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Review Article

Correlation between primary biliary cirrhosis and cancer risk: a meta-analysis

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Abstract: Primary biliary cirrhosis (PBC) is one auto-immune liver disease. Tumorigenesis is not only dependent on the properties of cancer cells but also by interaction with the immune system. However, the relationship between PBC and cancer risk remains poorly understood. The aim of this study is to systematically evaluate the correlation between PBS and cancer risk. Literature reviews on English database (PubMed, The Cochrane Library and OVID) and Chinese journal database (Chinese Journal Full-Text Database, Wanfang Data, VIP database, and Chinese Biological Medical Disc) were performed using computer and manual retrieval. In a time period until October 2015, all literatures studying the correlation between PBC and cancer risk were evaluated by Cochrane approach for determining 95% confidence interval (CI). After data extraction and quality evaluation, Stat 11 software was use to perform meta-analysis. A total of 17 studies in 16 literatures were included. Meta-analysis revealed the overall cancer risk of PBC patients at 5.5 (95% CI, 3.84-7.27). The combined test rate of cancer in PBC patients was 3.42 (95% CI, 2.39-4.45). Stratified analysis found higher cancer risk of PBC patients in Asia compared to those in America or Europe but lower than Oceanic regions. Those patients ≤56 years old had higher risk of liver cancer or total cancer compared to people >56 years old. Males PBC patients had higher cancer risk compared to females. Bias estimation revealed no publication bias, while sensitivity analysis found stable and reliable results. In summary, PBC patients had elevated risk of cancer, especially liver cancer risk.

Keywords: Primary biliary cirrhosis, liver cancer, meta-analysis

Introduction

Primary biliary cirrhosis (PBC) is one auto-immune liver disease with unknown reason. Pathological features of PBC mainly include chronic non-suppurative damage of minute bile duct, inflammation in portal area, chronic progressive cholestasis and liver fibrosis, and eventually liver cirrhosis or liver function failure [1-3]. PBC is commonly occurred in middle-aged females, with about 90% patients as females. With a slow and insidious onset, PBS disease course can be divided into asymptomatic stage, symptom stage and pre-terminal stage. Clinical symptoms of PBC include fatigue, skin itches and jaundice.

Increasing evidence demonstrated that tumorigenesis is not only dependent on the properties of cancer cells but also by interaction with the immune system [4]. Furthermore, tumors can evade immune destruction via the dysregulation of co-inhibitory or checkpoint signals [4], indicating abnormal immune response might play an important role in the development of tumor. Given the association of dysregulation of immune response with the pathogenesis of PBS, about 0.76%-5.9% PBS patients eventually had hepatocellular carcinoma even most of them developing into liver function failure [5], suggesting some risk factors might exist driving PBS into carcinoma, as furtherly demonstrated by a higher risk of malignant tumors such as breast cancer or pancreatic cancer observed in PBC patients. However, due to the lack of clear cancer risk factor in PBC patients, the correlation between PBC and malignant tumor is debatable so far, probably due to lower incidence, and variations in ethical group or sample size across studies [6]. This study thus collected all literatures regarding PBC and cancer risk and performed a meta-analysis, in

