Cancer Care Ontario

Burden of Cancer Caused by Infections in Ontario

Ontario
Cancer Care Ontario

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Foreword

Burden of Cancer Caused by Infections in Ontario is the seventh report in Cancer Care Ontario's Cancer Risk Factors in Ontario series.

The first report in the series summarized the epidemiologic evidence for a wide range of cancer risk factors, including infectious agents. The next five reports provided information on the prevalence, distribution and related cancer risk in the province of several behavioural risk modifiers, including tobacco, alcohol, environment and occupation, as well as healthy weights, healthy eating and active living. The report series supports one of Cancer Care Ontario's key strategic priorities to reduce chronic disease through prevention.

It has been known for several decades that certain infections, such as human papillomavirus (HPV), have the potential to cause cancer in humans. Information on the link between infections and cancer and on ways to prevent cancers resulting from infections, continues to evolve as new scientific evidence becomes available. *Burden of Cancer Caused by Infections in Ontario* examines bacteria, viruses and parasites that have been classified as "carcinogenic to humans" by the International Agency for Research on Cancer, with a focus on those relevant to Ontario. It describes the distribution of the included cancer-causing infections and their associated cancers in Ontario, estimates the number of cancer cases diagnosed in Ontario that are a result of infections, and outlines appropriate prevention efforts.

The Ontario-specific estimates of the cancer burden from the infections and discussion of current provincial efforts and future opportunities for reducing exposure to cancer-causing bacteria, viruses and parasites will support public health planners and policy makers in identifying priority areas for prevention efforts.

Sincerely,

Linda Rabeneck, MD MPH FRCPC
Vice-President, Prevention and Cancer Control
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Key Messages

Purpose

- This report describes the epidemiology and distribution of cancers associated with specific infectious agents (bacteria, parasites and viruses) in Ontario.
- It quantifies the cancer burden of these infections and describes current and potential prevention efforts.
- This report is intended to inform Ontario-specific cancer prevention programs and policies, and help prioritize areas for future prevention efforts.

Methods

- The cancer burden from infections was estimated for Ontario by calculating the proportion of cancer cases that could have been prevented if seven cancer-causing infections were removed from the Ontario population. This proportion was then applied to Ontario Cancer Registry incidence data for 2013.
- Where possible, plausible ranges around each input parameter used in the calculations were considered in order to account for uncertainty or variation around the input parameters.

Findings

- In 2013, approximately 3,100 (plausible range 2,443 to 3,591) new cancer cases diagnosed in Ontario (equivalent to about four percent of all new cancers) were attributed to seven infectious agents: human papillomavirus (HPV), *Helicobacter pylori (H. pylori)*, hepatitis C virus (HCV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), human herpesvirus 8 (HHV-8) and human T-cell lymphotropic virus, type 1 (HTLV-1).
- Of the 15 cancer types that are known to be wholly or partially caused by infection with one or more of the infectious agents examined in this report, 32 percent of their cases combined were attributable to infection.
- There are known measures to prevent infection and thereby reduce the number of cancers linked to HPV, *H. pylori*, HCV and HBV, which together account for most of the cancer cases attributable to infection in Ontario, and human immunodeficiency virus, type 1 (HIV), which plays an important role as a cofactor in causing cancer.

Importance of findings

- Cancers that are caused by these infections can, for the most part, be prevented by known methods and there is potential for improving current prevention strategies.
- By quantifying the burden of cancer associated with infections, it is possible to measure the impact of prevention strategies over time.

Next steps

- This report is intended to inform policy and prevention priorities for cancers caused by these infectious agents.
- Steps can be taken to reduce the burden of cancer associated with infections, such as:
  - vaccine and treatment administration to all of those who the National Advisory Committee on Immunization recommends;
  - preventing blood-borne and sexually transmitted infections among all who are susceptible; and
  - gaining a greater understanding of the prevalence and distribution of *H. pylori*, and the potential for targeted screening and treatment of this infection.

Executive Summary

Overview

Burden of Cancer Caused by Infections in Ontario is the seventh report in Cancer Care Ontario's Cancer Risk Factors in Ontario series. It addresses viruses, bacteria and parasites that the International Agency for Research on Cancer has determined to be "carcinogenic to humans,"[1] with a focus on infections relevant to Ontario. This report estimates the number of cancer cases diagnosed in Ontario that are a result of infection with these cancer-causing infectious agents, and outlines opportunities to improve prevention efforts for their associated cancer types.

Methods

For this report, population attributable fractions (PAFs) were calculated to determine the number of new cancer cases diagnosed in Ontario from infections. A PAF is an estimate of the proportion of disease cases that could be prevented if a given risk factor was eliminated from the population.[2] PAFs were calculated for the following infectious agents: human papillomavirus (HPV), *Helicobacter pylori (H. pylori)*, hepatitis C virus (HCV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), human herpesvirus 8 (HHV-8) and human T-cell lymphotropic virus, type 1 (HTLV-1). Because human immunodeficiency virus, type 1 (HIV) acts as a cofactor with some of the viruses described in this report, a PAF was not calculated, in order to avoid double counting cases.

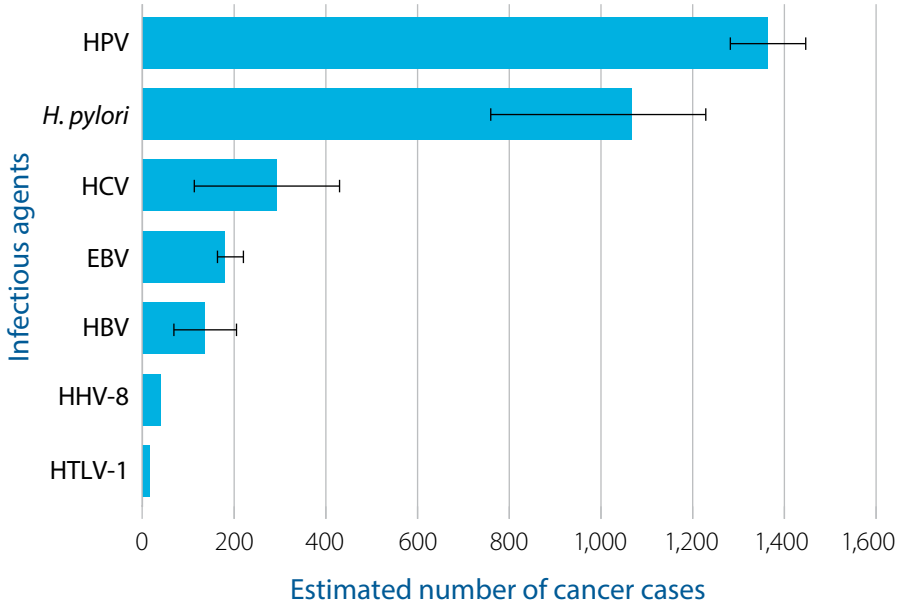
Ontario-specific PAFs were calculated for each cancer type associated with a given infection, using methods described in a previously published international study on the same topic. Inputs into each calculation included the Ontario-specific prevalence of the infection in the population (or among cases of a specific cancer type) and/or the relative risk associated with a given infection and cancer type. To account for uncertainty and variation in the input data, plausible ranges (based on relevant studies or reports) were calculated around each estimate. The total number of cancer cases linked to infections was estimated by calculating PAF estimates and plausible ranges by using the best available data and then applying these fractions to Ontario cancer incidence data for 2013.

> This report estimates the number of cancer cases diagnosed in Ontario that are a result of cancer-causing infectious agents, and outlines opportunities to improve prevention efforts for their associated cancer types.

Findings

In 2013, approximately 3,100 (plausible range 2,443 to 3,591) new cancer cases diagnosed in Ontario were from seven cancer-causing infections. These diagnoses account for roughly four percent of all new cancer cases in Ontario and 32 percent of the total cases of the 15 cancer types that are known to be associated with one or more of these infections. A summary of the number of cancers estimated to be attributed to each infection is presented in Figure ES-1.

FIGURE ES-1 Estimated number of cancer cases attributable to infectious agents, Ontario, 2013



SOURCE: Ontario Cancer Registry, 2016 (Cancer Care Ontario)
NOTES: HPV = human papillomavirus; *H. pylori* = *Helicobacter pylori*; HCV = hepatitis C virus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HHV-8 = human herpesvirus 8; HTLV-1 = human T-cell lymphotropic virus, type 1. ⊢⊣ represent plausible ranges (based on a range of studies or reports) for number of cancer cases attributable to each infectious agent, and no ⊢⊣ for HHV-8 and HTLV-1 reflect necessary but not sufficient relationships with associated cancers (i.e., PAF = 100%).

Compared to the carcinogens examined by Cancer Care Ontario in previous reports, infections are responsible for a larger cancer burden than alcohol consumption (responsible for between 1,000 to 3,000 cancer cases) or obesity (responsible for about 2,600 cancer cases), but less than the environment (responsible for between 3,500 to 6,500 cancer cases).[3-5] Tobacco is the modifiable risk factor responsible for the most cancer cases, which total almost 10,000.[6]

Because just under 3,000 cancer cases in Ontario were from HPV (plausible range 1,281 to 1,447 cancer cases per year), *H. pylori* (plausible range 759 to 1,229 cancer cases per year), HCV (plausible range 113 to 430 cancer cases per year) and HBV (plausible range 68 to 206 cancer cases per year), all of which have known means of prevention, efforts to improve prevention of these infections is the best way to reduce the burden of infection-associated cancer in Ontario.

Reducing the burden of cancer associated with infections

There has been a substantial increase in understanding of the role that infection plays in the development of cancer over the past few decades. A number of prevention measures are in place in Ontario to prevent and control cancer-causing infections and their associated cancers, such as blood supply screening, school-based vaccination programs, efforts to increase public awareness of the health risks of unsafe sex, harm reduction approaches (e.g., needle exchanges) and general infection control practices. Nonetheless, there are identifiable opportunities to decrease the cancer burden attributable to infections in Ontario.

The considerable cancer burden attributable to HPV, *H. pylori*, HCV and HBV, all of which have known means of prevention, suggests that prevention efforts to address these agents, along with efforts to improve the health and well-being of people infected with HIV, is the best way to decrease the cancer burden from infections in Ontario. Potential prevention opportunities include:

- **HPV:** Improving population coverage and the scope of the HPV vaccination program by providing the school-based vaccine earlier than Grade 7 and extending the catch-up period beyond Grade 12 for those who miss a dose; expanding public funding for the vaccine to a broader age range; rapidly adopting use of new vaccines as they become available; and increasing awareness that the vaccine is available in public health units to men who have sex with men up to age 26 (free of charge). Other opportunities to prevent HPV-associated cancers include continued education about the importance of cervical screening, integrating HPV testing into cervical screening and researching the value of screening for other HPV-associated cancer types.

- ***H. pylori*:** Continuing to monitor the results of treatment trials underway,[7] and assessing their potential value for preventing *H. pylori*-associated cancers.
- **HCV:** Improving early detection and the subsequent treatment of HCV infections, and promoting appropriate and consistent screening of high risk groups by primary care providers.
- **HBV:** Collecting and analyzing data on the effectiveness of the existing vaccination program on an ongoing basis, so that appropriate changes can be made as needed,[8] screening children for HBV before vaccinating them if their families have immigrated from endemic countries, providing HBV treatments more widely and following up with people who have been in contact with those who are infected.
- **Surveillance:** Ongoing tracking of infection prevalence, sub-types and cancer incidence is needed to prevent cancer-causing infections of all types and their associated cancers.

It is hoped that this report will inform Ontario-specific cancer prevention programs and policies, and help prioritize areas for future prevention efforts.

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Context

Objectives

The objectives of this report are to:

- describe the epidemiology and distribution of cancers associated with infections in Ontario;
- quantify the burden of cancer from infections in Ontario; and
- describe efforts and identify opportunities to prevent cancers associated with infections.

Infections as risk factors for cancer

It is well established that some infectious agents (bacteria, parasites and viruses) have the potential to cause certain cancers through mechanisms such as chronic inflammation, immune-suppression or interfering with cell processes and replication.[1] To date, the International Agency for Research on Cancer has classified 11 infectious agents as carcinogenic to humans (group 1 carcinogens), including human papillomavirus (HPV), *Helicobacter pylori (H. pylori)*, hepatitis C virus (HCV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), human herpesvirus 8 (HHV-8) (also known as Kaposi's sarcoma herpesvirus), human T-cell lymphotropic virus, type 1 (HTLV-1), liver flukes (*Opisthorchis viverrini and Clonorchis sinensis*), *Schistosoma haematobium* and human immunodeficiency virus, type 1 (HIV).[1] These infections and their associated cancers are shown in Table 1. With the evolving nature of human exposure to infectious agents and their sizable contribution to the global cancer burden,[9] infections that cause cancer remain an emerging area of research. Information on the links between cancer and infections, as well as ways to prevent infections and their associated cancers, continue to be updated as new scientific evidence becomes available.

