IJPSR (2021), Volume 12, Issue 11 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 October 2020; received in revised form, 27 June 2021; accepted, 19 July 2021; published 01 November 2021

AN OVERVIEW OF AETIOPATHOGENESIS AND PREVENTION OF INFECTIOUS CANCERS

Mandeep Kaur [1], Rahul Sandhu [2], Priya Datta [3] and Varsha Gupta [* 4]

Viral Diagnostic Laboratory (COVID-19) [1], Punjab Biotechnology Incubator, Phase 8 Mohali - 160071, Punjab, India.
Department of General Surgery [2], Armed Forces Medical College, Pune - 411040, Maharashtra, India.
Department of Parasitology [3], Post Graduate Institute of Medical Science and Research - 160012, Chandigarh, India.
Department of Microbiology [4], Government Medical College Hospital - 160031, Chandigarh, India.

Keywords:

Infection, Cancer, Prevention, Vaccination, Herd Immunity

Correspondence to Author:
Dr. Varsha Gupta

Professor,
Department of Parasitology 3, Post Graduate Institute of Medical Science and Research - 160012, Chandigarh, India.

E-mail: varshagupta_99@yahoo.com

ABSTRACT: Currently, the knowledge on the oncogenic behaviour exhibited by microbial agents is the result of long and laborious studies conducted over the years. It started with the liver fluke infection associated with bile duct carcinoma and bilharziasis with bladder cancer. Following this, multiple pathogens got implicated in carcinogenesis, including bacteria, many viruses, and even fungi. For some of these infections, the cancer-causal association has confirmatory evidence, but the data is limited for others. There is a need to understand the pathogenesis of these infectious cancers and the oncogenic mechanism of newly implicated infectious agents being added to the list of infectious cancer. Cancers arising out of infections are theoretically preventable either by vaccination or early treatment and careful drafting of public health policies can help to reduce the cancer burden. The concept of herd immunity in cancer prevention is new and emerging, but as it has an established role in preventing some infectious diseases, the same advantage can be conferred in the prevention of infectious cancers. Cancer research has a huge potential when it comes to cancer prevention, and the role of vaccination and herd immunity needs to be explored further.

INTRODUCTION: During the end of 19th century, for the very first time the parasitic infections, especially liver flukes and *Schistosoma* infections, were reported to cause cancers. This potential link between liver fluke's infection with liver cancer and chronic bilharziasis with bladder cancer was established by Askanazy and Goebel, respectively [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(11).5662-76

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(11).5662-76

Rous in 1911 was credited with the demonstration of infectious origin of chicken sarcoma, but it took further 50 additional years before evidence for a causal association of infections with human cancers emerged [1, 2].

The causative role of Epstein Barr virus (EBV) infection in Burkitt's lymphoma, hepatitis B virus (HBV) in hepatocellular carcinoma (HCC) and human papillomavirus (HPV) in carcinoma cervix was also studied. Most of these infections have human to a human mode of transmission and spread very easily. Thus, it can be inferred that the cancers associated with such infections are also transmissible and can be labelled as 'Infectious cancers'.

The global burden of infectious cancers was 17.8% and 16.1% of the total cancer burden in the year 2002 and 2008 respectively [3]. The human carcinogens, including biological agents, have been classified under different categories depending upon their oncogenic potential by International Agency for Research on Cancer (IARC), a working group of cancer research **Table 1**. A total of 17 microbes that include 12.1% viruses, 5.6% bacteria, and 0.1% helminths have been placed under different groups [1, 4]. *Helicobacter pylori*, HPV, HBV, and Hepatitis C virus (HCV) contribute maximally to the total cancer burden caused by the infectious agents, thus making the gastric, liver, and cervical cancers as the commonest amongst the list of infectious cancers [3, 5]. The annual prevalence of infectious cancers in underdeveloped nations is about 1.5 million. The reason for such high occurrence could be explained by a high prevalence of infections in this part of the world [1]. Secondly, overcrowding, poor hygiene, reuse of medical devices, drug abuse, and lack of access to medical care are other factors that predispose to one or other infections possessing carcinogenic potential [6].

TABLE 1: GROUP CLASSIFICATION OF HUMAN CARCINOGENS [1]

Agents classified groups	Carcinogenicity	Number of agents included in the group
Group 1	Carcinogenic to humans	120
Group 2A	Probably carcinogenic to humans	81
Group 2B	Possibly carcinogenic to humans	299
Group 3	Not classifiable as to its carcinogenicity to humans	502
Group 4	Probably not carcinogenic to humans	1

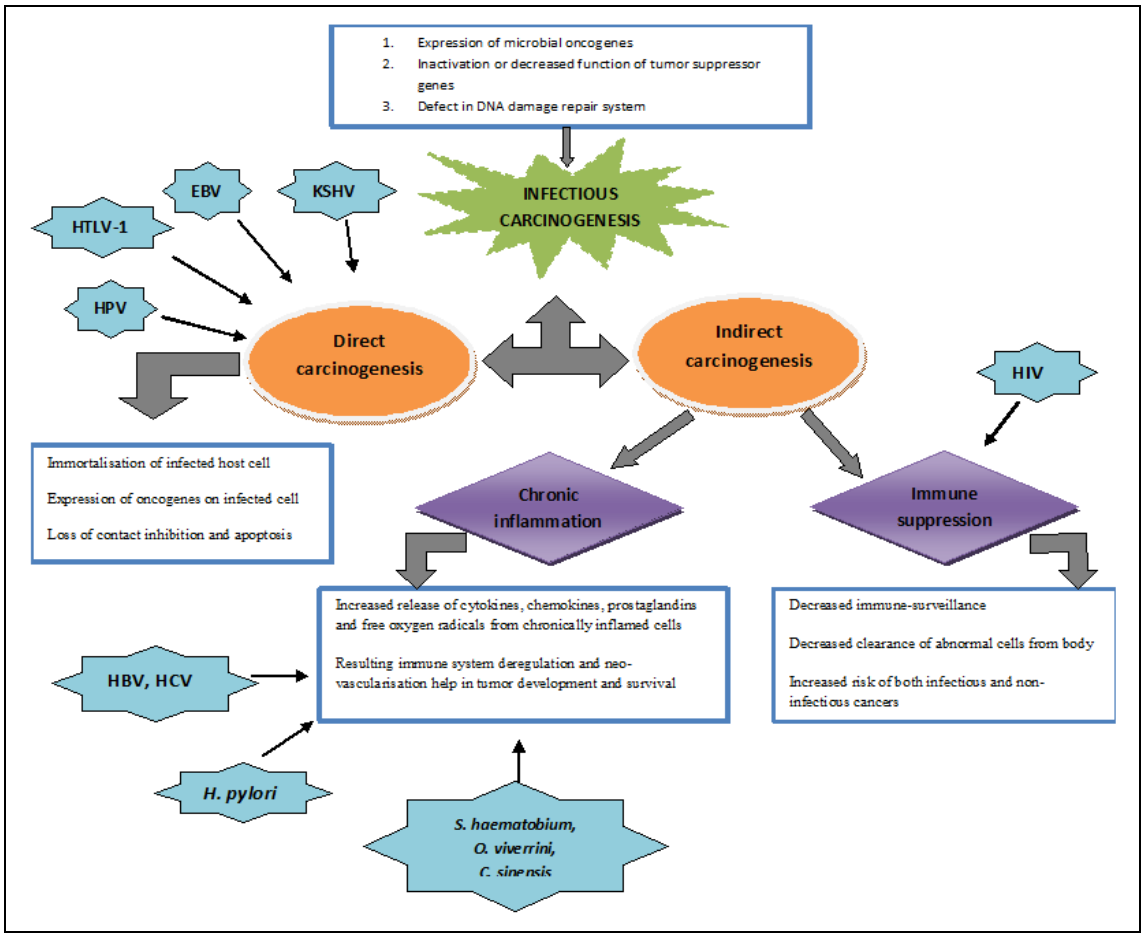

FIG. 1: SHOWS THE MECHANISM OF INFECTIOUS CARCINOGENESIS

Cancer Pathophysiology and Pathogenesis of Infectious Cancers: Cancer is a condition of abnormal and uncontrolled growth of cells accompanied with tissue invasion. Genetic and epigenetic alterations can cause a normal cell to be transformed into abnormal cells (also known AS

