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RESEARCH ARTICLE

DNA double-strand break repair gene *XRCC7* genotypes were associated with hepatocellular carcinoma risk in Taiwanese males and alcohol drinkers

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Abstract Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, the prevalence and mortality rates of which are very high in Taiwan. The study aimed at evaluating the contribution of *XRCC7* G6721T, together with cigarette smoking and alcohol drinking lifestyles, to the risk of HCC. In this hospital-based case-control study, the association of *XRCC7* single nucleotide polymorphism G6721T with HCC risk was examined by polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) among 298 HCC patients and 889 age- and gender-matched healthy controls. The results showed that the percentages of TT, GT, and GG *XRCC7* G6721T were 53.0, 41.3, and 5.7 % in the HCC patient group and 48.9, 43.1, and 8.0 % in the non-cancer control group, respectively. We have further stratified the populations by genders, cigarette smoking, and alcohol drinking status to investigate their combinative contributions with *XRCC7* G6721T genotype to HCC risk. The results showed that the GG genotype of *XRCC7* G6721T conducted a protective effect on HCC susceptibility which was obvious among males and drinkers, but not females, smokers, non-smokers, or non-drinkers (p=0.0058, 0.0069, 0.1564, 0.2469, 0.9354, and 0.3416, respectively). Our results suggested that the GG and GT genotypes of X-ray repair cross-complementing group 7 (XRCC7) G6721T had no effect on HCC risk to the whole population, but had a protective effect on HCC risk among males and alcohol drinkers.

Keywords Drinking · Genotype · Hepatocellular carcinoma · Polymorphism · Smoking · XRCC7

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Introduction

Liver cancer is the fifth cancer worldwide in men and the seventh in women. It also is the second and sixth leading cause of deaths in men and women, respectively. Statistically, over 80 % of the liver cancer cases were from low-income or middle-income countries, and about 50 % were from the China population alone [1]. Clinically, hepatocellular carcinoma (HCC) is the main type of liver cancer, accounting for over 90 % of cases. Environmental factors for HCC included chronic infections with hepatitis B and C viruses, alcohol and alcohol-related cirrhosis, tobacco consumption, overweight, diabetes, and contamination of cereal foodstuff with aflatoxin in selected countries [2–4]. Useful biomarkers for identifying high-risk populations as well as novel early detection and prediction tools together with preventive care are urgently needed. Low-penetrance susceptibility genes combined with environmental factors

have been believed to play an important role in carcinogenesis, and subtle polymorphic defects in the DNA repair may ruin the preventive system and initiate and progress the tumorigenesis.

One of the most detrimental forms of DNA damage is the double-strand break (DSB) because DNA may lose its physical integrity and information content on both strands in this case [5]. Homologous recombination (HR) and non-homologous end joining (NHEJ) are the two important pathways for removing the DSBs induced by endogenous and exogenous carcinogens. HR, which acts during the transition of S to G2 phases of the cell cycle, entails copying the missing information from an undamaged homologous chromosome. In NHEJ, which acts during all phases of the cell cycle, the broken DNA termini are first processed to make them compatible and then sealed by a ligation step. Among the NHEJ DNA repair proteins, human X-ray repair cross-complementing group 7 (XRCC7) (MIM: 600899; GenBank accession no.: NM_001469) plays a central role encoding the catalytic subunit of DNA-activated protein kinase (DNA-PKcs) of the NHEJ pathway [6]. It should be noted that NHEJ is the dominant subpathway for DSB repair in human cells [6]. The DNA-PK complex is also known as PRKDC, HYRC, and HYRC1. Whenever DSB is formed and detected, DNA-PKcs is recruited to the DSBs by the KU70/KU80 heterodimer to form an active DNA-PK complex that is essential for the progression of the NHEJ pathway [7]. Deficiencies in DNA-PK activity are clinically significant, and mice with inactivated components of DNA-PK show severe combined immunodeficiency as well as ionizing radiation hypersensitivity [8, 9]. There were three reports that investigated the association of *XRCC7* polymorphic genotypes with human diseases such as cancers [10–23], and most of them focused on the three polymorphic variants, rs7003908 (T>G), rs7830743 (A>G), and rs10109984 (T>C). Among them, G6721T of *XRCC7* (rs7003908) is located in intron 8 of the gene. It is speculated that this polymorphism may regulate splicing and cause messenger RNA (mRNA) instability [7]. Although several studies that examined the association of G6721T polymorphism of *XRCC7* with several types of cancer have been published [10–14, 16, 20], few have been focused on HCC [21].

