

# *Infectious Agents and Cancer*

*Dr A. O. Oluwasola, FWACP and Dr A. O. Adeoye, MBChB.*

*Department of Pathology, College of Medicine, University of Ibadan, Ibadan, Nigeria*

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## **SUMMARY**

*The epidemiology of several types of cancers indicate the involvement of several transmissible agents in their development, and in most cases, these seem to be viruses. The classic examples are Burkitt's lymphoma, nasopharyngeal carcinoma (EBV), hepatocellular carcinoma (HBV), and cervical carcinoma (HPV). Most of these cancers show substantial variations in their incidence in different parts of the world and in particular countries, they present significant health problems. Worldwide, infections account for up to 20% of all cancers. Also, there is now ample evidence implicating infection with the *Helicobacter pylori* in the occurrence of gastric carcinoma and gastric lymphoma, and infection with *Schistosoma haematobium* in the occurrence of the squamous cell carcinoma of the urinary bladder. The impact of these infections on the burden of cancer worldwide is becoming increasingly evident because they are largely responsible for the cascade of opportunistic malignancies associated with AIDS. The burden is heaviest among populations in developing countries, reflecting the impact of very early infection with these agents on subsequent risk of cancer. There are currently no vaccines available to prevent these chronic infections, other than for HBV. As a result, changes in behaviour hold the most promise for prevention.*

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### **All Correspondence to Dr A.O. Oluwasola**

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Department of Pathology,  
University of Ibadan,  
PMB 5116, Ibadan, Nigeria.  
E mail: oluwasol@yahoo.com  
Tel. 234-8023266338  
Fax: 234-2-2413545

## **INTRODUCTION**

The epidemiology of several types of cancers indicate the involvement of several transmissible agents in their development, and in most cases, these seem to be viruses. The classic examples are Burkitt's lymphoma, nasopharyngeal carcinoma (EBV), hepatocellular carcinoma (HBV), and cervical carcinoma (HPV). Most of these cancers show substantial variations in their incidence in different parts of the world and in particular countries, they present significant health problems. Worldwide, infections account for up to 20% of all cancers. Although it has been known for decades that naturally acquired viral infections in animals could cause malignancy, the evidence in humans has accumulated more slowly[1]. With the advent of new molecular research tools; there is now strong evidence for the role of several viruses in human malignancy. Also, there is now ample evidence implicating infection with the *Helicobacter pylori* in the occurrence of gastric carcinoma and gastric lymphoma, and infection with *Schistosoma haematobium* in the occurrence of the squamous cell carcinoma of the urinary bladder. Infectious agents constitute an important category of environmental agents causing cancer, as the cancers they cause are potentially preventable and in particular cases there are good prospects for cure using antimicrobial agents.

## **General Pathogenesis**

Carcinogenesis is a multistage process that originates in a single cell, and results from the development and accumulation of multiple genetic alterations. Cancer is a term used to describe a group of malignant tumours with a common characteristic of uncontrolled growth of abnormal cells that have acquired the capability to spread and metastasize to distant site through the circulation. Cancer is of

multifactorial aetiology involving an interplay between genetic and environmental factors (that include infectious agents) leading to a cascade of genotypic and phenotypic changes that culminates in the formation of a malignant tumour[3] (Figure 1).

(EBV), a member of herpes family, which is transmitted primarily via saliva. The EBV viral genes persist in conjunction with the host DNA in a subset of infected white cells and in the upper part of the throat for the remainder of the person's life. Periodically, the virus will replicate

**Figure 1:** Flow chart showing a simplified scheme of the molecular basis of cancer.

*(Modified from Robbin's Pathologic Basis Of Disease[3]).*

### **Chronic and Latent Infections**

Infectious agents implicated in tumorigenesis share in common the ability to either establish latency- that is, for the viral genes to persist in a subset of cells following infection or to become chronic infections under certain conditions. An example of a latent infection is the Epstein-Barr virus

producing new viral particles that are neutralized by the immune response of the individual. Almost all adults have had an EBV infection and are thus carriers of these viral genes [2].