Table 1. Basic information of included studies

First author	Year	Country	PBC case number	Sex	Age of diagnosis	Cancer type (N)	Follow-up period (year)	Sources of cases
Harada K [8]	2013	Japan	2946	F/M	56.5	Liver (71)	4.8	PB
Panjala C [9]	2007	Ireland	2192	F	65	Lymphoma (7)	4.5	PB
Howel D [10]	1999	UK	769	F/M	63	Total (50): Liver (8); Breast (6); Digestive tract (6); Respiratory system (10); Urinary system (1); Hematological system (4)	5.4	PB
Tomiyama Y [11]	2013	Japan	210	F/M	58	Liver (11)	8.5	HB
Rong G [12]	2015	China	1865	F/M	65.1	Liver (70)	5.5	HB
Kuiper EM [13]	2010	New Zealand	375	F/M	54.7	Liver (9)	9.7	HB
Su CW [14]	2008	China	96	F/M	55.6	Liver (5)	3.96	HB
Ngu JH [15]	2012	New Zealand	71	F/M	60	Total (50): Colon-rectum (1); Breast (1); Lung (3); Hematological system (2); Gynecologic organs (1); Non-melanoma (1); Others (2)	9	PB
Goldacre MJ [16]	2008	Germany	2120	F/M	NA	Total (29): Liver (8); Rectum (1); Stomach (2); Pancreas (3); Kidney (1); Gall bladder (3); Esophagus (1); Rectum (2); Breast (5); Lung (3)	NA	HB
Jackson H [17]	2007	Germany	930	F/M	NA	Total (42): Liver (7)	NA	PB
Cavazza A [18]	2009	Spain	389	F/M	52.2	Liver (13)	9.5	HB
Cavazza A [18]	2009	Italy	327	F/M	50.9	Liver (11)	9.1	HB
Nijhawan PK [19]	1999	USA	1689	F/M	NA	Total (93): Liver (15); Breast (15); Gastrointestinal tract (15); Gynecologic organs (13); Lung (9); Others (26)	4.4	HB
Shibuya A [20]	2002	Japan	396	F/M	59	Liver (14)	3.6	HB
Floreani A [21]	1999	Italy	109	F/M	50.8	Total (11): Liver (3); Breast (2); Melanoma (2); Endometrioma (1); Colon-rectum (1); Kidney (1); Non-Hodgkin's lymphoma (1)	6.8	HB
Landgren AM [22]	2011	USA	5718	M	50.74 or 57.67	Total (362): Liver (80); Oral cavity (124); Esophagus (35); Stomach (23); Rectum (46); Colon (21); Pancreas (33)	12.02 or 7.47	HB
Weinmann A, et al. [23]	2015	USA	480	F/M	68	Liver (36)	NA	HB

Table 2. Quality of literatures based on NOS scale

Study	Sample selection				Comparability (Correction of confounding factors)	Results			Total score
	Representativeness of exposure cohort	Selection of non-exposure cohort	Confirmation of exposure	Whether disease occurred before study		Measurement of results	Longer follow-up	Complete follow-up	
Harada K [8]	0	0	1	1	2	1	1	1	7
Panjala C [9]	0	0	1	1	0	1	1	1	5
Howel D [10]	1	1	1	1	1	1	1	1	8
Tomiyama Y [11]	0	0	1	1	2	1	1	1	7
Rong G [12]	1	1	1	1	2	1	1	1	9
Kuiper EM [13]	1	0	1	1	2	1	1	1	8
Su CW [14]	1	0	1	1	2	1	1	1	8
Ngu JH [15]	1	0	1	1	2	1	1	1	8
Goldacre MJ [16]	1	0	1	0	1	1	0	0	4
Jackson H [17]	1	1	1	1	2	1	0	1	8
Cavazza A [18]	0	0	1	1	1	1	1	1	6
Nijhawan PK [19]	0	0	1	1	1	1	1	1	6
Shibuya A [20]	0	0	1	1	2	1	1	1	7
Floreani A [21]	0	0	1	1	2	1	1	1	7
Landgren AM [22]	0	0	1	1	2	1	1	1	7
Weinmann A, et al. [23]	0	0	1	1	0	1	0	1	3

order to evaluate the correlation between PBC and risk of various cancers.

Material and methods

Literature search and evaluation

Both English database (PubMed, The Cochrane Library and OVID database) and Chinese database (Chinese Journal Full-Text Database, Wanfang Database, VIP database, and Chinese Biological Medical Disc) were searched using keywords “primary biliary cirrhosis”, “cancer or malignance” and “tumor or carcinoma” until October 2015. Two independent researchers performed screening of papers according to the inclusive and exclusive criteria, and extract data including first author, publication year, cancer type and case number, effect indicators and follow-up times. Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of all included literatures [6].

Literature screening criteria

Inclusive criteria: (1) Case-control or cohort study; (2) All patients fitted PBC diagnostic standard according to international guideline (1); (3) Using cancer as the final indicator; (4) Available cancer incidence, standardized rate, risk ratio and 95% confidence interval (CI).

Exclusive criteria: (1) Individual case report: (2) Duplicated reports; (3) Cancer diagnosis before onset of PBC.

Quality assessment

Quality assessment was performed using the Newcastle-Ottawa Scale (NOS) as previously described [6, 7]. For the assessment, a star system of the NOS has been developed. A maximum of one star represents each numbered item within the selection and exposure categories. Whereas, a maximum of two indicates comparability. In this study, 0-3 stars, 4-6 stars, or 7-9 stars are defined as a low-, moderate-, or high-quality study, respectively.

