ORIGINAL ARTICLE

CONTENTS

DNA repair RAD 18 rs373572 and OGG1 rs1052133 genes polymorphisms association with histological characterization of renal cell carcinoma

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ABSTRACT

Aim: Validate the association RAD18 Arg302Gln (rs373572) and OGG1 Ser326Cys (rs1052133) - with Renal Cell Carcinoma (RCC) susceptibility and histopathological characterization.

Materials and Methods: present study compromised of 37 patients with RCC and control group consisted of 28 healthy apparently individuals. A case control study was conducted using Hand E staining and allele-specific PCR for genes genotyping.

Results: The cohort comprised cases with subtypes clear cell, chromophobe, and variant RCC. A significant link was detected between OGG1 rs1052133 and RCC risk ($p = 0.006$), with the GG genotype being strongly linked to disease $p=0.005$. Haplotype demonstrated a significant relations of the GC with RCC ($p=0.013$). LD test revealed a significant association between RAD18 and OGG1 loci ($\chi^2 = 9.214$, $p = 0.027$), with r- value of 0 in cases and 0.14 in controls. Histopathological correlations revealed that OGG1 rs1052133 genotypes demonstrated a highly significant association with RCC $p<0.001$. RAD18 rs373572 genotypes were significantly closed link with tumor stage $p=0.001$. TNM classification revealed a significant relationship with RAD18 genotypes $p=0.017$.

Conclusions: A significant relationship between OGG1 rs1052133 and both RCC susceptibility and cancer histological subtype, proposed a potential role in the pathogenesis of disease. RAD18 rs373572 showed relevance to tumor stage and TNM classification, indicating a possible impact in disease progression rather than initiation.

KEY WORDS: DNA repair system, genes polymorphisms, RAD 18 rs373572, OGG1 rs1052133, renal cell carcinoma, histopathological characterization

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ABBREVIATIONS

RCC: Renal Cell Carcinoma
LD: Linkage Disequilibrium
PRR: Post-Replication Repair System
FFPE: Formalin-Fixed Paraffin-Embedded
HWE: Hardy-Weinberg Equilibrium

INTRODUCTION

Renal cell carcinoma (RCC) is the most commonly reported malignancy of the urinary system, accounting for over 90% of kidney cancers and approximately 2% of all cancer-related deaths worldwide [1-2]. The impact of DNA repair genes in tumorigenesis and cancer development has been extensively investigated [3]. The DNA repair p comprises some critical pathways, including base excision repair, mismatch repair and homologous recombination repair, all of which are vital for maintaining genomic integrity. Deficiencies or mutations in these systems can lead to genomic instability and the accumulation of mutations, thereby contributing to carcinogenesis [4]. Furthermore, DNA repair pathways have become key targets in cancer therapy. As well as, poly (ADP-ribose) polymerase inhibitors have enhanced efficacy in cancers with BRCA1/2 mutations, highlighting the therapeutic potential of targeting DNA repair deficiencies [5]. Renal cell carcinoma is well observed in both male and female, about 81610 patients of kidney and renal pelvis tumor were reported in the United States in 2024 with 14390 deaths. These accounts for about 4.1% of malignancies in adult [6]. The ratio between both sexes is 1.9:1. [7] RCC is different from kidney tumors that consist of renal pelvis or renal medulla, and it just applies to cancer that generate in the kidney bed lining. This summary does not classify non-RCCs of the kidney, as well as renal pelvis or renal

