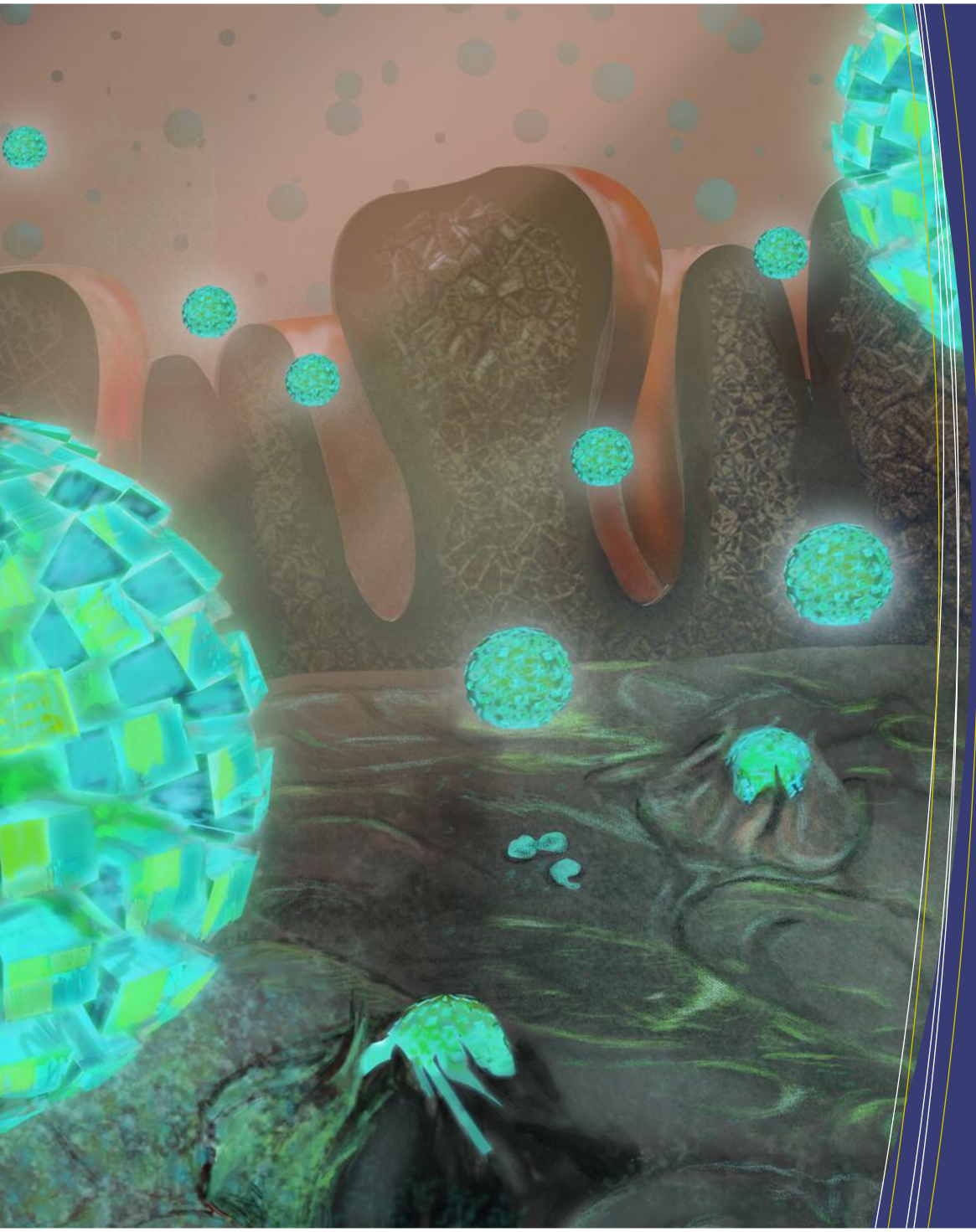
PERSPECTIVES on
infectious agents and cancer



HIGHLIGHTS

Evidence supports an association of one or more cancers with infection with:

- *Helicobacter pylori*
- Liver Flukes
- Schistosomes
- Epstein-Barr Virus
- Hepatitis B Virus
- Hepatitis C Virus
- Human Herpesvirus
- Human Immunodeficiency Virus
- Human Papillomavirus
- Human T-cell Lymphotrophic/ Leukemia Virus Type 1

Cancers associated with infectious agents are caused by a specific event (infection), and could, theoretically, be prevented.

Steps are being taken to prevent a number of cancer-causing infections and the cancers they cause, and prevention research is ongoing.

In time, it is possible that evidence will support an association between cancer and other infectious agents.

cancer care ontario | action cancer ontario

Better cancer services every step of the way

April 2010

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Published and distributed by Cancer Care Ontario. This document was written by staff of Cancer Care Ontario's Department of Population Studies and Surveillance:

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We would like to acknowledge Peter Campbell, Arold Davilmar, and Jocelyn Strath for their contributions during the early development of this report, and Gillian Frosst who secured images and managed the review process.

Thanks to the reviewers who provided input on the document:

Dr. David Fisman
University of Toronto

Mr. Jamie Forrest
Cancer Care Ontario

Dr. Nancy Kreiger
Cancer Care Ontario &
University of Toronto

Dr. Meb Rashid
Access Alliance

Dr. Terry Sullivan
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DEDICATION

This monograph is dedicated to the memory of Christine Powell, whose life was taken by a cancer associated with *Helicobacter pylori* infection. Thanks to her friends and family, a generous donation was provided to support the production of this monograph, whose purpose is to advance the agenda of reducing carcinogenic infectious agents' impact, and to increase awareness.

Cover image: original artwork of Lindsey Brake

Thanks to the many reviewers who provided valuable comments on specific chapters of this report:

Dr. Matthew Cheung
Sunnybrook Health Sciences Centre

Dr. Jo-Anne Chiavetta
EPI-STAT Research Inc.

Dr. Carlo Fallone
McGill University

Dr. Alan Fenwick (early draft)
Imperial College London

Dr. Alex Ferenczy
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Dr. Jenny Heathcote
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Dr. David Martin (early draft)
Health Canada

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Minas Gerais State Public Blood Center

Dr. Fernando Proietti
Federal University of Minas Gerais

Dr. Han-Jong Rim (early draft)
Korea University

Dr. Lorenzo Savioli
World Health Organization

Dr. Paiboon Sithithaworn
Khon Kaen University

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Government of Nunavut

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Public Health Agency of Canada

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FOREWORD

Just over a year ago, Professor Harald Zur Hausen was awarded the Nobel Prize in medicine for his part in discovering that certain subtypes of Human Papillomavirus (HPV) are in fact responsible for virtually all cervical cancer, which is a leading cause of cancer death among women in low income countries and the cause of about 500 cases and 140 deaths in Ontario last year.[1] In addition, Zur Hausen, his colleagues, and other researchers have highlighted the importance of these infectious precursors to cancer, both globally and in advanced countries.

Parkin and colleagues have estimated that approximately 18% of cancers worldwide are caused by infectious agents, 26% of these in developing countries, and 8% in developed countries.[2] The implication of this in a country like Canada and in a province like Ontario is that infectious agents are associated with a disease burden slightly greater than that of colorectal cancer (the lifetime probability of getting colorectal cancer is 7.4% in Canada).[1]

This publication highlights the range of infectious agents associated with cancer, including common infections such as HPV, *Helicobacter pylori (H. pylori)*, Hepatitis C Virus, some Herpes and other viruses, and some rare parasites. These infectious agents create the preconditions for cancer through a range of mechanisms, including chronic inflammation, direct mutagenesis, and immune suppression. The control of these infections through preventive mechanisms and effective treatment is unique to each of the infectious agents. The report highlights the new era of vigilance required to attend to infectious processes, responsible for a non-trivial burden of cancer in our population.

For the more common infections, including *H. pylori* and HPV, many primary care practitioners in Ontario are now familiar with both test and treat approaches and screening, respectively. Most primary care groups are also familiar with the introduction of the HPV vaccine in Ontario schools for grade eight girls. Over time, we anticipate some further reduction in cancer incidence and mortality from HPV, with a longer-term inoculation period and higher school-aged program participation.

The steps from infectious precursors to cancer are complex and evolving, and specialized journals have recently been introduced to help consolidate evolving knowledge in this area. The elegant simplicity of an infection is that its prevention or eradication through treatment reduces the likely burden of cancer. However, many of these infections are episodic; while some of them (such as Epstein-Barr Virus) are highly prevalent in the population, others (like HPV) may be intermittent at certain life stages. *H. pylori* has an overall weighted seroprevalence in Ontario of about 23%, with men having approximately double the prevalence of infection compared to women.[3]

The emerging knowledge of infectious precursors to cancer is a helpful tool in our effort to better control the disease and reduce its burden. We hope that this monograph is useful in stimulating new thinking about the best ways to approach the prevention and control of cancer. It is offered with the intent that fewer patients like Christine Powell will succumb to infectious processes that can trigger cancer in our population.

Terrence Sullivan, PhD
President and Chief Executive Officer
Cancer Care Ontario

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1. Canadian Cancer Society's Steering Committee. Canadian Cancer Statistics 2009. Toronto: Canadian Cancer Society; 2009.
2. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006;118(12):3030-44.
3. Naja F, Kreiger N, Sullivan T. *Helicobacter pylori* infection in Ontario: Prevalence and risk factors. Can J Gastroenterol 2007;21(8):501-6.

TABLE OF CONTENTS

OVERVIEW

The following document discusses bacteria, flukes and viruses as they relate to cancer, with each unique agent discussed in its own chapter. Agents included in this document are those classified by the International Agency for Research on Cancer (IARC) as **carcinogenic** to humans (known as Group 1) or probably carcinogenic to humans (known as Group 2A) (Table 1). Agents not yet classified by IARC as Group 1 or 2A are not included here. Group 2B agents are discussed if they are related to Group 1 or 2A agents. The authors acknowledge that not all possibly carcinogenic agents are discussed in this document, including polyomaviruses such as Simian Virus 40 (also known as Simian vacuolating virus 40), BK virus and JC virus.[1]

In this document, each agent is introduced with early historical information, followed by a discussion of its transmission and **prevalence**. Also discussed are: related epidemiologic information, risk factors, and infection prevention, treatment and control. An adequate characterization of the clinical response to available treatments, while of interest, is beyond the scope of this monograph. A general summary of the major points of this document can be found in Table 2.

