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REVIEW

# The role of infections in the causation of cancer in Kenya

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## Abstract

Cancer constitutes a major health care burden in the world today with the situation worsening in resource poor settings as seen in most Sub-Saharan African (SSA) countries. Infections constitute by far the most common risk factors for cancer in SSA and being a typical country in this region, Kenya has experienced an upsurge in the incidence of various types of cancers in the last few decades. Although there is limited population-based data in Kenya of infections-associated cancers, this review provides an up-to-date literature-based discussion on infections-associated cancers, their pathogenesis, and preventive approaches in the country. The primary infectious agents identified are largely viral (human immunodeficiency virus, human papillomavirus (HPV), Kaposi's sarcoma-associated herpes virus, Epstein–Barr virus, hepatitis B virus (HBV), hepatitis C virus), and also bacterial: *Helicobacter pylori* and parasitic: *Schistosomiasis haematobium.* Cancers associated with infections in Kenya are varied but the predominant ones are Non-Hodgkin lymphoma, Kaposi's sarcoma, Hodgkin lymphoma, Burkitt's lymphoma, cervical, liver, and gastric cancers. The mechanisms of infections-induced carcinogenesis are varied but they mainly seem to stem from disruption of signaling, chronic inflammation, and immunosuppression. Based on our findings, actionable cancer-preventive measures that are economically feasible and aligned with existing infrastructure in Kenya include screening and treatment of infections, implementation of cancer awareness and screening, and vaccination against infections primarily HBV and HPV. The development of vaccines against other infectious agents associated with causation of cancer remains also as an important goal in cancer prevention.

**Keywords** Infectious agents · Infections · Cancer · Pathogenesis · Prevention · Kenya

## Abbreviations

| | |
|---|---|
| AC | Anal cancer |
| AIDS | Acquired immunodeficiency syndrome |
| AIN | Anal intraepithelial neoplasia |
| ART | Antiretroviral therapy |
| BL | Burkitt's lymphoma |
| BLC | Bladder cancer |
| CagA | Cytotoxin-associated gene A |
| CVC | Cervical cancer |
| EBV | Epstein–Barr virus |
| GC | Gastric cancer |
| HAART | Highly active antiretroviral therapy |
| HBeAg | Hepatitis B e antigen |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HCV | Hepatitis C virus |
| HHV | Human herpes virus |
| HIV | Human immunodeficiency virus |
| HL | Hodgkin's lymphoma |
| *H. pylori* | *Helicobacter pylori* |

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| | |
|---|---|
| HPV | Human papillomavirus |
| hr-HPV | High-risk human papillomavirus |
| HSV | Human simplex virus |
| HTLV-1 | Human T-cell lymphotropic virus type 1 |
| IARC | International Agency for Research on Cancer |
| IL | Interleukin |
| KNH | Kenyatta National Hospital |
| LC | Lung cancer |
| KS | Kaposi's sarcoma |
| KSHV | Kaposi sarcoma- associated herpes virus |
| MALT | Mucosa-associated lymphoid tissue |
| MTRH | Moi Teaching and Referral Hospital |
| NADCs | Non-AIDS-defining cancers |
| NF-κB | Nuclear factor-kappa B |
| NHL | Non-Hodgkin lymphoma |
| NK/TL | Natural killer/T-cell lymphoma |
| OSCC | Oral squamous cell carcinoma |
| PLWA | People living with AIDS |
| ROS | Reactive oxygen species |
| *S. haematobium* | *Schistisoma haematobium* |
| SSA | Sub-Saharan Africa |
| STAT | Signal traducer and activator of transcription |
| WHO | World Health Organization |

