

Risk factors for primary liver carcinoma in Chinese population

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Abstract

AIM: To evaluate the risk factors for primary liver carcinoma (PLC) in Chinese population.

METHODS: Chinese Biomedical Literature Database, China Hospital Knowledge Database and MEDLINE were searched. All the related literatures were screened, and the risk factors for PLC in Chinese population were studied. Heterogeneity was evaluated by odds ratio (OR) q test. Combined OR and its 95% confidence interval (95%CI) were calculated, the association between the investigated risk factors and PLC was determined. Validity and bias of the findings were evaluated by sensitivity analysis and funnel plot analysis respectively.

RESULTS: Fifty-five of one hundred and ninety identified studies were accepted according to the inclusive criteria. Ten factors related to PLC were demonstrated by sensitive analysis and funnel plot analysis. They were cirrhosis (OR = 11.97, P = 0.000), HBV infection (OR = 11.34, P = 0.000), HCV infection (OR = 4.28, P = 0.000), family history of liver cancer (OR = 3.49, P = 0.000), unstable emotion (OR = 2.20, P = 0.000), depressed characters (OR = 3.07, P = 0.000), aflatoxin (OR = 1.80, P = 0.000), alcoholic (OR = 1.88, P = 0.000), intake of musty food (OR = 1.87, P = 0.000) and drinking contaminated water from pond (OR = 1.77, P = 0.003).

CONCLUSION: The main risk factors for PLC in China are liver diseases, family history of liver carcinoma, poor psychic status, aflatoxin, and some unhealthy behaviors.

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Key words: Primary carcinoma; Liver; Meta-analysis; Risk factor

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INTRODUCTION

Primary liver carcinoma (PLC) affects more than 500 000 people globally with 110 000 deaths annually. More than one-half of them were Chinese^[1]. The incidence rate is 14.58-46 per 100 000 people. In Qidong, Jiangsu Province and Fusui, Guangxi Zhuang Autonomous Region, the morbidity is higher than that in any other areas of China.

It is known that persistent hepatitis B virus (HBV) and HCV infection and aflatoxins are the main causes of PLC^[1]. However, most of the investigations were case-control studies. The real risk factors for PLC may be far more than the known causes. The results from different investigated areas are variable. Cohort study on risk factors for PLC in Chinese people is still not available. A meta-analysis confined to case-control studies published from January 1966 to December 2003 was carried out.

MATERIALS AND METHODS

Search strategy

The databases including Chinese Biomedical Literature Database (1979-December 2003), China Hospital Knowledge Database (1994-December 2003) and MEDLINE (1966-December 2003) were searched. The following keywords were used: liver cancer, liver carcinoma, primary liver cancer, primary liver carcinoma, malignant liver tumors, primary liver tumors, hepatocellular carcinoma, hepatocellular cancer, risk factor, cause, etiology, case-control study. In the search of MEDLINE, the keywords of Chinese population, Chinese and China were added. Further studies were identified through scanning reference lists of relevant articles, reviews, and textbooks. Articles published in both English and Chinese were accepted. To eliminate irrelevant studies, the title and abstract of the articles were screened at first, and then the whole texts of selected paper were examined for further screening based the inclusive criteria.

Inclusion and exclusion criteria

Inclusion criteria in the meta-analysis included case-control studies investigating the risk factors for PLC in Chinese population, the data from the articles including the background of population and time investigated, the articles that reported original data or statistical results of odd ratio (OR) and its 95% confidence interval (95%CI), the studies based on similar diagnostic criteria of PLC.

Exclusion criteria in the meta-analysis were poor methodological quality^[2], the republished studies, and no sufficient data and/or results in the article.

Data selection and study appraisal

Data used in this study included year of publication, number of case and control, characteristics of patients and control

(gender, age, native place, and living place), suspected risk factor and its definition of exposure, diagnostic criterion of PLC, and outcomes (OR value and its 95%CI of each factor should be provided, if the article did not report the results in the form of OR, we calculated OR and its 95%CI based on the given data).

Two researchers extracted the data from each study independently and any disagreements were discussed for consensus. Quality of the study was assessed by the guideline of Lichtenstein^[2].