Table 1:
Infectious agents included in this monograph

Bacteria

Helicobacter pylori (*H. pylori*)

Parasites

Liver Flukes

Clonorchis sinensis (*C.sinensis*)

Opisthorchis viverrini (*O.viverrini*)

Schistosomes

Schistosoma haematobium (*S. haematobium*)

Schistosoma japonicum (*S. japonicum*) †

Viruses

Epstein-Barr Virus (EBV)

Hepatitis B Virus (HBV)

Hepatitis C Virus (HCV)

Human Herpesvirus 8 (HHV-8)

Human Immunodeficiency Virus (HIV)

Human Papillomavirus (HPV) 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68*, and others (5, 8, 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, 97) †

Human T-Cell Lymphotrophic/Leukemia Virus Type 1 (HTLV-1)

* Group 2A
† Group 2B
All others Group 1

Table 2:[*]
Summary of infectious agents,[†] cancer types and mechanisms of carcinogenesis

Infectious agent	IARC Group	Cancers for which there is sufficient evidence in humans	Other cancers with limited evidence in humans	Established mechanistic events	Prevalence	Prevention & control
Bacteria						
Helicobacter pylori (*H. pylori*)	1	Non-cardia gastric, low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma[‡]		Chronic inflammation, direct mutagenesis	23.1% (Ontario)	• Treatment with antibiotic combinations • Vaccine development
Parasites						
Clonorchis sinensis (*C. sinensis*)	1[§]	Cholangiocarcinoma[‡]		Chronic inflammation, direct mutagenesis	15 million (global)[¶]	• Treatment with chemotherapeutic agents • Reduce source of infection • Vaccine development
Opisthorchis viverrini (*O. viverrini*)	1	Cholangiocarcinoma		Chronic inflammation, direct mutagenesis	9 million (global)[¶]	• Treatment with chemotherapeutic agents • Reduce source of infection • Vaccine development
Schistosoma haematobium (*S. haematobium*)	1	Urinary bladder		Chronic inflammation	200 million (global; all schistosomes)[¶]	• Treatment with chemotherapeutic agents • Environmental control • Vaccine development
Schistosoma japonicum (*S. japonicum*)	2B		Colorectal , liver		200 million (global; all schistosomes)[¶]	• Treatment with chemotherapeutic agents • Environmental control • Vaccine development

* Simplified. For more information, see agent-related chapters
† Agents IARC has included in their carcinogenic substance list (Group 1, 2A or related)
‡ Newly identified link between infectious agent and cancer
§ Recently reclassified by IARC working group
¶ Ontario prevalence unavailable
± Other HPV types are listed in Table 1

Source: Table adapted from Bouvard V, Baan R, Straif K, et al. on behalf of the WHO International Agency for Research on Cancer Monograph Working Group. Special report: Policy A review of human carcinogens--part B: Biological agents. Lancet Oncol 2009;10(4):321-2.

Table 2 continued:[*]
Summary of infectious agents[†] , cancer types and mechanisms of carcinogenesis

Infectious agent	IARC Group	Cancers for which there is sufficient evidence in humans	Other cancers with limited evidence in humans	Established mechanistic events	Prevalence	Prevention & control
Viruses						
Epstein-Barr Virus (EBV)	1	Nasopharyngeal, Burkitt's lymphoma, immune-suppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin lymphoma	Gastric[‡], lympho-epithelioma-like[‡]	Direct mutagenesis	90% (global)[¶]	• No treatment or prevention • Vaccine development
Hepatitis B Virus (HBV)	1	Hepatocellular carcinoma	Cholangiocarcinoma[‡], non-Hodgkin lymphoma[‡]	Chronic inflammation	0.002%-0.9% (Canada)[¶]	• Anti-viral therapy • Screening of pregnant women and children • Global immunization of infants and children
Hepatitis C Virus (HCV)	1	Hepatocellular carcinoma, non-Hodgkin lymphoma[‡]	Cholangiocarcinoma[‡]	Chronic inflammation	<1% (Ontario)	• Screening and treatment of high-risk individuals
Human Herpesvirus 8 (HHV-8)	1[§]	Kaposi's sarcoma[‡], primary effusion lymphoma[‡]	Multicentric Castleman's disease[‡]	Chronic inflammation, direct mutagenesis	<5% (North America)[¶]	• Treatment with anti-HIV drugs • Education of high-risk behaviours
Human Immunodeficiency Virus (HIV)	1	Kaposi's sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma[‡], cervix[‡], anus[‡], conjunctiva[‡]	Vulva[‡], vagina[‡], penis[‡], non-melanoma skin[‡], hepatocellular carcinoma[‡]	Immune suppression	0.2% (Ontario)	• Treatment of infected • Education of high-risk behaviours • Screening of blood donors • Vaccine development
Human Papillomavirus (HPV) type 16[±]	1	Cervix, vulva, vagina, penis, anus, oral cavity, oropharynx and tonsil	Larynx	Direct mutagenesis	11%-25% (Canada; women; all high prevalence types)[¶]	• Treat persistent changes • Screening of women • Vaccination (including types 18, 6, and 11)
Human T-cell Lymphotrophic/ Leukemia Virus 1 (HTLV-1)	1	Adult T-cell leukemia/ lymphoma		Direct mutagenesis	0.0014%-0.0018% (Canada)[¶]	• Education of risk factors • Screening of pregnant women and blood donors • Vaccine development

METHODS

Recent review articles and other literature on infectious agents and cancer were used as the basis of this document. Review articles focusing on infectious agents and cancer were identified using the National Center for Biotechnology Information PubMed search engine, using key terms and synonyms associated with each agent and cancer. Review articles were supplemented with recent original papers, also identified through PubMed. Peer-reviewed literature published from 2002 until 2009 were considered for this review. Older articles were included when relevant, and newer articles were added as recommended by reviewers.

To supplement the peer-reviewed literature, we used summary information from Canadian and international agencies: Health Canada, the Centre for Disease Control, Cancer Care Ontario, the International Agency for Research on Cancer, the Public Health Agency of Canada (including the Centre for Chronic Disease Prevention and Control), and topic-specific bodies such as the Helicobacter Foundation.

References

Referenced materials are numbered consecutively throughout the document. References appear at the end of the document.

Limitations of the evidence reviewed

The literature in this area is changing rapidly. The authors acknowledge the possibility that new information may be available by the time of publication.

Glossary items

The language in this document has been simplified where possible; due to the area of study, however, particularly in reference to the biological mechanisms of disease, many technical terms have been used. These items appear in the glossary at the end of the document. The first time these words appear in a chapter, they appear in **bold text**. Subsequent uses of the term within a chapter appear in normal text.

Italics

Italics are used to refer to specific bacteria, flukes, and schistosomes. *In vitro*/*in vivo* are also in italics.

Acronyms

A list of acronyms appears at the end of the document

HISTORY

Although the Nobel Prize for Medicine was awarded to Human Immunodeficiency Virus (HIV) and Human Papillomavirus (HPV) researchers only two years ago, the idea that infectious agents play a role in cancer development is not new. For example, the transmissible nature of cervical cancer was theorized as early as 1842, and schistosomes and liver flukes were identified as possible cancer-causing agents about 100 years ago.[2,3]

Early research carried out on birds found a relationship between transmissible agents and tumour formation. In 1908, Danish researchers Ellerman and Bang demonstrated that leukemia in chickens was transmitted by an agent small enough to pass through a filter that could remove intact cells. Later, American researcher Rous expanded on this work, showing similar results for chicken sarcoma and other bird species. This work created considerable controversy; at that time the medical community was not receptive to the notion of a transmissible cancer.[4,5]

In the 1930s, experiments performed on mammals implicated viruses as a cause of cancer. During this time, Bittner demonstrated that a predisposition to breast cancer in mice was transmitted to their offspring by an agent in their milk, again, fine enough to pass through a filter. This agent was referred to as a "milk factor" or "extra-chromosomal agent". In another important experiment conducted in the 1930s, Shope isolated virus particles from tumours on wild cottontail rabbits, and used these to inoculate domestic rabbits, which then developed similar tumours.[4,5]

While experiments on laboratory animals demonstrated the role of some viruses in the development of cancer, prior to the 1960s no clear links were established for human cancers. In 1958, Burkitt described a unique lymphoma in African children with high **incidence** in low lying tropical regions of Uganda, absent in nearby areas (with high elevation). This observation, along with a similarity to tropical diseases with known **arthropod** vectors, suggested that an infectious agent might be involved in the etiology of the disease.[6] In 1964, Epstein, Achong and Barr identified virus-like particles in cultured cell lines established from this tumour.[6] The virus was named the Epstein-Barr virus (EBV). Later, a **cohort study** conducted in Uganda reported a 30-fold higher risk of disease in African children with elevated blood levels of antibodies to EBV. The detection of EBV DNA in Burkitt's lymphoma, and lymphoma production in animals inoculated with the virus, together established a role for EBV in the development of a human cancer.[7]

In subsequent years, the results of sustained research efforts that began in the 1950s implicated more viruses and other infectious agents (schistosomes, liver flukes and *Helicobacter pylori*) in human cancer development.[2,8,9]

BIOLOGICAL MECHANISMS

Classifying cancer-causing biological agents

There are bacteria, flukes and viruses that can cause cancer in humans:

1. Bacteria are microscopic organisms that are extremely diverse in size, structure, lifestyle, habitat, and physiology. Typically 0.5 to 5.0 μm in length, bacteria are single-celled organisms found in soil and water.[10]

2. Flukes are parasitic, multi-celled organisms that spend a significant portion of their lifecycle associated with the living tissue of a host, and cause harm without immediately (or necessarily) causing death.

3. Viruses are genetic elements that require a host cell in which to replicate. Viruses are common microorganisms that infect all types of organisms.[10] At the simplest level, a virus is composed of genetic material (DNA or RNA), enclosed by a series of structural proteins. Viruses typically have a diameter between 10 and 300 nm. Although there is still discussion in the scientific community as to whether viruses should be classified as living creatures, the term "microorganism" includes them here, for convenience.

Biology of cancer

Cancer is a disease of uncontrolled cell growth, involving the interplay of many genes with multiple mutations in a stepwise fashion. The disease process begins when alterations occur in one or more of three main gene groups:[11]

1. Tumour suppressor genes or, more precisely, the proteins which they code, assist in the regulation of the cell cycle. Mature cells do not divide extensively, partly due to growth **inhibitors** expressed by these genes. The most well characterized tumour suppressor is the p53 gene,[11] the protein of which inhibits replication when damage to DNA is recognized. A cascade of cellular events either coordinates to fix the damage or commits the cell to apoptosis (programmed cell death). The protein p53 is absent or non-functional in more than half of all human tumours.[11]

2. **Oncogenes** are mutated genes that can contribute to cancer development by disrupting a cell's ability to control its own growth. Many viruses contain elements of precursors to oncogenes that, when inserted into a host **genome**, can induce cell transformation to a malignant phenotype.

3. **Carcinogenesis** also occurs when **DNA repair genes** are damaged. When this happens, mutations begin to accumulate.

Biological mechanisms of carcinogenesis

Advances in molecular biology have provided valuable insight into the role of infectious agents in malignancy. The three mechanisms by which infectious agents promote carcinogenesis are: 1. chronic inflammation due to a persistent infection; 2. mutagenesis, or changes to the genetic constitution of a cell due to alterations to its DNA by

oncogene insertion, or insertion of viral DNA that inhibit tumour suppressors or stimulate cell division; and
3. immunosuppression.

Chronic inflammation

An example of an agent that leads to cancer through chronic inflammation is *Helicobacter pylori (H. pylori)*. More specifically, infection with the bacterium has been established as a risk for the development of gastric cancer, likely through chronic inflammation of the gastric lining, for decades, leading to progressive structural changes.[12] The consistent turnover of cells in the mucous barrier results in circumstances that allow cancer development.[13] In addition to rapid cell turnover, inflammation attracts to the area white blood cells and other compounds that may interfere with normal **antioxidant** functions, and induce DNA damage to cells.

