ISSN (Print) : 0974-6846
ISSN (Online) : 0974-5645
Indian Journal of Science and Technology, *Vol 10(31), DOI: 10.17485/ijst/2017/v10i31/75684, August 2017*

Genetic Perspective of Hepatocellular Carcinoma (HCC) in Asian population - A Review

Anwayee Das and Kriti Menon*

Department of Genetic Engineering, SRM University, Kattankulathur – 603203, Tamil Nadu, India; kritimenon@gmail.com

Abstract

Hepatocellular Carcinoma (HCC) is the fifth most common cancer which causes thousands of death worldwide and the majority of the HCC sufferers are from Asia. Infection of Hepatitis B Virus and Hepatitis C Virus are major reasons for the development of HCC. The factors which add to its persistence are both environmental and genetic. Asia being a vast continent has a huge diversity of both. Polymorphisms in different genes linked with HCC lead to either increase or decrease in its risk. In this review we have focused on genetic factors responsible for HCC, with a special perspective based on the geography. According to the UN geo-scheme Asia is split into Eastern, Southeastern, Southern, Western and Central Asia. Here we have discussed on various genetic mutations which may or may not be the risk factor for HCC. The maximum HCC linked genetic mutations were observed in the Eastern region especially in China.

Keywords: Asian Population, Genetic Factor, Hepatocellular Carcinoma, Polymorphisms, UN geo-scheme

1. Introduction

Cancer is a chronic disease, which leads to an increase in death rate worldwide[1]. Benign or malignant tumor are formed because of the uncontrolled proliferation of under developed cells resulting in rapid spreading of this disease. At present there are over 100 known cancers affecting human species across the world[2]. In the survey carried out by world health organization (WHO) in 2011, Maldives, China, South Africa, Mongolia, Argentina and few countries of Europe show high death rate due to specific types of cancer[3]. Mexico, Bolivia, India, Pakistan, Iraq, Iran, Saudi Arabia and most of the African countries have low death rate due to cancer[3]. There is more than one causative agent for cancer. The major factors responsible for cancer are: Tobacco, obesity, poor sanitation, alcohol consumption, exposure to different types of toxins and radiation, infection due to Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) and so on. The genetic defects inherited from parents also play a major role in developing cancers[4]. About 5-10% of cancers develop due to genetic defects that are inherited[5]. Tobacco and infection caused by HBV, HCV and HIV serves the major sources for the development of lung cancer and liver cancer.

Although the cause of cancer is still being researched upon, with current evidence it is proved that one main cause for the development of cancerous cell is a mutation in the gene, leading to a complete change in the nucleotide sequence of genomic DNA and altering the stability

*Author for correspondence

of its protein production[6]. These mutated gene-containing cells when divide lead to tumor formation[7]. Thus genetic polymorphism is one of the root causes for the development of most types of cancers; for example, Breast Cancer type 1 (BRCA1) and Breast Cancer type 2 (BRCA2) gene mutations cause breast cancer, tumor necrosis factor-alpha (TNF-α) leads to the development of digestive system cancer and so on[8,9]. Genetic or the genes responsible for each type of cancers are different, there might be more than a hundred gene polymorphisms involved in a single cancer and its different stages.

Hepatocellular Carcinoma (HCC) is the fifth most common cancer, and the third leading cancer that causes death in the world, with over 500,000 fatalities annually[10]. HCC is also known as hepatoma or malignant hepatoma. It is the most common type of liver cancer. Most of the HCC are secondary to either a viral hepatitis (B or C) or cirrhosis. HCC is more common in men (4 to 8 times more) than in women of age group 50 or above. Major signs and symptoms of HCC involves change of skin colour (usually yellow skin), bloating due to accumulation of fluid in the abdomen, loss of appetite, abdominal pain, nausea, vomiting, feeling tired, etc.,

In this review we have focused on two most prominent populations, Asian and Caucasian suffering from liver disorders like chronic hepatitis infection, liver cirrhosis and HCC. We will be further proceeding and be focusing on the different geographical areas in Asia that are divided according to UN geo-scheme.

2. Discussion

Asia being world's largest and most populous continent has a vast geography. Asia is divided into different zones by the UN geo-scheme. The sub-regions included in the UN geo-scheme for Asia are Central Asia, Eastern Asia, Southern Asia, South-Eastern Asia and West Asia. Each population has one or more types of factors that lead to conditions like HCC. Table 1 shows a few genes involved in the development of HCC and few others which show no link with HCC, in the geographical area under Asia.

Out of several genes linked with HCC, few are discussed in detail. Most of these gene polymorphisms are found in Asian subjects. One such main genetic factor linked with HCC is tumor necrosis factor-alpha (TNF-α). TNF-α, is a multifunctional cytokine produced by the immune cells of our body, it helps in controlling the body's immune responses by inducing inflammation, apoptotic cell death and also inhibits tumorigenesis and viral replication. Published papers on TNF-α were studied and inferred that there are different gene polymorphisms like -308GG, -308G/A, -308AA and -238G/A which are risk factors for HCC. It was found that HCC patients had low frequency linkage with TNF-α-308GG as compared to healthy subjects. This showcased that -308GG was associated with decreased HCC risk in the Asian population. Another polymorphism -308G/A was found to have greater frequency linkage with HCC when compared with -308GG but it also acted as a protective factor for chronic Hepatitis B Virus (HBV) infection in Asian population but no significant association was studied in Caucasian patients. Thus it was inferred that -308G/A was a risk factor for HCC in Asian population[11]. TNF-a was also associated with various digestive system cancers and one of the polymorphisms, which had the highest risk in its progression, was -308AA[12]. Another important polymorphism TNF-α-238G/A was claimed as to be a risk factor for HCC from the study, but there were also studies showing that it might not be directly associated with the risk[13].

