

Cancer and Infectious Causes

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Abstract

Various kinds of organisms, including viruses, bacteria, trematodes and fungi are known carcinogens that cause cancer. Infectious identification related to cancer may lead to better treatment for both the prevention and targeting of cancer therapy. Although nearly 20% of all cancers are caused by an infection of a microbe, the amount of evidence and information regarding the mechanisms associated with oncogenesis varies dramatically from one organism to the next. This review cannot be exhaustive because we are not aware of all infections worldwide in addition to their potential mechanisms for oncogenesis. More research is required for all of the species mentioned in this review.

Keywords

Epstein Bar Virus, Hepatitis B Virus, Hepatitis C Virus, Human Herpes Virus 6, Human Herpes Virus 8, Human *Papillomavirus*, Human T-Cell Leukemia Virus Type 1, Merkel Cell *Polyomavirus*, *Chlamydia pneumonia*, *Helicobacter pylori*, *Mycoplasma*, *Salmonella typhi-1*, *Streptococcus bovis*, *Clonorchis sinensis*, *Opisthorchis viverrini*, *Schistosoma haematobium*, *Aspergillus flavus*, *Aspergillus parasiticus*, Cancer, Oncogenesis

1. Introduction

Out of all of the infectious diseases worldwide, there are only a few microorganisms that have a well-defined mechanism associated with oncogenesis. Many of the mechanisms hypothesized involve inflammation as a primary mechanism since inflammation is known to create an environment where there are more reactive oxygenated species in addition to providing an environment where aberrant methylation of oligonucleotides changes gene regulation from an epigenetic standpoint [1]. 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 [2]. Other microorganisms either provide or metabolize toxins related to mutagenesis [3]. Established oncogenes and oncoproteins are primarily limited to viral infections [4] [5]. The oncogenes involved in bacterial carcinogens are unknown since much of the information involved in the study comes from epidemiological evi-

dence and limited molecular biological studies. This means that although there is evidence regarding the microbe's ability to promote oncogenesis, other genes responsible for the promotion of cancer remains unknown.

While treating cancer with chemotherapy and radiation are fundamental, these processes wreak havoc on the immune system. A weak immune system increases the likelihood of developing various forms of cancer. While immune surveillance is a powerful mechanism for detecting and destroying precancerous and cancerous cells, it is important to keep in mind that the immune system also fights pathogens that are known carcinogens.

2. Viruses

Viral infections are more commonly associated with the development of cancer when compared to bacterial, trematode, and fungal infections. Viruses are known to have oncogenic potential by inserting its DNA into the host chromosome in addition to altering the cellular signaling with viral proteins. **Table 1** shows a breakdown of the known mechanisms of oncogenesis, the kinds of cancers associated with the viral infection, and treatments available. Each virus has its own characteristics or mode with regard to promoting oncogenesis.

2.1. Epstein Barr Virus

Epstein Barr Virus (EBV) is a gamma-1 herpes virus that is restricted to primate hosts and usually acts as a latent infection in host B lymphocytes. Although an EBV infection is typically asymptomatic, the virus has the potential inducing oncogenesis to form a wide array of tumors [6] [7]. The most common kinds of cancer caused by EBV include: Hodgkin Lymphoma, Burkitt Lymphoma, diffuse large B cell lymphoma (DLBCL), pyrothorax lymphoma, nasopharyngeal carcinoma, gastric carcinoma, and leiomyosarcoma of the immunocompromised [8]. However, healthy individuals with a typically asymptomatic EBV infection have an immune system that contains the virus via antigen specific memory CD8 T lymphocytes [9].

Oncogenes encoded by EBV include latent membrane protein 1 (LMP1) and LMP2A where LMP1 induces growth promoting signals while mimicking CD40 signaling pathways while LMP2A acts like a B cell receptor that activates AKT, NF-kB, NOTCH, and phosphatidylinositol 3 kinase [10] [11]. EBV nuclear antigen (EBNA) 3A/C silences tumor suppressor as a mechanism associated with oncogenesis [12] [13].

