SOUDMJ 2025 ; 1(1) :12-24
SUE ORAL & DENTAL MEDICINE JOURNAL

ONCOGENIC VIRUSES AND CANCER: A REVIEW OF LITERATURE ON THEIR GLOBAL BURDEN

BASANT H. ABOU ZAID
Associate Professor of Oral Pathology Oral and Maxillofacial Pathology Department, Faculty of Dentistry, Alsalam University, Tanta, Egypt.

ABSTRACT:
Oncogenic viruses represent a subset of viral pathogens capable of inducing cellular transformation and malignancy, significantly contribute to the global burden of human cancer. These viruses promote carcinogenesis through various mechanisms, including integration of viral DNA into the host genome, disruption of cellular signaling pathways, and evasion of immune surveillance, leading to uncontrolled cellular proliferation. Notable oncogenic viruses include Human Papilloma Virus (HPV), Epstein-Barr Virus (EBV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV). Prevention strategies primarily revolve around vaccination, with HPV and HBV vaccines demonstrating significant efficacy in reducing the incidence of cervical and liver cancers, respectively. In addition to prevention, effective treatment strategies for virus-associated cancers are essential. Therapeutic approaches include antiviral agents, immunomodulatory drugs, and targeted therapies that disrupt viral replication and control tumor growth. This review provides an overview of the role of oncogenic viruses in cancer development and discusses current prevention and treatment strategies.

KEYWORDS: Oncogenic Viruses; Viral Oncogenes; Carcinogenesis; Antiviral Vaccination; OncolyticVirotherapy

CORRESPONDING AUTHOR: Basant H. Abou Zaid, **E-Mail :**Basant.hamdy@sue.edu.eg
Associate Professor of Oral Pathology , Oral and Maxillofacial Pathology Department, Faculty of Dentistry, Alsalam University, Tanta, Egypt.

RECEIVED: *17.01.2025* **ACCEPTED:** *20.02.2025* **AVAILABLE ONLINE:** *05.03.2025*

DOI : 10.21608/SUODMJ.2025.361489.1001

ISSN : *3062-5041 SOUDMJ 2025 ; 1(1) :12-24*

OVERVIEW AND BACKGROUND

The human body has its unique defense mechanism to combat disease-causing agents. Suppressing the body's defense mechanisms, cells can act abnormally and divide without control ending up with cancer formation [1]. Cancer occurs following a consequence of DNA alterations that induce disordered cellular development, division, and death. Such cellular transformation is influenced by several intrinsic and extrinsic factors including aging, genetic mutations, immunological responses, as examples of intrinsic factors; while extrinsic influences involve nutrition, smoking, radiation, and infectious agents [2]. About 20% of human cancers are attributed to infectious agents with about 15% of this cancer burden can be assigned to viral infection [3]. The possibility of viral etiology of cancer was postulated in 1911 when the veterinarian P. Rous observed that sarcoma in hens might be transmitted by a filterable agent, which was further revealed to be a retrovirus [4,5]. In 1957, Soviet researchers led by L.A. Zilber demonstrated that the Rous sarcoma virus can provoke tumors in rabbits and laboratory mice and formulated the hypothesis that cancer may be initiated by viruses [6]. To date, there are seven known human oncogenic viruses: Kaposi's sarcoma-associated herpesvirus (KSHV), Epstein-Barr virus (EBV), human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T cell lymphotropic virus type I (HTLV-1), and Merkel Cell Poliomavirus (MCV) [3]. Despite diversity, these oncogenic viruses share common features including viral replication, integration into host genome, alteration of host genetic material, and immortalization of the infected cells [7]. Moreover, oncogenic viruses can induce cancer formation with the aid of many cofactors, such as persistent inflammation, suppression of cancer-specific immune agents, and involvement of cancer-causing mutagens [1]. The notion that some cancers are linked to specific viral infections has led to the development of

preventive, diagnostic strategies, and therapeutic measures in some clinical settings. These measures served to reduce the overall incidence of certain types of virus-related cancers such as cervical cancer and hepatocellular carcinoma (HCC) in some regions of the world [8]. In this review, a summary of the roles played by several kinds of oncogenic viruses in the development of cancer as well as the recent trends in prevention and treatment strategies are discussed.

Features of viral oncogenesis

To define the role of viruses in cancer pathogenesis, certain essential characteristics have been postulated. These include: (i) Persistent co-existence of cancerous cells and viral particles in cancer biopsy, (ii) Growth-promoting activity of viral genes, (iii) Presence of viral constituents modifying the host genomic material and mediating the malignant phenotype, and (iv) Epidemiological evidence supporting the viral role in cancer prevalence [9]. Oncogenic viruses maintain a state of persistence within the host cells. This occurs via mediating chronic infections in which there is no or little production of viral particles. Such conditions last for the entire life of the infected individual. This mechanism of viral persistency or latency is biologically compatible with the carcinogenic process since they avoid cell death, which characterizes acute lytic infections, and hide the infectious agent from the immune system. The intracellular viral existence occurs as either naked nucleic acid in the form of plasmid or episome, or integrated viral genome into host's own genome [10]. In addition, viral latency is typified by expression of proteins orchestrating cell death and proliferation; thereby sustaining infection with a controlled number of cells keeping the integrity of virus and host [11]. Besides the effect of persistent infection and viral transformation mechanisms, additional oncogenic hits are necessary for the full carcinogenic transformation [12]. In this context, latently infected cells by oncogenic viruses are more susceptible to further oncogenic insults, e.g., due to smoking, diet deficient in vitamins and antioxidants or/ and increased exposure to environmental carcinogens. All these insults, coupled with the viral-induced inflammatory responses compelled by host genetic makeup, end up in cell transformation and cancer development [11].

Mechanisms of viral carcinogenesis

Viral contribution to cancer could be mediated via direct and/or indirect mechanisms. Direct carcinogenic viruses own viral oncogenes that contribute directly to neoplastic transformation [10]. They help to keep the neoplastic phenotype via increased expression of viral-derived or cell-derived oncogenes [11]. The direct oncogenic viruses either integrate their viral genome into host's DNA thereby deregulating the expression of cellular oncogenes or tumor suppressor genes or express their own viral oncogenes without the need for integration such as EBV [11]. Indirect viral oncogenesis occurs via two main mechanisms (i) Provoking chronic inflammation and oxidative stress that constantly induce local tissue damage; and (ii) Creating immunosuppression which counteracts anti-tumor immune surveillance mechanisms [11]. The famous examples of the first category are the HBV and HCV in which the persistent infection induces chronic inflammation with subsequent increased risk of HCC [13,14]. On the other hand, the second category is best exemplified by human immunodeficiency virus (HIV) in which patients with low CD8 counts are at increased risk of a variety of malignancies such as lymphomas and Kaposi sarcoma [15]. It's noteworthy to mention that both direct and indirect pathways are not reciprocally restricted, subsequently some agents may utilize both mechanisms to induce carcinogenesis such as HCV and HBV [13,14].

