*Hemochromatosis and Hepatocellular Carcınoma**

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ABSTRACT

An autosomal recessive iron overload condition called hemochromatosis is characterized by increased dietary iron absorption and hepatic iron accumulation. It poses a risk for hepatocellular carcinoma, particularly prevalent in the European population. Hepatocellular carcinoma is one of the most common and deadly tumors globally, especially in Asia. Due to its tendency to be diagnosed in advanced stages, hepatocellular carcinoma has a poor prognosis. Early detection of tumors improves the chances of successful treatment and a longer life. Therefore, the EASL (European Association for the Study of the Liver) guidelines advocate for liver tumor screening using ultrasound every six months, irrespective of the liver's condition.

This review focuses on the relationship between hemochromatosis, a rare disorder that is among the risk factors, and hepatocellular carcinoma.

Keywords: hemochromatosis, hepatocellular carcinoma, HFE gene, iron, iron overload.

Jel Codes: *L26, O18, R11, B21.*

* Sorumlu yazar
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Hemokromatozis Ve Hepatosellüler Karsinoma

ÖZ

Hemokromatozis otozomal resesif kalıtılan, besinlerle alınan demirin emiliminin artmasıyla ve demirin karaciğerde birikmesiyle karakterize aşırı demir yükü bozukluğudur. Avrupa popülasyonunda sık görülen bir hastalık olması sebebiyle hepatosellüler karsinoma için bir risk faktörü olmaktadır. Hepatosellüler karsinoma dünya çapında özellikle Asya kıtasında yüksek insidans ve mortalite gösteren kanserler arasında yer almaktadır. Hepatosellüler karsinoma genellikle geç evrelerde teşhis edildiğinden prognozu kötüdür. Tümör erken tespit edildiğinde küratif tedavi oranları ve sağkalımda iyileşme sağlanmaktadır. Bu nedenle karaciğer hastalığı ne olursa olsun 6 ayda bir ultrason taraması ile karaciğerde tümör taraması yapılması EASL (European Association for the Study of the Liver) kılavuzlarında önerilmektedir.

Bu derleme, risk faktörleri arasında yer alan nadir görülen bir bozukluk olan hemokromatozis ve hepatosellüler karsinom arasındaki ilişkiye odaklanmaktadır.

Anahtar Kelimeler: hemokromatozis, hepatosellüler karsinoma, HFE geni, demir, aşırı demir yükü.

Jel Kodları: *L26, O18, R11, B21.*

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1. INTRODUCTION

According to GLOBOCAN 2020, liver cancer ranks fourth in terms of cancer-related mortality and is the seventh most common disease globally (Figure 1). Regarding incidence, it occupies the ninth position for women and the fifth position for men. In terms of cancer-related mortality, it is the sixth leading cause for women and the second for men. Men are more likely to develop liver cancer compared to women. Despite being ranked ninth among cancers affecting women, its high mortality rate is noteworthy; in fact, it is the sixth most prevalent cause of tumor-associated deaths among women.

Both primary and secondary liver cancers can occur. Primary liver malignancies are divided into two categories: intrahepatic cholangiocarcinoma (ICC) and hepatocellular carcinoma (HCC) (Chidambaranathan-Reghupaty et al.,2021). Less common cancers include hepatoblastoma, angiosarcoma, and hemangiosarcoma (Chidambaranathan-Reghupaty et al., 2021). Every type of cancer is named based

on the type of cell that turns into cancer, so liver cancer is a general term. HCC originates from hepatocytes, the primary parenchymal cells of the liver, whereas ICC originates from the bile ducts (Bray et al., 2018; Torre et al., 2015).

With almost 900,000 new instances of HCC and ICC globally in 2020, these malignancies were among the most frequent worldwide (Sung et al., 2021). Over 80% of cases of primary liver cancer worldwide are HCC patients (El-Serag & Rudolph, 2007). Among all liver malignancies, the relative incidence of ICC is between 10% and 15% (Sung et al., 2021). Hepatic angiosarcoma (HA), the third most frequent primary liver cancer, originates in blood vessel endothelial cells or lymphatic arteries (Mani & Van Thiel, 2001). With a roughly ten-month life expectancy following the first diagnosis, HA is a very uncommon form of liver cancer, accounting for only 2% of all liver malignancies, and it is also characterized by extremely fast disease development (Mani & Van Thiel, 2001).

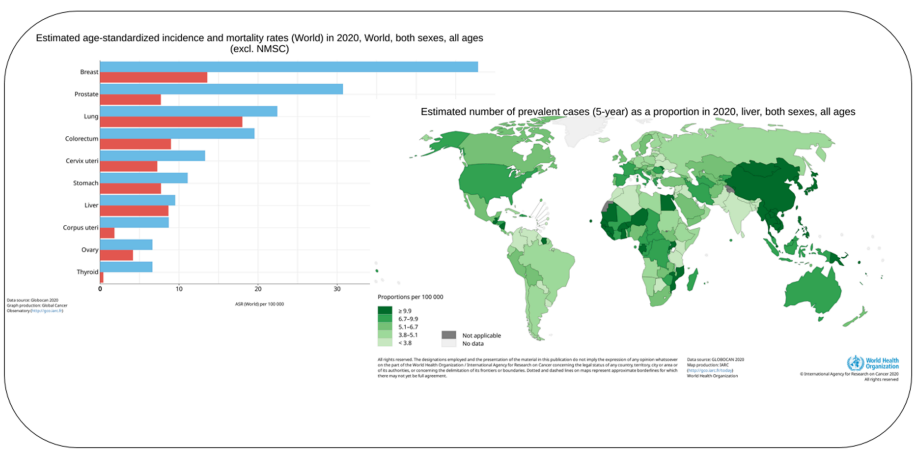

Figure 1: A comparison of liver cancer new cases and deaths in both genders with other types of cancer, according to GLOBOCAN 2020 data, and a 5-year prevalence map is shown (GLOBOCAN 2020).

Metastasizing from another region of the body to the liver has been named secondary liver cancer (Chidambaranathan-Reghupaty et al., 2021). The majority of secondary liver cancers originate from colorectal tumors, while certain malignancies from the breast, esophagus, stomach, pancreas, kindey, lung, and other organs can metastasis to the liver (Chidambaranathan-Reghupaty et al., 2021). Liver cancer is a secondary malignancy that affects around 70% of individuals with colorectal cancer (Valderrama-Trevino et al., 2017).

Twenty countries, most of which are in Sub-Saharan Africa (SSA) and Southeast Asia (SEA), have liver cancer as the main cause of death due to its link to

widespread viral infections in these regions (Bray et al., 2018). Despite being relatively uncommon in Germany, liver cancer ranks among the most common causes of tumor-associated fatalities because of its high fatality rate and dismal prognosis (Paganoni, 2021).

This review aims to examine current and available information to understand the genetic, molecular, and clinical relationships between hepatocellular carcinoma and hemochromatosis.