2.2. Hepatitis B Virus

Hepatocellular carcinoma (HCC) accounts for approximately 70% - 85% of all types of liver cancer [14]. Liver

Table 1. The following viruses each have different mechanisms associated with oncogenesis with regard to their respective oncogenes and oncoproteins. Each virus is known to cause various forms of cancer. The known antivirals to treat each virus, if available, are listed below. Many of the known antivirals are taken in various combinations to combat a given virus.

Virus	Genes and Proteins Involved in Cancer	Cancer	Treatment Available for Virus Infection
EBV	LMP1, LMP2A, AKT, NF-kB, NOTCH, and phosphatidylinositol 3 kinase	Hodgkin Lymphoma, Burkitt Lymphoma, Diffuse Large B Cell Lymphoma, Pyrothorax Lymphoma, Nasopharyngeal Carcinoma, Gastric Carcinoma, and Leiomyosarcoma	No specific antiviral treatment
HBV/HCV	TP53, CTNNB1, AXIN, ARID1A, AXIN1, and CDKN2A, and ARID1A	Hepatocellular carcinoma	Pegylated interferon, ribavirin, boceprevir, and telaprevir
HHV-6	ORF-1, p53, U95, NF-kB	Oral Squamous Cell Carcinoma, Hodgkin's Disease, non-Hodgkin's lymphoma, and cervical carcinoma	No specific antiviral treatment; immunotherapy
HHV-8	K1, vIRF, and cIL8R	Karposi's Sarcoma and Primary Effusion Lymphoma	Ganciclovir and Foscarnet
HPV	E5, E6, and E7	Cervical Cancer	Vitamin A and curcumin
HTLV-1	p53	Adult T-Cell Leukemia/Lymphoma	Corticosteroids, Plasmapheresis, Cyclophosphamide, Interferon, Valproic Acid, and Zidovudine
MCPyV	CD3G, CD3D, ZAP70, and IGHM	Merkel Cell Carcinomas	Nonspecific antiviral treatment

cancer is the third leading cause of deaths associated with cancer in addition to being the sixth most common cancer [15]. The likelihood of developing HCC while infected with hepatitis B virus (HBV) is between a 2500% - 3700% increase compared to patients without HBV [16] [17]. Elevated risk of HCC is correlated with a high viral load of HBV [18]. HBV is likely to cause liver cirrhosis and inflammation which is found in 80% - 90% of cases of HCC [18]. The regulation of HBV proliferation in the liver involves both natural killer cells and CD8+ T cells that actively fight the HBV infection [19].

HCC has three molecular mechanisms associated with an infection of HBV [20]. The first is cell proliferation and variability from the expression of viral protein HBX [2]. The second mechanism is related to HBV DNA integration which changes the expression of endogenous genes in addition to destabilizing the chromosome of the host genome [2]. The destabilization of the host chromosome is more common in HBV infections than it is in hepatitis C viral (HCV) infections. The third involves the accumulation of DNA damage caused by inflammation and hepatocyte division [2].

2.3. Hepatitis C Virus

130 - 170 million people world-wide are infected with HCV [21]. HCV infections are associated with some degree of liver fibrosis in addition to 15% - 25% of patients developing cirrhosis after 10 - 40 years of infection [22]. Patients with chronic hepatitis C (CHC), in addition to cirrhosis of the liver, increase the risk of liver failure and the formation of HCC [23]. Chronic infections are correlated to low NK cells titers despite the fact that NK cells usually high in the liver [24]. However, NK cells are activated and kill HCV-infected hepatocytes releasing antigens that prime specific CD8 and CD4 response [25].

Oncogenesis associated with oxidative stress has been examined in several mouse models including mice deficient in copper/zinc superoxide dismutase and mice with erythroid-2-related transcription factor-1 (Nrf1) knockout [26] [27]. Continued exposure to H₂O₂ can increase the activity of methylation of oligos, including the down regulation of catalase by affecting its promoter region [28] [29]. Increased methylation in HCC cells also respectively increases the expression of Snail [28] [30]. This methylation silences the expression of E-cadherin by a mechanism that first involves methylating the E-cadherin promoter via histone deacetylase 1 and DNA (cystosine-5)-methyltransferase 1, which increases expression of Snail [28]. The reduction of E-Cadherin is an early biomarker for both HCC and HCV-related cirrhosis [30].

