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ORIGINAL RESEARCH

Significant Contribution of DNA Repair *Human 8-Oxoguanine DNA N-Glycosylase 1* Genotypes to Renal Cell Carcinoma

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Introduction: DNA repair systems play essential roles in genomic stability and carcinogenesis. Therefore, genotypes at DNA repair loci may contribute to the determination of personal susceptibility to cancers. The contribution of *human 8-oxoguanine DNA N-glycosylase 1* (*hOGG1*) genotypes to renal cell carcinoma (RCC) is largely unknown. This study aimed to evaluate the contributions of *hOGG1* rs1052133 genotypes to the RCC risk.

Methods: We evaluated the contribution of *hOGG1* rs1052133 (G/C) genotypes among 118 cases and 590 controls and analyzed the interactions of *hOGG1* genotypes with smoking, alcohol drinking, hypertension, and diabetes status.

Results: The *hOGG1* rs1052133 CC genotype was significantly associated with a decreased RCC risk compared with that of the GG genotype (odds ratio [OR] = 0.25, 95% confidence interval [CI] = 0.09–0.72, p = 0.0049). The frequency of the rs1052133 C allele was significantly low in the RCC group (22.5% vs 31.2%; OR = 0.64; 95% CI = 0.46–0.89, p = 0.0074). Stratifying the analysis according to smoking, alcohol drinking, and diabetes status revealed no difference in the rs1052133 genotype distribution among these subgroups. A significant differential distribution of rs1052133 genotypes was observed among subjects with hypertension.

Conclusion: The CC genotype of rs1052133 may play a role in determining RCC susceptibility among Taiwanese people and may serve as a biomarker of RCC, particularly in patients with hypertension.

Keywords: *hOGG1*, genotype, polymorphism, renal cell carcinoma

Introduction

Renal cell carcinoma (RCC) imposes a serious disease burden; among the most frequently diagnosed cancers worldwide, RCC is the 6th one in men and the 10th in women.[1] Clinically speaking, RCC has been recognized as the most common renal cancer, and its subtypes can be distinguished from one another based on their differences in histology, genetic background, clinical course, and differential responses to treatment.[2,3] From a personalized medical viewpoint, several behavioral factors, such as personal physical activity, obesity, fruit and vegetable intake, cigarette smoking, and alcohol consumption, are identified as risk factors of RCC. Some clinical and medical comorbidities, including hypertension, diabetes, urinary stones, other forms of chronic kidney disease, and a family history of cancer, are associated with RCC.[3] However, to date, few clinically practical biomarkers in the

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genome have been identified as early predictors of the RCC risk. Many patients with RCC, even those with advanced stage tumors, are free of obvious symptoms,[2,4] and RCC is not detectable at the first visit to doctors. The worst situation is that up to 30% of patients with RCC treated with radical nephrectomy suffer from many adverse effects and face high odds of recurrence soon after their surgery.[5] Currently, personal identification as a patient with RCC is based on a series of labor-intensive and time-consuming histological validation processes. Therefore, genomic biomarkers should be elucidated for the precise detection and identification of RCC.

Several gatekeepers, such as DNA repair systems, including base excision repair (BER), mismatch repair, and nucleotide excision repair, which are responsible for maintaining the stability of our genome, have evolved and cooperated to prevent cells from undergoing carcinogenesis.[6–8] The most abundant oxidative DNA adduct 8-oxoguanine (8-oxoG), mainly produced by reactive oxygen species, is the cause of oxidative damage leading to a transversion from G:C→T:A and causing the development of carcinogenesis.[9,10] Human 8-oxoG DNA N-glycosylase 1 (hOGG1) is a pilot enzyme in the BER pathway for the detection and recognition of 8-oxoG in our genome.[6,11] Functional studies have shown that the genotype at rs1052133 (Ser326Cys) single nucleotide polymorphism (SNP) in exon 7 of *hOGG1* may determine the glycosylase activity[12,13] and serve as a genomic predictor of personal susceptibility to various cancer types.[14–19]

Therefore, in this study, we aimed to determine whether the *hOGG1* rs1052133 polymorphism is associated with the RCC risk in Taiwan and to elucidate the interactions of this SNP with several clinical and behavioral factors.

