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Liver Cancer: Contributory Factors, Diagnosis and Treatment

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Abstract:*Livercancerhave high mortality secondary to hepatitis B,hepatitis C and secondary to alcohol.Hepatocellular carcinoma (HCC),most common form of liver cancer with highest rates in China and in Sub-Saharan Africa.Approximately 75% of all primary liver cancer is HCC(also named hepatoma).Cholangiocarcinoma can form within liver as the bile duct.Liver fluke infection increases the risk of cholangiocarcinoma in Thailand.Tumor of blood vessles-angiosarcoma.Cancers produced from muscles in the liver are leiomyosarcoma.Many cancers in the liver are due to metastasis. Contributory factors of liver cancer includes: viral infection either with hepatitisC(HCV) or hepatitis B(HBV).Viruses cause HCC because massive inflammation, fibrosis and eventual cirrhosis within the liver. Aflatoxin exposure can lead to the development of HCC.High grade dysplastic nodules are precancerous lesions of the liver.Beckwith-Weidemann syndrome is associated with hepatoblastoma in children. Liver cancer is associated with abdominal mass, abdominal pain,emesis,anemia, packpain,jaundice, itching,weight loss and fever. Diagnosis mainly by ultrasound,CT,MRI, and magnetic resonancecholangiopancreatography(MRCP).Tests for tumor markers are helpful. Treatment bysurgery,antiviral drugs and liver transplant. Prevention by reducing exposure to risk factor for liver cancer, vaccination against hepatitis Bvirus, reducing alcohol abuse,prevention of carcinogenesis and treatment to prevent recurrence of liver cancer, by the chemotherapy drugs and antiviral drugs.With the advances in diagnosis and treatment the prognosis in liver cancer remains poor.*

Keywords:*Livercancer,Hepatocellular carcinoma(HCC),Cholangiocarcinoma,Treatment*

I. Introduction

Liver cancer, also known as hepatic cancer, is a cancer that originates in the liver[1].Globally, as of 2010,liver cancer resulted in 754,000 deaths, up from 460,000 in 1990,making it the third leading cause of cancer death after lung and stomach[2].In 2012,it represented 7% of cancer diagnoses in men the 5th most diagnosed cancer that year[3].Primary liver cancer is globally the sixth most frequent cancer, and the second leading cause of cancer death[4].0f these deaths 340,000 were secondary to hepatitis B,196,000 were secondary to hepatitis C, and 150,000 were secondary to alcohol[2].Hepatocellular carcinoma(HCC), the most common form of liver cancer, shows a striking geographical distribution, China has 50% of HCC cases globally, and more than 80% of the cases occur in Sub-Saharan Africa or East Asia due to hepatitis B virus [5,6].Cholangiocarcinoma also has a significantgeographically distribution, with Thailand showing the highest rates worldwide due to presence of liver fluke[5,,7].The leading cause of liver cancer is cirrhosis due to either hepatitis B, hepatitis C, or alcohol[1].Chronic infections with hepatitis B virus may be asymptomatic or may be associated with chronic inflammation of the liver (chronic hepatitis), leading to cirrhosis over a period of several years. This type of infection dramatically increases the incidence of hepatocellular carcinoma(liver cancer)[6]..Cholangiocarcinoma is associated with sweating, jaundice, abdominal pain, weight loss and liver enlargement[8].HCC is associated with abdominal mass, abdominal pain, emesis, anemia, back pain, jaundice, itching, weight loss and fever[9].Many imaging modalities are used to aid in the diagnosis of primary liver cancer[10].Treatment mainly by surgery, antiviral drugs and liver transplant. Prevention by reducing to exposure to a risk factor, and vaccination against hepatitis Bvirus.The paper provides an overview of the causes, diagnosis and treatment of liver cancer.

II. Hepatitis B virus and liver cancer classification

Hepatitis B virus(HBV)was not discovered until 1966 when Baruch Blumberg then working at the National Institute of Health (NIH),discovered the Australian antigen(later known to be hepatitis B surface antigen or (HBsAg) in the blood of Australian aboriginal people[11].Although a virus was suspected since the research published byMacCallum in 1947[12].Baruch Blumberg received the Nobel Prize in Physiology and

Medicine in 1976[13].By the early 1980s the genome of the virus had been sequenced, and the first vaccine were being tested [14,15].

