

RESEARCH ARTICLE

Relationship Between GSTT1 Gene Polymorphism and Hepatocellular Carcinoma in Patients from China

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Abstract

Objective: The results from studies on associations of the glutathione S-transferase T1 (GSTT1) gene polymorphism and hepatocellular carcinoma (HCC) risk in Chinese populations are still conflicting. This meta-analysis was performed to evaluate the relationship in detail. **Methods:** Eligible reports were recruited into this meta-analysis from the databases of PubMed, Embase, Cochrane Library and CBM-disc (China Biological Medicine Database). Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. **Results:** Eighteen investigations were identified for the analysis of association between polymorphic deletion of GSTT1 and HCC, consisting of 2,693 patients with HCC and 4,696 controls. Null genotype of GSTT1 was associated with HCC susceptibility in Chinese (OR=1.53, 95% CI: 1.28-1.82; P<0.00001). **Conclusion:** The GSTT1 null genotype is associated with HCC susceptibility in Chinese.

Keywords: Hepatocellular carcinoma - glutathione S-transferase T1 - gene polymorphism - meta-analysis

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and prevalent cancers in the human population, more than 50% of the world's HCC cases occur in China (Li & Jiang, 2011). It is well-documented that multiple risk factors contribute to hepatocarcinogenesis, including chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, cirrhosis, carcinogen exposure (such as aflatoxin B1), excessive alcohol drinking (Bayram et al., 2011). China is an important country in the Asia-Pacific region, and the HBV is the mainly risk factor for the onset of HCC. The present evidences show that the factor of gene polymorphism is associated with the risk of HCC susceptibility (Yuan et al., 2011; Dong et al., 2012). Glutathione-S-transferases (GSTs) are an enzyme superfamily involved in the Phase II metabolism, acting as primary intracellular detoxifiers and contributing to a broad range of physiological processes including cellular defense (Masoudi et al., 2011; Wang et al., 2012). Glutathione-S-transferase T1 (GSTT1) is a most important sub-group type of GSTs, and its gene polymorphism takes part in the pathogenesis of cancers. There were some investigations reporting that GSTT1 deletion was associated with cancer susceptibility (Xu et al., 2011; Aguiar et al., 2012; Ramalhinho et al., 2012).

In the past decades, most of the epidemiologic studies investigating the association of GSTT1 gene polymorphism with HCC susceptibility were conducted in Chinese populations. Unfortunately, the available

evidence is weak at present, due to sparseness of data or disagreements among the reported studies. The evidence from meta-analysis may be powerful than the individual investigation. This meta-analysis was performed to investigate whether the GSTT1 gene polymorphism was associated with the risk of HCC in Chinese population, by widely collect the reported investigations.

Materials and Methods

Search strategy for the association of GSTT1 gene polymorphism with HCC risk

The relevant studies were searched from the electronic databases of PubMed, Embase, Cochrane Library and CBM-disc (China Biological Medicine Database) on May 1, 2012. The retrieval strategy of (glutathione S-transferase T1 OR GSTT1) and (hepatocellular carcinoma OR liver cancer OR HCC) was entered into these databases mentioned above for search. The searches in Pubmed and Embase were limited in Human. Additional articles were identified through references cited in retrieved articles.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) The outcome had to be HCC; (2) There had to be at least two comparison groups (HCC group vs control group); (3) Investigation should provide the data of GSTT1 genotype distribution.

Exclusion criteria: (1) Review articles and editorials; (2) Case reports; (3) Preliminary result not on GSTT1 gene polymorphism or outcome; (4) Investigating the

Table 1. Characteristics of the Studies Evaluating the Effects of GSTT1 on HCC Risk in Chinese