Among many such genetic factors, which were thought to be linked with HCC, Tumor Protein 53 (TP53) codon 72 polymorphism which results in missense mutation of arginine to proline was also studied. TP53 which is a tumor suppressor gene, play a major role in cell cycle and in maintaining genomic integrity. Any mutation in TP53 can cause uncontrolled cell proliferation, which might lead to cancers. This study showed that the risk of cancer was reduced in Asians, when the comparison was made between HBV and HCV sufferers, it was found that there was no link between the TP53 polymorphism and HCC. Thus it may or may not be a risk factor for HCC[14].

Next risk factor were UDP-glucuronosyltransferases 1A7 (UGT1A7) gene polymorphisms, which lead to cancers. UGTs are major biochemical factors in detoxification and cellular defense, even a small mutation in

Table 1. Different gene polymorphisms responsible and not responsible for the increase in risk of HCC in Asia's geographical sub-divisions are tabulated

S.no	Geographical zones of Asia	Countries under this region	Factors responsible for HCC	Factor not responsible for HCC	Reference
1	Eastern Asia	China, Macau Special Administrative Region, Democratic People's Republic of Korea, Japan, Mongolia, Republic of Korea, Taiwan	rs11569017, ErbB4, LAPTM4B*2, XPC, miR-106b-25, GST, MRP-1	PIK3CA, IL27, mtDNA 9bp deletion, KIF1B	[21],[22],[23],[24],[25],[26], [27],[28],[29],[30],[31],[32]
2	Southern Asia	Afghanistan, Bangladesh, Bhutan, India, Iran (Islamic Republic of), Maldives, Nepal, Pakistan, Sri Lanka	TNF-a, INF-g, p53, XRCC1		[33],[34]
3	Southern Asia	Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, Viet Nam	Pre-S2(LC>HCC),FGFR4, IL-1B		[35],[36][,37]
4	Southern Asia	Armenia, Azerbaij, Bahrain, Cyprus, Georgia, Iraq, Israel, Jordan, Kuwait, Oman, Lebanon, Qatar, Saudi Arabia, State of Palestine, Syrian Arab Republic, Turkey, United Arab Emirates, Yemen	TNF-a, CCND1G870A, MDM2SNP309, miR-196a-2, Exo1 K589E, Arg72Pro of p53, Aurora A F31I	NQO1 C6091	[38],[39],[40],[41],[42],[43] , [44],[45]

UGT1A7 can cause change in coding for enzyme activities. Mutation in UGT1A7 can give rise to variants such as UGT1A7*1, UDT1A7*2, UGT1A7*3 and UGT1A7*4. UGT1A7*3 played a significant role in the development of various cancers among Asians especially HCC but UGT1A7*2 and UGT1A7*4 had no significant effect[15].

Mutation in MicroRNAs was associated with major cancer risks[16]. The study was conducted on four genetic variants in miRNAs namely rs11614913, rs2910164, rs3746444, rs229283. MiRNAs are single-stranded RNAs, which attach themselves to the mRNAs and inhibit translation mechanism. Studies carried out in these SNPs reveal that they act as both risk and protective factors for cancer. Comparison was done among the 3 polymorphisms of rs11614913 (TT, CT, CC). According to the statistical analysis, it was shown that rs11614913TT had decreased risk of colorectal, breast and lung cancers when compared with the CT and CC polymorphisms (TT<CT<CC)[16]. In rs2910164 there was no major risk observed in pooled analysis but in subgroup analysis when the comparison between polymorphisms CC and GG was conducted, there was a decrease in risk for HCC but increase in the risk of gastric cancers[16]. In sub-group analysis of ethnicity there was a reduced cancer risk for Asian population but increased risk for the Caucasian population. On studying about the polymorphism in rs3746444, it was found that the GG mutation had a higher risk of breast cancer among Asians especially in Chinese population. The study clearly showed that the four SNPs were associated with increase in risk for cancers in Asian population but no significant link was found with HCC[17].

A meta-analysis on interleukin-10 (IL-10) gene polymorphisms and HCC was studied to get a wider view on the various factors responsible for HCC worldwide. IL-10 is a cytokine produced by the immune cells of our body, which causes inflammatory actions during pathogenesis[18]. Any polymorphism in IL-10 can lead to various types of cancers such as breast, cervical, multiple myeloma, oral and gastric cancer. The important polymorphism of IL-10 studied was IL-10 1082G/A, IL-10 819T/C, IL-10 592C/A[18,19]. The former two polymorphisms had no association with HCC but the latter one was linked with an increased risk for HCC[19].