medulla cancer. The Genetic pathogenic variations have detected as the inherited tumor risk cause in several RCC-prone families; these variations are identified for only 5–8% of RCC cases [8-9], other undiscovered genes might have relations in the progression of familial RCC in addition to non-genetic risk factors. Numerous Studies have estimated a new genes variation which didn't associate with RCC hereditary, the results showed that the rate of germline changes in classic RCC genes aligns with prior detect and reported of other pathogenic variants, several of these variations observed in DNA repair encoding genes. The other pathogenic alteration rate was about (12.8-17.0) [10-14]. The other pathogenic incidence changes are more than would be founded in the different population. However, these studies are not population-based, and they are volubility enriched for cases of cancer who have been suggested for germline measurement. Many factors like Endogenous and environment like exposure to ionizing radiation, ultraviolet and some chemicals can lead to DNA damage that can be repaired by repair processing [15]. Most persistent DNA injury are efficiently took out by base and nucleotide excision repair pathways [16]. Meanwhile, several DNA injuries can stay at replication because DNA repair systems have limited capacity, which stimulate gaps in the newly synthesized strand. These gaps are repaired by post-replication repair system (PRR) [17]. Human *Rad18* gene is located on chromosome 3p24-25, the Rad18 protein link with the human Rad6 protein (HHR6A and HHR6B) that used by PRR [18]. The mutation in Rad18 or Rad6 lead to more sensitivity to different mutagens [19]. Oxoguanine glycosylase (OGG1) is the primary molecules used in the excision of modified nucleotide 8-oxoguanine (8-oxoG), a DNA lesion caused by exposure to reactive oxygen species, this enzyme linked with sequences rich in 8-O guanine in the promoter region, that lead to changing in DNA conformation, the downstream gene transcription activation, the recruitment of transcription factors [20]. The OGG1 involvement mechanism in the renal inflammatory through enhance binding of NF-κB/RelA with cis-elements resulted rapid production of inflammatory cell accumulation and chemokines/cytokines in the airways [21]. OGG1 also interacts directly with other proteins and impacts downstream biological mechanisms. It also enhance transformation of TGF-β1-induced cell via interacting with Smad7 [22]. OGG1 has been well investigated in cancer, but in renal tumors is less found. It is a common substitution mutation locus in renal cancer like RCC [23]. Researches have referred that the OGG1 gene is related to DNA injury with chronic kidney disease patients, and in its pathological process [24].

AIM

The present study aims to detect The RAD 18 Arg302Gln (rs373572) and OGG1 Ser326Cys (rs1052133) gene variations in renal cell carcinoma and association with histological characterization

MATERIALS AND METHODS

SAMPLE COLLECTION

This study included 37 cases with renal cell carcinoma (RCC), all of whom attended a Al-Sadir teaching hospital, Najaf city, Iraq, prior to receiving any treatment (chemotherapy or radiotherapy), control group consisted of 28 healthy apparently individuals. Formalin-fixed paraffin-embedded (FFPE) tumor tissue samples and relevant clinical data were collected from each case and blood samples were collected from control group for DNA extraction after obtaining written informed consent. DNA concentration and purity were detected via NanoDrop. The single nucleotide polymorphisms (SNPs) analyzed in this study were RAD18 Arg302Gln (rs373572), as previously reported by [25], and OGG1 Ser326Cys (rs1052133), as reported by [26]. PCR Conditions and Electrophoresis: For amplification of the RAD18 gene variant, PCR was implemented using allele-specific primers under the following conditions: annealing at 58 °C for 40 seconds and extension at 72 °C for 40 sec, for 35 cycles. The allele-specific PCR produced a 146 bp band for the Gln allele, a 106 bp band for the Arg allele, and a 206 bp control band. For the OGG1 Ser-326Cys polymorphism, PCR performed with annealing at 64°C for 1 minute and extension at 72 °C for 1 minute, over 30 cycles. The resulting products included bands of 194 bp, 252 bp, and a 406 bp internal control. PCR products were visualized by agarose gel electrophoresis under UV light following ethidium bromide staining.

ETHICAL APPROVAL

The study was approved by the Ethical Committee of the College of Science, University of Babylon (Approval No. B24006 IN 11/5/2024). DNA isolation and Oligonucleotides: whole DNA was isolated from FFPE tissue via the Geneaid™ DNA Isolation Kit Tissue (GET150), with a protocol modification involving overnight incubation with proteinase K to enhance lysis efficiency.

DATA ANALYSIS

Descriptive data were represented as mean ± standard deviation (SD) for age and as percentages for sex, histological classifications, and genotypes. Statistical asso-