Materials and Methods

Investigated Population

This case–control study was conducted in China Medical University Hospital. RCC was diagnosed by Dr. Wu's surgical team, while the grades and types of each patient with RCC were histopathologically confirmed by well-trained pathologists. Among 139 patients interviewed, 118 (85%) agreed to participate and were included in this study. For each patient with RCC, five controls were frequency-matched and recruited in the Health Examination Center of China Medical University Hospital. They had the same gender as the patients and ± 2 years of his/her age. None of the cancer-free controls had any biological relationship with one another. The inclusion criteria of the controls were the citizens of Taiwan without any history of any cancer type. All the controls were within the normal range of carcinoembryonic antigen (CEA) and identified as cancer-free. After the pre-screen first-term matching process, patients with incomplete demographic data about smoking, alcohol drinking status, hypertension, diabetes, or family history of cancer were excluded. Then, a further exclusion criterion among the control candidates was set as any symptom suggestive of RCC, such as hematuria. A five-fold number (590) of controls were retained for genotyping experiments and analytical processes. Each participant completed a written informed consent and provided 3–5 mL of his/her venous blood for the genotyping experiments under the guidance and supervision of the Institutional Review Board of China Medical University Hospital (DMR98-IRB-209). All the clinical investigations and records in this study were restrictively performed in accordance with the principles expressed in the Declaration of Helsinki. The selected demographic characteristics of all the participants are summarized and compared in Table 1.

DNA Preparation and Storage

Genomic DNA from the leukocytes of each study subject was extracted within 24 h after collection by using a QIAamp blood mini kit (Qiagen, Valencia, CA, USA), stored at −80°C, simultaneously diluted, aliquoted, and stored for genotyping as a working stock at −20°C as we previously reported.[20–24]

hOGG1 Genotype Discrimination Methodology

The *hOGG1* rs1052133 polymorphic site was genotyped as we previously described in 2013.[18,25] Polymerase chain reaction (PCR)–restriction fragment length polymorphism analysis was performed. The sequences of forward and reverse primers for *hOGG1* rs1052133 genotyping were 5′-ACTGTCACTAGTCTCACCAG-3′ and 5′-GGAAGG TGGGAAGGTG-3′, respectively. In detail, 100 ng of the genomic DNA of each sample was subjected to a typical PCR. In this procedure, a 25 μL reaction mixture contained 300 μM dNTP, 2 U *Taq* DNA polymerase, 1× PCR buffer, 1.5 mM $MgCl_2$, and 0.8 μM of each designed primer. After the mixture was thoroughly mixed, the overall reaction mixture was heated to 94°C for 4 mins and

Table 1 Analysis of the Distributions of Demographic Characteristics Among the RCC Cases and Healthy Controls

Characteristics	Cases (n = 118)		Controls (n = 590)		*p*-value
	N	%	N	%	
Age, mean ± SD	58.8 ± 9.9		58.2 ± 9.9		0.8256
≤ 60	61	51.7%	310	52.5%	0.8664
> 60	57	48.3%	280	47.5%	
Gender					
Male	76	64.4%	380	64.4%	1.0000
Female	42	35.6%	210	35.6%	
Smoking status					
Smokers	50	42.4%	229	38.8%	0.4701
Non-smokers	68	57.6%	361	61.2%	
Alcohol drinking status					
Drinkers	49	41.5%	217	36.8%	0.3312
Non-drinkers	69	58.5%	373	63.2%	
Hypertension					
Yes	79	66.9%	296	50.2%	0.0009*
No	39	33.1%	294	49.8%	
Diabetes					
Yes	26	22.0%	108	18.3%	0.3452
No	92	78.0%	482	81.7%	
Family cancer history					
Yes	11	9.3%	18	3.1%	0.0011*
No	107	90.7%	598	96.9%	
Histological types					
Clear cell	91	77.1%			
Non-clear cell	27	22.9%			
Histological grades					
Low	63	53.4%			
Middle and high	55	46.6%			

