Int J Clin Exp Med 2015;8(4):5667-5674
www.ijcem.com /ISSN:1940-5901/IJCEM0003234

Original Article

Interferon-γ polymorphism and hepatocellular carcinoma susceptibility: a meta analysis

Jing Sun*, Kai Liao*, Yuefei Wang, Leida Zhang

*Department of Hepatobiliary Surgery, Southwest Hospital, Third Military Medical University, Chongqing, China. *Equal contributors.*

Received October 18, 2014; Accepted December 31, 2014; Epub April 15, 2015; Published April 30, 2015

Abstract: Background: Interferon-gamma (*IFN-γ*) was first defined as an antiviral agent with potent antitumor effects in 1957 and this is supported by much subsequent research. *IFN-γ* rs2430561 polymorphism was found to increase *IFN-γ* production involved in the regulation of immune system. Previous studies of rs2430561 genotypes and hepatocellular carcinoma (HCC) susceptibility have produced inconsistent results. We thus summarized all epidemiologic and molecular data and carried out a meta-analysis to evaluate the effects of this functional polymorphism on HCC incidence. Methods: Human hospital- or population-based studies were identified by searching multiple databases (BIOSIS, Embase, PubMed, Web of Science, Chinese Biomedical Literature database). Six studies were selected for the meta-analysis. Crude ORs was calculated assuming the allele, homozygote, heterozygote, dominant and recessive model. The stability and reliability of the combined results were examined by using sensitivity analysis and publication bias tests. Results: Meta-analysis under the allele model showed that the T allele compared with the A allele showed a moderately but nonsignificantly increased risk of HCC (OR = 1.12, 95% CI = 0.92-1.35). Analyses under the remaining models revealed no evidence of a significant association. In subgroup analysis by infection type, summary ORs suggested no significantly elevated risk of HBV-infected HCC in relation to the allele or genotypes of rs2430561 polymorphism. The combined results were reliable according to sensitivity analysis and publication bias tests. Conclusion: We found no strong evidence supporting a statistically significant association between *IFN-γ* rs2430561 polymorphism and HCC susceptibility.

Keywords: Interferon-gamma, hepatocellular carcinoma, polymorphism, susceptibility

Introduction

A complex and heterogeneous human malignancy that ranks third only to lung cancer and gastric cancer as a commonest cause of deaths from cancer across the globe is hepatocellular carcinoma (HCC) [1]. According to previous experimental data, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are universally acknowledged causative agents of chronic hepatitis, liver cirrhosis and liver failure that are prone to the development of HCC [2-4]. Nevertheless, inherent genetic susceptibility to HCC has recently been hypothesized to associate with various gene polymorphisms because of the fact that HBV and HCV are detected in a small proportion of patients [5, 6]. In this investigation we focused on a mostly studied polymorphism at interferon-gamma (*IFN-γ*), a cytokine that produces useful substances important for the protection against viral infections via suppression of viral replication and determination of the predominant pattern of host response [7].

IFN-γ is a pro-inflammatory Th1 cytokine with a fundamental role in downregulating the gene expression of HBV in infected hepatocytes by disrupting the stability of viral RNA and abrogating HBV nucleocapsid particles [8]. Products of *IFN-γ* along with activation of T and NK cell increase body temperature and thus trigger the immune system [9-11]. A study in vivo showed that the level of IFN-γ increases from the 4th days post-infection [11]; increased IFN-γ serum expression has been reported to promote antitumor activity, whereas sustained low-level expression of IFN-γ triggers tumorigenesis [12]. *IFN-γ* has dual role as a tumor cell growth suppressor and apoptotic activity promoter, which