2. ETIOLOGY OF LIVER CANCER AND RISK AGENTS

The pathophysiology of HCC is intricate and encompasses several molecular dysfunctions including cell cycle dysregulation, DNA methylation modifications, chromosomal instability, immune system regulation, epithelial-mesenchymal transition, elevated levels of HCC stem cells, and dysregulation of miRNA (Hui et al., 1998). While the exact cause of the disease may vary, the overall mechanism involves liver damage, prolonged inflammation, fibrotic scarring (fibrosis), end-stage liver disease (cirrhosis), and HCC (Chidambaranathan-Reghupaty et al., 2021).

The kind of liver damage that develops is determined by the kind and extent of the lesion (Paganoni, 2021). Hepatocarcinogenesis is often a multistage, advancing procedure that begins with prolonged inflammation and proceeds to fibrotic scarring, cirrhosis, and liver cancer (Figure 2) (Paganoni, 2021). As the highest state of fibrotic scarring, cirrhosis raises the possibility of a malignant liver change into hepatocellular carcinoma (HCC) (Paganoni, 2021).

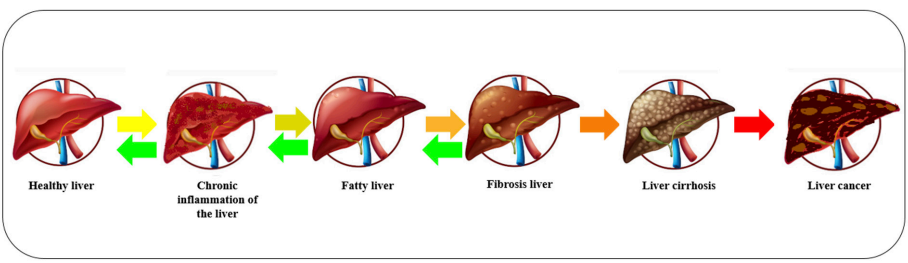

Figure 2: Hepatocarcinogenesis. While all stages up to cirrhosis are reversible, cirrhosis is an irreversible stage and results in cancer.

2.1. Infections by Viruses

Chronic hepatitis, resulting from viral infections such as hepatitis B and C, poses a substantial risk factor for the development of hepatocellular carcinoma (HCC). (Chidambaranathan-Reghupaty et al., 2021). HCV, like HBV, can be transmitted through various bodily fluids, not limited to blood, as both are pathogens primarily spread through bloodborne means (Chidambaranathan-

Reghupaty et al., 2021). The main modes of transmission include the sharing of needles, perinatal transmission, and any other contact involving the exchange of blood with an infected individual (Chidambaranathan-Reghupaty et al., 2021). The risk of HCC progression may increase with co-infection of HBV and HCV, especially in regions where both viruses are prevalent (Donato et al., 1998). The World Health Organization (WHO) estimates that approximately 257 million individuals, constituting 3.3% of the global population, are affected by chronic HBV infection, while around 71 million people are estimated to have chronic HCV infection (Chidambaranathan-Reghupaty et al., 2021). In 2018, new cases of hepatocellular carcinoma (HCC) were attributed to HBV and HCV transmissions, accounting for 54.5% and 21.2% of the global diagnoses, respectively (Bray et al., 2018). There are variations in the global prevalence of HBV and HCV based on geographical differences (Chidambaranathan-Reghupaty et al., 2021).

Antiviral medications have the potential to interrupt the progression of liver damage. While there is currently no cure for HBV infection, it can be prevented through vaccination, providing 98–100% protection against the virus (Reghupaty et al., 2021). Treating HBV poses a significant challenge (Zoulim, 2005). When there is an HBV infection, the immune system triggers both innate and adaptive responses (Chidambaranathan-Reghupaty et al., 2021). Adaptive immunity, involving T cells and HBV-specific antigens, is primarily responsible for eliminating HBV infection (Tan et al., 2015). Insufficient maturation of T cell memory results in a shortage of T cells specific to the hepatitis B virus (HBV) antigen, hindering the ability to mount an effective immune response (Lumley et al., 2018). This could result in an extended period of infection, repeated liver inflammation, the formation of fibrotic scars, advanced liver disease, and the development of HCC (Chidambaranathan-Reghupaty et al., 2021). Because HBV DNA may integrate and multiply within cells, causing persistent inflammation—the main cause of fibrosis and cirrhosis—the frequency with which HBV carriers develop HCC can be 20 times greater compared to non-carriers (Donato et al., 1998; Shi et al., 2005). Cirrhosis occurs in 1.3-2.4% of individuals who acquire HBV through transmission (Liaw et al., 1988), and chronic HBV infection leads to the development of HCC in 3.9% of affected individuals (Takano et al., 1995). In addition to random integration, the HBV can interfere with cell cycle checkpoints and induce chromosomal instability through the action of the HBx protein, ultimately fostering the development of malignancies in hepatocytes (Paganoni, 2021).

In addition to the prolonged duration of hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection presents a substantial risk for the development of liver cirrhosis (Fattovich et al., 1997). Remarkably, individuals with hepatitis C virus (HCV) infections face an almost 17-fold increased risk of developing HCC

(Donato et al., 2002). Due to its RNA genome, the pathways through which HCV promotes hepatocarcinogenesis differ significantly from those induced by HBV (Paganoni, 2021). Research findings thus far indicate that the structural and non-structural proteins of HCV play a role in promoting the oncogenic transformation of hepatocytes. This occurs by triggering inflammatory processes like insulin resistance, steatosis, DNA synthesis, oxidative stress, and mitochondrial dysfunction. These events can culminate in DNA damage, oxidative stress, and genetic instability, ultimately leading to the development of cirrhosis and HCC (Irshad et al., 2017). In six months after infection, about 30% of HCV-positive individuals spontaneously recover from the virus (Chidambaranathan-Reghupaty et al., 2021). Seventy percent of individuals with HCV infections develop chronic HCV infections (Chidambaranathan-Reghupaty et al., 2021). Antiviral medications have the capability to effectively treat over 95% of HCV infections (Chidambaranathan-Reghupaty et al., 2021). Chronic HCV infection, by contributing to fibrosis and cirrhosis, ultimately results in the development of HCC (Chidambaranathan-Reghupaty et al., 2021). The accumulation of fat in the liver, known as hepatic steatosis, hastens the progression of fibrosis, especially in individuals with HCV genotype 3 (Asselah et al., 2006).

2.2. Diabetes mellitus (DM)

Diabetes mellitus (DM) is a metabolic disorder with multiple contributing factors characterized by increased blood sugar levels due to impaired insulin production, function, or both, ultimately leading to cardiovascular complications (Chawla et al., 2016). While diabetes is increasing worldwide, Asia exhibits a higher prevalence of the condition (Jafri & Kamran, 2019). Globally, it is estimated that 366 million individuals are affected by this life-threatening disease, with 36 percent of those affected residing in the Western Pacific region, which encompasses a significant East Asian population (Federation, 2014). In some Western research studies, diabetes mellitus alone has been linked to a two- to fourfold increased risk of HCC (Davila et al., 2005). Similar observations have been documented in Asians (Ohishi et al., 2008).