Ras Association domain family 1A (RASSF1A) tumor suppressor gene is located in 3p21.3 locus. The inactivation of this gene has a major link with the development of various type of cancer including HCC in human. Epigenetic aberrant methylation of RASSF1A leads to hepato-carcinogenesis. So, the methylation status of RASSF1A was analyzed by calculating the gene expression level of RASSF1A mRNA. The analysis revealed that 86% of HCC sufferers were detected with RASSF1A hyper methylation (those subjects who did not receive chemotherapy)[20].

As described earlier we have segmented Asia into different geographical area according to the UN geo-scheme and studied the genetic factors responsible for the development of HCC in these population.

2.1 Eastern Asia

This region covers countries like China, Macau, Korea, Japan, Mongolia and Taiwan. The maximum number of studies were carried out in Chinese population as this country is geographically vast with the world's highest population; This population is prone to genetic mutations based on its geographical and environmental factors.

Due to the rapid development in economy, China has higher burdens of population. The trends show that there is a steep increase in the number of cancer patients in this country. Out of various studies done, we have narrowed down few factors that contribute towards the development of HCC. Among many factors responsible for the HCC, the Epidermal Growth Factor (EGF), EGF Receptor (EGFR) and EGF family receptor tyrosine kinases, which consists of four members, ErbB1, ErbB2, ErbB3 and ErbB4 were found to have link with the development of cancer[21,22]. The former two were linked with the hindering of tumor cell apoptosis, cell proliferation and metastasis of tumor cells, Whereas among the latter two mutations, a common genetic polymorphism in ErbB4 was found to have a link with HCC. Eight Single Nucleotide Polymorphisms (SNPs) of EGFR were studied, among which rs11569017T allele was associated with the susceptibility of HCC in patients suffering from Chronic Hepatitis B (CHB)[21].

Polymorphism in Lysosomal Protein Transmembrane 4 beta (LAPTM4β) mRNA and polymorphism in microRNA-106b-25 (miR-106b-25) also were threats leading to HCC. LAPTM4β mRNA and protein has the ability to up-regulate the normal hematopoietic progenitor cells and lead to development of HCC. LAPTM4β has 2 allele polymorphisms, *1 and *2 out of which, *2 was found to be more in HCC sufferers than in control and was significantly associated with HCC risk whereas the other polymorphism was not associated with increase in

HCC risk[23]. A polymorphism in the promoter region of microRNA-106b-25 (miR-106b-25) in the HBV affected people may lead to HCC. This cluster was studied and it has been found that it was linked to tumorigenesis and progression of cancers like HCC[24]. Studies revealed that a SNP rs999885 in this region was associated with increase in HCC risk in HBV persistent patients[25]. The risk of this polymorphism increased when the G allele was replaced with the A allele and the people with GG or AG genotype had greater life expectancy than the people with AA genotype thus showing that A allele was linked with an increase in HCC risk and higher mortality rate[24,25].

Mutations in Glutathione S Transferase (GST), Multidrug Resistant related Protein-1 (MRP-1) and Xeroderma Pigmentation Completion group C (XPC) codon 939 also serves for the increase in HCC risk. GSTM1 and GSTT1 are well studied GST genes. The null genotypes (homozygous deletion of GST genes) of these polymorphisms showed association with the increase in HCC risk and the sub group analysis showed that GST was related to increase in HCC in people living in the high incidence areas as compared to the subjects living in low incidence areas. The study revealed that GSTT1/GSTM1 polymorphisms were linked with the increase in HCC in the Chinese population[26].

A study on G-1666A polymorphism in MRP-1 was analysed and its relation with HCC was studied. MRP-1 belongs to the ATP-binding cassette superfamily of cell surface transport proteins. It helps in transport of the endogenously produced and exogenously administered molecules in an ATP-dependent way. It also plays a significant role as a transport protein in carcinogenesis. Analysis showed that the people with GG homologues had a reduced 4-year disease-free survival as compared with people having at least one A allele and the Electrophoretic Mobility Shift Assay (EMSA) showed that G allele had a stronger binding affinity for the nuclear proteins[27]. Thus the people with 1666GG polymorphism had a poorer survival rate and it was found to be most common in the South-eastern part of China[27].

Mutation in codon 939 of XPC is caused due to carcinogens like aflatoxin B1 (AFB1) and is involved in nucleotide excision repair, but studies have shown that this polymorphism might lead to HCC risk[28]. Aflatoxin B1 can break open the double stranded DNA, causes DNA base damage and oxidative damage, which leads to cancers. It was also found that the genotypic distribution of XPC Lys939Gln was high in the HCC sufferers. Therefore, XPC codon 939 was found to be associated with the AFB1 related HCC in this population[28].

Phosphatidylinositol 3 kinases (PIK3CA) polymorphism may be a major factor related to HCC in the Korean population. PIK3CA interacts with phosphatidylinositol 3,4,5 trisphosphate (PIP3) at the membrane and catalyzes the phosphorylation of Akt (Protein kinase B), which activates the down streaming signalling of the pathway. The frequency of PIK3CA mutation was checked in HCC sufferers by sequencing the exon 1, 3, 4, 6, 7, 8, 9, 19 and 20 and there was no mutations detected in the exons 3, 6, 8 and 19. However unknown SNPs where detected in exons 1,4,7,9 and 20, but these were found to have no direct relationship with increased HCC risk. The study suggested that this mutation rate in the Korean population was similar to the rates seen elsewhere in the world[29].