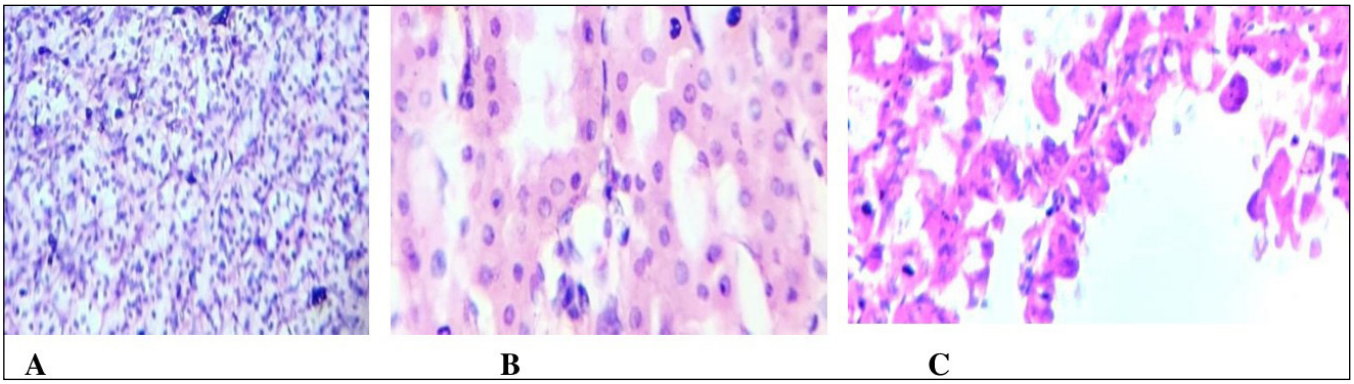

Fig. 1. Histopathological characterization of RCC types (A) 10X Clear cell variant of renal cell carcinoma, (B) 25X chromophobe variant of renal cell carcinoma and (C) 10X papillary variant of renal cell carcinoma

ciations were calculated using odds ratios, Chi-square tests, Fisher's exact tests, with a significance threshold of $p < 0.05$. Linkage disequilibrium and haplotype analysis were conducted using SHEsis software.

RESULTS

The present study was carried out to investigate the association between histopathological changes and critical SNPs in the OGG1 and RAD18 DNA repair genes in renal carcinoma (RCC) cases. The results revealed a significant association between cases age and the incidence of RCC. In addition, the male: female ratio was 2.6, indicating a higher prevalence of RCC among males compared to females, table (1).

Histopathological characterizations of renal carcinoma (RCC) were analyzed in the current study. Tumor grading showed that Grade I was the most prevalent, found in 81.08% of cases, while Grade III was the least frequent, accounting for only 2.70%. Three histological subtypes were observed: clear cell, chromophobe, and papillary carcinoma. Among these, clear cell carcinoma was the most common subtype, representing 75.67% of cases, the least common was papillary carcinoma at 10.81%. Tumor classification based on size and extent (T stage) demonstrated that T1 tumors (including subtypes T1a and T1b) were found in about 83.78% of cases, while T2 and T3 were less frequent. All cases were categorized under Nx and Mx. Overall, belong to the TNM staging system, 83.78% of the cases were categorized as T1NxMx, table (2).

The histopathological changes in the current study are illustrated in figure (1). Figure (1A) depicts renal cell carcinoma (RCC) of the chromophobe subtype, characterized by eosinophilic cells with prominent borders and reticular cytoplasm. Figure (1B) clarifies the papillary subtype, showing distinct papillary architecture with fibrovascular cores lined by neoplastic cells. Figure (1C)

The histopathological changes of this study are clarified in figure (1), figure A shows 10X Clear cell variant of RCC of the kidney show proliferating clear cells in diffuse growth patterns infiltrate the renal parenchyma tissue elements. Figure B explores 25X chromophobe variant of renal cell carcinoma of kidney show atypical malignant cells With dense eosinophilic cytoplasm and pleomorphic nuclei arranged in sheets and solid growth pattern, and figure C elucidates 10X papillary variant of renal cell carcinoma of kidney show atypical malignant papillary architecture composed of fibrovascular core with atypical malignant cells arranged in single layer pattern of growth. In this study, two SNPs RAD18 rs373572 and OGG1 rs1052133 were identified for their association with renal carcinoma. The rs373572 variant did not find a statistically significant association with renal carcinoma (χ^2=1.82, p=0.204), has odds ratio (OR) of 1.645 (95% CI: 0.796~3.399), suggesting no substantial difference in allele distribution between cases and controls. In contrast, the rs1052133 variant in the OGG1 gene revealed a significant protective association (χ^2=8.464, p=0.006), with an OR of 0.3 (95% CI: 0.13–0.689). The C allele was less frequent in cases 15.7% compared to controls 38.4%, refer to a potential protective role of the C allele against RCC table (3).

