INFECTIOUS AGENTS ASSOCIATED WITH CANCER (REVIEW)

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ABSTRACT: *Although cancer research is growing rapidly, there is no potential cure and the disease remains one of the leading causes of mortality worldwide. Cancer is a genetic disease, due to mutation in the genome which may occurs at any time during life span. Cancer due to infectious diseases considered as one of the main causes of cancer, it contributes 15% to 25% of all human cancer worldwide. The infectious organisms either directly involved in the cancer development by interrupting the host cell genome resulting to cancerous cell, or indirectly by increasing the risk of cancer development, like some viruses can affect signaling that normally keeps cell growth and proliferation in under regulation. DNA viruses use cellular epigenetic processes to control their life cycles during infection. Also, some infections weaken the immune system, making the body less able to fight off other cancer-causing infections. Others may cause chronic inflammation, which may lead to cancer. Most of the viruses that are linked to an increased risk of cancer can be passed from one person to another through blood and/or other body fluids. Examples of Infectious agents, like hepatitis B and C viruses, Epstein-Barr virus (EBV), human papillomavirus (HPV), human immunodeficiency virus type 1 (HIV-1), Helicobacter pylori (H. pylori) and Streptococcus bovis (S. bovis). These cancers include hepatocellular carcinoma, Burkitt's lymphoma, nasopharyngeal carcinoma, cervical cancers, non-Hodgkin lymphoma, Kaposi sarcoma, adenocarcinoma and lymphoma. There are fewer reports on the molecular mechanism and tumorigenesis due to infectious agents. Most reported papers address genetic mutation, but not infectious agents such as viruses, bacteria and parasites. The purpose of this review is to update the latest understanding on the development of cancer due to infectious microorganisms as well the possible strategy for cancer prevention and diagnosis.*

Keywords: Viral agent,Hepatitis B virus,Hepatitis C virus,Human papillomavirus, Aflatoxin, Helicobacter pylori,and Oncogenic parasite

INTRODUCTION

Worldwide in 2015, the most common causes of cancer death were lung cancer (1.6 million deaths), liver cancer (745,000 deaths and stomach cancer (723,000 deaths) [1]. Estimates place the worldwide risk of cancers from infectious causes (agents) at 16.1% [2]. Viral infections are risk factors for cervical cancer,80% of liver cancers, and 15-20% of other cancers [3].This proportion varies in different regions of the world from high of 32.7% in sub-Sharan Africa to 3.3% in Australia and New Zealand [2].Occasionally there are mechanisms associated with a genetic transfer of viral DNA to the host genome, potentially causing an opportunity for mutagenesis that leads to oncogenesis [4].In addition to viral causes, bacterial, fungal and parasitic agents are also assorted with cancer. Viruses that cause cancer include human papillomavirus (cervical carcinoma), Epstein-Barr virus (B –cell lymphoproliferative disease and nasopharyngeal carcinoma), Kaposi's sarcoma herpesvirus (Kaposi's Sarcoma and primary effusion lymphomas), hepatitis B and hepatitis C viruses (hepatocellular carcinoma), and Human T-cell leukemia virus-1(T-cell leukemia). Bacterial infection may also increase the risk of cancer, as seen in *Helicobacter pylori*-induced gastric carcinoma [5]. The oncogenes involved in bacterial carcinogen are unknown since much of the information involved in the study comes from epidemiological evidence and limited molecular and biological studies [6,]. Parasitic infection strongly associated with cancer include *Schistosoma haematobium* (squamous cell carcinoma of the bladder), and the liver flukes,*0pisthorchis viverini and Clonorchis (cholangiocarcinoma).* [7]. The paper reviews the infectious viral, bacterial and parasitic agents associated with cancer.

VIRAL AGENT

Viruses are one of the most important risk factors for cancer development in humans [3]. Infection by some hepatitis viruses, especially hepatitis B and hepatitis C, can induce a chronic infection that leads to liver cancer in 1 in 200. 0f people infected with hepatitis B each year (more in Asia, fewer in North America), and in about 1 in 45 of people infected with hepatitis C each year [8]. People with hepatitis B infection are more than 200 times more likely to develop liver cancer than uninfected people [8]..Liver cirrhosis, whether from chronic viral hepatitis infection or alcohol abuse or some other cause, is independently associated with development of live4r cancer, and the combination of cirrhosis and viral hepatitis presents the highest risk of liver cancer development. Because chronic viral hepatitis is so common and liver cancer so deadly, liver cancer is one the most common causes of cancer related deaths in the world and is especially common in East Asia and parts of sub-Saharan Africa [8].