Statistics and analysis

Stata 11 software was used to perform meta-analysis on all included literatures. Heterogeneity test was firstly performed on all included data. Based on the study variation, a fixed-effect model ($P \geq 0.1$, $I^2 < 50\%$) was selected for meta-analysis. Otherwise, random-effect model was used in meta-analysis. Further subgroup or sensitivity analysis was employed regarding those factors that possibly result in heterogeneity. Begg’s rank correlation method was used in quantitative test for plotting funnel plot, whose symmetry indicated effective management of publication bias.

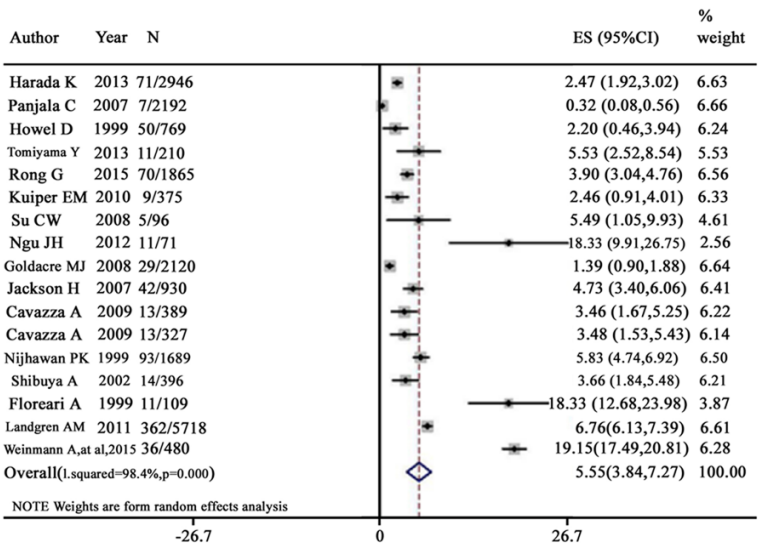

Figure 1. Meta-analysis of PBC and overall cancer risk.

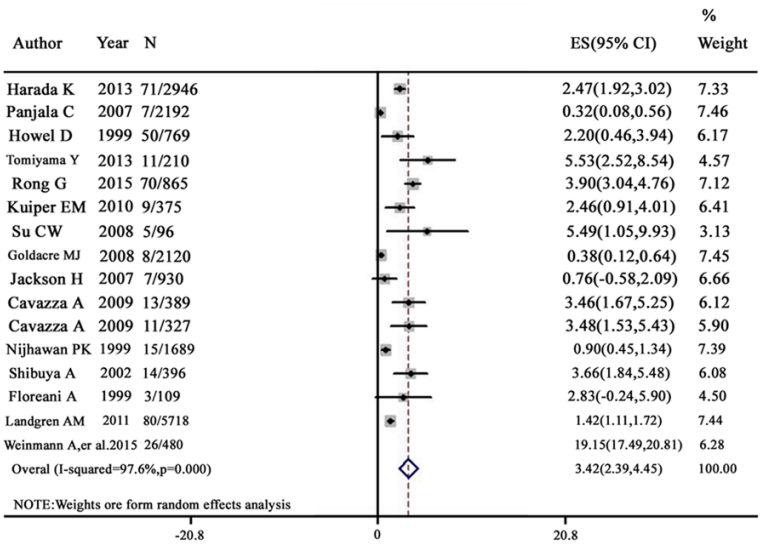

Figure 2. Meta-analysis of PBC and liver cancer risk.

Results

Literature search

A total of 49 English literatures were obtained from primary screening based on title and abstract. 15 of them were included based on criteria. In searching Chinese papers, 5 were automatically obtained and 1 of them was included. In sum, a total of 17 independent studies from 16 publicized papers were included in this analysis (**Table 1**).

Evaluation of method quality in all included studies

Using NOS scale to perform quality evaluation on all included studies. In all 8 items of NOS including sample selection, comparability, exposure evaluation/result, most of papers included in this study were of high quality, as all literatures had NOS score higher than 7, except for 5 papers at moderate quality (4-6 points) [9, 16, 18, 19, 23]. See **Table 2** for details.

