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ORIGINAL PAPER

Association between polymorphisms in tumor suppressor genes and oncogenes and risk of hepatocellular carcinoma: a case–control study in an HCC epidemic area within the Han Chinese population

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Abstract Data concerning the risk of hepatocellular carcinoma (HCC) and specific single nucleotide polymorphisms (SNPs) in an HBV-free population are currently limited. Therefore, we performed a case–control study to investigate the association between SNPs and the risk of HCC in individuals without chronic HBV infection. A total of 160 Han Chinese patients with HCC and an identical number of healthy controls were enrolled in this study. *rs1042522*, *rs10814325*, *rs17401966*, and *rs2279744* genotypes were determined using matrix-associated laser desorption ionization–time of flight–mass spectrometry (MALDI–TOF–MS). CG and GG genotypes in *rs1042522* and heterozygote and homozygote in *rs2279744* were significantly associated with an elevated risk of HCC. Homozygous mutation of *rs1081432* conferred a 2.68-fold risk of HCC (95 % CI 1.35–5.34); however heterozygosity was not statistically significant. *rs17401966* heterozygosity or homozygosity was not significantly associated with a increased risk of HCC. Several polymorphisms associated with a significantly increased risk of HCC were identified. These may serve as biomarkers in evaluating HCC risk in the general population.

Keywords HCC risk · Tumor suppressor gene · Polymorphism · Case–control study

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Introduction

According to the statistics published by the World Health Organization, liver cancer is currently the fifth most common cancer in males and the seventh most frequent cancer in the female population. The incidence and mortality of liver cancer varies significantly according to geographic region and gender. For example, the incidence of liver cancer in the male population in Eastern Asia is 35.5 per 100,000, compared to only 12.6 among their counterpart. In contrast, the incidence of liver cancer in more developed regions worldwide is relatively low, with an incidence of 8.2 per 100,000 in males and 2.7 per 100,000 in women [1]. Hepatocellular carcinoma (HCC) now qualifies as the third most common cause of death from cancer globally because of its high mortality rate. It also contributes significantly to the disease burden worldwide, especially in less-developed regions with vulnerable healthcare services.

It is generally accepted that chronic HBV infection is the major risk factor for primary liver cancer, and the prevalence of HBV infection largely reflects cancer occurrence [2]. To be more accurate, HBV infection is responsible for 60 % of liver cancer cases in less-developed regions, but only 23 % in more developed regions [3]. HCC accounts for approximately 70–85 % of all liver cancers, worldwide [4]. Other factors, including HCV infection and exposure to aflatoxin B1 [5], have also been associated with the development of liver cancer in parts of Africa and Asia [6]. Despite the diversity of risk factors involved in the development of liver cancer, hepatitis B vaccination is currently the most effective and economic

prevention against liver cancer. Following the establishment of immunization programs, remarkable and long-lasting protection against carriage and a reduction in HCC rates in adolescents and young adults were observed in multiple study areas [7]. The regular application of antiviral therapy is also capable of lowering the risk of disease among patients with chronic infection, and this protective effect has been observed within the Japanese population [8]. Based on these results, we infer that HBV vaccination and antiviral therapy are effective countermeasures against HBV-related HCC. However, the etiology of hepatocellular carcinoma among HBV-free patients remains unclear; therefore, no specific prevention strategies against HCC are currently available for individuals without HBV chronic infection. Recently, single nucleotide polymorphisms (SNPs) in multiple genes have been associated with the development of HCC, including *TP53* [9], *IL-6* [10], and several DNA repair genes [11]. However, these studies were predominantly performed in HBV-positive populations or populations with a high infection rate. To date, there is little data regarding SNPs and HCC risk within the HBV-free population. Xiamen is located in the southeast of China and is an epidemic area of HCC. According to statistics, the incidence of HCC in Xiamen is approximately threefold higher than the average incidence in China. Therefore, we conducted a case–control study to assess the association between specific polymorphisms and the risk of HCC in the Han Chinese population without HBV infection, in Xiamen.