Co-factors influencing the outcome of viral infections

At the cellular level, the status of cell cycle checkpoints and apoptosis, senescence, autophagy pathways affect the outcome of infection.Whereas, at the organism level, the host's immune status is probably the most crucial guard against

virus-induced cancers. Consequently, the incidence of virus-related cancers tends to be more prevalent in elderly and immunosuppressed patients with exceptionally high prevalence among AIDS patients [16,17]. Also, co-infection with other pathogens likely plays a role in certain virus-induced cancers [16]. For example, in Burkitt's lymphoma, the co-infection with malaria parasites induces growth of germinal center lymphocytes, which in turn extends the cellular population prone to EBV infection [18]. Additionally, the limited geographic distribution of certain viral-induced cancers would raise suspicion of some genetic and environmental influences [19,20].

I. Human oncogenic viruses and associated cancers

Many viruses show direct cellular transformation characteristics; however, there is no sufficient scientific evidence that could support their link to human neoplasia so that they are not included by the International Agency for Research on Cancer (IARC) [11]. The oncogenic viruses identified by the IARC as group 1 human carcinogens are listed in table 1. The MCV is not included in the table since it is classified by the IARC as group 2A (probably carcinogenic to humans) [8].

Table.1: Group 1 cancer-related viruses are listed and divided by virus family, virus name, cellular tropism, associated neoplasia and cancer cases. The percentage of cancer cases is based on 2,300,000 worldwide oncogenic infections with Group 1 pathogens (updated 2020), available from GLOBOCAN, the global cancer observatory and reference [21].

Virus family	Virus name	Cellular tropism	Associated neoplasia	Cases n (%)
Papillomaviridae	HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Keratinocytes	Cervical, anal, vulva, vagina, penis and head and neck cancers	730,000 (31.1%)
Hepadnaviridae	HBV	Hepatocyte	Hepatocellular carcinoma	380,000 (16.4%)
Flaviviridae	HCV	Hepatocyte	Hepatocellular carcinoma and other non-Hodgkin lymphomas	170,000 (7.4%)
Herpesviridae	EBV (HHV-4)	Epithelial cells and B cells	Hodgkin lymphoma, Burkitt lymphoma and nasopharyngeal carcinoma	156,600 (6.8%)
Herpesviridae	KSHV (HHV-8)	Epithelial cells and B cells	Kaposi sarcoma	42,000 (1.8%)
Retroviridae	HTLV-1	T and B cells	Adult T-cell leukemia and lymphoma	3600 (0.16%)

HPV: human papilloma virus, HBV: hepatitis B virus, HCV: hepatitis C virus, EBV: Epstein Barr virus, HHV: human herpes virus, KSHV: Kaposi sarcoma herpes virus, HTLV-1: human T cell lymphotrophic virus.

I.1. DNA viruses

•Human Papillomavirus (HPV)

According to the IARC monographs, presently there are more than 100 HPV subtypes with twelve subtypes classified as carcinogenic to humans [7]. HPV types 16, 18, 31, and 33 have been implicated in more than 90% of cervical cancer cases. Apart from cervical cancer, over 90% of anal cancers, 70% of vaginal and vulvar cancer, 60% of penile cancers, and 63% of oropharyngeal cancers have been associated with high-risk HPV infection [2]. HPV is a double-stranded, circular DNA (dsDNA) genome of approximately 7.9 Kilobase (kb) [21] encoded with two sets of genes named after order of their transcription: early genes (E) and late genes (L). The early genes consist of E1, E2, E4, E5, E6, E7 and E8 which are involved in viral replication and cellular transformation whereas the late genes encode the L1 and L2 are engaged in the assembly of viral particles. The usual mode of infection is via direct sexual contact where the virus gains access to the epithelial cells following any minor trauma to the skin or mucous membrane of an infected individual [7]. Sexually acquired HPV will usually be cleared off by the immune system over time resulting in asymptomatic or transient lesions. But in a few cases, HPV can get itself integrated into the host genome thereby achieving viral persistence [8]. This is one of the key steps in HPV-induced carcinogenesis. Following integration into the host genome, viral oncogenes E6 and E7 are expressed in their unique way [7]. The E6 oncogene induces accelerated degradation of P53 gene while the E7 oncogene inactivates the pRb gene, both are crucial cellular tumor suppressor genes responsible for regulating normal cell proliferation and preventing uncontrolled cell growth [22]. Subsequently, E6 and E7 oncogenes synergistically induce genomic instability leading to accumulation of mutations and cancer development [2].

•Epstein-Barr Virus (EBV)

Like HPV, the IARC has classified EBV as group I carcinogen since it is associated with Burkitt's lymphoma, Hodgkin's lymphoma, B cell lymphoma, gastric carcinoma and nasopharyngeal cancer [23]. Moreover, it is involved in the development of head and neck cancers mainly in nasopharyngeal and less commonly oral squamous cell carcinomas (OSCC).EBV is a member of the herpes family, spreads via saliva and other body fluids causing infectious mononucleosis, a common childhood infection [7]. The EBV genome is a linear dsDNA, about 170–180 kb in size encoding 80 genes and surface glycoproteins. Most of the viral genes are silent during the latent phase of infection with only 10 % of them being actively expressed. The genes encoding proteins duringthis phase are called latent genes. On the other hand, genes expressed during the lytic phase of infection lular signaling pathways inducing carcinogenesis [7,24].Most of the genes seen in EBV-associated carcinomas are latent genes which encode nuclear antigen proteins such as EBNA-LP (EBV nuclear antigen leader protein), EBNA1, EBNA2, EBNA3A, EBNA3B and EBNA3C and latent membrane proteins such as LMP2A (latent Membrane Protein 2A) and LMP2B[7].One of the important traits of EBV is its dual tropism since it can infect both naïve B-cells and epithelial cells via switching surface glycoprotein molecules [25]. The increased expression of EBNA2 promotes excessive growth of B-cells, thereby inducing carcinogenesis [2]. One of the main latent genes linked to oropharyngeal carcinomas is EBNA1 [26] which can reduce the activity of P53 gene [27] stimulate angiogenesis [28], and deregulate genes involved in epithelial-mesenchymal transition (EMT) [29].Following infection of epithelial cells by KSHV, the viral DNA becomes integrated into the host cells then either enters a state of latency or passes through the lytic phase. During the latency phase, several events take place. The KSHV episomes are spread to dividing host cells during mitosis therefore sustaining the presence of virally infected cells. Furthermore, the virus releases the latency-associated nuclear antigen (LANA) which is a crucial factor in the processes of viral persistence/ latency as well as contributing to carcinogenesis

and evasion of immunity in cells infected with KSHV [2].

