Cancer: Infection and Vaccines

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1 Introduction

Microbial infection by viruses, bacteria and parasites are known to be an important cause of cancers in various organ systems of the human body. According to the International Agency for Research on Cancer (IARC), 15.4% of all cancers have an infective aetiology [1]. That roughly translates to around 2.2 million cancers worldwide in a year. However, the incidence of such infection-attributable cancers is not the same in all parts of the world, with more incidence noted in the less developed nations (23.4%) compared to less incidence in the developed regions (9.2%). The other remarkable fact is that although around 20 distinct cancers have been identified to have association with such infective oncogenic agents, only three such cancers (non-cardia gastric cancer, liver cancer and cervical cancer) account for more than 4/5th of the entire burden [2]. The knowledge of the life cycles, infectivity, infective mechanism, pathogenicity and putative and proven carcinogenesis pathways is important for oncologists, epidemiologists and researchers to develop effective strategies to diminish their adverse impact specifically in terms of cancer burden and on human health at large.

IARC has labelled 12 micro-organisms as carcinogenic agents and this includes eight viruses, three parasites and one bacterium [3] (Table 1). These pathogenic organisms have been known for a long time to mankind but their association with cancers took time to discover. For an example, even though the parasites mentioned below have been known to humankind since the nineteenth century, it was only in 2009 that IARC declared them as carcinogens [4].

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Table 1 List of infective pathogens causing cancer

Pathogen	Year of discovery	Malignancy
Virus		
Epstein–Barr virus (EBV)	1964	Burkitt's lymphoma Diffuse large B-cell lymphoma Hodgkin lymphoma Undifferentiated nasopharyngeal carcinoma Gastric adenocarcinoma Leiomyosarcoma Post-transplant lymphoproliferative disease
Hepatitis B virus (HBV)	1965	Hepatocellular carcinoma
Human T-lymphotropic virus-1 (HTLV-1)	1980	Adult T-cell leukaemia (ATL)
Human genital papillomavirus (HPV) (Subtypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 59 and 59)	1983	Cervical carcinoma Squamous cell head and neck carcinoma Squamous cell anal cancer, penile cancer and vulvar cancer
Hepatitis C virus (HCV)	1989	Hepatocellular carcinoma
Kaposi sarcoma herpesvirus (KSHV/HHV8)	1994	Kaposi's sarcoma Primary effusion lymphoma Multicentric Castleman disease
Merkel cell polyomavirus (MCV)	2008	Merkel cell carcinoma
Bacterium		
Helicobacter pylori	1982	Gastric mucosa associated lymphoid tissue (MALT) lymphoma Gastric non-Hodgkin lymphoma (NHL) Gastric adenocarcinoma
Parasites		
Schistosoma haematobium	1851	Urinary bladder carcinoma
Clonorchis sinensis	1875	Cholangiocarcinoma
Opisthorchis viverrini	1886	Cholangiocarcinoma

2 Mechanism of Action

All the above-mentioned organisms are believed to exert direct carcinogenic effect with one exception, which is HIV-1. The retrovirus HIV-1, by virtue of immunosuppression, indirectly potentiates carcinogenesis by creating favourable conditions for persistent infections by other oncogenic pathogens [5–7]. Examples of direct oncogenicity include cellular gene products such as HPV E6 and E7, EBV LMP1, MCPyV T antigen and HTLV-1 Tax, which influence proliferative and anti-apoptotic activities [8]. The other mechanism is by propagation of chronic tissue injury and a consequent chronic inflammatory response that acts as a fertile ground for development of cancer. Organisms such as HBV, HCV and helicobacter pylori are well-known to do that [9].

3 Oncogenic Viruses

3.1 Papillomaviruses

In the mid-nineteenth century, Dominico Rigonni-Stern observed that nuns rarely contracted cervical cancer whereas prostitutes had more incidence of the disease than other females and linked uterine cancer with sexual behaviour [10]. A century later, subtypes of human papillomavirus (HPV) were linked with cervical cancer. A majority of HPV-induced cancers arise in the zones of transition between stratified squamous epithelia and the single layer (columnar) epithelia of the endocervix, anal canal and the tonsillar crypts. The theory is that there may be dysregulation of the normal coupling of the HPV life cycle to keratinocyte differentiation [11].