TABLE 1 Infectious agents and their associated cancer types

Infectious agents	Cancer types with sufficient evidence[a]	Cancer types with limited evidence[b]
Human papillomavirus	Cervix, penis, anus, vulva, vagina, oropharynx, oral cavity and tonsil	Larynx
Helicobacter pylori	Stomach (non-cardia gastric) and gastric non-Hodgkin lymphoma (mucosa-associated lymphoid tissue)	
Hepatitis C virus	Liver and non-Hodgkin lymphoma	Bile duct
Epstein-Barr virus	Burkitt lymphoma, Hodgkin lymphoma, nasopharynx, immunosuppression-related non-Hodgkin lymphoma and extranodal NK/T-cell lymphoma (nasal type)	Stomach and lympho-epithelioma-like carcinoma
Hepatitis B virus	Liver	Bile duct and non-Hodgkin lymphoma
Human herpesvirus 8	Kaposi sarcoma and primary effusion lymphoma	Multicentric Castleman disease
Human T-cell lymphotropic virus, type 1	Adult T-cell leukemia and lymphoma	
Opisthorchis viverrini, Clonorchis sinensis	Bile duct	
Schistosoma haematobium	Bladder	
Human immunodeficiency virus, type 1	Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, cervix, anus and conjunctiva	Vulva, vagina, penis, liver and skin (non-melanoma)

SOURCE: IARC, 2012[1]
NOTES:
[a]Indicates a causal relationship between the infectious agent and the cancer.
[b]Indicates that a causal relationship between the infectious agent and the cancer is possible, but chance, bias and confounders cannot be ruled out with confidence.

Prevention and control of cancer-causing infections and associated cancers

Preventing and controlling infections is a major goal of public health. Beyond addressing the serious health effects of infections, infection prevention and control are important tools for cancer prevention. Strategies to prevent the cancer types associated with infections include limiting exposure to these infections, vaccinating against infection and preventing the development of cancer once someone is infected.

In Ontario, initiatives that prevent exposure to cancer-causing infections are aimed at limiting exposure from infected blood and bodily fluids. For example, all blood donations are screened for the presence of HCV, HBV, HTLV-1 and HIV;[10] personal service settings, such as tattoo, nail and aesthetic services are inspected for infection prevention and control practices;[11] there is public and school-based education about safer sex practices; public health units trace people who come into contact with those who are infected;[12,13] routine practices are used in healthcare settings, wherein all bodily fluids are treated as infectious (e.g., gloves are worn, waste is disposed safely);[14] and harm reduction approaches have been adopted, such as needle exchanges and drug equipment distribution.[15]

In Ontario, vaccines to prevent against infection with HPV and HBV are provided to students in Grade 7 and to some high risk groups.[16,17] High risk groups for HBV include people with multiple sex partners, injection drug users, men who have sex with men, people with a history of one or more sexually transmitted infections, children of families who emigrated from endemic countries and infants of infected mothers shortly after birth.[13] Ontario currently provides publicly funded HPV vaccination to men who have sex with men up to age 26 through the public health units.[18]

Initiatives that prevent cancer from developing once infection occurs are also important for cancer prevention. In Ontario these include cervical screening for HPV-associated pre-cancerous cells (and their subsequent removal)[19] and in some cases, the treatment of *H. pylori*, HBV, HCV and HIV infections, either to cure the infection, limit the health impact of infection or decrease the likelihood of transmission.[20-24] These prevention opportunities are important in light of the fact that several cancer types associated with infections have poor survival (e.g., liver and stomach) and increasing mortality rates (e.g., liver).[25]

Rationale for report

While much is being done to prevent the development of cancers associated with infections, the overall burden of cancer from infections has not yet been calculated for Ontario. Quantifying cancer burden attributable to infections can inform Ontario-specific cancer prevention programs and policies, and prioritize areas for future prevention efforts.

Methods

All infectious agents that the International Agency for Research on Cancer has classified as carcinogenic to humans (group 1) and their associated cancer types were included in this report (Table 1). Population attributable fractions (PAFs) were calculated to quantify the number of new cancers diagnosed in Ontario that could be attributed to each infectious agent. A PAF is an estimate of the proportion of disease cases (e.g., cancer) that could be prevented if a given risk factor was eliminated from the population.[2] PAFs were only calculated for the infectious agents that were deemed relevant to the Ontario population, which resulted in the exclusion of liver flukes and *Schistosoma haematobium*, as these are very rare in Ontario. Human immunodeficiency virus, type 1 (HIV) is discussed in detail but estimates of attributable burden were not calculated. This approach was taken to avoid double-counting cancer cases attributable to HIV because the carcinogenic effect of HIV is considered to be indirect and requires co-infection with other carcinogenic infectious agents (e.g., human herpesvirus 8).[1] For each infectious agent, separate PAFs were calculated for each of the cancer types that the International Agency for Research on Cancer has classified as having "sufficient" evidence of an association with an infection (see Appendix A).

The methods used for calculating PAFs were based on those used by de Martel et al.[2] Depending on the availability of data, one of three PAF formulas was used to estimate the proportion of cancer cases associated with a given infectious agent (see Appendix A). Inputs into each PAF calculation included the prevalence of the infections in the population (or among cases of a specific cancer type) and/or the relative risk (risk of an event occurring in one group compared to the risk of the same event in another group) associated with a given infection and cancer type.

The literature was reviewed to identify the appropriate PAF inputs specific to the Ontario population. Full details on the data sources used in the PAF calculations can be found in Appendices A and B. In general, prevalence and relative risk estimates were extracted from a cancer registry, population-based surveys, case-control studies with population-based controls, systematic reviews or meta-analyses. Ontario-specific estimates were used whenever possible. When Ontario estimates were unavailable, Canadian estimates or estimates from jurisdictions that were deemed comparable to Ontario based on regional proximity or similar level of development were substituted.

Plausible ranges (based on relevant studies or reports) were calculated around each PAF estimate to reflect uncertainty and variation in the input data. These plausible ranges and PAF point estimates were then applied to the 2013 cancer incidence data from the Ontario Cancer Registry to estimate the number of cancer cases attributable to each infectious agent (see Appendix B).

The methodological limitations and assumptions of the data are outlined in Appendix C.

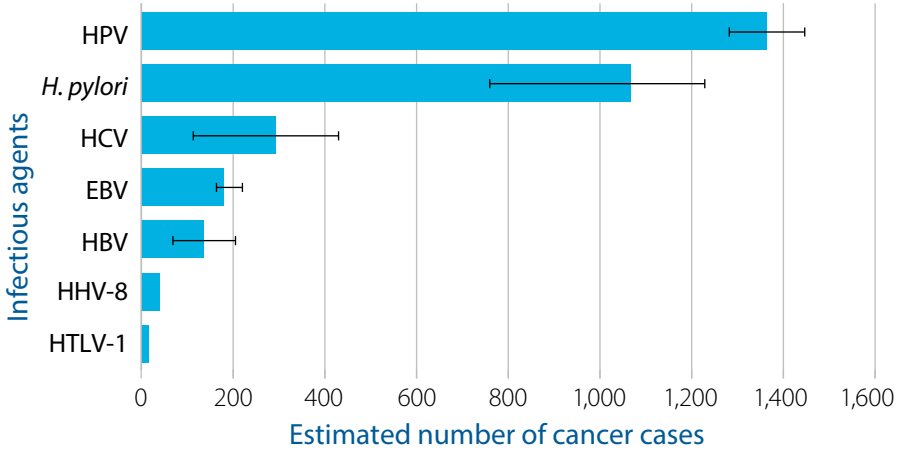
Findings

Overview

In 2013, approximately 3,100 new cancer cases (plausible range 2,443 to 3,591) diagnosed in Ontario could be attributed to human papillomavirus (HPV), *Helicobacter pylori (H. pylori)*, hepatitis C virus (HCV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), human herpesvirus 8 (HHV-8) and human T-cell lymphotropic virus, type 1 (HTLV-1) (see Figure 1). These diagnoses account for roughly four percent of all new cancer cases in Ontario and 32 percent of the total cases of the 15 cancer types that show sufficient evidence of an association with one or more of these infections. Cancer types that have sufficient evidence are cervix, oropharynx, anus, penis, vulva, vagina, oral cavity, tonsil, larynx, stomach (non-cardia gastric), liver (hepatocellular carcinoma), non-Hodgkin lymphoma (including mucosa-associated lymphoid tissue or MALT lymphoma), Hodgkin lymphoma, nasopharynx, Burkitt lymphoma, Kaposi sarcoma, and adult T-cell leukemia and lymphoma. Together, HPV, *H. pylori*, HCV and HBV account for over 90 percent of all cancer cases attributable to infections, which was just under 3,000 cancer cases in 2013. The majority of these cases were due to HPV and *H. pylori*. The remaining infections (EBV, HHV-8 and HTLV-1) combined account for a small number of cases per year.

> Infections are responsible for about 3,100 new cancer cases each year in Ontario.

FIGURE 1 Estimated number of cancer cases attributable to infectious agents, Ontario, 2013



SOURCE: Ontario Cancer Registry, 2016 (Cancer Care Ontario)
NOTES: HPV = human papillomavirus; *H. pylori* = *Helicobacter pylori*; HCV = hepatitis C virus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HHV-8 = human herpesvirus 8; HTLV-1 = human T-cell lymphotropic virus, type 1. ⊢⊣ represent plausible ranges (based on a range of studies or reports) for number of cancer cases attributable to each infectious agent, and no ⊢⊣ for HHV-8 and HTLV-1 reflect necessary but not sufficient relationships with associated cancers (i.e., PAF = 100%).

Human Papillomavirus (HPV)

There are over 100 types of HPV that primarily infect skin surfaces or the lining of mucosal areas of the body in humans (e.g., oral cavity, oropharynx, genitals).[1] HPV is divided into low and high risk types according to their association with cancer.[1] To date, there are 12 known high risk HPV types: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59.[1,26] While most HPV infections are asymptomatic and the immune system clears them spontaneously within one to two years, some infections persist.[1] Persistent infection with high risk HPV types can lead to cell changes that can result in cancer. Similarly, infection with low risk types can lead to genital warts and the development of benign wart-like growths in the upper airways (recurrent respiratory papillamatosis).[1]

The link between HPV and cancer

The evidence that persistent infection with HPV causes cervical cancer is well established.[27] HPV is also an established cause of cancer of the penis, anus, vulva, vagina, oropharynx, oral cavity and tonsil, and possibly larynx.[1] Although all of the known high risk types are associated with cervical cancer, at the moment HPV 16 and HPV 18 account for over 70 percent of cases.[28] There is strong evidence that HPV 16 and 18 are also associated with cancers of the penis, anus, vulva, vagina, oropharynx and oral cavity.[29-31]

Persistent infection with a high risk HPV type is a necessary, but not sufficient, cause of cervical cancer,[32] and therefore not all persistent HPV infections with high risk types result in cervical cancer.[27] The risk of a persistent infection with a high risk HPV type leading to cancer is increased by cofactors, such as a weakened immune system (e.g., transplant recipients and people with HIV), number of pregnancies, tobacco smoking, use of oral contraceptives and co-infections with other sexually transmitted infections (e.g., *Chlamydia trachomatis,* herpes simplex virus).[1] Smoking may increase the risk of HPV-associated oral cancers because it can promote infection.[29] People infected with HPV and HIV can develop invasive cervical cancer, which signifies progression to AIDS.[1]

Descriptive epidemiology of HPV

HPV infection is easily transmitted through skin-to-skin or skin-to-mucosa contact. The number of sexual partners is the main determinant of infection of the anus and genitals.[1,33] Other determinants of infection have been explored, but their evidence is inconsistent.[1,34-36] Prevalence of HPV infection in anogenital areas is higher than in the oral cavity.[1,37] Recent data suggest that HPV infections account for an increasing proportion of oropharyngeal cancers in Canada.[38] However, recent prevalence estimates of HPV infection in Ontario's general population is unknown.

HPV is the most common sexually transmitted infection. Without vaccination, most sexually active adults will acquire an HPV infection at some point in their lives.[1] Before the HPV vaccine, the incidence of new infections with high risk HPV types among Ontario females was highest in those ages 15 to 19.[33] Teen and young adult males and females have the highest incidence of anogenital infection, with a slight increase in middle-aged women.[1,39]

With the introduction of the HPV vaccine and Ontario's school-based HPV immunization program, the number of new HPV infections (primarily types 16 and 18) occurring in the population is expected to decrease. A decreasing trend has already been observed in Ontario and in other regions with more long-standing HPV immunization programs.[40-42]

Cancer burden associated with HPV in Ontario

An estimated 1,365 (plausible range 1,281 to 1,447) new cancers diagnosed in Ontario in 2013 were attributed to HPV infection. This means that over 1,300 cancer cases could be prevented if high risk HPV infections were eradicated in the province.