First author, year	Publication language	Location	Hepatitis virus status	Control Source	Case			Control			Null frequency(%)	
					Null	Positive	Total	Null	Positive	Total	Case	Control
Dong 1997	Chinese	Jiangsu,Guangxi, Hebei	HBV	Population	63	47	110	42	70	112	57.27	37.01
Yu 1999	English	Taiwan	HBV	Hospital	41	42	83	181	194	375	49.4	48.28
Sun 2001	English	Taiwan	HBV	Population	30	37	67	77	51	128	44.78	60.16
Liu 2002	Chinese	Jiangsu	HBV	Population	34	50	84	36	108	144	40.48	20.01
Liu 2003	Chinese	Guangxi	HBV	Hospital	28	23	51	18	35	53	54.9	33.96
McGlynn 2003	English	Jiangsu	HBV	Population	116	115	231	100	156	256	50.16	38.96
Li 2004	Chinese	Jiangsu	HBV	Population	108	99	207	97	110	207	52.17	46.87
Zhang 2005	Chinese	Hubei	HBV	Population	38	22	60	34	39	73	63.33	46.58
He 2005	Chinese	Guangxi	HBV	Population	43	62	105	50	101	151	40.95	33.12
Chen 2005	English	Taiwan	HBV	Population	289	279	577	199	190	389	50.09	51.17
Deng 2005	English	Guangxi	HBV	Population	108	73	181	154	206	360	59.67	42.79
Guo 2005	Chinese	Henan	HBV	Population	58	37	95	45	58	103	61.05	43.69
Long 2005	Chinese	Guangxi	HBV	Hospital	82	58	140	234	302	536	58.71	43.67
Ma 2005	Chinese	Guangxi	HBV	Population	35	27	62	21	52	73	56.45	28.77
Long 2006	English	Guangxi	HBV	Hospital	146	111	257	297	352	649	56.81	45.77
Yang 2009	Chinese	Guangxi	HBV	Hospital	33	67	100	11	49	60	33	18.33
Kao 2010	English	Taiwan	HBV	Hospital	51	51	102	200	186	386	50	51.82
Wei 2010	Chinese	Guangxi	HBV	Population	104	77	181	276	365	641	57.46	43.06

Table 2. Meta Analysis of the Association of GSTT1 Gene Polymorphism with Risk of HCC

Group and subgroups	Studies number	Q test P value	Model selected	OR (95%CI)	P
Non-sensitivity analysis					
Overall	1-19	1-1	Random	1.53(1.28,1.82)	<0.00001
Sensitivity analysis					
Population	1-13	1-1	Random	1.56(1.23,1.98)	1-1
Hospital	1-7	1-1	Random	1.46(1.12,1.92)	1-1
≥ 100	1-12	1-1	Random	1.50(1.25,1.80)	<0.0001
< 100	1-8	1-1	Random	1.62(1.03,2.53)	1-1

role GSTT1 gene expression to disease; (5) If multiple publications for same data from the same study group occurred, we only recruited the later one into our final analysis.

Data extraction and synthesis

Two investigators independently extracted the following information from each eligible study: f first author’s surname, year of publication, publication language, location of the study performed, control source of the control group and the number of cases and controls for GSTT1 genotypes. Frequencies of null genotype of GSTT1 were calculated for case group and control group, from the corresponding genotype distribution. The results were compared and disagreement was resolved by discussion.

Statistical Analysis

Cochrane Review Manager Version 5 (Cochrane Library, UK) was used to calculate the available data from each study. The pooled statistic was counted using the fixed effects model, but a random effects model was conducted when the P value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. P < 0.05 was required for the pooled OR to be statistically significant. I² was used to test the heterogeneity among the included studies. Sub-group

analysis was also performed according to source of the controls (population vs hospital), sample size of case (< 100 vs ≥ 100). Stata 11.0 was used to test the publication bias. The Begg adjusted rank correlation test (Begg & Mazumdar, 1994) was used for exploring publication bias (P<0.1 was considered significant), when the number of the included studies was more than ten.

Results

Study characteristics for GSTT1 null genotype with HCC risk

Eighteen studies (Dong et al., 1997; Yu et al., 1999; Sun et al., 2001; Liu et al., 2002; Liu et al., 2003; McGlynn et al., 2003; Li et al., 2004; Chen et al., 2005; Deng et al., 2005; Guo et al., 2005; He et al., 2005; Long et al., 2005; Ma et al., 2005; Zhang et al., 2005; Long et al., 2006; Yang et al., 2009; Kao et al., 2010; Wei et al., 2010) were recruited into our investigation to study the relationship between GSTT1 null genotype and HCC risk. Eleven studies were published in Chinese and others were reported in English (Table 1). The data of our interest were extracted, and the frequencies of null genotype of GSTT1 for case group and control group were calculated (Table 1). Those 18 investigations contained 2693 case series and 4696 controls. The average distribution frequency of GSTT1 null genotype in HCC case was 52.04% and the average frequency in controls was 40.78%. The average distribution frequency of GSTT1 null genotype in cases was markedly increased when compared with that in control group (HCC/Control = 1.28).