cancer cells) with changed gene expression and host signalling pathways [7]. The changes associated with cancer occur at the three non-exclusive levels: (a) physiological level, which is related to a modification in the physiology of cells, tissues, and organs, (b) cellular level, that is, the alterations in the signalling pathways involved in critical cellular processes resulting in increased cancer risk, and (c) molecular level, that includes changes in key cellular structures at the molecular level such as genotoxicity [1]. Neoplastic transformation can occur due to hormones, drugs, infectious agents, chemicals, physical or mechanical trauma, or chronic irritations [8]. A variety of infectious agents show persistence in the host population, which is thought to be the main mechanism involved in the carcinogenic process. Their removal from the host may sometimes reverse the tumor process confirming their carcinogenic role [2]. The three important mechanisms by which an infection can initiate or promote carcinogenesis are depicted in **Fig. 1.**

Infectious Cancer Agents: Mostly viruses, few parasites and one bacterial infection have proven role in cancer occurrence. Fungi have shown no proven cancer association, though such infections commonly occur during the course of cancer. The list of microorganisms showing causal association with cancers is discussed in **Table 2.**

TABLE 2: CLASSIFIED INFECTIOUS AGENTS AND THEIR ASSOCIATED CANCERS [5, 63]

Infectious agents	Cancer site	Route of infection transmission	Mechanisms of carcinogenesis	Prevention (if any)
Viruses				
Epstein Barr Virus	Nasopharyngeal Carcinoma, Burkitt lymphoma, immune-suppressed related non-hodgkin lymphoma, extranodal natural killer/ T cell lymphoma (nasal type), Hodgkin lymphoma	Through saliva (also called as 'Kissing disease')	Direct carcinogenesis	Anti-viral agents
Hepatitis B virus and Hepatitis C virus	Hepatocellular carcinoma	Percutaneous, sexual and mother to child transmission	Indirect carcinogenesis via chronic inflammation	Vaccination, antivirals and screening of donors
Human Herpes Virus 8	Kaposi sarcoma, primary effusion lymphoma	Sexual contact, through saliva	Direct carcinogenesis	No specific treatment
Human Immunodeficiency virus-1	Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, carcinoma of the cervix, anus	Percutaneous, sexual and mother to child transmission	Indirect carcinogenesis via immune suppression	Highly active antiretroviral treatment (HAART)
Human papilloma virus serotypes 16 & other serotypes 18, 31, 35, 39, 45, 51, 52, 56, 58, 59	Carcinoma cervix, vulva, vagina, penis, anus, oral cavity, oropharynx and tonsil.	Sexual contact, through saliva	Direct carcinogenesis	Vaccination and Pap smear screening
Human T- cell lymphotropic virus type-1	Adult T cell leukemia, and lymphoma	Sexual contact, Percutaneous transmission and through milk *via* breastfeeding	Direct carcinogenesis	No specific treatment
Merkel cell polyoma virus	Merkel cell cancer	Through saliva	Both direct and indirect carcinogenesis	No specific treatment
Parasites				
Schistosoma haematobium	Urinary bladder cancer	Contaminated water	Direct role through inflammation-induced DNA damages and Indirect role in immune facilitation	Anti-helminthic drugs
Opisthorcis sinensis & Clonorchis viverrini	Cholangiocarcinoma	Contaminated food	Indirect carcinogenesis via chronic inflammation	Anti-helminthic drugs
Bacteria				
Helicobacter pylori	Non cardia gastric carcinoma, low-grade B-cell MALT gastric lymphomas	Contaminated food and water, poor sanitation and through saliva also.	Indirect carcinogens that act via chronic inflammation	Antibiotic treatment

TABLE 3: MICROORGANISMS WITH POSSIBLE ONCOGENIC POTENTIAL

Infectious agents	Cancer site	Mechanism	References
Parasites			
Trichomonas vaginalis	Carcinoma cervix, prostate cancer	Indirect carcinogenesis by increasing HPV virulence (cervix) and chronic persistent inflammation (prostate)	64-67
Toxoplasma gondii	Primary ocular tumour, meningioma, leukemia, lymphoma, pituitary adenoma	By modifying microRNA in brain cells	68
Taenia solium (Neurocysticercosis)	Glioblastoma multiforme, Cerebral glioma, malignant haematological disease.	By chronic inflammation and release of nitric oxide, decreasing immune surveillance and causing damage to host DNA	69
Schistosoma japonicum and *Schistosoma mansoni*	Colorectal cancer and hepatocellular carcinoma	Direct and indirect carcinogenesis by increasing the risk of acquiring HBV and HCV infection during parenteral treatment for Schistosomiasis	1
Strongyloides stercoralis	T-cell leukemia (with HTLV), Colon adenocarcinoma	Stimulate HTLV-1 replication, Oligoclonal expansion of HTLV-1-infected lymphocytes	70-72
Trypanosoma cruzi (Chagas' disease)	Gastrointestinal cancer, Uterine leiomyoma	Unknown	72
Plasmodium falciparum	Burkitt's lymphoma	Acts as a cofactor and plays synergistic role with EBV in causing Burkitt's Lymphoma in Malaria endemic regions	7,71
Fungi			
Candida species	Oral squamous cell carcinoma	Direct carcinogenesis by causing malignant change in chronic leukoplakia	73
Bacteria			
Salmonella typhi	Gall bladder cancer	Indirect carcinogenesis *via* chronic inflammation in gall bladder carriage	74,75
Streptococcus bovis/S.gallolyticus	Colon cancer	Indirect carcinogenesis via chronic inflammation	76
Chlamydia trachomatis	Cancer cervix	Indirect carcinogenesis *via* chronic inflammation	77,78
Borrelia burgdorferi	Lymphoma marginal zone B cell	Chronic antigen-dependent immunostimulation triggering sustained lymphoid proliferation with oligoclonal and ultimately, monoclonal B-cell selection	79, 80
Fusobacterium fusiforme and *Borrelia vincentii*	Squamous cell carcinoma arising from tropicalphagedenic ulcer	Indirect carcinogenesis via chronic inflammation	71
Campylobacter jejuni and *Vibrio cholerae*	Associations with immunoproliferative small intestinal disease (IPSID), non-Hodgkin's lymphoma	Direct carcinogenesis by causing hypertrophy of lymphoid tissue in the small intestine which later turns malignant.	71,79,81
Viruses			
Simian virus 40	Malignant mesotheliomas, Bone cancer, Brain and spinal cord tumors	Large and small T Ags produced during early replication blocks various tumour suppressor proteins	82
JC virus	Colon cancer	Direct carcinogenesis and indirect via chronic persistence	83,84

Viruses: Globally, approximately 12% of human infectious cancers are viral in origin, and more than 80% of them occur in developing countries. Despite their high prevalence, public health importance, and availability of suitable immunoprophylaxis, still the control, prevention and treatment of such virus-induced cancers face formidable challenges [9].

Hepatitis B and C Virus: Hepatocellular carcinoma (HCC) is the sixth most common cancer globally, causing one-third of cancer-related deaths globally. Chronic viral hepatitis caused by HBV and HCV is the major cause of HCC. An age-adjusted worldwide incidence of HCC is 10.1 per 1 lakh person-years, and hepatitis B, and hepatitis C collectively resulted in 4.9% of worldwide cancers in 2007.In 2018, the death toll of HCC was 810,000 persons, and the attributable fractions of HCC due to HBV and HCV were 33% and 21%, respectively [10, 11].