Cancers of the cervix, oropharynx and anus account for over three-quarters of the cancer burden attributable to HPV infections. Cervical cancer accounts for the largest proportion of the HPV-associated cancer burden in Ontario. Because HPV infection is a necessary cause of cervical cancer,[32] all 523 cases of cervical cancer diagnosed in Ontario in 2013 are considered to be caused by persistent HPV infection. Attributable cases for cervical cancer and seven other cancer types are provided in Table 2. Over 90 percent of anal cancers were attributed to HPV infection, accounting for roughly 200 new cases diagnosed in 2013. HPV infections also account for a substantial proportion (roughly 50 percent or greater) of penile, vulvar, vaginal and oropharyngeal cancers diagnosed in Ontario (Table A6).

Figure 2 highlights the trends in incidence of the three cancer types with the highest estimated number of cancer cases caused by HPV infection. HPV is a necessary risk factor for cervical cancer. The decreasing incidence of cervical cancer starting in the 1980s was largely due to organized cervical screening. Screening detects and leads to the treatment of pre-cancerous lesions, which then prevents the development of cervical cancer. More recently, cervical cancer incidence has plateaued, possibly due to a decreasing cervical screening rate in Ontario over the same period and the continued presence of those who are under- or never-screened for cervical cancer.[43] Figure 2 also shows that rates of oropharyngeal cancer have increased by 50 percent among males, from four per 100,000 in 1985 to seven per 100,000 in 2012, while rates have remained relatively stable among females. This figure also shows that anal cancer rates have remained relatively stable

among males and females (ranging from two per 100,000 to three per 100,000). Increased HPV-associated oropharyngeal cancer is likely related to changes in sexual practices (i.e., increased oral sex).[44]

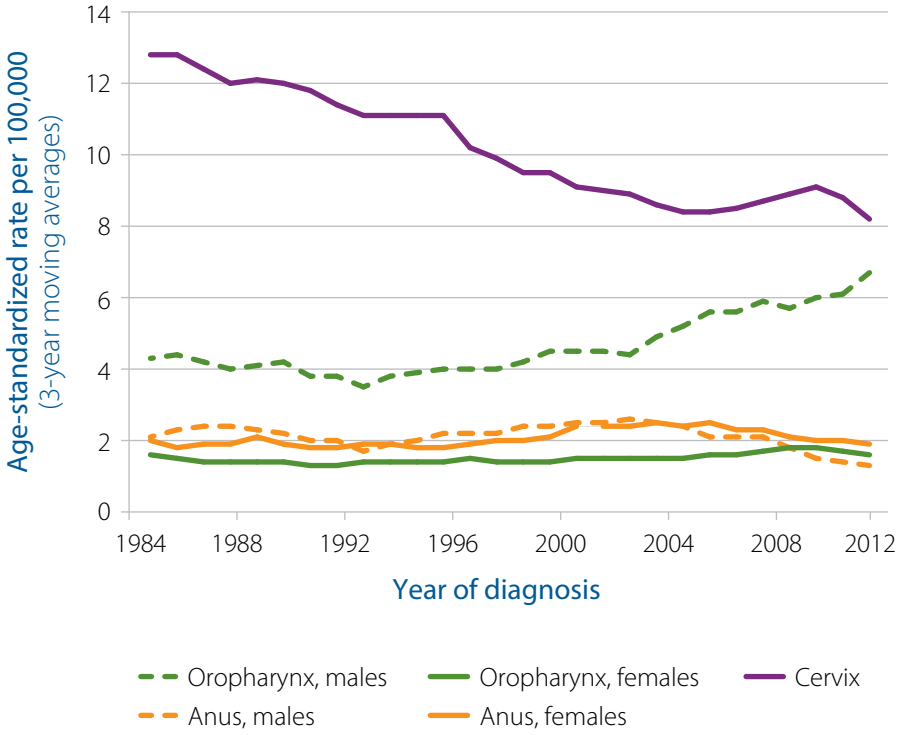
The HPV vaccine is expected to lead to decreases in cervical cancer in the province. It is also possible that over time, we may see decreases in other HPV-associated cancers.

TABLE 2 Estimated percentage and number of cancers cases attributable to human papillomavirus (HPV) infections, Ontario, 2013

Cancer types	Estimated percentage (%) of attributable cancers	Estimated percentage (%) of attributable cancers (plausible range)	Estimated number of attributable cancers	Estimated number of attributable cancers (plausible range)
Cervix	100	.	523	.
Oropharynx	53	48–58	319	287–351
Anus	92	83–100	202	182–220
Vulva	48	43–53	146	132–161
Vagina	78	70–86	65	58–71
Penis	53	48–58	57	52–63
Oral	4	4–5	33	30–36
Larynx	5	4–5	19	17–21
All cancer types associated with HPV	45	42–48	1,365	1,281–1,447

NOTE: For data sources, see Table A6 in Appendix B.

FIGURE 2 Incidence rates for selected cancer types associated with human papillomavirus (HPV), Ontario, 1984-2013



SOURCE: Ontario Cancer Registry, 2016 (Cancer Care Ontario)
NOTES: Incidence rates are standardized to the age distribution of the 2011 Canadian population. All oropharyngeal cancers, including HPV associated. For ICD-O-3 site and histology codes for cancer type, see Table A4 in Appendix A.

Helicobacter Pylori (H. Pylori)

H. pylori is a bacterium commonly found in the stomach. Infection with *H. pylori* can lead to chronic inflammation of the stomach lining that can result in the development of ulcers and, in a relatively small percentage of people infected, lead to abnormal cell changes that may progress to cancer.[1,45] *H. pylori* is the only bacterium that has been confirmed to be carcinogenic to humans.[1]

The link between *H. pylori* and cancer

H. pylori infection is associated with stomach (non-cardia gastric) cancer and gastric non-Hodgkin lymphoma (mucosa-associated lymphoid tissue or MALT).[1] Although the relationship between *H. pylori* and non-cardia gastric cancer is well-established, recent evidence has found that people infected with *H. pylori* have a much higher risk of developing this cancer than originally believed. People with an *H. pylori* infection have a roughly 17 times greater risk of developing non-cardia gastric cancer than those who are not infected.[46] Pooled studies show that the relative risk of someone with an *H. pylori* infection developing gastric non-Hodgkin lymphoma (MALT) is about seven times greater than that of someone who is not infected.[2] The ability of specific *H. pylori* strains to cause severe infections depends on modifiable risk factors (dietary and smoking tobacco) and individual genetic susceptibility, which determine how severe the infection will be and whether it will result in cancer.[45,47]

Descriptive epidemiology of *H. pylori*

In developed countries such as Canada, close personal contact—particularly within families—is a risk factor for *H. pylori* transmission.[1,48,49] *H. pylori* is transmitted by exposure to contaminated saliva, feces or water, or during medical procedures.[1,50] Factors that increase the likelihood of infection include low socio-economic status, especially during childhood, the number of children in a home, household crowding/density, living in a rural area and poor hygiene.[1,51,52]

Although the prevalence of *H. pylori* infection is over 50 percent globally, it is less common in developed areas.[1,53] In Ontario, survey data of adults ages 50 to 80 showed prevalence of infection to be approximately 23 percent.[54] This same study found that prevalence was higher in males (29 percent) than females (15 percent).[54] Infection is more common among some groups in Ontario, such as immigrants and First Nations people in northwestern Ontario.[54,55] The prevalence of *H. pylori* infection has been decreasing in developed countries, likely due to smaller families and improved housing and hygiene.[47,53,56]

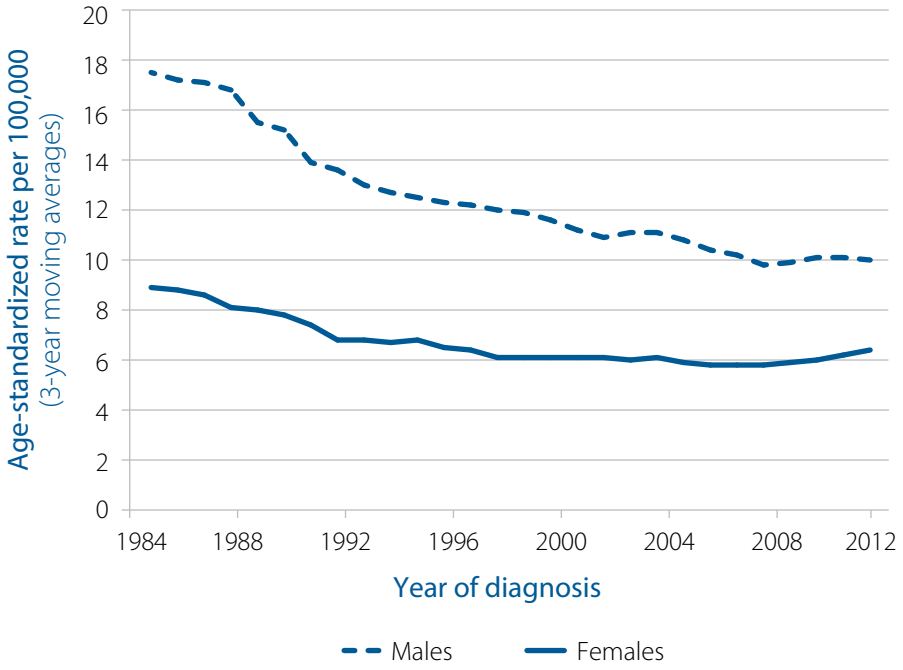
Cancer burden associated with *H. pylori* in Ontario

In 2013, an estimated 79 percent (plausible range 53 to 89 percent) of non-cardia gastric cancer cases diagnosed in Ontario were attributed to *H. pylori* infection. This percentage is equivalent to 897 cases (plausible range 605 to 1,015) that could have been prevented if *H. pylori* were eliminated from the population. In the same year, an estimated 59 percent (plausible range 53 to 74 percent) of gastric non-Hodgkin lymphoma cases diagnosed were attributed to *H. pylori* infection in Ontario, which is equivalent to 170 cases (plausible range 154 to 214).

In recent years, stomach cancer has been decreasing consistently in males, but its decrease has plateaued in females in Ontario (Figure 3). Changes in some of the known risk factors for stomach cancer may contribute to this decrease. Smoking prevalence has also decreased, diet and food preservation methods have changed (less salted food), and there is a greater recognition of the risk posed by and how to treat *H. pylori* infection.[57-59] Despite these decreasing trends, *H. pylori* remains an important cause of non-cardia gastric cancer in Ontario.[29]

> Almost 900 non-cardia gastric cancers were attributed to *H. pylori* infection.

FIGURE 3 Non-cardia gastric cancer incidence rates, Ontario, 1984-2013



SOURCE: Ontario Cancer Registry, 2016 (Cancer Care Ontario)
NOTES: Incidence rates are standardized to the age distribution of the 2011 Canadian population. For ICD-O-3 site and histology codes for cancer type, see Table A4 in Appendix A.

Hepatitis C Virus (HCV)

HCV is a virus that causes liver inflammation.[60] Infection can be acute or chronic; however, about 25 percent of infections clear on their own.[61-65] It is estimated that over 40 percent of people with HCV in Canada do not know that they are infected, which suggests that research is needed to clearly define predictors of clearance and to guide treatment strategies.[64,66,67] Of what is known, factors associated with improved viral clearance are being female and acute clinical infection.[64]

The link between HCV and cancer

Chronic HCV infection is a known cause of liver cancer (hepatocellular carcinoma) and non-Hodgkin lymphoma (NHL). There is also an association between chronic HCV infection and cancer of the bile duct (cholangiocarcinoma).[1]

In countries with a low prevalence of HCV, such as Canada, the likelihood that someone with a chronic HCV infection would develop liver cancer is estimated to be 24 times higher than that of an uninfected person.[68] The likelihood of someone with a chronic HCV infection developing NHL is three times higher than an uninfected person.[69] Development of liver cancer usually follows a long duration of advanced liver fibrosis or liver cirrhosis.[1] The progression to severe liver disease and cancer is accelerated in males and people over age 50, as well as by heavy alcohol consumption, fatty liver disease, insulin resistance and a compromised immune system (e.g., from infection with HIV).[1,70-73]

> The likelihood of someone with chronic HCV infection developing liver cancer is estimated to be 24 times higher than that of an uninfected person.