Some genes, which were thought to be risk factor for HCC, were found to have no link with it . One such gene is cytokine interleukin 27. IL27 is a part of the IL12 family, which plays a role in protection against tumor. It is an early mediator for the proliferation of naive T cells. Two particular SNPs of IL27, SNP -964A/G and -2905T/G were studied but no significant differences were found between the genotype and allelic frequencies in the patients suffering from HCC as well as the controls. It was found that IL27 was not linked to HCC development[30].

The mitochondrial DNA 9-bp (mtDNA) was also thought to be related to HCC. Its 9bp deletion polymorphism is caused due to the loss of one copy of 9bp tandem repeated sequence (CCCCCTCTA) and it causes an alteration in oxidative phosphorylation and in the level of oxidative stress[31]. But it was found that this gene deletion was not directly linked to HCC, it might indirectly influence HCC risk through specific microRNA-mediated regulation[31]

Kinase family factor 1B (KIF1B) was accounted as a risk factor which might be related to development of CHB in Chinese population[32]. But rs17401966 AG and GG genotypes and rs8019 and rs17401927 had no significant association with CHB. Also, it was confirmed that the three SNPs of KIFB1 were not associated with the development of CHB[32].

2.2 Southern Asia

Compared to other geographical area, southern Asia is not linked to factors that leads to the development of HCC, though it is geographically near to China, which

has maximum number of cases related to HCC. This part of Asia covers regions like India, Pakistan, Maldives, Sri Lanka and so on. In the above discussion it was claimed that TNF-a (-308) is an important cause for development of HCC in Asia population but in a study carried out on 398 subjects and 146 healthy controls in Indian population it was found that both TNF-a and IFN-g, the two important pro-inflammatory Th1 cytokines had no direct link with increased HCC risk[33]. The studies gave evidences for a viral negative association of IFN-g +874 TA and AA genotype with HBV-HCC risk and no clear association of TNF-a -308G/A genotype but the level of TNF-a was elevated as disease progressed to HCC whereas the level of IFN-g +874 was increase only in HCC subjects[33]. It was also observed that the IFN-g mRNA levels and not TNF-a level was elevated in cirrhosis patients. As there was increase in level of both cytokines during progression and different stages of HCC further studies are required revealing the root cause for development of HCC.

An analysis on the link between p53 and XRCC1(X-ray Cross Complimenting group 1) was done in the Indian population. It was observed that individually these genes did not show any risk for HCC but when they were combined a marked increase was seen in the susceptibility of HCC[34].

2.3 South-Eastern Asia

The South-eastern region includes Brunei Darussalam, Cambodia, Indonesia, Malaysia, Thailand, Myanmar, Singapore, Philippines, Lao People's Democratic Republic, Timor-Leste and Viet Nam. A study showed that HBV pre-S2 mutation rate was high in Indonesian population as compared to other Asian countries. But the presence of pre-S2 codon polymorphism was found to be more common in liver cirrhosis patients than in HCC sufferers, and it serves as a biomarker for all the liver diseases[35].

Another mutation in Fibroblast growth factor receptor 4(FGFR4) was studied and analyzed. Eight missense mutations were found on sequencing FGFR4, out of which 3 known mutations were present (V10I, L136P and G338R). V10I and G338R mutations were found to have higher frequency, as compared to the other SNPs. But significant difference was not found in the genotype distribution of these two alleles among patients and controls. The study also revealed that, homozygous G338R mutation showed increased secretion of Alphafetoprotein (AFP), which is a marker for HCC. Thus it was concluded that FGFR4 may contribute to HCC progression[36].

In the Thai population, the effect of Interleukin-1 beta (IL-1B) promoter region C511T and IL-1 receptor antagonist (IL-1RN) polymorphisms of patients with chronic HBV infection were studied. It was seen that IL-1B-511 genotype C/C, was significantly increased in people suffering from HCC as compared to the non-sufferers. But IL-1RN gene did not show any significant association among the subjects. Hence it was concluded that IL-1B might be a genetic marker for development of HCC in HBV affected people of Thai population[37].

2.4 West Asia

West Asia includes countries like Iraq, Saudi Arabia, Israel, Kuwait, Jordan, Turkey, United Arab Emirates and so on. Few risk factors that are seen in Turkish population is discussed here.TNF-α is a pro-inflammatory cytokine. A mutation in the promoter region of this gene, at position -308, is susceptible to various types of cancer. A study on HCC patients and controls confirmed the association of the TNF-α gene G-308A polymorphism as a risk factor for HCC[38].

A study on cyclin D1 (CCND1) was conducted on Turkish population. And was found that G870A polymorphism, present in the splice donor region of exon 4 of CCND1 gene is associated with an increased risk of HCC[39].

