



Ontario

Cancer Care Ontario

Action Cancer Ontario



Cancer Risk Factors in Ontario

Infectious Agents



INFECTIOUS AGENTS

Risk factor/exposure	Cancers with sufficient evidence ^a	Cancers with limited evidence ^a
Epstein-Barr virus (EBV)	Nasopharynx, Burkitt's lymphoma, immune-suppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin lymphoma	Stomach, lympho-epithelioma-like carcinoma
Hepatitis B virus (HBV)	Liver*	Bile duct [†] , non-Hodgkin lymphoma
Hepatitis C virus (HCV)	Liver*, non-Hodgkin lymphoma	Bile duct [†]
Human herpes virus 8 (HHV-8) [‡]	Kaposi sarcoma, primary effusion lymphoma	Multicentric Castleman's disease
Human immunodeficiency virus, type 1 (HIV-1)	Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, cervix, anus, conjunctiva	Vulva, vagina, penis, skin (non-melanoma), liver*
Human papillomavirus (HPV) [§]	Cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, tonsil	Larynx
Human T-cell lymphotropic virus, type 1 (HTLV-1) [‡]	Adult T-cell leukemia, lymphoma	
<i>Helicobacter pylori</i>	Stomach , low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma	
Liver flukes (<i>C. sinensis</i> , <i>O. viverrini</i>)	Bile duct [†]	
<i>Schistosoma haematobium</i>	Bladder	
<i>Schistosoma japonicum</i>		Liver

Source: ^aIARC, 2012

* Association is with hepatocellular carcinoma.

[†] Association is with cholangiocarcinoma.

[‡] Agent is a necessary but not sufficient cause of at least one of the associated cancers listed.

[§]HPV types classified by IARC as Group 1 carcinogens: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59.

^{||} Association is with non-cardia gastric carcinoma.

EPSTEIN-BARR VIRUS

Background

- » Epstein-Barr virus (EBV) is a human herpes virus, transmitted primarily through saliva. Some evidence also suggests a potential for sexual transmission.¹⁹⁰
- » EBV infection is common and usually does not cause serious illness. Childhood infections are generally asymptomatic or cause only mild illness, while infection during adolescence and young adulthood (most common in developed countries) can appear as infectious mononucleosis.¹⁹⁰
- » Following primary infection, EBV will enter and, in most cases, remain in a life-long latent state.¹⁹⁰

- Epstein-Barr virus (EBV) causes nasopharyngeal carcinoma, Burkitt's lymphoma, non-Hodgkin lymphoma (immune-suppression-related), extranodal NK/T-cell lymphoma (nasal type), and Hodgkin lymphoma. Limited evidence suggests that EBV may cause gastric carcinoma and lympho-epithelioma-like carcinoma.¹⁹⁰
- EBV is most strongly associated with nasopharyngeal carcinoma and various lymphomas:
 - » EBV DNA can be detected in the tissue of nearly 100% of nasopharyngeal cancers of the undifferentiated form, endemic Burkitt's lymphomas and extranodal NK/T-cell lymphomas (nasal type).¹⁹⁰ In western countries, EBV DNA is found in roughly 40%–50% of Hodgkin lymphomas.¹⁹¹
 - » Several observational studies have found biomarkers of EBV infection associated with nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma and nasal type extranodal NK/T-cell lymphoma.¹⁹⁰ Some cancers appear to have a positive [dose-response](#) relationship with EBV antibodies.^{192,193}
- EBV may [interact](#) with several other factors to modify the risk of developing cancer:
 - » For Burkitt's lymphoma, particularly the endemic type, EBV seems to act as a co-factor with malaria.^{192,193}
 - » The risk of Hodgkin lymphoma is increased for EBV-infected individuals with compromised immune systems or human immunodeficiency virus (HIV) infection.¹⁹⁴
- EBV may induce cancer through several biologic mechanisms: EBV gene products can induce cell proliferation, inhibit [apoptosis](#), induce genomic instability before or during tumour development, and promote tumour maintenance and cell growth.¹⁹⁰