Descriptive epidemiology of HCV

HCV is transmitted through exposure to infected blood. This exposure most commonly occurs through shared needles and other injection drug use equipment.[1,72] Less frequently, transmission of infection can occur through sexual activity or between a mother and her child during pregnancy or childbirth.[1]

Before testing blood donors for HCV began in the early 1990s, blood transfusions and receiving blood products were significant sources of HCV infection in Ontario.[1,66] It is thought that there is a group of undiagnosed people who were exposed to the virus before routine practices in medical settings and blood testing were put in place.[74] A Canadian study that modelled HCV prevalence by age group estimated that approximately 77 percent of those infected were born in the mid-1940s to mid-1970s.[75,76] People who have the highest risk of acquiring a new HCV infection include injection drug users, those who have been incarcerated and healthcare providers who have had needle stick injuries.[66,77] First Nations populations also have higher rates of HCV infection.[22,66,78] In Ontario, HCV infection is more common among males than females.[66,79] HCV-infected people have higher rates of other blood-borne infections, such as hepatitis B virus and HIV, because sharing needles can result in transmission of all three infections.[66] In 2006, it was estimated that three percent of people with an HCV infection also had HIV, and 12 percent of people with HIV had HCV.[66]

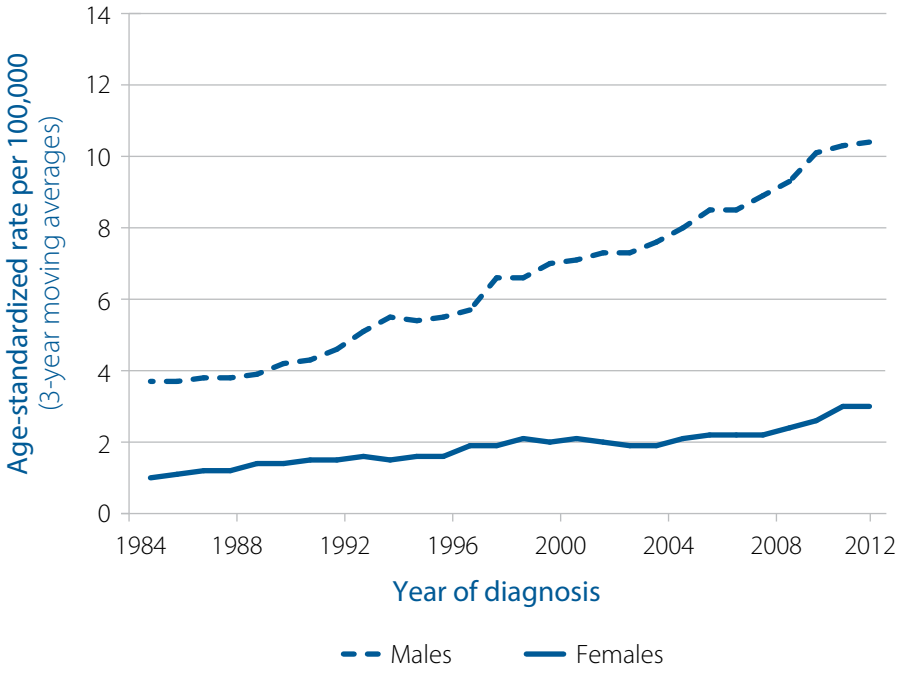
HCV affects all regions of the globe; however, the eastern Mediterranean has the highest prevalence of infection (two percent), followed closely by the European region;[80] Canada's prevalence is lower.[1] While current reporting does not differentiate chronic from acute cases, the rate of reported HCV in Canada decreased from 40 per 100,000 in 2005 to 30 per 100,000 in 2013.[81] In Ontario, this rate decreased from 37 per 100,000 in 2005 to 31 per 100,000 in 2015.[22] It is notable that the provincial rate of newly diagnosed infections in 2015 ranged from a low of 14 per 100,000 in York Region to a high of 148 per 100,000 in the Northwestern region.[82]

Cancer burden associated with HCV in Ontario

In 2013, an estimated 225 new cases (plausible range 98 to 352) of liver cancer and 68 cases (plausible range 16 to 78) of NHL diagnosed in the province were attributed to HCV infection. This accounts for roughly 24 percent (plausible range 10 to 37 percent) of liver cancer cases and two percent (plausible range zero to two percent) of NHL cases.

In Ontario over the past 30 years, the incidence rate of liver cancer has been increasing significantly, especially in males (Figure 4). Hepatocellular carcinoma is the most common type of liver cancer, and these trends may strongly reflect increasing cases of this cancer type. The rising incidence may be due to long-term, undiagnosed infections that have progressed to cancer in groups with a historically higher prevalence of HCV[66] or due to increasing immigration from countries where HCV is endemic.[83]

FIGURE 4 Liver cancer incidence rates, Ontario, 1984–2013



SOURCE: Ontario Cancer Registry, 2016 (Cancer Care Ontario)
NOTES: Incidence rates are standardized to the age distribution of the 2011 Canadian population. Liver cancers exclude intrahepatic bile duct cancers. For ICD-O-3 site and histology codes for cancer type, see Table A4 in Appendix A.

Epstein-Barr Virus (EBV)

Infection with EBV is very common, and usually occurs in childhood or young adulthood. Following initial infection, EBV remains inactive in most individuals without causing serious health issues.[1]

The link between EBV and cancer

EBV infection is most strongly associated with cancer of the nasopharynx, but it is also associated with an increased risk of Hodgkin lymphoma, Burkitt lymphoma, non-Hodgkin lymphoma (immune-suppression-related) and extranodal natural killer/T-cell lymphoma (nasal type).[1] Limited evidence suggests that EBV may cause gastric cancer and lympho-epithelioma-like cancer.[1]

EBV is more likely to cause cancer in people who are immunocompromised, such as those with HIV or transplant recipients.[84] EBV may act as a cofactor with HIV in causing cancer; AIDS-related lymphomas are frequently EBV-positive.[84]

Descriptive epidemiology of EBV

EBV is commonly transmitted through saliva and may be transmitted through sexual activity.[85] Although prevalence estimates are not available for Ontario, EBV is extremely common throughout the world (more than 90 percent of adults have been infected).[1,86] Infection is more likely to occur at a younger age in less developed regions than in more developed countries, such as Canada, where EBV infections commonly occur in young adulthood.[87] In early childhood, EBV infections are believed to be asymptomatic due to protective maternal antibodies.[88] If acquired during adolescence, EBV can cause infectious mononucleosis.[1]

Cancer burden associated with EBV in Ontario

In 2013, an estimated 181 new cancer cases (plausible range 163 to 221) were attributed to EBV in Ontario. Hodgkin lymphoma and nasopharyngeal cancer each accounted for roughly half of the EBV-associated cancer cases; a small number of cancer cases attributable to EBV were Burkitt lymphoma (Table 3). EBV accounted for the largest proportion of nasopharyngeal cancers, with an estimated 80 percent of cases of this cancer type attributable to EBV infections.[9]

TABLE 3 Estimated percentage and number of cancer cases attributable to Epstein-Barr virus (EBV) infection, Ontario, 2013

Cancer types	Estimated percentage (%) of attributable cancers	Estimated percentage (%) of attributable cancers (plausible range)	Estimated number of attributable cancers	Estimated number of attributable cancers (plausible range)
Hodgkin lymphoma	24	22–32	93	83–124
Nasopharynx	80	72–88	83	75–92
Burkitt lymphoma	20	18–22	5	5–6
All cancer types associated with EBV	35	32–43	181	163–221

NOTE: For data sources, see Table A6 in Appendix B.

Hepatitis B Virus (HBV)

HBV is a blood borne infection that is frequently asymptomatic and undiagnosed. Similar to HCV, infection with HBV can be acute or chronic in humans.

The link between HBV and cancer

There is sufficient evidence that chronic HBV infection causes liver cancer (hepatocellular carcinoma). A positive association has also been found between chronic HBV infection and cancer of the bile duct (cholangiocarcinoma) and non-Hodgkin lymphoma.[1]

In regions with low prevalence of HBV, such as Ontario, people with a chronic infection are estimated to have a 20 times greater risk of developing liver cancer than those who are not infected.[68] HBV-related cancers tend to occur in the presence of cirrhosis.[1] While co-infection of HBV and HCV is possible, HBV and HCV are independent risk factors for liver cancer.[68]

Descriptive epidemiology of HBV

HBV is transmitted through contaminated blood during transfusions, needle stick injuries, sexual contact, birth or close household contact.[1,89] In low endemic countries, populations at high risk for new infections include injection drug users, men who have sex with men and healthcare workers.[1]

The prevalence of chronic HBV infection varies globally, with low prevalence in developed nations and higher prevalence in China, Korea, sub-Saharan Africa, the Amazon Basin and several countries in Southeast Asia.[1] In endemic areas, infections occur mostly during infancy and childhood. Most infections (80 to 90 percent) with HBV in the first year of life become chronic, while under five percent of adult acquired infections become chronic.[90] Infection occurs most often in adolescence and young adulthood in low endemic areas, such as Ontario, where HBV is a reportable disease for which new cases must be reported to the local public health unit by law.[1,91]

In Ontario, the number of newly reported chronic HBV infections has been decreasing since 1991.[92] In 2005, there were 3,717 (30 per 100,000) chronic cases diagnosed in Ontario and by 2015, this number had dropped to 1,739 (13 per 100,000).[93] Within Ontario, there is significant regional variation in the incidence of reported HBV infections. In 2015, the incidence of newly diagnosed chronic HBV infection by public health unit ranged from zero per 100,000 in many regions, such as Porcupine and Grey Bruce, to 33 per 100,000 in York Region and 23 per 100,000 in Toronto.[93] This geographic pattern likely reflects the large immigrant population in the Greater Toronto Area. Higher rates of infection are found among Ontarians who have emigrated from high endemic areas, where they were more likely to have been infected as children.[94,95] Some data suggest that immigrants from countries with a high prevalence of HBV account for up to 70 percent of people with a chronic HBV infection in Canada.[20] Similar to HCV infection, our understanding of the prevalence of HBV infection in Ontario is limited because it is commonly asymptomatic and frequently goes undiagnosed.

Cancer burden associated with HBV in Ontario

Chronic infection with HBV accounts for an estimated 14 percent (plausible range seven to 22 percent) of liver cancer cases diagnosed in the province, equivalent to 137 cases (plausible range 68 to 206).

In Canada and in Ontario, liver cancer incidence is increasing rapidly (Figure 4).[96-98] This trend may partly be explained by a greater number of immigrants from countries where HBV and HCV infections are endemic.[29]

Human Herpesvirus 8 (HHV-8)

HHV-8 is also known as Kaposi sarcoma herpesvirus.[1,99] While a healthy immune system is usually able to manage the infection, people who are immunocompromised, e.g., those with HIV, are less able to fight off the infection and are therefore more likely to develop Kaposi sarcoma.[9,100,101]

The link between HHV-8 and cancer

A casual association between HHV-8 infection and Kaposi sarcoma has been established.[1] HHV-8 infection is necessary, but not sufficient, for the development of Kaposi sarcoma and cancer generally develops in people who are immunocompromised (e.g., co-infection with HIV or transplant recipients).[1] An HHV-8 infection can also cause primary effusion lymphoma and has a positive association with multicentric Castleman disease,[1] a condition that can lead to lymphoma.

Descriptive epidemiology of HHV-8

While HHV-8 can be transmitted through sexual and non-sexual routes (e.g., blood transfusion, tissue transplants), saliva is the primary means of transmission.[1,99] With no recent data on HHV-8 prevalence or incidence in Ontario or Canada, it is assumed that Canada is a region with a low infection prevalence.[102] The prevalence of HHV-8 varies globally, with a lower prevalence (less than 10 percent) in Asia, the United States or northern Europe; a moderate prevalence (10 to 30 percent) around the Mediterranean; and a higher prevalence (more than 50 percent) in sub-Saharan Africa.[1] In regions with high prevalence, HHV-8 infection usually occurs before age 10.[103,104] In countries with a low population prevalence, such as Canada, HHV-8 is more common in males with HIV, people with multiple sexual partners, men who have sex with men, injection drug users and immunocompromised people.[1,105-109]

Cancer burden associated with HHV-8 in Ontario

In 2013, all 41 cases of Kaposi sarcoma diagnosed in Ontario were attributed to infection with HHV-8. Kaposi sarcoma was rare before the AIDS epidemic, but rates rose substantially in the 1990s.[107] Kaposi sarcoma rates have decreased since the mid-1990s.[110]

Human T-Cell Lymphotropic Virus, Type 1 (HTLV-1)

HTLV-1 is a retrovirus that is in the same class as HIV.[1,111,112]

The link between HTLV-1 and cancer

HTLV-1 infection is a necessary cause of adult T-cell leukemia and lymphoma (ATLL); indicators of HTLV-1 infection are used to identify ATLL. Following decades of infection, HTLV-1 carriers have a lifetime risk of developing ATLL of two to four percent.[1]

The risk of cancer among HTLV-1 carriers is estimated to be three to five times higher for males than for females.[1] Childhood infection may pose a higher risk for cancer than an infection later in life.[1,113,114] Other determinants of disease progression are not fully understood.[112]

Descriptive epidemiology of HTLV-1

HTLV-1 is transmitted through bodily fluids from mother to child (primarily through breastfeeding), through sexual contact and through exposure to contaminated blood.[111,112]

In Canada (and Ontario), where HTLV-1 has low prevalence and ATLL is rare, transmission is primarily through sexual activity.[115] In endemic countries, such as areas of Japan and sub-Saharan Africa, South America and the Caribbean, transmission is mostly through breastfeeding (risk of 10 to 30 percent), followed by sexual transmission and exposure to blood.[1,115] In endemic countries, prevalence of HTLV-1 infection tends to be higher among females than males and increases with age.[1]

In Canada, the odds of infection are about 18.7 times higher in people born outside Canada or the United States.[115] Canadian rates of HTLV-1 infection among blood donors decreased from nine per 100,000 in 1990 to one per 100,000 in 2010.[115] Among HTLV-1-positive donors, nearly two-thirds were female and most (80 percent) were residents of Ontario, particularly Toronto, which has a high proportion of immigrants.[115]

Cancer burden associated with HTLV-1 in Ontario

In 2013, 100 percent of ATLL cases diagnosed in Ontario were attributed to HTLV-1 infection. This is equivalent to 17 cases.