Mouse double minute 2 (MDM2) gene is one of the main factors involved in the p53 pathway. T/G polymorphism, SNP309 (rs2279744) present on the intronic promoter region of MDM2 showed an effect on MDM2 expression and p53 activity. This SNP was also found to be associated with an increased rate of tumor formation in both hereditary and sporadic cancer. On analyzing MDM2 SNP309 polymorphism in Turkish subjects, it was found to be associated with HCC risk[40]. Guanine (G)/adenine (A) polymorphism at first position of codon 589 in Exonuclease 1 (Exo 1), an important gene involved in the mismatch repairing activity results in the substitution of amino acid glutamic acid (Glu, E) to lysine (Lys, K) (K589E). It alters cancer risk by influencing the activity of Exo 1 protein[41]. A study carried out on HCC sufferers and controls showed that Exo1 K589E polymorphism is associated with increased risk of HCC development in the Turkish population.[41].

A study on precursor MiRNA, miR-196a-2 rs11614913 (C→T) polymorphism showed that, it will alter mature miR-196a-2 expression and target mRNA

binding. The association of this polymorphism was studied among subjects with HCC and control group and was found to be a risk factor for HCC, especially among the males and HBV-infected patients in the Turkish population[42].

In the 4th exon of p53 gene, guanine (G)/cytosine (C) polymorphism at second position of codon 72 results in the substitution of amino acid arginine (Arg) to proline (Pro) (Arg72Pro). This polymorphism's effect was studied on HCC suffers and was found to be associated with increased risk for HCC development in the Turkish population[43].

Aurora A is considered as a potential cancer susceptibility gene. A Polymorphism in the coding region of Aurora A gene, F31I is linked to several human cancers. A study revealed that the genotypes containing I31 allele in HCC patients was significantly higher than that in controls, proving that Aurora A F31I polymorphism is suspected to be a risk factor for HCC[44].

Studies carried out in Turkish subjects showed that there was no involvement of NAD(P)H: Quinone oxidoreductase 1 (NQO1) C609T polymorphism with development of HCC. NQO1 is a cytosolic enzyme that protects our cell from oxidative stress, by catalyzing the two-electron reduction of numerous Quinone compounds into their less toxic form. NQO1 C609T polymorphism is suspected to cause depletion in p53 levels. Due to which a significant reduction of apoptosis and increase in genomic instability in hepatocytes can lead to HCC. But the allelic frequency and genotype distribution of NQO1 C609T showed no significant difference between subjects and controls[45].

2.5 Inherited or Early Onset of HCC

Since there are involvement of different genetic factors and polymorphism, studies were done to reveal that HCC can be inherited or developed in early stages of life. In a study carried out on 2242 HCC patients of the Korean population, it was observed that a total of 165 (7.4%) out of 2242 patients had a positive family history for HCC in one or more family members, whereas 2077 (92.6%) patients had no family history of HCC. Among those 165 patients with positive family histories, 159 had a positive family history of HCC in one or more first-degree relatives

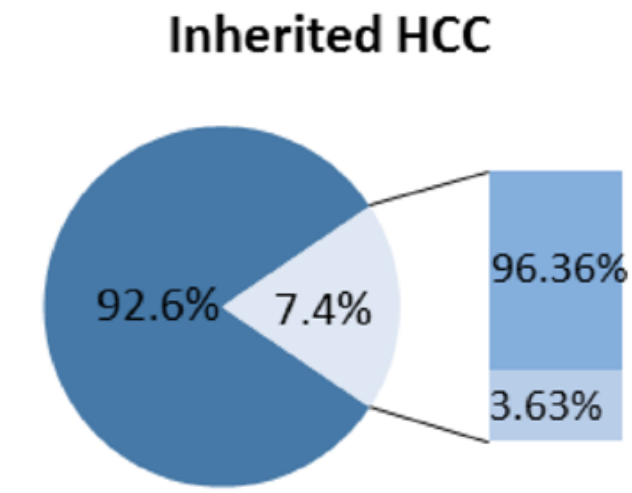

Figure 1. Percentage of inherited HCC.

Figure 1 shows a total of 7.4% patients had a positive family history of HCC in one or more family members and 92.6% patients had no family history of any HCC. Among 7.4% patients with positive family histories, 96.36% had a positivefamily history in one or more first-degree relatives which includes parents and siblings..

which includes parents and siblings, as shown in Figure 1. Out of these positive family history group, 61 (37.0%) patients were diagnosed in their fifties and 48 (29.1%) in their forties[46]. Another study carried out in 340 HCC patients and 292 controls selected from Chinese population showed a pattern of X linked recessive inheritance of HCC genes with the help of HCC pedigree. There were few patterns observed in the study. Mothers and brothers of the male HCC sufferers were more prone to get affected by HCC than other family members. At the same time HCC incidence was found to be higher among brothers as compared to brother-sister or sister-sister. It was also observed that there is a higher prevalence of HCC in the off-springs of female sufferers as compared to the male sufferers. These indicated that an X-linked recessive inheritance pattern runs in the family of few subject[47].