As for the overall DSB repair system, some previous reports showed that the genotypes of DSB repair genes, especially those NHEJ genes, may interact with environmental factors such as smoking or hepatitis C virus infection in determining the relative risk of HCC [24–26]. In this study, we aimed at revealing the genotypic frequencies of genotypes of G6721T polymorphism of *XRCC7* and focusing on the combined effects of *XRCC7* genotypes with environmental factors on HCC susceptibility among Taiwanese people.

Materials and methods

Investigated population and sample collection

Two hundred and ninety-eight patients diagnosed with HCC were recruited at the Department of General Surgery at the China Medical University Hospital, Taiwan, in 2004–2010. Each patient and non-cancerous healthy person completed a self-administered questionnaire and provided their peripheral blood samples. Originally, three times as many non-cancer healthy volunteers as controls were selected by matching for age and gender after initial random sampling from the Health Examination Cohort of our hospital. The exclusion criteria of the controls included previous malignancy, metastasized cancer from other or unknown origin, and any genetic or familial diseases. The included control population was 898. Our study was approved by the Institutional Review Board of the China Medical University Hospital (DMR103-IRB-094), and written informed consent was obtained from all participants.

Genotyping conditions

Genomic DNA was extracted from peripheral blood leukocytes using the QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and stored as previously published [27–29]. The paired primers used for G6721T polymorphism of *XRCC7* were forward 5′-TGGTGCTCAGCTTCTGGCTT-3′ and reverse 5′-CATCCCTGCCAGCTCTTCTG-3′. The *XRCC7* G6721T polymerase chain reaction (PCR) conditions were 1 cycle at 94 °C for 5 min; 35 cycles of 94 °C for 30 s, 55 °C for 30 s, and 72 °C for 30 s; and a final extension at 72 °C for 10 min.

Restriction fragment length polymorphism conditions

After the PCR process of *XRCC7* G6721T, the resultant 301-bp PCR product was mixed with 2 U *Taq*$^{\alpha}$I and incubated for 3 h at 65 °C in CutSmart™ Buffer (New England BioLabs, Taipei, Taiwan). The G form PCR products could be further digested while the T form could not. Two fragments, 235 and 66 bp, were present if the product was digestible G form. Then, 10 μl of product was loaded into a 3 % agarose gel containing ethidium bromide for electrophoresis. The genotype analysis was performed by two researchers independently and blindly. During this process, five of the control samples were excluded since their PCR products were not sufficient for clear genotyping recognition after PCR-restriction fragment length polymorphism (RFLP).

Statistical analyses

Further, four of the controls without records of their smoking and drinking status were also excluded. Finally, 889 of the

Table 1 Distributions of selected demographic data of the 298 hepatocellular carcinoma patients and the 889 matched controls

Characteristic	Controls (n=889)			Patients (n=298)			p value[a]
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			55.4 (4.9)			52.3 (4.5)	0.7418
Gender							
Male	636	71.5		213	71.5		
Female	253	28.5		85	28.5		0.9830
Smoking status							
Ever smokers	579	65.1		224	75.2		
Non-smokers	310	34.9		74	24.8		0.0017*
Drinking status							
Ever drinkers	518	58.3		206	69.1		
Non-drinkers	371	41.7		92	30.9		0.0011*

*p<0.05

[a] Based on chi-square test

controls and 298 cases with genotypic and clinical data were analyzed and the data were shown in the tables. Pearson's chi-square and Fisher's exact (when one or more cells were less than five) tests were used to compare the distribution of the genotypes between case and control groups. Data were recognized as significant when the statistical p value was less than 0.05. The HCC risk associated with the genotypes was estimated as an odds ratio (OR) and 95 % confidence interval (CI) by logistic regression.

Results

The frequency distributions of selected characteristics for the 298 HCC patients and 889 non-cancer controls are summarized in Table 1. Since we have applied frequency matching to select the non-cancer healthy controls, distributions of age and gender were comparable among the cases and the controls (Table 1). The cases had a significantly higher percentage of smokers (71.5 vs. 65.1 %, p=0.0522) and drinkers (69.1 vs. 58.3 %, p=0.0011) than the controls (Table 1).