Liver cancer Classification

The most frequent liver cancer, accounting for approximately 75% of all primary liver cancers, is hepatocellular carcinoma (HCC)(also named *hepatoma*, which is a misnomer because adenomas are usually benign).HCC is a cancer formed by liver cells, known as hepatocytes, that become malignant. Another type of cancer formed by liver cell is hepatoblastoma,which is specifically formed by immature liver cells[16].It is a rare malignant tumor that primarily develops in children, and accounts for approximately !% of all cancers and 79% of all primary liver cancers under age of 15.Most hepatoblastoma form in the right lobe[17].

Liver cancer can also form from other structures within liver as the bile duct, blood vessels and immune cells. Cancer of the bile duct(cholangiocarcinoma and cholangiocellular cystadenocarcinoma) account for approximately 6% of primary cancers[16].There are also variant type of HCC that consists of both HCC and cholangiocarcinoma[18].Tumors of the blood vessels(angiosarcoma and hemangioendothelioma, embryonal sarcoma and fibro -sarcoma are produced from a type of connective tissue known as mesenchyme. Cancers produced from muscles in the liver are leiomyosarcoma.Other less common liver cancers include carcinosarcomas,teratomas,yolk sac tumors, carcinoid tumors and lymphoma. Lymphomas usually have diffuse infiltration to liver, but it may form a liver mass in rare occasions [16].Many cancers found within the liver are not true liver cancers but are from other sites in the body that have spread to liver(metastases).Frequently, the site of origin is the gastrointestinal tract(such as colon cancer and carcinoid tumors mainly of the appendix),but also from breast cancer, ovarian cancer, lung cancer, renal cancer, prostate cancer[16].

III. Contributory factors

Viral infection

Viral infection with either hepatitis C virus(HCV) or Hepatitis B virus(HBV) is the chief cause of liver cancer in the world today, accounting for 80% of hepatocellular carcinoma(HCC)[19,20,21].The viruses cause HCC because massive inflammation, fibrosis and eventual cirrhosis occurs within the liver.HCC usually arises after cirrhosis, with an annual incidence of 1.7% in cirrhotic HCV-infected individuals [22].Around 5-10 of the individuals that become infected with HBV become chronic carriers, and around 30% of these acquire liver disease, which can lead to HCC[19].HBV infection is also linked to cholangicarcinoma[23].The role of other viruses other than HCV and HBV in liver cancer is much less clear, although there is some evidence that co-infection of HBV and hepatitis D virus may increase the risk of HCC[24].

Many genetic and epigenetic changes are formed in liver cells during HCV and HBV infection, which is a major factor in the production of liver tumors. The viruses induce malignant changes in cells by altering gene methylation, affecting gene expression and promoting or repressing cellular signal transduction pathways. By doing this viruses can prevent cells from undergoing a programmed form of cell death (apoptosis) and promote viral replication and persistence [19,22].

Liver cirrhosis

In addition to virus related cirrhosis, other causes of cirrhosis can lead to HCC. Alcohol intake correlates with risk of HCC, and the risk is far greater in individuals with an alcohol-induced cirrhotic liver. These are a few disorders that are known to cause cirrhosis and lead to cancer, including hereditary hemochromatosis and primary biliary cirrhosis [25].

Mycotoxin-Aflatoxin

The term"aflatoxin" is derived from the name of one of the molds that produce it,*Aspergillusflavus*.It was coined around 1960 after its discovery as the source of "Turkey X disease". Aflatoxins form one of the major groupings of mycotoxins[26].They are regularly found in improperly stored staple commodities such as cassava,chili peppers, corn, cotton seed,millet,peanuts,rice, sorghum, sunflower seeds, tree nuts, wheat, and a variety of species.When contaminated food is processed, aflatoxin enters the general food supply where they have been found in both pet and human foods, as well as in feedstocks for agriculture animals. Animal fed contaminated food can pass aflatoxin transformation products into eggs milk products and meat[27].For example, contaminated poultry feed is suspected in the findings of high percentage of samples of aflatoxin contaminated chicken meat and eggs in Pakistan[28].In a 2015 analysis of plant-based dietary supplements, the highest mycotoxin concentrations were found in milk thistle based supplements, at up to 37 mg/kg [29].

