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Original Article

Association of XRCC1 and APE1 DNA repair gene single nucleotide polymorphisms with hepatocellular carcinoma in Egyptians

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Abstract

***Background**: Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Genetic polymorphisms of base excision repair genes (BER), like X-Ray repair Cross Complementing group 1 (XRCC1) and AP endonuclease 1 (APE 1), could influence the repair capacity of DNA and elevate carcinogenesis risk. The current study aimed to investigate the association of these variants with increased risk of HCC and their potential use as noninvasive biomarkers of HCC in Egyptian population.* ***Subjects and methods:** APEX1 Asp148Glu and the XRCC1 Gln399Arg genotyping was performed by PCR-RFLP on blood and tissue samples from 100 HCC patients who underwent surgical resection of hepatic lesions and blood samples from 100 healthy individuals.* ***Results:** Individuals with the XRCC1 Gln399Arg (Gln/Gln) genotype had 31.8-fold increased risk of developing HCC (OR=31.8, p<0.001), while XRCC1 Gln399Arg (Arg/Gln+ Gln/Gln) genotype carriers demonstrated a greater risk with a 62.7-fold increase (OR= 62.7, p<0.001). Additionally, participants having APEX1 Asp148Glu (Glu/Glu) genotype exhibited a 33.77- fold higher risk of HCC (OR=33.77, p<0.001) and those with APEX1 Asp148Glu (Asp/Glu+Glu/Glu) showed 40.86-fold increased risk (OR=40.86; P < 0.01). There was an agreement of XRCC1 and APEX1 genotyping results between peripheral and HCC tissue samples in the HCC studied group.* ***Conclusion:** The XRCC p. Gln399Arg and APEX1 p. Asp148Glu polymorphisms may serve as genetic risk factors for developing HCC in Egyptians. They could also be utilized as noninvasive molecular markers for HCC in this population.*

Introduction

Hepatocellular carcinoma (HCC) is a significant global health concern, particularly in Egypt where it is the primary cause of cancer-related deaths and illnesses[1]. The development of HCC is closely associated with established risk factors such as chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, as well as exposure to aflatoxin B1[2]. These factors are implicated in cellular repair and tissue remodeling, processes that can ultimately result in chromosomal damage and the development of cirrhosis, thereby initiating the progression towards liver cancer[3]. Diverse DNA repair mechanisms are employed by cells to ensure genome stability[4]. The base excision repair (BER) pathway is a crucial cellular DNA repair system that corrects small base lesions, such as damaged or mismatched bases, in the DNA molecule. This pathway involves a series of coordinated steps that are carried out by specific enzymes to detect and repair damaged bases. BER plays a vital role in maintaining the integrity of the genome and preventing mutations that can lead to diseases such as cancer[5,6]. The *XRCC1* and APEX1 genes are essential components of the BER pathway, encoding core proteins that are crucial for maintaining genome stability[7,8]. The *XRCC1* gene is situated on chromosome 19q13.2[9], and encodes the XRCC1 protein, which acts as a scaffold for other repair enzymes involved in the recognition and repair of single-strand DNA breaks[10]. The *APEX1* gene, located on chromosome 14q11.2-q12, encodes the APEX endonuclease protein[11], with apurinic/apyrimidinic activity. APEX1 cleaves AP sites that occur after the removal of damaged or abnormal bases. This process helps in restoring the intact double-strand DNA by allowing gap filling and ligation by polymerase β/*XRCC1*/DNA ligase[12]. The integrity of DNA repair mechanisms, and consequently cancer risk, can be influenced by naturally occurring genetic variations within DNA repair genes[13]. Identifying these polymorphisms can assist in identifying individuals at a higher risk for certain cancers and tailoring personalized treatment strategies. The *XRCC1* p. Gln399Arg (rs25487) polymorphism is one of the most extensively studied. This polymorphism involves a G > A genotypic conversion, resulting in an arginine-to-glutamine (Arg-to-Gln) amino acid change at position 399, leading to the Arg399Gln gene polymorphism. This change could impact *XRCC1* repair activity and potentially increase susceptibility to malignancies[14]. The most common genetic polymorphism identified in APEX1 is APEX1 p. Asp148Glu (rs1130409), which involves a T to G allele conversion. This genetic change results in the substitution of aspartate (Asp) with glutamate (Glu) at amino acid position 148 within the 5th exon of the *APEX1* gene[15,16]. The *APEX1* p. Asp148Glu genetic polymorphism may decrease its interaction with other enzymes, leading to reduced efficiency of the BER mechanism[17]. Previous studies have examined the relationship between the *XRCC1* p.Gln399Arg and *APEX1* p.Asp148Glu polymorphisms and the risk of different types of cancer, but the results have been inconsistent. In terms of the risk of hepatocellular carcinoma (HCC), some studies have shown an increased risk, while others have suggested a decreased risk or no association at all[5,13,18,19]. Given the known impact of ethnicity and geographical location on allele frequencies, it is essential to