- *Hepatitis B virus (HBV)*

HBV is a small dsDNA virus with a genome of 3.2 kb which encodes four overlapping genes namely, S, C, P and X. Comparable to EBV, HBV exhibits dual tropism infecting both naïve B-cells and epithelial cells [32]. Following entry to the host cell, the virus integrates into the genomic DNA of human cells. HBV infection is known for its close association with HCC in addition to broad spectrum of other cancers such as gastric, nasopharyngeal and anal cancers, intrahepatic bile ducts tumors, as well as diffuse large B-cell lymphoma [33]. However, the incidence of HBV associated head and neck cancer remains relatively low [7]. The mechanisms underlying HBV-related carcinogenesis are still not fully understood, though this virus can exert oncogenic effects independently [34]. There is some evidence suggesting the role of HBV X protein in the repression of p53 tumor suppressor activity [35].

- *Merkel Cell Poliomavirus (MCV)*

Polyomaviruses are tiny non-enveloped dsDNA viruses, with a size of around 5.400 Kb. MCV is the sixth polyomavirus strain identified to infect the human population. The association between MCV and development of Merkel cell carcinoma, a rare and very aggressive neuro-endocrine skin cancer, is well-established [2]. The precise etiopathogenesis of MCV is still not fully understood, however integration of the viral genome into host DNA is a crucial step in carcinogenesis rendering the cells enhanced proliferation and resistance to apoptosis. Furthermore, oncogenic transformation seems to result from loss of immune surveillance since Merkel cell carcinoma mainly occurs in immunocompromised individuals [11].

I.2. RNA viruses

- *Hepatitis C Virus (HCV)*

The HCV is a member of the Flaviviridae family which is widely recognized as an etiological factor of HCC and human lymphomas.It is a single stranded RNA (ssRNA) virus with a genome of 9.6 Kb in length, encoding 10 viral proteins [7]. HCV exhibits triple tropism as it can infect naïve B-cells, hepatocytes and even salivary gland cells. Once HCV infects a host cell, it initiates a plethora of pro-malignant pathways via inhibiting cell cycle arrest and apoptosis [36]. The mechanism of HCV-induced liver cancer is well-elucidated. However, its potential link with non-liver cancers including OSCC requires further investigations [37].One of the closely observed extrahepatic signs of HCV infection is oral lichen planus, a precancerous condition that may progress to OSCC [38]. The mechanism of HCV induced carcinogenesis appears to resemble that of HPV infections. Like HPV E6/E7 oncoproteins,HCV has NS3 (non-structural protein 3) and NS5A (non-structural protein 5A) which can interfere with P53 and Rb tumor suppressor functions [39]. Furthermore, the persistent infection of HCV is associated with disruption of immune responses through various mechanisms such as suppression of interferon production, impaired functions of T-cells and natural killer cells, generation of reactive oxygen species (ROS), nitric oxide, harmful cytokines which all create an environment favorable for cancer development and progression [2,40].

- *Human T-cell Lymphotropic Virus type 1 (HTLV-1)*

The HTLV-1, the first known human retrovirus, was originally isolated from the cell line of T-cell lymphoma [33]. It has been implicated in the pathogenesis of a rare neoplastic disorder termed adult T-cell leukemia/lymphoma (ATLL). HTLV1 is endemic of Japan, the Western African coast, Central America and the Caribbean. The virus infects T- and B lymphocytes and dendritic cells in vivo [11]. HTLV-1 is predominantly transmitted via sexual contact,receiving blood transfusions, and nursing [2]. The virus primarily targets T-lymphocytes and can integrate into the host's DNA. The key viral proteinslinked to cancer development are Tax and HBZ which are responsible for tumor formation and maintenance respectively [41].

Potential role of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cancer progression

The emergence of SARS-CoV-2 in 2019 has shifted global interest toward the pathogenesis, prevention, and management of such detrimental infectious disease. The disease is generally characterized by fever, cough, headache, sore throat, diarrhea, tiredness, and the loss of taste or smell [42]. One of the most severe symptoms of coronavirus disease 2019 (COVID-19) is acute respiratory distress symptom, which can trigger a series of several inflammatory events in the lung [43]. The genome of this virus consists of ssRNA which is 26–32 Kb. One of its structural proteins is the spike protein (S protein) which enables viral invasion into target cells via the interaction of receptor-binding domain of the S1 subunit with angiotensin-converting enzyme 2 (ACE2) on the host cell surface [44]. Mutations in the S protein prevent the circulating antibodies from binding to the virus which weakens the protection against recurrent infection with this virus. It is suggested that SARS-CoV-2 would have long-term life-threatening complications that will be revealed over time as compared to common chronic viral infections including HIV, HBV, HCV, HPV, and EBV[42]. Some reports suggest SARS-COV-2 as a potential oncogenic virus [45].

The possible mechanisms of SARS-COV-2 oncogenesis

- *Disturbed renin-angiotensin-aldosterone system (RAAS)*

In SARS-COV-2, the virus binds to ACE-2 with subsequent dysregulated RAAS which triggers inflammation, vasoconstriction, fibrosis, oxidation, and capillary permeability which can all serve as important factors for cancer development and progression [46–48]. Furthermore, dysregulated RAAS is linked to increased production of the potent proangiogenic vascular endothelial growth factor (VEGF) which increases blood supply necessary for solid tumor growth and metastasis [49].

- *Viral mutagenicity*

Like the classic examples of oncogenic viruses, SARS-COV-2 may stimulate the human oncogenesor disrupt the tumor suppressor genes [42]. Infection with SARS-COV-2 can result in increased production of viral proteins nsp15 and nsp3 which interfere with the tumor suppressor functions of pRb and P53 genes respectively [50,51]. Moreover, SARS-COV-2 can induce epigenetic changes which are important for both viral infection and cancer progression [42].

- *Inflammatory cascade*

SARS-COV-2 can trigger the release of a plethora of inflammatory cytokines, a phenomenon known as the cytokine storm [52]. Among the inflammatory cytokines released in this process is IL-6 which is important in pathogenesis of COVID-19 and becomes a prognostic factor of disease severity via monitoring its elevated serum levels [53]. The upregulation of IL-6 results in several events that eventually leads to enhanced expression of cellular protooncogenes as well as increased-chances of metastasis via stimulating EMT[54,55].