The genotypes distribution for RAD18 rs373572 GA did not statistically significant relation to RCC (χ^2=4.807, p=0.092). In spite of the heterozygous GA genotype observed more frequently in cases 64.8% than in controls 73%, the AA genotype was exclusively found in the case group 16.2% and didn't find in controls, suggesting a possible but not statistically confirmed trend. The GG genotype was found in 18.9% of cases and 26.9% of controls. Conversely, OGG1 rs1052133 GC exhibit a statistically significant association with RCC (χ^2=10.194, p=0.005). The GG genotype was markedly more prevalent among cases 81.5% than controls 46.1%, while the heterozygous GC genotype and the CC genotype were

Table 1. Distribution of study samples by sex and mean of age

Categories	Case	Control	p
Age	55.75±11.24	31.50±1.99	0.000
Sex Male Female	 27(72.22)% 10(27.77%)	 25 (89.30)% 3(10.70)%	0.093

Table 2. Classification renal carcinoma cases according to the histopathological changes

Cases	Histolopathogical changes		
Grade	I	II	III
	30 (81.08%)	6(16.21%)	1(2.70)
Cell type	Clear	Chromophobe	Papillary
	28(75.67%)	5(13.51%)	4(10.81%)
T	T1	T2	T3
	(a)12 (32.43%) (b)19 (51.35%)	(a)5 (13.51%) (b) 0	(a) 1 (2.70) (b) 0
N	Nx	N0	N1
	37 (100%)	0	0
M	Mx	M0	M1
	37 (100%)	0	0
TNM	T1NxMx	T2NxMx	T3NxMx
	31(83.78%)	5(13.51%)	1(2.70%)

Table 3. RAD18 (rs373572) and OGG1 (rs1052133) Single Locus Association Test in renal carcinoma and control group (odd ratio / p <0.05)

SNP	Chi²	Fisher's p	OR [95% CI]	Detail		
					G	A
rs373572	1.82	0.204	1.645 [0.796~3.399]	Case	38(0.513)	36(0.486)
				Control	33(0.634)	19(0.365)
					G	C
rs1052133	8.464	0.006	0.3 [0.13~0.689]	Case	64(0.842)	12(0.157)
				Control	32(0.615)	20(0.384)

Table 4. RAD18 (rs373572) and OGG1 (rs1052133) genotypes Test in renal carcinoma and control group (odd ratio/p<0.05)

SNP	Chi²	Fisher's p	Detail			
				GA	AA	GG
rs373572	4.8073	0.092	Case	24(0.648)	6(0.162)	7(0.189)
			Control	19(0.73)	0(0)	7(0.269)
				GG	CC	GC
rs1052133	10.194	0.005	Case	30(0.815)	5(0.135)	2(0.054)
			Control	12(0.461)	6(0.23)	8(0.307)

more common in the control group 30.7% and 23%, respectively than in cases 5.2% and 13.1%, respectively. These results suggest that the presence of the C allele may exert a protective effect against renal carcinoma table (4).

According to Hardy-Weinberg Equilibrium (HWE) analysis for RAD18 rs373572 presented no significant deviation in the case group ($\chi^2 = 3.29$, $p = 0.523$) or the control group ($\chi^2 = 8.618$, $p = 0.081$), although the control group approached borderline significance. In the same manner, when both groups were analyzed together, the finding ($\chi^2 = 9.45$, $p = 0.07$) showed statistically non-significant, suggesting that the allele frequencies at this locus are largely stable and consistent with HWE assumptions in the studied population (table 5). On the other hand, the OGG1 rs1052133 polymorphism demonstrated a significant differences from Hardy-Weinberg equilibrium in the case group