Direct mutagenesis

An example of an agent that leads to cancer through direct mutagenesis is Hepatitis B Virus (HBV). HBV is a DNA virus and an established cause of hepatocellular carcinoma (HCC).[14] In a process called insertional mutagenesis, following infection, the DNA of HBV integrates into the host cell genome, transforming the cell into the malignant type. The DNA may be altered or amplified as a result of HBV integration.[15] Furthermore, one of the four proteins encoded by the HBV genome, X protein, plays an important role in HCC.[16] The X protein enhances cellular gene activity by interacting with the proteins that participate in RNA synthesis, with a DNA template. The X protein may also interrupt the function of p53 and other components of the DNA repair system, resulting in further molecular insults to the cell.[15]

Immune Suppression

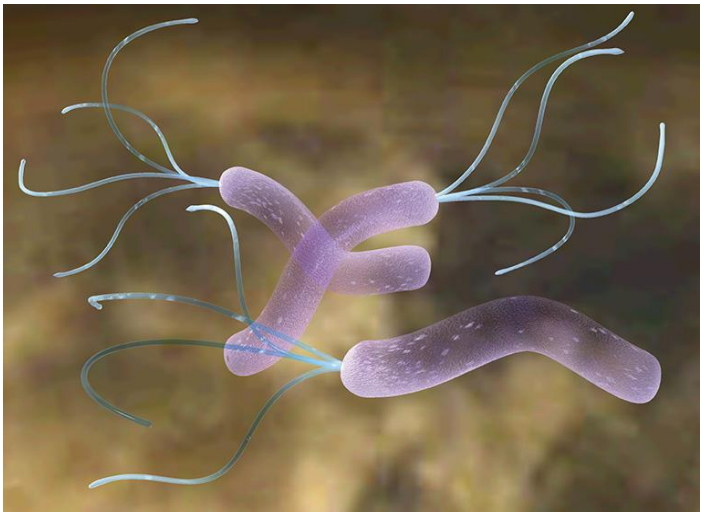
Human Immunodeficiency Virus (HIV) is an agent that can lead to cancer through immune suppression. HIV type 1 (HIV-1) and type 2 (HIV-2) are known to induce the clinical state of Acquired Immunodeficiency Syndrome (AIDS).[10] Infection with HIV is linked with Kaposi Sarcoma and is a known **carcinogen** for non-Hodgkin lymphoma.[17] The dampened ability of the compromised immune system to control cell growth after HIV infection is critical in the process that leads to cancer development. HIV-1 and HIV-2 infect white blood cells (called CD4 **lymphocytes**) that play a critical role in the production of cytokines that are involved in the regulation of cell growth. Depletion of CD4 lymphocytes is the primary marker for HIV infection and predicts an individual's risk of developing cancer. It is also thought that the HIV regulatory protein, **Tat**, has a growth-promoting effect on Kaposi Sarcoma lesions. HIVs are currently the only known microorganisms to induce carcinogenesis through immunosuppression.

H. pylori

What is *Helicobacter pylori*?

Helicobacter pylori (H. pylori) is a small, curved, whip-like, motile (capable of movement) **gram-negative** bacterium that lives in the protective mucus layer overlying the stomach mucosa (Figure 1).[18] Humans and some other primates are susceptible to the bacterium, which can colonize the human stomach and lead to stomach inflammation. There are many diverse strains of *H. pylori*, and it is possible for different varieties to be found in the same stomach.

Figure 1. *Helicobacter pylori*



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Although observed by earlier scientists, over 100 years ago, Polish clinical researcher Jaworski was the first to suggest that the microorganism had a role in gastric pathology. At the time, the bacterium could not be cultured, so these findings were largely ignored.[8] In the 1970s, an Australian pathologist, Warren, re-discovered the bacterium, which he found in the mucus overlying inflamed stomach mucosa. In 1982, Warren and Marshall cultured the organism, and demonstrated an association between its presence and inflammation in gastric biopsies.[8]

In time, the organism was placed in a new **genus** and given the name *H. pylori.* It was also discovered that people who carry the organism were more likely to develop peptic ulcers and stomach cancer. In 1994, *H. pylori* was classified as a Group 1 **carcinogen**, i.e., as causing cancer in humans.[18]

The only significant reservoirs of *H. pylori* are the human stomach, and the stomachs of some other primates and possibly cats. For the most part, infection is thought to occur during childhood, through the following means:

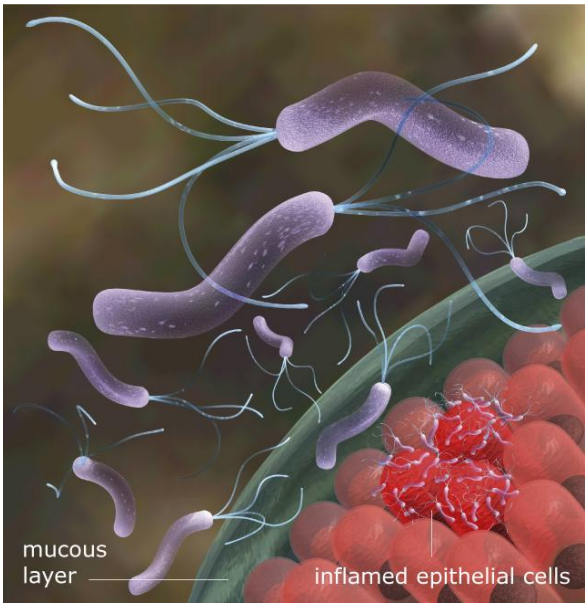
1. **Fecal-oral**: through exposure to feces, and possibly through contaminated water or food. This is the most common route of transmission.
2. **Oral-oral**: this has been observed among African women who pre-chew food given to their infants.
3. **Gastric-oral**: possibly through exposure to infected vomit.
4. **Iatrogenic**: through contaminated instruments (tubes, endoscopes or specimens) or occupational exposure e.g., endoscopists. This is the least common route of transmission.[19,20]

Without treatment, an established infection with *H. pylori* will typically persist for life. *H. pylori* is protected by

the mucus in which it lives, and it is able to counteract stomach acid with an enzyme called urease. Urease converts urea in the stomach into bicarbonate and ammonia, which act as an antacid bath.[8] The immune system responds to the infection with **T-cells** and other infection fighting agents. These potential *H. pylori* eradicators cannot easily get through the stomach lining, yet they remain as the immune response grows. In this process, **superoxide radicals** (which are destructive to the stomach lining) are left behind, and nutrients intended for the white blood cells are consumed by *H. pylori.*[21]

H. pylori infection is most often associated with poor water supply, crowding, and poor sanitation. In developing countries, socioeconomic factors such as low income, use of a stove for heating, and number of children are important risk factors.[22] The risk for infection decreases when a country experiences rapid socioeconomic improvement. Within industrialized nations, the risk varies by geography, ethnicity, age, and socioeconomic status. Higher risk groups include African Americans, Hispanics, and immigrants from areas where **prevalence** is high.[23] Adequate nutrition, particularly frequent consumption of vitamin C, fruits, and vegetables appear to protect against infection.[24]

Figure 2. *H. pylori* invading epithelial cells



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Infection with *H. pylori* often does not have symptoms, but once established, it causes stomach inflammation in virtually all who are infected (Figure 2).[23] *H. pylori* is the main cause of most cases of chronic **gastritis**.[18]

When *H. pylori* infection does produce symptoms, they are non-specific and related to gastritis. *H. pylori* can cause peptic ulcer disease, and eradication results in reduced peptic ulcer recurrence.[23] The body's own inflammatory response is the more likely cause of peptic ulcer, rather than the bacterium itself.[21] *H. pylori* may contribute to abdominal pain, discomfort, bloating, nausea, and early satiety. Some extra-gastric diseases have been associated with *H. pylori* infection, e.g., atherosclerosis (a buildup of plaque in the arteries) and skin disease, although these associations are controversial.[23,25]

Globally, *H. pylori* is the most common bacterial infection. *H. pylori* is present in half the world's population, with prevalence ranging from 20% to 30% in industrialized nations, and up to 70% in developing countries, where infection is usually acquired in childhood.[26,27] In industrialized nations, prevalence of infection: is lower at all ages; gradually increases with age; and varies with ethnicity and immigrant status.[28] The organism is found in a very high

proportion of those with duodenal ulcers, and in those with gastric ulcers.[23]

A recent *H. pylori* prevalence study in Ontario found:

- the overall weighted (reflecting proportional prevalence) **seroprevalence** is 23.1%;
- Ontario men have a significantly higher prevalence of infection than do women (29.4% vs. 14.9%);
- seroprevalence follows the pattern of other developed countries, with low prevalence in childhood, and rates that peak after age 70; and,
- prevalence is higher among immigrants, particularly in those who immigrated at age 20 or older.[29]

The decline in organism prevalence in the industrialized world is thought to be the result of improved hygiene and the widespread use of antibiotics. In Ontario, where prevalence is low in comparison to the developing world, the **incidence** of stomach cancer has also been declining over time in both sexes.[30]

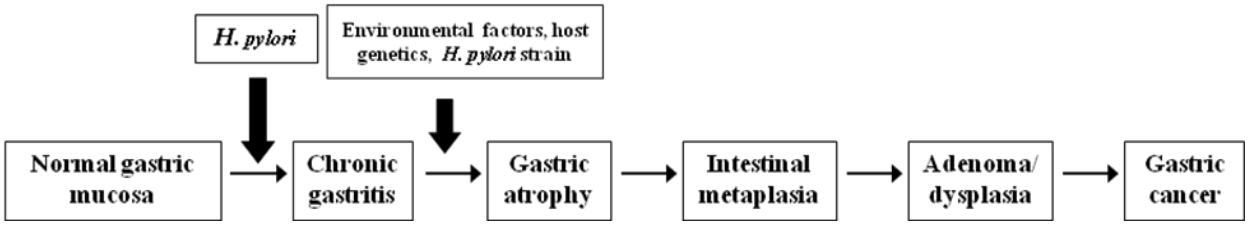
H. pylori infection can be detected by non-invasive or invasive means, the selection of which depends on the clinical setting. Non-invasive tests include blood, breath, and stool testing. The urea breath test is the non-invasive diagnostic test of choice for active infection (with **sensitivity** and **specificity** of about 95%), and can be used to confirm the eradication of infection following treatment.[31] Invasive testing is reserved for those with symptoms that may suggest more severe disease, such as gastrointestinal bleeding or weight loss, and in those over 50 years of age. During endoscopy, the stomach and duodenum are viewed through a lighted tube, and a biopsy of stomach mucosa is taken, which is then assessed for presence of *H. pylori*.[25]

H. pylori and Cancer

In Canada, it was estimated that 1,150 males and 720 females died from stomach cancer in 2009.[30] Stomach inflammation is the greatest known risk factor for peptic ulcer disease and for distal stomach cancer.[32] *H. pylori* is strongly associated with damage to the stomach lining (known as **atrophic gastritis**), which is a precursor to stomach cancer.[19] *H. pylori* infection leads to cancer through a sequence of steps in the stomach mucosa, from chronic inflammation through atrophic gastritis, to abnormal cells, followed by abnormal tissue (Figure 3). Once a susceptible individual has experienced many years of infection and tumour promotion, the elevated risk of stomach cancer remains, even if the infection is eradicated.[23] *H. pylori* is estimated to cause 5.6% of all cancers worldwide.[28] Strains of *H. pylori* more common in the Western world are associated with less gastric atrophy and inflammation than East Asian strains.[33] Although infection appears to be necessary for inflammation and atrophic gastritis, it does not appear to be necessary for the subsequent steps leading to cancer.

