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(Review)

Hepatocellular Carcinoma Incidence and risk factors: Insights into the Significance of Genetic Heterogeneity

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ABSTRACT

Regarding mortality rates, hepatocellular carcinoma (HCC) ranks third among all cancers and sixth among all primary malignancies in frequency. Preexisting diseases include hepatitis C, hepatitis B viruses, and nonalcoholic cirrhosis; all these factors increase the risk of developing HCC. Regarding population, Egypt is third in Africa and fifteenth around the globe, making HCC a major issue. The greatest HCV prevalence was formerly seen in Egypt. It is critical to investigate the probable relationship between HCV and HCC. In Egypt, the government has implemented a mass screening program for the detection and treatment of HCV, and this strategy is anticipated to result in a future decline in the incidence of HCC. It is vital to investigate genetic markers that may assist in identifying high-risk groups and, hence, adjust screening technique indications. microRNAs and single nucleotide polymorphisms may influence multiple cellular signaling pathways connected to tumor growth and angiogenesis, making diagnosing, prognosis, and treating HCC easier. As a result, further research is required to understand liver carcinogenesis completely. The current research focuses on HCC, its risk factors, and the examination of gene polymorphisms in affected patients.

Keywords: HCC; HCV; SNPs.

1-Introduction

Hepatocellular carcinoma (HCC) is a cancer that has spread to liver cells. This subtype of primary hepatic malignancy accounts for over 80% of all liver cancer diagnoses (1). Liver cancer ranks sixth in overall mortality and fourth among cancers globally and in Egypt, respectively, according to the World Health Organization (WHO) (2)**.** In 2020, there were 905,700 cases worldwide, and 830,200 people died (3). If current incidence and death rates remain unchanged, in 2040, scientists predict that liver cancer will affect 1.4 million people worldwide this year, with an estimated 1.3 million deaths. Improvements in diagnosis and therapy for HCC have been made in recent years, and this is great news since early detection is crucial for improved results (1).

In Egypt, HCC ranks second among male cancers and sixth among female cancers, which ranks third and fifteenth in Africa and the globe in the population (4). HCV and HCC are the main points of study in Egypt. First, evidence indicates a correlation between HCV and the initiation of HCC. Egypt has a high rate of HCV transmission, with an estimated 416,000 new infections annually. Both diseases have increased frequently due to government screening and follow-up efforts (5, 6).

Single nucleotide polymorphism (SNP) related to cancer was discovered via case studies investigating. SNPs involved in biological systems altered during cancer development. SNPs associated with iron metabolism of Human homeostatic iron regulator protein1 (HFE1), this text discusses various factors related to Inflammation, including Tumor necrosis factor A (TNFA), Interleukin 10 (IL-10), Interleukin 1beta (IL1B), Transforming growth factor beta (TGFB), cell cycle, oxidative stress (Glutathione S-transferase Mu 1 (GSTM1), Myeloperoxidase (MPO), Superoxide dismutase 2 (SOD2), iron metabolism (Human homeostatic iron regulator protein (HFE1), and DNA repair (Tumor protein (TP53), Mouse double minute 2 homolog (MDM2), X-ray repair cross complementing3 (XRCC3), Methylenetetrahydrofolate reductase (MTHFR) were identified (7).

Some inherited factors play a role in the pathogenesis of HCC (8). Early detection is critical for improved outcomes, and HCC monitoring, diagnosis, and therapy have progressed dramatically over the last 10 years. The two most often performed surveillance tests are liver ultrasound and serum alpha-fetoprotein levels. However, they are inaccurate in diagnosing HCC in its early stages (9). According to a recent meta-analysis, ultrasound has an 84% of diagnostic

accuracy for HCC at any stage but only 47% for diagnosing early-stage illness. The addition of serum fetoprotein raises the sensitivity of surveillance tests by 63% (48% to 75%) (10).