Statistical analysis

OR q test for heterogeneity was used to examine gross statistical heterogeneity among included studies. If K studies were included, $OR_i (i = 1, 2, \dots, K)$ was OR of the investigated factors in each study, OR_{ui} and OR_{li} were the upper and lower limit of its 95%CI respectively. V_i was variance calculated by the formula of $V_i = [\ln(OR_i/OR_{li})/1.96]^2$ or $V_i = [\ln(OR_{ui}/OR_i)/1.96]^2$. Weight (W_i) was calculated by $W_i = 1/V_i$. Supposed $y_i = \ln(OR_i)$ and $y_w = (\sum W_i y_i) / (\sum W_i)$. The heterogeneity among included studies was tested by $q = \sum [W_i (y_i - y_w)^2]$. If the q value was low ($P > 0.05$), the results of the included studies were considered as significant homogeneity, otherwise significant heterogeneity existed among studies^[3,4].

The association between investigated factors and PLC was presented as OR and its 95%CI. If the studies had no significant heterogeneity demonstrated by OR q test, fixed-effect model was used to calculate the combined OR and its 95%CI. Otherwise, random-effect model was used. Combined OR value greater than one indicated a risk factor for PLC. The significance of the combined OR was tested by $\chi^2 = (\sum W_i y_i)^2 / (\sum W_i)$ with $g = 1$ ^[3,4], and the significant level was $P = 0.05$.

Sensitivity analysis was performed through fixed-effect model and random-effect model. Coherence of the results from two models indicated a valid outcome^[4].

Funnel plot analysis was used to assess the potential bias, and its symmetry was tested through linear regression model. Intercept 95%CI of linear regression function spanning 0 and its significant level greater than 0.1 indicated symmetric funnel plot^[4].

RESULTS

Description of studies

Fifty-five of 190 identified studies were included in meta-analysis after the quality assessment of each study. They were published in Chinese in 1984-2002. The investigated people were from 24 cities located in 13 different provinces of China.

The investigated factors included liver diseases, family history, psychic status, past history of exposure to poison and style of living. The factors for liver diseases were from 26 studies of HBV infection, 15 of HCV infection, 9 of liver cirrhosis, and 20 of hepatitis history. There were 25 studies on family history of liver carcinoma. Psychological factors for PLC included 10 for negative living events, 6 for unstable emotions, and 6 for depressed characters. The past history of exposure to poison was from five studies of

pesticide and four of aflatoxin. The living style included nine factors: drinking (22 studies), smoking (15 studies), intake of musty food (3 studies), intake of pickle (5 studies), intake of bean product (4 studies), tea (4 studies), drinking water from pond (8 studies), drinking water from river (2 studies), and drinking water from well (5 studies).

Heterogeneity of studies

OR q test was carried out in included studies (Table 1). No significant heterogeneity existed among the studies on HCV infection, unstable emotion, past history of exposure to aflatoxin, and intake of musty food ($P > 0.05$). The remaining factors in the studies all had significant heterogeneity ($P < 0.05$).

Association of outcomes

Association between the factors and PLC was shown by combined OR and its 95%CI. If heterogeneity was significant, OR was combined with random-effect model, otherwise, fixed-effect model was used (Table 2). The OR and its 95%CI of five factors including past history of exposure to pesticide, intake of bean products, tea, drinking water from river and well had no statistical significance ($P > 0.05$). According to the value of OR, the strength of association in descending turn was liver cirrhosis, HBV infection, history of hepatitis, HCV infection, family history of liver carcinoma, depressed character, negative living events, unstable emotion, alcoholic, intake of musty food, aflatoxin, drinking water from pond, intake of pickle, and smoking, with their OR value greater than one, 95%CI beyond one. There was a statistical significance ($P < 0.05$).

Sensitive analysis

The combined OR and its 95%CI of each factor were calculated by both fixed-effect model and random-effect model, and coherence of the results was assessed. The factors of exposure to pesticide and drinking water from well showed conflicting results from two models (combined OR and its 95%CI of fixed-effect model were 1.69 (1.24 and 2.29) and 0.74 (0.58 and 0.96) respectively). Other factors showed similar results from two models.

Funnel plot

Since only two studies were involved in the factor of drinking water from river, funnel plot analysis was insignificant. According to the linear regression models of funnel plots, four factors including history of hepatitis, negative living events, smoking, and intake of pickle existed as asymmetric funnel plots with their intercept 95%CI beyond 0 and $P < 0.1$. Other factors showed symmetry funnel plots with their intercept 95%CI spanning 0 and $P > 0.1$ in their linear regression models.