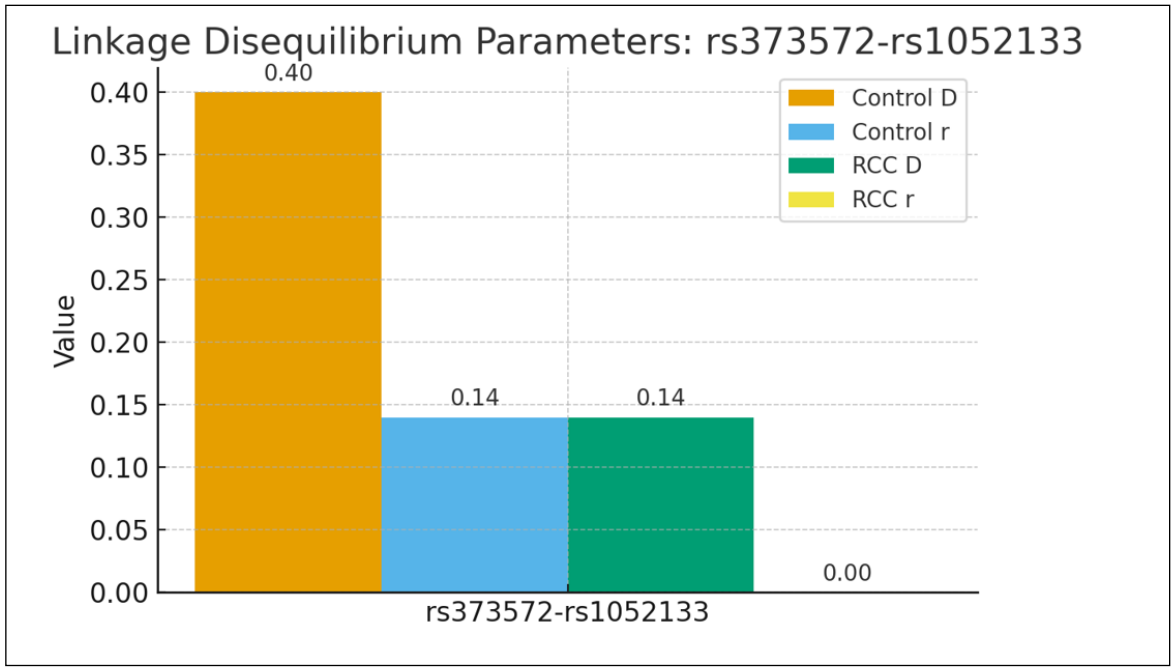

Fig. 2. Linkage Disequilibrium Analysis between RAD 18 (rs373572) and OGG1 (rs1052133) in case and control

Table 5. RAD18 (rs373572) and OGG1 (rs1052133) Hardy-Weinberg Equilibrium Test in renal carcinoma and control group (odd ratio/p<0.05)

SNP	Chi² in case	Fisher's p in case	Chi² in ctrl	Fisher's p in ctrl	Chi² in both	Fisher's p in both
rs373572	3.291	0.523	8.618	0.081	9.457	0.07
rs1052133	24.446	0.003	3.185	0.344	21.777	0.008

Table 6. Gene Interaction Analysis between RAD18 (rs373572) and OGG1 (rs1052133) in renal carcinoma and control group (odd ratio/p<0.05)

SNPs	Case Interaction	Control Interaction	diff	p
rs373572,rs1052133	-0.089	-0.095	0.005	0.456

Table 7. Haplotype Analysis of RAD18 (rs373572) and OGG1 (rs1052133) in renal carcinoma and control group (odd ratio / p <0.05)

Haplotype	Case(freq.)	Control(freq.)	Chi²	Fisher's p	OR [95% CI]
GG	31(0.418)	19(0.365)	0.365	0.583	1.252 [0.603~2.596]
AG	31(0.418)	13(0.25)	3.834	0.059	2.162 [0.992~4.714]
GC	7(0.094)	14(0.269)	6.706	0.014	0.283 [0.105~0.763]
AC	5(0.067)	6(0.115)	0.876	0.359	0.555 [0.16~1.927]

(χ^2 = 24.446, p = 0.003), refer to potential selection pressure or population stratification relation to renal carcinoma. However, the control group exhibited no significant deviation (χ^2 = 3.185, p = 0.344). The analysis of combined group also showed a significant deviation from HWE (χ^2 = 21.777, p = 0.008), reinforcing the link of this SNP with disease status and supporting its potential involvement in RCC susceptibility.

The interaction between SNP–SNP analysis of RAD18 rs373572 and OGG1 rs1052133 showed minimal interaction differences between cases and controls. The interaction coefficient was –0.089 in cases and –0.095 in controls, with a difference of 0.005 (p = 0.456). This statistically non-significant result mean that no synergistic or antagonistic interaction between these two variants in contributing to RCC susceptibility in the current study (table 6).

The haplotype analysis of both SNPs demonstrated variable distribution between cases and controls. The GC haplotype elucidated a significantly lower frequency in cases 0.094 compared to controls 0.269, with a statistically significant association p=0.014 and a protective odds ratio of 0.283 [95% CI: 0.105–0.736], suggesting a protective impact against renal carcinoma. Other haplotypes (GG, AG, and AC) did not report statistically significant differences between groups p>0.05, although the AG haplotype showed a trend toward increased risk (OR=2.162).