Human papillomaviruses (HPV) are another particular common cancer-causing virus. HPV is well known for causing genital warts and essentially all cases of cervical cancer, but it can also infect and cause cancer in other parts of the body, including the larynx, lining of mouth, nose, and throat, anus, and esophagus .Papanicolaou smear ("Pap" smear) is widely used cancer screening test for cervical cancer DNA based tests to identify the virus are also available [9].

Herpesviruses are a third group of common cancer-causing viruses. Two types of herpesviruses have been associated with cancer: Epstein-Barr virus(EBV) and human herpesvirus B(HHV-8) [10].EBV appears to cause all non-keratinizing nasopharyngeal carcinomas and some cases of

lymphoma, including Burkitt's lymphoma-the association is especially strong in Africa-and Hodgkin's disease [10].EBV has also been found in a variety of other types of cancer cells, although its role causing other cancers is not well established.KSHV.HHV-8 [11]] causes all cases of Kaposi's sarcoma, and has been found in some cases of a cancer-related condition called Cattleman's disease[10].Studies involving other kinds of cancer, particularly prostate cancer, have been inconsistent [10].Both of these herpesviruses are commonly found in cancerous cells of primary effusion lymphoma [10].Herpesviruses are also cause cancer in animals, especially leukemia's and lymphomas [10].

Human T cell lympho-tropic virus (HTLV-1) was the first human retrovirus discovered by Robert Gallo and colleagues at NIH [12]. The viruses cause Adult T-cell leukemia, a disease first described by Takatsuki and colleagues in Japan, and other neurological diseases [13].

Merkel cell polyomavirus is the most recently discovered human virus,isolated Merkel cell carcinoma tissues in 2008, by the group that discovered KSHIV/HHV-8 in 1994,using a new technology called digital transcriptome subtraction. About 80% of Merkel cell carcinomas are caused by a separate histogenesis.This is the only member of this group viruses known to cause cancer but other polyomaviruses are suspects for being additional cancer viruses [14].

HIV does not directly cause cancer, but it is associated with number of malignancies, especially Kaposi's

sarcoma, on-Hodgkin's lymphoma, anal cancer and cervical cancer. Kaposi's sarcoma is caused by human herpesvirus- 8. AIDS-related cases of anal cancer and cervical cancers are commonly caused by human papillomavirus. After HIV destroys the immune system, the body is no longer able to control these viruses, and infection manifest as cancer [15]. Certain other deficiency states (e.g. variable Immunodeficiency and IgA deficiency) are also associated with increased risk of malignancy [16].

HEPATITIS B VIRUS

Liver cancer in the United States is primarily due to three main factors: hepatitis C virus (HCV) (22%), hepatitis B virus(HBV)(12%) and alcohol use (47 %)[17]. In 2017 there will be about 40,710 new cases of liver cancer in the United States [18].World-wide, liver cancer mortality is more often due to hepatitis B virus(HBV)(33%) less often due to hepatitis c virus (21%),and still frequently due to alcohol use (30%) [19].World-wide, liver cancer is the 4th most frequent cause of cancer mortality, causing 9% of all cancer mortality (total liver cancer deaths in 2015 being 810,500),and coming, in frequency, after lung, colorectal and stomach cancers [19]. The viruses cause HCC because massive inflammation, fibrosis and eventual cirrhosis occurs within the liver. HCC arises after cirrhosis, with an annual incidence of 1.7 % in chronic HCV infected individuals [20].Around 5-10 of the individuals that become infected with HBV become chronic carriers and around 30% of those acquire liver disease, which can lead to HCC [21].HBV infection is also linked to cholangiocarcinoma [22].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 [23].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 methylation, affecting gene expression and promoting or repressing cellular signal transduction pathways. By doing this virus can prevent cells from undergoing programmed form of cell death (apoptosis) and promote viral replication and persistence [20].