HEPATITIS B VIRUS AND HEPATITIS C VIRUS

Background

- » Hepatitis B virus (HBV) is a small hepadnavirus and hepatitis C virus (HCV) is a flavivirus. HBV and HCV are highly contagious and are transmitted through contact with infected blood via blood transfusions, injection drug use, childbirth and needle-stick injuries. Transmission through sexual contact is also common for HBV because it can be transmitted in body fluids other than blood.¹⁹⁰
 - » HBV or HCV infections can be symptomatic or asymptomatic and may be completely cleared by the host's immune system or may develop into a chronic infection that usually persists throughout life;¹⁹⁰ only 2%–5% of adults infected with HBV will become chronically infected, while most HCV infections will become persistent.¹⁹⁰
- Chronic infection with hepatitis B or hepatitis C causes liver cancer (hepatocellular carcinoma) and may cause cancer of the bile duct (cholangiocarcinoma). Chronic HCV infection (and possibly chronic HBV infection) also causes non-Hodgkin lymphoma, especially of the B-cells.¹⁹⁰
 - Estimates of cancer risk associated with HBV and HCV vary widely across studies, likely due to differences in HBV/HCV prevalence in study populations and in duration of infection:

- **Relative risk** estimates for hepatocellular carcinoma associated with HBV range from 9.6 to 74 and from 1.5 to 87.4 in **cohort** and **case-control studies**, respectively.¹⁹⁰
- Hepatocellular carcinoma risk in people infected with HCV is 2.5- to 88-fold greater than the risk in uninfected people in **cohort studies**¹⁹⁰ and 8.1- to 17.3-fold greater in **meta-analyses**.^{195–197} Non-Hodgkin lymphoma risk has been estimated at 2.5- to 5.7-fold greater among people infected with HCV.^{198,199}
- An increased risk of hepatocellular carcinoma may exist even in the absence of serological markers for current infection.¹⁹⁰
- Co-infection with HBV and HCV is associated with a greater increase in risk of hepatocellular carcinoma than infection with either virus alone. HBV and HCV infection both appear to interact with tobacco use to influence liver cancer risk (see tobacco section on page 7).¹⁵
- HBV and HCV cause **carcinogenesis** *indirectly* through the development of chronic inflammatory liver disease (fibrosis, cirrhosis and, less often, chronic hepatitis). These conditions involve greater turnover of liver cells, which increases the risk of acquiring genetic mutations and may allow for the acquisition of selective growth advantages. HBV and HCV may also directly promote **carcinogenesis** through integration of the viral genome into host DNA and/or expression of viral proteins; further research is needed to clarify the cancer-causing mechanisms of these infections.¹⁹⁰

HUMAN HERPES VIRUS 8 (HHV-8)

Background

- » Human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma herpes virus, is a gamma-2 type herpesvirus, primarily transmitted through saliva.¹⁹⁰
- » The risk of HHV-8 transmission is high among immunocompromised people, including individuals with end-stage renal disease, transplant recipients and individuals with HIV. Homosexual activity, the number of sexual partners and previous history of sexually transmitted infections are also associated with infection.¹⁹⁰

- Human herpes virus 8 (HHV-8) causes Kaposi sarcoma and primary effusion lymphoma, a rare B-cell non-Hodgkin lymphoma. HHV-8 has also been associated with multicentric Castleman's disease.¹⁹⁰
- Several observational studies, mostly in transplant recipients and people infected with HIV, have estimated the risk of Kaposi sarcoma to be at least 10-fold greater in people infected with HHV-8.¹⁹⁰ The excess risk of primary effusion lymphoma associated with HHV-8 infection cannot be quantified since HHV-8 is used in diagnosing this cancer.
- HHV-8 shows a positive **dose-response** relationship with Kaposi sarcoma risk, in people who are and who are not infected with HIV-1, with risk increasing relative to increasing titre of antibodies against HHV-8, a marker of viral load.^{200,201}
- HHV-8 is a necessary, but not sufficient, cause of Kaposi sarcoma. Co-infection with HIV and, to a lesser extent, other immunocompromised states are important co-factors in the development of Kaposi sarcoma.¹⁹⁰
- HHV-8 may induce **carcinogenesis** through several biologic mechanisms, such as promoting cell proliferation, blocking **apoptosis**, inducing genomic instability, and controlling cell migration and tumour progression.¹⁹⁰

