OPEN ACCESS
Saudi Journal of Biomedical Research
Abbreviated Key Title: Saudi J Biomed Res
ISSN 2518-3214 (Print) |ISSN 2518-3222 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article

An Overview on Viral Origin of Cancer in Human

Mohammad Salim[1*], Mohammad Shahid Masroor[2], Vivek Kumar Singh[1], Shagufta Parween[3]

[1]Sanjay Gandhi Smriti Govt. Autonomous P.G. College, Sidhi, A.P.S. University, Rewa (M.P.), India
[2]People's College of Dental Sciences & Research Center, People's University, Bhopal (M.P.), India
[3]Department of Human Anatomy, All India Institute of Medical sciences (AIIMS), Bhopal (M.P.) India

DOI: 10.36348/sjbr.2022.v07i02.002 | **Received:** 05.01.2022 | **Accepted:** 09.02.2022 | **Published:** 15.02.2022

***Corresponding author:** Dr. Mohammad Salim
Sanjay Gandhi Smriti Govt. Autonomous P.G. College, Sidhi, A.P.S. University, Rewa (M.P.), India

Abstract

This is very unfortunate that even in 21st century most of us are still unaware of the fact that the microbial origin of cancer exists in nature. And, this is all due to the lack of knowledge about their potentialities in causing cancer in human and animals. Further, as in recent past, some of these viruses having high rate of mutabilities and adaptabilities have already been proven their abilities to transform the host cells dividing indefinitely. The present review discusses some of the oncogenic viruses developing human cancers including their mechanisms of cancer development known so far in the same field.

Keywords: Viruses, Human Cancers, v-onc, HPVs, HPyVs, HHVs, Hepatitis viruses, HTLV-1, HIV.

INTRODUCTION

William Coley, M. D., a surgeon of New York in late 19th century, had proposed the parasitic origin of cancer. He, for the first time opined that the cancer might be of microbial origin. This theory in early 20th century faces many hardships as the link between bacteria and human cancers were not established; finally, a strong opposition stood up to pronounce the parasitic theory as dead. Even, in 1911, a biologist of Rockfeller Institute named Peyton Rous when clearly established the virus as a cause of cancer, then unfortunately, no one believed it (Rous 1911) [1]. It was not until 1966 when the same Peyton Rous was awarded a Nobel prize in physiology and medicine for his discovery of Rous chicken sarcoma virus was vindicated as a cause of cancer. It was a milestone contribution in the field of microbial origin of cancer (Weiss and Vogt 2011) [2].

Viral origin of cancer appears to be the second most important risk factor for cancer development in human (Zur Hausen 1991) [3]. Nearly, 20% of all human cancers worldwide may be attributed to viruses (Parkin 2006) [4]. These viruses play an important role in the development of cancer and new evidences link between these two. In fact, the virus by itself does not cause cancer, but it might influence tumor development when the changes occur. The relationship between these two is complicated and not yet very well understood.

An oncovirus is a virus capable of causing cancer having either DNA or RNA genome developing tumor. The possible role of viruses in the development of cancer has been the subject of much intensive studies during the past 50 years. In general, a viral genome, after entering into a living cell, must hijack the cells machinery in such a way to push the cell toward becoming cancer. These viral fragments containing oncogene (v–onc) transform the cells to produce tumors as soon as it expressed. It induces uncontrolled and unlimited growth of cells. Several oncomodulations confirming a strong link between these oncoviruses and the formation of cancer in experimental animals has been established. Perhaps, the most important motto at this juncture has been to work on the protection of tumor suppressor protein so that the tumor is not developed. But unfortunately, it couldn't happen as several viruses containing oncogenes (v-onc) deregulate the synthesis of tumor suppressor protein via the formation of their own proteins. It causes impairment in signal transduction pathways. At present, the identification of these viral proteins causing cancers are the key point in the understanding of viral origin of cancer (Krzysztof Reiss and Kamil Khalili 2003) [5].

Both DNA and RNA viruses have been shown to be capable of causing cancer in humans. DNA tumor viruses are a group of double stranded DNA viruses that alter the glucose metabolism of normal cells (Mustaq *et al.*, 2016) [6]. There are many DNA tumor viruses such as Human Papilloma viruses (HPVs), Human Polyoma Viruses (HPyVs), Human Herpes Viruses (HHVs) and Adenoviruses. Adenoviruses do not cause cancer in human. Similarly, some RNA viruses causing cancer are Hepatitis viruses, Human T-cell leukemia virus and the viruses associated with AIDS (Gaston 2012, Flora and Maestra 2015) [7, 8]. Further, some of the well noted cancers caused by these oncoviruses are described as under:

1. **HPVs –** Cervical, anal, mouth, throat, vaginal and penile cancers.
2. **HPyVs –** Merkel cell carcinoma of the skin; SV-40 causing primary brain and bone cancers; JCV causing lung, colon and brain tumor cancers and BKV causing nephrotic cancer after kidney transplant.
3. **HHVs –** HSV-1 causes thyroid tumor; HSV-2 causes melanoma, cervical and prostate cancers; Varicella zoster causes leukemia and breast tumor cancers; Epstein-Barr virus causes Burkitts lymphoma, nasopharyngeal and gastric carcinoma; Cytomegalovirus causes glioblastoma and salivary gland cancer; Roseolovirus causes demyelination in brain and tumor and HHV-8 causes Kaposis' sarcoma.
4. **Hepatitis viruses –** cause hepatocellular carcinoma.
5. **HTLV-1 –** causes human adult T-cell leukemia (ATL).
6. **HIV –** causes a variety of cancers in immunocompromised patients due to parallel infections.

The present review is an attempt to deal with the study of viral origin of cancer in the light of recent researches done so far in the same field.