PBC and the risk of overall cancer/liver cancer

By combined and heterogeneity analysis of effective rate on all 17 studies, I^2 value was determined as 98.4%, suggesting heterogeneity across studies. Random effect model was then used to combine all studies and obtained the overall cancer incidence of PBC patients as 5.5% (95% CI, 3.84%~7.27%). When checking all 16 studies mentioning liver cancer, the incidence of liver cancer in PBC patients was deduced as 3.42% (2.39%~4.45%). The forest graphs of effective rate and combined results were shown in **Figures 1** and **2**.

Stratified analysis of correlation between PBC and overall cancer/liver cancer risk

We utilized Stata 11.0 software to analyze possible factors affecting the correlation between PBC and overall cancer/liver cancer risk in a stratified manner, mainly considering three factors including sample population regions, age of PBC diagnosis and sex. From **Table 2**, sample population or diagnostic age was not the source of higher heterogeneity and combined effective rate. Such heterogeneity mainly

Table 3. Stratified analysis of overall cancer/liver cancer risk in PBC patients

Subgroup	Overall cancer				Liver cancer			
	N	Combined rate	95% CIs	I^2 (%)	N	Combined rate	95% CIs	I^2 (%)
By regions								
Asia	8	6.72	2.29-11.14	98.6	8	6.72	2.29-11.14	79.7
Europe	6	3.13	1.8-4.48	98.4	6	1.33	0.72-1.95	72.1
America	2	6.4	5.52-7.29	52.4	2	3.42	2.39-4.45	97.6
Oceanic	1	18.33	9.91-16.75	-	0	-	-	-
Sample population								
General people	5	3.06	1.15-4.97	98	4	1.4	-0.02-2.82	94.2
Hospital	12	6.32	3.9-8.74	96.1	12	4.26	2.74-5.78	98.0
Average age								
≤56 years	6	8.6	2.02-15.18	98.4	6	6.17	-0.06-12.4	98.2
>56 years	7	3.32	1.67-4.98	96.6	6	2.81	1.22-4.4	95.9
Unclear	4	4.67	1.57-7.77	98.4	4	0.88	0.26-1.49	88.4
Sex								
Male	11	5.99	3.88-8.11	59.3	12	3.91	2.71-5.10	24.1
Female	12	3.39	2.11-4.67	94.0	12	2.39	1.61-3.17	80.1

Table 4. Combined effective rate of all cancers

Cancer	N	Combined effective rate (%)	95% CI (%)	I^2 (%)
Overall	17	5.5	3.84-7.27	98.4
Liver	16	3.42	2.39-4.45	97.6
Breast	4	0.64	0.15-1.13	69.8
Lung	3	0.21	0.07-0.35	72.3
Colon	2	0.273	0.15-2.12	96.3
Colon-rectum	2	1.08	-0.42-2.57	0
Rectum	2	0.14	0.06-0.22	91.3
Pancreas	2	0.312	0.19-0.43	91.5
Gynecologic organs	2	0.79	0.39-1.20	1.2
Hematological system	2	0.561	0.06-1.07	31
Gastrointestinal tract	2	0.863	0.50-1.23	0
Stomach	2	0.224	0.121-0.33	88.2
Esophagus	2	0.164	0.08-0.25	96.2
Kidney	2	0.053	-0.04-0.15	0

came from females. Meanwhile, Asian PBC patients had higher risk of cancers than patients in America or Europe, but lower than Oceanic regions. The risk of liver cancer in Asian PBC patients was also higher than America or Europe. Those PBC patients with primary diagnosis on or before 56 years had higher cancer risk than those received primary diagnosis after 56 years old. Moreover, male PBC patients had higher cancer risk than females (**Table 3**).

PBC and other cancer risk

We analyzed all cancers that were reported in more than two literatures in our database. Combined effective rates were smaller than 1% in all cancer types except for overall, liver and colorectal cancer (**Table 4**).

Publication bias and sensitivity analysis

Using Begg rank correla-tion approach, the publication bias was quantitatively analyzed. As Z=0.66 (P=0.510, Z<1.96, P>0.05), there was little chance that publication bias existed in the current study. In sensitivity test, we rejected 3 articles [15, 21, 23]. The single rejection of those articles decreased the effective rate by 1.61%, 1.92% and 1.91%, respectively. No significant change occurred before and after rejection, suggesting stable and reliable of the combined result (**Figure 3**).

