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Risk Factors and Current Therapeutic Approaches for Hepatocellular Carcinoma

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Abstract. Hepatocellular carcinoma, known as HCC, is known to be the most common liver cancer. Currently, there is ongoing research on discovering the risk factors and treatment methods for HCC to find out new treatment methods for HCC that are more effective and have fewer side effects. In this research paper, the risk factors that can cause HCC and their mechanism, as well as current treatment methods for HCC, are listed. The risk factors include biological factors such as HBV, HCV, and NAFLD, chemical factors such as vinyl chloride, arsenic, and thorotrast, physical factors such as cirrhosis, excess iron absorption, and type 2 diabetes, and other factors such as gender can all cause HCC to develop. These factors can cause liver inflammation, fibrosis, cirrhosis, and finally HCC. Nowadays, the treatment methods for HCC include surgical resection, liver transplantation, ablative therapies, transarterial chemoembolization (TACE), targeted therapies, and immunotherapies. However, all these therapies have their limitations and none of the therapies can ensure that they cannot only cure HCC but also not lead to recurrence. This paper aims to provide an overview of the development process of HCC and the ways to treat HCC. In addition, this paper also provides inspiration for future treatment.

Keywords: Hepatocellular carcinoma; risk factors; treatment methods.

1. Introduction

Hepatocellular carcinoma, which is also known as HCC, is the most common liver cancer. HCC strongly relates to hepatitis B (HBV) and hepatitis C (HCV). HBV and HCV can both cause chronic infection. Ranking for the areas that are prevalent in HCC is: East Asia and Sub-Saharan Africa > Southeast Asia and Western Pacific > Italy and Greece > Northern Europe > North America and Northern Europe. The areas with a higher prevalence of HCC are usually because of the higher prevalence of HBV and HCV [1].

HCC develops through carcinogenesis, where normal liver cells transform into cancer cells. First of all, inherited or acquired mutations occur in DNA. This affects liver cell growth, division, and repair. Harmful mutations can cause liver cells to grow at uncontrollable rates. Mutations can cause proto-oncogenes, a gene to control liver cell growth, to become oncogenes, which cause liver cells to grow without stopping. Besides, mutations can cause tumor suppressor gene p53 gene to be unable to stop liver cell growth or initiate apoptosis. When mutated liver cells grow uncontrollably, they can form tumors, which can be non-cancerous or cancerous. Non-cancerous tumors do not spread through the body, while cancerous tumors invade liver tissues and cause further damage. Tumors usually grow beyond a certain size and require nutrients and oxygen to achieve that. Angiogenesis is the process that can help tumors grow by stopping new blood vessels from growing. Besides, metastasis allows liver cancer cells to invade liver tissues and enter blood vessels or lymph nodes. To avoid detection by the immune system, liver cancer cells suppress immune responses or mimic normal liver cells [2].

This paper focuses on the risk factors and their mechanisms that cause HCC, and current treatment methods for HCC. There are several different factors to cause HCC to develop, including biological factors, chemical factors, physical factors, and other factors. Biological factors that can cause are usually related to environment and lifestyle. Chemical risk factors cause HCC by accumulating toxic effects on the liver, leading to liver damage and eventually to cancer cells. Physical risk factors can cause liver damage and cirrhosis. In addition, other factors, such as genetics, gender, ethnicity, and

geographic location, can cause HCC. Fortunately, nowadays, there are a lot of treatment methods for HCC, which can help cure HCC or reduce HCC's symptoms.

2. Risk Factors for HCC

A lot of biological, chemical, physical, and other kinds of factors can cause cancer to develop. There are a lot of factors that can cause HCC to develop as well. For example, biological factors such as HBV, HCV, and Non-alcoholic fatty liver disease (NAFLD), chemical factors such as vinyl chloride, arsenic, and thorotrast, physical factors such as cirrhosis, excess iron absorption, and type 2 diabetes, and other factors such as gender can all cause HCC to develop. The mechanisms for these factors to cause HCC and the examples of these factors will be discussed.

2.1. Biological Factors

In this section, the mechanism for biological factors will be discussed first. Then, examples of biological factors and ways they can cause HCC to develop will be introduced.

2.1.1. Mechanism for biological factors

Biological factors can lead to liver inflammation, which can further release cytokines and reactive oxygen species (ROS) to cause liver damage and fibrosis. After fibrosis develops, scar tissue replaces normal liver tissue and disrupts the liver's functions. As fibrosis develops into cirrhosis, this can cause genetic mutations and cellular dysplasia, which can develop into HCC.