Association between COVID-19 and OSCC

Because of the severity of COVID-19 pandemic, the public concern toward acquiring infection would result in underestimation of the warning signs and symptoms of cancer; hence preventing patients from seeking medical or dental care [56]. Consequently, the COVID-19 pandemic may be a contributing and exacerbating factor for the delayed diagnosis of serious diseases, like OSCC, which increases morbidity and worsens prognosis [57].Apart from such indirect effect on OSCC progression and prognosis, SARS-COV-2 may trigger several pathways crucial for oral carcinogenesis. One of the cellular entry targets of SARS-COV-2 is the extracellular matrix metalloproteinase inducer (EMMPRIN) which shows high affinity for binding with the virus. EMMPRIN releases matrix metalloproteinases and cytokines which play important roles in cellular proliferation, growth, and homeostasis in many malignancies as well as primary and metastatic cell lines of OSCC [42].

II. Prevention strategies

Cancer vaccination is a potential treatment approach aims at inducing antitumor immune response [58].

The basic concept of cancer prevention by vaccination involves utilizing immune system to prevent cancer-causing viral infection via neutralizing the oncogenic virus thereby avoiding uptake by target cells, or to attack premalignant and latent or dormant cancer cells [59]. Cancer vaccines fall into four categories, nucleic acid-based vaccinations, viral-based vaccines, peptide-based vaccines, and cell-based vaccines [1].

- *Mechanisms of anti-cancer vaccines*

In viral-based vaccination, the viral genetic material can be altered to include sequences containing tumor antigens since viruses are naturally immunogenic [58]. Antigen-presenting cells (APCs), namely dendritic cells (DCs), recognize and capture the vaccine antigen components [60]. The antigen-loaded DCs go to secondary lymphoid organs where they present the antigen to naïve CD4+ T cells and CD8+ T cells with the aid of MHC I and II, thus activating T cell and/or interacting with B cells [59]. It is significant to highlight that the activation of CD8+ T cells and tumor immunity depend heavily on CD4+ T cell support and co-stimulatory molecules. The activated T cells migrate to the tumor microenvironment to limit tumor development via direct killing premalignant or malignant cells expressing the targeted antigen [61]. In addition, plasma cells secrete antibodies that can neutralize oncogenic viruses via preventing virus-host interactions [59].

- *Current vaccines and their efficacy*

There are two types of licensed cancer prevention vaccines targeting oncogenic viruses: prophylactic vaccines for HPV and for HBV [59]. The prophylactic HPV vaccines approved worldwide are as follows: (i) a bivalent vaccine (Cervarix®, GlaxoSmithKline, Wavre, Belgium) that targets the genotypes HPV16 and HPV18; (ii) a quadrivalent vaccine (Gardasil®, Merck & Co, Rahway, NJ, USA) against HPV6, HPV11, HPV16 and HPV18; and (iii) a nonavalent (Gardasil 9®, Merck & Co, Rahway, HPV6, HPV11, HPV16, HPV18, HPV31, HPV33, HPV45,, HPV52 and HPV58. They all showed efficacy in reducing ano-genital viral infections as well as pre-malignant and malignant lesions [62,63]. HPV vaccines is expected to prevent cervical cancer, the third leading cause of cancer-related mortalities in women globally and perhaps will prevent other HPV-related cancers [16]. Vaccination against HBV is the best protection against chronic HBV infection. HBV vaccine was introduced in 1980, representing the first vaccine capable of preventing a specific human cancer. The HBsAg contains multiple epitopes that elicit neutralizing antibodies, conferring protection from infection [64]. Engerix-B and Recombivax HB are approved in the United States for both pediatric and adult populations and are generally administered in three doses. Another two-dose hepatitis B vaccine, HEPLISAV-B, was licensed for adults in 2018 [59]. The widespread use of the universal HBV vaccination program would contribute to the decline of chronic HBV infection and HCC [65].

III. Oncolytic virotherapy

Oncolytic virotherapy is a novel cancer therapeutic modality in which the virus selectively replicates in and destroys tumor cells while skipping normal cells [66]. Oncolytic viruses can be equipped with exogenous genes to exert powerful antitumor effects [67]. In October 2015, the FDA approved the first oncolytic virus therapy, T-VEC, for the treatment of melanoma via promoting lysis of tumor cells [68].Oncolytic viruses are derived from single- or double-stranded DNA or RNA viruses[67].

- *Adenoviruses*

Adenovirus is the largest non-enveloped dsDNA virus (26–45 Kb) which are excellent vectors in terms ofmanipulability and tolerance of transgenes[69]. Adenoviral vectors have been broadly studied for their capacity to carry transgenes for gene therapy. They offer several benefits including the ability to produce high viral titers and the inherent lytic activity. Several adenoviral agents revealed favorable outcomes in clinical studies such as the adenovector encoding hypoxia-inducible

factor 1 alpha (AdHIF-1α). It has demonstrated neuroprotective effects in rats and is assumed to inhibit apoptosis in nerve cells [70].

- *Adeno-associated virus*

Adeno-associated virus (AAV), a member of the family Parvoviridae is a non-enveloped single stranded DNA (ssDNA) virus [69]. Its nonpathogenic nature makes it an ideal candidate for gene transfer, and it has already proved clinical efficacy in generating strong immune response in mice against SARS-COV-2 [71], and providing complete protection against Ebola virus in mice [72]. Considering cancer treatment, AAV has demonstrated the potential to eliminate cervical cancer both in vivo and in vitro via targeting the HPV E6 and E7 oncoproteins [73].

- *Herpesviruses*

Herpesvirus (HSV) is a dsDNA virus enclosed by the nucleocapsid. It has a large genome and a complex structure which enables the incorporation of several transgenes. Being a cytosolic virus, HSV can infect several types of cancer cells and undergo rapid replication, hence efficiently disseminating offspring viruses within the tumor. Currently, HSV-1 is one of the prevalent strains of oncolytic viruses that are frequently employed, whereas HSV-2 is still under investigation [2].

- *Vaccinia virus*

The Vaccinia virus is a dsDNA that belongs to the Orthopoxvirus genus [74]. Its selective targeting depends largely on the presence of thymidine kinase (TK) gene, which encodes a crucial enzyme for viral replication. Malignant cells commonly show upregulated expression of TK, whereas seldom do the normal cells. Accordingly, researchers successfully engineered a Vaccinia virus strain with a specific TK phenotype characterized by confined replication solely within cancerous cells [75].