Materials and Methods

Cases and controls

Han Chinese patients with newly diagnosed HCC ($n = 160$) were recruited from the Xiamen Traditional Medicine Hospital and Xiamen Zhongshan Hospital between November 2011 and August 2013. Histological or cytological specimens were available from all HCC cases recruited. Patients were excluded if any of the following conditions were met: (1) infection from the hepatitis B or C virus; (2) liver disease due to parasitosis, diabetes, fatty liver, metabolism disorders, or severe cardiovascular diseases; (3) the presence of tumors other than HCC; (4) autoimmune hepatitis or toxic hepatitis; (5) refusal or inability to participate in the investigation because of critical health. Healthy controls ($n = 160$) were pair-matched by gender and age within 3 years, to an eligible patient with HCC. Control subjects were Han Chinese residents from Xiamen city, with no prior history of HCC, liver cirrhosis, or infection of hepatitis B or C virus. To eliminate the possible risk of bias, control subjects were randomly selected from the National Nutrition Survey, and we confirmed that all study subjects were ethnically unrelated.

An identical questionnaire was used to collect information on demographic characteristics, family cancer history, food consumption, lifestyle, and environmental factors from all study subjects. Interviews were performed by extensively trained staff to improve data quality and to minimize inter-interviewer variation. All cases and healthy controls provided a 5-ml blood sample on the day of the interview. Blood samples were centrifuged at 4,000 rpm for 10 min to separate plasma and blood cells and frozen at −78 °C prior to DNA extraction. All study subjects provided written informed consent, in agreement with the Helsinki declaration and the policy of the Ethics Committee of Xiamen Center for Disease Control and Prevention approving this study.

DNA extraction and genotyping

Human genomic DNA was extracted from blood cells using the MagNA Pure LC DNA Isolation Kit I (Roche Applied Science, Mannheim, Germany). Genomic DNA extracted from blood cells was stored at −22 °C in aliquots in screw-capped tubes. All samples were genotyped using the Sequenom platform in accordance with the manufacture's iPLEX Application Guide (Sequenom, San Diego CA, USA). Initial PCR amplification was performed in a total volume of 5 μl with 10 ng of genomic DNA, 3.5 mM of $MgCl_2$, 0.5 U of HotStar Taq polymerase (Qiagen, Valencia, CA, USA), 500 μM of dNTPs (Invitrogen, Carlsbad, CA, USA), and 60 nM of each primer set, using the GeneAmp PCR system 9700 thermal cycler (Applied Biosystems). Amplification was performed as follows: denaturation at 94 °C for 15 s followed by 45 cycles of 94 °C for 20 s, 56 °C for 30 s, 72 °C for 1 min, followed by 72 °C for 3 min. Subsequently, PCR products were treated with a mixture of 1.53 μl H_2O, 0.17 μl 10× shrimp alkaline phosphatase (SAP) buffer and 0.3 μl SAP (1.7 U/μl) at 37 °C for 40 min and 85 °C for 5 min. The SAP-treated products were then subject to iPLEX extension, during which time the primers hybridized to their target regions, which were extended by a single mass-modified nucleotide. The final extension reaction contained 0.222 μl iPLEX buffer plus (10×), 0.2 μl iPLEX termination mix, 0.041 μl iPLEX enzyme, 0.619 μl H_2O, and 0.940 μl of iPLEX extend primer mix at optimized concentrations (Sequenom). The working conditions for SBE extension were as follows: 94 °C for 30 s, followed by a total of 200 nested PCR cycles comprising 40 main cycles of 94 °C for 5 s, 5 subcycles of 52 °C for 5 s and 80 °C for 5 s, and a final extension for 3 min at 72 °C. To minimize background noise, iPLEX reaction products were treated with

cationic exchange resin for 30 min to remove salts. At the end of the experiment, samples were spotted on Spectro-CHIP arrays (Sequenom, San Diego CA, USA) using a MassArray Samsung Nanodispenser and scanned using a MALDI–TOF system. Genotyping results were analyzed using MassArray Typer 4.0 software. A negative water control and reference DNA were employed as quality control measures during the genotyping assay. In addition, approximately 5 % of the samples were randomly selected and repeated for genotyping as duplicated controls. As a result, the genotyping call rate was 100 %, and the results of genotype quality are shown in Supplementary Table 1.