2.4. HBV and HCV Oncogenes Associated with HCC

HBV and HCV have similar mechanisms with regard to their effect on the host chromosomes. While these oncogenes are common in HBV and HCV infections, the likelihood of developing HCC depends on the insertion of the viral genes in addition to altered bases and changes in the epigenetic profiles of the host chromosome. Common genes effected by aberrant bases in HCC during an HBV and HCV infection include TP53, CTNNB1, and AXIN. Deletions and silencing of CDKN2A in HCC tissue is also common in HBV and HCV infected patients. Mutations in tumor suppressor genes including TP53, ARID1A, AXIN1, and CDKN2A and an oncogene known as ARID1A are common in 10% of HCC tumors [31].

2.5. Human Herpes Virus 6

Human Herpes Virus 6 (HHV-6) is associated with encephalitis in immunocompetent individuals, maternal fetal infections, hematological malignancies, and digestive problems in immunocompromised individuals [32]-[34]. The virus is known to infect oligodendrocytes and astrocytes in samples *in vivo* and *in vitro* in addition to being detected in brain tumors of both adult and children patients via PCR, immunohistochemistry, and *in situ* hybridization [35] [36]. The mechanism for oncogenesis may involve the expression of viral protein ORF-1, which can form a dimer and deactivate p53, and U95, which can bind and deactivate NF-kB [34] [37]. HHV-6 is best known for its ability to infect CD4+ T cells which may increase the immunological effect from HIV in AIDS patients [38]. The ability for HHV-6 to evade the immune system is largely due to its ability to remain dormant though the life cycle in the cell. However, the expression of viral proteins is known to alter the immunomodulation associated with the engagement of CD46 receptors as well as alter the expression of cell surface receptor in T cells [39].

2.6. Human Herpes Virus 8

At the time, presence of Human Herpes Virus 8 (HHV-8) or Kaposi's sarcoma-associated herpes virus (KSHV) was found in virtually all Kaposi's sarcoma (KS) tissue for both immune competent and incompetent patients and appeared to be specific of the virus since it was yet to be found present in nearly any other tissue or diseases [40]-[42]. HHV-8 is also found in primary effusion lymphoma (PEL) and multicentric Castlemann's disease (MCD) [43]. HHV-8 viral proteins contribute to the pathogenesis and can be found in both latent and lytic phases [44]. The ability for HHV-8 to evade the immune systems comprises of many factors which include evasion of NK and T cell response, blockage of apoptotic pathways, interference of interferon signaling, and host chemokine network alterations [45].

KS is a vascular tumor that forms nodular lesions on skin and mucosa before it becomes a more aggressive form of cancer found in multicentric lesions of lymph nodes [46]. The mechanism of oncogenesis remains unclear since much of the potential oncogenes are only present in the lytic phase where the KS samples collected suggest that the HHV8 is still in latent phase [47]. These genes include K1, vIRF, and cIL8R [47]. The mechanism of HHV8 in KS is still not understood and likely involves a multistep process of oncogenesis.

2.7. Human Papillomavirus

The worldwide leading cause of morbidity and mortality for women is cervical cancer [48] [49]. Even though human *Papillomavirus* (HPV) plays a very important part in the etiology of cervical cancer, the virus itself is not completely sufficient for cancer prognosis [50] [51]. With more than 120 HPV types, there are at least 15 HPV types with oncogenic potential when there is a persistent infection [52] [53]. Although NK cells have the capacity of recognizing and killing virus-infected transformed cells by granule-dependent cytotoxicity and apoptotic pathways, the tumor cells associated with HPV infections evade attacks by NK cells [54]. Dendritic cells are not able to promote T-cell immune response during a HPV infection which significantly attenuates the humoral immune response [55] [56]. Many of the biomarkers associated with oncogenesis include various surface proteins of HPV [57] [58]. The most notable oncoproteins, E5, E6, and E7, initiate continuous proliferation without genetic proofreading which causes mutations that can lead to cancer [4] [5]. The regulation of HPV genome post infection likely involves gene regulation from miRNA of the host [59] [60].