Many studies have been published to assess the risk of gastric cancer in the presence of *H. pylori* infection. The strongest evidence of association is found in **case-control studies** nested in **cohorts**, which use serological evidence of infection in samples taken many years before disease onset. **Meta-analyses** of these studies have also been published. The overall conclusion of six meta-analyses is that

Figure 3. Gastric carcinogenesis with *H. pylori*



Source: Image adapted[42-44]

H. pylori infection presents a two-fold increased risk for gastric cancer (range of pooled 95% **Odds Ratios**: 1.92-2.56).[34] About 2% of those infected with *H. pylori* develop gastric cancer, which represents approximately 593,000 cases (63.4% of all stomach cancers) globally. It has been suggested that this may be an underestimate, as the infection tends to disappear with increasing damage in the stomach.[28,35] Serological studies testing participants 10 or more years before diagnosis reported a summary **relative risk** of 5.9 (95% **Confidence Interval**: 3.4 to 10.3).[35]

The harmfulness (virulence) of the **pathogen**, environmental factors, and individual genetic susceptibility all play a role in determining the severity of inflammation, and the likelihood that infection will lead to cancer.[33] Different strains of *H. pylori* show different levels of cancer risk, and different host responses and exposure to environmental factors affect that risk. How gastric mucosa are colonized and what problems develop depend on factors related to the bacterium, such as its motility, type of *H. pylori* enzyme activity, and its ability to 'stick' to the stomach mucosa.[18] Numerous dietary factors play a role in gastric cancer. Enhancers of the precancerous process are stomach irritants, while **inhibitors** are mainly **antioxidants**. It is thought that a high-salt diet may work with *H. pylori* to promote gastric cancer and that fruits and vegetables inhibit the process.[33] It is also thought that that the effect of *H. pylori* is enhanced by the presence of *N*-nitroso compounds.[36]

Less well known are the relationships between *H. pylori* infection and other cancers, including Mucosa-Associated Lymphoid Tissue (MALT) lymphoma, an uncommon form of non-Hodgkin lymphoma found most often in the stomach. *H. pylori* infection is present in up to 90% of those with low-grade MALT lymphoma. Regarding non-Hodgkin lymphoma of the stomach, it is estimated that 74% of cases in industrialized countries (5,600 people) and 79% of cases in developing countries (5,900 people) can be attributed to *H. pylori*.[28] For MALT lymphoma, clearing the infection does lower the cancer risk; three quarters of those with the cancer experience a complete or partial remission following eradication of the infection,[23] as do 60% of those with early stage high-grade stomach lymphomas.[35]

A group of recent meta-analyses suggest a relationship between *H. pylori* and other cancers, including laryngeal,[37] colorectal,[38,39] and lung,[40] but further research is needed before conclusions can be drawn. Interestingly, an inverse association has been observed between the presence of *H. pylori* and the

frequency of asthma and allergies,[41] and esophageal diseases (discussed below).

Prevention, Treatment, and Control

Screening low-risk populations for *H. pylori* infection is not generally seen as useful. Only a small proportion of those infected will develop gastric cancer, therefore there are valid reasons not to screen and treat healthy people. These reasons include expense, undue concern, and the potential for antibiotic resistance.[45-47] While eradication of *H. pylori* is the first-line treatment for peptic ulcer disease and MALT lymphoma, the effect of primary prevention in those with premalignant gastric lesions is uncertain. Targeted intervention in those susceptible to *H. pylori*-related diseases (e.g., those with a family history of gastric cancer, those from a region of the world with high gastric cancer rates) is, however, supported by the evidence.[48]

A variety of treatment regimens are used for *H. pylori* infection. Treatments combine various antibiotics with proton-pump inhibitors (agents that block hydrogen ion transport into the stomach), or other anti-acid drugs, such as ranitidine bismuth citrate. These treatments fail in 5% to 20% of patients, due to non-compliance (treatment can cause nausea, abdominal pain and diarrhea), antibiotic-resistance,[26,49,50] or re-infection. More recent publications suggest that the effectiveness of standard therapy is as low as 60% to 70%,[51] possibly due to emerging antibiotic resistance. It has been reported that a proportion of those with duodenal ulcer, when treated for *H. pylori* infection, may develop reflux esophagitis.[52] The potential development of antibiotic resistance or reflux disease, and the possibility of esophageal cancer, render widespread testing and treatment of the infection unrealistic.[46] With respect to early gastric lesions, eradicating *H. pylori* may decrease their progression, while vitamin supplementation (thought to lower the risk of gastric cancer) does not seem to have a major impact.[53] It is unclear if antibiotic treatment can eradicate advanced precancerous lesions. At this time, it appears that early intervention at an asymptomatic stage is required to prevent cancer development.[35] A **randomized controlled trial** comparing *H. pylori* treatment to placebo found that for carriers without precancerous lesions, the risk of gastric cancer development was significantly decreased with *H. pylori* eradication.[54]

It would be useful to develop a vaccine against the organism. Worldwide, *H. pylori* is an important causal factor for a deadly cancer, with substantial attributable risk.[26] A good vaccine would eliminate the drawbacks of antibiotic treatment. A number of vaccine candidates have been tested in humans, with limited success.[26,55] In 2009, significant progress was made in the development of a vaccine for *H. pylori*; the first vaccine may be launched in the near future.[41]

Future Directions

Reduced *H. pylori* prevalence has coincided with a dramatic rise in diseases of the esophagus, such as acid reflux disease and esophageal cancer, however, the evidence is not conclusive, and this association may be coincidental. It has been theorized that the bacteria may protect against diseases of the esophagus, including esophageal adenocarcinoma.[25,56,57]

It is believed that those uninfected with *H. pylori* have lower risk of stomach cancer because they do not have the

inflammation it causes. These individuals may, however, lack important microbial controls over stomach acidity, leaving them vulnerable to problems when the lower esophagus is exposed to acidity. It is thought that the host and microbe exchange signals which allow the bacteria to remain, despite the immune system response.[58] Most people chronically infected with *H. pylori* do not develop cancer. It is important to examine the precancerous process, and determine what factors lead to cancer in some *H. pylori* infected people and not others.

Future investigations should address the complex relationship between bacteria, host, and environment,[58] and identify factors or combinations of factors that trigger the events leading to gastric cancer. Studies using sensitive molecular techniques might provide a better estimate of the risk of cancer in *H. pylori* infected individuals.[35] Further exploration into vaccine development would be valuable.

O. viverrini and *C. sinensis*

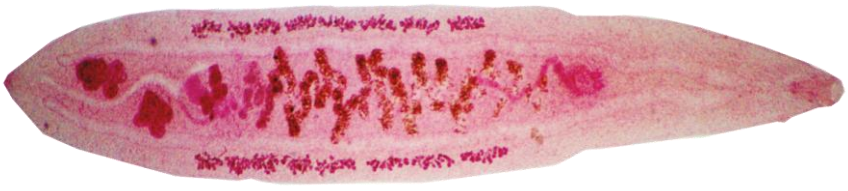
What are Liver Flukes?

Liver flukes are hermaphroditic (possessing both male and female organs), flat, leaf-shaped, transparent, parasitic worms also known as trematodes.[59] They are located in East and Southeast Asia.[60] Two liver flukes that infect humans, *Opisthorchis viverrini* (*O. viverrini*) (Figure 4) and *Clonorchis sinensis* (*C. sinensis*) (Figure 5), have been classified as Group 1 **carcinogens** by the International Agency for Research on Cancer (IARC).[12]

O. viverrini was first discovered in Thailand in 1911.[59] Although subsequent archaeological studies have found evidence of *C. sinensis* presence in China two thousand years ago, *C. sinensis* was first discovered in India in 1875.[61]

The liver fluke lifespan is 10 to 45 years, during which it continuously produces viable eggs.[12,62,63] This long lifespan is a substantial contributor to the stability of **endemic** areas and the sustainability of infection. Individuals who have emigrated to infection-free zones may develop symptoms years after leaving an endemic region.[64]

Figure 4. *Opisthorchis viverrini*



Source: Paiboon Sithathaworn

Upon human infection, liver flukes migrate to and mature in the human biliary tract, normally living within the smaller **intrahepatic bile ducts**.[12,62] Mature flukes can produce thousands of eggs per day, which are subsequently excreted in feces.[61] Excreted eggs infect snail hosts, mature, and hatch to produce free-swimming larvae which penetrate freshwater fish and develop into encysted metacercariae (cysts containing larvae in the infectious stage) (Figure 6).[12] Development from egg to mature liver fluke involves snail, fish, and human hosts.[60] This process requires roughly four months but is highly variable and dependent on several ecological conditions and the availability of hosts.[59,60]

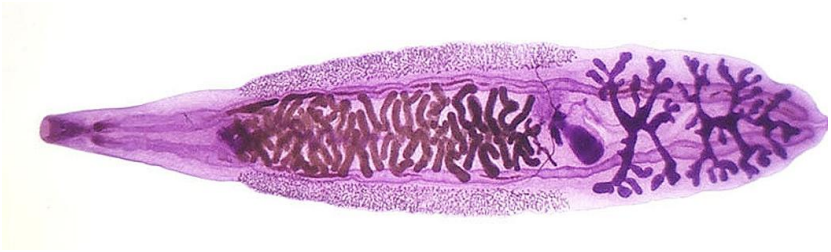
Although there is some evidence of accidental ingestion during the catching and handling of infected fish via unwashed hands, ingestion of raw or inadequately cooked (smoked, dried, salted, or pickled) fish containing the infectious stage of liver flukes is the cause of most human infection.[61,65-67] Infection intensity depends largely on cultural eating habits.[67]

Liver fluke infection is associated with poverty, lack of access to clean water and sewage treatment, widespread environmental pollution, and increasing population density.[67] Inhabitants of rural areas face a greater risk of infection.[12] Although similar rates of infected individuals are observed in both sexes, in endemic areas males may be more frequently and heavily infected than females, possibly a result of the custom of eating raw fish at drinking parties.[60,67]

Liver fluke infection is often present in the absence of clinical signs or symptoms. The majority of individuals who experience noticeable symptoms are heavily infected; symptoms depend on infection duration and number of worms.[62,65,68] Most symptoms result from adult worms directly or indirectly blocking the bile ducts.[65] *O. viverrini* infection leads to symptoms in 5% to 10% of infected people.[59] Marked gastrointestinal disturbances, in addition to weakness or general malaise, are significantly associated with *O. viverrini* infection.[59]

Symptoms of *C. sinensis* infection may include general malaise, fatigue, abdominal discomfort or distension, diarrhea, abnormally high production of white blood cells (eosinophilia), or fluctuating jaundice. Severe infection may lead to right upper quadrant pain, jaundice, liver and spleen enlargement, and edema (swelling caused by excess fluid in body tissues).[64,67] Infection with *C. sinensis* has a greater likelihood of leading to biliary and gallbladder stones than infection with other liver flukes.[12]