Despite major developments in HCC treatment, including curative surgery and nonsurgical treatment, the prognosis for HCC remains dismal, with most patients dying within 6-20 months (11). If diagnosed early enough, HCC may be treated. HCCs are detected at an advanced stage when individuals visit a doctor for symptoms (12). Cirrhosis, family history of a diagnosis of HCC, and either sex or age thresholds of 40 for men and 50 for women are used to determine who should undergo HCC monitoring (9). In this article, I outline much research on the relationship between hepatocellular carcinoma (HCC), its risk factors, and gene polymorphism in afflicted people.

1.1. Egypt's Epidemiology and Disease Burden

Hepatocellular carcinoma is ranked the sixth most prevalent type of cancer globally and the third leading cause of cancer-related deaths (13). The two regions with the greatest incidence rates globally are Asia and Africa. HCC contributes to about 85% of all liver cancer occurrences globally, making it the most frequent type (1). HCC incidence decreased in certain high-risk locations while rising in several low-risk areas. While the rate of HCC diminished in certain Asian countries and Italy between 1978 and 2020, it increased in Asia, the Americas, Oceania, and most of Europe (14).

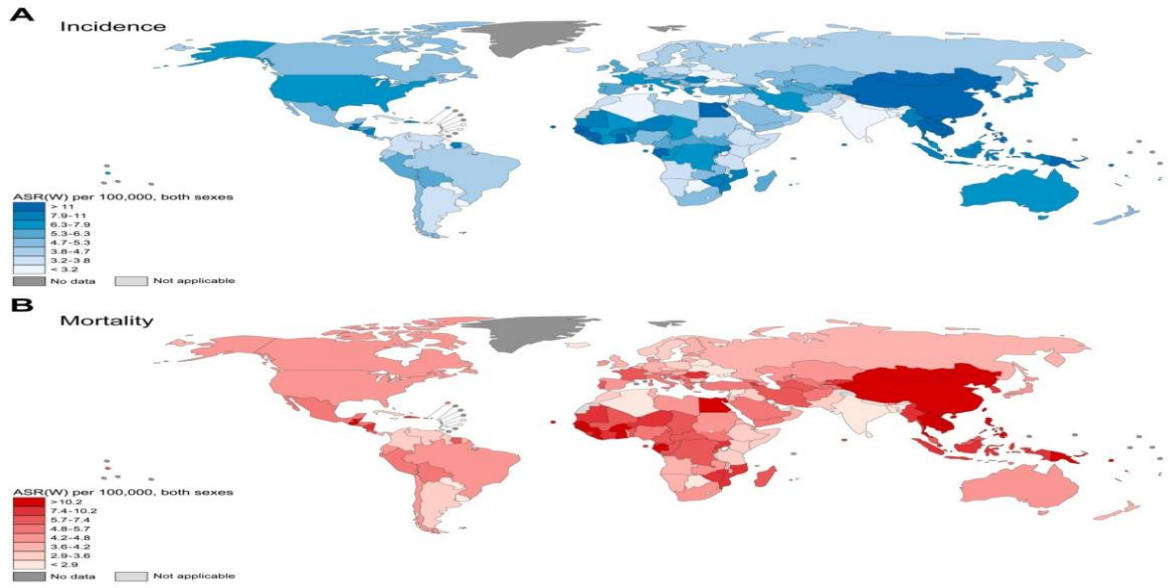

Figure 1: Age-standardized incidence and mortality rates (ASRs) for primary liver cancer per 100,000 people in 2020 by country (14).

Figure 1 demonstrates that in Northern Africa (15.2, 14.5 deaths), in 2020, the highest and lowest age-standardized incidence and mortality rates (ASRs) for liver cancer were recorded in Eastern Asia (17.8 new cases) and South-Eastern Asia (13.7 new patients) respectively. The ASRs for advanced patients and mortality per 100,000 were 9.5 and 8.7, respectively, with a 32% prevalence rate and a 31% death rate (2).

1.2. Risk factors/etiology

The most important hazards for HCC include Non-alcoholic fatty liver disease (NAFLD), continued viral reaction during hepatitis C, and a suppressed hepatitis B virus throughout therapy (15). Tobacco use, dietary pollutants such as aflatoxins, family or genetic factors, and the progress of HCC have all been related to carcinogenic environmental contaminants (16). **Figure 2** summarizes these risk factors.