There are numerous connections between DM and liver illness (Jafri & Kamran, 2019). In addition to HCC, DM is correlated with poorer overall outcomes and increased severity of liver fibrosis (El-Serag, 2004). Regardless of the root cause of liver disease, HCC tends to recur in individuals with diabetes mellitus even after receiving curative treatment (El-Serag, 2004). In nearly all individuals, cirrhosis is connected with impaired glucose tolerance (IGT) (Holstein et al., 2002). Individuals with end-stage liver disease demonstrate insulin resistance even in the absence of DM, yet 20% of individuals with cirrhosis develop clinically evident diabetes (Garcia-Compean et al., 2009).

In general, type 2 diabetes (DM2) is more commonly associated with chronic HCV infection than with the general population (Vanni et al., 2009). According to research conducted in Pakistan, 51% of these individuals were affected by insulin resistance (Kiran et al., 2013). A statistically significant association exists between DM2 and end-stage liver disease. Various studies conducted in this region of the world have shown that independent risk factors for DM2 in individuals with HCV include infection with HCV genotype 3, higher body weight, and older age (Memon et al., 2013). Kuske and her colleagues recently observed that diabetes serves as a risk factor for HCC in individuals with HCV infection (Kuske et al., 2012). In prospective research conducted by Fujino et al., the relative risk (RR) of DM for primary liver malignancies was nearly doubled, even after adjusting for confounding variables such as alcohol intake, smoking, and other comorbidities (Fujino et al., 2001). Moreover, in Pakistan, half of the individuals diagnosed with chronic HBV or HCC not related to hepatitis C virus (non-HCV) also had diabetes (Butt et al., 2013). Therefore, it is a logical conclusion that in individuals without additional risk factors, DM indeed elevates the risk of HCC (Jafri & Kamran, 2019).

2.3. Alcohol

Consuming alcohol increases the likelihood of developing stomach, colorectal, oropharyngeal, and breast cancers, as well as liver cancer (Chidambaranathan-Reghupaty et al., 2021). Alcohol consumption increases the risk of developing cancer in a proportionate manner (Chidambaranathan-Reghupaty et al., 2021).

In comparison to individuals who do not smoke, the risk of hepatocellular carcinoma increases by 46% with daily consumption of 50 grams of ethanol and by 66% with 100 grams (Turati et al., 2014). Approximately 30% of HCC cases result from alcoholic liver disease (ALD), encompassing situations where ALD coexists with other risk factors like obesity, diabetes, and hepatitis infections (Ganne-Carrie & Nahon, 2019).

Steatosis, commonly referred to as alcohol-related fatty liver (AFL), serves as the initial sign of liver damage associated with alcohol abuse and is often asymptomatic (Chidambaranathan-Reghupaty et al., 2021). While alcohol-related fatty liver (AFL) impacts more than 90% of individuals who engage in heavy drinking, only 30% progress to severe alcoholic liver disease (ALD) since AFL is a reversible condition (Chidambaranathan-Reghupaty et al., 2021). The reduction of NAD^+ to NADH occurs in hepatocytes during the conversion of alcohol to acetate and finally to CO_2 and H_2O (Figure 3). Elevated intracellular $NADH/NAD^+$ ratios and interference with mitochondrial fatty acid β-oxidation are outcomes of heightened ethanol metabolism (Chidambaranathan-Reghupaty et al., 2021). Through the electron transport chain, an elevation in $NADH/NAD^+$

has the potential to cause an upsurge in reactive oxygen species (ROS) (Donohue, 2007). Specific factors, like variations in ADH and ALDH genes, can lead to the accumulation of acetaldehyde molecules. These molecules can bind to proteins, DNA, or both, hindering their normal functions or eliciting a robust immune response (Brooks & Theruvathu, 2005; Setshedi et al., 2010).

The presence of steatosis renders the liver more vulnerable to additional factors that could lead to hepatic inflammation or alcoholic hepatitis (AH) Chidambaranathan-Reghupaty et al., 2021). The procedure produces cytokines and is characterized by the influx of leukocytes such as neutrophils, monocytes, and macrophages into hepatic tissue. Additionally, resident liver macrophages become activated (Chidambaranathan-Reghupaty et al., 2021). For alcohol-related HCC, alcoholic cirrhosis is also reversible, and discontinuing alcohol consumption serves as the remedy (Szabo & Bala, 2010).

Alcohol-induced fibrosis leads to heightened activity of hepatic stellate cells and a reduction in the number and activity of natural killer (NK) cells (Chidambaranathan-Reghupaty et al., 2021). Moreover, the histological characteristics of fibrosis in hepatitis-related cases and non-alcoholic steatohepatitis (NASH) differ (Lackner & Tiniakos, 2019; Schuppan et al., 2018). Ceasing alcohol consumption can lead to the regression of early fibrosis, and there is promising research in the development of anti-fibrotic medications (Chidambaranathan-Reghupaty et al., 2021). However, prolonged fibrosis is the underlying cause of cirrhosis and HCC (Chidambaranathan-Reghupaty et al., 2021).

2.4. Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD covers a range of liver disorders, starting from the buildup of fat in tissues to its more advanced manifestation, known as non-alcoholic steatohepatitis (NASH) (Chidambaranathan-Reghupaty et al., 2021). It stands as the most common form of liver disease, constituting nearly 25% of all cases globally (Maurice & Manousou, 2018). In individuals with early NAFLD or hepatic fat accumulation, 20% progress to end-stage liver disease due to non-alcoholic steatohepatitis (NASH), and 2.6% develop HCC (Ascha et al., 2010). NAFLD is mainly associated with DM and obesity, and the worldwide prevalence of NAFLD has increased in correlation with the rise in these conditions over the past ten years (Younossi, 2019).

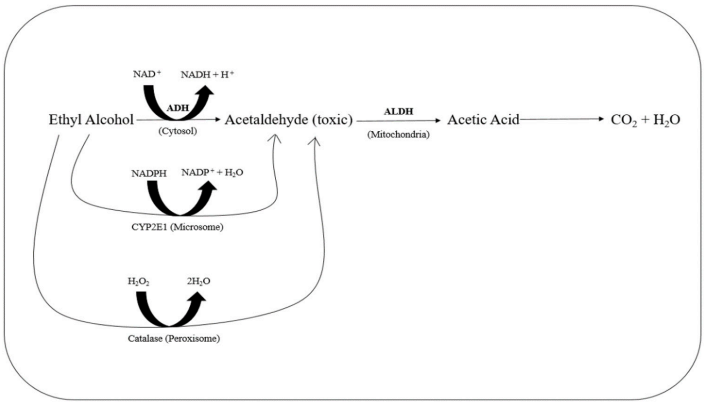

Figure 3: Decomposition of ethyl alcohol into CO2 and H2O. (ADH: alcohol dehydrogenase; ALDH: aldehyde dehydrogenase).