3. Conclusion

Among all the studies carried out in Asia, the maximum number of studies on HCC were carried in China. When the different polymorphism studies were done on the whole of Asia, it was found that the majority of polymorphisms which were risk factors for HCC were found in Eastern Asia. The country with the highest number of polymorphisms in this area was China. This was followed by South Korea and Japan. The Turkish population in Western Asia also showed several polymorphisms linked to increase in risk for development of HCC. A few polymorphism studies were carried out in Southern Asia and South-Eastern Asia which showed that not much polymorphisms were linked to increased link of HCC in these regions. The minimum number of polymorphisms linked to HCC was seen in Central Asia.

4. References

1. Stewart BW, Wild CP. World cancer report 2014. World. 2015 Nov 13.
2. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, Maertens J, Lortholary O, Kauffman CA, Denning DW. Revised definitions of invasive fungal disease from the European organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (EORTC/MSG) consensus group. Clinical Infectious Diseases. 2008 Jun 15; 46(12):1813–21. PMid:18462102, PMCid:PMC2671227. CrossRef.
3. Alwan A. Global status report on noncommunicable diseases 2010. World Health Organization; 2011.
4. Anand P, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B, Aggarwal BB. Cancer is a preventable disease that requires major lifestyle changes. Pharmaceutical Research. 2008 Sep 1; 25(9):2097–116. PMid:18626751, PMCid:PMC2515569. CrossRef.
5. Sawyers CL, Abate-Shen C, Anderson KC, Barker A, Baselga J, Berger NA, Foti M, Jemal A, Lawrence TS, Li CI, Mardis ER. AACR Cancer progress report 2013. Clinical Cancer Research. 2013 Oct 15; 19(20 Supplement):S1–98. PMid: 24045178. CrossRef.
6. Croce CM. Oncogenes and cancer. New England Journal of Medicine. 2008 Jan 31; 358(5):502–11. PMid: 18234754. CrossRef.
7. Knudson AG. Two genetic hits (more or less) to cancer. Nature Reviews Cancer. 2001 Nov 1; 1(2):157–62. PMid: 11905807. CrossRef.
8. Peto J, Collins N, Barfoot R, Seal S, Warren W, Rahman N, Easton DF, Evans C, Deacon J, Stratton MR. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. Journal of the National Cancer Institute. 1999 Jun 2; 91(11):943–9. PMid: 10359546. CrossRef.
9. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: A cancer journal for clinicians. 2011 Mar 1; 61(2):69–90. PMid: 21296855. CrossRef.
10. Block TM, Mehta AS, Fimmel CJ, Jordan R. Molecular viral oncology of hepatocellular carcinoma. Oncogene. 2003 Aug 11; 22(33):5093–107. PMid: 12910247. CrossRef.
11. Hu Q, Lou GG, Liu YC, Qian L, Lv BD. The tumor necrosis factor-α-308 and-238 polymorphisms and risk of Hepatocellular Carcinoma for Asian populations: a meta-analysis. Current Therapeutic Research. 2014 Dec 31; 76:70–5. PMid:25352937, PMCid:PMC4209508. CrossRef.
12. Guo XF, Wang J, Yu SJ, Song J, Ji MY, Cao Z, Zhang JX, Wang J, Dong WG. TNF-α-308 polymorphism and risk of digestive system cancers: a meta-analysis. World journal of gastroenterology: WJG. 2013 Dec 28;19(48):9461
13. Tian X, Ma P, Sui C, Li Y, Fu L, Jiang T, Wang Y, Jiang Y. Comprehensive assessment of the association between tumor necrosis factor alpha G238A polymorphism and liver cancer risk. Tumor Biology. 2014 Jan 1; 35(1):103–9. PMid: 23943369. CrossRef.
14. Ding C, Yu H, Qin H. Tp53 codon 72 polymorphism with hepatocellular carcinoma: a meta-analysis. Journal of International Medical Research. 2012 Apr 1; 40(2):446–54. PMid: 22613405. CrossRef.
15. Han SX, Wang L, Wu DQ. The association between UGT1A7 polymorphism and cancer risk: A meta-analysis.

