RESEARCH ARTICLE

Chronic Hepatitis B Virus Infection and Risk of Pancreatic Cancer: A Meta-analysis

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Abstract

Objectives: A number of studies have shown that chronic hepatitis B virus infection is implicated in susceptibility to pancreatic cancer. However, the results are still controversial. This meta-analysis aimed to quantitatively assess the relationship between chronic hepatitis B virus infection and incidence of pancreatic cancer of cohort and case-control studies. Methods: A literature search was performed for entries from 1990 to 2012 using PUBMED and EMBASE. Studies were included if they reported odds ratios (ORs) and corresponding 95% CIs of pancreatic cancer with respect to the infection of hepatitis B virus. Results: Eight studies met the inclusion criteria, which included five case-control studies and three cohort studies. Compared with individuals who have not infection of hepatitis B virus, the pooled OR of pancreatic cancer was 1.403 (95%CI: 1.139-1.729, P=0.001) for patients with hepatitis B virus infection. Sub-group analysis by study design showed that the summary OR was 1.43 (95%CI: 1.06-1.94, P=0.021) when pooling case-control studies and 1.31 (95%CI: 1.00-1.72, P=0.05) when pooling cohort studies. Conclusion: Findings from this meta-analysis suggest that chronic hepatitis B virus infection may increase the risk of pancreatic cancer. This relationship needs to be confirmed by further follow-up studies.

Keywords: Chronic hepatitis B virus infection - pancreatic cancer - cohort study - case-control study - meta-analysis

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Introduction

As one of the most lethal human malignant tumors, pancreatic cancer accounts for 3% of all reported cases of cancer (Jemal et al., 2008). It is estimated to be responsible for more than a quarter of a million deaths and be the fifth leading cause of cancer death in worldwide (Epstein et al., 2012). The prognosis is extremely poor, with 5-year survival rate of less than 5% even with the surgical and chemotherapy intervention (Le Scodan et al., 2009).

Many studies have been conducted to explore potential risk factors of pancreatic cancer. Heavy alcohol consumption can increase the risk of pancreatic cancer (Lucenteforte et al., 2012), as well as smoking (Iodice et al., 2008), sucrose-intake6 (Aune et al., 2012), processed meat consumption (Larsson et al., 2012) and high body mass index (Li et al., 2010), while folate intake (Bao et al., 2011) and coffee consumption (Dong et al., 2011) are not appreciably related to pancreatic cancer risk.

Several studies find that hepatitis B virus can replicate in human pancreatic tissue and that patients with hepatitis B infection have impairments of pancreatic function (Hoefs et al., 1980; Yoshimura et al., 1981; Shimoda et al., 1981; Dejean et al., 1984; Katakura et al., 2005). Also, some cohort and case-control studies (de Gonzalez et al., 2008; Hassan et al., 2008; Iloeje et al., 2009; Gordon et al., 2009; Hong et al., 2010; Zhu et al., 2011; Wang et al., 2012; Ben et al., 2012) have been conducted to estimate the relationship between chronic hepatitis B virus infection and pancreatic cancer. But the results were controversial. Therefore, a meta-analysis was performed to quantitatively assess the relationship of hepatitis B virus infection and the risk of pancreatic cancer in humans.

Materials and Methods

Inclusion Criteria

We screened the relevant studies from the search engines of PUBMED, EMBASE (last search update performed on 05/2012), using the Medical Subject Heading (MeSH) term "hepatitis B virus infection combined with pancreatic cancer or pancreatic neoplasm or pancreatic carcinoma" without language limit. Furthermore, we reviewed reference lists of retrieved articles to search for more studies. If sequential or multiple publications from the same data occurred, the publication that reported data from the largest or most recent study was included.