While the cause of NAFLD is not connected to prolonged alcohol consumption, its pathophysiology shares similarities with alcohol-induced fatty liver disease (Chidambaranathan-Reghupaty et al., 2021). Accumulation of triglycerides in hepatocytes is a characteristic feature of simple steatotic liver, which represents the initial stage of NAFLD (Chidambaranathan-Reghupaty et al., 2021). This condition can be triggered by the intake of a high-fat diet, increased breakdown of fat in the splanchnic fat tissue transferred to the liver, or excessive de novo lipogenesis (DNL) within the liver (Chidambaranathan-Reghupaty et al., 2021).

TNF superfamily member 14 (*TNFSF14*) and IFN-γ are produced by NK T cells and lymphocytes that are drawn to the liver in reaction to hepatocyte damage (Chidambaranathan-Reghupaty et al., 2021). Moreover, signals from the gut through Toll-like receptors (TLRs) can initiate congenital immune responses, subsequently resulting in inflammation (Chidambaranathan-Reghupaty et al., 2021). This initiates the secretion of inflammatory cytokines by macrophages present in the liver tissue, leading to persistent inflammation and the development of HCC (Chidambaranathan-Reghupaty et al., 2021).

2.5. Obesity

Obesity is a condition characterized by an excess accumulation of body fat (Jafri & Kamran, 2019). Body mass index (BMI)—kg (weight)/m^2 (height)—is the method recommended by the WHO for classifying body weight (Consultation, 2004). The current World Health Organization (WHO) recommended threshold criteria for overweight and obesity are 25 kg/m^2 or higher and 30 kg/m^2 or higher, respectively (Consultation, 2004). The application of the recommended BMI cutoff points to Asians has been a subject of ongoing debate (Jafri & Kamran, 2019). Two primary factors contribute to this discrepancy. Firstly, even with

a BMI below 25 kg/m^2, these communities exhibit a significant prevalence of DM2 and cardiovascular risk factors. Secondly, there is considerable variation in BMI, distribution, and body fat percentage among diverse Asian population groups (Consultation, 2004). Hence, the International Association for the Study of Obesity (IASO), the International Obesity Task Force (IOTF), and the WHO recommend BMI thresholds of 23.0–24.9 kg/m^2 for individuals classified as overweight and 25.0 kg/m^2 for those categorized as obese in Asian populations (IOTF, 2000). Metabolic syndrome, which includes its hepatic component, NASH is closely associated with obesity and diabetes mellitus. This condition raises the risks of cardiovascular diseases, stroke, and other health issues (Jafri & Kamran, 2019).

Generally, there is an elevated relative risk of cancer-related mortality associated with obesity (Jafri & Kamran, 2019). Obesity has been linked to several cancers, including colorectal, endometrial, breast, renal cell, and esophageal adenocarcinomas (Calle & Kaaks, 2004). Another independent predictor of HCC is obesity (Jafri & Kamran, 2019). Numerous epidemiological studies conducted on both the general population and a cohort of individuals with cirrhosis have provided clarification on this situation (Saunders et al., 2010). Research conducted on Japanese patients with decompensated end-stage liver disease indicated that the risk of HCC increased with higher BMI (Muto et al., 2006). Particularly intriguing are several studies that demonstrate the combined impact of DM and obesity on HCC without persistent hepatitis B and C infections (Polesel et al., 2009). In individuals with existing HBV and HCV infections, this influence becomes even more pronounced (Chen et al., 2008). Much like diabetes mellitus, obesity can contribute to inflammation in hepatocytes, initiating a series of events such as lipid peroxidation and oxidative stress within intracellular membranes. This process ultimately leads to cellular damage, necrosis, and the development of HCC (Chen et al., 2008).

2.6. Aflatoxins

Mycotoxins, known as aflatoxins, are created by fungi such as *Aspergillus flavus* and *A. parasiticus*. These compounds, chemically classified as furanocoumarins, are generated through secondary metabolic pathways in fungi and consist of a furan ring fused to a coumarin (Chidambaranathan-Reghupaty et al., 2021). Most contamination in cereals and nuts occurs during the processes of harvesting, transportation, or storage (Chidambaranathan-Reghupaty et al., 2021). Aflatoxin exposure can lead to hepatic toxicity, teratogenic effects, and immunotoxicity in both plants and animals. Although more than 20 aflatoxins have been identified, aflatoxins B1, B2, G1, and G2 are the most significant, with aflatoxin B1 (AFB1) being the most potent hepatocarcinogen (Kumar et al., 2016).

Aflatoxins, classified as hepatotoxins, can induce either acute or chronic poisoning. Numerous outbreaks of severe aflatoxin poisoning have resulted in fatal contagious diseases in countries such as Tanzania, Bangladesh, India, Nepal, and Kenya (Sarma et al., 2017). Acute poisoning leading to liver failure can be fatal, presenting symptoms such as jaundice, nausea, and abdominal discomfort (Chidambaranathan-Reghupaty et al., 2021). Prolonged exposure to aflatoxin poisoning is carcinogenic and specifically linked to HCC (Chidambaranathan-Reghupaty et al., 2021). The regions most commonly affected by aflatoxin B1 (AFB1)-associated HCC are Sub-Saharan Africa (SSA) and Southeast Asia (SEA), where the dry and humid climatic conditions provide an ideal environment for fungal growth (Chidambaranathan-Reghupaty et al., 2021). The most frequently observed mutation in individuals with HCC associated with aflatoxin is the AGGarg→AGTser missense mutation, located at codon 249 of the TP53 gene (Aguilar et al., 1993). Due to its effects on metastasis and differentiation, this mutation is known to encourage HCC (Peng et al., 1998). Aflatoxin exposure can result in chromosomal strand breakage and abnormalities in human cells (Turkez & Sisman, 2012). The combined impact of aflatoxin exposure and HBV infection may elevate the risk of HCC by up to 70%, in contrast to the risks associated with aflatoxin alone (ranging from 0.3% to 17.4%) or HBV infection alone (ranging from 4.8% to 17.4%) (Kew, 2003).

2.7. Hereditary Elements

Certain hereditary elements lead to the elevated risk of HCC, in addition to environmental influences (Chidambaranathan-Reghupaty et al., 2021). HCC usually arises as a secondary consequence of the underlying genetic disorder later in life (Chidambaranathan-Reghupaty et al., 2021). A secondary risk factor must typically interact with these genetic abnormalities to prevent HCC from developing (Chidambaranathan-Reghupaty et al., 2021). These genetic alterations are also predisposing (Chidambaranathan-Reghupaty et al., 2021).

2.7.1. Alpha 1-Antitrypsin Deficiency (A1ATD)

Alpha 1-antitrypsin (A1AT) belongs to the SERPIN (SERin Proteinase INhibitor) protein superfamily. The family members share common structural features, including three beta sheets (A, B, and C) and a flexible reactive loop. This loop acts as an inhibitor of the target proteinase by presenting a peptide sequence resembling a pseudo-substrate, with more than 30% structural similarity among family members (Chidambaranathan-Reghupaty et al., 2021). Alpha 1-antitrypsin (A1AT) predominantly inhibits neutrophil elastase (NE), a major protease responsible for breaking down various connective tissue substrates (Chidambaranathan-Reghupaty et al., 2021). Produced in reaction to tissue injury and inflammation, it is an acute-phase reaction anti-inflammatory protein that obstructs TNF-α's actions (Chidambaranathan-Reghupaty et al., 2021).