Figure 5. *Clonorchis sinensis*



Source: Bob Kistler

Due to the scarcity of specific symptoms, the most widely used and accurate method of infection diagnosis is the identification of fluke eggs in feces; however, eggs may not be present in individuals who are lightly infected or in those who have obstructions of the biliary tract caused by severe infection. In addition, the eggs of minute intestinal flukes can be confused with liver fluke eggs.[12,69] Recently, the number of residents of endemic areas willing to provide stool samples has been decreasing, leading to the need for and introduction of alternative diagnostic techniques including skin tests, blood serum tests, and radiologic examinations.[69] In some endemic areas, ultrasound, computer tomography, magnetic resonance imaging, and tissue harmonic imaging have been used to varying degrees of success.[61] **Immunodiagnostic** techniques have developed rapidly with improved **sensitivity** and **specificity**, although they are still used primarily as supplementary techniques.[64,67] A promising new **polymerase chain reaction** diagnostic method is displaying high sensitivity and specificity and may be a suitable tool for detection of *O. viverrini* in a large number of samples at a time.[70,71] In practice, incidental diagnosis of infection during sonographic examinations of the abdomen performed for separate concerns has become increasingly common.[69] To ensure maximal detection of infection, diagnosis should not be limited to one technique.[69]

Human liver fluke infection is endemic in China, Japan, South Korea, Laos, Thailand, Viet Nam, Cambodia, and Taiwan.[60] There is evidence that the geographic distribution of infection is broadening due to immigration and increased travel to endemic areas, accounting for cases reported in non-endemic areas, including North

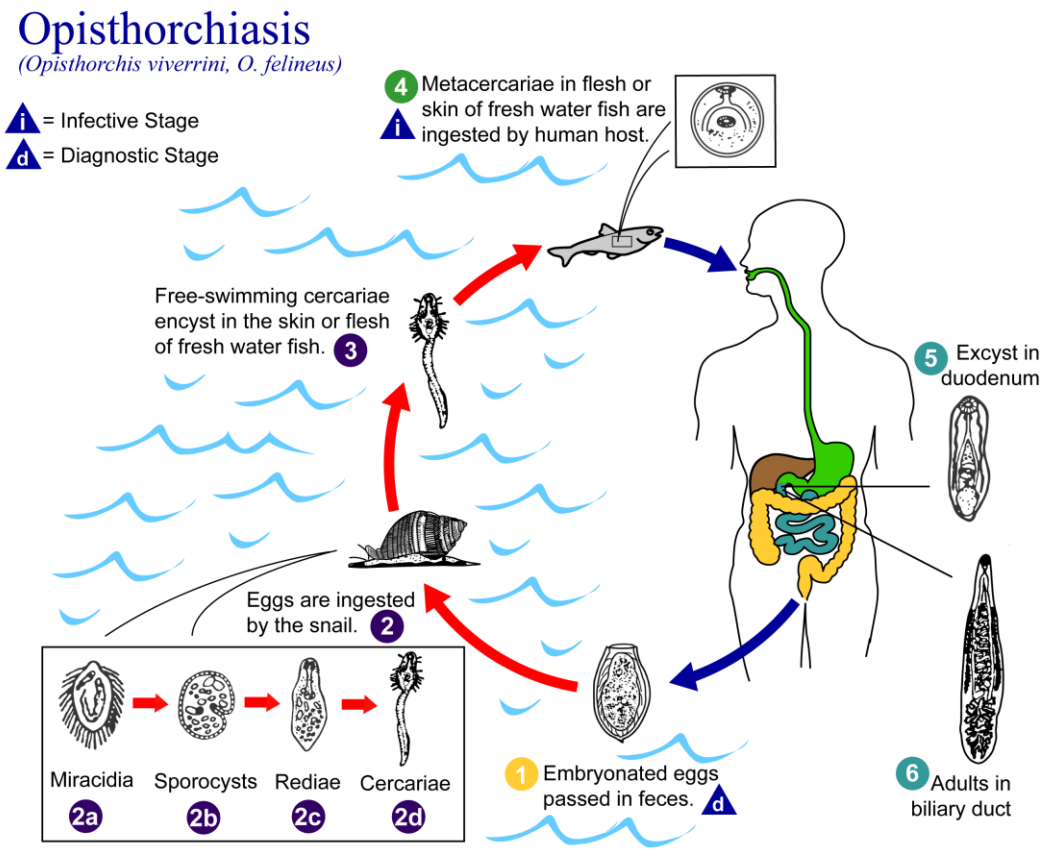
America.[63,68] Children have the lowest **incidence** of infection, with rates rising through the lifespan to peak around 40 to 50 years of age.[67]

O. viverrini has been estimated to infect nine million individuals worldwide. The highest **prevalence** is in Thailand, where an estimated six million inhabitants are infected.[12,60] Prevalence as high as 70% has been reported in some endemic areas of Thailand.[72] Globally, an estimated 67.3 million individuals are at risk of contracting an *O. viverrini* infection.[73]

Fifteen million individuals are estimated to be infected with *C. sinensis* within endemic areas, with infection occurring in all parts of the world where Asian immigrants are present.[12,65,67] According to recent estimates, more than 600 million people are currently at risk of *C. sinensis* infection, 95% of whom are residents of China or Thailand.[73]

Among immigrants to North America from countries with areas of endemic infection, liver fluke prevalence ranges from 11% to 26%.[63,64] Physicians in North America have diagnosed both chronic and acute infections in immigrant

Figure 6. Life cycle of *Opisthorchis viverrini*



Source: Alexander J. da Silva and Melanie Moser

populations. Food imported illegally from endemic areas or short and long-term visits to endemic countries by North Americans are known sources of acute infection within North American residents.[63]

Liver Flukes and Cancer

Cholangiocarcinoma (CCA) is a cancer arising from any portion of the bile duct **epithelium**.[64] CCA accounts for 15% of liver cancers worldwide. In the absence of flukes or endemic infections, development of CCA is quite rare although incidence is increasing in many high-income countries for unknown reasons.[12,74] In endemic areas, CCA occurs more frequently than Hepatocellular Carcinoma (HCC), the most common type of liver cancer in areas where liver fluke infections are uncommon or non-existent.[12] Khon Kaen, Thailand has the highest CCA incidence in the world. Infection is endemic to this area and 71% of liver cancers are classified as CCA.[75,76] Conservatively, liver flukes were responsible for 0.02% of all cancers worldwide in 2002.[28]

Given the evidence, *O. viverrini* has been classified as a known carcinogen.[12] A recent review found **odds ratios** of 1.3 to 27.1 of developing CCA in the presence of *O. viverrini*.[65] The vast majority of *O. viverrini* studies come from Thailand where liver cancer is the most prevalent of fatal cancers and CCA incidence is high.[75] A **case-control study** of CCA and HCC development in northeast Thailand found an odds ratio of 5.0 (95% **Confidence Interval**: 2.3-11.0) for development of CCA in the presence of *O. viverrini* infection. Infection with *O. viverrini* was not significantly associated with risk of developing HCC.[77,78] An additional study found an odds ratio of approximately four for early cancer development in the presence of *O. viverrini* infection.[76] With improved diagnostic and treatment methods lowering the risk of infection proceeding to CCA, a recent study suggested that host genetic background may play a role in the development of CCA and may help explain the high incidence of CCA in northeast Thailand.[79] In addition, this study identified past exposure to the infection in terms of elevated *O. viverrini* antibody levels as a risk factor for CCA development.[79]

Several studies support the notion of a causative role of *C. sinensis* in CCA tumour development.[67] Evidence of an association includes the greater prevalence of CCA in areas of endemic infection and the two- to five-fold greater development of CCA than hepatocelluar carcinoma in Korea, a country known to have endemic infection. Additional indications of an association include the estimated odds ratios of 2.7 to 13.6 of developing CCA following infection and the association of heavy intensity infections with cancer development.[12,65,67,69] In the past, the causal link between *C. sinensis* infection and CCA had been heavily disputed. As infection is extremely common, it was thought that the connection may be coincidental. Infection is not a requirement for development of CCA and development of this cancer is rare, even in those infected and at the greatest risk.[64] Given the emerging evidence, however, IARC has recently reclassified *C. sinensis* infection as carcinogenic to humans.[35,80]

CCA normally occurs in the sixth or seventh decade of life and is uncommon in those less than 40 years of age.[64] Possibly due to the likelihood that males in endemic areas are more frequently and heavily infected than females, males are at greater risk of developing CCA.

The male to female ratio for CCA ranges from 1.1:1 to 2.2:1.[76] Individuals with chronic inflammation as a result of liver fluke infection are also at greater risk. Chronic infection results in the production of several different oxygen and nitrogen species that work to combat the infection, but can also result in DNA damage. Prolonged liver fluke infection and the resulting harmful mutagens contribute greatly to development of CCA.[76] **Liver cirrhosis**, chronic infection with the Hepatitis C virus, heavy alcohol consumption, high fluke egg density in stool, obesity, consumption of nitrate-containing foods, history of familial cancer, and gallstones are also reported to be associated with CCA.[74,81] Fruit and vegetable consumption greater than 1.0 times per day may be a protective factor.[81]

Prevention, Treatment, and Control

Reducing the sources of infection is effective in theory but difficult to implement in practice.[61] The difficulty of detecting infected cases and the problem of re-infection are just two of the many obstacles facing health workers. However, the mounting number of infections and individuals at risk, in addition to the direct and indirect economic losses resulting from liver fluke infection, require the devotion of time and resources to prevention and control.[67] Ideally, improvements in hygiene and sanitation practices prevent transmission of eggs from feces, which disrupts the cycle of fluke maturation and transmission.[60,62] To be successful and long-lasting, prevention programs require broad community acceptance and participation.[60,82] Control efforts are primarily focused on the reduction and elimination of parasite transmission by ensuring proper food preparation, promoting the development of improved diagnostic techniques, providing chemotherapy, and improving sanitation.[61,73,82] A combination of health education, mass treatment, and governmental aid could significantly reduce liver fluke infection.[67]

In order to aid control measures, researchers have been pursuing a viable vaccine.[12] While none has been generated thus far, the recent development of gene catalogues for both *O. viverrini* and *C. sinensis* should accelerate vaccine development for liver fluke control.[67,72]

Liver fluke infections can be treated effectively with praziquantel, a chemotherapeutic agent shown to be very safe, with **efficacy** of over 90%.[61] Treatment often leads to the resolution of infection and reversal of disease-related abnormalities.[60] In some areas, where prevalence exceeds 20%, mass treatment of the entire population occurs on a yearly basis.[83] In other areas, where prevalence is between 5% and 20%, mass treatment occurs on a bi-annual basis.[83] Patients need to be followed up to evaluate the possibility of re-infection, which may be as high as 90% within one year of initial treatment.[59,60] In the most extreme cases, surgical removal of the flukes and infected tissues may be attempted, but this is both costly and dangerous.[61]

Future Directions

There is still much about liver flukes that is not understood. Efforts should be made to determine if reservoir hosts are contributing significantly to infection transmission.[61] In addition, there is a need to establish accurate estimates of the prevalence of CCA in infected individuals, as well as to determine the events that lead to **carcinogenesis**.[61,75] Specific *C. sinensis* antigenic bands have

improved the sensitivity and specificity of serodiagnosis; however, *C. sinensis* and *O. viverrini* share common **antigens** which cross-react with several other fluke infections.[84] Researchers should look to developing specific, non-invasive cancer screening techniques in at-risk populations.[75] In light of the recent voluntary screening difficulties and hesitancy of residents to comply with stool collection, there is a need for suitable mass screening techniques with adequate sensitivity and specificity that are acceptable among the general public.[64] Finally, the search for a viable vaccine should not be abandoned.

S. haematobium and *S. japonicum*

What are Schistosomes?