## Background

Current GLOBOCAN world estimates on cancer incidence and mortality produced by the International Agency for Research on Cancer (IARC) indicate that an estimated 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) and almost 10.0 million cancer deaths (9.9 million excluding nonmelanoma skin cancer) occurred in 2020 [1, 2]. This global burden of cancer is significant as currently, cancer is the first or second leading cause of death before the age of 70 years in 112 of 183 countries and ranks third or fourth in a further 23 countries as per World Health Organization (WHO) estimates in 2020 [2]. Being a typical example of a Sub-Saharan African (SSA) country, Kenya has experienced an upsurge in the incidence and mortality of various types of cancers in the last few decades as shown in Fig. 1 and these estimates are conservative and could be higher given that many cases go unreported and unaccounted [1, 2]. For instance, from 2012 to 2018, the incidence of cancer increased from 37,000 to 47,887 new cases and during the same period, the cancer mortality rose almost 16% from 28,500 to 32,987 [1, 2]. On the other hand, the number of new cancer cases in Kenya is projected to rise by more than 120% over the next two decades [3]. The increasing cancer incidence levels in Kenya is reflective of the effects of major

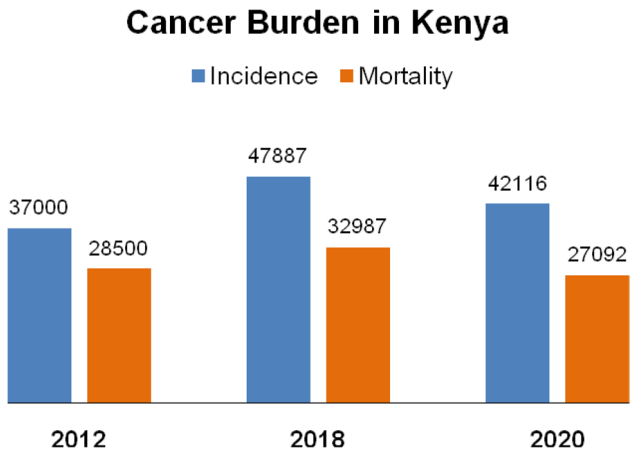


**Fig. 1** New cases and deaths of cancer in Kenya. Source: GLOBOCAN, accessible at https://gco.iarc.fr

societal and environmental changes that have occurred in the past few decades such as dietary transitions, aging population, increased environmental pollution, large-scale farming, occupational drift, industrialization, urbanization, excessive waste generation, climate changes, and the emergence of HIV/AIDS [4].

Infection-attributable cancer cases diagnosed worldwide were estimated to be 2.2 million in 2018 with the primary infectious causes being *Helicobacter pylori*, human papillomavirus (HPV), hepatitis B virus (HBV), and hepatitis C virus (HCV) [5]. In Africa, 24.5% of cancers and 28.7% in SSA were estimated to be due to infectious agents [5]. A recent study in Kenya reported that 30.8% and 48.2% of the total cancer cases sampled in Kenyatta National Hospital (KNH) and Moi Teaching and Referral Hospital (MTRH), respectively, were associated with infectious agents [6]. Among the top cancers attributable to infections in Kenya (Table 1), AIDS-defining cancers which are types of cancers that a person infected with HIV/AIDS is at high risk of developing occur among HIV/AIDS patients due to either poor access to antiretroviral therapy (ART) or poor screening of AIDS-related cancers [7]. Non-AIDS-defining cancers (NADCs), which are cancers not previously associated with HIV/AIDS, have also more recently added to the cancer burden among HIV/AIDS patients due to widespread use of highly active antiretroviral therapy (HAART) [7–9]. This use of HAART has increased longevity among HIV/AIDs patients and therefore they are able to reach risk age for NADCs. Additionally and due to their significant prevalence in the local community, chronic viral infections including the human papillomavirus (HPV), Epstein–Barr virus (EBV), Kaposi's sarcoma herpes virus (KSHV), hepatitis B virus (HBV), hepatitis C virus (HCV), and other parasitic infections such