Cancer Epidemiology. 2012 Aug 31; 36(4):e201–6. PMid: 22402308. CrossRef.
16. He B, Pan Y, Cho WC, Xu Y, Gu L, Nie Z, Chen L, Song G, Gao T, Li R, Wang S. The association between four genetic variants in microRNAs (rs11614913, rs2910164, rs3746444, rs2292832) and cancer risk: Evidence from published studies. PLoS One. 2012 Nov 14; 7(11):e49032. PMid: 23155448, PMCid: PMC3498348. CrossRef.
17. Xu Y, Gu L, Pan Y, Li R, Gao T, Song G, Nie Z, Chen L, Wang S, He B. Different effects of three polymorphisms in MicroRNAs on cancer risk in Asian population: Evidence from published literatures. PLoS One. 2013 Jun 1; 8(6). CrossRef.
18. Lu W, Pan K, Zhang L, Lin D, Miao X, You W. Genetic polymorphisms of interleukin (IL)-1B, IL-1RN, IL-8, IL-10 and tumor necrosis factor α and risk of gastric cancer in a Chinese population. Carcinogenesis. 2005 Mar 1; 26(3):631–6. PMid: 15579481. CrossRef.
19. Wei YG, Liu F, Li B, Chen X, Ma Y, Yan LN, Wen TF, Xu MQ, Wang WT, Yang JY. Interleukin-10 gene polymorphisms and Hepatocellular Carcinoma susceptibility:A meta-analysis. World J Gastroenterol. 2011 Sep 14; 17(34):3941–7. PMid: 22025883, PMCid: PMC3198024. CrossRef.
20. Saelee P, Wongkham S, Chariyalertsak S, Petmitr S, Chuensumran U. RASSF1A promoter hypermethylation as a prognostic marker for hepatocellular carcinoma. Asian Pac J Cancer Prev. 2010 Jan 1; 11(6):1677–81. PMid: 21338215.
21. Wu J, Zhang W, Xu A, Zhang L, Yan T, Li Z, Wu X, Zhu X, Ma J, Li K, Li H. Association of epidermal growth factor and epidermal growth factor receptor polymorphisms with the risk of hepatitis B virus-related Hepatocellular Carcinoma in the population of North China. Genetic Testing and Molecular Biomarkers. 2013 Aug 1; 17(8):595–600. PMid: 23790025, PMCid: PMC3732435. CrossRef.
22. Yu Q, Zhou CX, Chen NS, Zheng SD, Shen LM, Zhang JK. A polymorphism within ErbB4 is associated with risk for Hepatocellular Carcinoma in Chinese population. World J Gastroenterol. 2012 Jan 28; 18(4):383–7. PMid: 22294845, PMCid: PMC3261534. CrossRef.
23. Zhai G, Yang H, Ji X, Xiong F, Su J, McNutt MA, Li X. Correlation of LAPTM4B polymorphisms with Hepatocellular Carcinoma in Chinese patients. Medical Oncology. 2012 Dec 1; 29(4):2744–9. PMid: 22207410. CrossRef.
24. Qi F, Huang M, Pan Y, Liu Y, Liu J, Wen J, Xie K, Shen H, Ma H, Miao Y, Hu Z. A genetic variant in the promoter region of miR-106b-25 cluster predict clinical outcome of HBV-related Hepatocellular Carcinoma in Chinese. PloS one. 2014 Jan 8; 9(1):e85394. PMid: 24416400, PMCid: PMC3885710. CrossRef.
25. Castelli EC, Moreau P, e Chiromatzo AO, Mendes-Junior CT, Veiga-Castelli LC, Yaghi L, Giuliatti S, Carosella ED, Donadi EA. In silico analysis of microRNAS targeting the HLA-G 3′ untranslated region alleles and haplotypes. Human Immunology. 2009 Dec 31; 70(12):1020–5. PMid: 19664672. CrossRef.
26. Yu L, Wang CY, Xi B, Sun L, Wang RQ, Yan YK, Zhu LY. GST polymorphisms are associated with Hepatocellular Carcinoma risk in Chinese population. World J Gastroenterol. 2011 Jul 21; 17(27):3248–56. PMid: 21912475, PMCid: PMC3158402.
27. Zhao J, Yu BY, Wang DY, Yang JE. Promoter polymorphism of MRP1 associated with reduced survival in hepatocellular carcinoma. World J Gastroenterol. 2010 Dec 28; 16(48):6104–10. PMid: 21182225, PMCid: PMC3012574. CrossRef.
28. Long XD, Ma Y, Zhou YF, Ma AM, Fu GH. Polymorphism in xeroderma pigmentosum complementation group C codon 939 and aflatoxin B1–related Hepatocellular Carcinoma in the Guangxi population. Hepatology. 2010 Oct 1; 52(4):1301–9. PMid: 20658464. CrossRef.
29. Kim H, Park CK, Lee SJ, Rha SY, Park KH, Lim HY. PIK3CA mutations in hepatocellular carcinoma in Korea. Yonsei medical journal. 2013 Jul 1;54(4):883–7.
30. Peng Q, Qin X, He Y, Chen Z, Deng Y, Li T, Xie L, Zhao J, Li S. Association of IL27 gene polymorphisms and HBV-related Hepatocellular Carcinoma risk in a Chinese population. Infection, Genetics and Evolution. 2013 Jun 30; 16:1–4. PMid: 23395794. CrossRef.
31. Jin Y, Yu Q, Zhou D, Chen L, Huang X, Xu G, Huang J, Gao X, Gao Y, Shen L. The mitochondrial DNA 9-bp deletion polymorphism is a risk factor for Hepatocellular Carcinoma in the Chinese population. Genetic testing and molecular biomarkers. 2012 May 1; 16(5):330–4. PMid: 22283196, PMCid: PMC3354583. CrossRef.
32. Zhong R, Tian Y, Liu L, Qiu Q, Wang Y, Rui R, Yang BF, Duan SY, Shi JX, Miao XP, Wang L. HBV-related Hepatocellular Carcinoma susceptibility gene KIF1B is not associated with development of chronic hepatitis B. PLoS One. 2012 Feb 21; 7(2):e28839. PMid: 22363396, PMCid: PMC3283615. CrossRef.
33. Saxena R, Chawla YK, Verma I, Kaur J. IFN-γ (+ 874) and not TNF-α (– 308) is associated with HBV-HCC risk in India. Molecular and Cellular Biochemistry. 2014 Jan 1; 385(1-2):297–307. PMid: 24101445. CrossRef.
34. Kiran M, Chawla YK, Jain M, Kaur J. Haplotypes of microsomal epoxide hydrolase and X-ray cross-complementing group 1 genes in Indian Hepatocellular Carcinoma patients. DNA and Cell Biology. 2009 Nov 1; 28(11):573–7. PMid: 19754350. CrossRef. CrossRef.
35. Utama A, Siburian MD, Fanany I, Intan MD, Dhenni R, Kurniasih TS, Lelosutan SA, Achwan WA, Zubir N. Hepatitis B virus pre-S2 start codon mutations in Indonesian liver disease patients. World journal of gastroenterology: WJG. 2012 Oct 14;18(38):5418.