2.8. Human T-Cell Leukemia Virus Type 1

Human T-cell Leukemia virus type 1 (HTLV-1) is one of the oldest retroviruses and the first human retrovirus to be discovered [61]. Its discovery followed an epidemiological study of Adult T-cell leukemia/lymphoma (ATLL) where the cancer appeared to have been spreading like a pathogen in Japan [62]. ATLL is an aggressive lymphoproliferative disease that can be contracted from asymptomatic individuals [63] [64]. ATLL oncogenesis involves the HTLV-1 protein Tax to quell apoptosis, initiate a cascade reaction that leads to cellular inflammation, and inhibition of p53 in a cascade associated with DNA repair respectively [65]-[68]. The reason for HTLV-1 persistence in a manner that does not trigger an innate immune response still remains a mystery. The ability to detect HTLV-1 in serum is very difficult since an infection requires the transfer from infected cells [69]. Hypothesis of HTLV-1 spreading by mitosis of infected cells is a likely reason for its ability to evade the immune system [70].

2.9. Merkel Cell Polyomavirus

Merkel cell *Polyomavirus* (MCPyV) can be found in 80% of all Merkel cell carcinomas [71] [72]. A recent study showed a small presence of MCPyV in extrapulmonary small cell carcinomas [73]. The frequency of MCPyV, in the general population, is 80% of people who are over the age of 50 years [74]. The virus is also present in over 85% of homo- and bisexual HIV positive young men [74]. The incidence of developing MCC is very rare for immunocompetent individuals, the tumor is much more likely to occur in AIDS patients and those with chronic lymphocytic leukemia [75] [76]. Complete remission of an MCC tumor is possible for those immunosuppressed individuals who become immunocompetent [77]. MCPyV-positive tumors have up regulated CD3G, CD3D, ZAP70, and IGHM; however, the biological significance in oncogenesis remains unknown [78]. Although there is evidence of a link between ultraviolet (UV) radiation and specific mutations in TP53 and Ha-RAS, the mechanism associated with UV radiation in oncogenesis associated with MCPyV has yet to be determined [79].

3. Bacteria

Bacterial infections also contribute to the promotion of oncogenesis typically through mechanisms associated with inflammation. Although inflammation is a vague explanation of how bacteria promote oncogenesis, the bacteria none the less interfere by altering the environment surrounding tissue in a way that does promote an environment where mutations are more prominent and epigenetic gene regulation goes haywire. **Table 2** also shows the various modes of oncogenesis, kinds of cancer it is likely to cause, and treatments available.

3.1. *Borrelia burgdorferi*

Borrelia burgdorferi (Bb) is a spirochete that causes the zoonotic tick borne infection known as Lyme disease [80]. Erythema chronicum migrans (ECM), lymphocytoma cutis, and acrodermatitis chronica atrophicans (ACA) are a few of the cutaneous disorders associated with Bb infection [81]-[83]. Primary cutaneous B-cell lymphoma (PCBCL), in skin affected by ACA and patients with serology associated with previous exposure to Bb, shows evidence that PCBCL may be caused by Bb [84]-[86]. Bb can also be found in skin lesions of patients with PCBCL [87]-[89]. *Borrelia* induces a strong immunological response but has the ability to stave off the immune system despite dendritic cell (DC) activation and recognition of Bb surface lipoproteins [90]. The DC response is coupled with various effector T-cells.

3.2. *Chlamydia pneumoniae*

Chlamydia pneumoniae is an intracellular parasite, gram negative bacillus, and causes infection in 50% of adults exposed to the pathogen [91] [92]. The bacteria are transmitted through aerosol and respiratory secretions [91] [93]. An infection with *C. pneumoniae* can cause pneumonia, bronchitis, rhinitis, sinusitis, COPD or an asymptomatic infection. *C. pneumoniae* has the ability to evade innate immunity involving type 1 IFN by restricting the phosphorylation and nuclear translocation of IRF3 [94].