Besides, biological factors such as hepatitis viruses can integrate their DNA into the host gene and cause normal cellular functions to be disrupted, including tumor suppressor genes and oncogenes. After tumor suppressor genes are silent, cells can survive and grow uncontrollably. Furthermore, cancer cells can activate telomerase. This can cause cells to continue to divide without stopping, which can cause HCC to develop [2].

2.1.2. Examples of biological factors

In this section, different types of biological factors will be introduced. This includes HBV and HCV, mutations in tumor suppressor genes, epigenetic modifications, NAFLD and Non-alcoholic steatohepatitis (NASH), and other biological factors such as aflatoxins, iron accumulations, and alcohol abuse.

2.1.2.1. HBV and HCV

HBV and HCV are one of the biological factors that cause HCC. HBV integrates its gene into the host gene in liver cells because this allows the HBV to better promote the development of oncogene. HBV can cause continuous liver inflammation and further cellular damage. Different from HBV, HCV is an RNA virus and does not integrate into the host genes. Regardless, similar to HBV, HCV infection can cause persistent inflammation, fibrosis, and eventually cirrhosis, which is another risk factor that causes HCC. Cirrhosis can cause scar tissue to replace healthy liver tissue. This can cause cells to lose their normal functions and become cancer cells [3].

2.1.2.2. Mutations in tumor suppressor genes

Mutations in tumor suppressor genes are changes in the DNA sequence of tumor suppressor genes and can disrupt their normal functions. Tumor suppressor genes are a type of gene that can help control cell growth and division. When they function normally, they can help control cell division, repair DNA mistakes, and initiate apoptosis. When these genes mutate, their normal control over cell growth is lost, and this can contribute to HCC development. These mutations can both be inherited from a parent or acquired through the environment due to exposure to carcinogens, radiation, viruses, etc. Besides, these mutations can lead to a higher rate of mutations in other genes, further destabilizing genes and leading to more serious HCC symptoms [3].

2.1.2.3. Epigenetic modifications

Epigenetic modification is the changes that affect gene expression without changing the DNA sequence itself. This can change the expression of key genes involved in liver functions, cell cycle regulation, apoptosis, and DNA repair, and transform normal liver cells into cancer cells. In HCC, hypermethylation of DNA in the promoter regions of tumor suppressor genes can cause these genes to become silent. This can cause cells to lose their important functions and cause cell growth and division to lose the checking point. Besides, changes in histone acetylation and methylation patterns can cause either overexpression of growth-promoting genes or underexpression of growth-inhibiting genes, and cause HCC to develop [3].

2.1.2.4. NAFLD and NASH

NAFLD is an accumulation of excess fat in the liver of people who drink little or no alcohol. NASH is a more severe form of NAFLD since it not only involves significant fat deposition but also causes liver inflammation and damage to the liver cells. This inflammation and liver cell damage can lead to fibrosis, and progress to cirrhosis, liver failure, and eventually HCC. Some patients who have NAFLD can progress to NASH. They will have persistent inflammation, and cause oxidative stress, DNA damage, and eventually genetic and epigenetic modification that can cause HCC to form [3].

2.1.2.5. Other biological factors

Aflatoxins are toxic substances that are produced by certain types of molds. Aflatoxin is usually found in improperly stored staple commodities such as peanuts, maize, rice, and wheat. It is the most carcinogenic substance known and can pose significant risks to human bodies when taken. Aflatoxins, particularly aflatoxin B1 (AFB1), can bind to DNA and cause mutations. Besides, AFB1 can cause tumor suppressor gene TP53, an important gene for controlling cell division and apoptosis, to mutate. These mutations can cause the liver cells to grow uncontrollably and cause HCC to develop [3].

In addition, iron accumulation in the body refers to a buildup of excess iron, which usually occurs in the liver. Hereditary hemochromatosis is the most common precursor for iron accumulation. It causes the body to absorb too much iron from diets and excess iron can be deposited into the liver. This can cause free radicals to form in the liver and lead to oxidative stress. This stress can damage cellular lipids, protein, and DNA, and lead to HCC. Besides, oxidative stress can also cause liver inflammation, which can progress to HCC [3].

Lastly, alcohol abuse is also a risk factor since it can directly damage liver cells. Alcohol abuse refers to drinking too much that can cause harm to people's health. Drinking too much alcohol can cause cirrhosis to develop, which can cause normal liver cells to be replaced with scar tissue. This can cause liver damage and cause HCC. In addition, acetaldehyde, alcohol's by-product, is considered as a human carcinogen. It can form DNA adducts and lead to mutations and impaired DNA repair, which directly increase the risks of HCC development [3].