The high-risk HPV subtypes include 16, 18, 31, 33, 35, 45, 52 and 58 and these are implicated in the causation of several cancers in the human body including cervical cancer, vaginal and vulvar cancers in females and penile cancer in males and anal and oropharyngeal cancer in both sexes. The lifetime risk of sexual exposure to a high-risk HPV type has been estimated to be more

than 70% and individuals who are unable to clear the infection resulting in chronic or persistent infection are at high risk of developing precursor lesions and cancer [12].

The HPVs encode L1 and L2 capsid proteins and six key early region genes (E1, E2, E4, E5, E6 and E7). E6 protein of high-risk HPVs caused ubiquitin-protein ligase mediated destruction of the guardian of the genome, the tumour suppressor gene p53. It also caused activation of cellular telomerase. On the other hand, E7 proteins interact with the proto-oncogene pRB gene [13–16].

3.2 Polyomaviruses

In 2008, Chang and Moore discovered the fifth known human polyomavirus and named it MCV (Human Polyoma virus 5 or HPyV5) by virtue of its presence in Merkel cell carcinoma (MCC) [17]. Merkel cell carcinoma is a rare but highly aggressive cutaneous malignancy occurring in sun-exposed areas of the body. MCV DNA is present in approximately 80% of MCC cases [18]. The other polyoma virus that is implicated in the causation of cancer is the BK Polyoma virus with association being linked with a small percentage of bladder cancer [19].

3.3 Epstein–Barr Virus (Human Herpesvirus 4 or HHV4)

Nearly all cases of endemic Burkitt lymphoma are EBV-positive and one-fifth of sporadic cases of Burkitt lymphoma that occur in immunocompetent individuals outside of malaria-prone regions have EBV positivity. Half of HIV-associated lymphomas also contain EBV. In addition to these, EBV is also associated with a histologically diverse range of lymphoid cancers such as post-transplant lymphoproliferative disease (PTLD), mixed-cellularity and lymphocyte-depletion subsets of Hodgkin's lymphoma and natural killer (NK)/ T-cell lymphoma [20–22].

The other malignancy with almost universal EBV presence is nasopharyngeal carcinoma, irrespective of whether it occurs in endemic or non-endemic regions. In fact, individuals with rising or relatively high immunoglobulin A (IgA) antibody responses to EBNA1, EBV DNase and/or capsid antigens are at increased risk of developing nasopharyngeal carcinoma. This is one of the early detection methods for high-risk individuals [23–25].

EBV is present in 5 to 15% of gastric adenocarcinomas and more than 90% of gastric lymphoepithelioma-like carcinomas [26].

3.4 Kaposi Sarcoma Herpesvirus (KSHV or Human Herpesvirus 8 or HHV8)

It was in the nineteenth century that dermatologist Moritz Kaposi identified a rare type of indolent cutaneous sarcoma in older men and that was named Kaposi sarcoma. One century later, in the 1980s, with the onset AIDS pandemic, an aggressive counterpart of this sarcoma was reported among younger gay men and an association was established with this type of herpes virus. HHV8 or KSHV is responsible for all types of Kaposi sarcoma (KS), including the classical KS seen in elderly men, AIDS-associated (epidemic) KS, transplantation-associated KS and endemic KS which is seen in sub-Saharan Africa [27–32].

Apart from these, KSHV is also responsible for two forms of B-cell proliferative disorders, namely, multicentric Castleman disease (MCD) and primary effusion lymphoma (PEL).

3.5 Retroviruses

Human T-cell leukaemia virus (HTLV) subtype 1 (HTLV-1), which was identified in 1980, was the first human retrovirus discovered to have association with cancer. Only 2–5% of HTLV-1 infected individuals develop disease [33]. It is associated with various inflammatory disorders [uveitis,

polymyositis, pneumonitis, Sjogren syndrome, myelopathy apart from adult T-cell leukaemia/lymphoma (ATLL)].

HIV-1 is another retrovirus which is associated with a variety of malignancies but these occur through indirect effects of immunosuppression which gives the advantage to several oncoviruses like high-risk human papillomaviruses, polyomaviruses and herpesviruses [34].

3.6 Hepatitis Viruses

It was in 1966 that Blumberg discovered the Australia antigen which is now known to be hepatitis B surface antigen (HBsAg) and 4 years later, Dane discovered the virus. Hepatitis B virus is an enveloped DNA virus and even though HBV replication in the human body per se is not cytotoxic, it is the host immune response in the form of T-cell mediated and proinflammatory cytokine milieu that causes hepatocyte damage. About 5% infections in adults and approximately 90% of infections in neonates result in a chronic infection and one-fifth of those who have persistent infection go on to develop liver cirrhosis, in the background of which hepatocellular carcinoma is seen to arise [35, 36]. On the other hand, hepatitis C virus is a single-stranded RNA virus and although 30% of those who get exposed to this virus, will clear the infection on their own, the remainder will go on to develop chronic infection and subsequent cirrhosis, if left untreated. The risk of hepatocellular cancer is about 1% per year in patients with cirrhosis even after successful sustained virologic response to antiviral treatment [37].