Table 8. Association of renal carcinoma cell type (clear, chromophobe and papillary) with RAD 18 (rs373572) and OGG1 (rs1052133) genotyping (chi square, p <0.05)

Genotyping's	Clear	Chromophobe	Papillary	P
RAD18				
GG	5 (20%)	2(40%)	0	0.398
GA	17(68%)	2(40%)	5(71.4%)	
AA	3(12%)	1(20%)	2(28.6%)	
A	0.54	0.6	0.35	0.9364
G	0.46	0.4	0.64	
OGG1				
CC	2(7.7%)	2(50%)	1(14.3%)	0.000056
CG	0	2(50%)	0	
GG	24(92.3%)	0	6(85.7%)	
C	0.07	0.75	0.14	0.52913
G	0.92	0.25	0.85	

Table 9. Association of renal carcinoma grades (I, II and III) with RAD 18 (rs373572) and OGG1 (rs1052133) genotyping (chi square, p <0.05)

Genotyping's	Grade I	Grade II	Grade III	P value
RAD18				
GG	7(22.58%)	0	0	0.00134
GA	22(70.96%)	1(20%)	1(100%)	
AA	2(6.45%)	4(80%)	0	
A	0.58	0.1	0.5	0.7579
G	0.42	0.9	0.5	
OGG1				
CC	3(10%)	2(3.33%)	0	0.58552
CG	2(6.66%)	0	0	
GG	25(83.33%)	4(6.66%)	1(100%)	
C	0.13	0.33	0	0.8067
G	0.86	0.66	1	

Linkage disequilibrium between RAD18 (rs373572) and OGG1 (rs1052133) showed different patterns in case and control groups figure (2). In the case group (Figure 2), LD was weak, with a D' value of 0.14 and r^2 of 0, this mean almost complete recombination and absence of linkage between the two loci. On the other hand, the control group (Figure 2) clarified a moderate level of LD, with D' = 0.4 and r^2 = 0.11, proposed a non-random association between study SNPs. This difference in LD structure between case and controls may reflect underlying genetic instability in RCC or selection pressure influencing haplotype integrity in the diseased state.

ASSOCIATION HISTOLOGICAL CHANGES OF RENAL CARCINOMA AND GENOTYPING OF RAD 18 (RS373572) AND OGG1 (RS1052133)

The genotypic distribution of both SNPs polymorphisms was estimated across RCC histological subtypes including clear cell, chromophobe, and papillary. For the RAD18 gene, the GA genotype was most frequent among clear cell RCC (68%) and papillary RCC (71.4%), whereas chromophobe RCC reported equal frequencies of GG and GA genotypes (40% each). However, the distribution of RAD18 genotypes among the different histological types was not statistically significant (p = 0.398), this mean no clear link between RAD18 variants and RCC subtype. On the other hand, OGG1 genotypic frequencies showed significant variation among RCC subtypes (p = 0.000056). The GG genotype was predominant in clear cell (92.3%) and papillary RCC (85.7%) but entirely absent in chromophobe RCC, which recorded a higher frequency of CC (50%) and CG (50%) genotypes. These results suggest a potential association between OGG1 polymorphism and the chromophobe subtype of RCC, possibly implicating a histotypes-specific role in DNA repair pathways table (8).

Table 10. Association of renal carcinoma classification TNM (T1NxMx T2NxMx and T3NxMx) with RAD 18 (rs373572) and OGG1 (rs1052133) genotyping (chi square, p <0.05)

Genotyping's	T1NxMx	T2NxMx	T3NxMx	P
RAD18				
GG	7(22.58%)	0	0	0.01774
GA	22(70.96%)	1(12.5%)	1(100%)	
AA	3(9.67%)	3(87.5%)	0	
A	0.56	0.13	0.5	0.7947
G	0.43	0.87	0.5	
OGG1				
CC	3(10%)	2(40%)	0	0.43326
CG	2(6.66%)	0	0	
GG	26(86.66)	3(60%)	1(100%)	
C	0.13	0.4	0	0.75109
G	0.87	0.6	1	

Table 11. Association of renal carcinoma classification according to sex (male and female) with RAD 18 (rs373572) and OGG1 (rs1052133) genotyping (chi square, p<0.05)