**Table 1** The interplay between infections and cancer in Kenya

| Infection | Associated cancer | References |
|---|---|---|
| HIV | Non-Hodgkin lymphoma | [6, 20, 26] |
| | Kaposi sarcoma | [6, 20–23, 26] |
| | Squamous cell carcinoma of conjunctiva | [20] |
| | Oral squamous cell carcinoma | [26, 33] |
| | Squamous cell carcinoma of the cervix | [20] |
| HPV | Anal cancer | [6] |
| | Cervical cancer | [6, 39, 42] |
| | Penile cancer | [6, 29] |
| | Vaginal cancer | [6] |
| | Vulvar cancer | [6] |
| KSHV/ HHV-8 | Kaposi sarcoma | [6, 21, 47] |
| EBV/HHV-4 | Nasopharnyx cancers | [6] |
| | Hodgkin lymphoma | [6] |
| | Non-Hodgkin lymphoma | [6] |
| | Burkitt's lymphoma | [51, 52] |
| HBV/HCV | Liver cancer | [6, 32, 60–62] |
| *Helicobacter pylori* | Gastric cancer | [6, 32, 78–81] |
| *Schistosomiasis haematobium* | Bladder cancer | [6, 11, 85, 86] |
| *Opisthorchis viverrini* and *Clonorchis sinensis* | Bile duct cancer | [6] |

*EBV/HHV-4* Epstein–Barr virus/Human herpesvirus 4, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *HIV* human immunodeficiency virus, *HPV* human papillomavirus, *KSHV/HHV-8* Kaposi's sarcoma-associated virus/Human herpesvirus 8

as schistosomiasis or bilharziasis among other infectious agents may constitute important contributors to the rise of cancer in Kenya (Table 1) [6, 10–13]. In this review, we therefore performed an in-depth literature review and discussion on the role of infections on causation of cancers in Kenya.

## Methods

We undertook an electronic search in Medline (using PubMed interface), Scopus, and Clarivate Web of Science through July 2022 using the keywords such as 'cancer/neoplasm/malignancies or cancer type (e.g., cervical cancer, hepatocellular carcinoma/liver cancer, Burkitt's lymphoma, bladder cancer, gastric carcinoma/gastric or stomach cancer, and Kaposi sarcoma),' 'infections,' infectious agents (e.g., HIV, EBV, HCV, HBV, schistosomiasis, HPV, *H. Pylori*, HHV-8/ KSHV, HTLV-1, viruses, bacteria, and parasites),' 'Kenya,' 'Africa,' 'pathogenesis', 'risk factors,' or 'prevention.' The abstracts of all these papers were reviewed to determine whether they were eligible for inclusion if they majorly reported various cancer statistics, infections/infectious agents and cancer, cancer pathogenesis, and preventive/intervention approaches to cancers from infections in Kenya.

## Major infectious agents associated with causation of cancer in Kenya

### Viral agents

Viral agents comprise the largest contributors to infection-related malignancies. Although cancer is generally classified as non-communicable disease, causative association with infectious human viruses such as HIV, HPV, EBV, HBV, HCV, and KSHV among others makes it possible that through transmission of these viral infections, individuals can contribute to the spread of their associated cancers. We discuss below the viral agents associated with causation of cancer in Kenya.

### HIV

Many studies have linked the emergence of HIV/AIDs to an upsurge in various kinds of cancers [7, 9, 14–17]. Sexual transmission is one of the most common ways to acquire HIV and it can also be transmitted via blood [18]. With Kenya being among the highest ranked Sub-Saharan nations (which together constitute up to 71% of all HIV infected people in the world) with people living with AIDS (PLWA), behind South Africa and Nigeria [19], it is most expectable that AIDS-related diseases, complications and