Notes: *Statistically significant.

steadily amplified with My Cycler (Bio-Rad, Hercules, CA, USA) with 30 cycles of denaturation at 94°C for 60 s, annealing at 60°C for 60 s, and extension at 72°C for 60 s. A final extension step at 72°C for 5 mins was conducted. The volume of the restriction enzyme digestion was set at 12.5 μL that contained 8 μL of PCR products, 2 U Fnu4H *I* restriction enzyme, and 1× buffer. The reaction mixture was then incubated at 60°C for 16 hrs or overnight to allow complete digestion. The resultant DNA fragments were then subjected to 3.0% agarose gel electrophoresis at a constant voltage of 100 V for 30 mins. After electrophoresis, the gels were immediately stained with ethidium bromide and imaged under UV (260 nm) light to observe DNA fragments. For the C allele of *hOGG1* rs1052133, the single 200 bp fragment was no longer digested. For the G allele, two (100 and 100 bp) fragments were observed as a single band after gel electrophoresis. Any result with both types of bands was identified as the heterovariant CG genotype of *hOGG1* rs1052133.

Statistical Analysis

In this study, 590 cancer-free healthy controls and 118 patients with RCC were analyzed for their genotypic and clinical details as shown in Tables 1 and 2 and Figures 1–4. The deviation of the genotype frequencies of *hOGG1* SNPs in the control subjects from those expected under Hardy–Weinberg equilibrium was assessed using a goodness-of-fit test to ensure that the control subjects in this study were

Table 2 Analysis of *hOGG1* Rs1052133 Genotypic and Allelic Frequency Distributions Among the Renal Cell Carcinoma Patients and Healthy Controls

rs1052133	Controls		Patients		*p*-Value[a]	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
	Number	%	Number	%			
Genetic frequency							
GG	288	48.8%	69	58.5%		Reference (1.00)	Reference (1.00)
CG	236	40.0%	45	38.1%	0.2781	0.80 (0.53–1.20)	0.78 (0.56–1.13)
CC	66	11.2%	4	3.4%	0.0049*	0.25 (0.09–0.72) *	0.31 (0.14–0.69)*
P_{trend}					0.0188*		
P_{HWE}					0.0983		
GG	288	48.8%	69	58.5%		Reference (1.00)	Reference (1.00)
CG+CC	302	51.2%	49	41.5%	0.0554	0.68 (0.45–1.01)	0.55 (0.47–0.88)*
Allelic frequency							
Allele G	812	68.8%	183	77.5%		Reference (1.00)	Reference (1.00)
Allele C	368	31.2%	53	22.5%	0.0074*	0.64 (0.46–0.89)*	0.59 (0.43–0.83)*

Notes: *Statistically significant. [a]Based on Chi-squared test without Yates' correction or Fisher's extraction when the number is less than 5. [b]Adjust for age, gender, smoking, alcohol drinking, hypertension, diabetes and family history status.
Abbreviations: OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg Equation.

representative of the general Taiwanese population and to exclude the possibility of genotyping error (Table 2). Pearson's chi-square test and Fisher's exact test (when any cell was less than 5 persons) were adopted to compare the distribution of *hOGG1* genotypes between the cases and control groups and conduct stratification analysis. The difference in age, which is a continuous factor, was evaluated via Student's *t*-test. The association of *hOGG1* genotypes with the risk of RCC was estimated in terms of odds ratios (ORs) and their counterpart 95% confidence intervals (CIs) through logistic regression analysis with or without adjustment for possible confounders as indicated in table footnotes. Any $p < 0.05$ was considered to indicate a statistically significant result.