Genotyping's	Male	Female	P
RAD18			
GG	6(17.64%)	1(10%)	0.686297
GA	17(50%)	7(70%)	
AA	4(11.76)	2(20%)	
A	0.5	0.45	0.94355
G	0.5	0.55	
OGG1			
CC	4(11.76%)	1(10%)	0.71808
CG	1(2.94%)	1(10%)	
GG	22(64.70%)	8(80.0%)	
C	0.16	0.15	0.9819
G	0.83	0.85	

Both genes RAD18 and OGG1 genotypes distribution across RCC grades (I III) showed grade-specific variations in allelic and genotypic appearances. For RAD18, the GA genotype more frequent in grade I (70.96%) and was the only genotype found in grade III (100%), while the AA genotype was most frequent in grade II (80%). The GG genotype was not found in grade II and III. This distribution reported significant association with grade p=0.00134, imply a potential impact of RAD18 polymorphism in disease development. Whereas, OGG1 genotype frequencies did not exhibit significant variation regarding grades p=0.58552. The GG genotype remained predominant in all grades, especially in grade I and III (83.33%, 100%). The CC genotype found in grade I and II (10%, 33.3%), while CG was only found in grade I (6.66%). Allelic frequencies of both SNPs recorded no significant difference across tumor grades (RAD18 A allele p = 0.7579; OGG1 C allele p = 0.8067), this mean that while RAD18 genotypes may correlate with progression, allelic distribution alone may not be predictive table (9).

The RAD18 genotypes distribution across tumor grades demonstrated a statistically significant association (p = 0.01774). In the T1NxMx stage, the most frequent genotype was GA (70.96%), followed by GG (22.58%) and AA (9.67%). While, the T2NxMx stage clarified a predominance of the AA genotype 87.5%, with only one case carrying GA (12.5%) and none with GG. Notably, all cases in the T3NxMx stage carried the GA genotype 100%. The allele frequencies further supported this trend, with a higher A allele frequency in T1 and T3 stages, while the G allele was predominant in T2NxMx. Regarding the OGG1 gene, no statistically significant link was detected among tumor stages p=0.43326. In T1NxMx, GG was the dominant genotype 86.66%, followed by CC (10%) and CG (6.66%). In T2Nx-

Mx, 60% of individuals had the GG genotype and 40% had CC, with no heterozygous (CG) cases. In T3NxMx, only one case was present, carrying the GG genotype (100%). Allelic distribution showed a predominance of the G allele in all stages, especially in T3NxMx (100%) table (10).

The RAD18 and OGG1 genotypes distribution was detected according to sex. For the RAD18 gene, the most frequent genotype in both sexes was the heterozygous GA, found in 50.0% of males and 70.0% of females. The homozygous wild-type GG genotype appeared in 17.64% of males and 10.0% of females, whereas the mutant homozygous AA genotype was observed in 11.76% of males and 20.0% of females. Although of these differences in frequency, there was no significant link between RAD18 genotypes and gender p=0.686. Allelic distribution for RAD18 also reported comparable proportions between sexes: the A allele was found in 50.0% of males and 45.0% of females, while the G allele appeared in 50.0% of males and 55.0% of females. No significant gender-based difference was observed in allele frequency p=0.943. For the OGG1 gene, the GG genotype was the most common among both sexes, present in 64.70% of males and 80.0% of females. The CC genotype was observed in 11.76% of males and 10.0% of females, and the heterozygous CG genotype observed at lower frequencies (2.94% in males and 10.0% in females). There was no significant variation in genotype distribution between males and females p=0.718. Allele frequencies for OGG1 were also similar across sexes, with the G allele found in 83.0% of males and 85.0% of females, and the C allele in 16.0% and 15.0%, respectively. These differences were non-significant p=0.982 table (11).