Data collection and statistical analysis

Patient data were recorded with double entry verification using Epidata version 3.1. Unless specified, statistical analysis was performed using IBM Statistics SPSS version 19. Initially, demographic features between HCC patients and healthy controls were compared using a two-sided Chi squared test, to identify differences between these groups. Hardy–Weinberg equilibrium for each SNP was assessed using an online calculator with an alpha of 0.05. To establish univariate associations among environmental factors and polymorphisms, the odds ratio (OR) with a confidence interval of 95 % (95 % CI) was estimated using unconditional logistic regression.

Table 1 Demographic characteristic of hepatocellular carcinoma cases and controls

Variable	Cases ($n = 220$)		Controls ($n = 220$)		*P*
	N	%	*N*	%	
Age distribution					
≤30	3	1.8	3	1.8	
31–50	44	27.5	44	27.5	
51–70	86	53.8	86	53.8	
≥71	27	16.9	27	16.9	1
Gender					
Male	133	83.1	133	83.1	
Female	27	16.9	27	16.9	1
Education					
Elementary	98	61.3	92	57.5	
Middle school	36	22.5	31	19.4	
College or higher	26	16.3	37	23.1	0.289
Marital status					
Married	117	73.1	121	75.6	
Divorced	9	5.6	7	4.4	
Widowed	30	18.8	26	16.3	
Single	4	2.5	6	3.8	0.801
Alcohol consumption					
None	24	15	18	11.25	
Low	36	22.5	40	25	
Medium	68	42.5	76	47.5	
High	32	20	26	16.25	0.545
Age distribution					
≤30	3	1.8	3	1.8	
31–50	44	27.5	44	27.5	

Results

Subject Characteristics

The demographic characteristics of all study subjects are presented in Table 1. The match criteria applied in this study allowed for complete matching of age, gender, and ethnicity between the cases and healthy controls. Therefore, possible differences owing to these three above-mentioned factors were eliminated. Moreover, there were no statistically significant differences among cases and controls regarding education ($P = 0.289$) and marital status ($P = 0.801$). Alcohol consumption may be an important confounding factor among HCC cases without viral infection; therefore, we further examined the distribution of alcohol consumption between cases and controls; however, no statistical difference was observed ($P = 0.545$).

The genotype distributions of SNPs in *TP53*, *RECK*, *KIF1B*, and *MDM2* between HCC cases and controls are summarized in Table 2. The genotype distribution of four analyzed SNPs was in Hardy–Weinberg equilibrium in the control group ($P > 0.05$), suggesting that there was no sampling bias. The frequencies of CG and GG genotypes in *rs1042522* were significantly higher in cases than in controls, and the odds ratios were 2.46 (95 % CI 1.19–5.07) and 2.57 (95 % CI 1.21–5.43), respectively. Homozygous mutation of *rs1081432* conferred a 2.68-fold risk (95 % CI 1.35–5.34) of HCC; however, no statistical significance was observed in heterozygotes. In the case of *rs17401966* in *KIF1B*, neither hetero- nor homozygotes appeared to be at greater risk of HCC. Our analysis also revealed that the risk of HCC was significantly elevated in carriers of the TG or GG genotype in *rs2279744*, compared to subjects with the TT genotype. The odds ratios for homozygotes and heterozygotes were 3.04 (95 % CI 1.60–5.76) and 2.40 (95 % CI 1.33–4.33), respectively.

Discussion

Genetic variation in tumor suppressor genes or oncogenes is capable of altering gene function and, consequently, may contribute to the development of cancer. Significant research has been conducted to investigate the association