Results

Comparisons of Demographic Characteristics Among the Investigated Subjects

The frequency distributions of age, gender, and behavioral habits, such as smoking and alcohol drinking status, of the 118 patients with RCC and the 590 cancer-free control subjects were compared (Table 1). The control subjects were matched with the patients with RCC for age and gender during subject selection, so no difference was observed between the two groups in terms of age and gender ($p > 0.05$). No preferential difference was found in the frequencies of diabetes status or personal behavioral

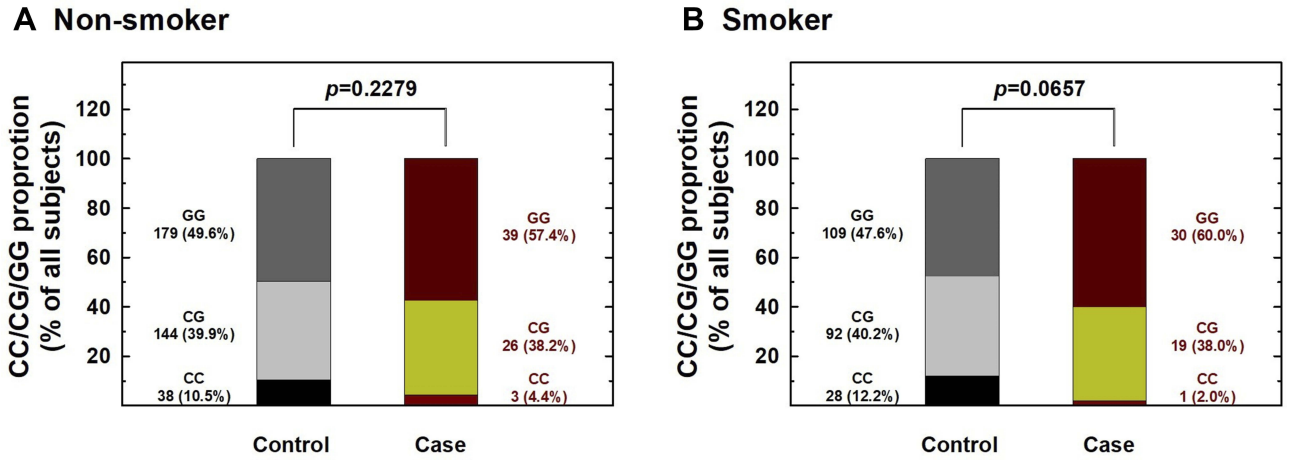

Figure 1 Contribution of *hOGG1* rs1052133 genotype to the risk of renal cell carcinoma after stratification by smoking status. The distributions of GG, CG, and CC genotypes at *hOGG1* rs1052133 among non-smokers (**A**) and smokers (**B**).