The distributions of the *XRCC7* G6721T genotypes among the controls and the HCC patients are provided and analyzed in Table 2. The frequencies of TT, GT, and GG genotypes at *XRCC7* G6721T were 53.0, 41.3, and 5.7 % in the HCC patients and 48.9, 43.1, and 8.0 % in the controls, respectively (Table 2). Statistically speaking, the *XRCC7* G6721T heterozygous GT and homozygous GG genotypes were not significantly associated with HCC risk.

There were more males than females of HCC patients in Taiwan, and we are interested in the genotypic contribution of *XRCC7* G6721T to gender difference of HCC susceptibility. After the stratification by the gender, it was found that the genotypes of *XRCC7* G6721T were differently distributed among males (p=0.0058) but not females (p=0.1564) (Table 3).

The interaction of the genotype of *XRCC7* G6721T and lifestyles such as cigarette smoking and alcohol drinking of the participants was of great interest since HCC is one of the

Table 2 Distribution of XRCC7 genotypes among the 298 hepatocellular carcinoma patients and the 889 matched controls

Genotype	Controls		Patients		OR (95 % CI)	p value[a]
	n	%	n	%		
rs7003908						
TT	435	48.9	158	53.0	1.00 (reference)	
GT	383	43.1	123	41.3	0.88 (0.67–1.16)	0.4148
GG	71	8.0	17	5.7	0.66 (0.38–1.15)	0.1813
p value for trend						0.2886
(GT+GG) vs. TT					0.85 (0.65–1.10)	0.2482
GG vs. (TT+)					0.70 (0.40–1.20)	0.2406

[a] Based on chi-square test

Table 3 Distribution of *XRCC7* genotypes among patients with hepatocellular carcinoma after stratification by genders

Variable	G6721T genotype			*p* value[a]
	TT (%)	GT (%)	GG (%)	
Males				
Controls	302 (47.5 %)	281 (44.2 %)	53 (8.3 %)	
Cases	121 (56.8 %)	86 (40.4 %)	6 (2.8 %)	0.0058*
Females				
Controls	133 (52.6 %)	102 (40.3 %)	18 (7.1 %)	
Cases	37 (43.5 %)	37 (43.5 %)	11 (13.0 %)	0.1564

*$p<0.05$

[a] Based on chi-square test

smoking- and alcohol-related cancers. The results in Table 4 showed that the genotypic distribution of the variant *XRCC7* G6721T genotypes was not different between the HCC and control groups, among whom were ever smokers ($p=0.2469$) or those who were non-smokers ($p=0.9354$) (Table 4). Interestingly, the results in Table 5 showed that the genotypic distribution of the variant *XRCC7* G6721T genotypes was different between the HCC and control groups who were ever drinkers ($p=0.0069$), but not different in the case among the non-drinkers ($p=0.3416$) (Table 5). Overall, it seemed that there was an interaction between *XRCC7* G6721T genotype and drinking lifestyle to the HCC susceptibility.

Discussion

The NHEJ genes such as *XRCC4*, *XRCC5*, *XRCC6*, and *XRCC7* take care of the genome integrity and consequently cell survival. Subtle genetic variations such as single nucleotide polymorphisms in these genes may escape the cell cycle checking point surveillance and lead to suboptimal overall DNA repair, allowing DNA damage to accumulate and trigger carcinogenesis [30]. As the catalytic subunit of the DNA-PK

Table 4 Distribution of *XRCC7* genotypes among patients with hepatocellular carcinoma after stratification by personal smoking habits

Variable	G6721T genotype			*p* value[a]
	TT (%)	GT (%)	GG (%)	
Smokers				
Controls	280 (48.4 %)	249 (43.0 %)	50 (8.6 %)	
Cases	114 (53.5 %)	87 (40.8 %)	12 (5.7 %)	0.2469
Non-smokers				
Controls	155 (50.0 %)	134 (43.2 %)	21 (6.8 %)	
Cases	44 (51.7 %)	36 (42.4 %)	5 (5.9 %)	0.9354

[a] Based on chi-square test

Table 5 Distribution of *XRCC7* genotypes among patients with hepatocellular carcinoma after stratification by personal alcohol drinking habits