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further investigate the association between *XRCC1* polymorphisms and HCC risk within specific ethnic groups. Obtaining hepatic tissue samples for genetic polymorphism studies can be challenging and invasive. Using peripheral blood as a source for genetic polymorphism analysis reduces the need for invasive tissue biopsies, making it easier to monitor patients over time and providing a more convenient option. This study aimed to examine the relationship between *XRCC1 p.Gln-399Arg* and *APEX1 p.Asp148Glu* gene polymorphisms and HCC development in the Delta region of Egypt, which has the highest incidence of HCC. The goal was to evaluate their potential as noninvasive genetic markers for HCC.

Subjects and Methods

Study subjects

This case-control study was conducted at the Gastroenterology Centre, Mansoura University Hospital in Egypt. The study included 100 patients with primary HCC who had undergone surgical resection and 100 healthy individuals. Participants with a history of previous chemotherapy or radiotherapy, or those with other cancers or significant organ diseases, were excluded. Informed consent was obtained from all participants following the medical research guidelines of Mansoura University, Egypt. Ethical approval for this research was obtained from the Institutional Review Board (IRB) of the Faculty of Medicine at Mansoura University, with the code [R.23.10. 2353]. Complete medical histories, clinical examinations, and radiological assessments including abdominal ultrasound and tri-phasic abdominal computed tomography (CT) were used to diagnose HCC.

Sampling

A venous blood sample was withdrawn from all participants and divided into two aliquots. The first aliquot was collected in plain tubes to obtain serum for laboratory investigations. The second aliquot was placed into EDTA blood collection vacutainers and frozen at -20°C until used for genotyping. Furthermore, HCC tissue samples were obtained only from HCC patients immediately after surgical resection and frozen at -20°C until genetic analysis was conducted.

Laboratory investigations

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, total bilirubin, and direct bilirubin levels were analyzed using a Cobas C 311 automatic biochemical analyzer (Roche Diagnostics). Serological parameters including antibodies to hepatitis C virus (Anti-HCV), surface antigen of hepatitis B virus (HBs Ag), and Alpha-fetoprotein (AFP) tumor marker levels were measured with the ARCHITECT i1000SR Immunoassay Analyzer.

Genetic analysis

DNA extraction

DNA extraction from 25 mg of HCC tissue and peripheral blood leukocytes was performed using the GeneJET Whole Blood Genomic DNA Purification Mini Kit (Fermentas-Thermo, USA; K0781) according to the manufacturer's protocol.