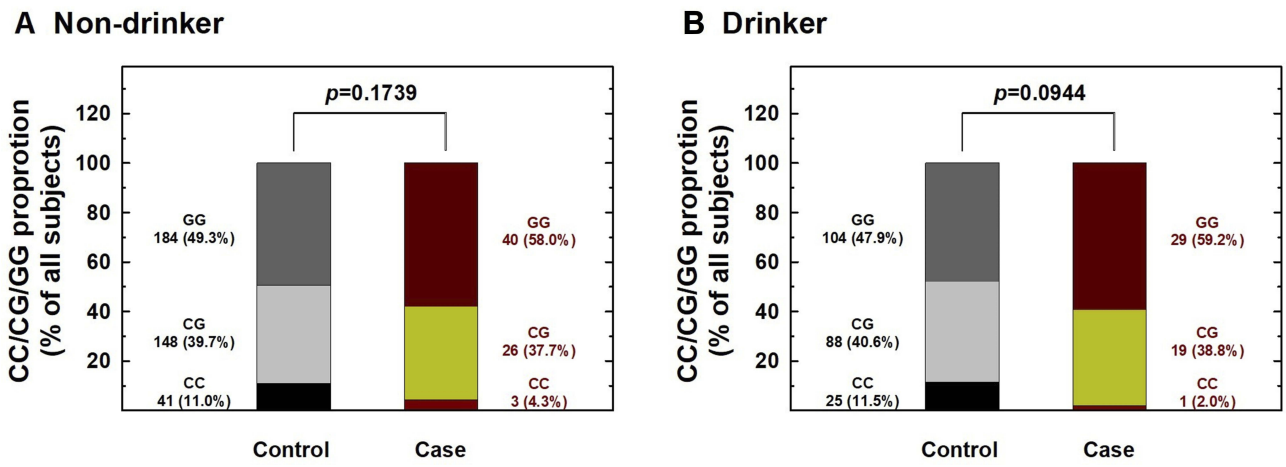

Figure 2 Contribution of *hOGG1* rs1052133 genotype to the risk of renal cell carcinoma after stratification by alcohol consumption status. The distributions of GG, CG, and CC genotypes at *hOGG1* rs1052133 among non-drinkers (**A**) and drinkers (**B**).

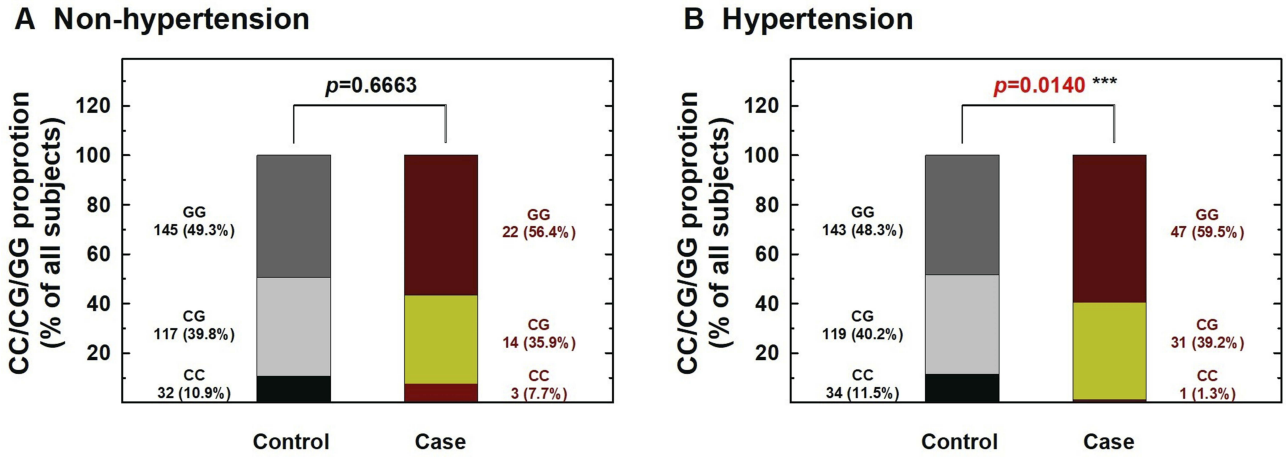

Figure 3 Contribution of *hOGG1* rs1052133 genotype to the risk of renal cell carcinoma after stratification by hypertension status. The distributions of GG, CG, and CC genotypes at *hOGG1* rs1052133 among individuals without (**A**) and with (**B**) hypertension. (*** Statistically significant between case and control groups).