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)

Background

- » Human immunodeficiency virus type 1 (HIV-1) is a human retrovirus that attacks the immune system. It is transmitted primarily through sexual contact, contact with infected blood (e.g., through blood transfusions or injection drug use) and mother-to-child transmission during pregnancy, childbirth or breastfeeding.¹⁹⁰
- » HIV infection leads to chronic, progressive illness that leaves the immune system unable to fight off other infections. This advanced stage of disease is known as acquired immunodeficiency syndrome (AIDS).¹⁹⁰

- HIV-1 causes Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, and cancer of the cervix, anus and conjunctiva. HIV-1 may also cause cancer of the vulva, vagina, penis and liver (hepatocellular carcinoma), as well as skin cancers other than melanoma.¹⁹⁰
- HIV infection increases the risk of developing Kaposi sarcoma by as much as several thousand times.¹⁹⁰ Individuals infected with HIV also have a 100–200 times greater risk of non-Hodgkin lymphoma (most often the B-cell type),²⁰² a roughly 30 times greater risk of anal cancer,²⁰² and approximately 10 times greater risk of Hodgkin lymphoma and cancer of the conjunctiva.^{190,202} Cervical cancer risk is 5–10 times greater in HIV infected people than the general population.^{190,202}
- For AIDS-defining cancers, including Kaposi sarcoma and non-Hodgkin lymphoma, an inverse [dose-response](#) relationship with immune competence is apparent; risk rises as immune competence declines over the duration of infection.^{190,203}
- Antiretroviral therapy generally reduces the risk of many HIV-associated cancers but risk still remains high compared to the uninfected population. Since the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s, the incidence of several AIDS-defining cancers, including Kaposi sarcoma and non-Hodgkin lymphoma, has declined.^{190,204,205} Hodgkin lymphoma incidence, however, has unexpectedly increased following the introduction of HAART.^{204,206}
- HIV primarily increases the risk of several cancers indirectly through immunosuppression, which allows increased replication of other oncogenic viruses such as EBV, HHV-8 and HPV.¹⁹⁰

HUMAN PAPILLOMAVIRUS (HPV)

Background

- » Papillomaviruses are small viruses that predominantly infect squamous epithelial cells and lead to abnormal tissue growth. There are over 120 types of human papillomavirus (HPV), transmitted mainly by skin-to-skin or skin-to-mucosa contact, most often during sexual activity.¹⁹⁰
- » HPV infections are most common in the anogenital tract, but can occur on the face, feet, hands, and in the mucosal area of the upper aero-digestive tract.¹⁹⁰
- » Most HPV infections are asymptomatic and will be cleared by the immune system within two years of infection. A small percentage of infections, however, become persistent.¹⁹⁰