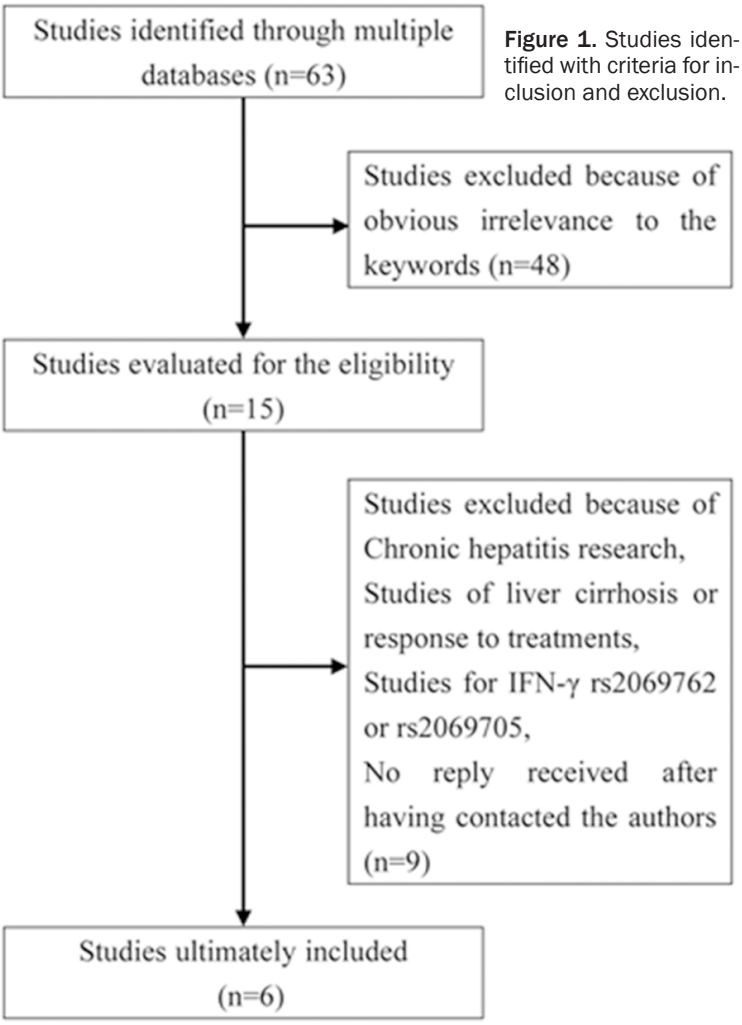

Figure 1. Studies identified with criteria for inclusion and exclusion.

has been described in human breast tumor cells [13]. An intronic single nucleotide polymorphism at *IFN-γ* (+874T/A, rs2430561) may affect the production of the cytokine and biologically change the function of regulatory elements by modifying their affinities to transcription factors [14]. A positive association of this T to A transition polymorphism with human diseases has been consistently reported [15]. The +874T allele, according to Pravica et al., functions more actively in increasing *IFN-γ* production relative to the +874A allele [16]. It is the important consequences that constitute the primary impetus for a number of investigators to examine the effects of *IFN-γ* rs2430561 on the HCC incidence [17-19]. Previous results for this polymorphism, however, are inconsistent. Discrepancy across the studies may arise from sampling variation or study design differences.

To increase the precision of effect estimations and to determine the role of rs2430561 genotypes in incident HCC, we decided to perform a meta-analysis of epidemiologic and molecular data from early-released case-control studies.

Methods

Search strategy, inclusion criteria, data abstraction

Online databases including BIOSIS, Embase, PubMed, Web of Science, and Chinese Biomedical Literature (CBM) were exhaustively searched until January 30, 2014. The possibly related studies were identified by using various search terms: hepatocellular carcinoma, hepatocellular cancer, hepatocarcinoma, polymorphism, genetic variants, genotypes, interferon-gamma, and *IFN-γ*. To maximize the number of our study, we imposed no restrictions on the computer-based literature search. In an effort to get additional data, we checked the references of all case-controlled studies. We also emailed the major authors when data of the original article were incompletely reported. The study was not considered in the final analysis if no reply was received.

We included the human hospital- or population-based studies that met all pre-defined criteria: Patients with HCC were investigated; IFN-γ rs2430561 polymorphism was genotyped; Genetic distributions of cases and controls were reported in detail, or the genetic data provided could be used to calculate an odds ratio (OR) for at least one contrast model tested.