Table 2 Distribution of selected SNPs and the risk of hepatocellular carcinoma

Genotypes	Cases	Controls	Odds ratio (95 % CI)	*P*
rs1042522 (*TP53*)				
CC	13 (8.1)	29 (18.1)	1 (Ref.)	–
CG	86 (53.8)	78 (48.8)	2.46 (1.19–5.07)	*0.015*
GG	61 (38.1)	53 (33.1)	2.57 (1.21–5.43)	*0.014*
rs10814325 (*RECK*)				
TT	19 (11.9)	32 (20.0)	1 (Ref.)	–
CT	74 (46.3)	86 (53.8)	1.45 (0.76–2.77)	0.261
CC	67 (41.9)	42 (26.3)	2.68 (1.35–5.34)	0.005
rs17401966 (*KIF1B*)				
AA	76 (48.8)	78 (48.8)	1 (Ref.)	
AG	60 (37.5)	66 (41.3)	0.93 (0.58–1.50)	0.773
GG	24 (15.0)	16 (10.0)	1.54 (0.76–3.12)	0.232
rs2279744 (*MDM2*)				
TT	23 (14.4)	49 (30.6)	1 (Ref.)	
TG	80 (50.0)	71 (44.4)	2.40 (1.33–4.33)	0.004
GG	57 (35.6)	40 (25.0)	3.04 (1.60–5.76)	0.001

between polymorphisms in tumor suppressor genes and oncogenes, and the risk of hepatocellular carcinoma; however, the results remain controversial. *TP53* possesses numerous anticancer functions and plays a crucial role in apoptosis, genomic stability, and inhibition of angiogenesis [12]. A common polymorphism in codon 72 (rs*1042522*), which causes a C-to-G transversion, has been associated with increased susceptibility to multiple types of cancer, including hepatocellular carcinoma. This polymorphism has been shown to compromise the activity of TP53, including DNA repair, apoptosis, and cycle arrest activities [13]. Specifically, cell assays indicate that TP53 harboring the wild-type codon 72 exhibits an increased capability of transactivating p21 and inducing growth arrest compared to the variant, which can be a crucial step in the repair of DNA damage [14]. Compared to the variant, the wild-type form demonstrated a protective effect on mtDNA integrity and its function, by suppressing the heteroplasmy level, in vivo. Lower levels of mtDNA damage caused by rotenone stress were accumulated among wild type, and the wild type co-localizes with polymerase gamma more than wild type [15]. Gene knockout is widely accepted as the optimal technique to investigate gene function and provides solid evidence with detailed data. Various types of p53 knock-in mice have been generated, and these demonstrate different abilities to induce apoptosis in response to gamma irradiation. Immunohistochemical analysis revealed marked differences in apoptosis, with a twofold increase in the number of apoptotic cells in P72 mouse tissues compared to R72 mice [16]. In epidemiological studies, a case–control study conducted among hepatitis C virus-positive carriers revealed no association between codon 72 and HCC risk [17]. In contrast, Ezzikouri et al. [18] observed a 1.57-fold elevated risk of HCC among male individuals with the GG genotype, and the odds ratio reached 4.4 in women. The association remains constant after match with the HCV-free condition; the odds ratio was 3.3 in study subjects. According to our research, the GG genotype conferred a 2.57-fold risk of HCC (95 % CI 1.21–5.43), while carriers of the CG genotype exhibited a 2.46-fold risk of developing HCC (95 % CI 1.19–5.07). Our results are keeping with a recent meta-analysis involving 2,718 cases and 3,752 controls, which indicated that both GG and CG genotypes significantly elevated the risk of HCC among Asian and European populations [19].

MDM2 is an important negative regulator of the TP53 tumor suppressor. Additionally, the *rs2279744* polymorphism, which causes a T-to-G transversion, can further enhance the expression of *MDM2*, thereby attenuating the function of TP53. We identified that both homozygous and heterozygote *rs2279744* genotypes were positively correlated with increased risk of HCC, with ORs of 3.04 (95 % CI 1.60–5.76) and 2.40 (95 % CI 1.33–4.33), respectively. As previously discussed, MDM2 is capable of interacting with TP53 and is one of the central nodes in the *TP53* pathway. Animal experiments have shown that even slight changes in the expression of *MDM2* may compromise the TP53 pathway in mice and induce cancer [20]. Western blot analysis was performed to determine the expression level of alternatively spliced *MDM2* transcripts, and elevated levels were observed in cells with the GG genotype. Interestingly, colony formation assays revealed that the expression of this alternatively spliced *MDM2* transcript could enhance colony formation, suggesting the existence of TP53-independent tumorigenic properties [21]. Dong et al. [22] investigated the *rs2279744* genotype among 173 patients with chronic lymphocytic leukemia (CLL) and 260 healthy controls by polymerase chain reaction–restriction fragment length polymorphism, and found that the unfavorable GG genotype significantly increased the risk of developing CLL, with an OR of 2.84. Furthermore, the expression of *MDM2* mRNA was also elevated in the CLL patient group. According to a systematic review of pooled data extracted from 10 independent studies [23], the GG genotype conferred a 1.831-fold risk of developing HCC when compared to the TT genotype. However, data for HBV-free subjects were not available for a subgroup analysis; therefore, we were not able to compare our results with this meta-analysis. Taken together, we conclude that the *rs2279744* GG genotype is positively correlated with

HCC risk and may serve as a marker for evaluating and assessing risk in the general population.