Schistosomes are flat, parasitic worms (flukes or trematodes) that live in the blood streams of mammals.[12] From a global health perspective, schistosomiasis (an infection caused by schistosomes) is the most significant water-borne disease.[85] Of all the parasitic diseases, schistosomiasis ranks second only to malaria in terms of public health and socioeconomic impact.[85,86] Two schistosomes that infect humans have been implicated in the development of cancer: *Schistosoma haematobium* (*S. haematobium*) (Figure 7) and *Schistosoma japonicum* (*S. japonicum*).[12] A third species, *Schistosoma mansoni* (*S. mansoni*), is also highly prevalent in **endemic** areas and causes severe morbidity, but to date has not been associated with an increased risk of cancer.[12]

Figure 7. *Schistosoma haematobium*

Source: WHO/TDR/Sinclair Stammers

Schistosomiasis is an ancient disease.[85] There is evidence of infection in Egyptian mummies from the time of the Pharaohs and in two thousand year old Chinese corpses.[87,88] A 'new form of **liver cirrhosis**' initially attributed to *S. haematobium* infection was described in 1904 and later credited to *S. mansoni*.[89] Shortly thereafter, *S. japonicum* was also collected and shown to be a distinctly different species.[90]

The primary mode of human schistosome infection is exposure to water containing cercariae, the infective stage of schistosomes.[12] Cercariae swim near the surface of water and penetrate human skin by release of lytic enzymes stored in anterior penetration glands.[12] During penetration of the skin, a process which takes a few hours, the cercariae lose their tails and transform into immature larvae (schistosomula) which enter the blood stream.[12] These schistosomula migrate to veins that drain either the bladder (*S. haematobium*) or the intestine (*S. japonicum*) where they finish their maturation and mate.[12] While adult worms cannot multiply in humans, they do continue to reside in the human body, where as mated pairs, they can produce eggs for up to 30 years.[66] Each day, *S. haematobium* worms produce an estimated 300 eggs and *S. japonicum* worms produce up to 3,000 eggs.[12,66] Approximately 50% of these eggs will leave the body, excreted in feces or urine, and subsequently hatch, releasing miracidia that infect snail hosts. While inhabiting a snail, miracidia mature into cercariae and are released into fresh water, regenerating the cycle of infection (Figure 8).[12]

In endemic areas such as Africa and southeast Asia, characteristics of the place of residence are the most important determinants of infection status and intensity. These characteristics include land use, snail population, and water resources.[91] Individuals residing in rural and agricultural areas, especially those communities that are irrigation-dependent, are at increased risk.[87] The construction of dams and other water resource development projects have been shown to lead to an increase in the **prevalence** of schistosomiasis in local inhabitants.[85,92]

Although schistosomiasis is often asymptomatic in its early stages, its long-term impact can be considerable.[93] Recent estimates have attributed 150,000 deaths per year to *S. haematobium* infection in sub-Saharan Africa alone.[92] In addition, schistosomiasis is responsible for an estimated annual loss of 1.7 to 4.5 million **disability-adjusted life years**, although a recent **meta-analysis** suggests the estimate could be several-fold higher.[85]

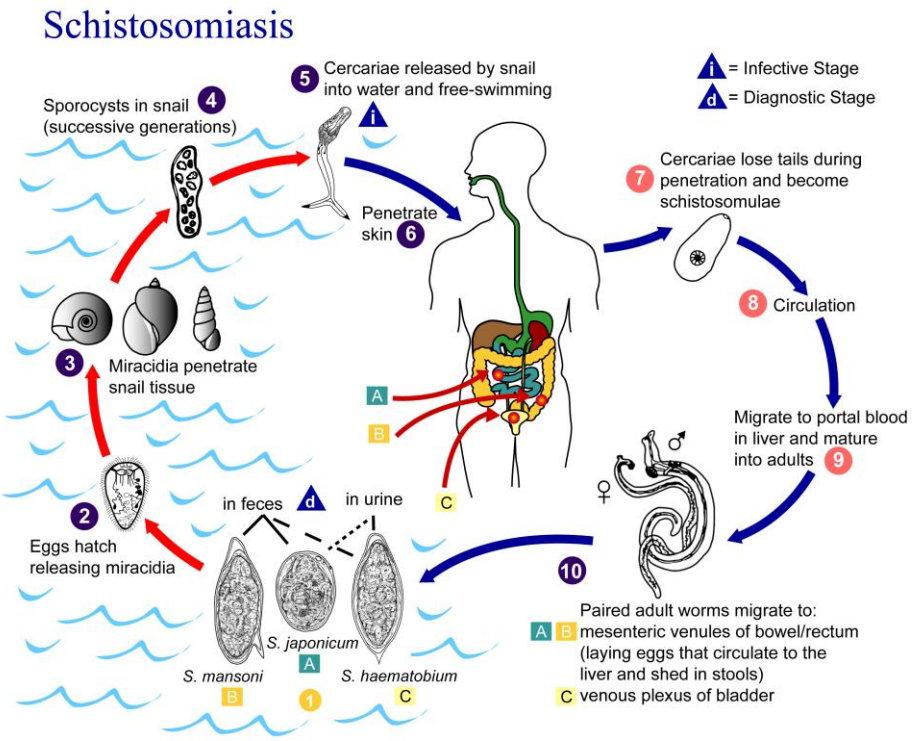
Chronic tissue inflammation is a signature characteristic of a schistosome infection.[93] Eggs that are not excreted become trapped in tissues, eliciting an immunologically-driven inflammatory response.[12] Although the urogenital system (*S. haematobium*) or liver and intestines (*S. japonicum*) are primarily affected, there are reports of pathological changes in many other organs.[12,89] Diarrhea, chronic pain, fatigue, anemia, malnutrition, and reduced exercise tolerance have been significantly associated with schistosomiasis.[93] Schistosomes have also been associated with bladder, liver, and colorectal cancers. Stomach and uterine cancers have also been linked with schistosomiasis, but evidence is inconclusive.[12,87]

The primary indicator of schistosomiasis is the detection of schistosome eggs in feces (*S. japonicum*) or in urine (*S. haematobium*).[12] In *S. haematobium* infections, eggs can also occasionally be detected in seminal fluid samples; cervical, bladder, or rectal tissue can also be biopsied.[94] The **sensitivity** of these methods is lessened when intensity of infection is low.[88] In addition, a single examination can lead to underestimation of egg output and egg excretion may be reduced in chronic infections.[89] Indirect screening techniques for *S. haematobium* infections include questionnaires regarding past occurrence of hematuria (the presence of blood in urine), visual inspection of urine for blood, and use of reagent strips to detect haematuria and proteinuria (the presence of an excess of proteins in urine).[95]

Schistosomiasis is endemic in 76 countries and territories.[85] *S. haematobium* is primarily found in Africa and the Middle East, while *S. japonicum* is found in southeast Asia and the Philippines.[12]

More than 200 million people are estimated to be infected with schistosomes. Eighty-five percent of infected individuals inhabit the African continent, although this may be an underestimation.[85,92] A further 779 million individuals are estimated to be at risk of contracting schistosomiasis.[85] The highest prevalence and intensity of infection are often found in school-age children, adolescents, and young adults.[85] In addition, *S. japonicum* infects animals and can be transmitted via zoonosis.[96] The number of domestic livestock that pose a risk to both humans

Figure 8. Life cycle of *S. haematobium* and *S. japonicum*



Source: Alexander J. da Silva and Melanie Moser

and water resources is estimated to be in the hundred thousands.[96]

Neither *S. haematobium* nor *S. japonicum* is endemic to Canada and there are no reported Canadian prevalence estimates. The only Canadian statistics available come from a study of Canadian travelers and new immigrants visiting the Tropical Disease Unit of the Toronto General Hospital. Of the 3,528 individuals who visited the hospital during the study period, 48 individuals had contracted a schistosome infection while overseas.[97] These individuals were younger and had a longer duration of travel or residence abroad than the study population as a whole. Immigrants or Canadians who visited overseas friends or relatives had an increased risk of arriving in Canada with acute schistosomiasis.[97,98] As Canada is a global hub for migration and travel, physicians should be aware of the possibility of infection, particularly in immigrants or travelers with a longer duration of stay abroad. Post-infection schistosomiasis complications are prevalent in immigrants from schistosoma-endemic areas long after disease interruption.[98]

Schistosomes and Cancer

S. haematobium is identified as a known cause of urinary bladder cancer and has been classified as a Group 1 **carcinogen** by the International Agency for Research on Cancer (IARC).[12] Bladder cancer **incidence** is amplified in *S. haematobium* endemic areas and is histologically and pathologically distinct

from the non-*S. haematobium*-associated bladder cancer of North America and Europe.[12,87] In countries free of schistosoma infection, the majority of bladder cancers develop in individuals between 65 to 75 years of age, compared to 40 to 49 years in countries where *S. haematobium* infection is endemic.[87] Studies have found **odds ratios** of developing bladder cancer in the presence of *S. haematobium* infection ranging from 1.8 to 23.5.[9,65,99-102] The range is vast due to the methods used.[77] Nevertheless, each study found a significant association between bladder cancer and schistosomiasis.[77] Based on studies with markers of current infection, an estimated three percent of global bladder cancer cases are attributable to infection with *S. haematobium*.[28]

The incidence of schistosomal-associated bladder cancer is much greater in males than females, with a ratio of 5:1 in endemic countries. Comparatively, in non-endemic countries, the male to female bladder cancer incidence ratio is 3:1.[87] This disparity in rates may be a result of the higher frequency of water contact associated with agricultural duties, which are performed primarily by males in endemic countries.[87] The elevated incidence rates in males may also be related to the higher prevalence of smoking, a co-factor in the development of bladder cancer, among males in non-endemic countries.[87] One study found that smoking and occupational exposure to chemicals and solvents (e.g., automotive trades, painters) were co-factors that increased the risk of bladder cancers associated with urinary schistosomiasis.[100]

S. japonicum has been implicated as a causative agent in the development of liver cancer in Japan and colorectal cancer in China.[12,87] In experimental animals that have been deliberately exposed to a known carcinogen, the development of liver cancer appears earlier and occurs in greater numbers in those infected with *S. japonicum,* compared to those not infected.[12,86] From **case-control studies**, the **relative risk** of developing cancer associated with *S. japonicum* ranges from 2 to 10 for liver cancer and 1.2 to 2.5 for colon cancer.[12] A single case-control study found a relative risk of 8.3 for developing rectal cancer in the presence of *S. japonicum*.[12] Other studies have not established a positive association for the role of *S. japonicum* in the development of cancer.[86] Given the evidence, IARC has classified *S. japonicum* as a possible carcinogen (Group 2B).[12]

Prevention, Treatment, and Control

Endemic schistosome infection generally occurs in the least developed countries where infrastructure is poor and resources are strained.[87,92,103] Large-scale preventive chemotherapy interventions are required to achieve short-term control of schistosomiasis morbidity and are the mainstay of the current public health strategy recommended by the World Health Organization.[91,104] Instead of reducing the number of infected individuals, many control programs focus on reducing the number of worms per person, thereby improving current health and preventing possible future development of complications.[92,104] Improvement of education, hygiene, diet, employment, and living conditions together with environmental management, are crucial elements to achieve reduction of transmission.[87] Large-scale control programs, socioeconomic development, and environmental changes have resulted in transmission interruption or disease elimination in nine countries, and

considerable reductions of infection prevalence and morbidity in many more.[85] The governments of countries with endemic schistosomiasis, however, frequently lack the funds required to support continued initiatives without the support of outside sources. Although these programs are successful over short periods, they often fail to continue when external funding is terminated.[103] Furthermore, large-scale efforts may have unintended consequences that spread other carcinogenic microbes; the high prevalence of Hepatitis C virus infection in Egypt, for example, is suspected to have resulted from a mass treatment program that lacked appropriate infection control safeguards.[85] Recently, there has been support for integrating schistosome control with existing control programs, thereby dramatically reducing costs and increasing program sustainability and longevity.[104]