Opisthorchis Viverrini (O. Viverrini), Clonorchis Sinensis (C. Sinensis)

O. viverrini and *C. sinensis* (liver flukes) are parasitic flatworms that have the potential to cause cancer.[1] Infection occurs when humans eat raw or under-cooked freshwater fish that are contaminated with fluke larvae.[1]

The link between liver flukes and cancer

C. sinensis can survive in humans for up to 26 years and *O. viverrini* can survive for up to 10 years.[116,117] Chronic infection with these liver flukes can cause persistent inflammation in the lining of the bile ducts, which can lead to cellular damage/changes and cancer of the bile duct (cholangiocarcinoma).[1,118]

Descriptive epidemiology of liver flukes

The prevalence of liver flukes is thought to be negligible in Ontario.[1,119] However, clonorchiasis, a disease caused by *C. sinensis* infection, has been reported in up to 26 percent of Asian immigrants to North America.[120,121] Prevalence of infection with liver flukes is generally higher in males and increases with age, peaking in middle age (people ages 40 to 59).[119] Globally, an estimated 45 million people are infected with liver flukes, which are endemic in China, Korea, Thailand, Viet Nam, Cambodia and Lao People's Democratic Republic.[1]

In Ontario, bile duct cancers are rare and liver flukes are not native to Ontario. Probably the best way to prevent their associated cancers is awareness among recent immigrants from endemic areas, travelers and physicians, and treatment of those infected.

Schistosoma Haematobium (S. Haematobium)

S. haematobium are parasitic flatworms that can cause infection in the human bladder.[1] Infection with *S. haematobium* can lead to schistosomiasis (snail fever).[122]

The link between *S. haematobium* and cancer

S. haematobium is a leading risk factor for bladder cancer in northern and sub-Saharan Africa.[123] It is believed that half of the eggs produced by *S. haematobium* are retained in the infected person's bladder, leading to inflammation, which over time can cause cancer.[1]

Descriptive epidemiology of *S. haematobium*

S. haematobium infections can occur when someone comes into direct contact with contaminated fresh water. Without treatment, an infection can last three to five years.[1]

S. haematobium is not endemic in Canada and cases of infection are usually linked to Canadians visiting or emigrating from endemic regions.[124] The majority of these infections originate in regions of Africa and the Middle East, where infection peaks from ages five to 15 and is more likely to affect agricultural workers.[1] While it may be difficult to know the global prevalence of *S. haematobium* infection, the World Health Organization reported that 66.5 million people were treated for schistosomiasis in 2015.[125]

Because these infections are not common in Ontario, the best way to prevent their associated cancers is awareness among recent immigrants from endemic regions, travelers and physicians, and treatment of those infected.

Human Immunodeficiency Virus, Type 1 (HIV)

HIV is a retrovirus that attacks cells of the immune system (i.e. T cells) and reduces their number. As HIV infection progresses, it leaves the immune system unable to fight off other infections. The advanced stage of disease, known as AIDS, is defined as having both a confirmed HIV infection and being diagnosed with one or more AIDS-related diseases, such as an associated cancer, opportunistic infection or wasting syndrome.[1,126]

The link between HIV and cancer

Although HIV is classified as carcinogenic to humans, it causes cancer mainly through immunosuppression, which leaves an infected person susceptible to other carcinogenic infections. There is strong evidence that HIV can cause Kaposi sarcoma, non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma, as well as cancers of the cervix, anus and conjunctiva.[1] There is also a positive association between HIV infection and penis, vulva and vagina, liver (hepatocellular carcinoma) and non-melanoma skin cancers.[1]

The risk of cancer among people infected with HIV is greater than that of the general population. Most of the cancers seen in those with HIV and not in the general population are caused by infections with viruses discussed in this report (e.g., HHV-8, HPV and EBV).[127] Compared to the general population of the United States, the HIV infected population had an estimated 50 percent excess burden of any cancer, as well as a 100 percent excess burden of Kaposi sarcoma, an 88 percent excess burden of NHL and a 66 percent excess burden of cervical cancer.[127]

Descriptive epidemiology of HIV

HIV is transmitted via exposure to blood, semen, vaginal secretions or breast milk.[1,89,128] Populations at risk for infection include people having unprotected sex, injection drug users and healthcare workers who may be exposed to the virus through contaminated needles or sharp objects.[1,128] People with sexually transmitted infections are also more susceptible to getting HIV during sex.[1,128] When an infected person follows an antiretroviral treatment regimen, their viral loads can be lowered to a level that greatly reduces the risk of transmission to others.[1,129]

While mother-to-child transmission is a risk factor globally, in developed regions such as Ontario, transmission to infants whose mothers are on antiretroviral therapy is exceedingly low. Of those diagnosed with HIV in Ontario in 2013 and 2014, 65 percent were men who have sex with men, 14 percent were heterosexuals, eight percent were injection drug users and 13 percent were from HIV endemic regions, such as Africa and the Caribbean.[130,131] Due to blood screening, the risk of HIV infection through blood products is almost non-existent in developed countries.[1,132] Occupational transmission of the virus through sharps, such as needles, is possible, but very rare.[1]

In Ontario, while there are over 16,000 persons living with HIV, the number of new infections has been decreasing.[133] In 2005, there were over 900 new cases (seven per 100,000) and this number had dropped to 759 (six per 100,000) by 2015.[134] In Ontario, most of the new cases reported in 2015 were among males (616 cases) and very few were reported among those under age 15 (six cases).[134]

Within Ontario, there is regional variation in the incidence of HIV infections reported. In 2015, more than half (433) were reported in Toronto (15 per 100,000) and none were reported in areas such as North Bay/Parry Sound and Brant County.[134]

In recent years, there has been a sharp decrease in AIDS cases reported in Ontario, from two per 100,000 in 2005 to less than one per 100,000 in 2015.[22] In Ontario, the incidence of some AIDS-related cancers has decreased in recent years as a result of highly effective treatments that suppress HIV and reduce the cancer-inducing effects of HIV-related immunosuppression.[110]

In Ontario, as described in the Context section of this report, the prevention of blood borne infections and the use of anti-retroviral medications prevents HIV transmission and reduces the long-term effects of other infections, including their associated cancers. Further, the Ontario government moved to cover the cost of pre-exposure medication for those at high risk of contracting HIV.[24]

Reducing the Burden of Cancer Associated with Infections

In the last few decades, there has been a substantial increase in understanding of the role that infection plays in causing cancer. As described in the Context section of this report, a number of infection control measures are in place within Ontario, such as blood supply screening, school-based vaccination programs, efforts to increase public awareness of the health risks of unsafe sex, harm reduction approaches (e.g., needle exchange and drug equipment distribution) and general infection control practices.

Despite these initiatives, approximately 3,100 cancer cases (plausible range 2,443 to 3,591) diagnosed in Ontario per year are estimated to be attributable to seven infections combined, some of which are enabled by the immunosuppression caused by co-infection with HIV. Of these cases, most (almost 3,000) are attributable to infections with known means of prevention: human papillomavirus (HPV), *Helicobacter pylori (H. pylori)*, hepatitis C virus (HCV) and hepatitis B virus (HBV). Focusing prevention efforts on these four infections, as well as on HIV, all of which can be prevented or treated, has the greatest potential to reduce the burden of cancer from infections in Ontario.

Focusing prevention efforts on infections that can be prevented or treated, has the greatest potential to reduce the burden of cancer from infections in Ontario.

Human papillomavirus (HPV)

HPV makes the largest contribution to the cancer burden attributable to infections in Ontario. Nearly 1,400 new cancer cases diagnosed in the province per year are estimated to be attributable to persistent infection with HPV. Infection with HPV is a necessary cause of cervical cancer and accounts for a very high percentage of anal cancers. Approximately 50 percent or more of each penile, vulvar, vaginal and oropharyngeal cancers are attributable to the infection. Preventing HPV infections through vaccination—or in the case of cervical cancer, interrupting the development of associated cancers through screening and treatment—has the potential for the largest decrease in the number of new cancer cases attributable to HPV infection in the province.

Vaccination

The burden of HPV-attributable cancers could be lowered by improving population coverage with and the scope of the HPV vaccination program, within recommendations of the National Advisory Committee on Immunization. In Canada, three HPV vaccines are used for females ages nine to 45 and two for males ages nine to 26.[135] All of the available vaccines protect against HPV 16 and 18, which together account for approximately 75 percent of cervical and up to 90 percent of anal cancers.[135] The 9-valent vaccine also protects against high risk types 31, 33, 45, 52 and 58.[135] Vaccination before sexual activity is most effective in preventing HPV infections and HPV-associated diseases. However, vaccination can prevent new HPV infections among people who previously had an infection with a different HPV type.[136] Accordingly, Canada's National Advisory Committee on Immunization recommends that females and males ages nine to 26 be vaccinated, and indicates that vaccination may be used in people over age 26 who have not been previously vaccinated.[135]

Ontario's school-based HPV vaccination program currently offers Grade 7 boys and girls the 9-valent vaccine that protects against high risk types 16, 18, 31, 33, 45, 52 and 58 and low risk types 6 and 11.[137] Children who were eligible for a vaccine in the school-based program, but missed a dose or didn't start it, may get it at a public health unit until the end of Grade 12.[137] Due to their greater risk of infection, men who have sex with men can also get vaccinated for free up to age 26 at public health units.[138] People who want to be vaccinated, but who are not eligible for publicly funded vaccination, can pay for the vaccine out-of-pocket or use private health benefits to cover the cost. Among 13-year-old girls in the 2015–2016 school year, vaccine series coverage was 61 percent (up-to-date immunization coverage[i]). Of the 13-year-old girls tracked in this period, 71 percent began the vaccine series, and of this 71 percent, 85.6 percent completed it.[17] The target for HPV vaccination in Ontario is 90 percent completion of the series.[17,139,140]

To improve coverage and scope of the publicly funded HPV vaccination programs, the province of Ontario may benefit from extending the catch-up age for publicly funded vaccination beyond Grade 12. Other opportunities include publicly funding the vaccine for a broader age range (British Columbia, for example, provides the vaccine to unvaccinated females born from 1994 or later, up to age 26)[141] and rapidly adopting the use of new vaccines, as they become available.

In Ontario, providing the school-based HPV vaccine earlier than Grade 7 may improve the impact of the vaccine on HPV-associated cancers. This strategy takes advantage of the fact that children in lower grades are unlikely to have been exposed to HPV, vaccinating earlier would extend the time that children who miss a dose could get the vaccine and the immune response is stronger among those vaccinated earlier.[142,143] For example, Quebec offers the HPV vaccine at Grade 4 and Alberta offers it at Grade 5.[144,145]

Efforts to increase awareness that the vaccine is available free of charge in public health units to men who have sex with men up to age 26 may increase vaccine uptake in this at-risk group. These efforts could take place in family practice, public health or clinic settings.

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[i]The school-based program began offering the vaccine to boys in the 2016–2017 school year, so these data are for females only. Up-to-date coverage is the proportion of a population that has received recommended vaccine doses by a certain age; children with some, but not all, doses are not included in this number.

> Vaccination against HPV infection, and cervical cancer screening are the best ways to decrease the number of new cancers associated with HPV.