IV. Review of previous literature

A multitude of research was conducted addressing the role of viruses in human carcinogenesis. In (2021), Vat et al. extensively reviewed the biological effects of the HPV oncogenes E6 and E7 whose combined effect is necessary for cancer development cellular tumor suppressor genes, Vat et al. highlighted several dysregulated pathways due to E6 and E7 oncogenes including their ability to induce epigenetic modification, genomic instability, activate angiogenic switch in cervical carcinoma cells, evade immune response, and activation of telomerase [76]. Furthermore, Akagi et al. (2014) performed a genome wide analysis on 10 head and neck cancer cell lines and found that HPV undergoes integration into host's genome at several insertional points leading to genomic instability which is a hallmark of viral carcinogenesis [77]. More recently, Zheng et al. (2020) evaluated the EBV positivity in undifferentiated, non-keratinizing and squamous cell nasopharyngeal cancers and found EBV DNA in 100% of the study population [78]. Interestingly, a few studies pointed out the co-infection of HPV and EBV in the head and neck cancers with an incidence rate of 0–7.8 % [79–81]. In their review, Payaradka et al. (2022) explained that such co-infection is said to augment the tumorigenic potential since oncogenes from either virus are known to upregulate the anti-apoptotic proteins thereby changing the course of normal physiological cell death [7]. A more recent comprehensive review of oncogenic viruses, Ameya and Birri (2023) discussed the molecular mechanisms of HBV, HCV, KSHV, and HTLV induced cancers. They reported the production of potent oncogenes such as HBx by HBV which enhance the invasive and metastatic potential of the infected cells, inhibit apoptosis, promote cell proliferation, and induce malignant transformation. On the other hand, the oncogenic potential of HCV is mediated via alteration of P53 and induction of liver cirrhosis which enhances the state of genomic instability necessary for cancer development.They also reported several complex molecular pathways mediated by KSHV, HTLV, and MCV that trigger the process of oncogenesis [82]. In (2020), Cantuti-Castelvetri et al. conducted an experimental in vitro study using human kidney cell lines and lentiviral particles typed with SARS-COV-2 S protein and observed that SARS-COV-2

increases the expression of neuropilin-1 (NRP-1) [83] which can promote carcinogenesis in different ways. One of these ways was explained by Norouzi et al. (2023) who reviewed the role of COVID-19 in OSCC progression and found that NRP-1 can facilitate tumor invasion, stimulate stemness features which enhance proliferation and chemo-resistance in OSCC, and support proliferation, survival, and migration of OSCC cells via increased VEGF. Furthermore, they highlighted that COVID-19 infection causes hyperactivation of P2X7 receptor which is associated with progression of OSCC as well as other types of cancers [84]. Moreover, Jahankhani et al. (2023) extensively reviewed the mutagenic perspectives of COVID-19 infection and indicated that SARS-COV-2 may lead to cancer development at many sites including lung, colon, pancreas, and breast. Their conclusion was based on the ability of SARS-COV-2 to exert several organ-specific effects such as fibrosis and chronic inflammation of the lung, dysbiosis of intestine, upregulated pancreatic cancer genes, and increased EMT of breast cells [42].

Evidence of oncogenic viruses in cancer prevention and therapy

A randomized clinical trial was conducted by Herrero et al. (2013) on 7,466 women aged 18–25 years old who were divided into two groups to receive HPV 16/18 vaccine (Cervarix) or hepatitis A vaccine as a control. At the final blinded 4-year study visit, 5,840 participants provided oral specimens to evaluate vaccine efficacy against oral infections. Cervarix vaccine has showed a 93% reduction in the prevalence of oral HPV16/18 infections suggesting that HPV vaccination could protect against the progression of oral cancer [85]. Regarding HBV, Yu et al. (2022) analyzed the impact of HBV immunization in infants on the incidences of HBV infection and HCC after three decades of vaccination in Shanghai. They found that the incidence of HBV infection in Shanghai population decreased by more than 80% and age-standardized rates of HCC by around 50% [86]. In (2023), Lin et al. evaluated different strategies employing oncolytic virotherapy in preclinical settings. They emphasized the better efficacy of oncolytic viruses when used in combination with chemotherapy, radiotherapy, or immunotherapy approaches [67]. After administration of combined therapy, there was an enhanced anti-tumor response in the form of increasedlevels of CD4+ and CD8+ cells,and decreased suppressor Treg cells infiltrating the tumor region [2].

Conclusions

Viral infections are believed to be responsible for nearly 15–20 % of all human malignancies with only seven viruses currently listed as pathogens with oncogenic potential. Several viral proteins can alter signaling pathways of host cells with subsequent deranged cellular processes including cell growth and maintenance. SARS-COV-2 and its proteins employ different strategies that would induce the development of cancer. A dramatic drop in incidence of certain virus-associated cancers is observed after vaccine administration. More research is needed to better characterize the oncolytic capacity of different viruses and to avoid the potential threats before human trials can start. More studies on post COVID-19 patients are required to address the possible impact of

References

1. Chowdhary S, Deka R, Panda K, Kumar R, Solomon AD, Das J, et al. Recent Updates on Viral Oncogenesis: Available Preventive and Therapeutic Entities. Mol Pharm 2023;20:3698–740. https://doi.org/10.1021/acs.molpharmaceut.2c01080.

2. Dash SR, Kundu A, Kundu CN. The role of viruses in cancer progression versus cancer treatment: A dual paradigm. Life Sci 2024:122506. https://doi.org/10.1016/j.lfs.2024.122506

3. White MC, Wu X, Damania B. Oncogenic viruses, cancer biology, and innate immunity. Curr Opin Immunol 2022;78. https://doi.org/10.1016/j.coi.2022.102253.

4. Rous P. A SARCOMA OF THE FOWL TRANSMISSIBLE BY AN AGENT SEPARABLE FROM THE TUMOR CELLS. Journal of Experimental Medicine 1911;13:397–411.https://doi.org/10.1084/jem.13.4.397.

5. STEHELIN D, VARMUS HE, BISHOP JM, VOGT PK. DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA. Nature 1976;260:170–3. https://doi.org/10.1038/260170a0.

6. ZILBER LA, KRYUKOVA IN. Haemorrhagic disease of rats due to the virus of chick sarcoma. Acta Virol 1957;1:156–60.

7. Payaradka R, Ramesh PS, Vyas R, Patil P, Rajendra VK, Kumar M, et al. Oncogenic viruses as etiological risk factors for

head and neck cancers: An overview on prevalence, mechanism of infection and clinical relevance. Arch Oral Biol 2022;143. https://doi.org/10.1016/j.archoralbio.2022.105526.

8. Galati L, Chiantore MV, Marinaro M, Di Bonito P. Human Oncogenic Viruses: Characteristics and Prevention Strategies—Lessons Learned from Human Papillomaviruses. Viruses 2024;16:416. https://doi.org/10.3390/v16030416.

9. Elkhalifa AME, Nabi SU, Shah OS, Bashir SM, Muzaffer U, Ali SI, et al. Insight into Oncogenic Viral Pathways as Drivers of Viral Cancers: Implication for Effective Therapy. Current Oncology 2023;30:1924–44. https://doi.org/10.3390/curroncol30020150.

10. Mui U, Haley C, Tyring S. Viral Oncology: Molecular Biology and Pathogenesis. J Clin Med 2017;6:111. https://doi.org/10.3390/jcm6120111.

11. Morales-Sánchez A, Fuentes-Pananá EM. Human viruses and cancer. Viruses 2014;6:4047–79. https://doi.org/10.3390/v6104047.