HBV, a small, partially double-stranded DNA virus, is a major contributor to chronic liver disease. The virus persists in the hepatocyte nuclei and results in immune-mediated hepatic

inflammation and injury. The persistent and chronic hepatic inflammation may induce mutagenic changes by viral integration into the host genome, thereby altering cellular gene expression or certain HBV proteins can directly cause malignant transformation [10].

The HBV prevalence varies among geographical regions, with the highest chronic infection rates reported from sub-Saharan Africa and East Asia. High rates in the Amazon and southern parts of eastern and central Europe and moderately affected regions with 2-5% prevalence are Middle East Indian subcontinent. Western European and North American countries report less than 1% chronic infection in the population [10].

HCV, a single-stranded (ss) RNA virus from family *flaviviridae* is transmitted *via* parenteral routes, intravenous drug abuse or by invasive sexual practices. Rarely mother to child transmission is reported. The estimated global prevalence of HCV infections are around 140 million infections. High mutation rate and prevalence of heterogenous but closely related quasi-species in HCV is due to the high replication rates and the lack of proof-reading capacity of the HCV-encoded polymerase [12].

The viral replication and other pro-oncogenic events occur in the cytoplasm of hepatocytes, but the mechanism by which it damages host cell DNA to initiate oncogenesis is still unknown. The persistent HCV infection leads to chronic inflammation, fibrosis, steatosis, and oxidative DNA damage, thus can promote carcinogenesis. Secondly, HCV proteins like core protein, E1/E2 glycoproteins, p7, NS2, NS3, NS4, and NS5 can have direct oncogenic effects and/or upregulate the mitogenic processes. HCV prevalence is varied and depends on demographic factors, with most affected regions being Central and East Asia and North Africa while approximately 1.6% in the USA, less than 0.5% in Northern Europe, and up to 3% in rural regions of Romania [12].

Major difference between HBV and HCV remains that currently no anti-HCV vaccine is available due to genetic variability exhibited by this RNA virus that acts as a major hurdle in the development of an effective vaccine [13]. Recently, effective antiviral agents have become available for the treatment of HCV infection and thus prevention of cancer. NS3-4A protease inhibitors (directly acting anti-hepatitis C agents) telaprevir, simeprevir, parita-previr and boceprevir, in combination with PEG IFNα (pegylated interferon α) and ribavirin have been approved for treatment of HCV infection and have resulted in elimination of virus from blood especially in infections by HCV-1 genotype.[14,15]

Epstein-Barr Virus: Infectious mononucleosis caused by Epstein-Barr virus, is a worldwide infection and tends to occur more in children aged 3-4 years in developing countries and among adolescent children in developed nations [16]. Oropharynx is the primary site of infection, but the virus is capable of infecting B cells in addition to epithelial cells and frequently exhibits switching between the two sites. EBV has shown a causal relationship with a number of malignancies, namely B and T cell lymphomas, Hodgkin's disease, post-transplant lymphoproliferative disease, leiomyo-sarcomas, nasopharyngeal and gastric carcinomas [17]. The binding of major viral glycoproteins gp350/220 to the CD21 receptor on B cells causes cell transformation and establishes latent infection. During the latency period, EBV latent membrane proteins 1 and 2 affect the cellular gene expression and cell growth through anti-apoptotic mechanisms further contributing to cancer development [17].

Nasopharyngeal carcinoma, is maximally reported from South China, Singapore and Malaysia and also from a certain population group in North Africa, Alaska and Canada [18]. For Burkitt's lymphoma, Papua New Guinea and sub-Saharan Africa are seen as the endemic areas where 95% of its occurrence has been attributed to EBV infection. Burkitt's lymphoma is the most common childhood malignancy in the central part of Africa, where EBV and malaria are considered cofactors in its carcinogenesis. In endemic areas, 95% of children get infected by 3 years of age, compared to the United States, where the infection is usually delayed until adolescence [19].

Standard therapy for EBV-associated carcinomas consists of multi-agent chemotherapy, radiation therapy combined with surgery of the cancers associated with EBV infection, Burkitt's lymphoma, post-transplant lymphoproliferative disease and leiomyosarcomas are frequently seen

among immunodeficient individuals suggesting the role of immunosurveillance in cancer prevention. Hence, the immune-therapy for EBV-associated tumours has been the target of research, and the work centered on adoptive transfer of EBV-specific cytotoxic T-cells has shown success, but the obstacles such as potential graft *vs.* host disease and resistance due to mutation of selected EBV epitopes need to be overcome. Vaccines capable of preventing primary EBV infection or boosting immune responses against EBV-associated tumours are under investigation [20].

Human Herpes Virus 8/ Kaposi Sarcoma Herpes Virus (KSHV): The HHV-8 or KSHV is a lymphotropic virus that has a predilection for epithelial cells such as skin, blood vessels, and organs (commonly lung and gastrointestinal tract) where it undergoes lytic replication and has a tendency to establish latent infections for a lifetime. After its first description in 1872 as a rare hemangiosarcoma-like tumor in elderly men, Kaposi's sarcoma is now regarded as an AIDS-defining condition with HHV-8 as the causative agent in 95% of the cases regardless of the HIV/AIDS status [21].

KS is a type of malignancy characterized by skin lesions that pass through patchy, plaque, and nodular stages, mostly appearing on extremities. In advanced stages, systemic involvement of lung and GIT often leads to fatal outcome.[21]Similar to EBV, HHV-8 infects B cells predominantly, but unlike EBV, lytic cycle is embraced rather than repressed [14]. Viral genes, micro RNAs, and modulation of cellular immunity result in increased cell survival while viral, and host cytokines promote cell proliferation, angiogenesis, and enhances viral spread, thus promote the occurrence of Kaposi sarcoma [5, 20].

Apart from KS, HHV-8 infection has been implicated in primary effusion lymphoma, which is a rare form of B cell non-Hodgkin lymphoma comprise less than 2% of HIV-1 related lymphomas, and Castleman's disease (polyclonal lymphoproliferative disease), which itself is a non-cancerous condition, but on rare occasions can progress to cause plasmablastic lymphoma [1, 3, 5]. In high prevalence areas, HHV-8 infection is acquired during childhood (between 6-10 years), usually from within the family, and sometimes can progress to cause cancer later in life. In USA, Europe, and Australia, KSHV is seen more among HIV-1 positive homosexual men, and this finding was supported by a strong decline observed in KS incidence following the introduction of highly active antiretroviral therapy (HAART) for HIV treatment [22].

The therapeutic options to treat KS, PEL and MCD include surgery, radiation, and chemotherapy depending upon the disease stage. Ganciclovir/ valganciclovir, foscarnet/ cidofovir, and valacyclovir/ famciclovir combinations have been shown to treat HHV-8 associated diseases and may also prevent the formation of KS [21, 22].

Human papillomavirus: Human papillomavirus, a member of papovaviridae family, is a small non-enveloped double stranded (ds) DNA virus and 50-60 nm in diameter [5, 20]. The genome of HPV consists of cDNA encoding sequences for six early (E1, E2, E4, E5, E6, and E7) and two late proteins (L1 and L2). Early proteins E1 and E2 are needed for replication and translation of virus, E2 additionally controls E6 and E7 expression while E4 and E5 help in viral assembly and growth stimulation. The late proteins L1 and L2 form minor and major capsid proteins [23]. The viral genome has three functional regions; first is a noncoding upstream regulatory region (URR), that regulates DNA replication, second is an "early" region, containing genes E1-E8 that are involved in viral replication and oncogenesis, and third is the "late" region, which encodes the viral capsid proteins (L1 and L2 structural proteins). Expression of the early gene products determines whether an HPV infection will be active or latent or will lead to malignant transformation [1, 24].