DISCUSSION

The results revealed a significant association between cases age and the incidence of RCC. In addition, the male-to-female ratio was 2.6, indicating a higher prevalence of RCC among males compared to females, these finding are consistent with previous studies showing sex-based differences in the incidence of non-reproductive tumors. Especially, males are approximately twice as likely to develop kidney cancer and present higher mortality rates as female [27], potentially according to the protective role of sex hormones in females [28]. This findings further reported by an earlier study [29] found that females had slower tumor development and a 19% lower risk of RCC-specific mortality compared to males. furthermore, a correlation between age and sex in RCC incidence has also been illustrated in previous investigation [30]. Highlights neoplastic cells with clear cytoplasm arranged in a nested pattern interspersed with blood vessels [29]. RCC is not a uniform disorder but encompasses a group of histologically distinct tumors, each with unique clinical behavior, genetic variation, and therapeutic responses. In one report involving 843 RCC cases, the distribution included 488 clear cell, 274 papillary, and 81 chromophobe subtypes. The analyses of Genomic and phenotypic of these subtypes have presented distinct molecular profiles, demonstrate the progression of subtype-specific management and medication strategies [31]. Understanding the shared and unique features among RCC subtypes is essential for detection different processing and improving targeted therapies. Additionally, some reports propose that cancer cells reprogram their metabolism to improve cellular survival and proliferation, introduce novel diagnostic and medication targets. RCC subtypes metabolic network analyses have been suggested to uncover system-level alterations and detection potential metabolic markers for precise intervention strategies [32]. Despite of the RAD18 gene has not been extensively validated in the context of RCC, its role in DNA lesion tolerance and post-replication repair suggested a potential intervention to renal tumorigenesis. RAD18 encodes an E3 ubiquitin ligase critical for monoubiquitination of proliferating cell nuclear antigen, enhance translation synthesis and enabling replication past DNA injury [33]. Variations or Mutations in RAD18 gene may effect this function, leading to replication fork stalling, increased mutational burden, and instability genomic hallmarks of tumor development. In this study, certain RAD18 genotypes (especially GA and AA) demonstrate significant relationships with histological subtypes and stages of tumor, referring a potential impact in disease development. Moreover, RAD18 has been involved in oxidative DNA lesions response, which is especially relevant in RCC, a cancer highly influenced by hypoxia and oxidative stress [34]. The outputs focusing on the essential genetic contributions of DNA repair gene variations in RCC etiology and progression. The rs1052133 (Ser326Cys) polymorphism found to be affected in enzymatic function and genomic stability. The histological association to chromophobe RCC, where C alleles were more found, propose OGG1 variation may have a distinct role in tumors of different origins, likely due to differences in oxidative index susceptibility. On the other hand RAD18 is involved in post-replication repair by ubiquitination of PCNA, trigger translation DNA synthesis. In spite of no overall relation to RCC risk was observed, the AA genotype illustrated exclusive presence in stage II tumors, while GA was predominant in stages I and III, implying a potential link to tumor development rather than initiation. Other literatures

have linked RAD18 variation with other malignancies, such as esophageal and colorectal cancer, though data on RCC is limited [35-36]. The significant deviation from HWE in the case group of OGG1 imply selection pressure or disease linkage, supporting a functional impact of these alleles in RCC progression. The GC haplotype (RAD18 G + OGG1 C) was significantly less frequent in patients, indicating a protective synergistic effect. While, LD patterns differed between studies groups, stronger in controls possibly due to loss of LD in case associated genomic instability, a known phenomenon in tumorigenesis [37]. Regarding No sex-related differences in genotype or allele frequencies, aligning with prior RCC reports suggesting genetic risk factors act independently of sex, while hormonal or environmental factors may modulate expression [38]. Genetic variation like Ser326Cys (rs1052133) have been found to decrease OGG1 activity, defecting DNA repair and promoting mutagenesis. In this study, the GG genotype was predominant, but change genotype observation in specific histological and clinical subgroups propose a modulatory impact in RCC risk and development. Other studies prove the potential effect of OGG1 polymorphism in renal carcinogenesis like, Audebert et al. [39] observed OGG1 mutations in RCC tissues, highlighting a possible link between impaired DNA repair and renal cancer development. These outputs collectively underscore the relevance of genomic maintenance processing, especially DNA repair mechanisms, in RCC pathophysiology. The correlation of RAD18 and OGG1 variations with tumor stage and histological subtypes highlights their potential as markers for RCC progression and prognosis. Moreover, the interaction between DNA repair deficiency and oxidative index represents a promising area for medications targeting, particularly considering the kidney high susceptibility to oxidative damage.

CONCLUSIONS

The OGG1 rs1052133 variation is significantly related to a reduced risk of renal carcinoma and point to histological subtype specificity, while RAD18 rs373572 may influence tumor development rather than susceptibility. These findings prove a role for DNA repair gene variants especially OGG1 in modulating RCC risk and progression, providing a potential avenue for genetic screening and personalized risk assessment in RCC.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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