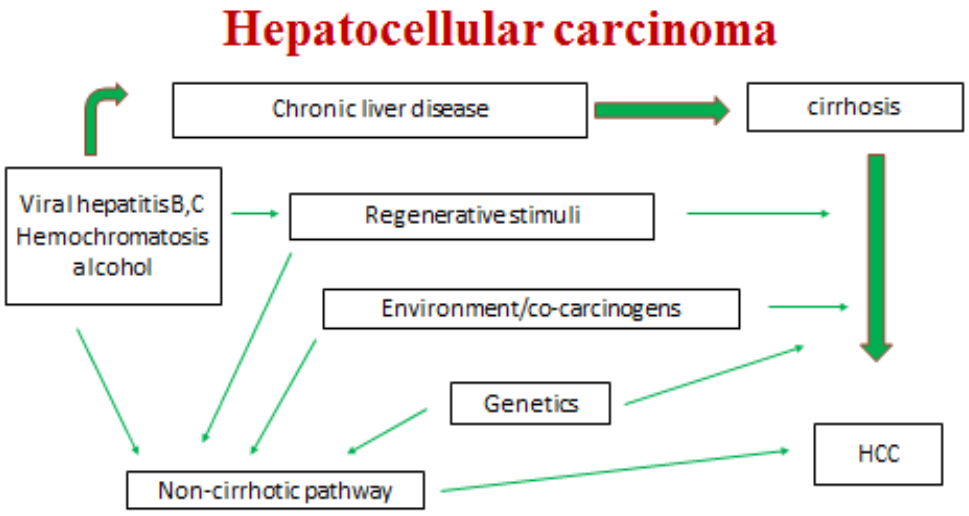

Figure 2. Summary of risk factors for hepatocellular carcinoma in Egypt.

1.2.1 Hepatitis C Virus

Around the globe, 71 million people suffer from HCV. There were 1.75 million new cases of hepatitis C in 2015. Transmission occurs mostly via unsafe healthcare-associated infections and medication injections, with the highest rates observed at 62.5 per 100,000 in the Eastern Mediterranean Region and 61.8 per 100,000 in the European Region (17). HCV's positive-sense, single-stranded RNA genome makes it a relatively modest encapsulated virus of

about 9.6 kb in size. Untranslated regions (UTRs) of 5' and 3' lengths are found in its DNA (18). According to phylogenetics and HCV genome sequencing research, there are 7 genotypes of HCV strains and 67 subtypes after the various genotypes have been further categorized (19).

In Egypt, Genotype 4 of HCV is the most common (20). However, the prevalence of certain genotypes varies from one location or country to another. Infection with the HCV genotype (GT) 1, which accounts for 46.2% of all HCV infections, is widespread worldwide. In South Asia, where 30.1% of all HCV infections occur, it was found that GT3 is the most frequent genotype (21).

The start of widespread anti-schistosomiasis treatment programs in the 1950s and 1960s is often cited as the cause of Egypt's high incidence of HCV today (22). HBV and HCV co-infection has been related to an elevated danger of HCC (23). Even though HBV is recognized as a significant risk indicator for liver cirrhosis and HCC, Egypt may have the highest HCV prevalence in the world. The prevalence of HBV infection in Egypt has declined over the last two decades as HCV has increased (24). For the previous 20 years, Chronic HCV infection has been the underlying cause of fibrosis, cirrhosis, and related molecular and genetic changes that occur in 50% of all patients of hepatic cancer in the United States of America (USA) (25). The continued viral reaction of HCV infection includes the development of cirrhosis-related diseases (26). HCV infection is the leading cause of chronic hepatitis, and HCV interacts with tumor suppressor proteins and cell cycle regulatory proteins. These interactions can interrupt the proteins' normal functioning, the proliferation of aberrant hepatocytes, and the formation of hepatocarcinogenesis (27).

For 20 years, doctors have tried treating HCV with interferon-based medications, which have failed in at least 50% of patients and caused serious adverse effects (28). Direct-acting anti-HCV antivirals (DAAs) have a greater healing rate with a sustained virologic response (SVR) of over 90% compared to interferon-based therapy when administered correctly and with minimum side effects (29).