Data extraction

According to the MOOSE (Meta-analysis Of

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Table 1. Baseline Characteristics of Included Studies in Meta-analysis

Reference	country /region	year	Numbers of individuals	mean age	diagnostic criteria	Matchof controls	ORs and 95% CIs
Wang	China	2012	645	56.56	1	Age and sex matched	1.610(1.125-2.304)
Hassan	USA	2008	476	60	1	Age and sex matched	2.500(1.500 -4.200)
Zhu	China	2011	553	NA	1	Age and sex matched	2.935(1.048-8.220)
Hong	Korea	2010	506	63.5	2	Age and sex matched	0.900(0.520-1.560)
Ben	China	2012	943	61	1	Age and sex matched	1.600(1.150 -2.240)
Iloeje	China Taiwan	2009	22471	NA	2	Age matched	1.95(1.159-2.011)
de Gonzalez	Korea	2009	201975	NA	1	Age matched	1.130(0.840-1.520)
Gordon	USA	2009	74851	NA	1	Age and sex matched	1.411(0.877-2.271)

NA, not mentioned in the study; 1, diagnosed by histology; 2, diagnosed by histology or by CT

Observational Studies in Epidemiology) guideline for reporting on meta-analyses of observational studies (Donna et al., 2000); data was extracted by two investigators (Libo Yang and Bo Wu) independently. The information of each study was extracted as following: first author's last name; region/country where the study was conducted; year of publication; numbers of cases; mean age of cases and controls; diagnostic criteria; manner in which the controls were selected; ORs, RRs or HRs of pancreatic cancer and corresponding 95% CIs for hepatitis B virus infection; and covariates adjusted in the statistical analysis. Discrepancies were resolved by discussion with a third investigator (Fuchun Jing) and a consensus was reached.

Statistical analysis Methods

The study-specific most adjusted OR, RR or HR was used to compute a summary OR and its 95%CI. RRs and HRs were directly considered as ORs. The statistical heterogeneity among the studies was estimated by the Chi square-test based Q-statistic (Cochran et al., 1954), and a significant Q-statistic (P<0.10) indicated heterogeneity across studies. The pooled OR was calculated by a fixed effect model (using the Mantel-Haenszel method) or a random effect model (using the DerSimonian-Laird method) according to the heterogeneity among studies (Mantel et al., 1959; DerSimonian et al., 1986). The potential publication bias was evaluated using Both Begg's funnel plot and Egger's test and P<0.05 was considered statistically significant in publication bias (Egger et al., 1997). Analyses were performed by using Stata version 12.0 (StataCorp LP, College Station, TX, USA). A P- value less than 0.05 was considered statistically significant, and all the P values were two sided.

Results

Literature search and studies characteristics

The results of the literature search are shown in Figure1. 30 articles were retrieved from our preliminary search. Of these, ten articles were identified for full review. After review, two studies were excluded with the following reasons: a study of HCV infection (El-Serag et al., 2009); a case report (Yoo et al., 2009). Thus, eight articles met the inclusion criteria (de Gonzalez et al., 2008; Hassan et al., 2008; Gordon et al., 2009; Iloeje et al., 2009; Hong et al., 2010; Zhu et al., 2011; Ben et al., 2012; Wang et al., 2012), six of these studies were conducted only in East

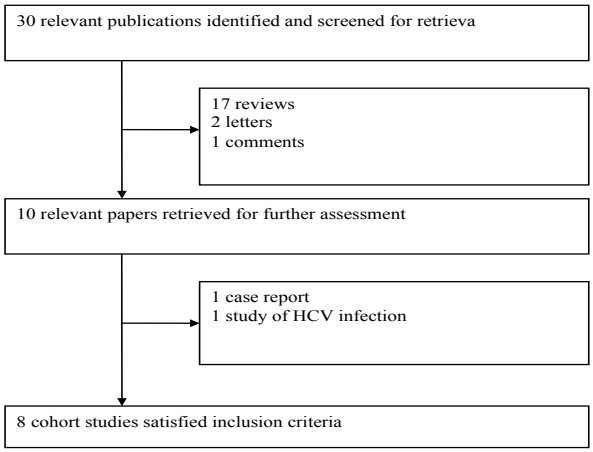

Figure 1. Flow Diagram of Search Strategy and Study Selection

Asia (de Gonzalez et al., 2008; Iloeje et al., 2009; Hong et al., 2010; Zhu et al., 2011; Ben et al., 2012; Wang et al., 2012) and two in USA (Hassan et al., 2008; Gordon et al., 2009).