Although the mechanism for *C. pneumoniae* to cause lung cancer is unknown, there are a few possible mechanism associated with its oncogenesis. One possible mechanism involves mediators associated with inflammation [95]. Inflammation can cause damage of DNA through reactive oxygenated species. Inflammation can also damage cells including the cells ability to repair itself in addition to increasing the rate of cellular division [96]. *C. pneumoniae* can localize and infect preferentially to the lungs of smokers [97]. Monocytes secretion of IL-1 β , IL-8, superoxide oxygen radicals, and tumor necrosis factor act as mediators of inflammation and can also cause damage to lung tissue and DNA which can result in carcinogenesis [98].

Table 2. Mechanisms of each bacteria is either known to cause cancer with regard to specific oncogenes, the toxins produced or metabolized by the host, or is likely caused by mechanisms associated with inflammation. The loci of the various bacteria is generally proximal to the region associated with the cancer. The various treatment options are often taken in combination to treat bacterial infection in a manner that minimizes the opportunity for the bacteria to become resistant to antibiotics.

Bacteria	Mode of Oncogenesis	Types of Cancers	Treatment Available for Bacterial Infections
<i>Borrelia burgdorferi</i>	Oncogenes Unknown/ Inflammation	Primary Cutaneous B-Cell Lymphoma	Doxycycline, Amoxicillin, Cefuroxime Axetil, Ceftriaxone and Penicillin.
<i>Chlamydia pneumoniae</i>	Oncogenes Unknown/ Inflammation	Lung Cancer	Macrolides, Doxycycline, and Quinolones
<i>Helicobacter pylori</i>	Oncogenes Unknown/ Inflammation	Gastric Carcinoma	Amoxicillin, Clarithromycin, Lansoprazole, Omeprazole, Metronidazole, Bismuth Subsalicylate, Metronidazole, and Tetracycline
<i>Mycoplasma</i>	P53 suppression, NF-kB activation, and inducing genetic instability	Gastric and Colon Carcinoma	Azithromycin, Clarithromycin, and Erythromycin
<i>Salmonella typhi-1</i>	Deconjugation of toxins and bile acid as a byproduct of glucuronidase and bind to DNA causing mutagenesis and inflammation	Cholangiocarcinoma	Ampicillin, Trimethoprim-Sulfamethoxazole, Chloramphenicol Quinolone, Macrolide, and Cephalosporin
<i>Streptococcus bovis</i>	Oncogenes Unknown/Carcinogenic Byproducts and Inflammation	Colorectal Cancer	Penicillin G, Ceftriaxone, and Gentamicin

3.3. *Helicobacter pylori*

Helicobacter pylori chronic infections are associated with peptic ulcerations and atrophic gastritis in addition to being associated with the development of gastric carcinoma, which is the second leading cause of deaths related to cancer in the world [99] [100]. Most *H. pylori* infected individuals are asymptomatic and never develop neoplasms even though *H. pylori* infection is very prevalent in patients with gastric cancer [101]. It is important to note that there are an abundant amount of *H. Pylori* strains and many individuals harbor more than one strain [102]-[104]. *H. Pylori* induces a robust immune response associated with an increase in IL-1, IL-8, and IL-6 concentration [105]. An increase in the number of CD4 and CD8 T-cells of infected individuals as compared to pre-infected individuals is also common [106].

The mechanism for oncogenesis associated with gastric carcinoma is unknown. However, *H. pylori*'s association with chronic inflammation, which leads to aberrant methylation genes including tumor suppressor genes, suggest a potential epigenetic mechanism is involved [107] [108]. Human gastric mucosae have high levels of methylation in the presence of *H. pylori* [109] [110].