Variable	G6721T genotype			*p* value[a]
	TT (%)	GT (%)	GG (%)	
Drinkers				
Controls	243 (46.9 %)	239 (46.1 %)	36 (7.0 %)	
Cases	116 (56.3 %)	86 (41.8 %)	4 (1.9 %)	0.0069*
Non-drinkers				
Controls	192 (51.8 %)	144 (38.8 %)	35 (9.4 %)	
Cases	42 (45.7 %)	37 (40.2 %)	13 (14.1 %)	0.3416

*$p<0.05$

[a] Based on Fisher's exact (drinkers) and chi-square (non-drinkers) tests

complex, XRCC7 plays a role in NHEJ via recognition and repair of the DNA DSBs [31]. Mice with DNA-PK inactivation were ionizing radiation hypersensitive and immunodeficient [8, 9]. In addition, cells defective in DNA-PK components are incapable of repairing DSBs and hypersensitive to ionizing radiation [32]. The *XRCC7* G6721T may regulate alternative splicing and cause the instability of its mRNA [7], and is further associated with increased cancer risk [10–13, 16, 19]. In this study, we have strengthened our analyzing power via enrolling a larger population of controls than our previous papers [24, 33, 34]. In Table 1, the cigarette smoking and alcohol drinking lifestyles were found to be risky environmental factors for HCC, although the former seemed to be at the borderline (Table 1). From the results, the GT and GG genotypes of *XRCC7* G6721T were not associated with HCC risk in the whole population (Table 2); however, they seemed to be a protective factor of HCC for only the Taiwanese males (Table 3). As for the females, the frequency of wild-type TT genotype was lower in the case group (43.5 %) than in the control group (52.6 %), but the difference did not reach the statistically significant level; either were not of the same trend (TT frequency higher in the cases than in the controls) as in the males (Table 3). As liver cancer is recognized to be one of the tobacco- and alcohol-related cancers [4, 35], the combined effects of *XRCC7* genotypes with smoking and drinking lifestyles on HCC risk in Taiwan were also of interest. As for the smoking lifestyle, it is found that there was no association between the *XRCC7* genotype with HCC risk among either ever smokers or non-smokers (Table 4). As for the alcohol drinking lifestyle, the association between *XRCC7* genotypes with HCC risk was obvious among ever drinkers but not non-drinkers (Table 5). The detailed explanation of the difference among the subgroups needs further investigation. Very possibly, the role of XRCC7 in hormone- or alcohol-induced DNA DSBs was somehow different from that in tobacco-induced DNA DSBs. Overall, although the genetic variation of *XRCC7* G6721T was not found to directly result in an amino

acid coding change, it might influence the expression level or stability of the XRCC7 protein as well as its function in NHEJ and genome maintenance. The low penetration of XRCC7 genetic variation may contribute to only specific patients' HCC carcinogenesis so that we could not find a significant association in the whole HCC population (Table 2), but did in a special subgroup (Tables 3, 4, and 5). Overall, male people carrying the T allele in *XRCC7* G6721T may have a lower capacity than those carrying the G allele in the DSB-removing capacity, especially for alcohol-induced HCC development.

The current study has several limitations and improving directions. First, the hospital-based study could enhance the representative power by enlarging the sample size of the cases. Second, other confounding factors such as obesity and virus infection status could not be taken into consideration and adjusted. In 2011, Long and his colleagues found that the *XRCC7* G6721T genotype was associated with HCC risk and closely related to aflatoxin B1 exposure among people in Guangxi, China [21]. The sample size of that study contained 348 HCC cases and 597 controls, much similar to the level of the current study. In vivo studies could be performed to reveal the contribution of *XRCC7* to HCC carcinogenesis, such as those comparing the expression alterations at mRNA and protein levels for *XRCC7* between the paired tumor and non-tumor sites from the same group of HCC patients with specific *XRCC7* genotypes. Also, the role of *XRCC7* genotypes among various cancers and populations is still inconclusive in the previous papers and needs further investigations [36].

In conclusion, our findings suggested that the G allele of *XRCC7* G6721T had no effect on HCC risk to the whole population, but had a protective effect on HCC risk among males and alcohol drinkers.

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Conflicts of interest None

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