DISCUSSION

Currently, the viral origin of cancer is well documented by the researches done so far in the past several decades. The present review described different viruses developing the various kinds of cancers comprising of their nature, disease causing ability and the disease complications causing cancer in human. A number of infectious viral agents have been suspected or recognized to be associated with human cancers including human papillomaviruses (HPV), human polyomaviruses (HPyVs), human herpes viruses, hepatitis viruses, human T-cell leukemia virus-1 and human immunodeficiency viruses (Table 1). They are being discussed in the light of recent researches as under:

Table 1: A List of Viral Origin of Cancer

S. N	Name of Oncogenic Viruses	Types of Cancer (Suggestive Link)	References
1.	**Human papillomaviruses (HPV)** (DNA Tumor Virus)	Cervical, vaginal, penis and anal cancer	Flora and Maestra 2015 [7] Masroor *et al.*, 2020 [9]
2.	**Human polyomaviruses (HPyV5)** (DNA Tumor Virus)	Mesotheliomas and brain tumor	Delianis and Hirch 2013 [10] Toptan *et al.*, 2016 [11] Salim *et al.*, 2014 [12]
	Merkel cell polyomavirus (MCV, MCP_yV_5 or HP_yV_5)	Merkel cell carcinoma	Carter *et al.*, 2009 [16] Faust *et al.*, 2014 [17]
	Simian virus- 40 (SV-40)	Brain and bone cancer	Regis *et al.*, 2004 [19] Biochuk *et al.*, 2010 [20] Qi *et al.*, 2011 [21]
	JC virus (JCV, HP_yV_2)	Brain tumor and lung cancer	Del Valle *et al.*, 2001 [22] Khalili *et al.*, 2003 [23] Zheng *et al.*, 2007 [24]
	BK virus (BKV, HP_yV_1)	Bladder and prostate cancer	Das *et al.*, 2008 [25] Abend *et al.*, 2009 [26] Pino *et al.*, 2013 [27] Syed *et al.*, 2013 [28]
3.	**Human Herpes Virus**		
	Human simplex viruses (HSV_1 and HSV_2) subfamily- α	Malignant thyroid, prostate, vulvar and cervical cancer, Melanoma	Kulomaa *et al.*, 1992 [30] Gupta *et al.*, 2007 [35] Anderson *et al.*, 2016 [41]
	Herpes zoster virus (HHV_3) subfamily- α	Breast, head and neck cancer	Mina *et al.*, 2012 [44] Qian *et al.*, 2019 [46]
	Epstein Barr virus (HHV_4)	Burkitts' lymphoma	Epstein *et al.*, 1964 [47] Masroor 2020 [48]

	Subfamily- γ		
	Human cytomegalovirus (HHV_5) subfamily-β	Mucoepidermoid carcinoma of salivary gland, prostate and breast cancer, glioblastoma	Geder *et al.*, 1977 [64] Melnic *et al.*, 2011 [63] Georges and Amit 2014 [65]
	Human Roseoloviruses (HHV_6 and HHV_7) subfamily- β	Associated with disturbed apoptosis and Li-Fraumeni syndrome causing brain tumor and cancer in various body parts	Kofman *et al.* 2011 [67] Henri *et al.*, 2015 [68]
	Kaposi's sarcoma herpes virus (HHV_8) subfamily - γ	Kaposis' Sarcoma	Pagano *et al.*, 2004 [54] Peng *et al.*, 2020 [69] Salim 2021 [71]
4.	**Hepatitis viruses (HAV, HBV & HCV)** (DNA & RNA Virus)	Hepatocellular carcinoma	Beasley *et al.*. 1981 [72] Choo *et al.*, 1989 [73] Baruch Blumberg 2010 [74]
5.	**Human T-cell leukemia virus –1 (HTLV-1)** (RNA Virus)	T-cell leukemias	Seiki *et al.*, 1982 [75] Gallo 2005 [76] Yoshida *et al.*, 2005 [77] Bellon and Nicot 2007 [78]
6.	**Human immunodeficiency virus (HIV)** (RNA Virus)	AIDS indirectly causing cancers	Silverberg *et al.*, 2011 [79] Silverberg *et al.*, 2013 [80] Gopal *et al.*, 2014 [81] Geoffrey *et al.*, 2020 [82]

1. Human Papillomaviruses (HPVs)

About a dozen of HPVs have been allocated carcinogenic by the IARC in Group 1. They cause cervical cancer in human, which is the third leading cancer in the world in terms of mortality. In addition to cervix uteri HPV can also target sites in the anogenital regions of both the sexes including upper aerodigestive tract (Flora and Maestra 2015) [7]. They are mainly transmitted by vaginal, anal or oral sex. Nearly, 70 % of all cervical cancers are caused by the HPV-16 and HPV-18. These two viruses causing cervical cancer were investigated by a Nobel laureate Zur Hausen, 2010. HPVs inhibits the function of tumor suppressor protein p53 of the host cells (Masroor *et al.*, 2020) [9].

2. Human Polyomaviruses (HPyVs)

Human Polyomaviruses are DNA tumor viruses whose infection is widespread but largely asymptomatic causing non-neoplastic diseases in immunocompromised patients. Today, the human polyomavirus (HPyV) family consists of:

1. Merkel Cell Polyomavirus (MCV or $MCPyV_5$) $HPyV_5$
2. Simian Virus-40 (SV-40)
3. *Trichodysplasia spinulosa* Virus (TSV) $HPyV_8$
4. JC Virus (JCV) $HPyV_2$
5. BK Virus (BKV) $HPyV_1$
6. KI Virus (KIPyV) $HPyV_3$
7. WU Virus (WUPyV) $HPyV_4$
8. MW Virus (MWPyV) $HPyV_{10}$
9. $HPyV_6$
10. $HPyV_7$
11. $HPyV_9$
12. $HPyV_{12}$
13. $HPyV_{13}$

These human polyomaviruses (HPyVs) have been linked to a variety of diseases causing cancer (Delianis and Hirch 2013 and Toptan *et al.*, 2016) [10, 11]. Four viruses of polyomaviridae named as SV40, MCV, BK and JCV have been reported as cancer causing viruses in human. Simian Virus 40 develops mesothelioma in human and has been allocated by the IARC in Group B carcinogen. Merkel cell virus causes Merkel cell carcinoma and its carcinogenicity is classified in Group 2A; the probably carcingenic to humans because their carcinogenicity has not yet been proved in experimental animals. Similarly, the other two viruses as BKV and JCV have been classified as still to be proved cancer causing in human (Salim *et al.*, 2020) [12].