3.4. *Mycoplasma*

Mycoplasma is the smallest self-replicating prokaryote and acts as a parasite that infects vertebrates. An infection of *Mycoplasma* can alter the cellular metabolism and physiology of a host and can act as an opportunistic pathogen under rare circumstances [111] [112]. Chronic *Mycoplasma* infections have the capacity to induce genetic instability and malignant transformation [113]-[118]. The metastasis of tumor cells can be influenced by the presence of *Mycoplasma in vivo* in addition to being a factor in increasing the invasiveness of tumors *in vitro* [114] [116] [118]. P53 suppression and NF- κ B activation are influenced by an infection of *Mycoplasma* [119]. Although there are studies that begin to correlate the effect of *Mycoplasma* to various cancers, the results remain in conjecture.

3.5. *Salmonella typhi-1*

The presence of cholangiocarcinoma is common Southeast Asia, Japan, Chile, Bolivia, and northern India [120]-[124]. Cholangiocarcinoma is of greater risk if the patient has gallstones [125] [126]. However, patients that are chronic typhoid are 167 times more likely to develop cholangiocarcinoma [127].

There are several potential mechanisms associated with the development of cholangiocarcinoma from *Salmonella typhi*. The first mechanism is associated with cholangiocarcinoma formation involves the deconjugation of conjugated toxins and bile acid to form carcinogenic biproducts by the enzyme β -glucuronidase of the bacteria [128] [129]. These byproducts of glucuronidase are mutagens that bind to DNA and create the opportunity for oncogenesis [3]. Chronic typhoid carriers that are not treated by antibiotics have an increased concentration of free radicals, which are known to promote oncogenesis [130]. The site of the infection of *S. typhi-1* is known to cause inflammation [131]. It is also important to note that *S. typhi-1* infection has the capacity to survive macrophage phagocytosis [132]. The lifetime of the *S. typhi-1* and its overall effect on macrophages remains unclear.

3.6. *Streptococcus bovis*

Streptococcus bovis is a bacteria that is commonly associated with colorectal cancer. Although there is some discrepancy on the prevalence of *S. bovis* and the rate of colorectal tumors, there is evidence that 25% - 80% of those infected with *S. bovis* have colorectal tumors with 18% - 62% having colonic neoplasia [133]-[139]. The etiology of the development of cancer associated with a bacterial infection usually involves chronic inflammation and the production of carcinogenic metabolites [140]. Many cancers associated with bacterial infections originate at the sight of the infection, causing chronic irritation, and inflammation [141]. Finding the proper metabolite in the microbiome, where there is a lot of competing floras, is very difficult but there remains a potential for the bacteria to create a microclimate that allows mutagens to flourish [140].

4. Trematodes

Trematodes act as microscopic parasites that use the host as a means to feed and reproduce. Often times the host

will excrete the eggs of the trematodes through feces and urine. The majority of trematode infections occur in the Asia-pacific region and are a consumed through either undercooked fresh water fish or contaminated drinking water. **Table 3** describes what is known about the mechanism associated with oncogenesis as well as describes what the kind of cancers the trematodes induce in addition to known treatments.

4.1. *Clonorchis sinensis*

Clonorchis sinensis is a hermaphroditic trematode liver fluke found primarily in Southeast Asia. *C. sinensis* was reported to have infected 7 million people in southern China, Korea, Taiwan, and Vietnam [142]. The liver fluke is commonly transmitted by consuming the muscle and connective tissue of undercooked fresh water fish in the endemic region. The matured worms begin to attach to intrahepatic bile ducts and sometimes even the gall-bladder and pancreatic duct [143]. *C. sinensis* is known to cause biliary tree inflammation, epithelial cell hyperplasia, mucin-producing cells in the mucosa mataplasia, and periductal fibrosis [144]-[148]. The second most prevalent liver cancer is cholangiocarcinoma behind only hepatocellular carcinoma. *C. sinensis* can cause an inflammatory response that induces the likelihood of forming cholangiocarcinoma [149]. Although rats are resistant to *C. sinensis*, the resistance is not from specific immunity and instead involves primarily local inflammation [150].