At least 14 different aflatoxins are produced in nature. Aflatoxin B1 is considered the most toxic and is produced by *Aspergillus flavus* and *Aspergillus parasiticus*.Aflatoxin M_1 is present in the fermentation broth of *Aspergillus parasiticus*,but it and aflatoxin M_2 are also produced when an infected liver metabolizes aflatoxin B_1 and B_2 [30].Aflatoxin poisoning has been reported worldwide that includes:

a) 2003 Kenya: acute poisoning,120 people died [31].
b) February-March 2013: Romania, Serbia, Croatia imported into western Europe-2013 aflatoxin contamination [32].
c) February 2013: Iowa contamination [33].
d) 2014(ongoing): Nepal and Bangladesh, neonatal exposures, found in umbilical cord blood [31].

Aflatoxin and HCC

Aflatoxin exposure can lead to the development of HCC.Food contamination by fungi leads to ingestion of the chemicals, which are very toxic to the liver. Common foodstuffs contamination with the toxins is cereals, peanuts, and other vegetables. Contamination of food is common in Africa, South-East Asia and China. Concurrent HBV infection and aflatoxin exposure increases the risk of liver cancer to over three times than seen in the HBV infected individuals without aflatoxin exposure. The mechanism by which aflatoxin cause cancer is through genetic mutation of a gene required for the prevention of cancer [34].

Miscellaneous risk factors in adults and children

Risk factors for liver cancer in adults include:
i). High grade dysplastic nodules are precancerous lesions of the liver. Within 2 years, there is risk of cancer arising from these nodules of 30 -40%[35].
ii). Obesity has emerged as an important risk factor as it can lead to steatohepatitis [36].
iii). Diabetes increases the risk of HCC[36].
iv). Smoking increases the risk of HCC compared to non-smokers and previous smokers [36].
v). There sis round 5-10% lifetime risk of cholangiocarcinoma in people with primary sclerosing cholangitis [37].
vi). Liver fluke infection increases the risk of cholangiocarcinoma, and is the reason Thailand has particularly high rates of this cancer (liver cancer)[5].

Increased risk of liver cancer in children can be caused by Beckwith-Weidemann Syndrome (associated with hepatoblastoma) [38],familial adenomatous polyposis(associated with hepatoblastoma)[38],low birth weight(associated with hepatoblastoma) [17]. Progressive familial intrahepatic cholestasis (associated with HCC),[39],and Trisomy 18(associated with hepatoblastoma)[38].

IV. Diagnosis

Many imaging modalities are used to aid in the diagnosis of primary liver cancer. For HCC these include sonography (ultrasound), computed tomography (CT) and magnetic resonance imaging (MRI).When imaging the liver with ultrasound, a mass greater than 2 cm has more than 95% chance of being HCC.The majority of cholangiocarcinoma occur hilar region of the liver, and often present as bile duct obstruction. If the cause of obstruction is suspected to be malignant, endoscopic retrograde cholangiopancreatography (ERCP), ultrasound, CT,MRI and magnetic resonance cholangiopancreatography(MRCP) are used[10].
Tumor markers, chemicals sometimes found in the blood of people with cancer, can be helpful in diagnosing and monitoring the course of liver cancers. High levels of alpha-fetoprotein (AFP) in the blood can be found in many cases of HCC and intrahepatic cholangiocarcinoma. Cholangiocarcinoma can be detected with these commonly used tumor markers:
*carbohydrate antigen 19.9(CA19.9)
*carcinoembryonic antigen (CEA)
* And cancer antigen 125(CA125).
These tumor markers are found in the primary liver cancers, as well as in other cancers and certain other disorders [40,41].

V. Treatment

Treatment of Hepatocellularcarcinoma(HCC).

Surgical resection is often the treatment of choice for non-cirrhotic livers. Increased risk of complications such as liver failure can occur with resection of cirrhotic livers. Five –year survival rates after resection has massively improved over the past few decades and can now exceeds 50%.Recurrence rates after resection due to the spread of the initial tumor or formation of new tumors exceeds 70%[42].Liver transplantation can also be used in cases of HCC where this form of treatment can be tolerated and the tumor fits specific criteria(such as Milan criteria).Less than 30-40% of the individuals with HCC are eligible for surgery and transplant because the cancer often detected late stage. Also HCC can progress during the waiting time for liver transplant, which can prevent transplant due to strict criteria [42].

Percutaneous ablation is the only non-surgical treatment than can offer cure. There are many forms of percutaneous ablation, which consist of either injecting chemical into the liver (ethanol or acetic acid) or

producing extremes of temperature using radio frequency ablation, microwaves, lasers or cryotherapy. OF these, radio frequency ablation has one of the best reputations in HCC, but the limitations include inability to treat tumors close to other organs and blood vessels to heat generation and heat sync effect, respectively [43,44].