Screening

Cervical screening can prevent cervical cancer. Despite the availability of cervical screening, during 2013–2015 only 61 percent of screen-eligible women in Ontario were considered up to date for cervical screening.[43]

The Ontario government recently announced that primary HPV testing will be integrated into cervical cancer screening for women ages 30 to 69.[146] This change to the Ontario Cervical Screening Program has the potential to improve the effectiveness of cervical cancer screening because the HPV test is more sensitive than the Pap test,[147] particularly for women age 30 and older.[148] HPV testing also offers the opportunity for self-sampling, which may increase participation in cervical screening.[149,150]

As more women who are vaccinated for HPV reach the screen-eligible age (the first cohort in the school-based program reached screen-eligible age in 2016), changes may occur in cervical cancer screening participation. While it is unknown how HPV vaccination will impact screening behaviour, some research suggests that vaccinated women are more likely to get screened.[151-153] Continual public education on the importance of regular screening will be necessary. It will also be important to address the potential impact of HPV vaccination on the Ontario Cervical Screening Program, including a re-assessment of screening recommendations.[154]

While organized screening programs do not exist for other HPV-associated cancers, cancer screening opportunities exist, such as checking for oral cancers by dentists during exams.[155] While studies are exploring the possibility of anal cancer screening[156] and testing for HPV on sites other than the cervix, further research is needed.[29]

Helicobacter pylori (H. pylori)

In Ontario, over 1,060 (plausible range 759–1,229) cancer cases per year are estimated to be attributable to infection with *H. pylori*. Population screening and treatment of asymptomatic people is not done in Ontario, even though *H. pylori* infection can be detected (typically using the urea breath test) and treated with a combination of medications. Population-based screening is not done for *H. pylori* due a lack of evidence in populations that are not endemic for the infection[157,158] and increasing concerns about antibiotic resistance.[23,159] The benefits of treating an *H. pylori* infection also vary with the gastric cancer incidence in a population.[23,157] Treatment is strongly associated with the remission of low-grade lymphomas.[1,23,158]

In Ontario, research should be conducted to determine the prevalence of infection in the general population, understand the sub-groups most likely to benefit from treatment, and gain a better understanding of the risks and benefits of treatment.[159] Although there may be benefits to targeted screening and treating people at higher risk for the infection in Ontario, such as First Nations people in the northwest and immigrants from endemic regions,[55,158] evidence on the prevalence of infection and who is at risk for associated cancers is needed. Prevention initiatives for *H. pylori*-associated cancers should consider the results of treatment trials underway,[7] and assess the impact and potential value of prevention strategies for *H. pylori*-associated cancers.

Hepatitis C virus (HCV)

It is estimated that over 200 new cases of liver cancer and almost 70 new cases of non-Hodgkin lymphoma (NHL) annually are attributable to chronic HCV infection. In addition to current efforts to limit transmission, such as harm reduction programs, the burden of HCV-attributable cancers could be lowered in Ontario by improved early detection and the subsequent treatment of HCV infections.

Detection and treatment of infection

With direct-acting antiviral (DAA) therapy, HCV infection is now almost entirely curable. Although the cost of DAA drugs was initially a barrier to widespread treatment of HCV infection, they have been made more accessible thanks to the pan-Canadian Pharmaceutical Alliance's successful negotiation with pharmaceutical companies in February 2017 for substantial DAA price reductions.[160] Accordingly, the Ontario Drug Benefit program has recently expanded access to HCV antiviral treatment.[21,22]

It is important to improve efforts to detect HCV infection and subsequent access to treatment because many people who are chronically infected are unaware of their infection and go untreated.[79] The Canadian Task Force for Preventive Health Care recommends screening for HCV infection among people who are at elevated risk (e.g., immigrants from endemic countries, people with a history of injection drug use, people who received blood transfusions before 1992 or people who are incarcerated), but advises against screening those without apparent risk of HCV.[77] Some organizations such as the American Association for the Study of Liver Diseases and the U.S. Centers for Disease Control and Prevention recommend one-time age-based screening for HCV.[74,161,162]

To prevent HCV-associated cancers, it is important to educate primary care providers about appropriate and consistent screening of high risk groups and to treat people who are infected with HCV.

Hepatitis B virus (HBV)

HBV is an important cause of liver cancer in Ontario; over 130 cases, or 14 percent of all liver cancer cases, per year are estimated to be attributable to chronic HBV infection and liver cancer incidence continues to rise. Therefore, addressing HBV infection represents an important prevention opportunity. In addition to Ontario's current efforts, which include sexual health education, steps to limit transmission and immunization programs, there are other opportunities for reducing HBV infection rates. Efforts to increase the uptake of HBV vaccination, and improve follow-up of those infected are ways to prevent HBV infection and lower the HBV-associated cancer burden.

Vaccination

The burden of HBV-attributable cancers could be lowered by improving population coverage for HBV vaccination. While a vaccine against HBV has been available to people meeting high risk eligibility criteria and in a publicly funded school-based program since the 1990s, the coverage among 12-year-olds was 70 percent for the 2015–2016 school year, which falls below the target of 95 percent.[17] Because most (80 to 90 percent) infections with HBV in the first year of life become chronic, while less than five percent of infections among adults become chronic,[163] one option for the province of Ontario is to vaccinate children earlier (e.g. in infants) as is the case in New Brunswick,[164] Prince Edward Island, British Columbia and Quebec.[165] The province of Ontario may benefit from the collection and consideration of data on the effectiveness of the existing vaccination program on an ongoing basis, so that appropriate changes can be made as needed.[8]

It would also be beneficial to screen children from endemic countries for the infection before vaccinating them because they may have been exposed to the virus in the home or by visiting their country of origin. Clinical guidelines for immigrants and refugees recommend screening and vaccination of susceptible people from countries with moderate or high prevalence.[166]

Case and contact management

People with chronic infection require follow-up, monitoring and treatment. The contacts of those infected also need to be checked. Available treatment reduces the risk of liver cancer, but public reimbursement for treatment is provided based on severity of disease and age.[20] Providing these treatments more widely to those infected and their contacts may lessen the number of liver cancer cases.

Human immunodeficiency virus, type 1 (HIV)

Although the attributable cancer burden for HIV was not calculated in this report, this virus is important in the development of cancers associated with other infections and there were over 16,000 Ontarians living with diagnosed infection,[133] and over 750 newly diagnosed cases of HIV were reported in Ontario in 2015.[134] Much is done in Ontario to prevent the infection, and treatments to suppress HIV increase the life expectancy of those infected by decreasing their likelihood of progressing to AIDS (and developing AIDS-related cancers) and simultaneously decreasing their chance of transmitting the virus.[106,110,167] However, not everyone who begins treatment continues with it, which has implications for the health of people who are infected and the risk of transmission.[168,169] An HIV/AIDS strategy was recently developed that, among other goals, seeks to further improve the health and well-being of the populations most affected, including preventing new HIV, HCV and sexually transmitted infections.[168] Ontario will benefit from the deployment of this strategy.

> **High-quality surveillance data are important in evaluating the overall disease burden and the impact of prevention efforts.**

Surveillance

To prevent cancer-causing infections of all types and their associated cancers, ongoing measurement of infection prevalence, sub-types and cancer incidence is important. In the absence of high-quality surveillance data, it is difficult to determine where efforts are successful and where there are opportunities for improvement.

To monitor the impact of Ontario's school-based HPV vaccination program, it will be necessary to track trends in the distribution of the different HPV types in the population, as well as the incidence of HPV-associated cancer types in the Ontario population and non-cancer-associated HPV health effects, including anogenital warts. It is promising that the incidence of anogenital warts has decreased with population-based female HPV vaccination programs in Ontario and other high income regions.[40,42,170] With vaccination targeting HPV 16 and 18, and the recent addition of other high risk types it is expected that these HPV types will gradually become less common. HPV vaccination is expected to eventually lead to a decrease in HPV-associated cancers, particularly cervical cancer.

Linking HPV vaccination coverage data with data from the Ontario Cervical Screening Program may help assess the impact of HPV vaccination on cervical cancer screening participation and cancer incidence and mortality. It will also be important to modify screening recommendations, as warranted, based on ongoing monitoring of the prevalence of HPV infections (and detection of high-grade cervical abnormalities and cervical cancer) among screen-eligible women.

To support the possibility of targeted screening and treatment of high risk groups for *H. pylori*, descriptive epidemiologic and surveillance studies that help identify high risk sub-groups and advance our understanding of the prevalence and distribution of *H. pylori* infection in Ontario are required. Enhanced cancer surveillance focused on high risk groups (e.g., First Nations and immigrant populations) or people who present with gastritis or ulcer-like symptoms may improve knowledge of which populations are going on to develop *H. pylori*-associated cancers.

While there are data that measure participation in the school-based HBV vaccination program, overall population coverage is unknown because Ontario does not systematically track vaccination in high risk groups or those who receive the vaccine outside the school-based program. Expanding surveillance of vaccine coverage in the Ontario population presents a potential opportunity for better evaluating population risk for HBV and associated health effects, including cancer.

Conclusion

In Ontario, there are many effective initiatives in place to prevent and control cancer-causing infections and their associated cancers.

Despite these efforts, approximately 3,100 new cancer cases (plausible range 2,443 to 3,591) diagnosed in Ontario in 2013 were attributable to infection with one of seven cancer-causing infectious agents: human papillomavirus (HPV), *Helicobacter pylori (H. pylori)*, hepatitis C virus (HCV), Epstein-Barr virus, hepatitis B virus (HBV), human herpesvirus 8 and human T-cell lymphotropic virus, type 1. Over 90 percent of these cancers were attributable to four infections (HPV, *H. pylori*, HCV and HBV), all of which have known means of prevention, suggesting a large opportunity for cancer prevention.

By quantifying the burden of cancer attributable to specific infections, it is possible to expand and strengthen initiatives already in place to prevent infections, such as school-based vaccination programs, as well as improve the early detection and treatment of carcinogenic infections and their associated cell changes. Continuing surveillance of these infections, their sub-types and their associated cancers over time is also important.

The information presented in this report is intended to help specialized cancer organizations (e.g., Cancer Care Ontario, Regional Cancer Programs, Canadian Partnership Against Cancer, Canadian Cancer Society), regional health organizations (e.g., Local Health Integration Networks, public health units), the provincial government and agencies that deal with public health develop appropriate prevention efforts.

Appendix A

Methods for Calculating Population Attributable Fractions

To estimate the number of new cancers that were attributed to each infectious agent diagnosed in Ontario, population attributable fractions (PAFs) were calculated. The methods used for calculating PAFs were based on those used by an international study on the global burden of cancers attributable to infectious agents published by de Martel et al., 2012[2] and then updated by Plummer et al., 2016.[9]

Selection of infectious agents and cancer sites

- Infectious agents classified as group 1 carcinogens ("carcinogenic to humans") by the International Agency for Research on Cancer (IARC) were considered for inclusion in this report.
- Of the 11 carcinogenic infectious agents, PAFs were calculated for seven of them: human papillomavirus (HPV), *Helicobacter pylori (H. pylori)*, hepatitis C virus (HCV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), human herpesvirus 8 (HHV-8) and human T-cell lymphotropic virus, type 1 (HTLV-1).
  - Human immunodeficiency virus (HIV) was excluded to avoid double-counting cancer cases attributable to infectious agents because it is a cofactor that causes cancer primarily through immunosuppression, which enables the cancer-causing effect of infections with other carcinogenic agents (e.g., EBV, HHV-8 and HTLV-1);[1] and
  - Liver flukes, *S. haematobium* and *S. japonicum* were excluded because they are very rare in Ontario.
- For each infectious agent, separate PAFs were calculated for each of the cancer types that IARC has classified as having "sufficient" evidence of an association with an infectious agent (Table A1). Exceptions are as follows:
  - for HPV, the PAF for laryngeal cancer (an additional type not classified with sufficient evidence) was calculated due to recent studies drawing an association between the two;
  - for EBV, PAFs were not calculated for immunosuppression-related non-Hodgkin lymphoma and extranodal natural killer/T-cell lymphoma (nasal type) due to a lack of data on the prevalence of EBV in these cancers; and
  - for HHV-8, the PAF was not calculated for primary effusion lymphoma due to the rarity of this cancer type.

TABLE A1 Infectious agents and associated cancer types included in Ontario population attributable fraction estimates

Infectious agents	Cancer types[a]
Human papillomavirus	Cervix, penis, anus, vulva, vagina, oropharynx, oral cavity, tonsil, and larynx
Helicobacter pylori	Stomach (non-cardia gastric) and gastric non-Hodgkin lymphoma (mucosa-associated lymphoid tissue and diffuse large B-cell)
Hepatitis C virus	Liver (hepatocellular carcinoma) and non-Hodgkin lymphoma
Epstein-Barr virus	Burkitt lymphoma, Hodgkin lymphoma and nasopharynx
Hepatitis B virus	Liver (hepatocellular carcinoma)
Human herpesvirus 8	Kaposi sarcoma
Human T-cell lymphotropic virus, type 1	Adult T-cell leukemia and lymphoma

NOTE:
[a] IARC, 2012[1]

Data sources

In general, prevalence estimates were extracted from population-based surveys, case-control studies with population-based controls, systematic reviews and meta-analyses; relative risk estimates from systematic reviews and meta-analyses; and cancer incidence data from the Ontario Cancer Registry. Ontario-specific estimates were used wherever possible. When Ontario estimates were unavailable, Canadian estimates or estimates from jurisdictions that were judged as comparable to Ontario based on regional proximity or similar level of development were substituted.