The studies would be excluded based on: Duplicate data; Lack of useful data; Studies of chronic hepatitis or liver cirrhosis; Published in forms of abstract, case report, comment letter, editorial, or systematic review.

Table 1. Baseline information of studies included in this meta-analysis

First author	Publication year	Sample		Gender (male/female)		Mean age		Ethnicity	Quality	Study country	Description of controls
		Case	Control	Case	Control	Case	Control				
Ben-Ari [25]	2003	10	48	59/16	/	48.1 ± 14.0	/	Caucasian	High	Israel	10 healthy individuals recovered from HBV infection; 48 healthy controls
Bouzgarrou [17]	2009	58	103	20/38	42/61	61.6 ± 9.8	46	Caucasian	High	Tunisia	Healthy control subjects selected from blood donors
Migita [18]	2005	48	188	39/9	127/67	62.5 ± 8.9	51.5 ± 15.6	East Asian	High	Japan	HBV patients without HCC
Teixeira [27]	2013	111	202	92/20	145/57	55.6 ± 11.5	33.3 ± 8.3	Caucasian	Low	Brazil	Healthy subjects from the same geographic region
Saxena [26]	2014	59	146	/	/	/	/	Caucasian	High	India	Healthy subjects
Nieters [19]	2005	249	250	/	/	49.3 ± 9.6	/	East Asian	High	China	Hospital controls without history of cancer or clinical liver cirrhosis

HBV-hepatitis B virus; HCC-hepatocellular carcinoma.

Table 2. Overall and stratified analyses of association between IFN-γ rs2430561 SNP and HCC risk

Variables	No. of studies	Allele (T vs. A)		Homozygote (T/T vs. A/A)		Heterozygote (A/T vs. A/A)		Dominant (T/T + A/T vs. A/A)		Recessive (T/T vs. A/T + A/A)	
		OR (95 % CI)	P_{Het}	OR (95 % CI)	P_{Het}	OR (95 % CI)	P_{Het}	OR (95 % CI)	P_{Het}	OR (95 % CI)	P_{Het}
Total	6	1.12 (0.92, 1.35)	0.795	1.29 (0.87, 1.92)	0.505	1.05 (0.79, 1.38)	0.984	1.06 (0.84, 1.35)	0.989	1.07 (0.85, 1.34)	0.150
Infection type											
HBV-infected†	4	1.20 (0.87, 1.66)	0.582	1.88 (0.87, 4.02)	0.403	1.05 (0.69, 1.62)	0.886	1.09 (0.74, 1.61)	0.868	1.04 (0.80, 1.35)	0.067
Other‡	2	1.07 (0.84, 1.36)	0.604	1.12 (0.71, 1.79)	0.582	1.04 (0.73, 1.49)	0.709	1.05 (0.78, 1.41)	0.975	1.05 (0.74, 1.77)	0.266

†-hepatitis B virus-infected; ‡-hepatitis C virus-infected or both HBV-infected and HCV-infected patients.

Two authors independently scanned titles, abstracts, even the whole text whenever necessary and excluded the records violating one or more requirements listed above. For the qualified studies, information was collected on the following items: surname of authors, study country, year of online publication, ethnicity, number of men and women, mean age of case and control groups, characteristics of controls, number of cases and controls, genotypying data, and matching methods of controls to cases. A senior author was consulted in case of discrepancies.

Quality assessment

The Newcastle-Ottawa Scale (NOS), a quality assessment tool for case-controlled or cohort studies, was chosen to check the quality of eligible studies in this meta-analysis [20]. NOS comprises three parts (selection of population, comparability, and exposure or outcome) involving eight items with nine points. The studies that scored six or more points (≥ 6) were grouped into 'high-quality' category, and those less than six scores (< 6) were classified into 'low-quality' category. One score would be taken away if the genotype distribution in control showed deviation from Hardy-Weinberg equilibrium (HWE).