4 Oncogenic Bacteria

4.1 Helicobacter pylori

It is associated with non-cardia gastric adenocarcinoma and lymphoma of the stomach. It is a spiral shaped bacterium that grows in the mucus layer over the epithelial lining of the stomach and is able to survive the harsh acidic environment by secreting an enzyme called urease that converts chemical urea to ammonia and locally neutralizes the acidity [38, 39]. H. pylori infection is widespread all around the world and caused well-tolerated gastritis in most people. In a small fraction of infected people, it induces gastric mucosal atrophy, metaplasia and eventually, cancer (a well-defined sequence of events and elucidated by Correa) [40]. Even then, it is estimated that approximately 75% of the global gastric cancer burden is attributable to this bacterium induced inflammation [41]. Two toxin-encoding genes cytotoxin associated gene A (cagA) and vacuolating gene (vacA) are present in virulent strains of H. pylori [42]. The use of eradication protocols with antibiotics targeting this infection (anti H pylori regimens) and improved hygiene have decreased the incidence of significant H. pylori infections in developed countries. The flip-side to this is the increased risk of gastric cardia and oesophageal carcinoma seen with people in whom H. pylori is eradicated related to gastro-esophageal reflux of acidic gastric content.

5 Parasites Causing Cancer

5.1 Schistosoma haematobium

This was the first blood fluke discovered by Theodor Bilharz in Cairo (Egypt) in 1851 and hence the terminology bilharziasis applied to infections caused by this parasite [43]. Humans are the definitive hosts and freshwater snails are the intermediate hosts for this trematode. Schistosomiasis causes chronic granulomatous cystitis leading to squamous metaplasia of the transitional epithelium and subsequently, development of squamous cell carcinoma of the urinary bladder.

5.2 Opisthorchis viverrini and Clonorchis sinensis

These liver flukes are seen to cause infections mostly limited to the South-east Asian nations (like Thailand, Laos, Cambodia and Vietnam).

The freshwater snails are the first intermediate hosts and certain varieties of freshwater fish become the second intermediate host and thereafter, the metacercarial stage of these flukes become infective to humans and other fish-eating mammals like dogs and cats. These parasites are implicated in causation of intrahepatic cholangiocarcinoma by effecting bile duct chronic inflammation, periductal fibrosis and epithelial hyperplasia and goblet cell metaplasia [44].

6 The Microbiome and Carcinogenesis

An interesting development in cancer research is the increasing importance attributed to the microbiological flora (microbiome) within the body. There is growing evidence to support a function of the microbiome in cancer development in human beings. Studies have shown that enrichment and depletion of particular bacterial taxa were associated with colonic adenomas and carcinomas. There is also suggestion that the faecal microbiome may itself become a screening tool for colorectal cancer. On the other hand, the oral microbiome may harbour potential risk markers for oral and oesophageal cancers. The intactness of the intestinal barrier function is also vital to keep in check bacterial translocation and consequent chronic inflammation at various body sites. Dietary components do play an important role in modifying this barrier function. Future research is destined to unravel the secrets of the microbiome and its association with cancer [45, 46].

7 Infection Control and Prevention in Cancer Patients

Cancer patients are particularly susceptible to community-acquired and hospital-acquired infections (HAI). The basic infection control measures such as hand hygiene, transmission-based precautions, environmental hygiene, aseptic techniques, HAI "bundles" and antimicrobial stewardship are essential components of any hospital infection prevention programme, and the same applies for cancer treatment hospitals with heightened importance. The key components of the infection prevention and control programmes can be discussed under the following headings:

7.1 Hygiene

Personal and environmental hygiene is important in preventing infections in patients, and this is even so more important in the cancer patients who are immunocompromised. Routine inspection of the skin, especially at the sites which are more to infection like intravascular catheter sites, drain sites and areas prone to maceration like the axilla and the perineum is important. Digital rectal examinations, rectal thermometers, enemas and suppositories must be avoided during periods of neutropenia to avoid mucosal breakdown. Chlorhexidine bathing is recommended to reduce transmission of multidrug-resistant organisms (MDROs) and prevent infections. The oral cavity and the gut microbiota are important sources of infections and so stringent periodontal health and healthy diet are important. Especially in the management of head and neck cancers, complete periodontal examination followed by necessary treatment is recommended, especially in patients receiving high-dose chemotherapy, stem cell transplantation and any cancer regimen that is expected to lead to significant immunosuppression. To minimize the risk of mucositis and pneumonia, oral rinses with sterile water or normal saline are recommended 4–6 times per day. Neutropenic patients should routinely brush their teeth with soft bristles, taking care to minimize gingival trauma. Antivirals and antifungals are included in the prophylactic regimen according to the institutional protocols and are often given to patients considered at high risk for serious infection.

7.2 Device Associated Infection

In cancer patients, there is an increased use of intravascular catheters, implantable ports and

peripherally inserted central catheter (PICC) lines and these are often kept in the body for a long duration of time. These predisposes these patients to catheter related infection and complications. Central line associated blood stream infection (CLABSI) prevention "bundle" strategies are aimed to counter such infections by frequently training nursing staff and care givers in these procedures with full barrier precautions, rigorous exit site care with daily assessment and infection control audit [47].

7.3 Environmental Hygiene

The overall environmental hygiene has an important impact in infection prevention. Surveillance of air, water and food quality and prompt corrective action is crucial in preventing infection in cancer patients.

7.4 Education and Awareness of Health Care Personals

Special care should be given to educate patients and healthcare workers regarding measures to reduce risk of exposure to infectious pathogens, such as common bacteria, community respiratory viruses and fungi. In addition, hospital infection control team, clinicians should be aware of the local epidemiology and devise an antibiotic stewardship programme and implement measures to reduce the exposure and spread of antibiotic-resistant pathogens in the institute.

8 Cancer Vaccines

The infectious aetiology of certain cancers provides us an opportunity to take preventive measures to counter the burden of these cancers by means that prevent these infections. One such potent method is development and use of prophylactic vaccines.

8.1 Hepatitis B Vaccines

Hepatitis B vaccine was the first licenced prophylactic vaccine against an infectious cause of cancer [48]. The commercial vaccines available in the 1980s were based on sub virion 22-nm HBV surface antigen (HBsAg) particles purified from the blood of chronically infected people. These were made safe for use by inactivation and absence of the 42-nm virion particles

The second-generation vaccines used recombinant DNA technology and produced HBsAg vaccines in genetically engineered yeast like *Saccharomyces cerevisiae.* These contain HBs protein spikes embedded in 22-nm lipid particles and they closely resemble the HBsAg particles produced during human infections. The method of delivery of this vaccine is by intramuscular injection at 0, 1 and 6 months. A recent development is an HBsAg containing CpG adjuvant (a Toll-like receptor 9 agonist) which is delivered as a two-dose regimen in adults [49].

In 1992, World Health Organization (WHO) recommended universal vaccination programmes targeting infants, with the first dose optimally delivered within 24 h of birth. This is very important because of the fact that the earlier age of infection, the more the chances of chronic infection and hepatocellular carcinoma eventually. A reduction of chronic HBV infection rates of more than 90% have been seen in countries with successful infant vaccination programmes [36]. An example of the effectiveness of HBV vaccination in preventing hepatocellular carcinoma (HCC) is seen from Taiwan. In that country, universal infant vaccination was started in the year 1984 and the observed incidence of HCC in 6- and 26-year-old cohorts born before and after initiation of the programme were 9.2 and 2.3 cases per ten million person-years, respectively, with a striking relative risk (RR) of 0.24 (Confidence interval 0.21–0.29) [50].

8.2 Human Papillomavirus Vaccines (HPV Vaccines)

The overwhelming importance of these particular vaccines is due to the fact that essentially all cervical cancer occurs from HPV infection. Whereas HPV16 and18 are responsible for 70% of cases of cervical cancer, other subtypes, namely HPV31, 33, 35, 45, 52 and 58, cause most of the remaining cancers [51]. Apart from cervical cancers, a vast majority of anogenital cancers (anal cancer, vaginal and vulvar cancer, penile cancer) and a good proportion of oropharyngeal cancers are attributable to HPV infections. HPV16 and 18 are responsible for the lion's share of these cases.