Genotyping

For the detection of the *XRCC1 p.Gln399Arg* and *APEX1 p.Asp148Glu* single nucleotide polymorphisms (SNPs), enzymatic amplification was performed using a Biorad Thermal cycler (Biorad PTC-100 Peltier, USA) and Dream Taq Green PCR Master Mix (2X) (K1081). The primer sequences for *XRCC1* genotyping were: forward 5'TTGTG CTTTCTCTGTGTCCA'3, and reverse 5'TCCTCCAGCCTT TTCTGATA'3[20], and for APEX1 genotyping were forward 5'CTGTTTCATTTCTATAGGCTA'3, and reverse 5'AGGA ACTTGCGAAAGGCTTC'3[21]. PCR amplification involved an initial denaturation (95°C for 5 min), followed by 35 cycles of denaturation (94°C for 50 s), annealing (56°C for *XRCC1* p.Gln399Arg and 54°C for *APEX1* p.Asp148Glu, both for 30 s), and extension (72°C for 30 s), with a final extension at 72°C for 10 min. For the *XRCC1* and *APEX1* SNP, the PCR products were digested with Thermo Scientific fastDigest MSPI and BfaI enzymes, (Lithuania, EU), respectively. The reaction mixture was incubated for 2 hours at 37°C for *XRCC1 Arg399Gln* and 2 hours at 37°C then 20 min at 65˚C for *APE1 Asp148Glu*. The resulting DNA fragments underwent separation based on size through electrophoresis on a 3.5% agarose gel. The separated fragments were then made visible by staining with ethidium bromide and subsequently observed under ultraviolet light. The G→A mutation of the *XRCC1* SNP was recognized by the *MSPI* restriction endonuclease. This resulted in one 615 bp fragment for the wild-type homozygous GG (Arg/Arg). The mutant homozygote AA (Gln/Gln) was cleaved into two fragments of 377 bp and 238 bp, respectively. The heterozygous AG (Arg/Gln) showed three fragments of 377 bp, 238 bp, and 615 bp, respectively, **fig. 1**.

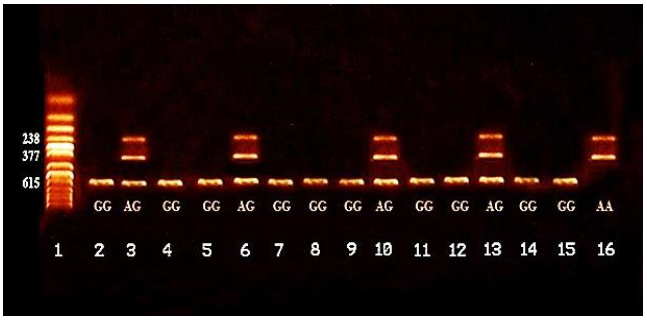

Figure 1: Agarose gel electrophoresis of PCR fragments produced by MSPI restriction enzyme digestion for the detection of the *XRCC1*Arg399Gln genetic polymorphism.

The T→G mutation of the *APE1* SNP was recognized by the BfaI restriction endonuclease, yielding a single 165 bp fragment for the wild-type homozygous TT (Asp/Asp) genotype. The mutant homozygous GG (Glu/Glu) genotype was cleaved into two fragments of 146 bp and 19 bp (the latter being too small for visualization on the gel). The heterozygous TG (Asp/Glu) genotype resulted in three fragments of 146 bp, 19 bp, and 165 bp, respectively, **fig. 2**.

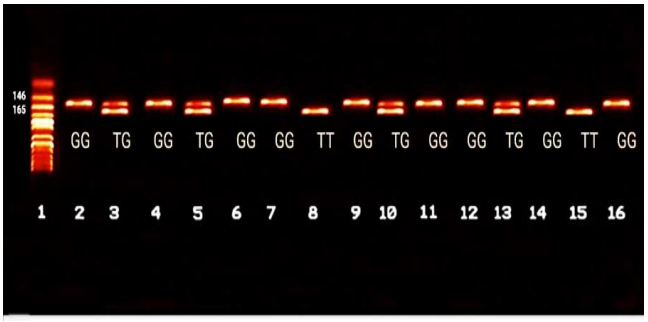

Figure 2: Agarose gel electrophoresis of PCR fragments produced from BfaI restriction enzyme for the detection of the APE1 Asp148Glu genetic polymorphism