HEPATITIS C VIRUS

An estimated 130 to 200 million people or 3% of the world population are living with chronic hepatitis [24].About 3.4 million people are infected per year and more than 350,000 die yearly from hepatitis C related diseases[24].During 2010,it is estimated that 16,000 people died of acute infections while 196,000 death occurred from liver cancer secondary to infection [25].It occur most commonly in Africa and Central and East Asia [26].About 343,000 deaths due to liver cancer and 358,000 due to cirrhosis occurred in 2013 due to hepatitis C[27].In the United States, about 2% of people have chronic hepatitis C [28].The number of deaths has increased to 15,000 in 2008,having overtaken HIV/AIDS as a cause of death in the USA in 2007 [29].In 2014 it was the single greatest cause of infectious death in the United States [30].In Europe the percentage of people with chronic infection has been estimated to be between 0.13 and 3.26 [31].Countries with particularly high rates include Egypt (22%),Pakistan,(4.8%),and China (3.2 %) [24].Transmission of HCV is primarily by blood –to blood contact with intravenous drug use, poorly sterilized equipment, needle stick injuries in the healthcare and transfusion[32]. Hepatitis C virus is a a small, enveloped, single stranded, positive –sense RNA virus [33]. It is a member of of the *Hepacvirus* genus in the family *Flaviridae*[34].There are seven major genotypes of HCV of HCV, which are known as genotypes one to seven [35].The genotypes are divided into several subtypes with the number of subtypes depending on the genotypes. In the United States, about 70% of cases are by genotype 1,20% by genotype two and !% by each other genotypes [28].Genotype 1 is also the most common in South America and Europe [33,].The half of the virus in the serum is around 3 hours and may be as short as 45 minutes [36].In addition to replication in the liver the virus can multiply in lymphocytes [37]

ACUTE AND CHRONIC INFECTION

Hepatitis C infection causes acute symptoms in 15% of cases [38].Symptoms are generally mild and vague, including a decreased appetite, fatigue, nausea, muscle or joint pain, and weight loss[28],and rarely acute liver failure result [39].Most cases of acute infection is not associated with jaundice [40]..The infection can be resolved spontaneously in 10-50 % of cases, which occurs more frequently in individuals who are young female [40].HCV RNA can be detected in blood within days of exposure and is followed by elevation in serum levels of liver specific enzyme and alanine aminotransferase (ALT),aspartate aminotransferase (AST) and in some cases bilirubin [41]. About 80% of those exposed to virus develop chronic infection [42].This defined as the presence of detectable viral replication for at least for at least for six months [43].Chronic infection after several years may cause cirrhosis or liver cancer [33].Worldwide hepatitis C is the cause of 27% of cirrhosis and 25 % hepatocellular carcinoma [44].Cirrhosis is more common in those also

infected with hepatitis *B, schistosoma*, or HIV, in alcoholics and those male gender [28].In those with hepatitis C, excess alcohol increases the risk of developing cirrhosis 100 fold [45].Those who develop cirrhosis have a 20 fold greater risk of hepatocellular carcinoma. This transformation occurs at a rate of 1-3 % per year [33,28].Being infected with hepatitis B in addition to hepatitis C increases the risk further [46].Liver cirrhosis may lead to portal hypertension, ascites (accumulation of fluid in the abdomen) easy bruising, or bleeding varicose (enlarged veins, especially in the stomach and esophagus),jaundice, and symptoms of cognitive impairment known as encephalopathy [47].Ascites occurs at some stage in more than half of those who have chronic infection [48].

A review by Takeda et *al* [49]. HCV and HBV cause carcinogenic DNA damage and genomic instability by a number of mechanisms. HBV, and especially HCV, cause chronic inflammation in the liver, increasing reactive oxygen species (ROS) formation. ROS interact directly with DNA causing multiple types of DNA damage (26 ROS-induced DNA damage are described by Yu et al [50]. It also appears that chronic inflammation caused by HCV infection triggers the aberrant up-regulation of activation – induced cytidine deaminase (AID) in hepatocytes. AID creates mutations in DNA by deamination (a DNA damage) of the cytosine base, which converts cytosine into uracil. Thus,it changes a C:G base pair into a mutagenic U:G mismatch. In a still further cause of DNA damage,HCV core protein binds to the base NBS1 protein and inhibits the formation of the Mre11/NBS1$_1$/Rad50 complex, thereby inhibiting DNA binding of repair enzymes. As a result, the reduced DNA repair mutagenic DNA damages can accumulate [51].

HEPATOCELLULAR CARCINOMA-HCC

HCC is the most common tumors worldwide. HCC HCC is one of the deadliest cancers in China where chronic hepatitis B is found in 90% of cases. In Japan, chronic hepatitis C is associated with 90% of HCC cases. Food infected (contaminated) with *Aspergillus flavus* (especially peanuts and corn stored during wet season) which produces aflatoxin poses risk factor [52]. Most malignant tumors of the liver discovered in western patients are metastasis(spread) from tumors elsewhere [53].In the west HCC is generally seen as a rare cancer, normally of those with-pre-existing liver disease. It is often detected by ultrasound screening and so can be discovered by health-care facilities much earlier than in developing regions such as sub-Saharan Africa [53]. In Japan, Saudi Arabia, Egypt Pakistan, HCV is the cause of HCC. The markers of hepatitis C infection (positive anti HCV) are found 80% - 90% in Japan,70 % in Egypt,40-50% in Pakistan, and 35-40% in Saudi Arabia [54].