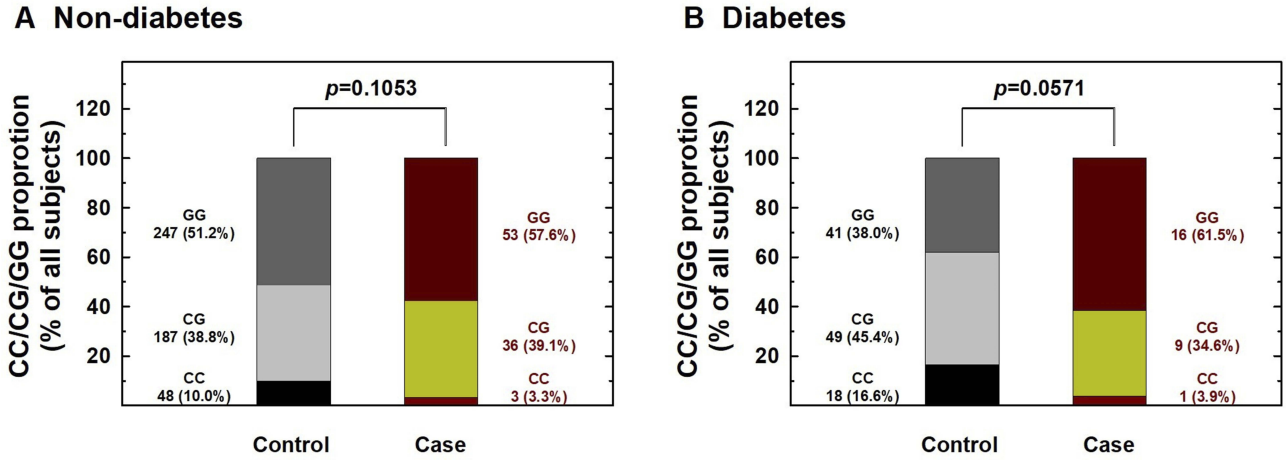

Figure 4 Contribution of *hOGG1* rs1052133 genotype to the risk of renal cell carcinoma after stratification by diabetes status. The distributions of GG, CG, and CC genotypes at *hOGG1* rs1052133 among individuals without (**A**) and with (**B**) diabetes.

habits, such as smoking or alcohol consumption ($p > 0.05$) between the two groups (Table 1). Interestingly, the rate of family history of cancer of patients with RCC was higher than that of the controls (9.3% versus 3.1%, $p = 0.0011$). This result indicated that RCC is an inherited disease. The results also showed that the percentage of subjects with hypertension in the RCC group (66.9%) was higher than that of the control group (50.2%; $p = 0.0009$). From a histological angle, 77.1% of patients had the most frequently occurring RCC subtype, namely, clear cell RCC (ccRCC). The proportions of patients with low-grade and middle- and high-grade RCC were 53.4% and 46.6%, respectively (Table 1).

Analysis of the Association of hOGG1 Genotypes with RCC Risk in Taiwan

The observed genotypic and allelic frequencies of *hOGG1* rs1052133 among RCC cases and controls and their associations with the risk of RCC are summarized in Table 2. The *hOGG1* rs1052133 genotypes among healthy controls were in a Hardy–Weinberg equilibrium ($p = 0.0983$). In the trend analysis, the distributions of *hOGG1* rs1052133 genotypes significantly differed between the control and case groups ($p = 0.0188$). In detail, the *hOGG1* rs1052133 CG and CC variant genotypes were present at frequencies of 40.0% and 11.2% in the control group and 38.1% and 3.4% in the case group, respectively (Table 2, top panel). In multivariate logistic regression analysis, after adjustments were made for age, gender, smoking, alcohol drinking, hypertension, diabetes, and family history status, the *hOGG1* rs1052133 homovariant CC was associated with an altered RCC risk (OR = 0.31 and 0.78, 95% CI = 0.14–0.69 and 0.56–1.13, for *hOGG1* rs1052133 CC homozygotes and CG heterozygotes, respectively; Table 2, top panel). The *hOGG1* rs1052133 variant CG and CC genotypes were subsequently combined to construct a dominant genetic model, and our results revealed that the combined genotypes conferred a significantly reduced RCC risk (OR = 0.55, 95% CI = 0.47–0.88; Table 2; middle panel). We examined the distributions of the allelic frequencies of *hOGG1* rs1052133 among the cases and controls and found a significant association between the *hOGG1* rs1052133 C allele and a decreased RCC risk in Taiwan (OR = 0.59, 95% CI = 0.43–0.83). Considering that 77.1% of patients had ccRCC, we found that the risk estimates were similar to the overall analysis when we restricted our analysis to patients with ccRCC (data not shown).