Data analysis

We calculated crude ORs with 95% CIs (95% confidence interval) by comparing data on the rare homozygous genotype to data on the wide-type homozygous genotype (homozygous model) in order to evaluate the association of *IFN-γ* rs2430561 genotypes with HCC susceptibility. The combined effects were also estimated for the allele, heterozygous, dominant and recessive models. To see whether the individual susceptibility differed between HBV-infected and other virus infected HCC, we performed subgroup analysis by infection type [the limited data only allowed further analysis in subgroup of HBV-infected HCC and 'other' subgroup comprising one study for HCV-infected HCC and one study for both HBV-infected and HCV-infected HCC]. Inter-study heterogeneity was evaluated using the Cochran Q test [21]. P values below 0.05 corresponded to the presence of heterogeneity. We used a Mantel-Haenszel meta-analysis of data derived from the samples in order to evaluate the overall evidence of association when no significant heterogeneity was indicated [22]; otherwise, the method of DerSimonian and Laird was applied to provide a pooled OR [23]. Statistical significance of the combined meta-analysis results was determined using the Z statistic, the ratio of the point estimate to its standard error. We used the Chi-square goodness of fit to test for HWE among controls for each study. Sensitivity analysis was conducted to by omitting the single studies, one at a time and recalculating the pooled ORs and 95% CIs to examine if the independent data sets exerted notable influence on the combined results. Publication bias was evaluated using the funnel plots and Egger's liner regression test [24]. The significance level was fixed at *P* values less than 0.05 unless specially stated. All statistical analyses were done using STATA software, version 12.0 (Stata Corporation, College Station, TX) and Review Manager, version 5.2 (Revman, the Cochrane Collaboration).

Results

Characteristics of studies

A flow diagram detailing selection process of eligible studies is displayed in **Figure 1**. Online searches using the search strategy yielded 63 records in total. We initially excluded 48 records after screening the titles and abstracts for obvious irrelevance to the keywords. We then evaluated the eligibility of the remaining 15 studies, of which 9 studies were removed due to studies of chronic hepatitis, liver cirrhosis, response to treatments, *IFN-γ* rs2069762 or rs2069705, or no reply received after having contacted the authors. Therefore, 6 studies reporting available data were included in the final meta-analysis [17-19, 25-27]. Most studies were small-sampled (No. of cases < 100 and No. of controls < 100). Four studies were conducted in Caucasian samples and two studies in East Asian samples. One Caucasian study included controls with a history of HBV infection, and an East Asian study used HBV patients without HCC as references. All studies were in HWE except for Teixeira et al., the only study in 'low-quality' category (**Table 1**). In addition, only the recessive model (T/T vs. A/T + A/A) analyzed the data from all studies, as the relatively larger study reported data for AA + AT, and TT [19].