2.2. Chemical Factors for HCC

In this section, the mechanism for chemical factors that can cause HCC will be discussed first. Then, examples of different types of chemical factors and the pathways they follow to cause HCC will be introduced secondly.

2.2.1. Mechanism for chemical factors

Chemical factors can accumulate toxic effects on liver cells, resulting in DNA damage and mutation, causing HCC. Chemicals can cause mutations in tumor suppressor genes and uncontrollable cell growth. Besides, chemicals can form DNA adducts and create lesions to disrupt DNA replication and transcription.

In addition, many chemicals can produce ROS in liver cells. Excessive ROS can damage cellular proteins, lipids, and DNA, which disrupt cells' function and lead to cell death. Then, fibrosis develops, and then cancer forms. Environmental toxins, such as pesticides and dioxins, can cause inflammation

in the liver, which releases cytokines and growth factors. This damages hepatocytes and stimulates liver cells to grow, which leads to mutations and malignant transformation in cells.

In addition, chemicals disrupt normal cell signaling pathways. Arsenic exposure interrupts cell cycle regulation and apoptosis transfers normal liver cells to oncogenes and helps tumor growth. Additionally, arsenic can cause cells to be unable to correct DNA replication errors, which accumulate mutations and increase the risks of getting HCC [2, 4].

2.2.2. Examples of chemical factors

In this section, chemical factors that can cause HCC and how they can cause HCC will be discussed. This includes vinyl chloride, arsenic, thorotrast, nitrosamines, and anabolic steroids.

2.2.2.1. Vinyl chloride

Vinyl chloride is a colorless gas that is primarily used to make polyvinyl chloride, a plastic product. Vinyl Chloride is also known as a carcinogen and can lead to HCC. The higher the level of exposure is, the higher the risks of developing HCC can be. Exposure to vinyl chloride can cause reactive metabolites to form in the liver, which can bind to DNA and form DNA adducts. These adducts can cause mutations in genes that control cell growth and division. Besides, vinyl chloride can cause oxidative stress by producing reactive oxygen species, which can damage cellular components [4].

2.2.2.2. Arsenic

Arsenic is a naturally occurring element that is found in the Earth's crust, which can enter human bodies through water, air, and food. Organic arsenic is highly toxic and can cause HCC. Exposure to arsenic, especially through contaminated water and food can cause liver damage. Besides, arsenic interferes with cellular signaling and DNA repair pathways while promoting oxidative stress, causing cellular damage and eventually developing into HCC. Additionally, arsenic exposure can cause immunosuppression, which can impair the body's ability to detect and destroy cancer cells, further increasing the risks of developing HCC [4].

2.2.2.3. Other chemical factors for HCC

Other chemical factors that can develop HCC include thorotrast, nitrosamines, and anabolic steroids. First of all, thorotrast, which is a radioactive contrast agent, has a long half-life and remains in the liver. Thorotrast continues to emit radiation and damage the liver. This leads to an increased risk of HCC. Secondly, nitrosamines, which are found in tobacco smoke and some foods, form N-nitroso compounds in the liver. N-nitroso compounds are strong carcinogens and can cause HCC. Lastly, anabolic steroids, also known as anabolic androgenic steroids (AAS), are derivatives of testosterone, the primary male sex hormone. Anabolic steroids usually mimic the effects of testosterone in the body and promote skeletal muscle growth. However, steroids can cause liver damage and HCC by developing tumors and creating an anabolic environment that supports hepatocytes to proliferate. Some hepatocytes may be cancerous, which leads to HCC to develop [4].

2.3. Physical Factors for HCC

In this section, a mechanism for physical factors that can cause HCC will be discussed first. Then, examples of different physical factors and how they can cause HCC to develop will be discussed secondly.

2.3.1. Mechanisms for physical factors

Physical factors typically induce liver damage, inflammation, and eventually HCC. Firstly, regenerative nodules in the liver can regenerate liver cells. If mutations are happening in these nodules, the liver cells have a high possibility of becoming cancer cells.

Secondly, hereditary hemochromatosis can cause excessive iron in the liver and produce free radicals, which are ROC. ROC can damage DNA, proteins, and lipids, and lead to mutations. Therefore, when people keep having iron levels higher than normal in their bodies, it can lead to fibrosis and cirrhosis.

Thirdly, insulin resistance and hyperinsulinemia typically have increased levels of insulin and insulin-like growth factors. These growth factors can help cells proliferate and inhibit apoptosis, which causes HCC to develop.