Although these infectious agents are transmissible from person to person, any subsequent malignancy that may develop is not transmissible to

another person. Table 1 gives a list of infectious agents that have been associated with tumour formation.

and 18 produce three proteins with growth –stimulating and transforming capabilities, E5, E6 and

**Table 1:** *Agent* Oncogenic infections associated with tumour formation. *Malignancy*

<i>Agent</i>		<i>Malignancy</i>
Epstein-Barr Virus (EBV)	-	Non-Hodgkin's lymphoma, Hodgkin's lymphoma, Nasopharyngeal carcinoma
Human T-cell leukaemia/ Lymphoma virus –1 (HTLV-1)	-	Adult T-cell leukaemia/ lymphoma.
Hepatitis B virus (HBC)	-	Hepatocellular carcinoma.
Hepatitis C virus (HCV)	-	Hepatocellular carcinoma.
Human papilloma virus (HPV)	-	Cervical cancer, other anogenital cancers, laryngeal cancer, oral cavity cancers
Oncorna virus	-	Lymphomas, leukaemia.
Human herpes virus type 8	-	Kaposi's sarcoma, primary effusion lymphoma
SV 40	-	Mesothelioma
<i>Helicobacter pylori</i>	-	Gastric carcinoma, gastric lymphoma.
<i>Campylobacter jejuni</i>	-	Intestinal lymphoma
<i>Schistosoma haematobium</i>	-	Urinary bladder squamous cell carcinoma
<i>Schistosoma japonicum</i>	-	Liver cell carcinoma
<i>Opistorchis viverini</i>	-	Cholangiocarcinoma.
<i>Clornorchis sinensis</i>	-	Cholangiocarcinoma.
<i>Chlamydia trachomatis</i>	-	? cervical cancer

### HPV and Cervical Cancer

Dr. Zur Hausen and co-workers were the first to demonstrate that specific types of HPV DNA could be identified by southern blot hybridization in the majority of invasive squamous cell carcinomas of the cervix and a substantial number of cervical cancer precursors[4]. Shortly there after, HPV DNA was isolated in tissues from metastatic cervical carcinoma, [5] and in tumour cell lines established from cervical carcinoma, indicating that the HPV was an integral component of the tumours[6]. Case control studies [7] and long term prospective follow-up studies have provided evidence of a central role for persistence of infection with high – risk types of HPV in the pathogenesis of invasive cervical cancer and precursor lesions.

#### *Mechanism of malignant transformation.*

Molecular studies using tissues culture cells have shown that certain types of HPV such as HPV-16

E7. E5 is not essential for transformation as the E5 region is frequently deleted in cervical carcinoma cells[8]. The expression of the E6 and E7 open reading frames (ORFs) from high oncogenic risk HPVs such as types 16 and 18, in established tissues culture cell lines cause the cells to become completely transformed [9].

HPV E7 oncoprotein accounts for the major transforming and immortalizing activity in high risk types of HPVs[10]. It co-operates with activated ras oncogenes for transformation of cervical epithelial cells[11]. The binding of the HPV E7 protein to retinoblastoma (Rb) and the Rb-related pocket proteins block the cell proliferation – inhibitory function of these endogenous tumor suppressors. E7 also sensitizes p53 reactive cells to undergo apoptosis and enhance mutagenicity of chemical carcinogens[12].

The presence of E6 significantly enhance the immortalizing and transforming activities of E7

oncoprotein.. In HPV infected cells, p53 levels are low because E6 –associated, protein-mediated binding of p53 to the E6 protein results in the rapid proteolytic degradation of the bound p53 through an ubiquitin-dependent pathway [13]. This reduces the amount of p53 present within the cell and causes a loss of the p53 repair mechanism. Another possible important role of E6 is telomerase activation, which may occur through the myc oncogene.

Compelling epidemiologic evidence has supported the role of HPV in the development of invasive cervical carcinoma. However, it should be noted that other co-factors have been found to be important in the pathogenesis of HPV- associated invasive cervical carcinoma. These include high parity, low socioeconomic status, smoking, increasing number of sexual partners and a history of sexually transmitted diseases [14]. Based on data obtained from epidemiologic studies, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) has classified HPV 16 and 18 as carcinogens in humans [15].

*Some other cancer-associated viruses:*

EBV is involved in the aetiopathogenesis of Burkitt's lymphoma; including almost all cases occurring among children in central Africa and about 20 percent of the cases elsewhere[2]. Malaria endemicity has also been identified as an important aetiological factor in the development of this tumour. EBV is also clearly involved in about 35 percent to 50 percent of cases of Hodgkin's disease [16]. In addition; EBV is implicated in the occurrence of nasopharyngeal carcinoma. In this tumor, ethnically related genetic factors are thought to be important because the disease is most common in persons of southern Chinese origin [17].

