to distort the magnitude of the association between DM and risk of CC (including ECC and ICC). Moreover, some subgroup analyses were based on few studies and the results need to be interpreted with caution. Nevertheless, given the relative prevalence of these two types (type 2 DM accounts for 90–95% of all diagnosed cases of DM), it is likely that the vast majority of cases included in this study are type 2 DM. Third, confounding is also likely to be present, because the history of DM may also reflect other factors related to an unhealthy lifestyle, such as smoking, heavy alcohol consumption, and obesity. Such unhealthy lifestyles have generally been associated with an increased risk of cancer. Thus, the observed increased risk of CC (including ECC and ICC) associated with a history of diabetes may in part reflect confounding by these factors. Although most studies controlled for these lifestyle factors, the possibility of residual confounding cannot be completely excluded. Fourth, all the included studies did not consider the role of antidiabetic drugs on the development of CC (including ECC and ICC). Many studies have increasingly suggested that metformin and thiazolidinediones, two common antidiabetic drugs, could exert a protective role against the development and progression of malignancies (Li and Abbruzzese, 2010). In contrast, use of insulin and insulin analog was recently indicated to be associated with an increased risk of some cancers (Werner *et al.*, 2011). Finally, as in all meta-analysis, the possibility of publication bias is of concern, because small studies with null results tend not to be published. However, the results obtained from formal statistical tests and funnel plot analysis did not provide evidence for such bias.

In a western population, the most important risk factors for CC include PSC, other biliary diseases, IBD, and infection with HCV. None of the studies included in this meta-analysis provided results controlled for PSC or IBD. We therefore cannot examine whether risks may be modified by these two important factors. Two case–control studies controlled for biliary diseases (Grainge *et al.*, 2009; Tao *et al.*, 2010), and in these two studies, one reported an increased risk in patients with diabetes compared with individuals without diabetes; however, the other did not. The summary RR was slightly lower for studies controlled for infection with HCV/HBV than those not controlled for infection with HCV/HBV (summary RR, 1.32 vs. 2.05). This could reflect a residual confounding from infection with HCV/HBV.

Tao *et al.* (2010) from China found that diabetes was positively associated with the risk of ECC; however, it was inversely associated with the risk of ICC (although not significant). The latter result was different from other studies on diabetes and ICC risk. It was possible that too small a sample and retrospective design (which is susceptible to selection and recall biases) might distort the true association between diabetes and the risk of ICC.

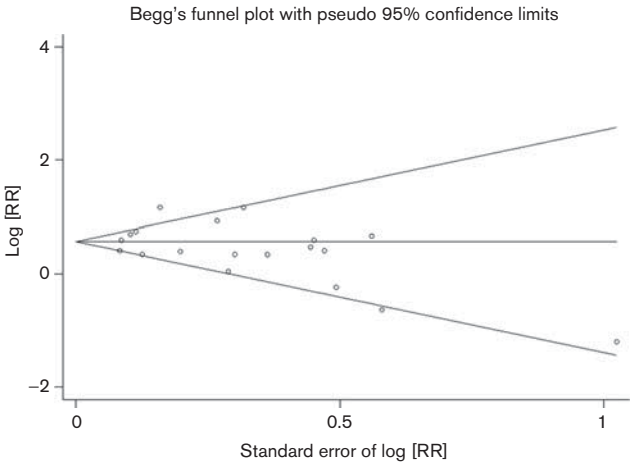
Several biological mechanisms have been proposed to potentially underlie the development of CC (including ECC and ICC) in individuals with diabetes. Type 2 DM

Table 3 Summarized relative risks for the association between diabetes and ECC and ICC by study characteristics

Subgroup	Number of studies	Relative risk (95% CI)	Tests for heterogeneity		
			Q	*P*	I^2(%)
ECC					
Geographical region					
Asia	4	1.32 (0.58–2.99)	9.54	0.023	68.6
Non-Asia	5	1.64 (1.31–2.06)	12.54	0.014	68.1
Study design					
Case–control study					
Hospital based	2	2.16 (0.96–4.84)	2.94	0.086	66.0
Population based	2	1.31 (0.78–2.19)	1.66	0.199	39.3
Cohort studies	5	1.61 (1.14–2.29)	13.78	0.008	71.0
ICC					
Geographical region					
Asia	5	1.94 (1.26–2.97)	13.09	0.011	69.4
Non-Asia	4	1.80 (1.54–2.01)	1.73	0.63	0
Study design					
Case–control study					
Hospital based	4	1.36 (0.80–2.33)	3.48	0.323	13.9
Population based	4	2.07 (1.59–2.69)	11.58	0.009	74.1
Cohort studies	1	1.60 (0.67–3.83)	–	–	–
Adjustment for HCV					
Yes	4	1.54 (0.82–2.91)	5.58	0.134	46.2
No	5	2.05 (1.61–2.61)	11.64	0.020	65.6

CI, confidence interval; ECC, extrahepatic cholangiocarcinoma; HCV, hepatitis C virus; ICC, intrahepatic cholangiocarcinoma.

Fig. 2



Funnel plot of studies evaluating the association between diabetes and risk of cholangiocarcinoma (CC) (including intrahepatic CC and extrahepatic CC). There is no evidence for publication bias. Begg's adjusted rank correlation test ($P=0.529$) and Egger's regression asymmetry test ($P=0.376$). RR, relative risk.

is associated with insulin resistance, compensatory hyperinsulinemia. Insulin has been shown to stimulate the growth of many cancer cell lines by binding to insulin receptors on cancer cells. In addition, insulin can result in decreased levels of insulin-like growth factor binding protein 1 and thus an upregulated level of IGFs. IGFs may stimulate cellular proliferation and inhibit apoptosis within the cholangiocytes, through activation of MAPK and PI3K/AKT pathways, and eventually lead to transformation (Levine *et al.*, 2006; Samani *et al.*, 2007; Cai *et al.*, 2008; Gallagher *et al.*, 2010). In-vivo studies also demonstrated that carcinogenesis of ICC was modulated by IGF-1R antagonists (Alvaro *et al.*, 2006). In addition, in some, but not all studies, diabetes has been found to be independently associated with a higher risk of biliary stones (Stone and Van Thiel, 1985; Biddinger *et al.*, 2008; Festi *et al.*, 2008; Shebl *et al.*, 2010), which are one of the major risk factors for CC. Shebl *et al.* (2010) found that in a Chinese population, DM was associated with a two-fold risk of gallstones, and approximately 60% of the effect of DM on bile duct cancer was mediated by gallstones. Furthermore, the researchers also found that DM was related to several key factors important in the process of stone formation (Stone and Van Thiel, 1985; Shebl *et al.*, 2010). In line with these findings, Biddinger *et al.* (2008) found that insulin resistance might result in increased production of biliary cholesterol and lithogenic bile salt, which directly promoted the formation of gallstones. In addition, researchers have found a graded dose–response association between bile duct cancer risk and both fasting and postprandial glucose levels, which also supports a causal relationship between the two variables (Gapstur *et al.*, 2000; Jee *et al.*, 2005).

In total, the results from this meta-analysis suggest an association between diabetes and increased risks of CC (including ICC and ECC). Nevertheless, it cannot be ruled out that the positive association may be due to bias or confounding among these studies. More studies, both epidemiological and mechanistic, are needed to further clarify this association in the future.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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