DISCUSSION

A considerable number of chemical agents have been proved to be directly carcinogenic for liver malignant tumor in animal experiments, and also most likely in human beings^[5]. But still no evidence is presented as yet. It was reported that the risk factors for PLC include hepatitis viruses, liver

Table 1 Heterogeneity of investigated factors

Factors	Included studies	<i>q</i>	<i>P</i>
Liver diseases			
HBV infection	26	74.72	0.000 ^b
HCV infection	15	10.68	0.711
Liver cirrhosis	9	23.61	0.003 ^b
History of hepatitis	20	104.13	0.000 ^b
Family history			
Family history of PLC	25	96.95	0.000 ^b
Psychological factors			
Negative living events	10	25.54	0.002 ^b
Unstable emotion	6	3.46	0.630
Depressed character	6	12.69	0.027 ^a
Past history of exposure to poison			
Pesticide	5	16.99	0.002 ^b
Aflatoxin	4	3.47	0.325
Living style			
Alcoholic	22	82.13	0.000 ^b
Smoking	15	24.58	0.039 ^a
Intake of musty food	3	3.72	0.156
Intake of pickle	5	23.73	0.000 ^b
Intake of bean products	4	18.56	0.000 ^b
Tea	4	16.03	0.001 ^b
Drinking water from pond	8	649.10	0.000 ^b
Drinking water from river	2	9.05	0.003 ^b
Drinking water from well	5	10.44	0.034 ^a

The values of *q* shown are statistical values of OR *q* test. ^a*P*<0.05 vs significant difference. ^b*P*<0.01 vs very significant difference.

Table 2 Summary of the association between factors and PLC

Factors	Total case/control	Combined OR	95%CI	χ^2 (<i>g</i> = 1)	<i>P</i>
Liver diseases					
HBV infection	3 390/4 604	11.34	8.72-14.75	327.60	0.000 ^b
HCV infection	1 737/2 534	4.28	3.30-5.56	119.93	0.000 ^b
Liver cirrhosis	1 689/2 609	11.97	6.19-23.19	54.46	0.000 ^b
History of hepatitis	3 625/4 903	5.71	4.11-7.92	108.12	0.000 ^b
Family history					
Family history of PLC	3 681/4 932	3.49	2.68-4.53	87.24	0.000 ^b
Psychological factors					
Negative living events	1 688/2 096	2.65	1.69-4.15	17.90	0.000 ^b
Unstable emotion	1 502/2 086	2.20	1.74-2.77	44.48	0.000 ^b
Depressed character	1 355/1 777	3.07	2.10-4.47	33.99	0.000 ^b
Past history of exposure to poison					
Pesticide	755/969	1.55	0.82-2.93	1.84	0.175
Aflatoxin	327/327	1.80	1.44-2.25	26.90	0.000 ^b
Living style					
Alcoholic	3 207/3 983	1.88	1.53-2.32	35.60	0.000 ^b
Smoking	2 408/3 347	1.24	1.09-1.41	10.90	0.001 ^b
Intake of musty food	623/723	1.87	1.42-2.47	19.74	0.000 ^b
Intake of pickle	1 233/1 602	1.69	1.34-2.13	47.56	0.000 ^b
Intake of bean products	814/1 158	0.74	0.29-1.90	0.13	0.718
Tea	656/870	0.69	0.31-1.51	0.88	0.348
Drinking water from pond	1 561/1 614	1.77	1.09-2.87	8.65	0.003 ^b
Drinking water from river	379/437	1.41	0.38-5.19	0.27	0.603
Drinking water from well	636/856	0.79	0.45-1.36	7.99	0.392

The values of χ^2 shown are statistical values of significant test of combined OR. ^b*P*<0.01 vs significant difference.

diseases, mycotoxins or phytotoxins, nutrition, social drugs, metabolic diseases, chemical agents, inorganic substances, medication, and ionizing radiation. However, in 10–15% of patients, there is no risk factor for the development of PLC^[5]. This study investigated the association between possible risk factors and PLC in Chinese population by meta-analysis of case-control studies published in the past 37 years, and demonstrated the risk factors for PLC in Chinese population.

This study analyzed 19 suspected risk factors for PLC.