2.1. Merkel Cell Polyomavirus (MCV or $MCPyV_5$)

Merkel cell carcinoma is a very aggressive type of skin cancer mostly found in older people who are generally immunocompromised with higher frequency of transplantations kept under the medication of immunosupressants (Williams *et al.*, 1998, Engels *et al.*, 2002 and Kassem *et al.*, 2008) [13-15]. Currently, no any proper medication or vaccinations are available for the treatment of the same cancer (Carter *et al.*, 2009, Faust *et al.*, 2014) [16, 17].

2.2. Simian Virus – 40

Simian virus-40 was discovered as a contaminant in polio vaccine. And, the people vaccinated during the period 1955 to 1963 for polio were accidently exposed to this oncogenic virus. Later on, it was discovered as a potent carcinogenic bio-organism developing brain and bone cancer, mesiothelioma and non-Hodgkin lymphoma in human (Stratton *et al.*, 2003, Regis *et al.*, 2004, Biochuk *et al.*, 2010 and Qui *et al.*, 2011) [18-21].

2.3. JC Virus (JCV, $HPyV_2$)

The John Cunningham virus or JC virus is only found in humans. The virus produces progressive multifocal encephalopathy (PML) in immunocompromised patients. It crosses the blood-brain barrier to infect the brain causing encephalopathy, demyelination and meningitis. The JC virus is found in huge amount in urban sewage worldwide whose infection took place in a very childhood stage. Nearly, 80% populations are infected with the same virus globally but the virus activated only in those who are immunocompromised. Immunosuppressants are contradicated in these patients (Del Valley *et al.*, 2001, Khalili *et al.*, 2003, Zheng *et al.*, 2007) [22-24].

2.4. BK Virus (BKV or $HPyV_1$)

BK virus is developed in those patients who have undergone kidney transplantations. The virus was isolated from urine in the same patient named as BK. It causes graft disorder as BK virus associated nephropathy (BKVAN) developing bladder and prostate cancer (Das *et al.*, 2008, Abend *et al.*, 2009, Pino *et al.*, 2013, Syed *et al.*, 2013) [25-28].

3. Human Herpes Viruses (HHVs)

Herpes viruses are the DNA viruses derived from the Greek word herpein (to creep) referring to the latent and recurring infections. Eight viruses have so far been identified belonging to the family herpesviridae infecting humans are categorized in subfamilies as α, β and γ. The α – sub family includes herpes simplex viruses (HSV) type 1 & 2 and Varicella zoster virus (VZV or HSV-3); β- subfamily contains cytomegalovirus (CMV or HHV-5) and roseoloviruses (HHV-6 & HHV-7); similarly, Epstein-Barr virus (EBV or HHV-4) and Kaposis' sarcoma virus (KSHV or HHV-8) belong to the γ sub family. The genetic material DNA of all 8 viruses replicated well in nucleus in a wide variety of animals including human. Some of the vertebrates they infected are horses, pigs, mice, cattle's and fishes. It has also been reported that more than 90% of adult humans are at least having one herpesvirus in their lifetime which can remain in a latent form lifelong. They cause either latent or lytic infections. Their latency and reactivation are enough to cause cancer (Grinde 2013) [29]. HSV-2 has also been reported to cause cervical cancer in women. The DNA fragments of genital herpes have been isolated in nearly half the patients suffering from cervical cancer. In addition to cervical cancer, these viruses are also suspected to cause Burkitts' lymphoma, nasopharyngeal carcinoma and possibly vulvar cancer, Kaposis' sarcoma occurring primarily in men of homosexual habit and the cancers of prostate and bladder (Kulomaa *et al.*, 1992, Whitley 1996, Haverkos *et al.*, 2000, Davidson 2010, Brown and Newcomb 2011) [30-34].

3.1. Human Herpes Simplex Viruses (HSVs)

There are two types of HSVs as HSV-1 and HSV-2. They cause oral and genital infections. While HSV1 develops herpetic labialis or cold sores, herpetic gingivostomatitis and herpetic gladiatorum, the HSV-2 is usually involved in producing genital warts, melanoma, thyroid, prostate and cervical cancers. These viruses are simply transmitted by close contact with body fluids via kissing and oral sex. Human herpes viruses have developed numerous mechanisms of immunoevasion causing cancer. Further studies are still needed to elaborate the role of these mechanisms in cercinogensis and to apply these knowledge in the development of novel cancer therapies. However, there are some antiviral drugs that are effective against some kinds of herpes viruses (Kulomaa *et al.*, 1992, Gupta *et al.*, 2007, Opstelten *et al.*, 2008, Jensen *et al.*, 2010, Thomas *et al.*, 2011, Mohan *et al.*, 2013, Chi *et al.*, 2015, Anderson *et al.*, 2016) [30, 35-41].

3.2. Varicella Zoster Virus (VZV, HHV_3)

Varicella zoster virus causes chicken pox and shingles in human. After an infection, the latency of virus is lifelong in human sensory ganglia and is reactivated when a body becomes immunocompromised in future. It produces several limphoproliferative disorders, leukemia, necrotic skin lesions and breast tumors. (Kurtaran *et al.*, 2009, Gilden *et al.*, 2012, Mina *et al.*, 2012, Chiu *et al.*, 2013, Qian *et al.*, 2019) [42-46].