The characteristics of the included studies are tabulated in Table 1. There were a total of 302420 individuals in the included eight studies. In most of the studies (de Gonzalez et al., 2008; Hassan et al., 2008; Gordon et al., 2009; Zhu et al., 2011; Ben et al., 2012; Wang et al., 2012), pancreatic cancer was diagnosed according the histology. In other studies (Iloeje et al., 2009; Hong et al., 2010), pancreatic cancer is confirmed by histology or diagnosed by symptoms, signs and more than two types of imaging tools. Enzyme-linked immunosorbent assay was used to test the presence of HBsAg and hepatitis B core antigen antibody (anti-HBc), hepatitis B e antigen (HBeAg) and hepatitis B e antibody (anti-HBe). Polymerase chain reaction (PCR) was used to assay the HBV DNA level.

Quality evaluation of included studies

Because the quality of the included studies can overestimate or underestimate the OR and CI, we perform a quality evaluation of each study, the result are tabulate in Table2. Of these eight studies, five were conducted in a hospital-based case-control study design (Hassan et al., 2008; Hong et al., 2010; Zhu et al., 2011; Ben et al., 2012; Wang et al., 2012), three in cohort design (de Gonzalez et al., 2008; Gordon et al., 2009; Iloeje et al., 2009). Six of the studies were performed in Eastern Asia (Korea and China) (de Gonzalez et al., 2008; Iloeje et al., 2009; Hong et al., 2010; Zhu et al., 2011; Ben et al., 2012; Wang et

Table 2. Quality Assessment of All Studies

case-control studies Studies	1	2	3	4	5A	5B	6	7	8
Wang	YES	YES	NO	NO	YES	YES	YES	YES	NO
Hassan	YES	YES	YES	NO	YES	YES	YES	YES	NO
Zhou	YES	YES	NO	YES	YES	YES	YES	YES	NO
Hong	YES	YES	NO	YES	YES	YES	YES	YES	NO
Ben	YES	YES	NO	NO	YES	YES	YES	YES	NO

1, adequate description of the case; 2, representativeness of the cases; 3, controls drawn from the community; 4, definition of Controls; 5A, study controlled for age; 5B, study controlled for other factor(s); 6, ascertainment of exposure; 7, Same method of ascertainment for cases and controls; 8, Non-Response rate

cohor studies Studies	1	2	3	4	5A	5B	6	7	8
Iloeje	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
de Gonzalez	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Gordon	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No

1, exposed cohort truly representative; 2, controls drawn from the same community; 3, ascertainment of exposure; 4, outcome of interest not present at start; 5A, cohorts controlled for age; 5B, cohorts controlled for other factor(s); 6, quality of outcome assessment; 7, follow-up long enough for outcomes to occur; 8, complete accounting for cohorts