12. J. Prindle M, J. Fox E, A. Loeb L. The Mutator Phenotype in Cancer: Molecular Mechanisms and Targeting Strategies. Curr Drug Targets 2010;11:1296–303. https://doi.org/10.2174/1389450111007011296.

13. Zucman-Rossi J, Laurent-Puig P. Genetic diversity of hepatocellular carcinomas and its potential impact on targeted therapies. Pharmacogenomics 2007;8:997–1003. https://doi.org/10.2217/14622416.8.8.997.

14. Coleman WB. Mechanisms of Human Hepatocarcinogenesis. Curr Mol Med 2003;3:573–88. https://doi.org/10.2174/1566524033479546.

15. Chadburn A, Abdul-Nabi AM, Teruya BS, Lo AA. Lymphoid Proliferations Associated With Human Immunodeficiency Virus Infection. Arch Pathol Lab Med 2013;137:360–70. https://doi.org/10.5858/arpa.2012-0095-RA.

16. Sarid R, Gao SJ. Viruses and human cancer: From detection to causality. Cancer Lett 2011;305:218–27. https://doi.org/10.1016/j.canlet.2010.09.011.

17. Schulz TF. Cancer and viral infections in immunocompromised individuals. Int J Cancer 2009;125:1755–63. https://doi.org/10.1002/ijc.24741.

18. Chene A, Donati D, Orem J, Björkman A, Mbidde ER, Kironde F, et al. Endemic Burkitt's lymphoma as a polymicrobial disease. Semin Cancer Biol 2009;19:411–20. https://doi.org/10.1016/j.semcancer.2009.10.002.

19. Li X, Fasano R, Wang E, Yao K-T, Marincola F. HLA Associations with Nasopharyngeal Carcinoma. Curr Mol Med 2009;9:751–65. https://doi.org/10.2174/156652409788970698.

20. Hjalgrim H, Rostgaard K, Johnson PCD, Lake A, Shield L, Little A-M, et al. HLA-A alleles and infectious mononucleosis suggest a critical role for cytotoxic T-cell response in EBV-related Hodgkin lymphoma. Proceedings of the National Academy of Sciences 2010;107:6400–5. https://doi.org/10.1073/pnas.0915054107.

21. SCHEURER ME, TORTOLERO-LUNA G, ADLER-STORTHZ K. Human papillomavirus infection: biology, epidemiology, and prevention. International Journal of Gynecological Cancer 2005;15:727–46. https://doi.org/10.1111/j.1525-1438.2005.00246.x.

22. Yim E-K, Park J-S. The Role of HPV E6 and E7 Oncoproteins in HPV-associated Cervical Carcinogenesis. Cancer Res Treat 2005;37:319. https://doi.org/10.4143/crt.2005.37.6.319.

23. Bakkalci D, Jia Y, Winter JR, Lewis JE, Taylor GS, Stagg HR. Risk factors for Epstein Barr virus-associated cancers: a systematic review, critical appraisal, and mapping of the epidemiological evidence. J Glob Health 2020;10. https://doi.org/10.7189/jogh.10.010405.

24. Di Pietro A. Epstein–Barr Virus Promotes B Cell Lymphomas by Manipulating the Host Epigenetic Machinery. Cancers (Basel) 2020;12:3037. https://doi.org/10.3390/cancers12103037.

25. Young LS, Rickinson AB. Epstein–Barr virus: 40 years on. Nat Rev Cancer 2004;4:757–68. https://doi.org/10.1038/nrc1452.

26. Tsao SW, Tsang CM, Lo KW. Epstein–Barr virus infection and nasopharyngeal carcinoma. Philosophical Transactions of the Royal Society B: Biological Sciences 2017;372:20160270. https://doi.org/10.1098/rstb.2016.0270.

27. McFadden K, Luftig MA. Interplay Between DNA Tumor Viruses and the Host DNA Damage Response, 2013, p. 229–57. https://doi.org/10.1007/978-3-642-37765-5_9.

28. O'Neil JD, Owen TJ, Wood VHJ, Date KL, Valentine R, Chukwuma MB, et al. Epstein–Barr virus-encoded EBNA1 modulates the AP-1 transcription factor pathway in nasopharyngeal carcinoma cells and enhances angiogenesis in vitro. Journal of General Virology 2008;89:2833–42. https://doi.org/10.1099/vir.0.2008/003392-0.

29. Wang L, Tian W, Xu X, Nie B, Lu J, Liu X, et al. Epstein -Barr virus nuclear antigen 1 (EBNA1) protein induction of epithelial- mesenchymal transition in nasopharyngeal carcinoma cells. Cancer 2014;120:363–72. https://doi.org/10.1002/cncr.28418.

30. Goncalves PH, Ziegelbauer J, Uldrick TS, Yarchoan R. Kaposi sarcoma herpesvirus-associated cancers and related diseases. Curr Opin HIV AIDS 2017;12:47–56. https://doi.org/10.1097/COH.0000000000000330.

31. Iannacone M, Guidotti LG. Immunobiology and pathogenesis of hepatitis B virus infection. Nat Rev Immunol 2022;22:19–32. https://doi.org/10.1038/s41577-021-00549-4.

32. Bogolyubova A V. Human Oncogenic Viruses: Old Facts and New Hypotheses. Mol Biol 2019;53:767–75. https://doi.org/10.1134/S0026893319050030.

33. Liang TJ, Heller T. Pathogenesis of hepatitis C—associated hepatocellular carcinoma. Gastroenterology 2004;127:S62–71. https://doi.org/10.1053/j.gastro.2004.09.017.

34. Geng M. Molecular mechanism of hepatitis B virus X protein function in hepatocarcinogenesis. World J Gastroenterol 2015;21:10732. https://doi.org/10.3748/wjg.v21.i38.10732.

35. McGivern DR, Lemon SM. Virus-specific mechanisms of carcinogenesis in hepatitis C virus associated liver cancer. Oncogene 2011;30:1969–83. https://doi.org/10.1038/onc.2010.594.

36. Borsetto D, Fussey J, Fabris L, Bandolin L, Gaudioso P, Phillips V, et al. HCV infection and the risk of head and neck cancer: A meta-analysis. Oral Oncol 2020;109:104869. https://doi.org/10.1016/j.oraloncology.2020.104869.

37. Nagao Y, Sata M, Noguchi S, Seno'O T, Kinoshita M, Kameyama T, et al. Detection of hepatitis C virus RNA in oral lichen planus and oral cancer tissues. Journal of Oral Pathology & Medicine 2000;29:259–66. https://doi.org/10.1034/j.1600-0714.2000.290604.x.