Association of GSTT1 null genotype with HCC risk

In this meta-analysis, we found that GSTT1 null genotype was associated with HCC risk in Chinese (OR=1.53, 95%CI: 1.28-1.82; P<0.00001; Figure 1 and Table 2).

Sub-group analysis

Sub-group analysis for GSTT1 was also performed

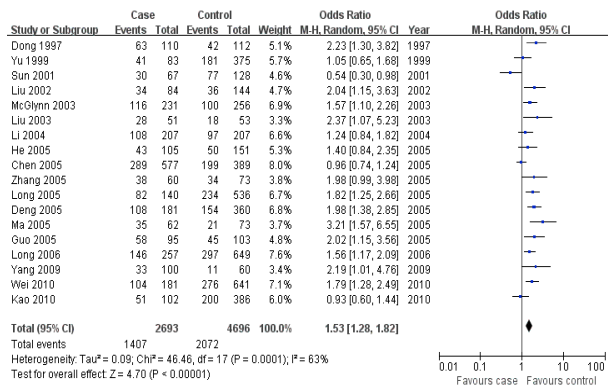


Figure 1. Association Between GSTT1 Null Genotype and HCC Susceptibility

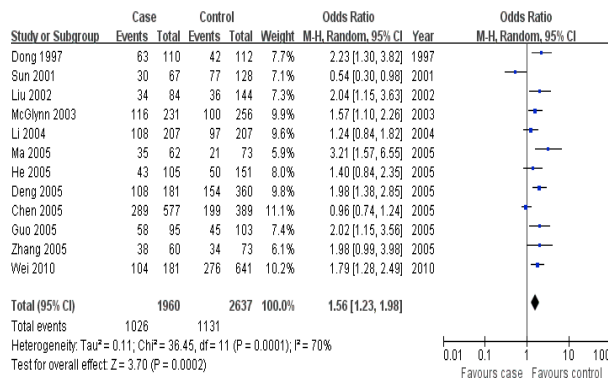


Figure 2. Association Between GSTT1 Null Genotype and HCC Susceptibility (according to the population source of the controls)

according to the source of the controls (population vs hospital), sample size of case (< 100 vs ≥ 100). We found that the results for GSTT1 from the sub-group analysis were consistent with the previous results (Figure 2 for the population source and Figure 3 for the sample size of case ≥ 100; Table 2).

Evaluation of publication bias

No significant publication bias was showed for overall Chinese population (P=0.112; Figure 4). In the sub-group analysis, there was also no significant publication bias for the meta-analysis according to the population source of the controls (P=0.244), and for the meta-analysis according to the sample size of case more than 100 (P=0.436).

Discussion

In our study, we found that the null genotype of GSTT1 was associated with the HCC risk in Chinese. Our results indicated that GSTT1 null genotype was associated with the susceptibility of HCC in Chinese, and it might become a useful indicator to predict the risk of HCC in Chinese population. In our study, we found that the average distribution frequency of GSTT1 null genotype in cases have a 1.28-fold increase when compared with that in control group. In the sub-group study according to according to source of the controls (population vs hospital), sample size of case (< 100 vs ≥ 100), we found that the results were consistent with the previous. There was no publication bias for overall Chinese population, the population source of the controls and the sample size of

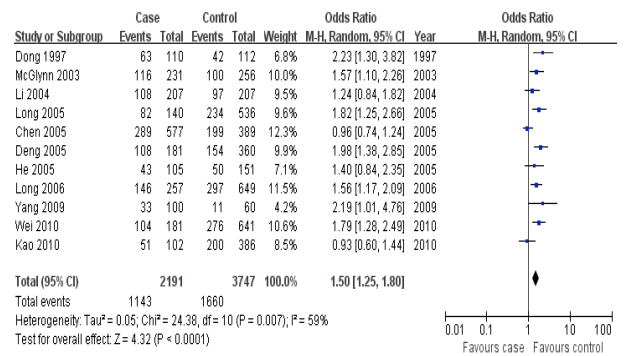


Figure 3. Association Between GSTT1 Null Genotype and HCC Susceptibility (according to the sample size of case more than 100)