1.2.2 Hepatitis B Virus

Annually, HCC accounts for more than 900,000 fatalities caused by chronic HBV. HBV is accountable for over 80% of virus-associated HCC cases worldwide, with a predominant prevalence of HCC incidences observed in Africa and East Asia (30). The majority of HBV in

Egypt was found to be 1.4%, with a co-infection risk of 0.06% for HBV (31). Chronic HBV significantly increases the risk of HCC by 15-20 times and is associated with a mortality rate of 30-45% in patients with chronic HBV infection (32). The Hepatitis B virus is characterized by its small size, enveloped structure, and double-stranded DNA genome of 3.2 kb, which is incomplete (33).

The Americas exhibit a high prevalence of HBV genotypes F and H. At the same time, Southeast Asia and the Middle East have a high majority of genotype E characterizes a widespread distribution of genotypes A and D. Sub-Saharan West Africa. Genotypes I and J are also primarily found in Asia, bringing the total number of HBV genotypes to 10, including the AJ genotype (34). According to an Asian study, infected individuals with HBV genotype C had a higher chance of getting HCC beyond 40 years than those infected with HBV genotype B. The risk of developing HCC is associated with the HBV genotype D. in Western Europe and North America than genotype A (35).

In endemic areas, transmission occurs mostly during pregnancy and the first few weeks of birth (vertical and perinatal exposure), while in developed regions, transmission occurs via sexual and parental contact with contaminated blood in drug addicts (36). Occult HBV infection occurs when a patient contains the viral particle, but tests are negative for hepatitis B surface antigen (HBsAg); however, liver disease and HCC are still possible (37).

HBsAg is not the only significant hematological. Patients with positive anti-hepatitis B core antibodies but no HBsAg are at risk of developing HCC (38). The vaccination prevents hepatitis B and HCC. Since the 1980s, it has reduced HCC incidence by 75% in highly endemic regions. In 1991, the WHO recommended adding this vaccination to the EPI. According to the WHO, all newborns should be vaccinated within 24 hours after delivery. The incidence of HBV has decreased considerably because of the universal immunization program (39).

1.2.3 Cirrhosis

Regarding clinical risk factors, cirrhosis appears to be the most relevant for HCC development (40). Age-standardized incidence of both chronic liver diseases (CLD) and liver cirrhosis is 20.7 per 100,000 people, and the worldwide prevalence of liver disease is determined to be 1.5 billion individuals. Approximately 1% to 8% of the world's population develops liver cirrhosis yearly. There are 26.0 new cases in Europe for every 100,000 individuals in the USA,

but in Asia, the incidence varies from 16.5% in East Asia to 23.6% in Southeast Asia (41). Inflammation caused by hepatic injury then induces necrosis and regeneration of hepatocytes, which gradually leads to hepatocellular carcinoma. Chronic liver disease progresses through fibrosis, cirrhosis, and hepatocellular carcinoma (42-43). HCC appears in about 70-90% of patients with macronodular cirrhosis, which is marked in Western nations by enormous nodules of varied sizes surrounded by fibrosis (44). In East Asia and West Africa, it is estimated that only 25%-50% of HCC patients had established liver cirrhosis at the time of diagnosis (45).

Some HCCs develop without cirrhosis, and it has been hypothesized that cirrhosis is necessary for hepatocarcinogenesis. HCC patients often have preexisting cirrhosis, and HCC is also detected at a higher rate in prospectively studied cirrhotic people (46, 47). Co-infection with HBV, HCV, and HIV; long-term infection; older age; male gender; alcohol use; low Cluster differentiation (CD4) count are all related to the severity of fibrosis progression. Fibrogenesis is supported by steatosis, obesity, and diabetes. Cirrhosis is not associated with viral genotype or viral load (28). The prevalence is 2% in cirrhotic individuals with HBV infection and 38% in those with HCV infection (48). Egypt has a serious public health crisis due to chronic liver disease caused by liver cirrhosis brought on by chronic HCV infection (49).