Progress is being made on generating a preventive vaccine for humans, which will aid control and prevention measures. A reduction in the number of worms is the vaccine gold standard.[96] Research has also focused on the exploration of a vaccine targeted at parasite fertility and egg viability as a means to reduce morbidity, as schistosome eggs are not just responsible for transmission of infection but also for the pathology.[96] In addition, some researchers are developing a veterinary vaccine that would block parasite transmission.[96]

Treatment of existing infection with chemotherapy is highly successful in terminating infection, halting progression to serious disease, reducing the infection cycle, and reversing some disease symptoms, particularly in children.[12,87,92] None of the drugs currently in use are significantly effective in eliminating immature worms.[12,92,96] Re-treatment at regular intervals is essential to maintaining low morbidity levels.[92] Recent price decreases have caused the cost of treatment to be drastically lower than the cost of screening.[104] As uninfected individuals can be safely treated, it is possible to treat all members of high-risk endemic groups at minimal cost and effort, regardless of infection status, a much more efficient approach than screening all individuals and treating only those who are infected.[104]

Future Directions

Monitoring systems and diagnostic techniques that are precise, inexpensive, and able to accurately gauge infection patterns are crucial to understanding global schistosome patterns.[87, 88] There is a need for health impact assessments, including schistosomiasis risk, in the planning, implementation, and follow-up phases of future water resource development projects.[85]

Effective treatment requires the provision of affordable, orally active, anti-schistosomal drugs able to treat both adult and immature worms.[88] To ensure sustainability, drugs must be provided free of charge to the poorest people who need them.[92] Developing the capacity of individual countries to plan, monitor, and evaluate sustainable control programs should be the long-term goal of development partners and of countries themselves.[87,92,103]

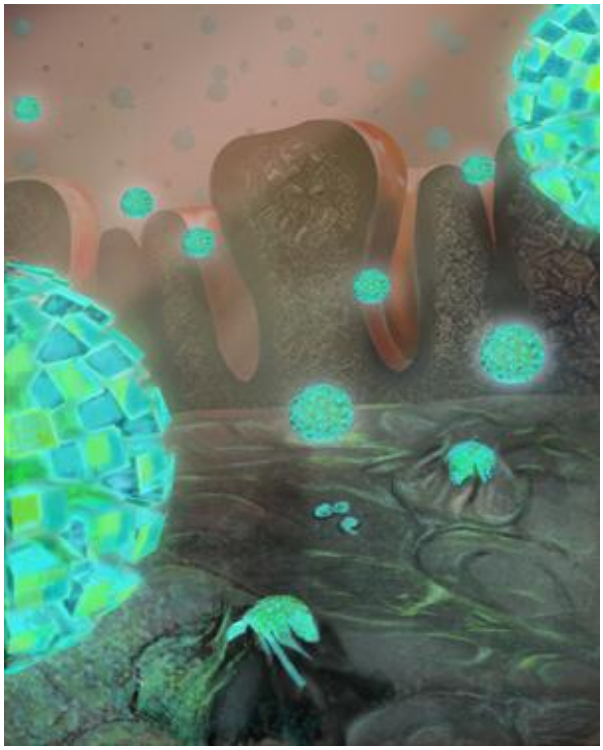
EBV

What is Epstein-Barr Virus?

Epstein-Barr Virus (EBV) is a member of the **herpesvirus** family (Figure 9).[7] In 1958, Burkitt described a unique lymphoma in African children and in 1964, Epstein, Achong, and Barr identified virus-like particles in Burkitt's lymphoma tumour cells. Further research helped establish a role for this virus in the development of Burkitt's lymphoma, and EBV became the first virus clearly implicated in the development of a human cancer. There are two subtypes of EBV: EBV-1 and EBV-2. EBV-1 is more common in developed nations.[6]

Initial EBV infection is followed by life-long **latent** infection, with the affected cells occasionally triggered into replication.[6] EBV is transmitted primarily through salivary contact, although there is some evidence suggesting that it is also sexually transmitted.[105] Transmission of the virus through the air or blood does not normally occur.[106,107] Since many healthy people carry and spread the virus intermittently for life, transmission is almost impossible to prevent.[107]

Figure 9. Epstein-Barr Virus



Source: Original artwork by Lindsey Brake

Most people with EBV infection do not experience serious consequences.[7] Infection generally occurs early in life. Many children infected with EBV experience either no symptoms, or symptoms similar to mild and brief childhood illnesses. In industrialized nations, infection often occurs after childhood. When infection occurs in adolescents and young adults, EBV causes **mononucleosis** 35% to 50% of the time, often with fever, sore throat, and swollen lymph glands.[107]

Generally, a clinical diagnosis of infectious mononucleosis can be made from the combination of fever, sore throat, and enlarged lymph glands lasting one to four weeks. A normal to moderately elevated white blood cell count, increased total number of **lymphocytes**, over 10% atypical lymphocytes, and a positive reaction to a mononucleosis antibody spot test indicate EBV infection and infectious mononucleosis. Additional laboratory tests may be needed when the diagnosis is ambiguous.[107]

EBV infects over 90% of the world's adult population.[35] Data are not available for Canada, but as many as 95% of adults in the United States are thought to be infected by 35 to 45 years of age.[107]

EBV and cancer

Laboratory studies point to a relationship between EBV and tumour formation. Viral DNA in tumour cells appear to come from a single EBV infecting a single cell (said to be in monoclonal form). Of note, EBV DNA is not integrated directly into the host DNA. EBV DNA exists as an **episome** associated with the chromosomes of infected cells, which implies that EBV was present before the tumour, and played a role in tumour development. Further evidence for the **carcinogenicity** of EBV comes from the observation that EBV induces **immortalization** of **B-lymphocytes *in vitro***, and a protein produced by EBV has been shown to play a role in tumour formation. Studies of experimental animals have shown EBV can induce fatal lymphomas in primates, and inoculation of **immunodeficient** mice with EBV infected human lymphocytes has been associated with the development of malignant tumours.[6]

EBV is most clearly implicated in the development of various lymphomas and nasopharyngeal carcinoma. EBV infection is thought to lead to lymphoma through the expression of specific EBV proteins that promote cell survival by interacting with cell regulatory mechanisms, resulting in a pool of cells that may become malignant. Other ways EBV proteins may promote lymphoma development are complex, vary with tumour type, and are not well understood.[108,109] With respect to nasopharyngeal carcinoma, it is unclear if EBV infection occurs early or late in the process. It is thought that after infection, EBV latent genes provide growth and survival benefits to the infected cells, leading to development into malignant tumours.[109,110]

According to the International Agency for Research on Cancer (IARC), EBV is a Group 1 carcinogen (i.e., is carcinogenic to humans).[111] The following discussion is restricted to cancers for which EBV is a Group 1 carcinogen, unless otherwise indicated.

Burkitt's lymphoma

Burkitt's lymphomas are classified into three types: **endemic**, sporadic (i.e., in an irregular pattern) and Acquired Immune Deficiency Syndrome (AIDS)-associated.

1. Endemic Burkitt's lymphoma is a predominantly pediatric disease found primarily in equatorial Africa and Papua New Guinea.[7] that correlates strongly with **holoendemic** malaria.[6,35,112] Here, repeated malarial infections are thought to make the cells more prone to the effects of EBV.

2. Sporadic forms of Burkitt's lymphoma (less frequently associated with EBV) have been described in Europe and North America, including Canada.[35] Sporadic Burkitt's lymphoma is distinguished from endemic Burkitt's lymphoma by its clinical presentation (abdomen instead of jaw), wider age range at diagnosis, occurrence primarily in whites and much lower **incidence**.

3. AIDS-associated Burkitt's lymphoma is also rare, estimated to be at least 1,000 times more common in AIDS patients than sporadic Burkitt's lymphoma is in the general population.[6,106]

In the United States, males are four times more likely than females to develop sporadic Burkitt's lymphoma.[113] Internationally, the proportion of sporadic Burkitt's lymphoma cases associated with

EBV ranges from 15% to 88%,[6] while data from the U.S. indicate fewer than 30% of cases are reported as associated with EBV.[114] It is difficult to infect uninfected Burkitt's lymphoma tumour cells with EBV, therefore, viral presence seems to indicate it was involved in disease progression.[6]

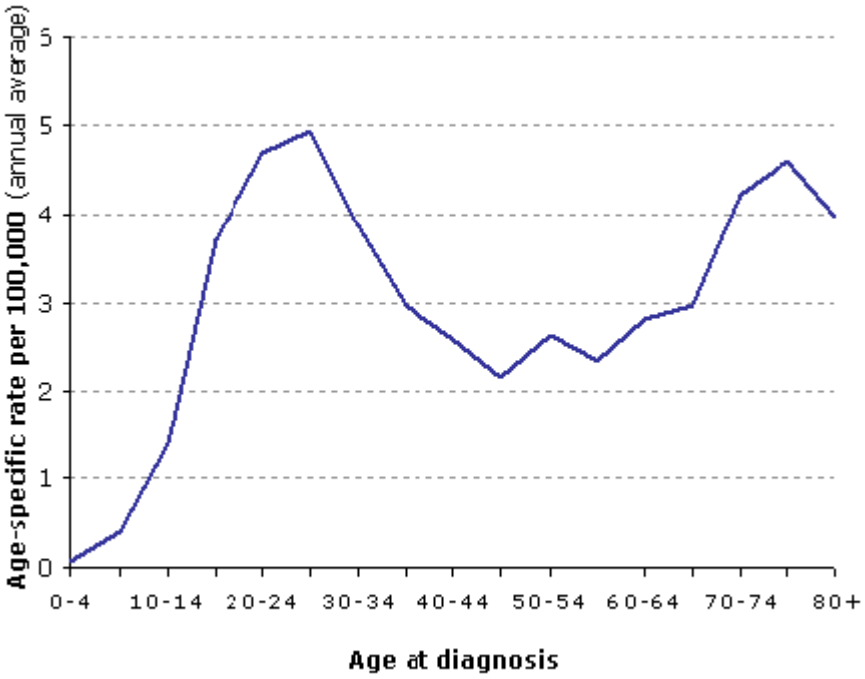
Hodgkin lymphoma

In 2009, an estimated 910 Canadians were diagnosed with Hodgkin lymphoma.[30] In industrialized nations, nodular sclerosis is the most common histologic subtype of Hodgkin lymphoma. This subtype peaks in people 15 to 34 years old. Another subtype, mixed cellularity, increases between the ages of 45 and 79. The age distribution of these two subtypes contribute to two age-specific incidence peaks for Hodgkin lymphoma, one around age 20 to 30, and the second around age 75 (Figure 10).