The combined outcomes showed that liver diseases were the most important factors for PLC with much a greater OR value than any other factor. Both liver cirrhosis and HBV infection were strongly associated with PLC, with their OR being 11.97 and 11.34 respectively (*P*<0.05). The association between HCV infection and PLC was moderate, with its OR being 4.28 (*P*<0.05). Though history of hepatitis was significantly associated with PLC, its funnel plot was asymmetric. Therefore this outcome might have bias, possibly due to the published bias, and heterogeneity from

the different definitions of history of liver diseases in the included studies. Family history of PLC was another risk factor for PLC, with its OR being 3.61 ($P < 0.05$), suggesting that people with family history of PLC have a higher risk. Poor psychological status can strengthen the risk for PLC. In this meta-analysis, the factors for unstable emotion and depressed character were significantly associated with PLC, with their OR being 2.20 and 3.07, respectively ($P < 0.05$). The funnel plot of negative living events was asymmetric though its combined OR was significant. The reason may be the published bias, and the conclusion on negative living events could not be made. In regard to exposure to poison, two factors including exposure to aflatoxin or pesticide were investigated. It was demonstrated that aflatoxin played an important role in PLC^[5]. In this meta-analysis, the outcome showed that aflatoxin was also a risk factor for PLC in Chinese population, with its OR being 1.80 ($P < 0.005$), but it seems to be trivial when compared to the factors for liver diseases, family history of PLC and poor psychological status. The results indicated that there was no significant association between exposure to pesticide and PLC, with its OR being 1.55 ($P > 0.05$). Furthermore, this result was unreliable because it was conflicting in sensitivity analysis. Hence, it is not clear whether exposure to pesticide is a risk factor for PLC. The living habits of drinking, intake of musty food and drinking water from pond were all significantly associated with PLC (OR was 1.88, 1.87, and 1.77 respectively, $P < 0.05$), suggesting that they may enhance the risk for PLC. Though the factors of both smoking and intake of pickle had a significant combined OR (1.24 and 1.69 respectively, $P < 0.05$), it was unable to draw conclusions because of the bias demonstrated by their asymmetric funnel plots ($P < 0.1$). Drinking water from river was not significantly associated with PLC (OR = 1.41, $P > 0.05$) and its bias was difficult to analyze by funnel plot due to its limited number of the included studies. Thus it is unknown whether it is a risk factor. The ORs of intake of bean products, tea and drinking water from well were all less than 1 (OR being 0.74, 0.69, and 0.79 respectively, $P > 0.05$). These results could not demonstrate that they are protective factors for PLC. Furthermore, the result of drinking water from well was unreliable because the results were conflicting in sensitivity analysis.

Meta-analysis is a tool, but bias in meta-analysis can cause invalid results. In this study, case-control studies were included in meta-analysis. Considering the design of the included studies, validity of their results was inferior to that of prospective studies. Thus, the significance of conclusion from this meta-analysis is limited due to the design of the included studies. Since lack of qualified cohort studies on the risk factor for PLC in Chinese population, the result of this meta-analysis is valuable for further research. Test of heterogeneity is a formal statistical analysis for examining if the observed variation in study results is compatible with

the variation expected by chance^[4]. When heterogeneity is statistically significant ($P < 0.05$), the observed different results should be explained individually. Nineteen factors in the included studies were involved in this investigation, fifteen of which had significant heterogeneity. The various risk factors for PLC were possibly interactive. When an investigated factor is involved in the included studies, the difference between other risk factors and their interaction is not easy to control among studies, thus leading to the heterogeneity. Furthermore, different studies are usually undertaken in different ways, but it is hard to attribute heterogeneity to any single factor^[4]. Since the differences in the included studies are of practical significance, random-effect model is used for the factor with significant heterogeneity to make a more conservative estimation of the combined result. In the current study, some original articles were unable to be used because of their deficient data. It is difficult to estimate the effect of these missing data on the combined results. Sensitivity analysis can test the reliability of the outcomes by assessing coherence of the combined results from fixed-effect model and random-effect model. In this study, most factors passed sensitivity analysis successfully (17/19), thus proving the reliability of the results in this meta-analysis. Publication bias is associated with funnel plot asymmetry. However, the reasons for asymmetric funnel plot may include publication bias and others such as selection biases, poor methodology of smaller studies, true heterogeneity and chance^[4]. Since the funnel plots of history of hepatitis, negative living events, smoking, and intake of pickle were found asymmetric, conclusions about these factors should not be drawn due to the bias.

In conclusion, the main risk factors for PLC in Chinese population are related to liver diseases, family history of liver carcinoma, poor psychological status, aflatoxin, and bad living style. Liver diseases are most important in all these factors. Control of HBV infection, HCV infection, and liver cirrhosis is the essential measure for the prevention of PLC. In addition, balanced psychological status, avoidance of musty food or food polluted by aflatoxin-contaminated food, and no alcoholic can reduce the risk for PLC.

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