Discussion

PBC is one autoimmune disease causing cholestasis with unclear reasons. It manifested as slow progression of conditions and may persist for couple of years without direct oncogenic factors [1]. Till now, there are several studies investigating risk of malignancy in PBC patients, however, no consensus has been achieved regarding the association of PBC with malignancy as some studies demonstrating an

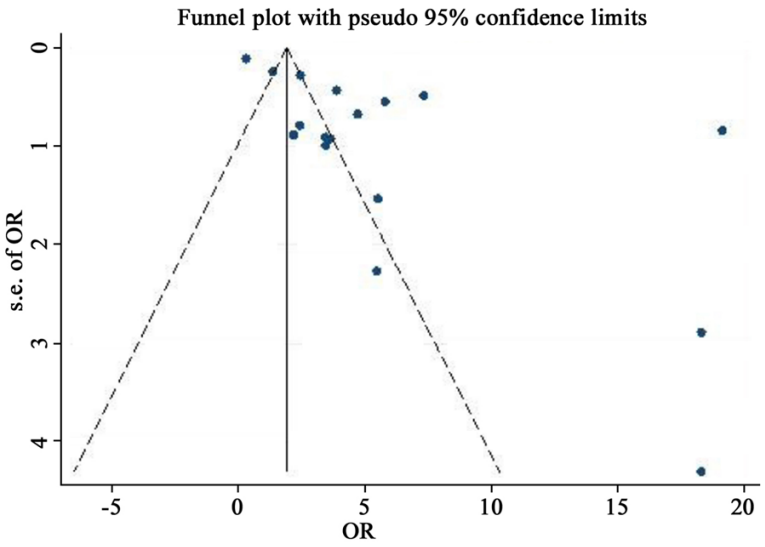

Figure 3. Funnel plot of PBC and overall cancer risk.

increased overall cancer risk in PBC patients and others not [10, 15, 16, 19]. In this study, through meta-analysis of several published studies, we investigated the cancer risk in PBC patients and demonstrated that the first four popular cancers in PBC patients were liver cancer, colorectal cancer, gastrointestinal cancer and breast cancer.

Liver cancer is one common malignant tumor with insidious onset, and atypical symptoms during early stage but with rapid progression [24]. At the time of diagnosis, liver cancer is frequently already at focal terminal stage or with metastasis, thus causing unfavorable prognosis and short survival time. its incidence in PBC patients remains poorly understood. Risk factors for liver cancer include viral infection, aspergillus toxicity, alcoholic toxicity and liver metabolic disorders [25]. Some studies reported that PBC might increase liver cancer risk. Other reports indicated that PBC patient had lower rate of liver cancer. One reason for the controversy is that PBC is a relatively rare disease. Thus, the sample size was usually small in the majority of studies. In this study, we performed a systematic analysis of all 15 articles included. A total of 20481 PBC cases were included, and 673 liver cancer cases were identified during the follow-up period. The combined effective rate of hepatocellular lesion in PBC patients was 3.42%, suggesting that PBC could increase liver cancer risk. Due to limited numbers of studies include in the present study, large cohort clinical studies as well as epidemiology surveys were required to confirm the correlation between PBC and liver cancer. Another reason for the controversy regarding the association of PBC with liver concer is that there are some geographical and environmental differences between studies. Therefore, in the present study, we also performed a stratified analysis including population regions, PBC diagnosis age and sex for the correlation between PBC and overall/liver cancer risk. Our results showed that Asian PBC patients had higher cancer risk than American or European patients but lower than New Zealand people. In addition, those people equal or younger than 56 years had higher overall/liver cancer risk than those PBC patients over 56 years old. In addition, male PBC patients were more susceptible to cancer than females.

A total of 16 papers regarding PBC and cancer risk were included in this study. NOS scale was used to evaluate the quality of literatures, and revealed 11 of them reaching high quality (≥7 scores) and 5 of them moderate quality (4-6 scores). Meanwhile we also performed bias analysis and sensitive analysis for all included articles. Bias analysis revealed minor publication bias in all literatures. Sensitivity analysis showed decreased combined effective rate after rejecting 3 articles, whilst no significant change of combined effective rate with the deletion of any of the remaining 13 articles, suggesting stable and reliable results.

In summary, this study showed that PBC patients had elevated risk of cancers, especially for liver cancer, suggesting regular screening for HCC with cross-sectional imaging with or without alpha-fetoprotein at 6- to 12-month intervals should be advised for PBC patients according to the AASLD Practice Guidelines,

Disclosure of conflict of interest

None.

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