1.2.4 Environmental toxins

Environmental behaviors could include occupational contact with a wide range of chemical compounds. The hepatic system is an important organ that helps with detoxification, metabolism, and excretion (50). As a result, exposure of the liver to potentially toxic organic and inorganic chemical substances may lead to HCC. Arsenic is one substance suggested as a possible HCC risk factor (51). Vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) are the most often used, as are organic solvents (OS) such as trichloroethylene (TCE), perchloroethylene (PCE), N-nitrosamines, dioxin-like compounds (DLC), polychlorinated biphenyls (PCB), and polybrominated biphenyls (PBB), aside from chloral and chloral hydrates, which were primarily employed in DDT and other pesticides. Herbicides and insecticides include ortho-toluidine (O-toluidine). Agriculture employs around (26%) of the Egyptian population. Pesticide exposure is the leading cause of HCC, particularly among rural males. The risk of HCC is increased in this population due to exposure to other risk factors (such as HBV and HCV) (26). Pesticides and fertilizers are considered independent hazards for HCC in Egypt's mid-delta area (27).

1.2.5 Lifestyle factors (alcohol consumption, smoking)

HCC may be influenced by heavy alcohol use over time. Ethanol metabolism produces acetaldehyde by inducing CYP2E1 (cytochrome P450 2E1), leading to elevated generation of reactive oxygen species, lipid peroxidation, and DNA damage. The observed effects include modifications to the antioxidant defense system and inhibition of DNA repair mechanisms, interference with methyl group transfer processes, decreased levels of hepatic retinoic acid, and accumulation of iron resulting in DNA strand breaks and mutations in the p53 gene (52). According to case-control studies from various nations, chronic ethanol intake leads to a roughly two-fold higher risk of HCC (29). In Egypt, this is very low danger. A 16% higher risk of HCC is associated with heavy alcohol drinking (53).

Tobacco components are typically metabolized in the liver, and their carcinogenic effects are known. A comprehensive review of 81 epidemiological research reported that cigarette users had an elevated risk of HCC and death (1). In Egypt, varying results have been discovered about the relationship between the consumption of cigarettes and the HCC (54). However, recent research found that the number of years after Individuals who gave up cigarettes more than 30 years ago had the same HCC risk as nonsmokers, indicating that giving up cigarettes was shown to be inversely related to HCC risk. (55). Egyptian research found that patients who smoked 20 cigarettes daily for over 29 years had a higher chance of getting HCC (33).

1.2.6 Aflatoxins

Ingestion and exposure to fungal aflatoxins is another risk factor for liver cancer. Four aflatoxins are known to be carcinogenic to both animals and humans: qB1, B2, G1, and G2. The most potent hepatotoxic and carcinogenic agent is aflatoxin B1. The induction of HCC by Aflatoxin B1 occurs as a result of the creation of deoxyribonucleic acid (DNA) adducts, leading to genetic mutations in the liver cells that are targeted. DNA adducts have been observed to form covalent bonds with guanine bases present in the DNA of liver cells. This interaction has resulted in the mutation of the p53 tumor suppressor gene, which is a potential precursor to The progress of HCC (56).

Several Research investigations have been conducted to measure the amounts of aflatoxins in food (locally and imported samples) by various Egyptian governorates. Aflatoxin levels were elevated in the samples. The collecting locale and the time of year are two major

variables influencing aflatoxin levels in these samples. A single nucleotide alteration in codon 249 of the tumor suppressor p53 gene is responsible for mutagenesis. This point mutation has been identified in a significant cohort of Egyptian individuals diagnosed with HCC associated with aflatoxin B1 (AFB1) (35).

1.2.7 Non-alcoholic fatty liver disease

The incidence of NAFLD is high in the USA, as evidenced by numerous studies. It has been associated with HCC, which typically develops in the context of liver cirrhosis. The incidence of this phenomenon is increasing concomitantly with the escalating prevalence of obesity, diabetes, and metabolic syndrome. Nonalcoholic steatohepatitis (NASH) exhibits comparable outcomes to HCV infection (57). In the NASH group, the incidence of HCC within 5 years was 11.7% in individuals without chronic HCV infection, whereas it was 30.4% in those with chronic HCV infection. Whenever a case of HCC arises, the mortality rate is similar in both groups (35).