Lastly, obese people have a lot of adipose tissue. Adipose tissue can secrete different adipokines and inflammatory cytokines, which cause systemic and hepatic inflammation. This can intensify liver damage and cancer risk [2, 5, 6].

2.3.2. Examples of physical factors

In this section, different physical factors that can cause HCC will be discussed. This includes cirrhosis and type 2 diabetes.

2.3.2.1. Cirrhosis

Cirrhosis is a late stage of fibrosis. Scar tissue forms at these stages and causes the liver to have abnormal functions. Cirrhosis develops from replacing normal liver tissue with scar tissue when there are liver diseases. This disrupts liver function and causes liver cancer to develop. Common causes of cirrhosis include HBV and HCV, alcoholic liver disease, andNASH. NASH is more severe than NAFLD, especially in Western countries. Both conditions can lead to the accumulation of fat in liver cells, cause inflammation and fibrosis, and further develop into cirrhosis and HCC. Alcohol consumption can cause fat accumulation, alcoholic hepatitis, and ultimately cirrhosis. Acetaldehyde, produced by alcohol, can cause oxidative stress and cellular damage, enhancing the risk of HCC [5].

2.3.2.2. Type 2 diabetes

Type 2 diabetes can affect the way of body processes glucose and is the most common form of diabetes. In addition, type 2 diabetes is characterized by insulin resistance, so people with type 2 diabetes cannot respond to insulin properly. Besides, Type 2 diabetes, which is linked with obesity, can increase the risk of HCC and cause NAFLD or NASH. Type 2 diabetes can also cause hyperinsulinemia and inflammation, which result in liver cell damage and fibrosis [6].

2.4. Examples of Other Factors

In addition to the biological, chemical, and physical factors that are discussed above, other factors can cause HCC to develop. In 2.4, the mechanisms and examples for other factors will be discussed. First, some genetic conditions and inherited diseases such as iron overload disorder, alpha-1 antitrypsin deficiency, and copper accumulation disorder can cause liver damage and develop into liver cancer. In addition, some genetic mutations can increase the risk of HCC. Secondly, gender is one of the factors that can lead to HCC. Men are more likely to develop HCC than women. Since different sex hormones can influence the rate of liver disease and liver cancer. For instance, androgens, which is male hormones, can promote the growth of hepatocellular carcinoma cells. Thirdly, certain ethnicities and populations have a higher risk of HCC largely because of different prevalence of HBV and HCV infections. For example, East Asia and sub-Saharan Africa have higher HCC incidence rates due to the high prevalence of HBV infection. Besides, food consumption can develop HCC. If foods are contaminated with aflatoxins, eating these foods can significantly increase the risk of HCC. Eating more processed foods than fresh fruits and vegetables can also contribute to the risk of HCC. In addition, the carcinogens in tobacco smoke can directly affect liver cells or exacerbate liver damage, which can develop into HCC. As discussed before, exposure to certain chemicals and toxins, such as vinyl chloride, arsenic, and thorotrast, has a higher risk of developing liver cancer [7].

3. Current Treatment Methods for HCC

In this section, current treatment methods that can be applied to HCC will be introduced. Besides, the mechanism for them to treat HCC and their limitations will be discussed.

3.1. Surgical Resection

Surgical resections can remove tumors without affecting the surrounding healthy tissue while eliminating all the cancer cells. When tumors are localized and patients have good liver functions, surgical resection can be used to treat the patients. In addition, to ensure the surgery and recovery are successful, patients should not have significant cirrhosis or portal hypertension if they are treated with surgical resections.

Even though surgical resection can have a great possibility to cure early-stage HCC, there is still a great risk of recurrence, especially when hepatitis or cirrhosis still occurs. Therefore, patients should still have regular follow-ups with imaging and blood tests after the surgical resections to ensure there is no recurrence or new tumors [8].

3.2. Liver Transplantation

Liver Transplantation is the process of replacing a diseased liver with a healthy liver. However, there is a requirement for liver transplantation, such as a patient's single tumor should be smaller than 5 cm or can have up to three tumors with each less than 3 cm. Liver Transplantation is especially beneficial for patients who have severe liver damage or meet Milan criteria that can select patients who are likely to have a successful transplantation outcome.

Liver transplantation can have a great possibility to cure patients since it can remove both tumors and cirrhotic liver tissue. This reduces the likelihood of liver cancer recurrence. However, the main challenge for liver transplantation is the availability of donor organs and it requires the patients to take lifelong immunosuppression medicine to prevent organs from rejecting the transplanted liver [8].