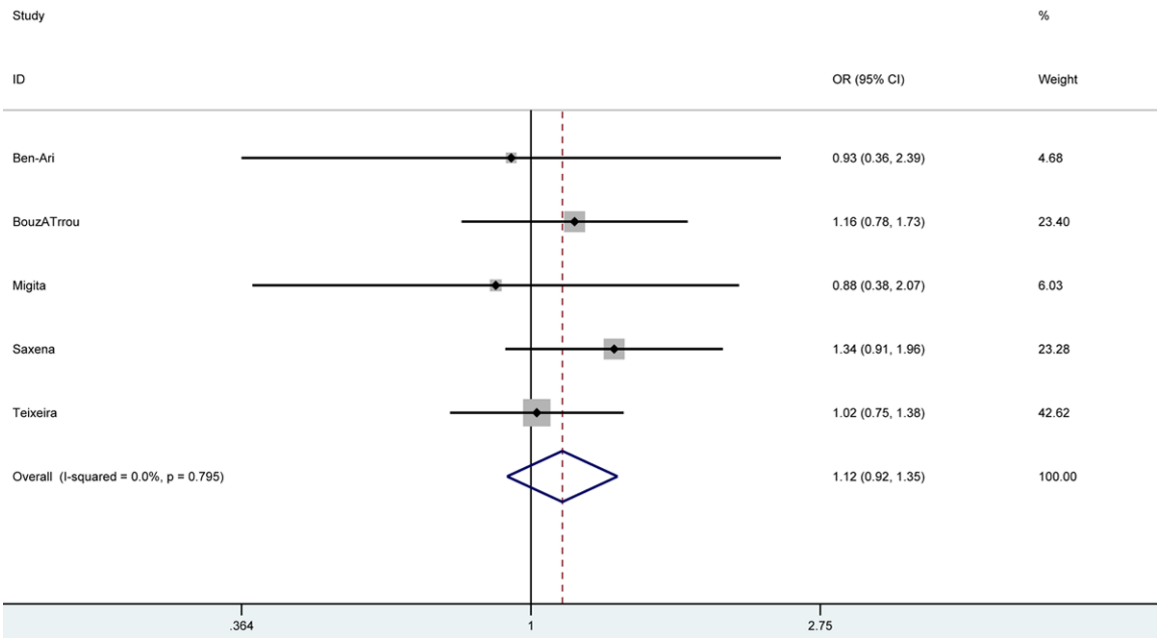

Figure 2. Meta-Analysis of the association between *IFN-γ* rs2430561 polymorphism and HCC susceptibility under the allele model. Squares correspond to the point estimate of effect for each study, and horizontal lines through the squares correspond to 95% CIs. The area of each square reflects the weight assigned to that study. The diamond represents the summary point estimate of effect, and the width of the diamond represents the 95% CI of the summary point estimate of effect.

Quantitative data synthesis

As shown in **Figure 2** and **Table 2**, the T allele compared with the A allele showed a moderately increased risk of HCC, although the association was not significant (OR = 1.12, 95% CI = 0.92-1.35). In subsequent analyses, we found nonsignificantly increased risk of HCC among people with the T/T, A/T, or both T/T and A/T genotypes (OR = 1.29, 95% CI = 0.87-1.92 under the homozygote model; OR = 1.05, 95% CI = 0.79-1.38 under the heterozygote model; OR = 1.06, 95% CI = 0.84-1.35 under the dominant model; OR = 1.07, 95% CI = 0.85-1.34 under the recessive model).

In subgroup analysis by infection type, all summary ORs were near the null value and this suggested no significantly elevated risk of HBV-infected HCC in relation to the allele or genotypes of *IFN-γ* rs2430561 (**Table 2**).

Sensitivity analysis, publication bias

Sensitivity analyses via sequentially omitting the single studies for *IFN-γ* rs2430561 showed no substantial difference between the primary ORs and the recalculated ORs, suggesting our results were stable. The funnel plots for all genetic models were symmetrical and the Egger's test detected no obvious evidence of significant publication bias across the studies. **Figure 3** displays the funnel plots under the recessive model (Egger's test: $P = 0.947$).

Discussion

In this largest investigation to date, we performed a meta-analysis and analyzed epidemiologic data from all published case-controlled studies addressing the association of *IFN-γ* rs2430561 genotypes with inherited susceptibility towards HCC. Using distinct genetic models, we found no strong evidence for a significantly increased risk of HCC. In further subgroup analysis, the *IFN-γ* rs2430561 polymorphism, both at the genotypic level and the allelic level, failed to show any association with HBV-infected HCC. Because of the sample inadequacy, it is unclear whether or not this lack of causal association is merely a false-negative finding. This issue, therefore, requires a large study to clarify.