38. Sillanpaa M, Melen K, Porkka P, Fagerlund R, Nevalainen K, Lappalainen M, et al. Hepatitis C virus core, NS3, NS4B and NS5A are the major immunogenic proteins in humoral immunity in chronic HCV infection. Virol J 2009;6:84. https://doi.org/10.1186/1743-422X-6-84.

39. Fasbender F, Widera A, Hengstler JG, Watzl C. Natural Killer Cells and Liver Fibrosis. Front Immunol 2016;7. https://doi.org/10.3389/fimmu.2016.00019.

40. Enose-Akahata Y, Vellucci A, Jacobson S. Role of HTLV-1 Tax and HBZ in the Pathogenesis of HAM/TSP. Front Microbiol 2017;8. https://doi.org/10.3389/fmicb.2017.02563

41. Jahankhani K, Ahangari F, Adcock IM, Mortaz E. Possible cancer-causing capacity of COVID-19: Is SARS-CoV-2 an oncogenic agent? Biochimie 2023;213:130–8. https://doi.org/10.1016/j.biochi.2023.05.014.

42. Notz Q, Schmalzing M, Wedekink F, Schlesinger T, Gernert M, Herrmann J, et al. Pro- and Anti-Inflammatory Responses in Severe COVID-19-Induced Acute Respiratory Distress Syndrome—An Observational Pilot Study. Front Immunol 2020;11. https://doi.org/10.3389/fimmu.2020.581338.

43. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;46:586–90. https://doi.org/10.1007/s00134-020-05985-9.

44. Alpalhão M, Ferreira JA, Filipe P. Persistent SARS-CoV-2 infection and the risk for cancer. Med Hypotheses 2020;143:109882. https://doi.org/10.1016/j.mehy.2020.109882.

45. Augustine R, S A, Nayeem A, Salam SA, Augustine P, Dan P, et al. Increased complications of COVID-19 in people with cardiovascular disease: Role of the renin–angiotensin-aldosterone system (RAAS) dysregulation. Chem Biol Interact 2022;351:109738. https://doi.org/10.1016/j.cbi.2021.109738.

46. Gressens SB, Leftheriotis G, Dussaule J-C, Flamant M, Levy BI, Vidal-Petiot E. Controversial Roles of the Renin Angiotensin System and Its Modulators During the COVID-19 Pandemic. Front Physiol 2021;12. https://doi.org/10.3389/fphys.2021.624052.

47. Gupta A, Madhavan M V., Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020;26:1017–32. https://doi.org/10.1038/s41591-020-0968-3.

48. Arrieta O, Villarreal-Garza C, Vizcaíno G, Pineda B, Hernández-Pedro N, Guevara-Salazar P, et al. Association between AT1 and AT2 angiotensin II receptor expression with cell proliferation and angiogenesis in operable breast cancer. Tumor Biology 2015;36:5627–34. https://doi.org/10.1007/s13277-015-3235-3.

49. Leng RP, Lin Y, Ma W, Wu H, Lemmers B, Chung S, et al. Pirh2, a p53-Induced Ubiquitin-Protein Ligase, Promotes p53 Degradation. Cell 2003;112:779–91. https://doi.org/10.1016/S0092-8674(03)00193-4.

50. Bhardwaj K, Liu P, Leibowitz JL, Kao CC. The Coronavirus Endoribonuclease Nsp15 Interacts with Retinoblastoma Tumor Suppressor Protein. J Virol 2012;86:4294–304. https://doi.org/10.1128/JVI.07012-11.

51. Blanco-Melo D, Nilsson-Payant BE, Liu W-C, Uhl S, Hoagland D, Møller R, et al. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. Cell 2020;181:1036-1045.e9. https://doi.org/10.1016/j.cell.2020.04.026.

52. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect 2020;9:1123–30. https://doi.org/10.1080/22221751.2020.1770129.

53. Shirogane T, Fukada T, Muller JMM, Shima DT, Hibi M, Hirano T. Synergistic Roles for Pim-1 and c-Myc in STAT3-Mediated Cell Cycle Progression and Antiapoptosis. Immunity 1999;11:709–19. https://doi.org/10.1016/S1074-7613(00)80145-4.

54. Gao X, Liu X, Lu Y, Wang Y, Cao W, Liu X, et al. PIM1 is responsible for IL-6-induced breast cancer cell EMT and stemness via c-myc activation. Breast Cancer 2019;26:663–71. https://doi.org/10.1007/s12282-019-00966-3.

55. Maciel PP, Martelli Júnior H, Martelli DRB, Machado RA, Andrade PV de, Perez DE da C, et al. COVID-19 Pandemic:Oral Repercussions and its Possible Impact on Oral Health.

56. Pesqui Bras Odontopediatria Clin Integr 2020;20. https://doi.org/10.1590/pboci.2020.135.

57. Park JY. Oral cavity cancer management during the COVID-19 pandemic. J Korean Assoc Oral Maxillofac Surg 2020;46:371–2. https://doi.org/10.5125/jkaoms.2020.46.6.371.

58. Liu C-H, Grandi N, Palanivelu L, Tramontano E, Lin L-T. Contribution of Human Retroviruses to Disease Development—A Focus on the HIV– and HERV–Cancer Relationships and Treatment Strategies. Viruses 2020;12:852. https://doi.org/10.3390/v12080852.

59. Enokida T, Moreira A, Bhardwaj N. Vaccines for immunoprevention of cancer. Journal of Clinical Investigation 2021;131. https://doi.org/10.1172/JCI146956.

60. Kim CW, Kim K-D, Lee HK. The role of dendritic cells in tumor microenvironments and their uses as therapeutic targets. BMB Rep 2021;54:31–43. https://doi.org/10.5483/BMBRep.2021.54.1.224.

61. Kaufman HL, Kohlhapp FJ, Zloza A. Oncolytic viruses: a new class of immunotherapy drugs. Nat Rev Drug Discov 2015;14:642–62. https://doi.org/10.1038/nrd4663.

62. Goldstone SE, Giuliano AR, Palefsky JM, Lazcano-Ponce E, Penny ME, Cabello RE, et al. Efficacy, immunogenicity, and safety of a quadrivalent HPV vaccine in men: results of an open-label, long-term extension of a randomised, placebo-controlled, phase 3 trial. Lancet Infect Dis 2022;22:413–25. https://doi.org/10.1016/S1473-3099(21)00327-3.

63. Patel C, Brotherton JM, Pillsbury A, Jayasinghe S, Donovan B, Macartney K, et al. The impact of 10 years of human papillomavirus (HPV) vaccination in Australia: what additional disease burden will a nonavalent vaccine prevent? Eurosurveillance 2018;23. https://doi.org/10.2807/1560-7917.ES.2018.23.41.1700737.