- Several types of human papillomavirus (HPV) are classified by the International Agency for Research on Cancer (IARC) as Group 1 [carcinogens](#) in humans (HPV 16,18,31,33,35, 39,45,51,52,56,58,59). HPV 16 causes cancer of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx and tonsil, and is associated with laryngeal cancer. Cervical cancer is also caused by other high-risk HPV types (18,31,33,35,39,45,51,52,56,58,59), with limited evidence supporting a role for several additional HPV types. HPV 18 may also cause cancer of the vulva, vagina, penis, anus, oral cavity and oropharynx. HPV 33 may cause cancer of the vulva and anus.¹⁹⁰
- The [carcinogenicity](#) for HPV is most established and strongest for cervical cancer, but increased risks are seen for other cancers, as well:
 - HPV DNA is found in almost all cervical cancer cases and HPV infection is considered necessary for its development.^{207,208} Women infected with HPV have at least a 50-fold increased risk of cervical cancer or its immediate precursor, cervical intraepithelial neoplasia grade three (CIN3).¹⁹⁰ Persistent infection is particularly important for this cancer's development.¹⁹⁰
 - HPV is found in 20%–50% of vulvar cancers,^{190,209} 60%–70% of vaginal cancers,^{190,209} roughly 45% of penile tumours,^{210,211} 80%–90% of anal cancers,^{190,209} 4%–74% of oral cavity tumours and 20%–70% of tumours in the oropharynx.¹⁹⁰ The HPV-associated risk increases for these tumours are generally less than 5- to 10-fold—far lower than for cervical cancer.¹⁹⁰
- The HPV-associated cancer risk is specific for the type of oncogenic HPV infection:
 - For cervical cancer, HPV 16 and 18 are the most common HPV types present in tumour tissues, detected in over half and over 15% of cases, respectively.²⁰⁸
 - The risk of cervical cancer associated with HPV 16 appears to be an order of magnitude higher than that for all other oncogenic types, although strong risks are also associated with HPV 18 (particularly for cervical adenocarcinoma). Risks are generally lower for other high risk HPV types, although these associations are difficult to study due to a high potential for co-infection with other, and potentially more potent, HPV types.¹⁹⁰
 - In addition, HPV 16 is the most common HPV type detected in tumours of the vulva,²⁰⁹ vagina,²⁰⁹ anus,²⁰⁹ penis,^{210,211} oral cavity and oropharynx,²¹² and it is the only type of HPV presently causally associated with these cancers. Although other HPV types (HPV 18 and 33 [vulva and anus only]) may also cause these cancers, studies of type-specific cancer risk are limited by small numbers of cases and co-infection with other HPV types.¹⁹⁰
- Infection with a high-risk type of HPV is a necessary, but not sufficient, cause of cervical cancer. Co-factors include tobacco smoking, parity, immunosuppression and co-infection with other sexually transmitted agents, such as *chlamydia trachomatis*, herpes simplex virus or HIV. Hormonal factors, diet and genetic susceptibility may also act as co-factors with HPV; more research is needed to investigate these hypotheses.¹⁹⁰
- *In vitro* and *in vivo* evidence supports a direct oncogenic role for HPV, particularly for cervical cancer. HPV may promote [carcinogenesis](#) by becoming incorporated into the host genome or through the production of viral proteins, potentially resulting in disordered cell replication, inhibition of [apoptosis](#), induction of genomic instability, and deregulation of the immune system.¹⁹⁰

HUMAN T-CELL LYMPHOTROPIC VIRUS, TYPE 1 (HTLV-1)

Background

- » Human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus in the same class as HIV, with three possible modes of transmission: vertical mother-to-child transmission, sexual contact and parenteral transmission through injection or blood transfusion. Breastfeeding is the most common transmission mode in endemic areas (e.g., South-west Japan, parts of sub-Saharan Africa, the Caribbean and South America), while sexual contact is most common in the Western world.¹⁹⁰
- » Most individuals infected with HTLV-1 will remain asymptomatic; however, up to 10% of infected people are at risk of developing a serious associated disease during their lifetime.¹⁹⁰

- Human T-cell lymphotropic virus, type-1 (HTLV-1) causes adult T-cell leukemia/lymphoma (ATLL).¹⁹⁰
- HTLV-1 is considered a necessary cause of ATLL and indicators of HTLV-1 infection are used in the ATLL diagnosis. HTLV-1 carriers have an estimated lifetime risk of ATLL of 2%–4%, with the latency period from infection to ATLL development estimated to be upwards of several decades.¹⁹⁰
- Several factors can modify ATLL risk among HTLV-1 carriers: male HTLV-1 carriers have a higher risk than female carriers; childhood infection may pose a higher risk than infection later in life; familial clustering of ATLL in endemic areas suggests genetic influences in ATLL development.¹⁹⁰
- HTLV-1 can induce ATLL in humans through the expression of viral proteins, particularly the Tax protein, which can immortalize and transform T-cells.¹⁹⁰