3.3. Epstein – Barr Virus (EBV or HHV_4)

Epstein-Barr virus is an oncogenic virus already placed in Group 1 carcinogenic agents by the IARC 2011. In 1964, Anthony Epstein, Bert Achong and Yunne Barr identified for the first time a new human oncovirus as Burkitt lymphoma virus (Epstein *et al.*, 1964) [47]. This was a type of herpes virus. This is a DNA tumor virus infecting B-cells of the immune system and epithelial cells. These infections are quite known in the society as "kissing diseases" or mononucleosis or "mono". The disease is very easily transmitted simply either by kissing or coughing, sneezing, sharing drinking or eating utensils. As with other herpes viruses, though, not everyone develops the symptoms of kissing disease, their infection is lifelong. Similarly, the prominent period of getting infection has been found to be the early teen age. EBV cancers are most common in Africa and Southeast Asia. The EBV in human causes harmless to life threatening infections causing cancer (Masroor 2020) [48]. A list of these cancers caused by the EBV are given as under:

1. Nasopharyngeal carcinoma (Alibek *et al.*, 2013 and Shinokuma *et al.* 2003)[49,50].
2. Burkitts' lymphoma (Zhang *et al.*, 2013) [51].
3. Hodgkins lymphoma (Gulfaraz 2005) [52].
4. B-cell lymphoproliferative diseases including post-transplant cases (Herrmann and Niedobeitek 2003, Pagano *et al*., 2004, Klein *et al*., 2007, Perez – Ordonez 2007 and Carbone *et al*. 2008) [53-57].
5. Gastric carcinoma (Kuzuschima *et al.*, 1999, McLaughlin Drubin and Munger 2008 and Sousa *et al.*, 2008) [58-60].

6. Epithelial malignancies (Tsao *et al.*, 2015) [61].

3.4. Human Cytomegalovirus (HCMV, HHV_5)

HCMV may cause serious diseases in people with a weakened immune system. Human cytomegalovirus (HCMV) infects most organs of the human body including brain, breast, colon, eyes, kidney, liver and lungs. However, their most preferable place has been reported to be the salivary glands (Koichi Yamanishi *et al.*, 2007) [62]. HCMV remains latent within the body throughout life but it might be reactivated at any time causing mucoepidermoid carcinoma of salivary gland and other malignancies like prostate cancer (Geder *et al.*, 1977 and Melnick *et al.*, 2011) [63, 64]. HCMV has also been reported to cause breast cancer in women (Georges and Amit 2014) [65] and the glioblastoma, a deadly form of cancer in brain (Price *et al.*, 2013) [66]. Most healthy children and adults infected with CMV will recover within time without any complications and do not require antiviral treatment. However, antiviral treatments may improve the prognosis in some patients. There is no commercially available CMV vaccine. Experimental vaccines are being studied.

3.5. Roseoloviruses (HHV_6 & HHV_7)

There are two types of roseoloviruses found in nature as HHV-6 and HHV-7 infecting humans. Surprisingly, these viruses are found in all human populations globally. *Roseola infantum* is characterized by the high fever with rose coloured rashes developed on face, neck, trunk, thighs and legs. This is widespread around the world causing brain cancer in children most commonly involving 6 months to 3 years. Since the salivary glands are the natural reservoir of these viruses, the disease is spread by saliva and not by rashes. The cells infected with the roseoloviruses cause disturbed apoptosis and necrosis developing cancer and death of cells respectively (Kofman *et al.*, 2011, Henri *et al.*, 2015) [67, 68].

3.6. Kaposis' Sarcoma Herpes Virus (KSHV, HHV_8)

Kaposi's sarcoma (KS), a kind of cancer usually developed in immunocompromised patients including AIDS and is caused by the KSHV or HHV-8. KS is characterized by the purplish red coloured lesions found on nose, around the lips, ear and eyes (Peng *et al.*, 2020) [69]. This is a sexually transmitted virus but it seems that it to be spread by some other ways also as direct contact through blood and saliva as well (Antman and Chang 2000, Pagano *et al.*, 2004) [54, 70] and cancer known as primary effusion lymphoma and in many people the multicentric Castleman disease i.e. cancer of the lymph nodes or lymphoma. Further, studies are still required to better understand the role of HSV- 8 in these cancers. Treatment of Kaposis control of HIV infections using HAART is an integral part of successful kaposis sarcoma therapy. Usual therapy may be combined with not only antiviral drugs but anticancer drugs too to prevent and treat infections. Since the KS grows and spreads slowly, their lesions are more often treated with surgery, radiations and intralesional therapies (Salim 2021) [71].

4. Hepatitis Viruses (HAV, HBV & HCV)

The inflammation of liver is hepatitis caused by the hepatitis viruses like A, B, C, D and E. Hepatitis B and C viruses are rather more potent carcinogenic viruses than hepatitis A virus. HBV was investigated in 1960 by Baruch Blumberg for which a Nobel prize in physiology and medicine awarded to him in 1976. In 1980, the oncogenicity of the same virus as potent hepatocellular carcinoma (HCC) in human was established by Palmer Beasley. HCV was investigated by Michel Houghton and Bradly in 1989 and their pathogenicity was established as developing hepatocellular carcinoma worldwide. Though, HAV is not involved in producing liver cancer, it has been linked with some other cancer like non-Hodgkin lymphoma. Similarly, HCV seens to be the more dangerous than HBV as it produces liver cancer asymptomatically. And, a patient dies within a year of infection developing hepatocellular carcinoma if not treated well within time. However, both the viruses as HBV and HCV are quite different in nature. While HBV is DNA virus belonging to the family hepadnaviridae, HCV is an RNA virus of flaviviridae. Both the viruses are classified by the IARC as Group 1 carcinogenesis. Further, both HBV and HCV can be treated with drugs and can be recovered completely within a few months. The effective vaccines are available for HAV and HBV. However, no effective vaccines are available for HCV. The therapies which can arrest the histological progression and the viral replications are followed. Such therapies include α-IFN and lamivudine for hepatitis B and α-IFN and ribavirin for hepatitis C as the drug of choice (Beasley *et al.*, 1981, Choo *et al.*, 1989, Baruch Blumberg 2010) [72-74].

5. Human T-cell Leukemia Virus -1 (HTLV-1)

HTLV-1 was investigated by Mitsuaki Yoshida Bernard Poiesz and Robert Gallo in 1980. It causes human adult T- cell leukemia (ATL). The incubation period of developing ATL is about 20 years or more with the probability of causing cancer is 5%. It causes disabling and fatal diseases in human with no satisfactory means of treatment available so far. HTLV-1 is a RNA virus belonging to a class of viruses known as retroviruses. The retroviruses for their multiplication must go through an extra step called reverse transcription for the formation of new DNA genes. Now, these genes when integrated with the host cell chromosome and expressed phenotypically it sometimes, lead to cancer. HTLV-1 is just like HIV, which is another human retrovirus but HTLV-1 does not cause AIDS. However, the modes of transmission are exactly the same as HIV. This cancer is mostly found in southern Japan, south America, the Caribbean

and in central Africa (Seiki *et al*., 1982, Gallo 2005, Yoshida *et al*., 2005, Bellon and Nicot 2007) [75-78].