HPVs are restricted in their host range to humans and primarily infect stratified epithelia at either cutaneous or mucosal sites. Genital HPVs infect primarily the cervix, vagina, vulva, penis, and anus. They are divided into high-risk types [16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 70] which are associated with anogenital cancer and low-risk types [6, 11, 42, 43, 44] that are associated with benign anogenital warts. Among low-risk types, HPV types 6 and 11 are responsible for 90% of all genital warts and can also cause recurrent

respiratory papillomatosis, a disease in which benign tumours can grow leading from the nose and mouth into the lungs [25, 26]. Among the anogenital cancers, cervical cancer has received the most attention, and in 90% of cases, HPV types 16, 18, 31, 45 are implicated. Other conditions associated with high-risk HPV types include carcinoma of the vagina, vulva, penis and anus and their precancerous lesions [27].

Sexually transmitted HPV infection is the most important risk factor for cervical intraepithelial neoplasia (CIN) and invasive cervical cancer. Unlike many other cancers, cervical cancer occurs and strikes early during the reproductive period of a woman's life. Incidence usually rises in 30-34 years of age and peaks at 55-65 years, with a median age of 38 years (21-67 years). Worldwide, the annual incidence of cervical cancer is approximately 510,000 new cases and approximately 288,000 deaths. In US and Europe, half of the cervical cancer cases are associated with HPV-16 [24, 27].

As per the Centers for Disease Control (CDC) estimates, more than 90% of sexually active men and 80% of women will get the infection with at least one type of HPV at any point in their lives [27]. AIDS patients, renal transplant patients receiving immunosuppressive therapy, and individuals with T cell deficiencies have increased rates of HPV persistence, anogenital lesions, and cervical cancer. Hence, the advent of a vaccine against HPV has stirred much excitement but much debate as well [28].

Human T Lymphotropic Virus-1: HTLV-1 (ssRNA), a slow transforming retrovirus, is associated with adult T-cell leukemia. Like other retroviruses, it has adiploid genome with two long terminal repeats (LTRs) and bears*gag*, *pol*, and *env* genes in addition to other accessory genes. HTLV-1 is transmitted through infected blood and blood products, sexual route, and mother to child via breastfeeding [5]. The virus displays a special tropism for CD4 cells, the clonal proliferation of which may lead to adult T cell leukaemia (ATLL). Certain viral proteins like HTLV-1 *Tax* and HBZ proteins may activate viral transcription and modify the infected cell growth and division, eventually leading to cause cancer [29]. Though the virus has a very long latent period of 20 to 30 years, but once the tumour formation sets in, there occurs rapid progression of the disease. Infected children particularly are at higher risk of developing ATLL later in life. Relapses are common even after adequate chemotherapy, and the median survival in affected individuals is just eight months [5, 19]. Approximately 10 million people around the world are infected by HTLV-1, but the disease is manifested only in 2-5% of the infected individuals [29].

The endemic areas for HTLV-1 infection are South-West Japan, the Caribbean countries, and parts of Africa and South America, with about 10% population infected with this virus. ATLL occurs exclusively in endemic areas with a cumulative incidence of 1-5% [5]. An effective preventive strategy for HTLV-1 infection is screening blood donors, and many countries in endemic areas have implemented systematic screening programs for blood donors [30]. New targets in the therapies like peptides, recombinant protein, DNA and viral vectors that can generate neutralizing antibodies against the virus and confer multivalent cytotoxic T cell response against *Tax* gene need to be studied [31].

Parasites: The contribution of parasitic worms in human cancers was initially suspected based on the occurrence of a particular infection and cancer in the same geographical setting [3]. Later on, the causal involvement of parasitic agents in cancers was documented in many studies. IARC (2011) has classified parasitic agents like *S. haematobium*, *C. sinensis* and *O. viverrini* in carcinogen group 1, *S. japonicum* in group 2B, and *S. mansoni* and *O. felineus* were assigned group carcinogen 3 depending upon their carcinogenic potential [1].

Schistosomes: Schistosomes are blood dwelling parasitic flukes that belong to genus *Schistosoma* and family Schistosomatidae. It has six human pathogenic species namely *S. haematobium, S. mansoni, S. japonicum, S. mekongi, S. interacalatum and S. guineesis* that mainly differ from each other with respect to the final location in the host [1].

Schistosomiasis is the second most common human infection after malaria in tropical and subtropical regions. *S. haematobium* and *S. mansoni* together contribute 95% of this infection. *S. haematobium*

infection is endemic in 53 countries of the Middle East and Africa, and in 2003 close to 200 million people got infected with *S. haematobium*, and 85% of them resided in sub-Saharan Africa [1].

Schistosoma haematobium infection is associated with 5 times increased risk of squamous cell cancer (SCC) of the urinary bladder. Soluble egg antigen released from miracidia induces the proliferation, hyperplasia and metaplasia in the organ epithelium. Furthermore, nitrosamine produced from its urinary precursors, urinary stasis, and raised urinary beta-glucuronidase levels are the other risk factors implicated in carcinogenic processes [32]. *S. japonicum* and *S. mansoni* have shown weak cancer association. In one study, *S. japonicum*, which is located in superior mesenteric veins, showed a strong association with rectal cancer, apart from earlier known associations with HCC and colonic cancer [33].

Blood transfusions and parenteral treatment provided for *S. mansoni* infection can indirectly increase the risk of HBV and HCV infections and thus HCC. Moreover, the depressed cell-mediated immune response in active intestinal schistosomiasis can prolong the carrier state of HBV and HCV viruses, further increasing the risk of developing HCC in such patients [3].

Opisthorcis and Clonorchis: *Opisthorchis* and *Clonorchis*, belonging family *Opisthorchidae* are pathologically important food-borne trematodes. The hermaphrodite adult worms of these parasites lay bile-stained operculated ovoid eggs that are indistinguishable between the two species [34]. Both these flukes inhabit the human liver and cause hepatobiliary diseases, including bile duct cancer and sometimes HCC. *Opisthorchis viverrini*, *O. felineus* and *C. sinensis* are the important species implicated in these cancers [1, 3]. *Opisthorchis viverrini*, is a definite human carcinogen and in endemic a rear, it is twice more commonly associated with cholangiocarcinoma than HCC. Otherwise, in a non-endemic region, cholangiocarcinoma is a rare tumour. The mechanism by which these flukes result in cancer includes the hyperplasia of the bile duct epithelium due to chronic irritation. The other carcinogenic factors include endogenous carcinogen production, formation of DNA methylating enzymes *via* p450 enzyme activation. Lastly, the production of cytotoxic nitric oxide from L-arginine can result in DNA damage helping the carcinogenic process [3].

The incidence of *O. viverrini* infection in Northeast Thailand is 2.4 times more common among males than females and remains one of the leading causes of death in this area. This particular species is also prevalent in Northeastern states of India, whereas its counterpart, *O. felineus* is not found in India but is prevalent in the North West Siberian region. Clonorchiasis is a common infection in China, Hong Kong, The Republic of Korea, and Japan. It is also quite prevalent and reported among the immigrants coming to North America from China and Laos. The maximum prevalence for C. sinensis is seen in Busan (previously known as Pusan), a metropolitan city in South Korea, hence the increased risk of cholangio carcinoma in that region [35, 36].

Bacterial Causes of Cancer: Bacteria do not generally show carcinogenic behavior except when factors like chronic inflammation and toxic bacterial metabolites have played a role in cancer occurrence. Till date, only *H. pylori* have shown a proven role in carcinogenesis by its propensity to cause chronic inflammation.