64. Gerin JL, Alexander H, Shih JW, Purcell RH, Dapolito G, Engle R, et al. Chemically synthesized peptides of hepatitis B surface antigen duplicate the d/y specificities and induce subtype-specific antibodies in chimpanzees. Proceedings of the National Academy of Sciences 1983;80:2365–9. https://doi.org/10.1073/pnas.80.8.2365.

65. Wu Q-J, Vogtmann E, Zhang W, Xie L, Yang W-S, Tan Y-T, et al. Cancer Incidence among Adolescents and Young Adults in Urban Shanghai, 1973–2005. PLoS One 2012;7:e42607. https://doi.org/10.1371/journal.pone.0042607.

66. Li Y, Shen Y, Zhao R, Samudio I, Jia W, Bai X, et al. Oncolytic virotherapy in hepato-bilio-pancreatic cancer: The key to breaking the log jam? Cancer Med 2020;9:2943–59. https://doi.org/10.1002/cam4.2949.

67. Lin D, Shen Y, Liang T. Oncolytic virotherapy: basic principles, recent advances and future directions. Signal Transduct Target Ther 2023;8. https://doi.org/10.1038/s41392-023-01407-6.

68. Sheridan C. First oncolytic virus edges towards approval in surprise vote. Nat Biotechnol 2015;33:569–70. https://doi.org/10.1038/nbt0615-569.

69. bin Umair M, Akusa FN, Kashif H, Seerat-e-Fatima, Butt F, Azhar M, et al. Viruses as tools in gene therapy, vaccine development, and cancer treatment. Arch Virol 2022;167:1387–404. https://doi.org/10.1007/s00705-022-05432-8.

70. Yang M-L, Tao T, Xu J, Liu Z, Xu D. Antiapoptotic Effect of Gene Therapy with Recombinant Adenovirus Vector Containing Hypoxia-inducible Factor-1α after Cerebral Ischemia and Reperfusion in Rats. Chin Med J (Engl) 2017;130:1700–6. https://doi.org/10.4103/0366-6999.209909.

71. Zabaleta N, Dai W, Bhatt U, Hérate C, Maisonnasse P, Chichester JA, et al. An AAV-based, room-temperature-stable, single-dose COVID-19 vaccine provides durable immunogenicity and protection in non-human primates. Cell Host Microbe 2021;29:1437-1453.e8. https://doi.org/10.1016/j.chom.2021.08.002.

72. van Lieshout LP, Soule G, Sorensen D, Frost KL, He S, Tierney K, et al. Intramuscular Adeno-Associated Virus–Mediated Expression of Monoclonal Antibodies Provides 100% Protection Against Ebola Virus Infection in Mice. J Infect Dis 2018;217:916–25. https://doi.org/10.1093/infdis/jix644.

73. Sato N, Saga Y, Uchibori R, Tsukahara T, Urabe M, Kume A, et al. Eradication of cervical cancer in vivo by an AAV vector that encodes shRNA targeting human papillomavirus type 16 E6/E7. Int J Oncol 2018. https://doi.org/10.3892/ijo.2018.4245.

74. Locker JK, Kuehn A, Schleich S, Rutter G, Hohenberg H, Wepf R, et al. Entry of the Two Infectious Forms of Vaccinia Virus at the Plasma Membane Is Signaling-Dependent for the IMV but Not the EEV. Mol Biol Cell 2000;11:2497–511. https://doi.org/10.1091/mbc.11.7.2497.

75. Inoue T, Tsai B. How Viruses Use the Endoplasmic Reticulum for Entry, Replication, and Assembly. Cold Spring Harb Perspect Biol 2013;5:a013250–a013250. https://doi.org/10.1101/cshperspect.a013250.

76. Vats A, Trejo-Cerro O, Thomas M, Banks L. Human papillomavirus E6 and E7: What remains? Tumour Virus Res 2021;11. https://doi.org/10.1016/j.tvr.2021.200213.

77. Akagi K, Li J, Broutian TR, Padilla-Nash H, Xiao W, Jiang B, et al. Genome-wide analysis of HPV integration in human cancers reveals recurrent, focal genomic instability. Genome Res 2014;24:185–99. https://doi.org/10.1101/gr.164806.113.

78. Zheng X, Wang R, Li X, Zhou T, Zhang J, Zhang P, et al. Detection of methylation status of Epstein-Barr virus DNA C promoter in the diagnosis of nasopharyngeal carcinoma. Cancer Sci 2020;111:592–600. https://doi.org/10.1111/cas.14281.

79. Jiang R, Ekshyyan O, Moore-Medlin T, Rong X, Nathan S, Gu X, et al. Association between human papilloma virus/Epstein–Barr virus coinfection and oral carcinogenesis. Journal of Oral Pathology & Medicine 2015;44:28–36. https://doi.org/10.1111/jop.12221.

80. Jalouli J, Ibrahim SO, Sapkota D, Jalouli MM, Vasstrand EN, Hirsch JM, et al. Presence of human papilloma virus, herpes simplex virus and Epstein-Barr virus DNA in oral biopsies from Sudanese patients with regard to toombak use. Journal of Oral Pathology & Medicine 2010;39:599–604. https://doi.org/10.1111/j.1600-0714.2010.00910.x.

81. Chowdhary S, Deka R, Panda K, Kumar R, Solomon AD, Das J, et al. Recent Updates on Viral Oncogenesis: Available Preventive and Therapeutic Entities. Mol Pharm 2023;20:3698–740. https://doi.org/10.1021/acs.molpharmaceut.2c01080.

82. Dash SR, Kundu A, Kundu CN. The role of viruses in cancer progression versus cancer treatment: A dual paradigm. Life Sci 2024:122506. https://doi.org/10.1016/j.lfs.2024.122506.

83. White MC, Wu X, Damania B. Oncogenic viruses, cancer biology, and innate immunity. Curr Opin Immunol 2022;78. https://doi.org/10.1016/j.coi.2022.102253.

84. Norouzi A, Liaghat M, Bakhtiyari M, Noorbakhsh Varnosfaderani SM, Zalpoor H, Nabi-Afjadi M, et al. The potential role of COVID-19 in progression, chemo-resistance, and tumor recurrence of oral squamous cell carcinoma (OSCC). Oral Oncol 2023;144. https://doi.org/10.1016/j.oraloncology.2023.106483.

85. Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, et al. Reduced Prevalence of Oral Human Papillomavirus (HPV) 4 Years after Bivalent HPV Vaccination in a Randomized Clinical Trial in Costa Rica. PLoS One 2013;8:e68329. https://doi.org/10.1371/journal.pone.0068329.

86. Yu S, Zhu Q, Zheng Y, Wu C, Ren H, Liu X, et al. Accelerating Decreases in the Incidences of Hepatocellular Carcinoma at a Younger Age in Shanghai Are Associated With Hepatitis B Virus Vaccination. Front Oncol 2022;12. https://doi.org/10.3389/fonc.2022.855945.