infections would occur at a similar rating. AIDS-defining cancers such as KS, cervical cancer (CVC) and NHL have increased in Kenya as is the case in other African countries like Nigeria and Uganda where there are large numbers of PLWA with many patients being diagnosed with late-stage disease [7, 20–23]. A study by Rogena et al. found that KS was the leading AIDS-defining malignancy in the biggest National hospital in Kenya from 2000 to 2011 [20]. These AIDS-defining cancers among PLWA are majorly due to infections, which are less well controlled due to HIV-associated immune suppression [18]. In addition, it has been found that non-AIDS-defining cancers (NADCs) such as anal cancer (AC), Hodgkin lymphoma (HL), hepatocellular carcinoma, and lung cancer (LC) have also increased among PLWA during the HAART era [24], with twice the number of cases among HIV/AIDS patients on highly active antiretroviral therapy (HAART) than in the corresponding general population [25, 26]. This use of HAART has increased longevity among HIV/AIDS patients enabling them to reach risk age for NADCs. A study by Rogena et al. found that invasive squamous cell carcinoma of the conjunctiva was the leading non-AIDS-defining malignancy in the biggest National hospital in Kenya from 2000 to 2011 [20]. Although the mechanisms by which HIV may promote the development of NADCs are presently not fully understood; oncogenic effects of the HIV virus, immunosuppression, chronic inflammation, higher rates of oncogenic viral co-infections, and traditional cancer risk factors, alongside the exposure to HAART used for HIV/AIDs treatment, have been described to play a role in pathogenesis [25, 27]. It has, however, been established that patients with advanced HIV disease and/or aging-related comorbidities are likely to experience worse outcomes and have poorer tolerance of therapy compared with those with less advanced HIV disease. The introduction and widespread use of HAART have prolonged the lives of PLWA leading to their prolonged exposure to environmental and lifestyle cancer risk factors and co-infection with oncogenic viruses. In light of their immunocompromised status, this prolonged exposure contributes to the emergence of NADCs malignancies. Conversely, HAART has been associated with a positive impact on the incidence of AIDS-defining infectious and malignant diseases including KS and NHL and persistence of oncogenic (high-risk) human papillomaviruses [8, 28]. Screening the populations for HIV and rapid initiation of HAART for positive cases may therefore help to reduce the incidence of AIDS-defining cancers. Whereas the way forward for NADCs malignancies is an ongoing discussion and investigation, efforts directed toward the development of better, cheaper, and readily accessible cancer screening methods may offer the opportunity for early discovery and treatment leading to better outcomes.

## Human papillomaviruses

The 'high-risk Human papillomavirus (hr-HPV) type', a sub-group of mucosal HPVs, is the cause of approximately 5% of all human cancers, which corresponds to one-third of all virus-induced tumors [18]. HPV is mainly transmitted through sexual contact including vaginal, oral, and anal sex and within this high-risk group, HPV16 and HPV18 are the most oncogenic types, being responsible for approximately 50% of all worldwide cervical cancers (CVC) [18]. HPV infects basal epithelial cells and after infection, they either exist in episomal form or can integrate into the cell genome causing genomic instability [18]. For instance, expression of HPV oncogenes E6 and E7 is also dependent on integration: in episomal form expression of E2 protein keeps expression levels of E6/7 low, but during integration, open reading frame of E2 gene is disrupted and E2 no longer is able to control HPV oncogenes [18]. Consequently, E6, E7, and E5 HPV oncoproteins retain keratinocytes in proliferative state, avoiding apoptosis and clearance by the immune system. A study conducted by Senba et al. in Kenya among penile cancer cases also concluded that NF-kappaB in penile cancer is expressed more frequently in the presence of HPV infection than in its absence [29]. Additionally, it has been reported that HPV is able to promote angiogenesis and deregulate cellular energetics [30].

CVC is the second most common female malignancy in Kenya, a trend that is mirrored globally, while oral squamous cell carcinoma (OSCC), another HPV-related cancer, is the sixth most common malignancy in the world whose rise in Kenya has been associated with HIV infection and now appears to present at a relatively young age [6, 31–33]. Chronic infection with the hr-HPV types including HPV16 is casually linked to the development of anal, head and neck, penile, and cervical cancer [6] with the spread of HPV infections being attributable to various forms of sexual intercourse including vaginal, anal, and oral sex [18]. Receptive anal intercourse, a major risk factor for HIV infection, also leads to a high prevalence of anal HPV16 co-infection and HPV-related anal intraepithelial neoplasia (AIN) [34, 35]. Whereas CVC incidence has been constantly decreasing in developed countries due to introduction of national cervical cancer screening programs, it remains among the top cancers in Kenyan women where efforts to boost both awareness and screening are still below par. In Kenya, efforts have been made to provide vaccination against HPV to women and adolescent girls as a way to reduce its spread. Studies showed that although HPV vaccine acceptability among Kenyan women was considerably high (95%, 95% confidence interval [CI]: 92%, 99%), the same group of women

had very little prior knowledge about HPV vaccine and its role in preventing cervical cancer [36] further highlighting the need to intensify awareness campaigns. Due to the above viral links, factors that may contribute to their transmission must become important factors to consider in the control of associated cancers especially cervical, anal, penile, and oral cancers [18]. One such factor that has drawn attention in Kenya is the practice of male circumcision. In a study conducted by Backes et al. among male participants in a randomized controlled trial of male circumcision in Kenya, from May 2006 to October 2007, it was shown that circumcised men had a lower prevalence of HPV-associated flat penile lesions at 0.7% versus uncircumcised at 26.0% and may ultimately reduce male-to-female HPV transmission [37]. It is also worth noting that based on studies conducted elsewhere, strong evidence shows that childhood/adolescent circumcision is also protective against invasive penile cancer [38].