RECK encodes a membrane-anchored glycoprotein of ~110 kDa, with multiple epidermal growth factor-like repeats and serine protease inhibitor-like domains. *RECK* was first identified by Takahashi et al. [24] in the *v-Ki-ras*-transfected NIH3T3 cell line and is thought to be a metastasis suppressor. Cell assays confirmed that *RECK* mRNA is expressed in normal human tissues and untransformed cells, while expression was not detectable in tumor-derived cell lines. The expression of *RECK* in malignant cells can lead to repression of invasive activity and decrease the level of matrix metalloproteinase-9 (*MMP-9*). Oh et al. [25] also found that *RECK* regulates *MMP-2* and *MT1-MMP*, which are involved in cancer progression. However, the mechanism by which RECK regulates the *MMP* family remains unknown. In a study of 64 patients with HCC, Furumoto et al. [26] found that cases with high expression of *RECK* mRNA exhibited better survival and less invasive tumors, suggesting that RECK may serve as a promising prognostic biomarker for HCC. A case–control study was performed to evaluate the impact of polymorphisms in the *RECK* gene with HCC risk in the Taiwanese population [27]. The crude ratio was 2.15 (95 % CI 1.21–3.82) for the CC genotype in *rs10814325* and 2.18 (95 % CI 1.28–3.70) for the TC genotype. After adjusting for age, gender, and other possible confounders, the adjusted ORs for the CC and TC genotypes were 2.18 (95 % CI 1.21–3.94) and 2.11 (95 % CI 1.11–4.03), respectively. Similarly, in our study, the CC genotype was significantly associated with elevated risk, with an OR of 2.68 (95 % CI 1.35–5.34). A modest increase in HCC risk was also observed among subjects with the CT genotype; however, this was not statistically significant. This may be partly attributed to the limited number of subjects enrolled in our study; therefore, additional studies involving a larger cohort of patients are required.

Genome-wide association studies (GWASs) allow us to identify SNPs associated with a disease on a large scale. Recently, a GWAS was conducted by Zhang et al. [28] to identify SNPs responsible for the development of HCC among carriers of the hepatitis B virus. This study revealed that a polymorphism in the *KIF1B* intron on chromosome 1p36.22 (*rs17401966*) was strongly associated with HBV-related HCC, and this finding was further validated in five additional samples, involving 1,962 cases with HCC and 1,430 controls. Direct sequencing was employed to genotype the *rs17401966* in 202 HCC patients of Thai origin with chronic HBV infection and 196 HBV carriers without HCC, and binary logistic regression analysis revealed no significant association [29]. Notably, a meta-analysis revealed that the G allele can significantly reduce the risk of HCC in the Chinese population, with a pooled OR of 0.76 (95 % CI 0.64–0.90). This significance was retained in a large sample size subgroup, regardless of ethnicity. These findings suggest that the G allele may confer a protective effect against the development of HCC. However, our data indicate that neither hetero- nor homozygosity of *rs17401966* is related to increased risk of HCC. We assume that it may attribute to the HBV-free subjects we enrolled, and this polymorphism may possibly interact with the chronic HBV infection and consequently involved with the change of disease risk. It is also possible that the lack of significance may owe to the limited number of subjects in our study; therefore, additional studies involving a larger cohort of patients are required to clarify this issue.

In summary, we demonstrated that polymorphisms in *TP53*, *MDM2*, and *RECK* may affect the risk of developing HCC in an HBV-free Chinese population. Our results suggest that polymorphisms can serve as biomarkers for evaluating HCC risk in the general population. However, further studies are still required.

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Conflict of interest The authors have no conflicts of interest to disclose.

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