Systematic chemotherapeutics are not routinely used in HCC, although local chemotherapy may be used in a procedure known as trans arterial chemo-mobilization .In this procedure, cytotoxic drugs such as doxorubicin or cisplatin with lipiodol are administered and the arteries supplying the liver are blocked by gelatin sponge or other particles. Because most systematic drugs have no efficacy in the treatment of HCC, research into the molecular pathways involved in the production of liver cancer produced sorafenib,a targeted therapy drug that prevents cell proliferation and blood cell growth. This drug provides a survival benefit for advanced HCC[44].Radiotherapy is not often used in HCC because the liver is not tolerant to radiation. Although with modern technology it is possible to provide well targeted radiation to the tumor, minimizing the dose to the rest of the liver. Dual treatment of radiotherapy plus chemo- mobilization,localchemotherapy, systemic chemotherapy or targeted therapy drugs may show benefit over radiotherapy alone [45].

Treatment ofCholangiocarcinoma

Resection is an option incholangiocarcinoma,but less than 30% of cases of cholangiocarcinoma are respectable at diagnosis. After surgery, recurrence rates are up to 60%[46,47].Liver transplant may be used where partial resection is not an option, and adjuvant chemo- radiation may benefit some cases[37].Up to 60% of cholangiocarcinoma form in the perihilar region and photodynamic therapy can be used to improve quality of life and survival time in these unrespectable cases. Photodynamic therapy is a novel treatment that utilizes light activated molecules to treat the tumor. The compounds are activated in the tumor region by laser light, which causes the release of toxic reactive oxygen species, killing tumor cells [46,48].Systemic chemotherapies such as gemcitabine and cisplatin are sometimes used in inoperable cases of cholangiocarcinoma[37].Radio frequency ablation ,trans-arterial chemo-mobilization and internal radiotherapy(brachytherapy)all show promise in the treatment of cholangiocarcinoma[46].Radiotherapy may be used in the adjuvant setting or for palliative treatment of cholangiocarcinoma[49].

Treatment ofHepatoblastoma

Removing the tumor by either surgical resection or liver transplant can be used in the treatment of hepatoblastoma.In some cases surgery can offer a cure. Chemotherapy may be used before and after surgery and transplant [50].Chemotherapy, including cisplatin, vincristine, cyclophosphamide,and doxorubicin are used for the systemic treatment of hepatoblastoma.Out of these drugs, cisplatin seems to be the most effective[51].
Hepcortespenlismut-L is an immunotherapy that is going through a phase 3 clinical trial for HCC[52].

VI. Prevention

Prevention of cancers can be separated into primary, secondary, and tertiary prevention.

Primary prevention

Preemptively reduces exposure to a risk factor for liver cancer. One of the most successful primary liver cancer preventions is vaccination against hepatitis BVaccination against hepatitis C virus is currently unavailable. Other forms of primary prevention are aimed at limiting transmission these viruses by promotion of safe injection practice, screening of blood donation products and screening of high risk individuals. Aflatoxin exposure can be avoided by post-harvest intervention to discourage mold, which has been effective in WestAfrica. Reducing alcohol abuse, obesity, and diabetes would also reduce of liver cancer. Diet control in hemochromatosis could decrease the risk of iron overload, decreasing the risk of cancer [53,].

Secondary prevention

Includes both cure of the agent involved in the formation of cancer (carcinogenesis) and the prevention of carcinogenesis if this is not possible.Cure of virus-infected individuals is not possible, but treatment with antiviral drugs such as interferon can decrease the risk of liver cancer. Chlorophyllin may have potential in reducing the effects of aflatoxin [53].

Tertiary prevention

Includes treatments to prevent the recurrence of livercancer.These include the use of chemotherapy drugs, and antiviral drugs [53].

VII. Conclusion

The leading cause of liver canceriscirrhosisdue to hepatitis B, hepatitis C or alcohol. China has 50% of hepatocellular carcinoma (HCC) cases, and high rates occur in Sub-Sahara Africa or East Asia due to hepatitis

B.Diagnosis by sonography, CT scan, and MRI.Treatment is mainly by surgery, antiviral drugs and liver transplant .Prevention by vaccination against hepatitis B.

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