6. Human Immuno Virus (HIV)

HIV causing AIDS does not cause cancer directly. In fact, it weakens the immune system by destroying the helper T-cells of WBCs. A weak immune system might let new cancer cells survive long enough to grow and form life threatening tumor. It increases a persons' risk of getting several cancers caused by some other viruses too such as Kaposis sarcoma, cervical cancer, Hodgkin disease, non-Hodgkin lymphoma, anal cancer, lung cancer, oral cancer, throat and skin cancer and many other types of cancers. HIV-2 is considered a Group 1 carcinogen by the IARC (Flora and Maestra 2015) and the role of HIV in genesis of many cancers is supported by the findings of several studies (Silverberg *et al.*, 2011 & 2013, Gopal *et al.*, 2014, Siegel *et al.*, 2019 and Geoffrey *et al.*, 2020) [79-83]. Perhaps, the very discovery of HIV virus causing AIDS in human population had surprised us a lot in such a way that we have forgotten the pain of AIDS patients and our whole energy of research has diverted in killing the virus from the society. If we are not exaggerating the fact, no one has died of AIDS virus itself, but the AIDS patients are dying due to parainfections caused by several microorganisms causing various ailments, diseases and cancers. And, this is all due to the immunity failure caused by the HIV simultaneously (Yarchoan and Uldrick 2018, Justiz and Naik 2021) [84, 85].

Moreover, HIV has always been an overlooked cause of cancer in AIDS patients. And, the AIDS patients are continuously suffering from cancers and they have never been included in any surveillance programme globally except the programmes framed for the reduction of STDs expected to contribute in controlling the HIV oriented cancers simultaneously. Therefore, currently, a better understanding on cancer incidences of HIV patients is required. Unfortunately, even today, there are no drugs and/or vaccines available to prevent the patients from HIV. However, antiretroviral therapy (ART) or highly active antiretroviral therapy (HAART) have been found to be associated with improved survival among patients with AIDS (Diamond *et al.*, 2006) [86].

Further, generally people with HIV go through the same cancer treatment people without HIV go through. Standard treatments for HIV patients having cancer include chemotherapy, radiation, immunotherapy, targated therapy and surgery. Unfortunately, all the antiviral drugs which are available in market can kill the human immunoviruses only outside of human body and still we could not make opportunity to kill them inside the human body. Certainly this is due to their nature of viruses as they are non-living outside the body but behaves like a living organism inside the human body. And, they are being treated as the connecting link between non- living and living matters. Lastly, as to be mentioned that despite all the efforts we made in past, we are still struggling to know the complete molecular biology of the viruses to kill them inside the host especially the AIDS viruses acquiring high rate of mutability and adaptability in the host cells. (Coghill *et al.*, 2015, Zucman *et al.*, 2018) [87, 88].

CONCLUSION

The present review deals with the study of a very paradoxial subject of cancer biology as the viral origin of cancer. Currently, the subject is now fully documented in the scientific society and should be acquainted to all of us that microbial origin of cancer exists. In fact, the story began with the award of a Nobel Prize to Peyton Rous in 1966 for the discovery of Rous sarcoma chicken virus as the casual organism in developing the sarcoma cancer in domestic fowl. Since then several viruses have been investigated to cause cancers in human. Some of them are as human papillomaviruses causing cervical, vaginal, penile and anal cancers: human polyomaviruses causing brain and bone cancer, Merkel cell carcinoma developing lung, bladder and prostate cancer; human simplex viruses causing thyroid, prostate, vulvar and cervical cancer and melanoma; herpes zoster virus causing breast, head and neck cancer; Epstein Barr virus causing Burkitts' lymphoma; human cytomegalovirus causing mucoepidermoid carcinoma of salivary glands, prostate and breast cancer and glioblastoma; human roseoloviruses causing brain tumor and cancer in various body parts; Kaposi's sarcoma herpes virus causing Kaposi sarcoma; hepatitis viruses causing hepatocellular carcinoma; human T- cell leukemia virus causing T- cell leukemias and human immunodeficiency virus causing AIDS and cancers in human.

ACKNOWLEDGEMENTS

This piece of research work is dedicated to the memory of Late Purva Singh, who died recently in her young age. We are also grateful to the institutions concerned for providing us necessary facilities during the course of this research work.

Ethical Clearance: Since the article is purely a review work hence it does not require an ethical clearance.

Conflict of Interest

The authors have declared that no competing interests exist amongst us. They have approved the final version of the manuscript contributing equally.

Financial support and sponsorship

No financial support was granted during the course of this research work.

Abbreviations

WBCs	:	White blood corpuscles
DNA	:	Deoxyribonucleic acid
RNA	:	Ribonucleic acid
HPVs	:	Human papillomavirus
HPyVs	:	Human polyomavirus
HHVs	:	Human Herpes viruses
HSV	:	Human simplex viruses
JCV	:	John Cunningham virus
BKV	:	BK virus
EBV	:	Epstein Barr virus
HIV	:	Human immuno virus
ATL	:	Adult T- cell leukemia
MCV	:	Merkel cell virus
MCPyV	:	Merkel cell polyomavirus
HZV	:	Herpes zoster virus
VZV	:	Varicella zoster virus
CMV	:	Cytomegalovirus
HCMV	:	Human cytomegalovirus
KS	:	Kaposi's sarcoma
KSHV	:	Kaposi sarcoma herpes virus
HAV	:	Hepatitis A virus
HBV	:	Hepatitis B virus
HCV	:	Hepatitis C virus
TSV	:	Trichodysplasia spinulosa virus
ART	:	Anti retroviral therapy
α -IFN	:	α- interferon
AIDS	:	Acquired immunodeficiency syndrome
SV-40	:	Simian virus-40
HTLV-1	:	Human T- cell leukemia virus-1
HCC	:	Hepatocellular carcinoma
p53	:	Tumor suppressor protein
STDs	:	Sexuallly transmitted diseases
PML	:	Progressive multifocal encephalopathy
IARC	:	International agency for research on cancer
BKVAN	:	Bk virus associated nephropahty