## The HIV and HPV interplay

The preceding two sections have discussed HIV and HPV viruses as independent risk factors associated with various cancer types in Kenya. Additional viral cancer link in Kenya was uncovered by studies conducted by De Vuyst et al. which found a connection between immunosuppression, mainly associated with HIV-positive status, and multiple HPV infection [39]. Since immunosuppression is a known role player in carcinogenesis, this therefore to some extent indirectly implicates HIV-HPV infection in the causation of cervical cancer (HPV-HIV-CVC link). Indeed, another recent Kenyan study showed that the prevalence of cervical cancer is higher among HIV-positive women than in the general population [40, 41] while in other studies in Kenya, prevalence of HPV types in cervical carcinoma in women with HIV have been reported [42, 43]. Being a communicable disease, this further implies that the spread of HIV may indirectly contribute to the spread of cervical cancer. HIV virus just like the HPV has been shown to be more easily transmitted to uncircumcised males therefore compounding the role that lack of circumcision may play, not just in the causation but also in spreading of cervical cancer. Due to the important role that a competent immune system plays in identifying and destroying altered cells, the immunocompromised status makes it easy for such aberrant cells which could eventually be cancerous to thrive, multiply, and spread. As a confirmation of this fact, various studies have shown that with the advent of HIV, the prevalence of various types of cancers, i.e., both AIDS-defining and non-AIDS-defining [20, 25, 26] have increased significantly with the latter being associated with the wide spread use of HAART. Factors that could contribute to the suppression of the immune system like HIV and other viral infections must therefore be treated not just as likely causes of different types of cancers, but further as opportunities for cancer prevention and control.

## Human herpes viruses and HIV interplay

Research findings have associated all human herpes viruses (HHVs) in almost every cancer-implicated branch of the immune system, namely tumor-promoting inflammation, immune evasion, and immunosuppression with some HHVs accomplishing these effects by inhibiting apoptotic pathways and by promoting proliferation [44]. Mechanisms related to immunosuppression and low-grade chronic inflammation could eventually result in the initiation and progression of cancer. HHV-8-HIV-KS has been established with human herpes virus-8 (HHV-8)/ Kaposi's sarcoma-associated herpesvirus (KSHV) and KS which is a rare cutaneous tumor that preferentially develops in cases of severe immunosuppression, such as in HIV/AIDS. In HIV patients with HHV-8 infection, a 20,000- to 50,000-fold increase of KS has been reported. KSHV is most commonly spread through saliva. A likely mechanism of KSHV for causation of cancer was proposed to be through transcriptional repression of the tumor suppressor gene PDZ-LIM domain-containing protein 2 (PDLIM2) [45], an effect that is essential for KSHV-induced persistent activation of NF-κB and signal transducer and activator of transcription 3 (STAT3) and subsequent tumorigenesis and tumor maintenance. NF-κB and its activation pathways are frequently targeted by viruses and aberrant constitutive activation of NF-κB is frequently found in human tumors of diverse tissue origin [31]. In their findings, Sun et al. showed that PDLIM2 repression by KSHV involves DNA methylation [45]. They further observed that the epigenetic repression of PDLIM2 can be reversed by 5-aza-2-deoxycytidine and vitamin D to suppress KSHV-associated cancer cell growth, an observation that bears therapeutic potential for KSHV-mediated cancers, particularly those associated with AIDS. A study conducted in Mombasa, Kenya, found that bacterial vaginosis and herpes simplex virus type two (HSV-2) have consistently been the largest contributors to HIV acquisition risk over the past 20 years [46]. Other studies in Kenya have shown an increasing prevalence of KS-associated herpes virus [6, 47] and also the presence of the open reading frame 75 (ORF75) gene associated with Kaposi's sarcoma herpes virus among HIV-1/AIDS patients [21]. As discussed earlier, HIV infections are a risk factor for the development of both AIDS and non-AIDS-defining malignancies in Kenya. On the other hand, Epstein–Barr virus (EBV) also known as herpesvirus 4 (HHV-4) has been for long associated with BL and now also some cancers such as Hodgkin's lymphoma (HL), nasopharyngeal carcinoma, a sub-type of gastric lymphoma, and NK/ T-cell lymphomas [48]. The detection of EBV in BL tumors is variable with almost all of the endemic form of