Subgroup Stratification Analysis of hOGG1 Rs1052133 Genotypes According to Personal Behavioral and Clinical Factors

We further performed stratification analysis to investigate the association between *hOGG1* rs1052133 genotypes and the risk of RCC based on potential Taiwanese-specific personal behavioral and clinical factors, such as cigarette smoking, alcohol consumption, hypertension, and diabetes status, which are listed in Table 1. First, the distributions of genotype frequencies between the RCC case and control groups were similar among nonsmokers and smokers ($p > 0.05$; Figure 1). The adjusted ORs of the carriers with the CG and CC genotypes at *hOGG1* rs1052133 were 0.81 and 0.38 for nonsmokers (95% CI = 0.44–1.37 and 0.14–1.22, respectively) and 0.81 and 0.24 for smokers (95% CI = 0.42–1.38 and 0.09–1.02, respectively; Figure 1), respectively. The results showed no obvious protective effect of *hOGG1* rs1052133 genotype on the risk of RCC in nonsmokers or smokers (Figure 1). Second, the distributions of the genotypic frequencies were similar among nondrinkers and alcohol drinkers between the case and control groups ($p > 0.05$; Figure 2). The adjusted ORs of the carriers with genotypes CG and CC at *hOGG1* rs1052133 were 0.82 and 0.37 among nondrinkers (95% CI = 0.51–1.33 and 0.18–1.26, respectively) and 0.76 and 0.18 among alcohol drinkers (95% CI = 0.42–1.53 and 0.09–1.17, respectively; Figure 2), respectively. The protective effects of *hOGG1* rs1052133 genotypes on the risk of RCC appeared to be nonsignificant among nondrinkers and alcohol drinkers (Figure 2). Interestingly, the distributions of the genotypic frequencies between the case and control groups were significantly different only in subjects with hypertension but not in subjects without hypertension (Figure 3). The adjusted ORs of the carriers with CG and CC at *hOGG1* rs1052133 were 0.80 and 0.67 among the subjects without hypertension (95% CI = 0.41–1.54 and 0.22–2.03, respectively) and 0.81 and 0.09 among the patients with hypertension (95% CI = 0.54–1.28 and 0.01–0.57, respectively; Figure 3). Notably, the protective effects of *hOGG1* rs1052133 genotype on the risk of RCC were obvious among people with hypertension, and only the genotype of the homovariant CC was protective (Figure 3). The distributions of *hOGG1* rs1052133 genotype frequencies were not significantly different between the case and control groups among the subjects in the subpopulations without or with diabetes (Figure 4). The

adjusted ORs of carriers with CG and CC at *hOGG1* rs1052133 were 0.91 and 0.16 among the subjects without diabetes (95% CI = 0.61–1.33 and 0.18–1.07, respectively) and 0.66 and 0.31 among those with diabetes (95% CI = 0.24–1.19 and 0.07–1.36, respectively; Figure 4), respectively. The effect of *hOGG1* rs1052133 genotype on the RCC risk appeared to be nonprotective regardless of the diabetes status (Figure 4). We also performed a stratified analysis in study participants without a family history and found that the results were similar to the overall analysis (data not shown). This result suggested that the effect of rs1052133 is independent of family history.

Discussion

hOGG1 encodes an 8-oxoguanine DNA glycosylase in charge of the recognition of the most common oxidative DNA adducts, namely, 8-oxoGs, and this gene acts as an AP-lyase to remove these adducts from the genome via the BER machinery.[9,10] As a glycosylase in the first step, hOGG1 not only recognizes 8-oxoGs but also cleaves the glycosylic bond between the modified base and the sugar moiety. Then, hOGG1 cleaves 3′ to the AP site, leaving 5′-phosphate, 3′-phospho-α, β-unsaturated aldehyde, and an apurinic/apyrimidinic site for further actions of DNA polymerase β and DNA ligases I and III.[6] The most recognizable polymorphic site of hOGG1 is the well-known rs1052133 (Ser326Cys, C to G), and several genotype–phenotype studies have provided evidence that the glycosylase activity of the "G" variant of the hOGG1 enzyme is more sensitive to the inactivating influence of oxidizing agents than that of the "C" wild type; cells carrying "G" alleles can accumulate mutations more readily under the same challenges of oxidative stress.[12,26,27]