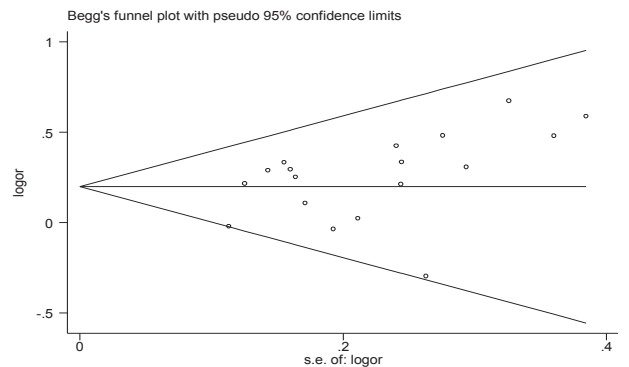


Figure 4. Funnel Plot to Assess Publication bias for GSTT1 in Overall Chinese Population. No significant funnel asymmetry was observed which could indicate publication bias. The horizontal line in the funnel plot indicates the random effects summary estimate, while the sloping lines indicate the expected 95% CI for a given standard error, assuming no heterogeneity between studies. logOR, natural logarithm of the OR; s.e. of: logOR, standard error of the logOR

case more than 100. The conclusion in our meta-analysis might be robust to extent.

Three meta-analyses were performed to investigate the association of GSTT1 gene polymorphism and HCC risk. White et al. (2008) performed a meta-analysis and included 13 eligible studies to study the relationship between GSTT1 genetic variants and found that there was no statistical difference in the null genotype distribution of GSTT1 between the HCC group and control group, and they did not performed the analysis for Chinese population or Asians. Wang et al. (2010) up-dated the meta-analysis from White et al. (2008) and included 18 studies for the association of GST gene polymorphism with HCC risk in Asians and found that null genotype of GSTT1 was associated with the risk of HCC. The conclusions were similar with ours. However, this meta-analysis not performed a sub-group study in Chinese population. Yu et al. (2011) conducted a meta-analysis in Chinese and included 16 studies for the relationship between GSTT1 gene polymorphism and HCC risk in Chinese, and they found that the null genotypes of GSTT1 was associated with increased risk of HCC. The number of included studies in our meta-analysis was larger than the previous meta-analyses. The conclusion from our study might be more robust.

GSTT1 null genotype might be an important factor for the morbidity and progression of cancers in Chinese

population. Wang et al. (2012) conducted a prospective study in Chinese population to detect the association between GSTT1 gene polymorphisms and survival of gastric cancer, and found that individuals carrying null-GSTT1 had a moderate higher risk of death from gastric cancer. Liu et al. (2012) performed a meta-analysis to explore the association between GSTT1 null genotype and risk for cervical cancer, and reported a modification on the association between GSTT1 null genotype and cervical cancer. Wang et al. (2010) conducted a meta-analysis to evaluate the association between polymorphism of GSTT1 and the risk of lung cancer in Chinese population, and this meta-analysis suggested that GSTT1 deletion polymorphisms might have an effect on the susceptibility of lung cancer in Chinese population. Those studies mentioned above might give us a message that GSTT1 null-genotype might be a risk factor to cause cancer in Chinese population. However, more studies should be performed in the future.

Our results indicated that there was an association between null genotypes of GSTT1 and HCC risk in Chinese population. The outcome might be robust to some extent. The GSTT1 null genotype might become a valuable indicator to predict the risk of HCC in Chinese population. Once it is confirmed, the early prevention would be conducted and the high mortality in Chinese would be improved. However, those findings should be regarded cautiously because many other ingredients, such as small sample size of the included report, limited statistical power, heterogeneity of enrolled cases, variable study designs and different interventions, were closely related to affect the results.

In conclusion, the results in our study support that null genotype of GSTT1 is associated with the risk of HCC in Chinese population. However, more association investigations are required to further clarify the role of the GSTT1 gene polymorphism in predicting the risk of HCC in Chinese population.