BL having EBV which is a pediatric cancer that occurs in regions where there is high levels of malaria transmission particularly in SSA [49] while less than 30% of the AIDS associated are EBV-positive and EBV is rarely detected in the sporadic form of BL [50, 51]. In Kenya, the incidence rate of BL was found to be highest in regions where malaria transmission was also high [52]. EBV infection is transmitted from host to host via mainly salivary contact, and the virus passes through the oropharyngeal epithelium to B lymphocytes, where it establishes a lifelong latent infection which has three main latency patterns, each of which has a role in avoiding host response while promoting B-cell survival/proliferation [18].

## Hepatitis viruses

Hepatocellular carcinoma (HCC) accounts for about 90% of liver cancer cases and the chronic infection of hepatitis B virus (HBV) and/or hepatitis C virus (HCV) has been independently implicated as a major risk factors in its development [53, 54]. Other risk factors of HCC also include aflatoxicosis, smoking, and hereditary conditions such as hemochromatosis and alpha-antitrypsin deficiency [54, 55]. With respect to aflatoxicosis, a study by Zhou et al. reported that aflatoxin B1, HBV, and HCV are directly associated with HCC and play a synergistic role on hepatic carcinogenicity [56] and this is of concern in Kenya as aflatoxin exposure remains a public health problem [57, 58] in the midst of HBV and HCV infections. Liver cancer has been reported to be the 6th most cancer in Nairobi, Kenya [6, 32], and Kenya belongs to the African Region-E characterized by high mortality and hyperendemicity of HBV. Further, strong association between hepatitis B surface antigen (HBsAg) and to some extent hepatitis B e antigen (HBeAg) and HCC has also been documented [59, 60]. Both HBV and HCV can be transmitted via blood, e.g., by sharing needles or through blood transfusions and from mother to baby at birth while HBV can also be transmitted via sexual contact. Mutuma et al. in a recent follow-up study in Kenya reported that of 88 liver biopsies obtained from four urban hospitals, 89% were positive for hepatocellular carcinoma (HCC) and that 75% of HCC positive biopsies were positive for HBsAg demonstrating a strong association between HCC and HBV [61]. Recently, liver cancer was also found to be more frequent among adults and subjects co-infected with HBV and HIV in Kenya [62]. The higher prevalence in males than females has been postulated to occur because of lifestyle differences among either gender; males are more prone to viral infection and alcoholic cirrhosis than females but it is important to note that hormones (testosterone, progesterone, and estrogens) also take part in viral infection and subsequent liver damages [53]. In HBV endemic areas like Kenya, perinatal infections are predominant and introduction of hepatitis B immunization program in newborns, complemented with administration of hepatitis B immunoglobulin for those born to mothers with chronic HBV infection could provide a promising course for the reduction of HBV infections that may ultimately lead to reduction in HCC cases [53]. On the other hand, there has been rising incidence of HCC in Western countries that appear to correlate with the increasing prevalence of HCV yet the biology of the two viruses, HBV and HCV, are remarkably different and consequently have differences in their oncogenic mechanisms [53]. HCV has also been associated with non-Hodgkin lymphoma (NHL) [63]. Generally, viral hepatitis infections are associated with cellular inflammation, oxidative stress, and DNA damage that may lead to subsequent hepatic injuries such as chronic hepatitis, fibrosis, cirrhosis, and finally HCC with other recent studies also having demonstrated that viral hepatitis could trigger the population of hepatic cancer stem cells. Specifically, HBV infection causes chronic, intermittently active inflammation that provides "fertile field" for “mutation, selection, and adaptation” of HBV and the infected hepatocytes, a long-term evolutionary process during HBV-induced carcinogenesis [64]. On the other hand, HCV infection leads to a release of inflammatory and fibrotic mediators such as reactive oxygen species (ROS) cell death signals, hedgehog ligands, and nucleotides which lead to activated hepatic stellate cell that promotes liver scarring through proliferation, contractility, fibrogenesis, matrix degradation, and inflammatory signaling [65]. Since HCC has various etiologies and primary preventive measures such as antiviral therapy therefore need to be combined with dietary modifications, weight loss, and tobacco/alcohol cessation, etc., to reduce HCC development particularly in chronic hepatitis patients.