4.2. *Opisthorchis viverrini*

Opisthorchis viverrini is a food borne trematode that transmits by ingesting the fins, skin, or musculature of raw or undercooked fish. The liver fluke is endemic in Thailand, Vietnam, Cambodia, and Lao [151] [152]. *O. viverrini* is associated with conditions including obstructive jaundice, periductal fibrosis, cholelithiasis, cholangitis, and hepatomegaly [153]. *O. Viverrini* is linked with the etiology of cholangiocarcinoma (CCA), as studied by epidemiological and experimental evidence [152] [154]-[156]. The leading cause of cancer mortality in Southeast Asia is CCA. There are multiple mechanisms for oncogenesis associated with an *O. viverrini* which include mechanical injury of epithelial cells, immunopathology associated with infection related inflammation, and the toxic excretory/secretory (ES) molecules from the parasite [157].

4.3. *Schistosoma haematobium*

Schistosomiasis is the second leading cause of morbidity and mortality of a parasitic disease after malaria [158]. The disease affects 10% of the world's population and is usually picked up by drinking water contaminated with *Schistosoma haematobium* in sub-Saharan Africa [159] [160]. The geographic areas that are endemic to *S. haematobium* have elevated numbers of bladder carcinomas. *S. haematobium* has both the ability to evade host immunity in addition to being able to effect the hormonal microenvironment in a way that suits its reproduction and growth [156].

The potential mechanisms of oncogenesis bladder carcinomas involve either environmental factors or the N-nitroso compounds associated with bladder inflammation [157]-[162]. The environmental factors including pesticides and cigarette smoke have the potential to work synergistically with *S. haematobium* infection by increasing the likelihood of bladder carcinoma [162] [163]. N-nitroso compounds are found in excess in the urine of infected individuals [164]-[167]. These compounds have been hypothesized to have come from endogenous

Table 3. The mechanism for oncogenesis are relatively unknown for trematodes. *Opisthorchisviverrini* excretes toxic cytokines which promote oncogenesis. However, most trematodes presence causes inflammation in the sight where the trematode has attached itself to; generally causing cholangiocarcinoma in that loci. Treatment of trematodes early significantly reduces the opportunity for oncogenesis.

Trematodes	Mode of Oncogenesis	Cancer	Treatment for Trematode Infection
<i>Clonorchis sinensis</i>	Oncogenes Unknown/ Inflammation	Cholangiocarcinoma	Triclabendazole, praziquantel, bithionol, albendazole, levamisole, and mebendazole
<i>Opisthorchis viverrini</i>	Mechanical Injury of Epithelial Cells, Inflammation, and Toxic Excretory/ Secretory Molecules	Cholangiocarcinoma	Praziquantel and Tribendimidine
<i>Schistosoma haematobium</i>	Oncogenes Unknown/Inflammation	Bladder carcinoma	Praziquantel and Biltricide

and exogenous sources. A potential endogenous source might be associated with the inflammatory response of the bladder while an exogenous source might come from the diet of the individual [166] [167].

5. Fungi

Fungi is not typically associated as being carcinogenic, however, *Aspergillus flavus* and *Aspergillus parasiticus* are attributed to the development of hepatocellular carcinoma. The known treatments and mechanisms are mentioned in **Table 4**.

Aspergillus flavus and *Aspergillus parasiticus*

Aspergillus flavus and *Aspergillus parasiticus* are pathogenic fungi that are known to produce carcinogenic and mutagenic Aflatoxins B1 (AFB1) [168] [169]. AFB1 is a hepatocarcinogen that is causally-related to the formation of hepatocellular carcinoma (HCC) [170]. HCC is a common form of cancer that accounts for 9.2% of all cancer formation [171]. HCC is seventh most common cancer in females and the fifth leading cause of cancer in males [172]. Epidemiological studies show a greater prevalence of HCC in regions where the fungus grows best; such as sub-Saharan Africa and Asia-Pacific regions [169]. The prognosis of HCC for the population of these regions is grim with 93% of those with tumors dying 12 months after the first symptoms [171]. These infections are in spite of a robust immune response comprising of both innate and adaptive mechanisms.

Possible mechanisms associated with the formation of HCC with regard to the exposure of AFB1 are thought to involve the 249ser mutation. This mutation is found in approximately between 36.3% and 66% of the patients with a lot of exposure to AFB1 [173]-[178]. *In vitro* research has shown a preferential codon switch associated with the mutagenesis of p53 at the third base of codon 249 [179].