As human cancer at various sites shares some common characteristics, such as the major causes of carcinogenesis, investigations into other cancers may have implications. Liu et al. analyzed thirty- two studies with 4524 cases and 5684 controls, attempting to determine

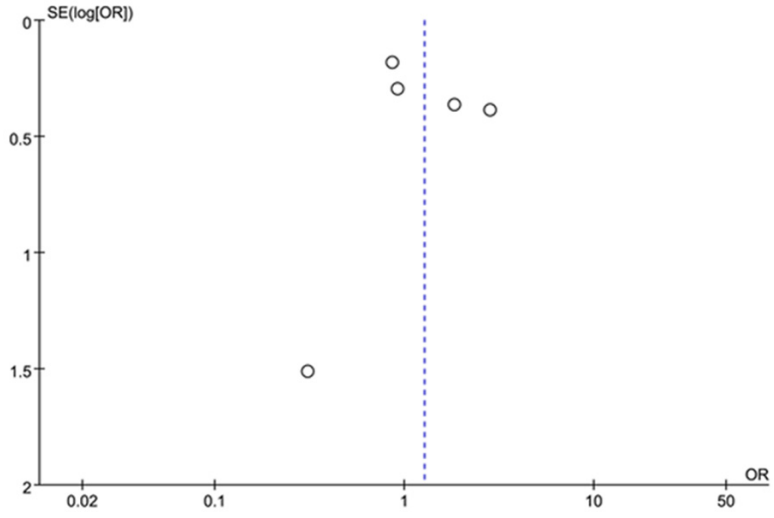

Figure 3. The funnel plot for publication bias test (the recessive model). Each point represents a separate study for the indicated association.

the role of *IFN-γ* rs2430561 in the development of cancer, with no overall cancer risk suggested in the work. Intriguingly, nearly 60% increased risk of breast cancer was shown in subgroup analysis by cancer type and significantly elevated risks were seen in African and European individuals when data were stratified by ethnicity [28]. The study by Ge et al., slightly larger than the previous study, demonstrated evidence not supporting a positive association in each subgroup [29]. Based on a large number of subjects, both analyses showed no evidence of significant associations with overall cancer risk, suggesting rs2430561 genotypes may not have major impact on the incidence of human cancers, including HCC. Several lines of evidence showed killer or cytotoxic T cells that produce proinflammatory cytokine *IFN-γ*, including CD4+ T cells and cytotoxic CD8+ cells, destroy infected and foreign cells [30, 31]. *IFN-γ* controls human innate and adaptive immune responses by suppressing proliferation and enhancing apoptosis to maintain the homeostasis of T cells [32]. These data implicate *IFN-γ* has a significant role in tumor immune surveillance. Conversely, a steady flow of recent studies has reported that the cytokine gene may have protumorigenic effects in some cases [33]. As early as 1957, Isaacs and Lindenmann for the first time defined *IFN-γ* as an antiviral agent due to the potent antitumor activity [34]. Nakashima et al. developed a mouse model and found a clear association between administration of *IFN-γ* and prevention of virally induced leukemia and extended overall survival time [35]. The antigrowth effects were further confirmed in a recent report by Bekisz and coworkers [36]. These theories hint that *IFN-γ* and the polymorphisms at the locus are likely to have protective effect against the incidence of HCC.

One of the high-risk countries is China, where more than 400,000 new HCC cases and 370,000 deaths were reported in 2008 [37]. According to El-Serag et al., the incidence rate vary widely across geographic regions and ethnic groups; such variance also manifests between men and women [38]. It is therefore worthwhile to investigate the role of *IFN-γ* rs2430561 in HCC in a number of ethnicities to identify if the polymorphism differentially confers inherent susceptibility to HCC among distinct ethnic groups.

The statistical power of this study was obviously enhanced by performing a meta-analysis, in which all individual datasets were incorporated and analyzed. However, it is noteworthy that each of the published studies included a small number of individuals, leading to an inadequate sample in the final meta-analysis. We thus can infer, but cannot conclude, that *IFN-γ* rs2430561 is not associated with HCC susceptibility. Moreover, the incidence of HCC varies considerably across the globe, the null association may be altered in a larger study when analysis is restrained to some specific ethnic group. Finally, the etiology of HCC is complicated and multifactorial in nature. It is better to consider the coeffects from environmental carcinogens and other predisposition genes such that the susceptibility role of *IFN-γ* rs2430561 could be well defined.