Helicobacter pylori: Worldwide, the fifth most common cancer is gastric cancer, with an estimated 952,000 cases and 723,000 deaths reported in the year 2012 [5]. Approximately 50% of the world's population harbours this organism in their stomach. *Helicobacter pylori*, a gram-negative bacillus, survives the gastric acidity and lives in a neutral pH niche between the mucus layer of the stomach and the gastric epithelium but never shows tissue invasion. Despite its non-invasiveness, *H. pylori* infection is invariably associated with inflammation but once established, the bacterium and associated inflammation are thought to last for decades [37]. This chronic inflammation by producing mutagenic free radicals and N-nitroso compounds induces cell proliferation, thereby resulting in cancerous changes. It is the first bacterial cause of human cancer and has been classed into group 1 human carcinogens by IARC. Chronic superficial gastritis is a precursor lesion of gastric adeno-carcinoma and increases the cancer risk two folds while its progressive form, *i.e.*, chronic atrophic gastritis, increases the risk more to 9 folds. Further

atrophic changes result in in metaplastic trans-formation of gastric epithelium to the intestinal epithelium, and cancer ensues thereafter [38, 39]. The most convincing evidence implicating *H. pylori* as carcinogenic came from four nested case-control studies from Hawaii, California, Great Britain and Taiwan, and it was further observed that the infection usually causes tumours distal to the gastric cardia [40]. While *H. pylorus is* an easily curable infection with a short course of antibiotics, it is tempting to think about creating a vaccine for the prevention of gastric cancer [37]. An oral recombinant *H. pylori* vaccine in phase 3 clinical trial in children in China has documented efficacy and safety and a future option to reduce *H. pylori* infections [41]. The mere persistence of a microbe can disturb the microbial harmony of that body part and is a significant risk factor involved in carcinogenesis. Many studies are being carried out worldwide to determine the oncogenic potential in other unclassified microbes. The number of microbes showing carcinogenic behaviour is increasing, but the cancer-causal association is still not established for most of them to label them as classified human carcinogens. The list of such unclassified microbe cancer associations with a brief mention of the possible carcinogenic mechanism is given in **Table 4**.

Prevention of Infectious Cancers: Cancer prevention is the practice of taking active measures to decrease cancer incidence and mortality and is dependent upon both individual efforts to improve lifestyle and seek preventive screening and socioeconomic or public policy related to cancer prevention. More than 75% of cancer deaths could be prevented by avoiding the risk factors involved, including prevention from cancer-associated infections. Infectious cancers are usually preventable, and their occurrences can be prevented if appropriate existing public health methods for infection prevention like vaccination, safe injection practices, and antimicrobial therapy are applied. The best prevention practice is avoidance of infectious exposure itself. Still, even if it occurs, prompt post-exposure management in the form of preformed antibodies or effective cell-mediated immune cells can confer protection [6].

Role of Vaccination in Cancer Prevention: Long before the immunization era had begun, infectious diseases were the major contributors to morbidity and mortality among the human population. The vaccine discovery, especially against these debilitating and sometimes fatal infections, has significantly brought down the burden of illness, death, and long-term disability in the population. Most of the research effort in the field of prevention of infectious cancer is in the line of harnessing body's immune system for protection against them. Thus today, the focus has shifted more into the cancer-preventive strategies [42]. Chronic inflammation due to persistent infection often plays a role in initiating the carcinogenic process like in HBV infection-causing HCC; HPV infection causing cervical cancer; EBV infection-causing nasopharyngeal cancer; and *H. pylori* infection leading to gastric cancer [1, 43]. The vaccines protect against infection by hampering the microbial process of causing damage to the body cells, but chronic infections can protect against the development of cancer [42]. Till date, effective vaccines are available for only two viral infections (HBV and HPV) that may lead onto cancer. Much research work is underway for the development of vaccines against other oncogenic microbes such as *H. pylori* and EBV.

To curtail the carcinogenesis, therapies to eliminate the microbial agent from the blood are required, which is a difficult task in persistent viral infection, and till date, this mechanism of cancer control has achieved little success [44].

Hepatitis B Vaccine: In areas endemic for HBV infection, liver cancer results from chronic HBV infection in approximately 60-90% of adults and almost 100% children [44]. Hence immunizing susceptible children at an early age becomes an important preventive measure. The first vaccine for HBV came in the early 1980s and was primarily started to target viral hepatitis. Later on, its preventive role in decreasing the occurrence of HCC was proved to be a major milestone in cancer prevention [19].

Hepatitis B surface antigen (HBsAg), also called 'Australia antigen' was first time used in 1971 for testing in blood banks. Later on, a heat-treated HBV vaccine based on HBsAg was developed in 1975. Improving upon this vaccine, in 1980stwo plasma-derived inactivated vaccines (known as

"first-generation vaccines") approved by the US Food and Drug Administration (FDA) came into existence and showed excellent efficacy [44, 45]. They were subunit vaccines containing 22-nm HBsAg particles made of plasma from chronic HBsAg carriers. The preparations underwent vigorous inactivation steps, purified, and aluminium hydroxide was added as an adjuvant. However, the concerns about human safety by using blood products led to its discontinuation after a genetically engineered DNA recombinant vaccine was introduced in 1990. This recombinant vaccine was a yeast-derived HBsAg vaccine ("second-generation vaccines") that also showed excellent results and was much safer than first-generation vaccine. Although the current vaccines are highly effective(94-98% efficacy)and provide 20 years of protection from chronic HBV infection, certain population groups such as elderly, smokers, obese, chronic hepatic or chronic renal diseases patients don't respond well to this vaccine [46]. Finally, the third generation vaccine was developed by recombinant DNA technology in mammalian cells using three components of the virus, *i.e.*, HBsAg, pre-S1 and pre-S2 HBV proteins, and improved adjuvants more immunogenic [45].

Currently, two different formulations of yeast-derived vaccines are in use worldwide. The vaccine should be kept at 2-8°C and never be frozen. It is heat stable and can be stored for one month at ambient temperature even in tropical areas, which increases the vaccine coverage to far-off areas where a refrigeration facility is not available [13].

The first dose of vaccine is recommended to be administered at birth, followed by three booster doses at 4 weeks intervals. The current dosing schedule has been observed to confer protection from chronic HBV-related hepatitis and HCC later in life [20]. This is the kind of the first vaccine that is given during infancy and eliminates the disease in adults [46]. Children born to mothers who are HBsAg positive should receive HBIG in addition to full HBV vaccination in order to protect them from the risk of chronic infection in case they have acquired infection from the mother [47]. Current HBV vaccination programme has certain limitations like multiple parenteral doses, high non-responder rate (10%), infection by escape mutants, and high cost of vaccination [19].

Newer pentavalent and hexavalent combination vaccines have addressed the issue of multiple doses and also have helped in increasing the vaccine coverage [13]. Oral vaccines for HBV would be the best option that may obviate the need for the trained personnel required for parenteral administration of vaccines [19].

Human Papillomavirus Vaccine: Cervical cancer is the second most common cancer occurring in women worldwide. It is also one of the most common causes of cancer death in developing countries. Infection by high-risk types of HPV (16 and 18) contributes to more than 70% of all cervical cancer cases. Certain non-oncogenic HPV serotypes (6 and 11) are responsible for the occurrence of benign genital diseases such as genital warts in 85% of cases. Routine screening procedures being followed in developing countries like India are not of much use as the estimates suggest that more than 80% of sexually active women usually acquire genital HPV by 50 years of age. Cervical cancer strikes early in life; hence the preventive strategies should also start at an early age, long before the first sexual exposure [48]. The excellent antibody response and high levels among young children suggest that the best time to initiate the vaccine series is before the exposure to HPV infection. Moreover, the fact that HPV infection is acquired up to 6 times more likely at a younger age (<15 years) than the infection acquisition at an older age (>18 years) and post-infection to have a cancerous conclusion takes another 20 years, which makes vaccination of young children a high priority [43, 44].