REFERENCES

1. Rous P. (1911). A sarcoma of the fowl transmissible by an agent separable from the tumor cells. J. Exp. Med. 13 (4) : 397-411.
2. Weiss R.A., Vogt P.K. (2011). 100 years of Rous sarcoma virus. J. Exp. Med. 208 (12) : 2351-2355.
3. Zur Hausen H. (1991). Human papillomaviruses in the pathogenesis of anogenital cancer. Virology 184 (1) : 9-13.
4. Parkin D.M. (2006). The global health burden of infection associated cancers in the year 2002. Int. J. Cancer 118 (12) : 3030-3044.
5. Krzysztof Reiss & Kamel Khalili (2003). Viruses and Cancer : lessons from the human polyomaviruses, JCV. Oncogene 22 : 6517-6523.
6. Mustaq M., Suhas Darekar & Elena Kashuba (2016). DNA tumor viruses and cell metabolism. Oxidative Medicine and Cellular Longevity 2016 (2016) Article 1D 646834,9 pages.
7. Flora D.S., Maestra L.S. (2015). Epidemiology of cancers of infectious origin and prevention strategies. J. Prev. Med. Hyg. 56 (1) : 15-20.
8. Gaston K. (editor) (2012). Small DNA Tumor Viruses. Caister Academic Press. ISBN 978-1-904455-99-8.
9. Masroor M.S., Salim M., Parween S., & Hidayat-Ulla Khan (2020). Human papillomaviruses capable of causing cancer in human. EC Emergency Medicine and Critical Care 4 (10) : 38-43.
10. Delianis T. & Hirch H.H. (2013) Human polyomavirus in disease and cancer. Virolgy 473 (2) : 63-72.
11. Toptan T., Samuel A. Yousem, Jonhan H.O. & Yuan Chang (2016). Polyomaviruses in cancer. JCI Insight 1(2): e85562.doi: 10.1172/ jci. Insight. 85562.
12. Salim M., Masroor M.S., Parween S. & Prajapati I.P. (2020). An overview on human polyomaviruses developing cancer in humans. The Journal of Medical Research 6 (4) : 125-127.
13. Williams R.H., Morgan M.B., Mathieson I.M., Rabb H. & Rabb (1998). Merkel cell carcinoma in reneal transplant patient : increased incidence ? Transplantation 65 (10) : 1396-1397.
14. Engels E., Frisch M., Goedert J., Biggar R. & Miller R. (2002). Merkel cell carcinoma and HIV infection. The Lancet 359 (9305) : 497-498.
15. Kassem A., Schopflin A., Diaz C. & Zur Hausen A. (2008). Frequent detection of Merkel cell Polyomavirus in Human Merkel cell carcinomas and identifications of a unique deletion in the VP1 gene. Cancer research 68 (13) : 5009-5013.
16. Carter J.J., Paulson K.G., Wipf G.C. & Galloway D.A. (2009). Association of Merkel cell polyomavirus- specific antibodies with Merkel cell carcinoma. J. Natl. Cancer Inst. 101 (21) : 1510-1522.
17. Faust H., Andersson K., Ekstrom J., Hortlund M., Robsahm T.E. & Dillner J. (2014). Prospective study of Merkel cell polyomavirus and risk of Merkel cell Carcinoma. Int. J. Cancer 15-134 (4) : 844-848.
18. Stratton K., Almario D.A. & McCormick M.C. (2003). Immunization safety review: SV-40 contamination of polio vaccine and cancer. The National Academies Press, Washington D.C.
19. Regis A. Vilchez & Janet S. Butel (2004). Emergent human pathogen Simian Virus 40 and its role in cancer. Clin. Microbiol. Rev. 17 (3) : 495-508.
20. Boichuk S., Hu L., Hein J. & Gjoerup O.V. (2010) Multiple DNA damage signaling and repair pathways deruglated by simian virus 40 large antigen. J. virol. 84 (16) : 8007-8020.
21. Qi F., Carbone M., Yang H., & Gaudino G. (2011). Simian virus 40 transformation, malignant mesothelioma and brain tumors. Expert Rev. Respir. Med. 5 (5) : 683-697.
22. Del Valle L., Gordon J., Assimakopoulou M. & Khalili K. (2001). Detection of JC Virus DNA sequences and expression of the viral regulation protein T- antigen in tumors of the central nervous system. Cancer Res. 61: 8287-8293.