Alpha 1-antitrypsin deficiency (A1ATD) affects approximately 1 in 1800 to 1 in 2000 live births and is characterized by reduced levels of alpha 1-antitrypsin in the blood (Chidambaranathan-Reghupaty et al., 2021). It is the most common hereditary cause of pediatric liver disease and increases the likelihood of end-stage liver disease and HCC (Chidambaranathan-Reghupaty et al., 2021). Liver problems are caused by a toxic gain-of-function mechanism, while A1AT-related lung illnesses are caused by reduced circulating A1AT and are linked to a loss-of-function process (Chidambaranathan-Reghupaty et al., 2021). AT1ATD is linked to melanoma cell adhesion molecule (MCAM) modulation (Chidambaranathan-Reghupaty et al., 2021), altered regulation of cyclin D1, mitochondrial dysfunction (Chidambaranathan-Reghupaty et al., 2021), delayed ER protein degradation (Chidambaranathan-Reghupaty et al., 2021), and the aggregation and polymerization of mutant A1AT in liver cells.

2.7.2. Autoimmune Hepatitis (AIH)

Autoimmune hepatitis (AIH) is a persistent liver disorder in individuals genetically predisposed, where the immune system directs its attack towards the hepatocytes (Chidambaranathan-Reghupaty et al., 2021). The disorder is intricate and polygenic, lacking any apparent inheritance pattern (Chidambaranathan-Reghupaty et al., 2021). A mutation in DR beta 1 (DRB1), a gene belonging to the human leukocyte antigen (HLA) class II and associated with $CD4^+$ T cell-mediated antigen presentation, is associated with autoimmune hepatitis (AIH) (Chidambaranathan-Reghupaty et al., 2021). Additionally, mutations in the genes responsible for cytotoxic T lymphocyte-associated protein 4 (CTLA4), TNFA, and the Fas cell surface death receptor (FAS) are associated with autoimmune hepatitis (AIH) (Chidambaranathan-Reghupaty et al., 2021). Depending on which autoantigens promote this illness, there are two primary forms of AIH (Chidambaranathan-Reghupaty et al., 2021). Anti-smooth muscle and anti-nuclear antibodies are signs of Type 1 AIH, which affects both adults and children (Chidambaranathan-Reghupaty et al., 2021). Anti-liver cytosol type 1and/or anti-liver/kidney microsomal type 1 (anti-LKM1) antibodies are characteristics of type 2 AIH, which primarily affects children (Chidambaranathan-Reghupaty et al., 2021).

The generation of autoantibodies is attributed to a phenomenon called "molecular mimicry" (Chidambaranathan-Reghupaty et al., 2021). For instance, cytochrome P450IID6, an autoantigen that shares molecular similarities with HCV antigens, is recognized by anti-LKM1 (Chidambaranathan-Reghupaty et al., 2021). Autoimmune hepatitis (AIH) affects women more frequently than men, with an annual incidence ranging from 11 to 25 cases per 100,000 individuals (Chidambaranathan-Reghupaty et al., 2021). According to a meta-analysis encompassing more than ten studies, the prevalence of end-stage liver disease

among AIH patients ranges from 12% to 83%, and approximately 5–6% of AIH patients develop (Chidambaranathan-Reghupaty et al., 2021).

2.7.3. Tyrosinemia Type 1 (HT1)

Hereditary tyrosinemia type 1 (HT1) is an autosomal recessive genetic disorder caused by a deficiency in the enzyme fumarylacetoacetate hydrolase. This enzyme is responsible for converting 4-fumarylacetoacetate (FAA) and water into acetoacetate, fumarate, and H^+ in the final stage of tyrosine degradation (Chidambaranathan-Reghupaty et al., 2021). Accumulation of harmful metabolites associated with FAA in the liver leads to severe liver dysfunction (Chidambaranathan-Reghupaty et al., 2021). The treatment for this condition involves the use of 2-(2 nitro-4-3 trifluoro-methylbenzoyl)-1,3-cyclohexanedione (NTBC), a compound that inhibits the early stages of the tyrosine catabolic pathway, preventing the accumulation of most harmful metabolites (Chidambaranathan-Reghupaty et al., 2021). Nevertheless, phenylalanine, the precursor of tyrosine, and tyrosine still accumulate and need to be controlled by diet (Chidambaranathan-Reghupaty et al., 2021). Individuals who received treatment with NTBC after the onset of symptoms or those who did not receive treatment have reported the development of HCC (Chidambaranathan-Reghupaty et al., 2021). Administering treatment to asymptomatic individuals with tyrosinemia type 1 can prevent the development of HCC (Chidambaranathan-Reghupaty et al., 2021). However, in situations where neonatal screening is insufficient, and access to NTBC is unavailable, untreated HT1 can still result in HCC. Between 25% to 75% of individuals who test positive for HT1 progress to develop HCC (Chidambaranathan-Reghupaty et al., 2021). Individuals who do not receive treatment may develop HCC due to various potential factors, including oxidative stress, apoptosis resistance, endoplasmic reticulum (ER) stress, disruption of the Golgi complex, and inhibition of DNA repair enzymes (Chidambaranathan-Reghupaty et al., 2021).

2.7.4. Glycogen Storage Diseases (GSD)

The body stores energy in the form of glycogen, a branching polymer consisting of linear chains of eight to twelve glucose monomers linked by alpha (1–4) glycosidic junctions. Glycogen storage diseases (GSDs) are rare metabolic disorders that impact the processes related to the synthesis or breakdown of glycogen. There are over a dozen different forms of GSD, each associated with the deficiency of a specific enzyme. Errors in these pathways primarily affect the liver, as it is the primary site for glycogen metabolism. The most common types of GSD are I, III, and IV (Chidambaranathan-Reghupaty et al., 2021).

The most common form of GSD is type I, commonly known as von Gierke disease. The likelihood of developing this autosomal recessive disorder is

approximately one in 100,000 (Chidambaranathan-Reghupaty et al., 2021). GSD type I is divided into four subtypes: 1a, 1b, 1c, and 1d, with Type 1a being the most common. Individuals with GSD type I have a deficiency in the enzyme glucose-6-phosphatase, which plays a role in both glycogenolysis and gluconeogenesis. This enzyme is primarily found in the hepatic tissue, renal tissue, and gut. It is involved in the final stage of both pathways, converting glucose-6-phosphate to glucose (Chidambaranathan-Reghupaty et al., 2021). The deficiency of this enzyme leads to a significant reduction in glucose availability, resulting in severe hypoglycemia (Chidambaranathan-Reghupaty et al., 2021). Additionally, glucose-6-phosphate serves as an allosteric inhibitor for the first enzyme in glycogenolysis, glycogen phosphorylase. This inhibition leads to the accumulation of glycogen in the hepatic tissue (Chidambaranathan-Reghupaty et al., 2021). Other biochemical abnormalities associated with GSD type I include hyperlipidemia, hyperuricemia, and lactic acidosis. Adenomas in the hepatic tissue occur in 57% of patients with type 1 GSD, while HCC occurs in 8% of cases. (Chidambaranathan-Reghupaty et al., 2021). Possible causes of type 1 GSD-associated HCC include impaired autophagy, mitochondrial dysfunction, metabolic reprogramming, oncogene activation, and down-regulation of tumor suppressors (Chidambaranathan-Reghupaty et al., 2021).