Prevalence data

To identify the appropriate PAF prevalence of infections specific to the Ontario population, a review of the literature was conducted with the aid of a professional librarian. The following search rules were applied:

- Ontario specific, otherwise expanded to Canada, else North America, developed nations and globally;
- population prevalence of infection and, when not available, prevalence of infection in cases;
- English language articles, published in the years 2000 to 2016; and
- data collected 1995 or later, to account for potential changes in prevalence estimates.

Table A2 shows the articles that were the sources with the best available prevalence estimates selected for Ontario:

TABLE A2 Data sources for prevalence estimates of infectious agents

Infectious agents	Cancer types	Selected sources	Regions	Types of study/data sources
Human papillomavirus	Cervix	N/A[a]	N/A[a]	N/A[a]
Human papillomavirus	Oropharynx	Nichols et al., 2013[171]	Ontario	Retrospective study, prevalence in cases
Human papillomavirus	Anus	Ouhoummane et al., 2013[172]	Quebec	Retrospective study, prevalence in cases
Human papillomavirus	Vulva	de Sanjosé et al., 2013[173]	Global	Retrospective study, prevalence in cases
Human papillomavirus	Vagina	de Vuyst et al., 2008[174]	Global	Meta-analysis, prevalence in cases
Human papillomavirus	Penis	Bethune et al., 2012[175]	Nova Scotia	Retrospective study, prevalence in cases
Human papillomavirus	Oral cavity	Plummer et al., 2016[9]	Global	Case series studies, prevalence in cases
Human papillomavirus	Larynx	Plummer et al., 2016[9]	Global	Case series studies, prevalence in cases
Helicobacter pylori	Stomach (non-cardia gastric)	Naja et al., 2007[54]	Ontario	Case-control study, prevalence in controls
Helicobacter pylori	Mucosa-associated lymphoid tissue	Naja et al., 2007[54]	Ontario	Case-control study, prevalence in controls
Hepatitis C virus	Liver[b] (hepatocellular carcinoma)	Rotermann et al., 2013[79]	Canada	Population survey, population prevalence
	Liver[c] (hepatocellular carcinoma)	Morris Sherman, 2017	Toronto, Ontario	Hospital patients, prevalence in cases
Hepatitis C virus	Non-Hodgkin lymphoma	de Sanjose et al., 2008[69]	British Columbia	Case-control study, prevalence in cases
Epstein-Barr virus	Hodgkin lymphoma	Lee et al., 2014[176]	North America	Meta-analysis, prevalence in cases
Epstein-Barr virus	Nasopharynx	Plummer et al., 2016[9]	Low incidence areas	Prevalence in cases
Epstein-Barr virus	Burkitt lymphoma	IARC, 2012[1]	Low endemic areas (Europe and North America)	Prevalence in cases
Hepatitis B virus	Liver[b] (hepatocellular carcinoma)	Rotermann et al., 2013[79]	Canada	Population survey, population prevalence
	Liver[c] (hepatocellular carcinoma)	Morris Sherman, 2017	Toronto, Ontario	Hospital patients, prevalence in cases
Human herpesvirus 8	Kaposi sarcoma	N/A[a]	N/A[a]	N/A[a]
Human T-cell lymphotropic virus, type 1	Adult T-cell leukaemia and lymphoma	N/A[a]	N/A[a]	N/A[a]

NOTES:
Reference numbers provided in the table correspond to the main reference list in this report.
[a] Population attributable fraction assumed to be 100% on the basis of evidence suggesting a "necessary but not sufficient" relationship between the relevant agent and cancer type.
[b] Liver cancer (hepatocellular carcinoma) prevalence value used for lower PAF estimate for the infectious agent.
[c] Liver cancer (hepatocellular carcinoma) prevalence value used for upper PAF estimate for the infectious agent.

Relative risk data

For all infectious agents under consideration and their associated cancer types, the relative risk estimates were primarily obtained from Plummer et al., 2016.[9] Where possible, relative risk estimates for populations comparable to Ontario's were used in our analysis, whether they were published in Plummer et al., 2016[9], or were in their citied studies. Table A3 provides an overview of the selected articles.

TABLE A3 Data sources for relative risk estimates of infectious agents and associated cancer types

Infectious agents	Cancer types	Articles	Regions	Relative risk estimates	Assumptions
Human papillomavirus	Cervix	IARC, 2012[1]	N/A	N/A	Necessary cause[a]
Human papillomavirus	Oropharynx, oral cavity, larynx, anus, vulva, vagina, penis	Plummer et al., 2016[9]	Global	Very large	Very large relative risk[b]
Helicobacter pylori	Stomach (non-cardia gastric)	Plummer et al., 2015[46]	Global	17.0	N/A
Helicobacter pylori	Mucosa-associated lymphoid tissue	Plummer et al., 2016[9]	Global	7.2	N/A
Hepatitis C virus	Liver (hepatocellular carcinoma)	Cho et al., 2011[68]	Low endemic countries	23.8	N/A
Hepatitis C virus	Non-Hodgkin lymphoma	San Jose et al., 2008[69]	Canada (British Columbia)	3.3	N/A
Epstein-Barr virus	Hodgkin lymphoma, nasopharynx, and Burkitt lymphoma	Plummer et al., 2016[9]	Global	Very large	Very large relative risk[b]
Hepatitis B virus	Liver (hepatocellular carcinoma)	Cho et al., 2011[68]	Low endemic countries	20.3	N/A
Human herpesvirus 8	Kaposi sarcoma	IARC, 2012[1]	N/A	N/A	Necessary cause[a]
Human T-cell lymphotropic virus, type 1	Adult T-cell leukaemia and lymphoma	IARC, 2012[1]	N/A	N/A	Necessary cause[a]

NOTES:
Reference numbers provided in the table correspond to the main reference list in this report.
[a] Population attributable fraction assumed to be 100% on the basis of evidence suggesting a "necessary but not sufficient" relationship between the relevant agent and cancer type.
[b] No relative risk (RR) estimate required for these prevalence in cases, as RR value assumed to be very large, to the point that PAF can be assumed to equal the prevalence of an infectious agent in particular cancer cases.

Cancer incidence data

Data on the number of new cancer cases diagnosed in Ontario (cancer incidence) were obtained from the Ontario Cancer Registry (OCR). Cancer Care Ontario maintains the OCR, which gathers information from administrative databases, laboratory reports and clinical records. Electronic records are linked at the person level and then "resolved" into incident cases of cancer using computerized medical logic. The four main data sources are:

- pathology reports;
- activity-level reporting from Regional Cancer Centres (RCCs) and non-RCC hospital records;
- surgery and discharge data records from the Canadian Institute for Health Information (CIHI); and
- death certificates received from the Ontario Registrar General.

Data are added to the OCR at multiple points in a year, potentially affecting case resolution and changing cancer incidence data, which means that the results of an analysis may be affected based on the date the data was extracted from the OCR. The cancer incidence data used in this report's PAF calculations and incidence trends were extracted from the OCR in November 2016, at which point the most recent year of available data were new cancer cases diagnosed in 2013. Definitions of the cancer types used for the PAF estimates are shown in Table A4.

TABLE A4 Definition of cancer types associated with infectious agents

Cancer types[a]	ICD O-3 Site/Histology code[b]
Cervix	C53
Oropharynx (including tonsil and base of tongue)	C01.9, C09, C10
Anus	C21.0–C21.2, C21.8
Penis	C60
Vulva	C51
Vagina	C52.9
Oral cavity	C02–C06
Larynx	C32
Stomach (non-cardia gastric)	C16.1–C16.9
Mucosa-associated lymphoid tissue	Histology 9699
Liver (hepatocellular carcinoma)	C22.0
Non-Hodgkin lymphoma	All sites with histologies 9590–9597, 9670–9719, 9724–9729, 9735, 9737, 9738; and All sites except C42.0–C42.1 and C424 with histologies 9811–9818, 9823, 9827, 9837
Hodgkin lymphoma	Histologies 9650–9667
Nasopharynx	C11
Burkitt lymphoma	Histology 9687
Kaposi sarcoma	Histology 9140
Adult T-cell leukaemia and lymphoma	C 42.1 with histology 9827
All cancers combined	C00–C80.9

NOTES:
[a] Cancer cases defined by SEER Site recode (see https://seer.cancer.gov/siterecode/icdo3_dwhoheme/index.html).
[b] Third Edition of the International Classification of Diseases for Oncology (2000). ICD-0-3 site/histology codes were based on the Surveillance, Epidemiology and End Results (SEER) site recode definition. See http://seer.cancer.gov/siterecode/icdo3_dwhoheme/index.html.

Statistical analyses: PAF formulas

To estimate the number and proportion of cancers in Ontario adults attributable to various infectious agents, the population attributable fraction (PAF) for each infectious agent was calculated using one of the standard formulas noted in Table A5, as described in De Martel et al., 2012.[2]

TABLE A5 Population attributable fraction (PAF) formulas

Levin's formula	**PAF = p_P(RR-1)/1+p_P(RR-1)**	Where p_P is the prevalence of a given infection in the general population, and **RR** is the relative risk of developing a specific cancer for populations that are infected compared to uninfected.
Alternate formula 1	**PAF = p_C(RR-1)/(RR)**	Where p_C is the prevalence of a given infection in patients with specific cancers, and **RR** is the relative risk of cancer for an individual infection vs. uninfected.
Alternate formula 2	**PAF = p_C**	Where p_C is the prevalence of a given infection in patients with specific cancers. Adapted from Alternate formula 1, the relative risk portion is assumed to equal 1, when the RR is large ([RR-1]/[RR]=1), leaving the PAF calculation to only reflect prevalence in cases.

NOTES:

p_P=prevalence of exposure in general population; **RR**=relative risk associated with exposure; and p_C=prevalence in cancer cases.

- Based on the type of infectious agent prevalence data (population vs. case) available and magnitude of the relative risk (RR) estimate, a single PAF formula was selected for each agent and associated cancer.
  - For situations where the best available prevalence data is the prevalence in cancer cases, and when the associated RR between the agent and cancer is very large ([RR-1]/[RR] approaches 1), the PAF can be represented by prevalence in cases. This was the situation for PAF calculations for HPV and EBV, as outlined in Table A6.
  - For instances where a single best prevalence value was not available, due to data limitations, the PAFs were calculated twice: (1) using Levin's formula and (2) using the alternate formula 1. With (1) considered to be an underestimate and (2) considered to be an overestimate, the final reported PAFs for HBV and for HCV were the average of their two PAF calculations.
- For each cancer type associated with an infectious agent, the PAF was calculated for the Ontario population as a whole. PAF estimates were not calculated for sub-groups, such as age or sex, due to limited data.
- To estimate the number of cancer cases diagnosed in 2013 that were attributable to each infectious agent, the resulting PAF point estimates were applied to the 2013 cancer incidence data from the OCR (see Table A7).
- The total number of cancer cases attributable to a given infection was obtained by summing the estimates for each associated cancer type. The estimates of the number of cancer cases attributable to a given infectious agent were then summed to obtain the total number of cancer cases diagnosed in Ontario attributable to any infectious agents.
- To account for uncertainty and variability in the prevalence and relative risk estimates used in the PAF estimates, plausible ranges were calculated around each PAF point estimate. These ranges were calculated by adjusting the PAF inputs by a relative 10 percent (plus and minus), and recalculating the PAF using these adjusted prevalence and RR values. This method provided upper and lower bounds around the PAF point estimates, with the following exceptions:
  - Liver cancer cases attributed to HBV and to HCV each had their lower bounds reflect PAF estimates based on reported population prevalence estimates from the 2007–2011 Canadian Health Measures Survey,[79] and the upper bound reflect the PAF estimates based on the prevalence of each infection in liver cancer cases at Toronto General Hospital between June 2016 and January 2017 (personal communication with Dr. Morris Sherman, Feb. 2, 2017). Each PAF estimate, for HBV and for HCV, was the average of the above two PAF estimates.
  - The lower bound of non-cardia gastric cancer associated with *H. pylori* infections was adjusted to a lower value calculated with a lower relative risk (5.9) based on enzyme-linked immunosorbent assay (ELISA) methodology that had been widely reported previously.[2]
  - The upper bound of *H. pylori* infections and EBV infection associated with Hodgkin lymphoma were adjusted to a higher PAF value reported in Plummer et al.[9]