Acknowledgements

The author(s) declare that they have no competing interests.

References

- Aguiar ES, Giacomazzi J, Schmidt AV, et al (2012). GSTM1, GSTT1, and GSTP1 polymorphisms, breast cancer risk factors and mammographic density in women submitted to breast cancer screening. *Rev Bras Epidemiol*, **15**, 246-55.
- Bayram S, Akkiz H, Bekar A, et al (2011). No association of the exonuclease 1 T439M polymorphism and risk of hepatocellular carcinoma development in the Turkish population: a case-control study. *Asian Pac J Cancer Prev*, **12**, 2455-60.
- Begg CB, Mazumdar M (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, **50**, 1088-101.
- Chen CC, Yang SY, Liu CJ, et al (2005). Association of cytokine and DNA repair gene polymorphisms with hepatitis B-related hepatocellular carcinoma. *Int J Epidemiol*, **34**, 1310-8.
- Deng ZL, Wei YP, Ma Y (2005). Polymorphism of glutathione S-transferase mu 1 and theta 1 genes and hepatocellular carcinoma in southern Guangxi, China. *World J Gastroenterol*, **11**, 272-4.
- Dong C, Yu S, Chen G, et al (1997). Polymorphisms of GSTT1 and M1 genotypes and their effects on elevated aflatoxin exposure and increased risk of hepatocellular carcinoma. *Zhongliu Fangzhi Yanjiu*, **24**, 327-9.
- Dong D, Gao X, Zhu Z, et al (2012). A 40-bp insertion/deletion polymorphism in the constitutive promoter of MDM2 confers risk for hepatocellular carcinoma in a Chinese population. *Gene*, **497**, 66-70.
- Guo H, Bian J, Jiang F, et al (2005). The null genotypes of GSTM1 and GSTT1 and the genetic susceptibility of primary liver cancer in Luoyang, China. *Zhongliu*, **25**, 58-61.
- He S, Jr Qin, Gu Y, et al (2005). Analysis of GSTM1, GSTT1 polymorphisms in liver cancer patients. *Guangxi Yike Daxue Xuebao*, **22**, 875-7.
- Kao CC, Chen MK, Kuo WH, et al (2010) Influence of glutathione-S-transferase theta (GSTT1) and micro (GSTM1) gene polymorphisms on the susceptibility of hepatocellular carcinoma in Taiwan. *J Surg Oncol*, **102**, 301-7.
- Li J, Jiang X (2011). Loss of runt-related transcription factor 3 expression associated with human hepatocellular carcinoma progression and prognosis. *Asian Pac J Cancer Prev*, **12**, 2285-90.
- Li S, Wu J, Ding J, et al (2004). Impact of genetic polymorphisms of glutathione S-transferase T1, M1 on the risk of primary hepatocellular carcinoma in alcohol drinkers. *Shiyong Aizheng Zazhi*, **19**, 229-32.
- Liu C, Bian J, Jiang F, et al (2002). Genetic polymorphism of glutathione S-transferase M1, T1, P1 on susceptibility hepatocellular carcinoma. *Zhongguo Gonggong Weisheng*, **18**, 935-6.
- Liu Y, Xu LZ (2012). Meta-analysis of association between GSTM1 gene polymorphism and cervical cancer. *Asian Pac J Trop Med*, **5**, 480-4.
- Liu Z, Wei Y, Ma Y, et al (2003) Population with GSTT1 gene deletion and the relationship to hepatocellular carcinoma from Guangxi. *Guangxi Yike Daxue Xuebao*, **20**, 161-3.
- Long XD, Ma Y, Wei YP, et al (2005) Study on the detoxication gene GSTM1-GSTT1-null and susceptibility to aflatoxin B1 related hepatocellular carcinoma in Guangxi. *Zhonghua Liu Xing Bing Xue Za Zhi*, **26**, 777-81.
- Long XD, Ma Y, Wei YP, et al (2006). The polymorphisms of GSTM1, GSTT1, HYL1*2, and XRCC1, and aflatoxin B1-related hepatocellular carcinoma in Guangxi population, China. *Hepato Res*, **36**, 48-55.
- Ma D, Chen Y, Li Y, et al (2005). Glutathione-S-transferase M1 and T1 polymorphisms (deficiency) and susceptibility to liver cancer in hepatitis B surface antigen positive (HBsAg positive) population. *Guangxi Yixue*, **27**, 656-7.
- Masoudi M, Saadat I, Omidvari S, et al (2011). Association between N142D genetic polymorphism of GSTO2 and susceptibility to colorectal cancer. *Mol Biol Rep*, **38**, 4309-13.
- McGlynn KA, Hunter K, LeVoyer T, et al (2003). Susceptibility to aflatoxin B1-related primary hepatocellular carcinoma in mice and humans. *Cancer Res*, **63**, 4594-601.
- Ramalhinho AC, Fonseca-Moutinho JA, LA Breitenfeld G (2012). Positive Association of Polymorphisms in Estrogen Biosynthesis Gene, CYP19A1, and Metabolism, GST, in Breast Cancer Susceptibility. *DNA Cell Biol*, **31**, 1100-6.
- Sun CA, Wang LY, Chen CJ, et al (2001). Genetic polymorphisms of glutathione S-transferases M1 and T1 associated with susceptibility to aflatoxin-related hepatocarcinogenesis among chronic hepatitis B carriers: a nested case-control