Statistical analysis

Statistical analysis of the compiled data was performed using the SPSS software package, version 26.0. For Parametric data, the mean with standard deviation [SD] was used, and the Student's t-test was used to compare the means of two study groups. Kappa statistics were calculated to estimate the agreement between methods. The chi-squared test was used to evaluate deviations from Hardy-Weinberg equilibrium expectations. Odds ratios with 95% confidence intervals were calculated, and statistical significance was set at a P value below 0.05. Logistic and ordinal regression analyses were performed to predict risk factors. To determine the necessary sample size, we utilized an online calculator available at http://osse.bii.a-star.edu.sg/ based on the minor allele frequency of the *APEX1* Asp148Glu gene (3), a significance level of 5% and a study power of 85%. The minimum required sample size was calculated to be 74 subjects in each group. To account for possible dropouts, a total sample of 100 subjects was included in each group.

Results

Table 1 presents the demographic, pathological, and laboratory characteristics of the participants in this study. The two studied groups were matched regarding age and gender (p> 0.05). The left lobe was affected in approximately one-third of HCC cases (34%), while the right lobe was affected in about two-thirds of cases (66%). Most cases presented a single focal hepatic lesion (92%) and were well-differentiated (41%) or moderately differentiated (43%). Regarding laboratory data, HCC patients showed significantly lower albumin, higher AST, ALT, bilirubin, and AFP concentrations (p<0.001 in all). The prevalence of HCV and HCV-HBV infection in HCC patients was significantly higher compared to the healthy individuals (p<0.001 in all). Two participants in the control group were tested positive HCV antibodies. They were retained as they tested negative for HCV RNA PCR, that indicated no active infection. The application of the Hardy-Weinberg (HW) equation revealed that peripheral and tissue *XRCC1* and APE1 genotypes in all studied groups were in HW equilibrium. Individuals with the *XRCC1 Gln399Arg (Gln/Gln)* genotype had 31.8-fold increased risk of developing HCC (OR=31.8, p<0.001), while *XRCC1 Gln399Arg (Arg/Gln+Gln/Gln)* genotype carriers demonstrated a greater risk with a 62.7-fold increase (OR= 62.7, p<0.001). Additionally, participants having *APEX1 Asp148Glu (Glu/Glu)* genotype exhibited a 33.77- fold higher risk of HCC (OR=33.77, p<0.001) and those with *APEX1 Asp148Glu (Asp/Glu+Glu/Glu)* showed 40.86-fold increased risk (OR=40.86; P < 0.01), **tab. 2**. This higher OR in the studied polymorphisms indicated a very strong association of these SNPs and increasing HCC risk, however small sample size may produce inflated OR, so this should be interpreted cautiously. No significant association was found between the studied polymorphisms and the clinical, laboratory and serological parameters (p > 0.05 in all) in the study population. Logistic regression analysis was performed to predict the development of HCC in apparently healthy subjects. Univariate and multivariate analysis revealed that higher AFP, *XRCC1 Arg/Gln+Gln/Gln*, and *APEX1 Asp/Glu+Glu/Glu* were associated with a higher risk of HCC development (*P* <0.001 for all), **tab. 3**. As shown in **tab. 4**, perfect agreement was found between peripheral blood and tissue *XRCC1 Arg399Gln* and *APE1 Asp148Glu* genotyping in all studied HCC patients.