1.2.8 Genetic Landscape in HCC

Genetic and environmental factors contribute to HCC vulnerability, according to growing evidence. Liver cancer involves several molecular, cellular, and histological steps. Chronic liver inflammation may damage, kill, and regenerate hepatocytes, changing their epigenetic and genetic makeup. Due to structural genetic alterations, oncogenes like MYC and tumor suppressor genes like TP53 are altered or mis-regulated (56). New research suggests that HCC may arise from mature hepatocytes or intrahepatic stem cells (58). Histologically, phenotypically aberrant precursor liver lesions such as cirrhotic nodules and low-grade and high-grade dysplastic nodules undergo a process of dedifferentiation and progress toward early and advanced HCCs (59).

The occurrence of cancer is attributed to genetic and epigenetic modifications. By utilizing New Generation Sequencing on patient HCC samples, it is possible to reconsider and investigate the comprehensive molecular profiles of HCC across various tiers, including copy number alterations (CNAs) and somatic mutations at the genomic level, gene expression at the transcription level, and epigenetic modifications at the gene level (60). HCC arises due to the dysregulation of genes that control the cell cycle, proliferation, apoptosis, and migration. The activation of signaling pathways associated with tumorigenesis is attributed to alterations in the regulation of oncogenes or tumor suppressor genes, which are hereditary factors for HCC (61).

1.2.8.1 Noncoding RNAs (ncRNAs)

Because of the wide variety of biological processes that noncoding RNAs (ncRNAs), such as long ncRNAs (lncRNAs) and microRNAs (miRNAs), play a part in, they have recently received enough attention to merit mentioning. Mutations or abnormal expression of ncRNAs are closely associated with many diseases, particularly cancer. The crosstalk research between lncRNAs, miRNAs, and their master-regulated proteins has become a newfangled passion for deciphering cancer's molecular mechanism, including HCC (62). miRNAs sponge when lncRNAs bind miRNAs and hide the targets of the miRNA (63).

1.2.8.2 miRNAs in HCC (clinical application and therapeutic application)

MiRNAs are a class of small non-coding RNA molecules consisting of a single strand. These molecules have been identified in various species. miRNAs are approximately 20 nucleotides long and serve as post-transcriptional modulators of gene expression. Most variations were discovered via case-control studies involving miRNAs and SNPs in biological signaling pathways altered in liver cancer (64). miRNAs play a crucial role in various physiological and pathological conditions, encompassing cellular processes such as growth, development, differentiation, proliferation, apoptosis, and metabolism. Several studies have demonstrated that modifications in miRNA genes and their expression significantly impact carcinogenesis by affecting the regulation of proto-oncogene or tumor suppressor gene expression (65).

Many patients with HCC are already at an advanced stage by the time they are diagnosed, giving them one of the worst prognoses of any cancer. High-risk patients are often screened for HCC using tumor biomarkers, including alpha-fetoprotein (AFP) and protein generated by vitamin K deficiency or antagonists-II (PIVKA-II). Traditional tumor markers, however, have failed to diagnose HCC adequately; their sensitivity and specificity for HCC distinction ranged from just 39-64% (66).

miRNAs are potential diagnostic biomarkers for early cancer because of their consistent expression and varied activities in the human genome. Scientists may measure blood miRNAs that have the potential to act as possible biomarkers for the diagnosis or prognosis of several diseases (63). Both miR-130b and miR-15a were shown to be overexpressed in HCCs serum when testing for HCC, miR-130b was 87.7% sensitive and 81.4% specific, whereas miR-15b was 98.3% sensitive but only 15.3% specific. Their combination as HCC biomarkers may be

good, particularly for early-stage HCC patients with low AFP levels (67). High levels of exosomal miRNA 32-5p expression, which targets PTEN, were observed in HCC patients, with downregulation of miRNA-137 and miRNA-940 (66).

miRNA exhibit differential expression in various types of cancer, with oncogenic miRs typically being significantly increased and tumor-suppressor miRs being significantly decreased. Some of the tumor-suppressor miRNAs play a role in tumor development. In contrast, others are responsible for the disease's proliferation, invasion, metastasis, and recurrence. Also, several oncogenic miRNAs are linked to tumor initiation, progression, and metastasis (68). For example, MiR-122, a tumor-suppressing liver-specific miRNA, accounts for 70% of the total miRNA in hepatic tissues. It modulates hepatic lipid metabolism and inhibits viral replication in HBV-related HCC by targeting N-MYC Downstream Regulated 3 (NDRG3), an N-MYC downstream-regulated gene family member. MiR-122 and NDRG3 are possible therapeutic targets for HBV-related HCC (69).