- study in Taiwan. *Carcinogenesis*, **22**, 1289-94.
- Wang B, Huang G, Wang D, et al (2010). Null genotypes of GSTM1 and GSTT1 contribute to hepatocellular carcinoma risk: evidence from an updated meta-analysis. *J Hepatol*, **53**, 508-18.
- Wang Y, Yang H, Li L, et al (2010). Glutathione S-transferase T1 gene deletion polymorphism and lung cancer risk in Chinese population: a meta-analysis. *Cancer Epidemiol*, **34**, 593-7.
- Wang ZY, Zhou J, Luo L, et al (2012). Predictive role of glutathione-S-transferase gene polymorphisms in the survival of gastric cancer cases. *Asian Pac J Cancer Prev*, **13**, 1515-8.
- Wei Y, Long X, Liu Z, et al (2010). Genetic Polymorphism of Glutathione-S-transferase M1 and T1 in Hepatocellular Carcinoma and Nasopharyngeal Carcinoma. *Cancer Res Prev Treat*, **37**, 1162-5.
- White DL, Li D, Nurgalieva Z, et al (2008). Genetic variants of glutathione S-transferase as possible risk factors for hepatocellular carcinoma: a HuGE systematic review and meta-analysis. *Am J Epidemiol*, **167**, 377-89.
- Xu D, Yan S, Yin J, et al (2011). Null genotype of GSTT1 contributes to colorectal cancer risk in Asian populations: evidence from a meta-analysis. *Asian Pac J Cancer Prev*, **12**, 2279-84.
- Yang Z, Xie Y, Kuang Z, et al (2009). Relationship between genetic polymorphisms of glutathione-S-transferase M1, T1 genes and susceptibility to hepatocellular carcinoma in population of Fusui District of Guangxi Zhuang Autonomous Region. *Zhonghua Zhongliu Fangzhi Zazhi*, **16**, 970-5.
- Yu L, Wang CY, Xi B, et al (2011). GST polymorphisms are associated with hepatocellular carcinoma risk in Chinese population. *World J Gastroenterol*, **17**, 3248-56.
- Yu MW, Chiu YH, Chiang YC, et al (1999). Plasma carotenoids, glutathione S-transferase M1 and T1 genetic polymorphisms, and risk of hepatocellular carcinoma: independent and interactive effects. *Am J Epidemiol*, **149**, 621-9.
- Yuan R, Jiang C, Hong K, et al (2011). Genetic Variation in the Fat10 Gene is Associated with Risk of Hepatocellular Carcinoma in a Chinese Population. *Asian Pac J Cancer Prev*, **12**, 2117-22.
- Zhang Y, Deng C, Zhu Y (2005). Study on genetic polymorphisms of xenobiotica metabolizing enzymes in hepatitis B virus-associated hepatic diseases. *Wenzhou Yixueyuan Xuebao*, **35**, 464-7.