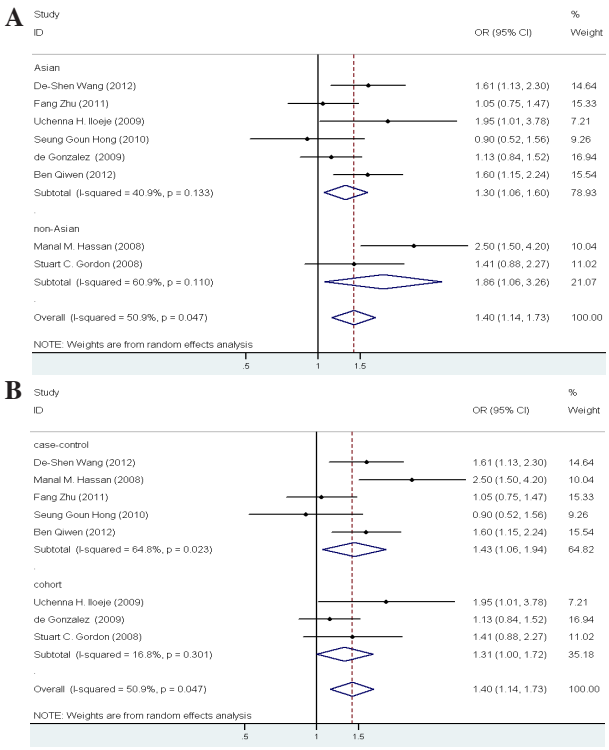

Figure 2. (A) Forest plot showing overall and subgroup analysis on the association between hepatitis b infection and risk of pancreatic cancer according to region. (B) Forest plot showing overall and subgroup analyses on the association between hepatitis B infection and risk of pancreatic cancer design of studies

al., 2012), two in USA (Hassan et al., 2008; Gordon et al., 2009). The selection of controls varied substantially. Controls were acute patients (Hassan et al., 2008; Hong et al., 2010; Zhu et al., 2011; Ben et al., 2012; Wang et al., 2012), patients with active HBV infection (Gordon et al., 2009), or volunteers for checkup (de Gonzalez et al., 2008; Gordon et al., 2009; Iloeje et al., 2009). All groups of controls appeared to be selected on the basis of convenience. The pantients and controls were frequency matched by age and sex in all the studies. The Newcastle-Ottawa Scale (Wells et al., 2000) was adopted in our

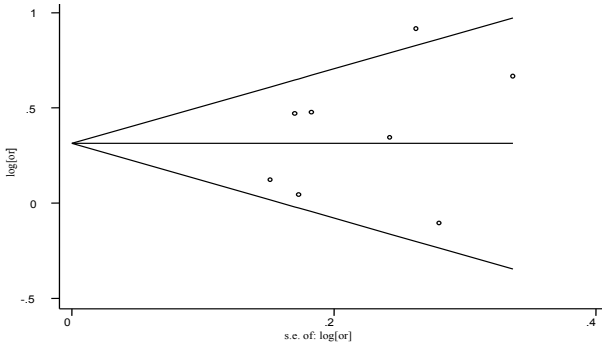

Figure 3. Begg's Funnel Plot with Pseudo 95% Confidence Limits

quality assessment. The assessment result was shown in Table2A and Table2B. The full score was nine and all studies scored six or higher.

Main results of analysis

In Figure 2, the overall OR was estimated for HBV positive patients vs negative people from all the studies. The summary OR of pancreatic cancer from all combined studies was 1.403 (95%CI: 1.139-1.729, *P*=0.001). There was significant heterogeneity across the studies (Q=14.27, *P*=0.047, I^2= 50.9%). Figure 2(A) showed the ORs from the studies conducted in Asia and two studies conducted in USA. The summary OR of Asian was 1.300 (95% CI: 1.057-1.600, *P*=0.013) for HBV positive patients, and OR of non-Asian was 1.862 (95% CI: 1.0063-3.260, *P*=0.030). There was no significant heterogeneity between the six studies conducted in Asia (Q=8.46, *P*=0.133, I^2=40.9%) and the two studies in USA (Q=2.56, *P*=0.110, I^2=60.9%). Figure 2(B) showed the ORs according to the five case-control studies as well as three cohort studies. The summary OR of the five case-control studies was 1.432 (95% CI: 1.056-1.942, *P*=0.021) with significant heterogeneity between studies (Q=11.37, *P*=0.023, I^2= 64.8%). The summary OR of the three cohort studies was 1.307 (95% CI: 0.996-1.716, *P*=0.054) with no statistical heterogeneity between studies (Q=2.40, *P*=0.301, I^2=16.8%). Because of the heterogeneity of the studies

included, a meta-regression was conduct but without identifying potentially important sources of between-study heterogeneity.