Studies have shown that miR associated with cell-cycle inhibition (miR-34a, miR-101, miR-199-a-5p, and miR-223) (70) were downregulated. In contrast, the ones associated with cell proliferation and the inhibition of apoptosis (miR-17-92 polycistron, miR-21, miR-96, miR-221, and miR-2240) are upregulated in HCC (71). When comparing Egyptian patients with HCC to healthy controls and those infected with HCV, researchers found that miR-122 and miR-483 were increased, whereas miR-335 was downregulated. miRNAs treat liver cancer and are non-immunogenic. miRNA mimics or inhibitors may enhance liver cancer treatment by targeting the pathogenic molecular mechanism of miRNAs (67).

According to a separate study, restoring tumor suppressor miR-122 makes HCC cells more sensitive to sorafenib treatment by downregulating multidrug resistance genes. In contrast, inhibition of oncogenic miR-221 led to improved survival and a significant reduction in the number and size of tumors. In addition, HCC cells transfected with anti-miR-221 were more sensitive to combined interferon- and 5-FU chemotherapy (72).

lncRNAs are defined as cellular RNAs with more than 200 nucleotides in length and are associated with diverse physiological and pathophysiological activities, such as cell development, differentiation, tumorigenesis, and metastasis (73)

The presence of genetic variants in lncRNA highly upregulated in liver cancer *(*HULC*)* and lncRNA Metastasis-associated lung adenocarcinoma transcript 1(MALAT1) has been linked

to a reduced likelihood of developing HCC in individuals who are persistent carriers of HBV. Furthermore, these variants positively correlate with the serum levels of lncRNA-AF085935 and lncRNAuc003wbd, two promising noninvasive diagnostic biomarkers for HCC. These findings suggest that genetic variations may contribute to the development of HCC following HBV infection (74). According to much research, susceptibility genes and abnormal gene expression are risk factors for HCC (75,76).

1.2.8.3 Gene polymorphism

SNPs are the most common sequence variations in the human genome. SNPs in miRNAs may cause cancer by interfering with transcription, processing, or target identification. Abnormal miRNA expression has been linked to several pathologic events, including the development of HCC. Consequently, genetic differences in miRNAs have been related to the development of HCCs. Numerous studies have shown that susceptibility genes and abnormal gene expression are risk factors for HCC (77).

An Egyptian study found that the TNF--308 G > A polymorphism was linked to an increased susceptibility to HCC. However, no significant correlation was observed between the cytokines interleukin (IL)-1 and IL-10 and the risk of HCC. In a previous study conducted on Egyptian patients, two genetic polymorphisms, namely X-Ray Repair Cross Complementing 1(XRCC1) G28152A (rs25487) and XRCC7 G6721T (rs7003908), were discovered and posited as plausible molecular risk factors for HCC in the Egyptian population. Differences in DNA repair mechanisms may result in the persistence of DNA lesions that are either inadequately repaired or remain unrepaired, potentially facilitating cancer development (78).

Despite extensive research, no SNPs have been shown to have an odds ratio high enough to be implemented into clinical practice as prognostic markers for HCC. Current HCC risk assessment may be enhanced by the future combination of genetic variations with clinical characteristics (79).