36. Ho HK, Pok S, Streit S, Ruhe JE, Hart S, Lim KS, Loo HL, Aung MO, Lim SG, Ullrich A. Fibroblast growth factor receptor 4 regulates proliferation, anti-apoptosis and alpha-fetoprotein secretion during Hepatocellular Carcinoma progression and represents a potential target for therapeutic intervention. Journal of Hepatology. 2009 Jan 31; 50(1):118–27. PMid: 19008009. CrossRef.
37. Hirankarn N, Kimkong I, Kummee P, Tangkijvanich P, Poovorawan Y. Interleukin-1 beta gene polymorphism associated with Hepatocellular Carcinoma in Hepatitis B Virus infection. World Journal of Gastroenterology. 2006 Feb 7; 12(5):776. PMid: 16521194, PMCid: PMC4066131. CrossRef.
38. Akkiz H, Bayram S, Bekar A, Ozdil B, Akgollu E, Sumbul AT, Demiryurek H, Doran F. G-308A TNF-α polymorphism is associated with an increased risk of Hepatocellular Carcinoma in the Turkish population: Case-control study. Cancer Epidemiology. 2009 Oct 31; 33(3):261–4. PMid: 19683483. CrossRef.
39. Akkiz H, Bayram S, Bekar A, Akgollu E, Ozdil B. Cyclin D1 G870A polymorphism is associated with an increased risk of Hepatocellular Carcinoma in the Turkish population: Case–control study. Cancer Epidemiology. 2010 Jun 30; 34(3):298–302. PMid: 20347627. CrossRef.
40. Akkiz H, Sumbul AT, Bayram S, Bekar A, Akgollu E. MDM2 promoter polymorphism is associated with increased susceptibility to Hepatocellular Carcinoma in Turkish population. Cancer Epidemiology. 2010 Aug 31; 34(4):448–52. PMid: 20447891. CrossRef.
41. Bayram S, Akkiz H, Bekar A, Akgollu E, Yildırım S. The significance of exonuclease 1 K589E polymorphism on Hepatocellular Carcinoma susceptibility in the Turkish population: a case–control study. Molecular Biology Reports. 2012 May 1; 39(5):5943–51. PMid: 22205538. CrossRef.
42. Akkiz H, Bayram S, Bekar A, Akgollu E, Ulger Y. A functional polymorphism in pre-microRNA-196a-2 contributes to the susceptibility of Hepatocellular Carcinoma in a Turkish population: A case–control study. Journal of Viral Hepatitis. 2011 Jul 1; 18(7):e399–407. PMid: 21692953. CrossRef.
43. Sumbul AT, Akkiz H, Bayram S, Bekar A, Akgollu E, Sandikci M. p53 codon 72 polymorphism is associated with susceptibility to Hepatocellular Carcinoma in the Turkish population: A case–control study. Molecular Biology Reports. 2012 Feb 1; 39(2):1639–47. PMid: 21607615. CrossRef.
44. Akkız H, Bayram S, Bekar A, Akgollu E, Ozdil B. Relationship between functional polymorphism in the Aurora A gene and susceptibility of hepatocellular carcinoma. Journal of Viral Hepatitis. 2010 Sep 1; 17(9):668–74. PMid: 20002563.
45. Akkiz H, Bayram S, Bekar A, Akgollu E, Ulger Y, Kaya BY, Sandikci M, Ozdil B. No association of NAD (P) H: Quinone oxidoreductase 1 (NQO1) C609T polymorphism and risk of Hepatocellular Carcinoma development in Turkish subjects. Asian Pac J Cancer Prev. 2010 Jan 1; 11(4):1051–8. PMid: 21133623.
46. Park CH, Jeong SH, Yim HW, Kim JD, Bae SH, Choi JY, Yoon SK. Family history influences the early onset of hepatocellular carcinoma. World J Gastroenterol. 2012 Jun 7; 18(21):2661–7. PMid: 22690075, PMCid: PMC3370003. CrossRef.
47. Jiang JH, Gao Q, Shen XZ, Yu Y, Gu FM, Yan J, Pan JF, Jin F, Fan J, Zhou J, Huang XW. An X-chromosomal association study identifies a susceptibility locus at Xq22. 1 for Hepatitis B virus-related hepatocellular carcinoma. Clinics and Research in Hepatology and Gastroenterology. 2013 Dec 31; 37(6):586–95. PMid: 24209690. CrossRef.