Table 1: Demographic, pathological and laboratory characteristics of the participants in this study

Variable		HCC patients (N=100)	Control (n=100)	P value
Age/years		61.4 ±4.8]	60.7 ±4.7	0.315
Gender				
▪ ***Male: (N/%)***		82 (82%)	73 (73%)	0.128
▪ ***Female*: (N/%)**		18 (18%)	27 (27%)	
Pathological criteria				
Site (N/%)				
Right lobe		66 (66%)		
Left lobe		34 (34%)		
Multiplicity (N/%)				
Single focal lesion		92 (92%)		
Multiple foci		8 (8.0%)		
Tumor differentiation (N/%)				
Well-differentiated		41 (41%)		
moderately-differentiated.		43 (43%)		
Poorly-differentiated		9 (9%)		
Undifferentiated		7 (7%)		
Biochemical and serological parameters				
ALT (u/L)	**Median (Min - Max)**	0.958 (0.23 – 4.116)	0.5 (0.22 -0.633)	**<0.001**
AST (u/L)	**Median (Min - Max)**	0.867 (0.267 – 3.883)	0.45 (0.05 -0.633)	**<0.001**
Albumin (g/L)	**Median (Min - Max)**	27 (20 – 42)	40 (37 – 48)	**<0.001**
T. ilirubin (µmol/L)	**Median (Min - Max)**	34.21 (1.71 – 494.3)	10.26 (1.71 – 17.1)	**<0.001**

AFP (µg/L)	**Median (Min - Max)**	48.5 (1.1 – 4230)	1.65 (0.4 - 4.2)	**<0.001**
HCV Infection				
Anti-HCV Positive (N/%)		94 (94%)	2 (2%)	**<0.001**
HBV/ HCV Co-infection				
Positive (N/%)		14 (%)	0 (%)	**<0.001**

Table 2: Genotypes and allele frequencies of APEX1 and XRCC1 variants

Gene	Genotypic frequencies	HCC N=100 (N/%)	Control N=100 (N/ %)	OR	P value	95% CI
XRCC1 Arg399Gln	***Arg/Arg***	3 (3%)	66 (66%)	0.016	<0.001	0.0047– 0.054
	Arg/Gln	30 (30%)	28 (28%)	1.1	0.755	0.59 – 2.03
	Gln/Gln	67 (67%)	6 (6%)	31.8	<0.001	12.6 – 80.2
	Arg/Gln+Gln/Gln	97 (97%)	34 (34%)	62.7	<0.001	18.5–212.8
	Allelic frequencies					
	Arg	36 (18%)	160 (80%)	0.054	<0.001	0.03 -0.09
	Gln	164 (82%)	40 (20%)	18.22		11.05 – 30.05
APE1 Asp148Glu	**Genotypic frequencies**					
	Asp/Asp	4 (4%)	63 (63%)	0.02	<0.001	0.008 -0.072
	Asp/Glu	32 (32%)	32 (32%)	1.000	1	0.55 – 1.81
	Glu/Glu	64 (64%)	5 (5%)	33.77	<0.001	12.58 – 90.69
	Asp/Glu+ Glu/Glu	96 (96%)	37 (37%)	40.86	<0.001	13.89 – 120.27
	Allelic frequencies					
	Asp	40 (20%)	158 (79%)	cv0.066	<0.001	0.04 – 0.11
	Glu	160 (80%)	42 (21%)	15.05		9.26 – 24.455

Table 3: Logistic regression for predicting HCC development among healthy subjects

	Univariate				Multivariate			
	P	**OR**	**95% CI**		***P***	**OR**	**95% CI**	
Age (years)	0.314	1.031	0.972	1.094				
Male gender	0.130	1.685	0.858	3.308				
AFP (ng/mL)	**<0.001**	**3.962**	2.093	7.498	0.008	2.953	1.321	6.604
XRCC1 (Arg/Gln+Gln/Gln)	**<0.001**	**62.765**	18.508	212.84				
APEX1 (Asp/Glu+Glu/Glu)	**<0.001**	**40.865**	13.885	120.26				
XRCC1 (Gln/Gln)	**<0.001**	**31.81**	12.62	80.18	**<0.001**	18.044	3.776	86.233
APEX1 (Glu/Glu)	**<0.001**	**33.77**	12.58	90.69	0.006	9.992	1.928	51.787