One in 100,000 individuals is affected by GSD type III, also known as Cori disease or Forbes disease. This autosomal recessive condition is characterized by a deficiency in the enzymes glycosyltransferase and glycosidase, responsible for branching and debranching glycogen, respectively (Chidambaranathan-Reghupaty et al., 2021). There are two subcategories: type IIIa, where the enzyme deficiency affects both the hepatic tissue and muscle (approximately 80% of cases), and type IIIb, which only affects the hepatic tissue (Chidambaranathan-Reghupaty et al., 2021). Glycogen is a branching molecule that contains α-1,6 glycosidic linkages at the branch locations. Since glycogen phosphorylase is limited to breaking down α-1,4 bonds, a debranching enzyme is responsible for breaking down the α-1,6 glycosidic link during glycogen breakdown. This process leaves a linear chain that can be further broken down by glycogen phosphorylase. Due to the deficiency of this enzyme, short-chain, branching glycogen molecules accumulate in the muscles and liver (Chidambaranathan-Reghupaty et al., 2021). In this case, liver involvement is minimal, and the primary source of morbidity in early adulthood is muscular illnesses (Chidambaranathan-Reghupaty et al., 2021). Less than 10 cases of HCC have been documented in individuals with Cori disease, and there are sporadic occurrences of end-stage liver disease in these patients (Chidambaranathan-Reghupaty et al., 2021).

Except within the elderly Mennonite population, where the condition has a frequency of 1 in 1000, Type VI, also known as Hers disease, is an extremely

rare disorder with an unclear prevalence (Chidambaranathan-Reghupaty et al., 2021). The autosomal recessive disorder Type VI, also known as Hers disease, is attributed to a deficiency in the glycogen phosphorylase enzyme responsible for glycogenolysis. Symptoms of this condition include hepatomegaly, impaired growth, elevated hepatic transaminases, low prealbumin levels, hyperlipidemia, and ketonic hypoglycemia (Chidambaranathan-Reghupaty et al., 2021). There is limited data available regarding the development of HCC in individuals with Hers disease (Chidambaranathan-Reghupaty et al., 2021). Nonetheless, data proves that these people may develop HCC, albeit rarely (Chidambaranathan-Reghupaty et al., 2021). Furthermore, in these patients, fibrosis is more prevalent than cirrhosis (Chidambaranathan-Reghupaty et al., 2021).

2.7.5. Hereditary Hemochromatosis (HH)

Hemochromatosis is a condition characterized by excess iron accumulation in the body, leading to elevated absorption of dietary iron and its buildup in organs such as the pancreas, liver, heart, and joints. There are two main types: primary, or hereditary (divided into types 1, 2, 3, and 4), and secondary, or non-hereditary. The most common form, type 1 hereditary hemochromatosis, responsible for 90% of cases, is caused by genetic mutations in the hemostatic iron regulator (*HFE*) gene. (Chidambaranathan-Reghupaty et al., 2021).

The cell surface protein encoded by HFE plays a role in maintaining iron balance by indirectly regulating the activities of two other proteins, transferrin and ferroportin (Chidambaranathan-Reghupaty et al., 2021). Ferroportin, primarily found in the intestinal epithelium, increases the concentration of plasma iron by transporting absorbed dietary iron from the cell to the circulation (Chidambaranathan-Reghupaty et al., 2021). Hepcidin, a protein, binds to ferroportin and degrades it, thereby decreasing the quantity of iron transported into the plasma (Chidambaranathan-Reghupaty et al., 2021). HFE regulates the expression of hepcidin through a mechanism that is currently not fully understood (Chidambaranathan-Reghupaty et al., 2021). Changes in HFE among individuals with hereditary hemochromatosis (HH) lead to reduced hepcidin levels, increased ferroportin expression, heightened iron absorption, and an accumulation of iron in the body (Chidambaranathan-Reghupaty et al., 2021). Transferrin receptor 1 is the iron-dependent receptor for transferrin and is involved in cellular iron absorption (Chidambaranathan-Reghupaty et al., 2021). *HFE* also inhibits iron uptake by cells by binding to transferrin receptor 1, preventing its relationship with transferrin (Chidambaranathan-Reghupaty et al., 2021). Because there is no functioning HFE protein in HH, cells take iron more readily (Chidambaranathan-Reghupaty et al., 2021). Increased cellular iron uptake and elevated levels of circulating iron lead to the accumulation of iron in hepatic tissue and other organs (Chidambaranathan-Reghupaty et al., 2021).

Iron overload can promote tumor formation through heightened cellular proliferation, increased levels of reactive oxygen species (ROS) can cause DNA damage, and peroxidative damage can adversely affect the membranes of subcellular organelles (Chidambaranathan-Reghupaty et al., 2021). Furthermore, an excess of iron may impede the growth of lymphocytes (Chidambaranathan-Reghupaty et al., 2021). In patients with HH, the new cases of end-stage liver disease between 10 to 25%, the new cases of HCC is from 8 to 10% (Chidambaranathan-Reghupaty et al., 2021), and the risk of developing HCC is enhanced by around twenty times when compared to healthy persons (Chidambaranathan-Reghupaty et al., 2021).

2.7.6. Porphyria

Porphyrin is a compound composed of four modified pyrrole subunits connected by methine bridges at alpha carbon atoms. Heme, a type of protoporphyrin, is a porphyrin with a chemical attachment to an iron molecule. Porphyrias, a group of rare disorders, are primarily inherited and result from deficiencies in enzymes related to heme biosynthesis. These deficiencies lead to the accumulation of porphyrins and their precursors in the body (Chidambaranathan-Reghupaty et al., 2021). It can be broadly categorized into two groups: cutaneous porphyria and acute porphyria. Acute porphyria (AP) predominantly impacts the nervous system and is marked by sudden episodes of severe abdominal pain that may persist for extended periods (Chidambaranathan-Reghupaty et al., 2021). Subtypes of acute porphyria include acute intermittent porphyria (AIP), variegate porphyria (VP), aminolevulinic acid dehydratase deficiency porphyria (ALAD), and hereditary coproporphyria (HCP), each characterized by the deficiency of a specific enzyme. Non-acute or cutaneous porphyrias, primarily triggered by sun exposure, exhibit symptoms such as skin blistering, swelling, redness, itching, and scarring (Chidambaranathan-Reghupaty et al., 2021). Porphyria cutanea tarda (PCT), X-linked dominant protoporphyria (XLDPP), congenital erythropoietic porphyria (CEP), and erythropoietic protoporphyria (EPP) are subtypes of porphyria. The two main categories of porphyria, acute hepatic porphyria (AHP) and erythropoietic porphyria, are differentiated based on the origin of the excess precursors (Chidambaranathan-Reghupaty et al., 2021). The precursors for acute intermittent porphyria (AIP), porphyria cutanea tarda (PCT), hereditary coproporphyria (HCP), and variegate porphyria (VP) are hepatic in nature and have their origin in hepatic tissue. Conversely, the precursors for congenital erythropoietic porphyria (CEP) and erythropoietic protoporphyria (EPP) are derived from erythropoietic processes in the bone marrow (Chidambaranathan-Reghupaty et al., 2021).