The vaccines for HPV are manufactured by recombinant DNA technology producing non-infectious virus-like particles (VLPs) comprising mainly HPV L1 protein. Three FDA-approved HPV vaccines, namely Gardasil, Gardasil 9, and Cervarix, are used in routine practice [48]. All three vaccines provide protection against HPV types 16 and 18, which are responsible for 70% of cases of cervical cancers, while Gardasil and Gardasil 9 provide additional protection against HPV types 6 and 11 infections. The vaccines don't confer any protection against the HPV serotypes acquired before vaccination [43, 44]. Cervarix provides protection against cervical cancer only. It contains L1 proteins of HPV serotypes 16 and 18 and

aluminium sulphate as an adjuvant. It has shown 90% efficacy in clinical trials with three doses given at 0, 1, and 6 months and is protective against type 16/18-related CIN-2/3 and AIS [43, 48].

Gardasil contains L1 proteins from HPV 16, 18, 6, and 11 serotypes and in clinical trials reported from five continents, including Asia, has shown 100% efficacy against types 16/18-related CIN-2/3 and AIS. The three-dose regimen (0, 2, 6 months) in women aged 16-26 years protects from almost 100% vaginal, cervical, and vulval cancers and genital warts [43, 48].

Gardasil 9 (HPV serotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58), the newest vaccine, has shown 97% efficacy in providing protection against all HPV-associated cancers (except oropharyngeal cancer). It is approved to be used in people aged between 9-26 years [44, 48].

Till date, none of the vaccines are currently approved to prevent oropharyngeal cancers, but it would not be surprising if future data prove that these cancers would also be prevented with current vaccination.

The vaccination schedule of HPV vaccines for special risk groups is as under: [48, 49]

a) In children and age group 9-14 years, 2 dose schedule is recommended at a gap of 6 months.

b) In immunocompromised persons and age group 15-26 years, 3 dose schedule (0, 4-8 weeks, and 6 months later) is recommended.

The dosage schedule differs with different types of vaccines like for Gardasil™ three doses are recommended at 0, 2, and 6 months or at 0, 1, and 6 months while for Cervarix™ (minimum interval of 4 weeks between the first and the second dose, 12 weeks between the second and third dose and 24 weeks between the first and third dose) is recommended. HPV vaccines don't interfere with other vaccines; hence can be given simultaneously with other vaccines such as Hepatitis B and Tdap [43]. But certain barriers like the high cost of the vaccine, safety concerns, misperceptions that vaccine is required only in sexually active females but not in children, and the risk of promiscuity are the reasons for low HPV immunization rates.

The strategies like a reminder/recall systems; focused interventions targeting staff, clinicians, parents, assessment and feedback activities; and school-based HPV vaccination programs can help in increasing HPV vaccine coverage [46].

HPV Vaccination in Males: The burden of HPV associated cancers in men is comparable to that among women in developed parts of the world such as those in Western Europe, but unlike women, there is no screening for anal cancer and oropharyngeal squamous cell carcinoma, the malignancies which are increasing in incidence particularly in men. Moreover, there is a difference in the level of humoral immune response against infection among the two genders.

While the majority of women ≥70% seroconvert after detectable cervical HPV infection with antibody to the major coat protein L1, in the case of men only ≥20–30% do so. Despite the poor antibody response in natural infection, 100% seroconversion has been observed in men post-vaccination. It is clear from all these facts that men will definitely benefit from HPV vaccination, still, only a few nations have included the recommendations for boys and men in their HPV immunization program [50]. Australia is the first country to approve the quadrivalent HPV vaccine use in men between age group 9 and 15 years, and in other developed nations, male vaccination is given between age group 9-26 years [35]. The protective efficacy of the quadrivalent vaccine in two studies against anal precancerous state and genital warts was observed as 75% and 90%, respectively [44, 51]. But to draw a proven conclusion about the vaccine efficacy in the male population, the results of the ongoing studies should be analyzed before introducing this vaccine for routine use in males, especially in developing nations [44].

Role of Herd Immunity in Cancer Prevention: Herd immunity is the prevailing level of immunity in the population acquired by either vaccination or natural infection that helps in reducing the risk of infection spread among susceptible individuals. The term 'herd immunity' was defined and used for the first time in year 1923. During 1930s, the role of herd immunity in disease prevention was realized when a temporary decrease in the incidence of measles cases occurred following

measles vaccination to a significant number of children in that area. Mass vaccination campaigns for disease prevention became very common and had achieved their goals of decreased infection transmission for many diseases [52-54]. The indirect benefits of vaccination to unvaccinated susceptible populations conferred by existing herd immunity and its importance were recognized in 1980 when this natural protection helped achieve the global eradication of smallpox [55]. Herd immunity acts in two ways for disease prevention; firstly, by breaking the chain of infection and secondly by reducing the source and total susceptible population [56].

Herd Immunity in High-Risk Groups: Following infection or post-vaccination, the development of immunity in an individual is based on host, type of agent, and environmental factors. Immunodeficient individuals like people suffering from HIV/AIDS, haematological cancers, dysfunctional spleen, and those receiving chemotherapy and radiotherapy get the maximum benefit of herd immunity [57-60].

A newborn whose immune system is not competent enough to fight against disease too is benefitted from prevailing herd immunity in the population [59]. Hence, among immune-deficient individuals rather than active vaccination, herd immunity plays an important role in the prevention against infectious diseases as they are unable to generate long-lasting immunity because of ineffective immune response to vaccine components [53].

Role in Infectious Cancers: Herd immunity doesn't confer protection for all infectious diseases. The infections that are easily transmissible from one person to another will be able to derive the benefit of herd immunity, *e.g.,* contact and droplet infections. In sexually transmitted infections, the high level of immunity in one gender can result in induction of immunity in the sexual partners due to herd effect.

Hence, herd immunity plays an important role in the control of STIs. Theoretically, vaccinating all sexually active females can ultimately confer protection to the opposite sex against a particular infection, but this doesn't hold true for homosexual men. Therefore, the vaccination of men also becomes necessary, especially when an effective herd immunity has to be established in a high-risk population [61]. The role of herd immunity in an infectious cancer is possible only when the spread of underlying infection leading to cancer can be prevented. Only two infectious cancers till date are preventable by vaccine *i.e.* HCC by HBV vaccine and carcinoma cervix by the HPV vaccine. Though the effect of herd immunity has not been observed with hepatitis B vaccination, where individual vaccination provides only individual immunity, for HPV, the herd immunity can play an important role in prevention from disease and later on from its carcinogenic effect.

A meta-analytical study supported the fact that a significant reduction [OR of 0.14 (95%CI 0.09–0.21)] in the frequency of high-grade cervical lesion was observed among women post-vaccination [62]. Although no indirect benefits of vaccination and herd effect were seen in the HPV vaccine field trials done in developed nations, in endemic regions, this highly effective vaccine can provide benefit to the susceptible unvaccinated and uninfected population against cervical cancers via herd immunity [55].

CONCLUSION: Cancer development is the result of a series of genetic modifications induced by a wide variety of external factors, including infections. This list of infections associated with cancers is on the rise, but the convincing evidence for most of the associations is still missing and calls for more research.

Such infectious cancers are easily preventable if the infections are treated in time. Few of them are vaccine-preventable, and the vaccines warrant the protection against infections and indirectly against their carcinogenic complications.

The concept of herd immunity is emerging as far as cancer prevention is concerned and encouraging, too, for its role in decreasing the cancer burden. But the possible mechanisms involved in conferring cancer protection is a topic of continuing research.

DISCLOSURE STATEMENT: This is submitted that none of the authors has any conflict of interest.

FUNDING: This research received no specific grant from any funding agency in public, commercial or not-for-profit sectors.