OR: *odds ratio*, **CI,** *confidence interval*, *Logistic regression test was used*

Table 4: Agreement between peripheral and tissue XRCC1 and APE1 in studied HCC patients

		Tissue XRCC1			K
		Arg/Arg	**Arg/Gln**	**Gln/Gln**	
Peripheral XRCC1 Arg399Gln	**Arg/Arg**	3	0	0	1
	Arg/Gln	0	30	0	
	Gln/Gln	0	0	67	
		Tissue APE1			**K**
		Asp/Asp	**Asp/Glu**	**Glu/Glu**	
Peripheral APE1 Asp148Glu	**Asp/Asp**	4	0	0	1
	Asp/Glu	0	32	0	
	Glu/Glu	0	0	64	

K: *Kappa statistic*

Discussion

Genetic polymorphisms in DNA repair genes can affect an individual's vulnerability to both external and internal carcinogens, impacting DNA repair capabilities and potentially elevating the risk of HCC. This study sought to explore the potential link between the *APEX1* p.Asp148Glu and *XRCC1* p.Gln399Arg SNPs and the likelihood of developing HCC among Egyptians in the Delta region, where HCC incidence is on the rise. The current study revealed that HCC is more prevalent in older individuals, which is consistent with previous studies showing an increase in HCC prevalence with age[2,23,24]. Furthermore, the incidence of HCC was significantly higher in males compared to females, with an observed male-to-female ratio of 4.55:1. This trend is consistent with the results of previous studies[17,24,25], indicating a male predominance in HCC. This gender difference could be attributed to both biological and environmental factors. In females, estrogen levels inhibit interleukin (IL)-6-mediated inflammation, thus reducing compensatory hepatocyte proliferation