In summary, our results did not indicate an association between the functional rs2430561 polymorphism at *IFN-γ* and HCC incidence. Future research based on a large quantity of individual studies representing various ethnicities is needed to evaluate the effects of *IFN-γ* rs2430561 on the genetic risk of human HCC.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Leida Zhang, Department of Hepatobiliary Surgery, Southwest Hospital, Third Military Medical University, 30 Gaotanyan Main Street, Shapingba District, Chongqing 400038, China. E-mail: zhangleidazz@163.com

References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[2] Boyer N and Marcellin P. Pathogenesis, diagnosis and management of hepatitis C. J Hepatol 2000; 32: 98-112.

[3] Rehermann B and Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection. Nat Rev Immunol 2005; 5: 215-229.

[4] Wright TL. Introduction to chronic hepatitis B infection. Am J Gastroenterol 2006; 101 Suppl 1: S1-6.

[5] Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, Hsiao CK, Chen PJ, Chen DS and Chen CJ. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002; 347: 168-174.

[6] Gupta E, Bajpai M and Choudhary A. Hepatitis C virus: Screening, diagnosis, and interpretation of laboratory assays. Asian J Transfus Sci 2014; 8: 19-25.

[7] Koziel MJ. Cytokines in viral hepatitis. Semin Liver Dis 1999; 19: 157-169.

[8] Sun QL and Ran W. Review of cytokine profiles in patients with hepatitis. World J Gastroenterol 2004; 10: 1709-1715.

[9] Huang WS, Cherng SC, Jen TK, Yu MH and Yeh MY. Effects of temperature on radiochemical purity and immunoreactivity of radiolabeled monoclonal antibody 1H10. J Nucl Med Technol 2000; 28: 182-185.

[10] Hasday JD, Fairchild KD and Shanholtz C. The role of fever in the infected host. Microbes Infect 2000; 2: 1891-1904.

[11] Karalyan Z, Zakaryan H, Sargsyan K, Voskanyan H, Arzumanyan H, Avagyan H and Karalova E. Interferon status and white blood cells during infection with African swine fever virus in vivo. Vet Immunol Immunopathol 2012; 145: 551-555.

[12] He YF, Wang XH, Zhang GM, Chen HT, Zhang H and Feng ZH. Sustained low-level expression of interferon-gamma promotes tumor development: potential insights in tumor prevention and tumor immunotherapy. Cancer Immunol Immunother 2005; 54: 891-897.

[13] Ruiz-Ruiz C, Munoz-Pinedo C and Lopez-Rivas A. Interferon-gamma treatment elevates caspase-8 expression and sensitizes human breast tumor cells to a death receptor-induced mitochondria-operated apoptotic program. Cancer Res 2000; 60: 5673-5680.

[14] Haukim N, Bidwell JL, Smith AJ, Keen LJ, Gallagher G, Kimberly R, Huizinga T, McDermott MF, Oksenberg J, McNicholl J, Pociot F, Hardt C and D'Alfonso S. Cytokine gene polymorphism in human disease: on-line databases, supplement 2. Genes Immun 2002; 3: 313-330.

[15] Hollegaard MV and Bidwell JL. Cytokine gene polymorphism in human disease: on-line databases, Supplement 3. Genes Immun 2006; 7: 269-276.

[16] Pravica V, Perrey C, Stevens A, Lee JH and Hutchinson IV. A single nucleotide polymorphism in the first intron of the human IFN-gamma gene: absolute correlation with a polymorphic CA microsatellite marker of high IFN-gamma production. Hum Immunol 2000; 61: 863-866.

[17] Bouzgarrou N, Hassen E, Farhat K, Bahri O, Gabbouj S, Maamouri N, Ben Mami N, Saffar H, Trabelsi A, Triki H and Chouchane L. Combined analysis of interferon-gamma and interleukin-10 gene polymorphisms and chronic hepatitis C severity. Hum Immunol 2009; 70: 230-236.