REFERENCES:

1. Khurana S, Dubey ML and Malla N: Association of parasitic infections and cancers. Ind J Med Microbiol 2005; 23(2): 74-9.
2. Mueller NE: Cancers caused by infections: unequal burdens. Cancer Epidemiol Biomarkers Prev 2003; 12: 237s.
3. International Agency for Research on Cancer. Monographs on the evaluation of carcinogenic risks to humans. A review of human carcinogens- Part 100 B: Biological Agents. Lyon, France: International Agency for Research on Cancer 2011.
4. Parkin DM: The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006; 118(12): 3030-44.
5. Oho JK and Weiderpass E: Infection and cancer: global distribution and burden of diseases. Ann Glob Health 2014; 80: 384-92.
6. Stransky N, Vallot C, Reyal F, Bernard-Pierrot I, de Medina SG and Segraves R: Regional copy number-independent deregulation of transcription in cancer. Nat Genet 2006; 38(12): 1386-96.
7. Benamrouz S, Conseil V, Creusy C, Calderon E, Dei-cas E and Certad G: Parasites and malignancies, a review, with emphasis on digestive cancer induced by *Cryptosporidium parvum* (alveolata: apicomplexa). Parasite 2012;19:101-15.
8. Mesri EA, Feitelson MA and Munger K: Human viral oncogenesis: a cancer hallmarks analysis. Cell Host Microbe 2014; 15: 266-82.
9. De Flora S and La Maestra S: Epidemiology of cancers of infectious origin and preventive strategies. J Prev Med Hyg 2015; 56: E15-E20.
10. Ringehan M, McKeating JA and Protzer U: Viral hepatitis and liver cancer. Phil Trans R Soc B 2017; 372: 20160274.
11. Forner A, Reig M and Bruix J: Hepatocellular carcinoma. Lancet 2018; 391: 1301-14.
12. Alqahtani SA and Colombo M: Viral hepatitis as a risk factor for the development of hepatocellular carcinoma. Hepatoma Res 2020; 6: 58.
13. Stoll-Keller F, Barth H, Fafi-Kremer S, Zeisel MB, Baumert TF: Development of hepatitis C virus vaccines: challenges and progress. Expert Rev Vaccines 2009; 8(3): 333-45.
14. Liaw YF and Chu CM: Hepatitis B virus infection. Lancet 2009; 373: 582e92.
15. Pawlotsky JM: Treatment of chronic hepatitis C: current and future. Curr Top Microbiol Immunol 2013; 369: 321e42.
16. Ferressini Gerpea NM, Vistaropa AG, Moyanoa A, De Matteob E, Preciadoa MV and Chabay PA: Distinctive EBV infection characteristics in children from a developing country. Int J Infect Dis 2020; 93: 139-45.
17. Farrell PJ: Epstein–Barr Virus and Cancer. Annu Rev Pathol 2019; 14(1): 29-53.
18. Tsao SW, Tsang CM and Lo KW: Epstein –Barr virus infection and nasopharyngeal carcinoma. Phil Trans R Soc B 2017; 372: 20160270.
19. Donati D, Espmark E, Kironde F, Mbidde EK, Kamya M, Lundkvist A, Bejarano MT and Falk KI: Clearance of circulating Epstein-Barr virus DNA in children with acute malaria after antimalaria treatment. J Infect Dis 2006; 193(7): 971-7.
20. Liao JB: Viruses and human cancer. Yale J Biol Med 2006; 79: 115-22.
21. Rewane A and Tadi P: Herpes Virus Type 8. [Updated 2021 Jan 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556023/.
22. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H and Robinson CA: Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. Roche Ganciclovir Study Group. N Engl J Med 1990; 340(14): 1063-70.
23. Bansal A, Singh MP, Rai B. Human papillomavirus-associated cancers: A growing global problem. Int J Appl Basic Med Res 2016;6(2):84-9.
24. Gómez DT and Santos JL: Human papillovirus infection and cervical cancer: pathogenesis and epidemiology. In: Méndez-Vilas A, editor. Communicating Current Research and Educational Topics and Trends in Applied Microbiology. Formatex Research Center, Spain 2007; 2007: 680-8.
25. Lowy DR and Schiller JT: Reducing HPV-associated cancer globally. Cancer Prev Res (Phila) 2012; 5(1): 18-23.
26. Centers for Disease Control and Prevention. Human papilloma virus-associated cancers-United States, 2004-2008. Morb Mortal Wkly Rep2012; 61(15): 258-61.
27. https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-vaccine-fact-sheet.
28. Kaarthigeyan K: Cervical cancer in India and HPV vaccination. Indian J Med Paediatr Oncol 2012; 33(1): 7-12.
29. Zhang LL, Wei JY, Wang L, Huang SL and Chen JL: Human T-cell lymphotropic virus type 1 and its oncogenesis. Acta Pharmacol Sin 2017; 38(8): 1093-103.
30. Proietti FA, Carneiro-Proietti AB, Catalan-Soares BC and Murphy EL: Global epidemiology of HTLV-1 infection and associated diseases. Oncogene 2005; 24: 6058e68.
31. Lynch MP and Kaumaya PT: Advances in HTLV- 1 peptide vaccines and therapeutics. Curr Protein Pept Sci 2006; 7(2): 137-45.
32. Jain S, Sengupta M and Jain P: Non-Viral parasites associated with carcinogenesis. Cancer Invest 2019; 37(9): 453-62.
33. Cheng MG, Mott Cheng MG and Mott KE: Progress in assessment of morbidity due to *Schistosoma japonicum*- A review of recent literature. In assessment of morbidity due to schistosomiasis. Trop Dis Bull 1988; 85: R1-R45.
34. Kaewkes S, Elkins DB, Sithithawom P and Haswell-Elkins MR: Comparative studies on the morphology of the eggs of Opisthorcis viverrini& lecithodendrid trematodes. Southeast Asian J Trop Med Public Health 1991; 22: 623-30.
35. Haswell-Elkins MR and Elkins DB: Food-Borne Trematodes. In: Gordon Cook, editor. Manon's Tropical Diseases. London: WB Saunders; 1996; 1458-61.
36. Srivatnakul P, Sontipong S, Chotiwan P and Parkin DM: Liver cancer in Thialand: Temporal and geographical variations. J Gatroenterol Hepatol 1988; 3: 413-20.
37. Parsonnet J: Bacterial infection as a cause of cancer. Environ Health Perspect 1995; 103(Suppl 8): 263-8.
38. Correa P, Cuello C, Duque E, Burbano LC, Garcia FT and Bolanos O: Gastric cancer in Colombia. III: Natural history of precursor lesions. J Natl Cancer Inst 1976; 57: 1027-35.
39. Ihamaki T, Kekki M, Sipponen P and Siurala M: The sequelae and course of chronic gastritis during a 30- to 34-bioptic follow-up study. Scand J Gastroenterol 1985; 20: 485-91.