Cancer of the liver can be caused by chronic infection with either HBV or HCV. Both viruses appear to act via chronic hepatitis, causing repeated cycles of cell death and regeneration. In these carriers, liver cancer usually occurs in the presence of cirrhosis. Chronic HBV infection is more common among Asian populations and among sub-Saharan Africans, including Mozambique and Nigeria.

### ***H. pylori and Gastric Cancer***

*H. pylori* infect approximately half the world's population and the infection has been linked to the development of gastric adenocarcinoma and gastric lymphoma. However, majority of infected persons remain asymptomatic throughout their lives,[18] suggesting that other factors such as genetic or environmental (particularly dietary factors) are involved in the pathogenesis. As far back as October 1994, The International Agency for Research on Cancer (IARC), has declared *Helicobacter pylori* infection in humans as carcinogenic and a definite cause of human gastric cancer based on epidemiological data [19].

An analysis of data from 13 countries showed a strong correlation between the incidence of gastric cancer and the prevalence of *H. pylori* infection[20]. Prospective serologic studies have reported that persons with *H. pylori* infection have a three to six fold higher risk of gastric cancer than those without infection[21,22]. This association seems largely restricted to intestinal – type cancers and cancers of the distal stomach[23]. A recent study, however, has shown that both intestinal type and diffuse- type cancers develop in the setting of *H. pylori* infection[24]. These studies have failed to demonstrate an association between gastric cancer and peptic ulcer disease, suggesting that the association of *H. pylori* with gastric cancer is independent of the link between the infection and ulcer disease [22].

Circumstantial evidence suggests that infection with *H. pylori* may also increase the risk of gastric non – Hodgkin's lymphomas. Sixty percent of gastric non – Hodgkin's lymphomas evolve from chronic gastritis a lesion usually caused by *H. pylori* [25]. A region in Europe with a high incidence of gastric non- Hodgkin's lymphoma had a higher rate of *H. pylori* infection than a region with low incidence. The validity of these associations has been given credence to by a report of the resolution of low-grade gastric lymphomas following eradication of *H. pylori* infection with antibiotic therapy [26].

### Pathogenesis Of *H. Pylori* Induced Tumours

The concept of a pre-cancer sequence in the stomach derive from longitudinal studies in Finnish workers [27] and Correa *et al* [28]. These workers studied the natural history of chronic gastritis in circumscribed populations over many years and demonstrated that the common form of intestinal type gastric carcinoma arises on a background of chronic atrophic gastritis and intestinal metaplasia, through a multi-step progression, occurring over a period of 15-20 years from onset of infection. The observation made in some African countries (including Nigeria) [29] and India [30], where high prevalence of *H. pylori* infection is noted alongside a low gastric cancer rate has suggested that *Helicobacter pylori*

is unlikely to be the sole factor driving the precancer-cancer sequence. The view being presently advanced is that *Helicobacter pylori* is a form of promoting agent that provides a continuing source of inflammatory damage [31]. Epidemiological and histopathological studies, [32,33] have shown that the development of diffuse – type cancer is also closely related to *H. pylori* infection.

Most *H. pylori* strains express 95 kD vacuolating cytotoxin, *VacA*, [34] and possess the *cag pathogenicity island* (*cag-PAI*) a 37 kb genomic fragment which encodes for a 120-kD protein CagA [35]. They also elaborate urease, alcohol dehydrogenase and mucolytic factors. All these agents contribute to the development of cancer following *H. pylori* infection. Accumulating evidence suggests that bacterial surface components, particularly BabA, a 78-kD outer membrane protein that binds to the fucosylated Lewis B blood group antigen and pro-inflammatory polymorphisms of the interleukin-1 $\beta$  gene favour the development of gastritis that precede the development of gastric carcinoma [36].

### Schistosoma Haematobium and Urinary Bladder Cancer

Chronic infection with parasitic trematode worms (Schistosomes) is associated with the development of urinary bladder carcinoma in Egypt and elsewhere [37]. Urinary tract disease is a specific trait of infection with *S. haematobium*. Squamous cell carcinoma of the bladder associated with *S.*

*haematobium* tend to be well differentiated and to metastasize locally. In Egypt, squamous cell carcinoma of the bladder accounts for 18 to 28% of all cancers, with an incidence of 10.8 per 100,000 population [38]. The association appears to be consistent in many sub-Saharan nations as well [39]. However, large autopsy series have failed to demonstrate a consistent association with a particular type of tumour [40] and squamous cell carcinoma of the bladder is prevalent in some countries that have a very low prevalence of *S. haematobium* or none at all. *S. haematobium*-associated bladder cancers are often associated with mutations of the p53 and cyclin – dependent kinase inhibitors-2 tumour – suppressor genes [39]. HLA-B16 and Cw2 have been associated with *S. haematobium*-related bladder cancer patients in Egypt [41]. At present, the evidence is sufficient to conclude that *S. haematobium* has a role in causing some type of bladder cancer. However, other risk factors including male sex, tobacco smoking and chemical substances play a role.