HELICOBACTER PYLORI

Background

- » *Helicobacter pylori* (*H. pylori*) is a small bacterium that lives in the stomach mucosa and can lead to stomach inflammation. *H. pylori* infection is thought to occur through four possible means: fecal-oral transmission through contaminated water or food, oral-oral transmission among mothers who pre-chew food given to infants, gastric-oral through exposure to infected vomit and iatrogenic through contaminated medical instruments or occupational exposure.¹⁹⁰
- » *H. pylori* infection may be treated by various combinations of antibiotics or other anti-acid drugs, whereas untreated infections will typically persist for life.¹⁹⁰

- *Helicobacter pylori* (*H. pylori*) causes stomach cancer (non-cardia gastric carcinoma) and low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma, a rare form of non-Hodgkin lymphoma.¹⁹⁰
- [Meta-analyses](#) have estimated a 2- to 3-fold increased risk for non-cardia gastric cancer from *H. pylori* infection;^{213–215} this may, however, be an underestimate since *H. pylori* infection often disappears as the stomach becomes increasingly damaged.¹⁹⁰ Individuals with *H. pylori* also have an approximately 3-fold increased risk of MALT lymphoma.²¹⁶

- Cancer risk in the presence of *H. pylori* is influenced by several other factors including *H. pylori* strain, host immune response and environmental factors.¹⁹⁰ Several dietary factors, for example, may **interact** with *H. pylori* to influence gastric cancer development; in the presence of *H. pylori*, high dietary salt may promote gastric cancer, while vegetables and fruit may inhibit the process.^{190,217} Tobacco smoking may **interact** with *H. pylori* in the development of gastric cancer.^{190,217}
- Antibiotic treatment for *H. pylori* infection can reduce the risk of MALT gastric lymphoma; 62%–100% of people with this cancer experience complete remission following eradication of the infection.¹⁹⁰ While *H. pylori* eradication may reduce the progression of early gastric lesions, its effect on advanced premalignant gastric lesions is unclear.¹⁹⁰
- *H. pylori* infection results in chronic inflammation of the stomach mucosa that progresses to permanent damage followed by abnormal tissue development and eventually cancer.¹⁹⁰

OTHER INFECTIOUS AGENTS

Background

- » Liver flukes (*O. viverrini* and *C. sinensis*) and schistosomes (*S. haematobium*) are flat, parasitic worms that can infect and live in the human biliary tract (particularly the intrahepatic bile ducts) and the bladder, respectively.¹⁹⁰
- » Human infection with liver flukes or schistosomes is often asymptomatic and is usually caused by ingesting raw or inadequately cooked fish containing liver flukes or water containing schistosomes in the infectious stage of their reproductive cycle.¹⁹⁰
- » Liver fluke infection is most common in East and Southeast Asia while schistosome infection is most common in Africa and Southeast Asia; both may appear in Canada due to travel or immigration.¹⁹⁰

- Liver flukes (*O. viverrini* and *C. sinensis*) cause cancer of the bile duct (cholangiocarcinoma) and schistosomes (*S. haematobium*) cause bladder cancer.¹⁹⁰
- Studies mostly conducted in Thailand (*O. viverrini*) or Korea (*C. sinensis*) have reported a 1.3- to 27.1-fold greater risk of developing cancer of the bile duct (cholangiocarcinoma) in the presence of *O. viverrini* and a 2.7- to 13.6-fold greater risk in the presence of *C. sinensis*.¹⁹⁰
- **Case-control studies** have found a 1.7- to 15-fold greater risk of urinary bladder cancer associated with *S. haematobium* infection,¹⁹⁰ with the most recent study reporting greater risk with first infection at younger ages (< 15 years) and a long time since diagnosis.²¹⁸
- Liver flukes and schistosomes likely contribute to the development of cancers by inducing chronic inflammation that may activate **oxidative stress** pathways and lead to potentially harmful DNA alterations. Liver flukes may also directly activate cell proliferation and inhibit **apoptosis**.¹⁹⁰