and damage[1]. In contrast, in males, testosterone boosts androgen receptor signaling, which results in increased hepatocyte proliferation[26]. Environmental factors that contribute to higher rates of exposure among males to hepatic carcinogenic agents include occupational exposure to chemicals, alcohol consumption, smoking, and hepatitis viral infection compared to women[27]. Patients with HCC exhibited significantly lower albumin levels and higher AST, ALT, and bilirubin levels compared to the control subjects. These findings align with those reported by Naguib et al[28]. AFP concentration and the prevalence of HCV and HCV-HBV co-infection were significantly higher in the HCC group compared to healthy controls, consistent with the findings of previous studies[17-29]. These results indicate that viral hepatitis plays a significant role in the development of HCC. Our study found that individuals with *XRCC1* p.Gln399Arg genotypes (Gln/Gln, Arg/Gln+Gln/Gln) and *APEX1* p.Asp148Glu genotypes (Glu/Glu, Asp/Glu+Glu/Glu) have a significantly higher risk of developing HCC, suggesting they may be genetic risk factors for HCC. HCV infection has oncogenic properties that inhibit DNA repair mechanisms in liver cells. Additionally, HCV induces chronic inflammation, increasing reactive oxygen species (ROS) production, causing genomic DNA damage that, if left unrepaired, can lead to cancer development[30]. In the present study, there was no significant association found between the *XRCC1* Gln399Arg and *APEX1* Asp148Glu variants and the presence of HCV infection or HCV-HBV co-infection in the HCC study group. This suggests that HCV or HBV infections may not influence the occurrence of these polymorphisms. Our study indicated that higher levels of AFP, the *XRCC1* Arg/Gln+Gln/Gln, and the *APEX1* (Asp/Glu+Glu/Glu) genotypes were linked to an elevated risk of HCC development and could serve as predictors for HCC. Our results are consistent with previous studies, all of which have demonstrated an association between the *XRCC1* variant examined and an increased risk of HCC[22, 31-34]. Conversely, previous studies in different populations[4-9] reported no association between this variant and increased HCC risk, while others[10,11] reported a higher risk of HCC with this variant. The *APEX1 p.Asp 148Glu* polymorphism played no role in HCC development in previous literatures[5,12,13]. Several studies have investigated the relationship between the studied SNPs and an increased risk of HCC in Egyptian subjects, though these studies were conducted in provinces outside the delta region of Egypt. Studies performed in the South Valley of Egypt[14], and in the Capital of Egypt[15], revealed a significant association between the *XRCC1* studied SNP with an increased risk of HCC. Other studies[10,16] found no relationship. In Menoufia, Egypt, a study[17] revealed that the *XRCC1 Gln/Gln* genotype had a protective role against HCC development (OR = 0.64), while the *APEX1 p.Asp148Glu* variant was associated with a higher risk of HCC. Our results align with previous studies reporting an insignificant correlation between the studied SNPs and susceptibility to HCC in HCV-positive patients[16-18]. These discrepancies may arise from a relatively small sample size, variation in specimen handling, the genotyping method applied, and the time of measurement relative to the disease onset. Furthermore, such inconsistencies in results could be attributed to the impact of racial differences and the diverse environmental and genetic factors present in geographically distinct populations. The *XRCC1 Arg399Gln* SNP has been suggested to be affected by environmental agents like smoking or associated with other genetic polymorphisms, such as *XRCC1 280His* allele[19]. This polymorphism occurs in close proximity to the *BRCA1 carboxyl-terminal (BRCT1)* domain of the *XRCC1* protein, that plays a crucial role in interacting with *PARP1*, an interaction essential for the effective repair of single-strand DNA breaks. Consequently, the presence of this variant in this region may disrupt the BRCT1-PARP1 binding, potentially resulting in impaired DNA repair and the buildup of DNA damage[20], thus increasing susceptibility to HCC. The expression levels of *XRCC1* and *APE1* in HCC were investigated in both peripheral blood and tumor tissue samples to assess the agreement between blood and tumor DNA specific repair activity. The current study demonstrated perfect agreement in SNPs between HCC tissue and peripheral blood samples from the same patients for both genes, indicating that the circulating levels reflect the tumor pathology. This suggests that the detection of these polymorphisms in both genes using tissue samples offers no apparent advantage, and peripheral blood samples could serve as a suitable surrogate for tissue biopsies in genetic studies of. However, molecular analysis of tissue samples remains important for accurate results and should complement peripheral blood sampling in clinical and research studies. This result is consistent with previous study[21] reported that formaldehyde-fixed paraffin-embedded (FFPE) colorectal cancer tissue samples can be a valid alternative to peripheral blood samples for genetic analysis. This high concordance supports the use of less invasive blood tests for genetic analysis

Conclusions

The present study concluded that the XRCC1 p.Gln399Arg and APEX1 p.Asp148Glu genetic polymorphisms were significantly associated with an increased risk of HCC in the Egyptian population and could serve as noninvasive predictive genetic markers for HCC, eliminating the need for tissue samples.

Limitations

The current study had some limitations, including its single-center design and limited sample size. Further studies using DNA sequencing are necessary to confirm these results. Studying other genetic polymorphisms within the *XRCC1* and *APEX1* genes could be beneficial.

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List of Abbreviations

AFP: Alpha-fetoprotein
ALT: Alanine aminotransferase
Anti-HCV: Antibodies of hepatitis C virus
AP: Apurinic/apyrimidinic
APEX1: AP endonuclease 1
AST: Aspartate aminotransferase

BER: Base excision repair
CI: Confidence interval
CT: Computed tomography
HBs Ag: Surface antigen of hepatitis B virus
HCC: Hepatocellular carcinoma
HW: Hardy Weinberg
IRB: Institutional research board
OR: Odds ratio
PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism
SD: Standard deviation
SNPs: Single nucleotide polymorphisms
XRCC1: X-Ray Cross Complementing group

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