[18] Migita K, Miyazoe S, Maeda Y, Daikoku M, Abiru S, Ueki T, Yano K, Nagaoka S, Matsumoto T, Nakao K, Hamasaki K, Yatsuhashi H, Ishibashi H and Eguchi K. Cytokine gene polymorphisms in Japanese patients with hepatitis B virus infection--association between TGF-beta1 polymorphisms and hepatocellular carcinoma. J Hepatol 2005; 42: 505-510.

[19] Nieters A, Yuan JM, Sun CL, Zhang ZQ, Stoehlmacher J, Govindarajan S and Yu MC. Effect of cytokine genotypes on the hepatitis B virus-hepatocellular carcinoma association. Cancer 2005; 103: 740-748.

[20] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-605.

[21] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA and Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-2012.

[22] Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.

[23] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

[24] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[25] Ben-Ari Z, Mor E, Papo O, Kfir B, Sulkes J, Tambur AR, Tur-Kaspa R and Klein T. Cytokine gene polymorphisms in patients infected with hepatitis B virus. Am J Gastroenterol 2003; 98: 144-150.
[26] Saxena R, Chawla YK, Verma I and Kaur J. IFN-gamma (+874) and not TNF-alpha (-308) is associated with HBV-HCC risk in India. Mol Cell Biochem 2014; 385: 297-307.
[27] Teixeira AC, Mendes CT Jr, Marano LA, Deghaide NH, Secaf M, Elias J Jr, Muglia V, Donadi EA, Martinelli AL. Alleles and genotypes of polymorphisms of IL-18, TNF-alpha and IFN-gamma are associated with a higher risk and severity of hepatocellular carcinoma (HCC) in Brazil. Hum Immunol 2013; 74: 1024-1029.
[28] Liu F, Li B, Wei YG, Chen X, Ma Y, Yan LN, Wen TF, Xu MQ, Wang WT and Yang JY. IFN-gamma+874 A/T polymorphism and cancer risk: an updated analysis based on 32 case-control studies. Cytokine 2011; 56: 200-207.
[29] Ge YZ, Wang YD, Xu Z, Xu LW, Wang YP, Gu MH, Ding AX, Zhu XB, Wu R, Li WC, Xu YD and Jia RP. Lack of association between interferon gamma +874 T/A polymorphism and cancer risk: an updated meta-analysis. Tumour Biol 2014; 35: 6405-6414.
[30] Schroder K, Hertzog PJ, Ravasi T and Hume DA. Interferon-gamma: an overview of signals, mechanisms and functions. J Leukoc Biol 2004; 75: 163-189.
[31] Billiau A and Matthys P. Interferon-gamma: a historical perspective. Cytokine Growth Factor Rev 2009; 20: 97-113.
[32] Schoenborn JR and Wilson CB. Regulation of interferon-gamma during innate and adaptive immune responses. Adv Immunol 2007; 96: 41-101.
[33] Zaidi MR and Merlino G. The two faces of interferon-gamma in cancer. Clin Cancer Res 2011; 17: 6118-6124.
[34] Isaacs A and Lindenmann J. Virus interference. I. The interferon. Proc R Soc Lond B Biol Sci 1957; 147: 258-267.
[35] Nakashima H, Miyake K, Clark CR, Bekisz J, Finbloom J, Husain SR, Baron S, Puri RK and Zoon KC. Potent antitumor effects of combination therapy with IFNs and monocytes in mouse models of established human ovarian and melanoma tumors. Cancer Immunol Immunother 2012; 61: 1081-1092.
[36] Bekisz J, Sato Y, Johnson C, Husain SR, Puri RK and Zoon KC. Immunomodulatory effects of interferons in malignancies. J Interferon Cytokine Res 2013; 33: 154-161.
[37] Li Q, Du J, Guan P, Qu CF and Dai M. [Estimation and prediction of incidence, mortality and prevalence on liver cancer, in 2008, China]. Zhonghua Liu Xing Bing Xue Za Zhi 2012; 33: 554-557.
[38] El-Serag HB and Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007; 132: 2557-2576.