Specifically, AHP is linked to a higher risk of HCC (Chidambaranathan-Reghupaty et al., 2021). Enzyme levels can be lowered to 50% with just one mutant allele

due to these autosomal dominant characteristics (Chidambaranathan-Reghupaty et al., 2021). For the disease phenotype to manifest, additional risk factors like viral infections, alcohol dependence, *HFE* mutations, or smoking must be present. This is because a reduction in enzyme activity greater than 50% is required for the emergence of the disease phenotype (Chidambaranathan-Reghupaty et al., 2021). Thorough controlled investigations are essential to fully evaluate the actual incidence and increased risk associated with acute hepatic porphyria (AHP). This is crucial because other susceptibility factors may independently contribute to the development of HCC (Chidambaranathan-Reghupaty et al., 2021). Patients with AHP had a 35-fold enhanced chance of developing HCC (Chidambaranathan-Reghupaty et al., 2021), with an incidence of 0.16–0.35% for AHP-associated HCC (Chidambaranathan-Reghupaty et al., 2021). Histological anomalies and abnormal liver enzymes are seen in PCT patients (Chidambaranathan-Reghupaty et al., 2021). There have been reports of a 20-fold enhance in the risk of HCC (Chidambaranathan-Reghupaty et al., 2021), and an annual incidence of 0.26% was found in research including 39 individuals. 4–27% of AIP patients (Chidambaranathan-Reghupaty et al., 2021) and 1.3-5.4% of VP patients had HCC.

3. HEPATOCELLULAR CARCINOMA IN HEMOCHROMATOSIS

Genetic testing indicates that hemochromatosis is the most common genetic disorder in the United States, with a frequency of 1 in 227 among individuals of Northern European heritage (Adams, 2023). Due to iron overload, many hemochromatosis patients will seek medical attention; phlebotomy therapy early on can avert the most serious consequences, including cirrhosis and HCC (Adams, 2023). Hemochromatosis, a hereditary condition characterized by elevated transferrin saturation and liver iron overload, does not exhibit anemia and/or reticulocytosis (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). In the early stages of the disease, the accumulation of iron in the liver primarily affects peri-portal hepatocytes, while Kupffer cells remain unaffected (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Normally, the spleen does not have an overload of iron (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Hemochromatosis, a disorder related to iron homeostasis, is characterized by increased iron release from macrophages, heightened iron absorption in the intestines, higher transferrin saturation, and the expansion of the circulating iron pool (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Accumulation of iron in the body, primarily in the liver, may occur as a consequence of this progressive process (European Association for the Study of the Liver. Electronic

address & European Association for the Study of the, 2022). Without treatment, hemochromatosis can lead to liver fibrosis, cirrhosis, and the development of HCC (Atkins et al., 2020; Pilling et al., 2019). Diabetes, osteoporosis, and arthropathy are common symptoms (Sahinbegovic et al., 2010). Individuals with severe or early-onset hemochromatosis may encounter hypothyroidism, hypogonadotropic hypogonadism, and heart failure as consequences of the disorder (Kelly et al., 1998). Common symptoms of hemochromatosis include weakness, fatigue, and a grayish-brown discoloration of the skin (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Hemochromatosis is more prevalent in males than females, and the risk of developing the condition increases with age (Hagstrom et al., 2021).

Hemochromatosis is an autosomal recessive disorder, and approximately 80% of individuals of European descent with the condition are homozygous for the p.Cys282Tyr (p.C282Y) mutation in the *HFE* gene (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). The prevalence of this genotype varies across Europe, with a frequency of 1 in 82 in Ireland and 1 in 2,500 in Southern Europe (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Hemochromatosis can be caused by occasional recessive pathogenic variants in genes such as hepcidin (*HAMP*), transferrin receptor 2 (*TFR2*), and hemojuvelin (*HJV*). Alternatively, versions with a dominant function in the ferroportin gene (*SLC40A1* or *FPN*) can also lead to hemochromatosis (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). However, in individuals with adult-onset hemochromatosis, the presence of the specific gene variation that causes the condition is neither sufficient nor necessary for a diagnosis of hemochromatosis based on phenotypic criteria (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Being homozygous for the p.C282Y variation in *HFE* increases the likelihood of hemochromatosis, although the precise penetrance of the disease varies with age and gender (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). In a comprehensive follow-up study involving 203 individuals aged 40 to 69 who were homozygous for the p.C282Y variation, the penetrance of the illness associated with iron overload was determined to be 28% (95% CI 18-40%) in men and 1.2% (95% CI 0.03-6.5%) in women (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). In the same study, elevated serum ferritin levels were observed at baseline in 81.8% of men and 55.4% of women, indicating higher rates of biochemical penetration (European Association for the Study of the Liver. Electronic address & European Association

for the Study of the, 2022).

The clinical manifestations of hemochromatosis depend on the stage of the disease and are determined by the degree of iron excess and organ damage (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). According to screening tests, the illness frequently has no symptoms in its early stages (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Fatigue and joint pain are typical hemochromatosis symptoms (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Skin pigmentation, impotence, and heart arrhythmia are also present in severe cases (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Individuals with hemochromatosis are at an increased risk of developing liver disorders such as chondrocalcinosis, rheumatoid arthritis, osteoarthritis, osteoporosis, and liver malignancies (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022).

Testing for hemochromatosis is recommended for individuals presenting with unexplained heart failure, abnormal amenorrhea in females, atypical sexual development in males, or, in childhood, as hemochromatosis is more frequently linked to cardiomyopathy and hypogonadotropic hypogonadism (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022).

Biochemical markers of hemochromatosis with iron overload contain increased saturation of transferrin, higher ferritin, and raised hepatic transaminases (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). From a clinical standpoint, if individuals with any of the mentioned disorders experience an elevation in both ferritin levels and transferrin saturation, they should undergo examination for hemochromatosis (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Iron and serum ferritin levels ought to also be assessed as components of the evaluation process for those whose liver blood tests are abnormal (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022) .

Considering the widespread occurrence of the p.H63D polymorphism in the general population, it is plausible that this genetic variation is benign (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). While compound heterozygosity for p.C282Y and p.H63D alone may not be sufficient to cause hemochromatosis, individuals with

this genotype may display phenotypic manifestations of hemochromatosis when combined with other genetic or environmental factors that pose a risk for hepatic disorders (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Among individuals with homozygous hemochromatosis without the p.C282Y variant, the prevalence of homozygosity for p.H63D is no higher than in the general population (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). There is ongoing debate over the p.H63D test's clinical use (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). p.C282Y and p.H63D were shown to be disorder-related versions when *HFE* was initially recognized as a hemochromatosis gene (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). In individuals with clinically diagnosed hemochromatosis, the combined prevalence of compound heterozygosity for p.C282Y/p.H63D was determined to be 4.1% (114 out of 2,802), surpassing the 1.6% (100 out of 6,243) observed in control groups, according to the study (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022).