23. Khalili K., Del Valle L., Otte J., Weaver M. & Gordon J. (2003). Human neurotropic polyomavirus, JCV and its role in carcinogenesis. Oncogene 22 (33) : 5181-5191.
24. Zheng H., abdel Aziz H.O., Nakanishi Y., Masuda S. & Saito H. (2007). Oncogenic role of JC virus in lung cancer. J. Pathol. 212 (3) : 306-315.
25. Das D., Wojno K. & Imperiale M.J (2008). BK virus as a cofactor in the etiology of prostate cancer in its early stages. J. virology 82 (6) : 2705-2714.
26. Abend J.R., Jiang M. & Imperiale M.J. (2009). BK virus human cancer: Innocent until proven guilty. Semin Cancer Biol. 19 (4) : 252-260.
27. Pino L., Rijo E., Nohales G., Frances A., Ubre A. & Arango O. (2013). Bladder transitional cell carcinoma and BK virus in a young kidney transplant recipient. Transpl. Infect. Dis. 15 (1) : 25-27.
28. Syed Hassan, Zaid Alirhayim, Syed Ahmed & Syed Amer (2013). Case Report: polyoma BK virus: an oncogenic virus? Case reports in Nephrology 2013 (2013), Article ID 858139, 2 pages, http://dx.doi.org/10.1155/2013/858139.
29. Grinde B. (2013). Herpesviruses : Latency and reactivation-viral strategies and host response. J. Oral Microbiol. 5. doi.10.3402/ Jom.V5i0.22766.
30. Kulomaa P., Pavonen J. & Lehtinen M. (1992). Herpes simplex virus induces unscheduled DNA synthesis in virus infected cervical cancer cell lines. Res Virol. 143 (5) : 351-359.
31. Whitley R. (1996). Human herpesviruses, biology, therapy and immunoprophylaxis, Cambridge: Whitley R. and Yamanashi K. (Eds). Cambridge.
32. Haverkos H., Rohrer M. & Pickworth W. (2000) The cause of invasive cervical cancer could be multifactorial. Biomed. Pharmacother. 54 (1) : 54-59.
33. Davidson AJ. (2010). Herpesvirus systematics. Vet. Microbiol. 143 : 52-69.
34. Brown J.C. & Newcomb W.W. (2011). Herpesvirus capsid assembly: insights from structural analysis. Curr. Opin. Virol. 1 : 142-149.
35. Gupta R., Warren T. & Wald A. (2007). Genital herpes. Lancet 370 (9605): 2127-2137.
36. Opstelten W., Neven A.K. & Eekhof J. (2008). Treatment and prevention of herpes labialis. Canadian Family Physician 54 (12) : 1683-1687.
37. Jensen K., Patel A., Larin A. & Vasko V. (2010). Human herpes simplex viruses in benign and malignant thyroid tumors. J. Pathol. 221 (2) : 193-200.
38. Thomas F., Elguero, Brodeur J., Goff Le & Misse D. (2011). Herpes simplex virus-2 and cancer: a medical geography approach. Infect. Genet. Evol. 11 (6) : 1239-1242.
39. Mohan R.P.S., Verma S., Singh U. & Agrawal N. (2013). Acute primary herpetic gingivostomatitis. BMJ Case Reports 2013; 2013: bcr 2013200074.doi10.1136/bcr2013-200074.
40. Chi C.C., Wang S.H. & Kanjirath P.P. (2015). Interventions for prevention of herpes simplex labialis (cold sores on the lips). The Cochrane Database of Systematic Reviews. 8: CD 010095. doi:1002/14651858. CD010095. pub 2.PMID 26252373.
41. Anderson B.J., Mc Guire D. & Ortiz D. (2016). Prophylactic Valacyclovir to prevent outbreaks of primary herpes gladiatorum at a 28-day camp: a 10 year review. Clin.J. Sports Med. 26 (4) : 272-278.
42. Kurtaran B., Payolas S., Candevir a., Komur S. & Aksu H.S.Z. (2009). Disseminated herpes zoster infection in a patient with lymphoma. Turk. J. Med. Sci. 39 (3) : 479-482.
43. Gilden D., Nagel M.A. & Cohrs R.J. (2012). Persistence of *Varicella zoster* virus DNA in salive after herpes zoster. J. Infect. Dis. 205 (7) : 1178-1179.
44. Mina E., Ali Z., Mirsaed M., Reza G. & Masood G. (2012). Detection of *Varicella zoster* in the benign and malignant breast tumors by polymerase chain reaction. Int. J. Mol. Clin. Microbiol. 2 : 153-157.
45. Chiu H.F., Chen B.K., & Yang C.Y. (2013). Herpes zoster and subsequent risk of cancer: a population based study. J. Epidemiol. 23 : 205-210.
46. Qian J., Anita E.H., karki S., Emily B. & Bette L. (2019). Risk of herpes zoster prior to and following cancer diagnosis and treatment: a population-based prospective cohort study. The Journal of Infectious Diseases 220 : 4-11.
47. Epstein M.A., Achong B.G. & Barr Y.M. (1964). Virus particles in cultured lymphoblast from Burkitts lymphoma. Lancet 1 (7335) : 702-703.
48. Masroor M.S. (2020). An oncogenic Epstein-Barr virus developing diseases and cancer in human. The Journal of Medical Research 6 (5) : 249-251.
49. Alibek K., Kakpenova A. & Baiken Y. (2013). Role of infectious agents in the carcinogenesis of brain and head and neck cancers. Infect Agent Cancer 8 (1) 7.doi: 10.1186/1750-9378-8-7.
50. Shinokuma A., Hirakawa N., Tamiya S., Oda Y. & Komiyama S. (2003). Evaluation of Epstein-Barr virus infection in sinonasal small round cell tumors. J. Cancer Res Clin. Oncol. 126 (1) : 12-18.
51. Zhang T., Fu Q., Gao D., Ge L. & Sun L. (2013). EBV associated lymphomas in 2008, WHO classification. Pathology, Research and practice. http://dx.doi.org/10.1016/J.prp.201.3.11.09.
52. Gulfaraz K. (2005).Epstein-Barr virus, cytokines and inflammation:a cocktail for the pathogenesis of Hodgkin's lymphoma? Experimental Haematology. 34 : 399-406.
53. Klein E., Kis L.L. & Klein G. (2007). Epstein- Barr virus infection in humans: from harmless to life endangering virus- lymphocyte interactions Oncogene 26 (9) : 1297-1305.
54. Pagano J.S., Blaser M., Buendia M.A. & Roizman B. (2004). Infectious agents and cancer: criteria for a causal relation. Semin. Cancer Biol. 14 (6) : 453-471.
55. Perez-Ordonez B. (2007). An update on Epstein-Barr virus and nasopharyngeal carcinogenesis. Head Neck Pathol. 1 (2) : 141-145.
56. Herrmann K. & Niedobitek G. (2003). Epstein- Barr virus associated carcinomas : facts and fiction. The J. Pathology 199 (2) : 140-145.
57. Carbone A., Gloghini A. & Dotti G. (2008). EBV-associated lymphoproliferative disorders: classifications and treatment. The Oncologist 13 (5) : 577-585.