There was no indication of publication bias from either Egger's (P=0.375) and Begg's (P=0.536) tests or visualization of the Begg's funnel plot (Figure3). A sensitivity analysis which was performed to evaluate the stability revealed that there was no significant impact on the overall results with removal of any of the studies.

Discussion

In this meta-analysis, we reviewed the case-control studies and cohort studies with the information of chronic hepatitis B infection and pancreatic cancer in four countries or regions. The overall result suggests that chronic hepatitis B virus infection can cause about 40.7% increase in the risk of pancreatic cancer. However, Sub-group analysis showed that this markedly increased risk was largely attributed to the summary risk estimates from case-control studies and only a borderline significant association was observed when combining all cohort studies. Given a cohort study was more powerful to detect a causal relationship than a case-control one; this result should be interpreted with caution.

Chronic hepatitis B virus infection is one of the most serious infections and a major risk factor for deaths from cirrhosis and liver cancer (Fattovich et al., 2004; EI-Serag., 2012). Although the prevalence of chronic hepatitis B virus infection decreased in most regions, the absolute number of chronic hepatitis B virus infection patients has increased, and in Eastern Asia, the disease is still endemic (Chang, 2011). Just like patients with hepatocellular carcinoma (HCC), cirrhosis of chronic hepatitis B, HBV antigens and hepadnaviral DNA can be found in pancreatic tissue also. In some cancers (cerval cancer, gastric cancer) associated with infectious organisms, direct infection plays an important role in the course of malignant transformation. The immune reaction of the host caused by virus can lead to a series of result such as inflammation and even cancer. With HBV DNA integrating into the cellular genome, the function of anti-oncogenes would be disrupted and oncogenes be stimulated (Mason et al., 1993). These may be the possible mechanisms whereby hepatitis B virus could cause pancreatic cancer.

The hepatitis B virus infection incidence is still heperendemic in Eastern Asia and in sub-Saharan Africa with the HCC incidence rates of more than 20 per 100000 persons (EI-Serag, 2012), so more attention was paid to the outcome of chronic hepatitis B virus infection in East Asia. HBV genotypes have different ethnic distributions. In Eastern Asia, HBV genotypes B and C are more common (Kao et al., 2003; Ni et al., 2004). Six of the included studies were conducted in Eastern Asia to focus on the injury on pancreas of HBV positive patients. The result of sub-analysis is significant.

Heterogeneity across studies is often a concern in a meta-analysis. It was not surprising that a certain degree of heterogeneity was observed given the between-study variation, such as race, study design and sample source et al. The degree of heterogeneity was somewhat attenuated among the studies conducted in Asian, suggesting that race may be a potential source of heterogeneity. However, meta-regression was adopted and no variables were identified as a potential contributor to heterogeneity.

Some potential limits should be considered in the current meta-analysis. First, studies have showed that the association between chronic hepatitis B virus infection and pancreatic cancer can vary by anti-HBc or anti-HBe or HBsAg. Our meta-analysis was based on estimates without adjust by assessment of hepatitis B virus, which could be one of potential limitations. Second, geographic and ethnic distributions of HBV genotypes may affect the result and indicate selection bias, population stratification, or genotyping errors. Third, since we only searched paper in English and Chinese, the completeness of evidence is impeded by language bias. The last but not the least is about the number of included studies. More studies especially cohort studies about the association of HBV infection and pancreatic cancer are need to be conducted to update the result.

In conclusion, the current meta-analysis showed that hepatitis B virus infection may increase the risk of pancreatic cancer. Well-designed cohort studies are warranted to confirm this association.

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