### Fungal Carcinogenesis

There are conflicting views on the association between fungi and tumour formation [42, 43]. Fungi are thought to act indirectly, by producing chemical substances (mycotoxins), which induce tumour formation. Chief among the fungal products examined was aflatoxin, a mold-produced contaminant of several important food commodities such as grains, cereals and groundnuts. A report in favour of a possible role for aflatoxin in the pathogenesis of hepatocellular carcinoma, based its conclusion on epidemiological studies and animal models, which suggested that aflatoxin and HBV act synergistically to increase the risk of HCC [42]. On the contrary, another study found aflatoxin to be a potent carcinogen for laboratory rats and suggested that humans are probably refractory to carcinogenic effect of aflatoxin [43]. This study flawed previous epidemiological evidence on the basis of not controlling for confounding cofactors such as HBV infections endemic in the study populations. However, further studies are needed in the area to further ascertain this relationship.

### **HIV/AIDS and Cancer**

Infection with HIV-1 is characterized by a progressive loss of T-cell function and is reflected clinically by opportunistic infections and neoplastic disease, especially virus associated cancers. This association of cancers with HIV infection has been recognized since the beginning of the AIDS pandemic and has served as an important AIDS defining condition.

Tumours arising in HIV infected persons are similar in many respects to those observed in other immunodeficiency disorders and include Kaposi's sarcoma, non-Hodgkin's lymphoma and anogenital carcinoma[44]. HIV weakens the hosts immune defense, consequently, the increased incidence of neoplasia in HIV infection reflects, at least partially, immune dysregulation and inefficient immune surveillance of cancer cells.

available to prevent the onset of carcinogenesis or at least limit the possibility of cell transformation. Two examples of cancer promoting factors that, with vaccination, could potentially reduce the risk of carcinogenesis have been identified [45]. "The first one is the hepatitis B vaccine, which, since 1985, has been in use in Taiwan. In that country every newborn baby is vaccinated against hepatitis B. There is already first data available, which seems to point to the preventive effect of the vaccination against liver cancer.

Furthermore intervention by immunization of infants at high risk – now underway in many populations in which the infection is prevalent – is likely to prevent the disease in future generations.

The other example cited was the human papillomaviruses 16 and 18 and their role in lesions of the cervix. Results of clinical trials currently being conducted in Germany demonstrate that the

**Table 2 :** HIV-associated cancers.

Kaposi's sarcoma	Leukaemia
Non-Hodgkin's lymphoma	Lung cancer
Primary CNS lymphoma	Skin cancers (Squamous cell carcinoma)
Squamous cell carcinoma of cervix	Multiple myeloma
Hodgkin's disease	Germ cell tumours in testis
Lip cancer	Leiomyosarcoma in children.

### **Pathogenesis**

HIV is currently, not thought to cause cancer directly. By crippling the immune system, infection with the virus increases a person's risk of getting several types of cancers, especially those linked to other viruses, e.g. HHV-8 and HPV. Loss of B-cell maturation control has been demonstrated by studies of immunoglobulins associated with AIDS related lymphoma. Many other tumours have been described in greater frequency in HIV –infected individuals, some of these cancers are listed in table 3, but they are not considered AIDS-defining illnesses.

### **Cancer Prevention**

The identification of infectious agents of cancer has become more and more important as vaccines are

vaccines protect against the high-risk papillomavirus infections, which are responsible for cervical cancer and most squamous lesions of the cervix. This provides a basis for hope that a vaccine will be also very effective. In view of the high number of cervical cancers globally, one could theoretically speculate that if every woman would be vaccinated at an age of 10 to 12 years that we would have a tremendous preventative potential, preventing in part close to 12 percent of all cancer cases, which occur presently in females on a global scale.

### **CONCLUSION**

The impact of these infections on the burden of cancer worldwide is becoming increasingly evident because they are largely responsible for the cascade

The burden is heaviest among populations in developing countries, reflecting the impact of very early infection with these agents on subsequent risk of cancer. There are currently no vaccines available to prevent these chronic infections, other than for HBV. As a result, changes in behaviour hold the most promise for prevention.

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