The most important predisposing or risk factors vary widely from country to country. In countries where hepatitis B is endemic, such as China hepatitis B is the predominant cause of HCC [55].Whereas in countries, such as United States, where hepatitis B is rare because of high vaccination rates, the majority cause of HCC is cirrhosis, often due to hepatitis C ,obesity or alcohol abuse [55].The main predisposing-risk factors for HCC includes: alcoholism, Hepatitis B, Aflatoxin, Hepatitis C,(25% of causes globally). [56], cirrhosis of liver, on-alcoholic steatohepatitis (if progression to cirrhosis has occurred)[57],hemochromatosis, alpha 1-anistrepsin deficiency ,Wilsons's disease (while some theorize the risk increases [58,hcc,25].Case studies are rare [59]],and suggest the opposite where Wilson's disease actually confer protection [60].

The risk of HCC in type 2 diabetes is greater (from 2.5 to 7.1 time the non-diabetic risk) [61], depending on the duration of diabetes and treatment duration. A suspected contributor to this increase risk is *circulating insulin concentration* such that diabetic with poor insulin control or on treatment that elevate their insulin output (both states that contribute to higher circulating insulin concentration) show far greater risk of HACC than diabetic on treatment that reduce circulating insulin concentration [61].The risk of obese patients (with body mass index (BMI) greater than 30) is increasing than cirrhotic patients [62]. Alcohol generally contributed to 15-45 % of HCC cases in the developed countries due to significant role in cirrhosis [63].Many studies have shown the association of heavy alcohol intake (>50 to 70 g/d for several years) and HCC [64].Aflatoxin is mycotoxin produced by *Aspergillus flavus*.This fungus grows easily on foodstuffs including peanuts, pistachio, etc.,which stored in warm and damp conditions [65].Several studies have revealed the association between aflatoxin and HCC [66].Also some studies in Asia, Shanghai and Taiwan, hepatitis B infection and a study in Taiwan reported that HBsAg carriers,who were susceptible to aflatoxin, were likely to develop HCC [67].

When hepatocellular carcinomas grow to a size of more than 6-8cm they are considered cancerous and thus become a risk of HCC.Although HCC commonly effects adults,children who are affected with biliary atresia,infantile cholestasis,glycogen-storage disease. and other cirrhosis diseases of liver are predisposed to developing HCC.Children and adolescent are unlikely to have chronic liver disease, however if they suffer from congenital liver disorders, this fact increases the chance of developing HCC [68]. HCC like any other cancer develops when there is mutation to the cellular machinery that causes the cell replicate sat a higher rate and/or results in the cell avoiding apoptosis. In particular, chronic infection of hepatitis B and/or hepatitis C can aid the development of HCC by repeatedly causing body's own immune system to attack the liver cells, some of which are infected by the virus, other merely bystanders [69].While this constant cycle of damage followed by repair can lead to mistakes during repair which in turn lead to carcinogenesis, this hypothesis is more applicable at present to hepatitis C .Chronic hepatitis C causes HCC through the stage of cirrhosis. In chronic hepatitis B, however, the integration of the viral genome into infected cells, can directly induce a non- cirrhotic liver to develop HCC [69]. Alternative, repeated consumption of large amount of ethanol can have a similar effect. The toxin aflatoxin from certain Aspergillus species of fungus is carcinogen and aid carcinogenesis of hepatocellular cancer by building up in the liver. The combined high prevalence of rates of aflatoxin and hepatitis B in settings like China and West Africa has led to relatively high rates of HCC in those regions. Other viral hepatitis such as hepatitis A have no potential to become a chronic infection and thus are not related to hepatocellular carcinoma [69].

HUMAN PAPILOOMAVIRUS-HPV

Worldwide, HPV causes the second largest infection associated cancers or 5.2% of the global cancer burden [70].In the United States, HPV causes most cervical cancers, as well as cancers of the vagina, vulva, penis, anus, rectum, and oropharynx(cancers of back of the throat, including the base of the tongue and tonsils) [71].Each year in the United States, about 39,800 new cases of cancer are found in parts of the body where HPV is often found. HPV causes about 31,500 of these cancers [71]. A review by Munger *et al*, [72] there are about 200 HPVs.They can be classified into mucosal and cutaneous HPVs.Within each of these HPV groups, individual viruses are designated high or low risk according to the propensity for malignant progression of the lesions that they cause. Among the HPV high –risk viruses, the HPV E6 and E7 oncoprotein functional inactive the p53 and retinoblastoma tumor suppressors respectively. In addition, the high-risk HPV E6 and E7 oncoproteins can each independently induce genomic instability in normal human cells. They generate miotic defects and aneuploidy through the induction of centrosome abnormalities.