40. Forman D, Newell DG, Fullerton F, Yarnell JW, Stacey AR and Wald N: Association between infection with Helicobacter pylori and risk of gastric cancer: Evidence from a prospective investigation. Br Med J 1991; 302: 1302-5.
41. Parikh NS and Ahlawat R: Helicobacter Pylori. 2020 Aug 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 30480966.
42. https://www.historyofvaccines.org/content/articles/cancer-vaccines-and-immunotherapy.
43. Read SA and Douglas MW: Virus induced inflammation and cancer development. Cance Lett 2014; 345(2): 174-81.
44. Clements D: Vaccination to prevent cancer. N C Med J 2016; 77(5): 337-40.
45. Ho JK, Jeevan-Raj B and Netter HJ: Hepatitis B Virus (HBV) Subviral Particles as Protective Vaccines and Vaccine Platforms. Viruses 2020; 12(2): 126.
46. Chen DS: Hepatitis B vaccination: the key towards elimination and eradication of hepatitis B. J Hepatol 2009; 50: 805-16.
47. Chen DS, Hsu NHM, Sung JL, Hsu TC, Hsu ST and Kuo YT: The Hepatitis Steering Committee, The Hepatitis Control Committee: a mass vaccination program in Taiwan against hepatitis B virus infection in infants of hepatitis B surface antigen carrier-mothers. JAMA 1987; 257: 2597-603.
48. Athanasiou A, Bowden S, Paraskevaidi M, Fotopoulou C, Martin-Hirsch P and Paraskevaidis E: HPV vaccination and cancer prevention. Best Pract Res Clin Obstet Gynaecol 2020; 65: 109-24.
49. Ward EM, Flowers CR, Gansler T, Omer SB and Bednarczyk RA: The importance of immunization in cancer prevention, treatment, and survivorship. CA Cancer J Clin 2017; 67: 398-410.
50. Stanley M: HPV vaccination in boys and men. Hum Vaccin & Immunother 2014; 10(7): 2109-11.
51. Giuliano A, Palefsky J, Goldstone S, Moreira E Jr, Penny M and Aranda C: Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med 2011; 364: 401-11.
52. Garnett GP: Role of herd immunity in determining the effect of vaccines against sexually transmitted disease. J Infect Dis 2005; 191(Suppl.1): S97-S106.
53. Fine P, Eames K and Heymann DL: "Herd immunity": a rough guide. Clin Infect Dis 2011; 52(7): 911-6.
54. Hinman AR, Orenstein WA and Papania MJ. "Evolution of measles elimination strategies in the United States". J Infect Dis 2004; 189(Suppl 1): S17-S22.
55. Kim TH, Johnstone J and Loeb M: Vaccine herd effect. Scand J Infect Dis 2011; 43: 683-9.
56. Merrill RM: Introduction to Epidemiology. Burlington, Massachusetts, USA: Jones & Bartlett Publis 2003; 68-71.
57. "Herd Immunity" (http://www.ovg.ox.ac.uk/herd-immunity). Oxford vaccine group.
58. Cesaro S, Giacchino M, Fioredda F, Barone A, Battisti L and Bezzio S: "Guidelines on vaccinations in paediatric haematology and oncology patients". Biomed Res Int 2014: 707691.
59. National Center for Immunization and Respiratory Diseases (2011). "General recommendations on immunization - recommendations of the Advisory Committee on Immunization Practices (ACIP)". MMWR. Recommendations and reports: Morbidity and mortality weekly report. Recommendations and reports/ Centers for Disease Control 2011; 60(2): 1-64.
60. Wolfe RM: "Update on adult immunizations". J Am Board Fam Med 2012; 25(4): 496-510.
61. http://www.cancerresearchuk.org/about-cancer/cancer in general/treatment/biological-therapy/types/cancer-vaccines.
62. Rambout L, Hopkins L, Hutton B and Fergusson D: Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. Can Med Assoc J 2007; 177: 469-79.
63. Jacqueline C, Tasiemski A, Sorci G, Ujvari B, Maachi F and Missé D: Infections and cancer: the "fifty shades of immunity" hypothesis. BMC Cancer 2017; 17(1): 257.
64. Shui IM, Kolb S, Hanson C, Sutcliffe S, Rider JR and Stanford JL: *Trichomonas vaginalis* infection and risk of advanced prostate cancer. Prostate 2016; 76(7): 620-3.
65. Rodriguez-Cerdeira C, Sanchez-Blanco E and Alba A: Evaluation of Association between vaginal infections and high-risk Human Papillomavirus Types in Female Sex Workers in Spain. ISRN Obstetrics and Gynecology 2012; 2012: 240190.
66. Marous M, Huang WY, Rabkin CS, Hayes RB, Alderete JF and Rosner B: Trichomonas vaginalis infection and risk of prostate cancer: associations by disease aggressiveness and race/ethnicity in the PLCO Trial. Cancer Causes Control 2017; 28(8): 889-98.
67. Zhang ZF, Graham S, Yu SZ, Marshall J, Zielezny M and Chen YX: *Trichomonas vaginalis* and cervical cancer- A prospective study in China. Ann Epidemiol 1995; 5(4): 325-32.
68. Thirugnanam S, Rout N and Gnanasekar M: Possible role of *Toxoplasma gondii* in brain cancer through modulation of host microRNAs. Infect Agent Cancer 2013; 8(1): 8.
69. Herrera LA, Ramirez T, Rodríguez U, Corona T, Sotelo J and Lorenzo M: Possible association between Taenia solium cysticercosis and cancer: increased frequency of DNA damage in peripheral lymphocytes from neurocysticercosis patients. Trans R Soc Trop Med Hyg 2000; 94(1): 61-5.
70. Catalano C, Aron J, Bansal R and Leytin A: Colorectal Cancer Associated with *Strongyloides stercoralis* Colitis.ACG Case Rep J 2017; 4: e104.
71. Persing DH and Prendergast FG: Infection, cancer, and the immune response. In: Knobler SL, O'connor S, Lemon SM, Editors forum on microbial threats, Board on global health, eds. The infectious etiology of chronic diseases defining the relationship, enhancing the research, and mitigating the effects. Workshop Summary. Washington DC: The National Academic Press 2004; 154-73.
72. Tong HV, Brindley PJ, Meyer CG and Velavan TP: Parasite Infection, Carcinogenesis and Human Malignancy. EBioMedicine 2017; 15: 12-23.
73. Bakri MM, Hussaini HM, Holmes AR, Cannon RD and Rich AM: Revisiting the association between candidal infection and carcinoma, particularly oral squamous cell carcinoma. J Oral Microbiol 2010; 2: 5780-5.
74. Gonzalez-Escobedo G and Gunna JS: Gallbladder Epithelium as a Niche for Chronic Salmonella carriage. Infect Immun 2013; 81(8): 2920-30.
75. Koshiol J, Wozniak A, Cook P, Adaniel C, Acevedo J and Azócar L: *Salmonella enterica serovar Typhi* and gallbladder cancer: A case–control study and meta-analysis. Cancer Med 2016; 5(11): 3310-25.
76. Abdulamir AS, Hafidh RR and Bakar FA: The association of Streptococcusbovis/gallolyticus with colorectal tumors: the nature and the underlying mechanisms of its etiological role. J Exp Clin Cancer Res 2011; 30: 11.
77. Antilla T, Saikku P, Koskela P, Bloigu A, Dillner J and Ikaheimo I: Serotypes of *Chlamydia trachomatis* and risk

for development of cervical squamous cell carcinoma. JAMA 2001; 285(1): 47-51.
78. Paavonen J: Chlamydia trachomatis and cancer. Sex Transm Infect 2001; 7(3): 154-6.
79. Mazza JJ: Infectious disease and cancer. Wis Med J 2010; 109(2): 66-9.
80. Schöllkopf C, Melbye M, Munksgaard L, Smedby KE, Rostgaard K and Glimelius B: Borrelia infection and risk of non-Hodgkin lymphoma. Blood 2008; 111(12): 5524-9.
81. Baginsky LA, Diss TC, Ye H, Wren B, Du MQ and Isaacson PG: *Campylobacter jejuni* infection in intestinal lymphoma: A strong association with immunoproliferative small intestinal disease. Blood 2004; 104(11): 1369.
82. Vilchez1 RA and Butel JS: Emergent human pathogen Simian virus 40 and its role in cancer. Clin Microbiol Rev 2004; 17(3): 495-508.
83. Rollison DE: JC virus infection- a cause of colorectal cancer? J Clin Gastroenterol 2010;44(7):466-8.
84. Enam S, Valle LD, Lara C, Gan DD, Ortiz-Hidalgo C and Palazzo JP: Association of Human Polyomavirus JCV with colon cancer: Evidence for interaction of viral T-Antigen and β-Catenin. Cancer Res 2002; 62: 7093-101.

How to cite this article:
Kaur M, Sandhu R, Datta P and Gupta V: An overview of aetiopathogenesis and prevention of infectious cancers. Int J Pharm Sci & Res 2021; 12(11): 5662-76. doi: 10.13040/IJPSR.0975-8232.12(11).5662-76.