58. Mc Laughlin- Durbin M.E. & Munger K. (2008). Viruses associated with human cancer. Biochimica et Biophysica acta 1782 (3) : 127-150.
59. Sousa H., Pinto-Correia A. L., Medeiros R. & Dinis-Ribeiro M. (2008). Epstein-Barr virus is associated with gastric carcinoma. The question is what is the significance? World J. Gastroenterol. 14 (27) : 4347-4351.
60. Kuzuschima K., Nakamura S., Nakamura T., Yamamura Y. & Yokoyama N. (1999). Increased frequency of antigen- specific CD8 (+) cytotoxic T-lymphocytes infiltrating an Epstein- Barr virus associated gastric carcinoma. J. Clin. Invest. I04 (2) : 163-171.
61. Tsao S.W., Tsang C.M., To K.F. & Lo K.W. (2015). The role of Epstein- Barr virus in epithelial malignancies. The J. Pathology 235 (2) : 323-333.
62. Koichi Yamanishi, Arvin A.M., Gabriella C.F., & Whitley R. (2007). Human herpes viruses: biology, therapy and immunoprophylaxis. Cambridge, UK; Cambridge University Press. ISBN 0-521-82714-0
63. Melnic M., Sedghizadeh P.P., Allen C.M. & Jaskoll T. (2011). Human cytomegalovirus and mucodermoid carcinoma of salivary glands: Cell specific localization of active viral and oncogenic signaling proteins is confirmatory of a causal relationship. Exp. Mol. Pathology 92 (1) : 118-125.
64. Geder L., Sanford E.J., Rohmer T.J. & Rapp F. (1977). Cytomegalovirus and cancer of the prostate : *in vitro* transformation of human cells. Cancer Treat. Rep. 61 : 139-146.
65. Georges Herbein & Amit Kumar (2014). The oncogenic potential of human cytomegalovirus and breast cancer. Front Oncol. 4 230.doi:10.3389/fonc.2014.00230.
66. Price R.L., Song K., Bingmer K. & Kwon C.H. (2013). Cytomegalovirus contributes to glioblastoma in the context of tumor suppression mutations. Cancer Research 73 (11): 3441. doi. 10.1158/0008.5472.CAN-12-3846.
67. Kofman A., Marcinkiewicz L., Dupart E. & Brown J. (2011). The roles of viruses in brain tumor initiation and oncomodulation. J. Neuro- Oncology 105 (3) : 451-466.
68. Henri A., Pascale B., & Agnes G.D. (2015). Laboratory and clinical aspects of human herpesviruses 6 infections. Clinical Microbiol. Reviews 28 (2) : 313-335.
69. Peng Z., Wang J., Zhang X., Wamg X. & Jiang L. (2020). Identification of AIDS-associated Kaposis sarcoma: a functional genomic approach. Front. Genetics 10 : 1376.
70. Antman K. & Chang Y. (2000). Kaposis sarcoma. The New England J. Medicine 342 (14) : 1027-1038.
71. Salim M., (2021). Advances in the study of Kaposi's sarcoma in human. Int J. Current Res. And Review 13 (8) : 171-177.
72. Beasley R.P., Hwang L.Y., Lin C.C. & Chien C.S. (1981). Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22707 men in Taiwan. Lancet 2 (8256) : 1129-1133.
73. Choo Q.L., Kuo G., Weiner A.J., Overby L.R., Bradley D.W. & Houghton M. (1989). Isolation of cDNA clone derived from a blood- borne non- A, non-B viral hepatitis genome. Science 244 (4902) : 359-362.
74. Baruch S. Blumberg (2010). Autobiography Nobelprize. org. Retrived 210-03-17.
75. Seiki M., Hattori S. & Yoshida M. (1982). Human adult T-cell leukemia virus: molecular cloning of the provirus DNA and the unique terminal structure. Proceedings of the National Academy of Sciences, U.S.A. 79 (22) : 6899-6902.
76. Gallo R.C. (2005). History of the discoveries of the first human retrovirus: HTLV-1 and HTLV-2. Oncogene 24 (39) : 5929-5930.
77. Yoshida Mitsuaki & Jeang Kuan-Teh (2005). Preface to 25 years of HTLV-1 and ATL research. Oncogene. 24 (39) 5925.doi:10.1038/sj.onc.1208967.
78. Bellon M. & Nicot C. (2007). Telomerase: a crucial player in HTLV-1- induced human T- cell leukemia. Cancer Genomics and Proteomics 4 (1) : 21-25.
79. Silverberg M.J., Chao C. & Leyden W.A. (2011). HIV infection, immunodeficiency, viral replication and risk of cancer. Cancer Epidemiol. Biomarkers Prev. 20 : 2551-2559.
80. Silverberg M.J., Leyden W. & Warton E.W. (2013). HIV infection staus, immunodeficiency and the incidence of non-melanoma skin cancer. J. Natl. Cancer Inst. 105 : 350-360.
81. Gopal S., Achenbach C.J. & Yanik E.L. (2014). Moving forward in HIV-associated cancer. J. Clin Oncol. 32 : 876-880.
82. Geoffrey K.C., Pauline E.J., Nelly Y., Omar M. & Walter G.J. (2020). Types and prevalence of HIV related opportunistic infections/conditions among HIV-positive patients attending Kenyatta National Hospital in Nairobi, Kenya. African Health Science 20 (2) : 615-624.
83. Sigel K., Park L. & Justice A. (2019). HIV and cancer in the veterans health administration system. Semin. Oncol. 46 (4-5) : 334-340.
84. Yarchoan R. & Uldrick T.S. (2018). HIV associated cancers and related diseases. New Engl. J. Med. 378: 1029-1041.
85. Justiz, V. A. A., Naik R. HIV-1 associated opportunistic infections. In: Stat Pearls (Internet). Treasure Island (FL): Stat Pearls Publishing, 2021.
86. Diamond, C., Taylor, T. H., & Im, T. (2006). Highly active anitiretroviral therapy associated with improved survival among patients with AIDS-related primary central nervous system non-Hodgkins lymphoma. *Current HIV Res*, 4, 375-378.
87. Coghill, A. E., Shiels, M. S., Suneja, G., & Engels, E. A. (2015). Elevated cancer-specific mortality among HIV-infected patients in the United States. *J Clinical Oncolgy*, 33(21), 2376-2383.
88. Zucman, D., Mellot, F., & Couderc, L. (2018). HIV-associated cancers and related disease. *New Eugl J Med*, 378(22), 2144-2145.