Appendix B

Details of Population Attributable Fractions and Attributable Numbers

TABLE A6 Population attributable fractions (PAF) of infectious agents and associated cancer types—formulas, inputs, results and plausible ranges

Infectious agents	Cancer types	PAF formulas	Prevalence estimates (%)	Relative risk estimates	PAF estimates (%)	Lower plausible range (%)	Upper plausible range (%)
Human papillomavirus	Cervix[a]	.	.	.	100	.	.
Human papillomavirus	Oropharynx	PAF = p_c	53.0[b]	.	53	48[q]	58[q]
Human papillomavirus	Anus	PAF = p_c	92.0[c]	.	92	83[q]	100[q]
Human papillomavirus	Vulva	PAF = p_c	48.0[d]	.	48	43[q]	53[q]
Human papillomavirus	Vagina	PAF = p_c	78.0[e]	.	78	70[q]	86[q]
Human papillomavirus	Penis	PAF = p_c	53.0[f]	.	53	48[q]	58[q]
Human papillomavirus	Oral cavity	PAF = p_c	4.3[g]	.	4	4[q]	5[q]
Human papillomavirus	Larynx	PAF = p_c	4.6[g]	.	5	4[q]	5[q]
Helicobacter pylori	Stomach (non-cardia gastric)	PAF = p_p(RR-1)/1+p_p(RR-1)	23.1[h]	17.0[n]	79	53[r]	89[t]
Helicobacter pylori	Mucosa-associated lymphoid tissue	PAF = p_p(RR-1)/1+p_p(RR-1)	23.1[h]	7.2[g]	59	53[q]	74[t]
Hepatitis C virus	Liver (hepatocellular carcinoma)	PAF = p_p(RR-1)/1+p_p(RR-1) PAF = p_c(RR-1)/RR	0.5[i] 38.6[j]	23.8[o] 23.8[o]	24[p]	10[s]	37[u]
Hepatitis C virus	Non-Hodgkin lymphoma	PAF = p_c(RR-1)/RR	2.4[k]	3.3[k]	2	0.4[s]	2[q]
Epstein-Barr virus	Hodgkin lymphoma	PAF = p_c	24.0[l]	.	24	22[q]	32[t]
Epstein-Barr virus	Nasopharynx	PAF = p_c	80.0[g]	.	80	72[q]	88[q]
Epstein-Barr virus	Burkitt lymphoma	PAF = p_c	20.0[m]	.	20	18[q]	22[q]
Hepatitis B virus	Liver (hepatocellular carcinoma)	PAF = p_p(RR-1)/1+p_p(RR-1) PAF = p_c(RR-1)/RR	0.4[i] 22.7[j]	20.3[o] 20.3[o]	14[p]	7[s]	22[u]
Human herpesvirus 8	Kaposi sarcoma[a]	.	.	.	100	.	.
Human T-cell lymphotropic virus, type 1	Adult T-cell leukaemia and lymphoma[a]	.	.	.	100	.	.

NOTES:

p_c=prevalence in cancer cases; p_p=prevalence of exposure in general population; and RR=relative risk associated with exposure.

[a] Causal association between infectious agent and associated cancer.

[b] Prevalence estimate obtained from Nichols et al., 2013.[171]

[c] Prevalence estimate obtained from Ouhoummane et al., 2013.[172]

[d] Prevalence estimate obtained from de Sanjosé et al., 2013.[173]

[e] Prevalence estimate obtained from de Vuyst et al., 2009.[174]

[f] Prevalence estimate obtained from Bethune et al., 2012.[175]

[g] Prevalence and relative risk values obtained from Plummer et al., 2016.[9]

[h] Prevalence estimate obtained from Naja et al., 2007.[54]

[i] Prevalence estimates obtained from Rotermann et al., 2013.[79]

[j] Prevalence estimates provided by Dr. Morris Sherman (personal communication, Feb. 2, 2017).

[k] Prevalence and relative risk values obtained from de San Jose et al., 2008.[69]

[l] Prevalence estimate obtained from Lee et al., 2014.[176]

[m] Prevalence estimate obtained from IARC, 2012.[1]

[n] Relative risk values obtained from Plummer et al., 2015.[46]

[o] Relative risk values obtained from Cho et al., 2011.[68]

[p] PAF estimate based on the average of PAF results from: (1) Levin's formula; and (2) Alternate formula 1.

[q] Upper and lower PAF plausible ranges calculated using ±10 percent of prevalence and of relative risk, respectively.

[r] Lower plausible range calculated using relative risk (5.9) from De Martel et al., 2012[2] based on ELISA method.

[s] Lower PAF plausible range calculated using prevalence estimates from Rotermann et al., 2013.[79]

[t] Upper plausible range obtained from Plummer et al., 2016.[9]

[u] Upper plausible range calculated using prevalence estimates provided by Dr. Morris Sherman (personal communication, Feb. 2, 2017).

TABLE A7 Estimated number of cancer cases attributable to infectious agents, Ontario, 2013

Infectious agents	Cancer types	Number of new cancer cases, 2013	Estimated number of cancer cases attributed to infection[a]	Lower plausible range[a]	Upper plausible range[a]
Human papillomavirus	Cervix	523	**523**	.	.
Human papillomavirus	Oropharynx	602	**319**	287	351
Human papillomavirus	Anus	220	**202**	182	220
Human papillomavirus	Vulva	305	**146**	132	161
Human papillomavirus	Vagina	83	**65**	58	71
Human papillomavirus	Penis	108	**57**	52	63
Human papillomavirus	Oral cavity	766	**33**	30	36
Human papillomavirus	Larynx	422	**19**	17	21
Helicobacter pylori	Stomach (non-cardia gastric)	1,140	**897**	605	1,015
Helicobacter pylori	Non-Hodgkin lymphoma of gastric (mucosa-associated lymphoid tissue)	289	**170**	154	214
Hepatitis C virus	Liver (hepatocellular carcinoma)	953	**225**	98	352
Hepatitis C virus	Non-Hodgkin lymphoma	4,088	**68**	16	78
Epstein-Barr virus	Hodgkin lymphoma	386	**93**	83	124
Epstein-Barr virus	Nasopharynx	104	**83**	75	92
Epstein-Barr virus	Burkitt lymphoma	27	**5**	5	6
Hepatitis B virus	Liver (hepatocellular carcinoma)	953	**137**	68	206
Human herpesvirus 8	Kaposi sarcoma	41	**41**	.	.
Human T-cell lymphotropic virus, type 1	Adult T-cell leukaemia and lymphoma	17	**17**	.	.
Total		9,758[b]	**3,102**	2,443	3,591

NOTES:
[a] The population attributable fraction estimates from Table A6 above were applied to the number of each cancer type diagnosed in Ontario in 2013.
[b] Total number of cancers cases in 2013 based on 15 cancer types, where liver cancer cases were counted once, and Burkitt lymphoma and non-Hodgkin lymphoma of gastric (mucosa-associated lymphoid tissue) cancer cases were considered part of non-Hodgkin lymphoma.

Appendix C

Considerations and Limitations

There are several considerations and limitations that should be kept in mind when reviewing the results of this report.

Analysis:

- **Population attributable fraction (PAF) point estimate:** The PAF values provided are best estimates for each infectious agent and associated cancer type, and are supported by a plausible range to account for uncertainty and variations in reported PAF inputs (prevalence and relative risk estimates).
- **Ontario-wide PAF:** There are individual- and group-level differences in exposure and susceptibility that have not been accounted for in the results. The analysis was meant to reflect PAFs for the entire province of Ontario; however, the attributable burden of cancer and infections varies for certain individuals or groups based on specific circumstances or exposures not common in the general population.
- **PAF and lag-time:** PAF estimates are based on exposure estimates from the current time period or recent past and do not account for the lag time needed for cancer to develop. As a result, the PAF estimates provided in this report may not reflect future estimates of the cancer burden attributable to infectious agents.
- **PAF and co-infections:** In the PAF estimates, it was assumed that a single infectious agent accounts for a proportion of cancer burden in Ontario; however, many of the risk groups for these infections overlap and individuals may have concurrent infections. Therefore, it is important to note that, this report does not account for additive or synergistic effects of co-infections.
- **Human papillomavirus (HPV) and relative risk of developing oral cancer:** Based on an assumption that all cancer types associated with HPV have either an association that is causal or a high relative risk,[9] our analysis assumed the prevalence of cancer cases could approximate the PAF. This may have been a limitation when considering HPV infection and oral cancers, where the association may not be as strong. However in the absence of a relative risk estimate, we assumed that the likelihood of developing oral cancer due to HPV would be high.
- **Cancer incidence rates:** Among the 15 cancer types discussed, incidence trends were provided for eight cancer types caused by associated infectious agents that had relative risk greater than five or PAFs above 50 percent. These cancer types included cervix, penis, anus, vulva, vagina, oropharynx, non-cardia gastric and liver (not including intrahepatic bile duct).
- **Hepatitis B virus (HBV) and hepatitis C virus (HCV) prevalence estimates:** The PAF estimates for HBV and HCV were based on two different prevalence estimates with the following limitations:
  - Canadian Health Measures Survey provides prevalence estimates for all of Canada and cannot provide Ontario-specific data. It also excludes people living in locations such as territories, reserves and institutionalized centres who may be more likely to be infected with HBV or HCV, leading to potential underestimates of the prevalence of each agent in Ontario.[79]
  - Liver cancer (hepatocellular carcinoma) cases reported at Toronto General Hospital account for approximately half of all cases in Ontario (personal communication with Dr. Morris Sherman, Feb. 2, 2017); however, the associated HBV and HCV prevalence estimates may be overestimates for Ontario because the population around Toronto General Hospital includes a higher proportion of immigrants and other at-risk groups than the rest of Ontario.

Data sources:

- **Incidence of chronic HBV:** An HBV infection is considered to be chronic if detectable HBV surface antigens or HBV DNA persists for more than six months after the initial infection. However, in practice, distinguishing chronic HBV infections (greater than six months in duration) from acute HBV infections is difficult because up to a quarter of chronic HBV cases may have markers of an acute infection or acute flare ups can lead to detection of a previously undiagnosed chronic infection.[92] Chronic HBV infections can also remain asymptomatic or share symptoms with liver cirrhosis, meaning the reported chronic HBV incidence rate likely underreports the true incidence of this infection.[177]
- **HBV and HCV prevalence from the Canadian Health Measures Survey (CHMS):** The CHMS cannot distinguish chronic HBV and HCV infections from acute infections due to the methods used to detect them. However, most of the current infections detected by the CHMS were likely chronic.[79] The CHMS may also underestimate the population-prevalence of both HBV and HCV, since it is based on a household sample that excludes some groups that tend to have high prevalence of these infections (e.g., homeless populations, people living on First Nations reserves, inmates, and residents of long-term or mental health institutions).
- **HBV and HCV prevalence from cases:** The number of liver cancer (hepatocellular carcinoma) cases due to HBV or HCV at Toronto General Hospital may overestimate prevalence in cases for each agent in comparison to the rest of Ontario because the Greater Toronto Region's population includes a higher proportion of immigrants and other groups who are more likely to have an HBV or HCV infection.
- **HPV prevalence in oropharyngeal cancer cases:** HPV prevalence estimates for head and neck cancers used in the PAF estimates for this report were based on studies that used p16 presence detected by polymerase chain reaction as a surrogate marker for HPV. This was done due to a limited availability of studies that have used E6/E7 mRNA detection, which is considered the gold standard for identifying HPV infection.[178]
- ***Helicobacter pylori (H. pylori)* and immunoblot detection:** The relative risk of developing non-cardia gastric cancer due to an *H. pylori* infection used in the PAF estimate was 17.0 based on studies that used the immunoblot (western blot) method for detecting *H. pylori*.[46] This relative risk is higher than the 5.9,[2] previously estimated based on the enzyme-linked immunosorbent assay (ELISA). This higher estimate was selected because the immunoblot has been shown to be more sensitive at detecting anti-*H. pylori* antibodies than the ELISA method.[46] The resulting PAF estimates for *H. pylori* and non-cardia gastric cancer in this report are likely higher than those in previous studies.
- ***H. pylori* and mucosa-associated lymphoid tissue (MALT) relative risk:** The relative risk estimate (7.2) was based on studies that include mucosa-associated lymphoid tissue (MALT) and diffuse large B-cell lymphomas (DLBCL) because the two types are not distinguishable in most cancer registries.[9] As a result, the relative risk used in the PAF calculation reflects the risk of developing MALT or DLBCL, and may suggest a higher risk than developing MALT alone.
- **Relative risk estimates:** In the PAF estimates, the relative risk values or assumptions were based, for the most part, on findings of the global cancer burden of infectious disease studies.[2,9] Studies examining the likelihood of developing specific cancers were based on research from various regions in the world that are assumed to be comparable to Ontario's population (e.g., developed countries).

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