HELICOBACTER PYLORI-H PYLORI

H.pylori is highly associated with gastric ulcer disease. The pathogenic role of *H.pylori* in chronic active gastritis and its association between *H.pylori* and duodenal ulcer in 95 to 99% of patients is well established [73].Gastric adenocarcinoma is 3 to 12 times more likely to develop in individuals infected with *H.pylori* [74].There are a number of postulated mechanisms whereby *H.pylori* can cause injury to mucosa, urease can result in ammonia production and hemostatic factors and cytotoxins (e.g.,protease,lipases and phospholipase A and vacuolating cytotoxin) can cause injury [75].*H.pylori* more likely associated with the early or initial states of primary gastric lymphoma than advanced tumors.*H.pylori* can disappear during progression of gastric lymphoma [76].Eradication of *H.pylori* is associated with significant reduction in duodenal ulcer recurrence [77],and is also useful in differentiating between *H.pylori* and gastric MALT lymphoma (mucosa-associated lymphoid tissue) [78].In *H.pylori* infected patients who develop gastric cancer, serum IgG against CagA is 94% sensitive and 93% specific, indicating that detection of antibodies to CagA is useful marker for diagnosis of duodenal and gastric cancer [79].

H.pylori causes over 63% of all stomach cancers, which corresponds to more than 5.5% of all cancers in the world [80].As reviewed by Chang and Personnel [81], chronic *H.pylori* infection in the human stomach is characterized by chronic inflammation [81].This accompanied by epithelial cell release of reactive oxygen species (ROS) and reactive nitrogen species (RNOS), followed by the assembly of activated macrophages at stomach site of infection. The macrophages also release ROS and RNOS.Levels of 8-oxo 2-deoxyguanosine (8-OHdG), one of the predominant forms of free radical-induced oxidative DNA damages [82] are increased more than 8-fold in DNA after infection by *H.pylori*, especially if *H.pylori* are cagA positive [83].The increase in 8-0HdG likely increase mutation [19].In addition, oxidative stress, with high levels of 8-0HdG in DNA,also affects genome stability by altering chromatin status. Such alterations can lead to abnormal methylation of promoters of tumor suppressor genes [84].

MISCELLANOUS BACTERIA

Onocogenic bacteria includes:

Borellia burgdorferi(primary cutaneous B-cell lymphoma-PCBCL), [85].,*Chlamydia penumonaie* (Monocytes secretion of IL-IB,IK-8,superoxide oxygen radicals and tumor necrosis factor as mediator of inflammation and can also cause damage to lung tissue and DNA which can result in carcinogenesis) [86],*Mycoplasma*(have the capacity to induce genetic instability and malignant transformation [87],*Salmonella typhi*-1 (patients with chronic typhoid are 167 times more likely to develop cholangiocarcinoma)[88].and *Streptococcus bovis* (commonly associated with colorectal cancer, colorectal tumors,25% to 80%,and patients with colorectal tumors with 18%-62 % colonic neoplasia),[89].

ONCOGENIC PARASITES

The parasites that cause schistosomiasis (biharzia),especially,can cause bladder cancer and cancer at other sites [90].Inflammation triggered by the worm's eggs appears to be the mechanism by which squamous cell carcinoma of the bladder is caused. In Asia,infection by *S.japonicum* is associated with colorectal cancer [90].Distomiasis caused by parasitic liver flukes, is associated with cholingioncarcoma (cancer of bile duct) in East Asia [90].Malaria is associated with Burkitt's lymphoma in Africa, especially when present in combination with *Epstein-Barr virus*, although it is unclear whether it is causative [90].Parasites are also a significant cause of cancer in animals. *Cysticercus fasciolaris*,the larval form of the common tapeworm of the cat. *Tania taeniaformis*,causes cancer in rats[90],*Spirocerca lupi* is associated with esophageal cancer in dogs, at least within the southern United States [90].A novel type of case reported in 2015,involved an immunocompromised man whose tapeworm underwent malignant transformation, causing metastasis of tapeworm cell neoplasia throughout his body. This was not a cancer of his own cells but of parasite's. This isolated case has no substantive bearing on public health but is interesting for being "a novel disease mechanism that links infection and cancer [91].

CONCLUSION

In conclusion**,** number of infectious agents have been identified which either cause or contribute to specific human cancer, they do so by changing the genome of the host cells. Therefore, understanding the molecular interaction of these agents with the host genome is highly important in dealing with the diagnosis and treatment of the disease.

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