To our knowledge, only one study has investigated the contribution of *hOGG1* to RCC and focused on rs1052133 as we did.[28] The G allele at *hOGG1* rs1052133 is associated with a 1.4-fold increased risk of RCC in a Chinese population. They found that the contribution is extremely significant in the subgroups of subjects with overweight (defined as a body mass index >24 kg/m^2) and nonsmokers.[28] This conclusion is consistent with our results that the CC genotype at *hOGG1* rs1052133 was associated with a lower risk of RCC than that of the GG genotype (Table 2). In the current study, we further found that the determinant value of *hOGG1* rs1052133 of the RCC risk was high among patients with hypertension. Hypertension is a common risk factor of RCC, so this SNP could represent a potential prognosis biomarker of patients with RCC. However, the sample size was limited, and the detailed underlying mechanisms should be further investigated. Their study and ours are both valuable because we have provided genomic information from Eastern populations with relatively representative sample sizes. Studies have rarely investigated the genomic factors contributing to the RCC risk possibly because of the low prevalence of RCC relative to other cancers worldwide. As such, collecting enough samples from patients with RCC for case–control studies is difficult. Additional studies involving larger sample sizes and focusing on various populations are necessary to validate the present findings. To the best of our knowledge, this study was the first to show an association between the *hOGG1* rs1052133 polymorphism and the RCC risk in the Taiwanese population. Our novel finding was that *hOGG1* genotypes might interact with hypertension to determine the risk of RCC.

The majority of RRCC is ccRCC, and other minor subtypes include papillary, chromophobe, and Bellini collecting duct types. Among our RCC cases, 91 (77.1%) patients had ccRCC, 15 (12.7%) had a papillary type, 9 (7.6%) had a chromophobe type, and 3 (2.5%) had a Bellini collecting duct type. In our stratified analyses, the association of rs1052133 with ccRCC was similar to the overall RCC, whereas the numbers of other non-ccRCC subtypes were too small for meaningful analysis. Although the prognosis of these different subtypes varies, their etiology and risk factors are similar. Genetic susceptibility may also be similar. Nevertheless, future studies with a sufficient number of minor subtypes are warranted to clarify the associations in minor subtypes.

CG and GG at *hOGG1* rs1052133 are associated with an increased risk of various cancer types, including oral cancer,[19] lung adenocarcinoma,[15] breast cancer,[29] laryngeal cancer,[30] esophageal cancer,[31] colorectal cancer,[14] gallbladder cancer,[16] prostate cancer,[32,33] and leukemia.[34] Few negative findings have shown no association between *hOGG1* rs1052133 genotypes and several cancer types.[25,35] Some reports have described controversial findings that the G allele may cause a reduced glycosylase hOGG1 activity, leading to an overall downregulation of the BER capacity.[12,13] The link between hOGG1 genotype, DNA repair capacity, and cancer risk still requires further investigations, especially those focusing on genotype–phenotype correlations and measuring the DNA repair capacity of cells with various genotypes. These inconsistencies may be attributed to differences in genomic background, sampling methodology, and small sample sizes. The role

of *hOGG1* in carcinogenesis is much more complicated than that in BER because few alternative mechanisms can take over the function of hOGG1 when its capacity is downregulated.

In conclusion, our data suggested that *hOGG1* rs1052133 genotype is associated with the RCC risk in Taiwan. More functional examinations will contribute to studies on genotype–phenotype correlation. Larger sample sizes with more detailed information about environmental exposure for precise stratification analysis will help reveal the etiology of RCC.

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Disclosure

The authors declare no conflicts of interest related to this study.

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