## Human T-cell lymphotropic virus 1

There is a close association between adult T-cell leukemia/lymphoma and the presence of antibodies to human T-cell lymphotropic virus 1(HTLV-I) but there are few documented studies in Kenya and Africa [6, 50, 66] probably due to lack of diagnostic facilities, although when series of lymphoma cases are reviewed, some 10–20% have characteristics of T-cell Leukemia/lymphoma [67]. HTLV-I spreads via blood, through sexual contact, and from mother to child in the womb or via breastfeeding.

### Bacterial agents; *Helicobacter pylori* as the main player

The prevalent relationship between solid tumors and bacteria has been suggested to be mainly opportunistic rather than causative [68, 69] except *Helicobacter pylori* which is a well-recognized gastric carcinogen [70] and there is also increasing evidence on its causal relationship with colorectal

neoplasia [71, 72] as well as its potential in causing stomach ulcers. It is worth noting that studies have also shown that *H. pylori* is also associated with an increased risk of pancreatic cancer [73]. There is also emerging evidence pointing toward association between *H. pylori* infection and HCC [74]. Furthermore, high prevalence of *H. pylori* has been observed in HCV-positive patients with chronic liver disease [75, 76] but the role of this *H. pylori* in chronic liver disease and HCC progression remain unclear despite the finding that *H. pylori* eradication is beneficial in treating chronic liver disease and HCC patients [77]. Other bacteria that have been suggested to have causative links to cancer include *Mycoplasma* sp. (LC and ovarian cancer), *Chlamydophila pneumonia* (LC), *Salmonella typhi* (gall bladder cancer), *H. hepaticus* (gall bladder cancer), *H. bilis* (gall bladder cancer), *Streptococcus gallolyticus* (colorectal cancer), *C. psittaci* (Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma and ocular adenexa MALT lymphoma), *Chlamydia pneumonia* (Pulmonary MALT lymphoma) and *C. trachomatis* (Pulmonary MALT lymphoma) [69]. Despite declining incidence rates in many Western countries, gastric cancer (GC) remains the second top-most cause of cancer deaths worldwide [72]. In Kenya, incidence rates and trends of gastric carcinoma as well as its association with *H. pylori* infections have also been reported [6, 32, 78, 79]. In a cross-sectional prospective study undertaken in Nairobi, Kenya, among subjects with a history of uninvestigated dyspepsia, *H. pylori* was significantly associated with gastric pathologies investigated and allele T of IL-1 β -511 and long allele of IL-1 RN-L/L was found to play a role in *H. pylori* disease [80]. Recently, from whole genome sequencing of *H. pylori* strain KE21 in a native Kenyan patient diagnosed with a gastric cancer, it was found to be potentially virulent and could trigger oncogenic pathways in gastric epithelial cells [81]. *H. pylori* infection insults gastric mucosa leading to the occurrence of atrophic gastritis which progress to intestinal metaplasia, dysplasia, early gastric cancer, and consequently to advanced GC that occur over decades after infection [82]. The roles of the bacterial genotypes, gene polymorphisms, and host's factors in GC formation have been postulated to be important since GC develops in only 1%-3% of *H. pylori* infected people [83]. Further, the risk of GC is enhanced when individuals are infected by strains expressing the oncoprotein CagA, in particular if CagA has a high number of repeats containing the EPIYA sequence in its C'-terminal variable region or particular amino acid sequences flank the EPIYA motifs. Besides *H. pylori* infections, genetic background and environmental factors particularly, high salt intake, *N*-nitroso compounds, smoking and alcohol drinking have also been implicated in gastric carcinogenesis and/or potentiating the carcinogenic effects of cagA-positive *H. pylori* strains [82]. The mode of transmission of *H. pylori* infections is commonly by close person to person contact, fecal–oral and oral-oral routes and the infection prevalence usually exhibit inverse relationship to indicators of socioeconomic status. Therefore, for Kenya and other similar economies, the improvement of socioeconomic status of the populace and sanitation as well as eradication of the *H. pylori* in the gut through a combination of antibiotics [84] might reduce *H. pylori*-related gastric carcinogenesis mainly among high-risk individuals.