The HPV prophylactic vaccines [52–56] are based on VLPs or non-enveloped virus-like particles, which are composed of copies of the L1 major virion protein in the shape of an icosahedron, mimicking the outer shell of HPV. Cervarix (GlaxoSmithKline, Brentford, United Kingdom) is a bivalent vaccine containing VLPs of subtypes 16 and 18. Gardasil (Merck, Kenilworth, New Jersey) is a quadrivalent vaccine containing the VLPs of subtypes 6, 11, 16 and 18. The HPV subtypes 6 and 11 cause genital warts and are never implicated in cancer. Gardasil-9 offers protection against HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58.

The current CDC (Centres for Disease Control and Prevention, USA) recommendation is for HPV vaccination for all boys and girls at ages 11–12 years to protect against HPV-related infections and cancers. Anyone starting the series before the age of 15 years should receive two doses of the vaccine, with at least 6 months between the first and second doses. Adolescents who receive the two doses less than 5 months apart, need a third dose. The recommendation is for HPV vaccination of all through the age 26 years. Those who start their doses at ages 15–26 years, still need three doses. Three doses are recommended for those who have immunocompromised conditions, between age 9 and 26 years. Adults aged 27–45 years, who are not vaccinated, may opt to get the vaccine after discussion with a physician about their risk of acquiring infection and possible benefit of vaccination [57].

The Indian Academy of Paediatrics Committee on Immunization (IAPCOI) recommends offering HPV vaccine to all females who can afford the vaccine. Vaccination can be given to females as young as 9 years as well as in those aged 13–26 years who have not previously completed vaccination [58].

The impact of HPV vaccination can be understood from the example of Scotland which has high coverage rate of 80% of adolescent girls having completed the complete three doses of Cervarix and approximately 90% having received at least one dose. Decrease was noted in the incidence of cervical intraepithelial neoplasia (CIN) type 3 at the first cervical screening between the 1988 birth cohort and the 1994 birth cohort with values of 11.9 per 100,000 and 2.9 per 100,000, respectively, with the former cohort being the one before the launch of national vaccination programme [59]. However, it should be noted that even after vaccination, girls should get PAP smear done as per guidelines.

9 Therapeutic Vaccines

It is believed that cancer cells arise in the body from time to time but are scavenged or destroyed by the immune system. This process is known as immunosurveillance and it is when the immune system fails to destroy such aberrant cells that a tumour may arise [60]. This idea is not a new concept. In 1890, an American surgeon William Coley reported about the complete regression of a sarcoma in a patient with high fever due to bacterial infection and he put this observation into clinical practice by trying to treat cancer patients with bacteria (Coley's toxin) to induce immune reaction [61]. His approach was highly criticized at that time. In the early 21st century significant response rates were to high dose interleukin 2 against malignant melanoma and renal cell carcinoma [62]. Since then, there has been tremendous development in the immunologic therapies for cancer. In this perspective the immunogenicity of oncogenic microbial agents deserves special mention.

9.1 Bacillus Calmette Guerin (BCG)

It is a vaccine primarily used against tuberculosis but it also has an approved oncologic use. It is used by intravesical route to prevent recurrences in the treatment of non-muscle invasive bladder cancer.

9.2 Sipuleucel-T

It is a cellular vaccine composed of dendritic cells presenting the fusion protein PA2024, which is expressed in prostate cancer cells. Full-length prostatic acid phosphatase is co-expressed with the cytokine GM-CSF to form PA2024. This is then loaded on to autologous dendritic cells isolated from individual patients by leukapheresis. This vaccine was approved in 2010 for the treatment of patients with metastatic castrate-resistant prostate cancer (mCRPC) with minimal or no symptoms [63].

9.3 Talimogene Laherparepvec (T-VEC)

It is an oncolytic, genetically modified herpesvirus that generates an "in situ vaccine" effect. This genetically engineered herpes simplex virus (HSV) is only capable of replicating in cancer cells, where it generates the cytokine GM-CSF. The high levels of local GM-CSF recruit dendritic cells and macrophages and make them antigen-presenting cells (APCs) leading to priming of tumour-specific T cells in the tumour microenvironment after direct intra-tumoral injection. It is approved to treat stage III and IV malignant melanoma patients for whom surgical intervention is not appropriate and with tumours which can be directly injected [64].

10 Conclusion

The world of microbiology is intricately related to the various processes of cancer in the human body, right from the evolution to the existing and future therapies and a detailed knowledge of the same is paramount for the entire community involved in cancer care. Indeed, it is undeniable that a good medical microbiology team is an indispensable component in the multidisciplinary management of cancer.

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