3.3. Ablative Therapies

Ablative therapies can destroy or remove the diseased tissue. Ablative therapies include different types, such as radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation. Firstly, RFA uses high-frequency electrical currents to heat and destroy cancer cells and is most effective for small tumors, which are typically less than 3 cm. RFA involves a probe being inserted into the target area, and radiofrequency energy can be transmitted through the probe to heat and destroy the liver tissue. Like RFA, MWA uses microwave energy to heat and destroy the tumor cells at a faster speed to reach higher temperatures than RFA. In addition to RFA and MWA, cryoablation can also be used to treat HCC. Cryoablation freezes cancer cells and kills them by using liquid nitrogen or argon gas to create extremely cold temperatures.

Ablative therapies are very useful for small tumors and patients who are not able to be treated with surgical resection. However, even though ablative therapies can cure the patients, it is less effective for larger or multifocal tumors. Ablative therapies are often used when surgery is not able to apply on the patients because tumors are not in a proper location, or patients don’t have good liver functions [9].

3.4. Transarterial Chemoembolization (TACE)

TACE combines chemotherapy with an embolic agent that can block the blood supply to the tumor. This combination not only kills the cancer cells through chemotherapy but also suppresses the oxygen and nutrients they need to survive.

TACE is applied when patients have larger or multifocal tumors that are not suitable for surgical resection. TACE is effective for controlling symptoms and slowing the disease’s development. While TACE is not able to cure the patients, it can significantly prolong survival for patients [8].

3.5. Targeted Therapy

Targeted therapy includes Sorafenib and Lenvatinib. Firstly, sorafenib can inhibit kinases that are involved in tumor cell development and angiogenesis. Besides, lenvatinib works by targeting cancer

cell growth and blood vessels that support them. Targeted therapies can be used for advanced HCC and extend survival for patients. They are especially useful for patients who have manageable side effects from the treatments [10].

3.6. Immunotherapy

Nivolumab and Pembrolizumab are immune checkpoint inhibitors that help the immune system recognize and attack cancer cells. They block the PD-1 protein on immune cells, thereby boosting the immune response against cancer cells.

Nivolumab and Pembrolizumab are very useful for patients who do not respond to conventional treatments. They can improve overall survival and are generally well tolerated since the immune system can attack the side effects they cause [8].

4. Conclusion and Discussion

In conclusion, HCC is caused by several different factors. First of all, biological factors can cause liver inflammation and release cytokines and ROS, which cause liver damage, fibrosis, and further HCC. Secondly, chemical factors can accumulate toxic effects on liver cells, causing DNA damage and mutation, further leading to HCC. Thirdly, physical factors lead to liver damage, inflammation, and eventually HCC. Lastly, other factors such as genes, gender, ethnicity, food sources, and lifestyle, can cause HCC to develop as well.

Nowadays, there are several different treatment methods for HCC. First of all, surgical resection is the most effective way to cure patients, but it can cause a great risk of recurrence, and patients should meet certain criteria for this treatment. Secondly, liver transplantation is another effective way to cure the patients, but there is a lack of donors and requirements for taking the immunosuppression lifelong. Thirdly, ablative therapies are very useful for small tumors when patients cannot receive surgical resection, but it is less effective for large or multifocal tumors. Fourthly, TACE can be applied for large or multifocal tumors, but it cannot cure the patients. Fifthly, targeted therapies are useful for patients who have manageable side effects. Lastly, Nivolumab and Pembrolizumab are very useful for patients who cannot respond to conventional treatment.

Although there are treatments that are very effective to treat HCC, every treatment has its own limitations. The limitations include side effects and lead HCC to recur. Besides, there are some treatments that won't have side effects but they are unable to cure HCC. Hence, the aims for the treatment methods that will be developed in the future are not only effective on curing HCC, but also have less side effects or even no side effects on patients.

First, future HCC treatments will be more specific to identify the mutations that cause HCC. This can target patients' tumors more specifically and help treat patients more effectively. In addition, new immune checkpoint inhibitors and combination therapies will be developed, which can strengthen the immune system's ability to fight against HCC. Additionally, personalized HCC vaccines and cell transfer therapies will be developed in the future. More advanced techniques for radiology and surgery, such as real-time imaging and guidance systems, will also be developed. This can improve the accuracy of the treatment methods and develop more effective ablative therapies. Finally, early detection methods, such as screening and surveillance, will also have improvements and are particularly useful for high-risk populations.

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