The diagnostic percentage of compound heterozygosity for p.C282Y/p.H63D was substantially lower than the diagnostic rate of homozygosity for p.C282Y in the 39,000-person eMERGE cohort (2.3% against 14% in females and 3.5% versus 24.4% in males, respectively (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Individuals with both compound heterozygosity for *HFE* and iron overload, along with disease-modifying factors like obesity, a fatty liver, diabetes, or alcohol consumption, face a greater risk than those with homozygosity for p.C282Y (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). A large prospective population-based research including 31,192 people of Northern European descent revealed that serum iron indices in males who were compound heterozygotes for p.C282Y/p.H63D did not alter over middle age, and although ferritin levels increased with age in women, disease due to iron overload was rare (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). In a substantial UK population sample comprising volunteers of European descent aged 40 to 70, the diagnosis of hemochromatosis over a mean follow-up of 7 years was notably higher in individuals heterozygous for p.C282Y/p.H63D. The hazard ratios (HR) were 33.63 (95% CI 21.44–52.76; $p < 0.001$) for men and 34.74 (95% CI 16.47–73.29; $p < 0.001$) for women compared to participants without the p.C282Y or p.H63D variant. However, after considering multiple testing, the increased morbidity ceased to be statistically

significant (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022).

Only a small number of patients with secondary hemochromatosis have been reported to experience improvement in HCC (Yamauchi et al., 2019). In conclusion, there is a potential association between secondary hemochromatosis and the development of HCC (Yamauchi et al., 2019).

Hemochromatosis is recognized for its association with cirrhosis and HCC, and the incidence of these complications varies based on the type of research conducted, whether it involves estimates of lifetime cumulative penetrance, cross-sectional studies, or patient- or population-based studies (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). The relative risk of primary hepatocellular carcinoma in cohorts with hemochromatosis was estimated to be between 20 and 200 (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022), including definitions of biliary differentiation (hepato-cholangiocarcinoma or cholangiocarcinoma) in up to 35% of cases in the hepatocarcinoma series (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). In a recent study involving a substantial population cohort from the UK Biobank, men aged 40 to 70 who were p.C282Y homozygous exhibited an elevated estimated effect size for the incidence of any hepatic disorder (HR 2.34, 95% CI 1.60–3.43, p <0.001) and hepatocellular carcinoma (HR 8.88, 95% CI 4.79–16.45, p <0.001) compared to individuals without the p.C282Y or p.H63D variant (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). A subsequent study utilizing the same community population substantiated these results: male p.C282Y homozygotes had a higher likelihood of developing primary hepatic malignancy, including hepatocellular and intrahepatic bile duct carcinomas, compared to individuals without p.C282Y or p.H63D variants (HR 10.5, 95% CI 6.6–16.7, p < 0.001). Furthermore, the risk of all-cause mortality was significantly elevated (HR 1.2, 95% CI 1.0–1.5, p = 0.046) (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). In females, there was no statistically significant association observed between p.C282Y homozygosity and hepatocellular carcinoma or mortality (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). While the majority of HCC cases were identified in individuals with p.C282Y homozygosity, a recent extensive multicenter cohort study that compiled retrospective data from eight university hospitals in Sweden revealed an increased risk of HCC in patients with either p.C282Y homozygosity or p.C282Y/H63D compound heterozygosity (HR 21.32, 95% CI 10.34–43.97)

(European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Compared to a population-based reference group matched for age, sex, and county of residence, individuals with p.C282Y homozygosity or p.C282Y/H63D compound heterozygosity had a higher risk of all-cause mortality (HR 1.16, 95% CI 1.04–1.30)(European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022).

Although the exact annual incidence of cancer related to hemochromatosis is not well-defined, approximations suggest it is at or above 1.5% (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Patients with hemochromatosis frequently exhibit an overall occurrence of HCC ranging from 10% to 30%, and this is predominantly observed in individuals with cirrhosis (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022)and occurs regardless of iron deficiency (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). HCC has been documented to occur in a small series of patients with advanced fibrosis at non-cirrhotic stages (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022) and in rare uncommon case reports of individuals who had minimal, modest, or indeed no fibrosis (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022).

Individuals with hemochromatosis who have diabetes, elevated iron levels, prolonged exposure to excess iron, older age at the time of disease diagnosis, and co-carcinogenic factors such as alcohol use, smoking, and HBV and HCV infections are at an increased risk of developing cancer related to hemochromatosis (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Certain individuals may also be influenced by additional risk factors contributing to cancer development, such as radiation exposure, NAFLD, exposure to chemicals, obesity, use of medications, exposure to toxins, genetic variations, and a family history of HCC (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022).

4. CONCLUSION

A late diagnosis is generally linked to a poor prognosis for HCC (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Despite the lack of randomized controlled trials in cirrhotic patients, overall statistics indicate that HCC monitoring is linked with considerable improvements in early tumor discovery, curative treatment rates,

and survival (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022).

Irrespective of the underlying liver disease, the recommendations from the European Association for the Study of the Liver (EASL) strongly recommend the regular monitoring for early tumor detection through biannual ultrasound examinations (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022).

Most studies assessing the accuracy of serum alpha-fetoprotein (AFP) focused on its diagnostic capability for hepatocellular carcinoma (HCC) rather than its suitability for monitoring (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022), and the results show significant variation in both sensitivity and specificity (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Although AFP measurement by itself as a tool for regular HCC surveillance is inadequate (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022), rigorous meta-analysis has demonstrated that combining AFP with ultrasonography boosts individuals with end-stage liver disease and the frequencies of early or any stage HCC diagnosis concurrently while simultaneously raising false-positive rates (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Accordingly, AFP can be included in ultrasonography for the monitoring of HCC in patients with hemochromatosis, despite the fact that it is optional in current standards from Europe and America (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022).

Other techniques, such as contrast-enhanced CT or MRI, may be useful in addition to ultrasound when the examination of the liver by ultrasound is technically poor (for example, significant parenchymal heterogeneity, hepatic steatosis, vigorous obesity) (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022). Lastly, only those who qualify for liver transplantation or cancer therapy should undergo HCC screening, as its main objective is to increase patient survival (European Association for the Study of the Liver. Electronic address & European Association for the Study of the, 2022) .

The challenges of doing several costly and time-consuming tests to identify a small percentage of patients with HCC make other options, such as imaging-based screening, more problematic (Adams, 2023). Since the average age of a patient with hemochromatosis is higher than that of most other forms of cirrhosis, the

issue that needs to be answered is whether early diagnosis (typically by imaging) in an older patient with hemochromatosis can result in liver transplantation or curative surgery (Adams, 2023).

The C282Y genetic test, which detects iron overload and, less frequently, hemochromatosis early in the illness, is probably the best screening test for hemochromatosis-related HCC (Adams, 2023).

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