6. Discussion

It is clear that there are many pathogens that have the capability of inducing oncogenesis. It is also clear that more research is necessary to find more infectious causes of cancer, to better understand the mechanism of oncogenesis, and to delineate treatments that target both the cancer and the infectious cause of cancer.

Of the microbes and trematodes listed in this article, there are most likely many more pathogens that could act as a carcinogen. Many of these oncogenic pathogens require extended exposure to the host organism in order to create the conditions necessary for the development of cancer. Being able to prevent the spread of these microbes and trematodes can reduce the likelihood of people who get infected, thus reducing the opportunity for an infection to become cancerous. Treating long term infections from microbes and trematodes could pay dividends since the treatment could have a direct or tertiary opportunity to reduce the risk associated with prolonged exposures of organisms that could induce oncogenesis.

The immune system plays a major role in reducing the opportunity for an infection to cause cancer. HIV/AIDS patients are more likely to acquire Kaposi sarcoma (herpes virus 8), Hodgkin's and non-Hodgkin's lymphoma (EBV), liver cancer (HBV and HCV), and anal and cervical cancer (HPV) [180]. Therefore, a healthy immune system can significantly reduce the risk of acquiring a cancer from viral oncogenic pathogens.

Diseases like malaria can increase the likelihood of developing endemic Burkitt lymphoma by creating an environment of either T-cell suppression and/or a mechanism associated with stimulation of B-cells [181] [182]. The prevalence of developing endemic Burkitt lymphoma could be reduced by taking artemisinin to protect patients against malaria. Suppression of the immune system by a pathogen like *Aspergillus flavus* and *Aspergillus parasiticus* via hepatocarcinogenic AFB1 toxin, reduces the opportunity for a healthy immune system to fight off the infection associated with carcinogenic fungi [183].

Table 4. *Aspergillus flavus* and *Aspergillus parasiticus* both have similar mechanisms with regard to oncogenesis in addition to similar forms of cancer and treatment.

Fungi	Mode of Oncogenesis	Types of Cancers	Treatment for Fungal Infection
<i>Aspergillus flavus</i> and <i>Aspergillus parasiticus</i>	Aflatoxin Production, 249ser Mutation, and Potentially a Mutation in p53	Hepatocellular Carcinoma	Voriconazole and Amphotericin B

Vaccines against HPV are aimed primarily at preventing mechanisms associated with the development of cervical cancer. Modalities for treating the cause of cancer by protecting the patient from an oncogenic virus are a significant step toward preventative measures against certain cancers by vaccines. However, gynecological screening alone might be the best preventative measure from cervical cancer.

On the other hand, treating the cancer with chemotherapy can reduce the body's ability to fight off infections in a way that allows opportunistic infections, associated with the development of cancer, to thrive unregulated. This is particularly true with HBV infections where chemotherapy reduces the body's ability to regulate the spread of HBV [184]. In addition to chemotherapy, immunotherapy might be necessary to help stave off infectious causes of cancer while treating the cancer itself.

Inflammation and oxidative stress need to be more thoroughly investigated with regard to cancer causing infections, particularly with bacterial infections. Although the causation of oncogenesis from an inflammatory response has been deliberated, the effect it has on the molecular biology of organisms is relatively unknown. The oncogenes, genetic damage, epigenetic malfunction, and tumor suppresser genes are understood to be contributing factors to cancer caused by inflammation but the details of how these microorganisms and trematodes remains a mystery. We suggest that a significant amount of research is necessary to elucidate what is really happening in cells with regard to oncogenesis and metastasis.

Screening of infectious diseases that cause cancer should become more readily available to patients, particularly in regions where individuals are more likely to be infected by oncogenic microorganisms or trematodes. Although HPV is commonly screened with regard to cervical cancer, many other carcinogenic microorganisms do not have the same kind of attention. Although many of the viral treatments associated in combatting oncoviruses are not available in addition to being asymptomatic, there should at least be screening to alert the patient that they have an elevated risk of contracting cancer.

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