Pathogen recognition receptors (PRRs) are biomolecules that recognize the pathogen and damage-associated molecular patterns (PAMPs/DAMPs). These patterns can potentially trigger the development of HCC (80). Research on the involvement of PRRs in the development of HCC has focused mostly on Toll-like receptors (TLRs), particularly TLR4. At least 12 kinds of cancer, including HCC, have been linked to variations in the TLR4 gene (81). In another study,

miRNA499SNPs were shown to decrease the risk of HCC; thus, researchers set out to learn more about the function of miRNAs and the processes by which they contribute to the formation of primary liver cancer (82). The development of HCC is believed to be influenced by various factors, including persistent infections caused by hepatitis B or hepatitis C viruses, exposure to carcinogenic substances, cirrhosis, and multiple SNPs (83).

Common genetic hazards for HCC have been the focus of many genome-wide association studies and candidate gene analyses. However, identifying SNPs associated with susceptibility to HCC is crucial for advancing our knowledge of disease biology and developing more accurate diagnostic and prognostic tools. Some documented SNPs that have been linked to an increased risk of developing HCC include in **Table 1.**

Table 1. **Some documented SNPs have been linked to an increased risk of developing HCC.**

SNP	Gene(s), at or near locus, variant type	Chromosome Locus	OR	Risk	Reference
rs2240688	CD133, protein-coding	4P13	1.465	C	(84)
rs2275959	LINC01605, genic upstream transcript variant, intron variant	8p13	1.45	A or C	(85)
rs4721888	MACC1, missense variant, coding sequence variant	7p15.3	1.16	C	(86)
rs11776545	LINC01605, genic upstream transcript variant, intron variant	8p13	1.4	A	(85)
rs7975232	Apa1, Intron Variant	12 p14	1.687	T	(87)
rs3957357	GSTA1 TT, 2KB_upstream_variant, upstream transcript variant	6p13	2.1	T	(88)
rs1008547	LINC01605, genic upstream, transcript variant, intron variant	8p13	1.45	C	(85)
rs1010273	PRDM1, coding sequence variant, Synonymous Variant	6p13	2	AA	(89)
rs2267401	APOBEC3B, upstream_transcript_variant,2KB_ upstream_variant	22q11.23	1.9	G	(90)
rs1012068	DEPDC5, protein-coding	22q12	10.50	G	(91)
rs755622	MIF,2KB_upstream_variant, upstream transcript variant	22p14	6.303	G	(92)

2. Conclusion

HCC is becoming a major problem in Egyptian culture. The most significant threat to our nation is HCV. While HBV is Egypt's second most significant etiology, HCV is the primary risk factor. It is important to look for genetic characteristics that may be used to identify high-risk groups and adjust screening guidelines accordingly. In addition, new preventative methods for high-risk people may be developed if predictive characteristics are uncovered. As a result of the microRNAs and SNPs' ability to influence several cellular pathways, including those with strong links to tumor growth and angiogenesis, HCC may be better diagnosed, prognoses, and treated. So, further research on hepatic carcinogenesis is required.

Conflict of Interest

The Authors declare no conflict of interest.

List of Abbreviations: Single nucleotide polymorphism (SNP), Hepatocellular carcinoma (HCC), World Health Organization (WHO), Human homeostatic iron regulator protein1 (HFE1), Tumor necrosis factor A (TNFA), Interleukin 10 (IL-10), Interleukin 1beta (IL1B), Transforming growth factor beta (TGFB), Glutathione S-transferase Mu 1 (GSTM1), Myeloperoxidase (MPO), Superoxide dismutase 2 (SOD2), Human homeostatic iron regulator protein (HFE1), Tumor protein (TP53), Mouse double minute 2 homolog (MDM2), X-ray repair cross complementing3 (XRCC3), Methylenetetrahydrofolate reductase (MTHFR), age-standardized incidence and mortality rates (ASRs), Non-alcoholic fatty liver disease (NAFLD), Untranslated regions (UTRs), Hepatitis C Virus (HCV), genotype (GT), Hepatitis B virus (HBV), Hepatitis B surface antigen (HBsAg), Cluster differentiation (CD4), deoxyribonucleic acid (DNA), United States of America (USA), Nonalcoholic steatohepatitis (NASH), noncoding RNAs (ncRNAs), long ncRNAs (lncRNAs), microRNAs (miRNAs), N-MYC Downstream Regulated 3 (NDRG3), X-Ray Repair Cross Complementing 1(XRCC1), Toll-like receptors (TLRs).

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