### Parasitic agents; *Schistosomiasis haematobium* as the main player

Several parasitic infections have been associated with different human cancers. They include schistosomiasis (urinary bladder cancer), the liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis* (chongiocarcinoma or bile duct cancer) and the *Plasmodium* species (BL) [5, 6, 49]. Noteworthy and based on available data, are some cases of urinary bladder cancer (UBC) that have been reported in Kenya which are typically characterized by hematuria [6, 85]. A study conducted at the Kenyatta National Hospital (KNH) found that this cancer was most prevalent among people from Central and Eastern parts of the country with Kikuyu, Kamba, and Meru ethnic communities being the most affected [86]. Other than its association with alcohol drinking, smoking and farming, BLC has been linked to *Schistosomiasis haematobia* infection [87]. In Kenya, Schistosomiasis or bilharzias, one of the so-called neglected tropical diseases, which is caused by the parasitic fluke worm schistosoma, is prevalent in the Lake Victoria basin, Eastern province and the inland coastal strip. People become infected when infectious free-swimming worm larvae burrow into skin that has come into contact with contaminated fresh water. Like other parts of the continent, BLC in Kenya is mostly of the squamous cell type, a malignant disease that arises in a background of schistosomiasis or bilharziasis [11], yet in spite of it being preventable, a national control program similar to those found elsewhere in Africa is yet to be instituted in Kenya. The pathology is characterized by serious and irreversible lesions in the urogenital tract induced by chronic infection with the parasite that can eventually lead to squamous cell carcinoma of the bladder. In Angola, an African country with comparable lifestyle to Kenya's, rural environment and agricultural exposure were found to be the main factors responsible for exposure to *S. haematobium* [87]. Primary prevention of bilharzial-related BLC is possible in Kenya if programs are put in place to control the vector (*Bulinus spp.* snails), preventive chemotherapy to those at risk and ultimately by eradication approaches [88].

## Conclusion

Chronic viral infections including human immunodeficiency virus, human papillomavirus (HPV), Kaposi's sarcoma-associated herpes virus, Epstein–Barr virus, hepatitis B virus (HBV), hepatitis C virus, and bacterial infections especially *Helicobacter pylori* and parasitic infections majorly *Schistosomiasis haematobium* constitute major cancer risks in Kenya. Cancers associated with infections in Kenya are varied but the predominant are Non-Hodgkin lymphoma, Kaposi's sarcoma, Hodgkin lymphoma, Burkitt's lymphoma, cervical, liver, and gastric cancers. Since the etiology of cancer is multifactorial, and for the fact that it is a genetic disease highly influenced by environmental factors, the mechanisms of infections-induced carcinogenesis are varied but they mainly seem to stem from disruption of signaling, chronic inflammation, and immunosuppression. There are scant data in Kenya on the role of the Human T-cell lymphotropic virus 1 in causing T-cell leukemia/lymphoma and the liverflukes, *Opisthorchis viverrini* and *Clonorchis sinensis* in causation of cholangiocarcinoma. Based on our findings, actionable cancer-preventive measures that are economically feasible and aligned to existing infrastructure in Kenya include screening and treatment of infections, implementation of cancer awareness and screening, and vaccination against infections primarily HBV and HPV. The development of vaccines against other cancers-associated infectious agents remains also as an important goal in cancer prevention.

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## Declarations

**Conflict of interest** The authors declare that they have no competing interests.

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