EBV-positive tumours (where the EBV **genome** or gene products are detected in tumour cells) are found in 30% to 50% of Hodgkin lymphoma cases, although this proportion varies considerably from country to country.[6,111] EBV-positive tumours are most commonly associated with the mixed cellularity tumour subtype, with 60% found to be EBV-positive in a representative sample (16 to 74 years old) from a Scottish and English population. The same study reported EBV positivity associated with nodular sclerosis, but the percentage of EBV-positive tumours was just under 24%.[115] Children and older adults are more likely to have EBV-positive tumours than young adults,[7] and EBV positivity is more common in males. In the 15 to 49 year age group, males are twice as likely as females to develop EBV-positive tumours.[6,116] International data indicate that children from economically less developed regions are more likely to develop EBV-positive lymphoma, as are Hispanics.[116] Variation in strain does not appear to explain the variation in EBV positivity. Immune compromised individuals however, show greater incidence of EBV-2-positive disease.[6,7]

Detection of monoclonal viral DNA in tumour cells provides the molecular evidence for a link between EBV and Hodgkin lymphoma, although the role that EBV plays in development of the

Figure 10. Age-specific incidence rates of Hodgkin lymphoma in Ontario for both sexes combined, 1998-2002



Source: Cancer Care Ontario, Ontario Cancer Registry, 2006

disease is still not fully understood.[7] Results from a **cohort study** found that blood serum markers indicating enhanced EBV activation are associated with an elevated risk of Hodgkin lymphoma, ranging from 2.6 to 4.0.[117]

Infectious mononucleosis is an indicator of later infection (generally in adolescents or young adults) by EBV. Results from a number of cohort studies indicate a three-fold excess of Hodgkin lymphoma incidence among young adults following infectious mononucleosis when compared to the general population.[118] An association between infectious mononucleosis and EBV-positive Hodgkin lymphoma is supported by several (but not all) studies of young adults.[119-122]

The association between infectious mononucleosis and risk for EBV-positive Hodgkin lymphoma is consistent with the hypothesis that later infection with EBV increases the risk of EBV-associated Hodgkin lymphoma.[119] Risk appears to be greatest immediately following infection, decreasing with time, although some increased risk may remain for 10 to 20 years following infection.[121,122] Infectious mononucleosis is a more severe form of primary infection by EBV, and the association with EBV-associated Hodgkin lymphoma might also be explained by a more severe infection increasing the risk for this disease. Another possible explanation is that infectious mononucleosis indicates a lifestyle predisposing individuals to late infection by viral agents (other than EBV) that increase risk.[120]

Other factors may interact with EBV infection to increase risk of Hodgkin lymphoma. Individuals with a compromised immune system are at increased risk, and Human Immunodeficiency Virus (HIV) infection is associated with a particularly virulent form of EBV-associated Hodgkin lymphoma.[6] Genetic factors also may be of importance in Hodgkin lymphoma. In a study that examined identical twins under age 50, a 99-fold increase in risk (95% **Confidence Interval**: 44-182) for Hodgkin lymphoma was reported, whereas non-identical twins experienced no increase in risk.[118] While similar data are not available for EBV-positive and EBV-negative Hodgkin lymphoma, the role of genetic factors in both of these disease types needs further exploration.[118] Genes in the Human Leukocyte **Antigen** region, which plays a key role in immune response, are of particular interest since they may be associated with Hodgkin lymphoma risk.[118]

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma is rare in Canada and other Western countries. There is substantial international variation, with high incidence in southern China (particularly Hong Kong), Singapore, and Malaysia.[7,35] Studies indicate that the risk of developing nasopharyngeal carcinoma among Chinese immigrants to Canada (a large proportion of whom are from southern China) is much higher than that found in the rest of the Canadian population.[123] Due to the rarity of the disease, data from Western countries regarding EBV's association with nasopharyngeal carcinoma are limited. Most nasopharyngeal carcinomas diagnosed in China, Southeast Asia, the Mediterranean, Africa and the United States are associated with EBV-1 infection. Among Alaskan Inuit, cases are almost always EBV-2 related.[7]

Nasopharyngeal carcinoma is classified into three histologic subtypes: squamous, non-keratinizing and undifferentiated

(World Health Organization types I, II, and III).[7] Almost all undifferentiated nasopharyngeal carcinoma tumours contain monoclonal EBV genomes, providing support for a causal relationship between EBV and tumours of this histologic subtype. There is some debate regarding the association of EBV with the squamous and non-keratinizing subtypes, although association of EBV with these subtypes of nasopharyngeal carcinoma has been observed.[7,109]

Antibodies to various components of EBV are elevated in nasopharyngeal carcinoma cases compared to controls, and data from follow-up studies indicate a greatly increased risk of nasopharyngeal carcinoma among individuals with EBV-specific antibodies.[28] For example, in Taiwanese men with two types of EBV-specific antibodies, a 33-fold increase in risk of developing nasopharyngeal carcinoma (**Relative Risk**=32.8, 95% Confidence Interval: 7.3-147.2) was reported after 16 years of follow-up.[124]

Smoking and the consumption of Cantonese-style salted fish are known risk factors for nasopharyngeal carcinoma, and epidemiologic studies indicate that greater risk is associated with the consumption of other types of preserved foods.[125] Because this cancer is rare in Western countries, research into other risk factors and their effect on the risk associated with EBV is limited.

Other cancers

Lymphoproliferative disorders are those where lymphatic system cells grow excessively. EBV-associated lymphoproliferative disorders in **immunocompromised** individuals are related to: 1) an inherited immunodeficiency, called X-linked lymphoproliferative disorder; 2) lymphomas associated with immunosuppressive drugs given to transplant recipients; and 3) AIDS.[126] EBV-associated **T-cell** lymphoproliferative disorders have also been reported.[126]

According to IARC, there is conclusive evidence of carcinogenicity for non-Hodgkin lymphoma in **immunosuppressed** subjects, and sino-nasal angiocentric T-cell lymphoma. Evidence for lymphoepithelial carcinoma (primarily a cancer of the salivary glands) and smooth muscle tumours in immunosuppressed subjects is inconclusive.[28] Associations between EBV and breast cancer are neither strong nor consistent.[127]

With respect to gastric carcinoma, new evidence indicates that EBV has a role in 5% to 10% of cases worldwide. EBV-positive gastric carcinoma has a distinct structure, is more likely to develop in the young and in men, and is correlated with ethnicity (more prevalent in Caucasians and Hispanics than Asians).[128] The monoclonal form of the viral genome, and the expression of EBV-transforming proteins indicate the involvement of EBV.[80]

Prevention, Treatment, and Control

A recent, double-blind, **randomized controlled trial** of Belgian university students evaluated an EBV vaccine in relation to infectious mononucleosis.[129] This trial found that infectious mononucleosis frequency was reduced among vaccine recipients, compared to those who received the placebo. The vaccine did not prevent asymptomatic infection, and the study did not determine the duration of protection from infectious mononucleosis. It is not clear if the vaccine will prevent EBV-related

cancers.[129] The testing of other vaccines in humans is either in the planning or preliminary stages.[130,131] A successful vaccine would have greatest impact on areas with a high incidence of EBV-related malignancies, such as China and Africa.[35]

Future Directions

There is no treatment for EBV infection. Without an effective vaccine, little can be done to prevent transmission of this common virus. While current work with vaccination is promising, research is needed to determine whether vaccines might be effective in reducing cancer-related to EBV infection.

Studies are also needed to explore the role of EBV as a co-factor in the development of other cancers. As well, the association of EBV with squamous and non-keratinizing subtypes for nasopharyngeal carcinoma needs clarification. Studies examining the association of specific genes in the HLA region with EBV-positive Hodgkin lymphoma should continue as there is some evidence for an association of this region with Hodgkin lymphoma in general. The immune system consequences of delayed infection with EBV (resulting in infectious mononucleosis) and the possible relationship with the development of Hodgkin lymphoma, are other areas worth exploring.

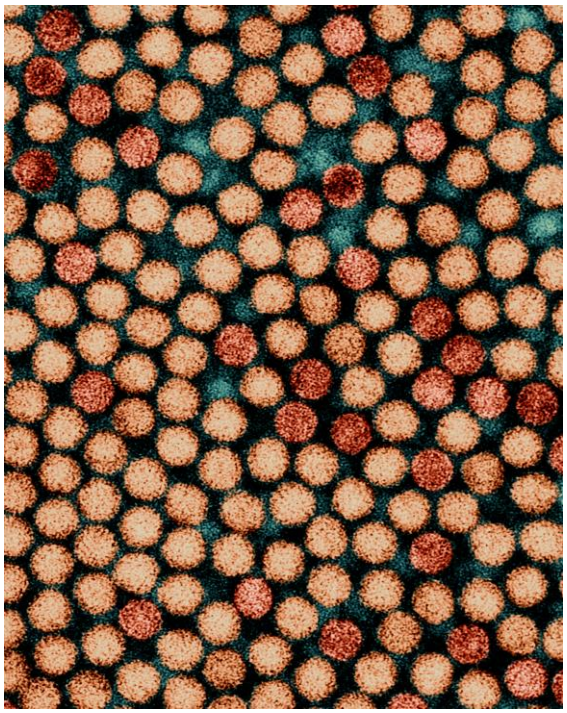
Although difficult to study in Western populations, investigations into the interaction between EBV risk factors and nasopharyngeal carcinoma risk are needed.

HBV

What is Hepatitis B Virus?

Hepatitis B Virus (HBV) (Figure 11) is a small, partially double stranded DNA virus that has been classified as a Group 1 **carcinogen**.[14,106] During the 1950s, it was first proposed that chronic (viral) liver infections could lead to liver cancer.[132] Hepatitis B surface **antigen** (HBsAg), previously called Australian antigen, was discovered in 1965 and was subsequently identified as a component of HBV.[133,134] Since then, the role of HBV in the development of liver cancer has been determined.[14,106]

Figure 11: Hepatitis B virus



Source: Image copyright Dennis Kunkel

HBV can be divided into eight **genotypes** (labeled A through H) and several **serotypes**.[135] Genotype A, which is globally widespread, is the most prevalent genotype in North America, followed by genotypes C, B, D, and G.[135,136] HBV infection is classified as acute or chronic. Approximately 90% of healthy adults infected with HBV will clear the virus within six months.[137] If a sufficient immune response is not mounted, individuals will become chronic Hepatitis B carriers.[138]

In Asia and Africa, transmission most often occurs in childhood via infected mothers or other children, while in Canada and other developed countries, transmission occurs primarily in adolescents and adults through sexual contact and injection drug use, although contact with infected blood or other bodily fluids can also lead to infection.[35,136-140] The risk of contracting infection is low for **hemophiliacs**, individuals who undergo **hemodialysis**, and health care workers.[133] Risk of chronic Hepatitis B development is dependent on sex, immune function, viral factors, and age at the time of infection; children infected during pregnancy and infants born to infected mothers are at the highest risk (80% to 90+%) while risk is lowest among adults (<10%).[14,106]

Although the majority of children (90%) and adults (50%) will remain asymptomatic following the onset of HBV infection (average 60 to 90 days), individuals may experience symptoms including nausea, vomiting, joint and stomach pain, development of jaundice, loss of appetite, and fatigue.[133,141,142] Once chronic infection develops, individuals are often asymptomatic until the appearance of **liver cirrhosis**-related complications and/or Hepatocellular Carcinoma (HCC).[136]

Diagnosis of infection is based on the detection of HBV antigens, antibodies, and viral DNA, and is determined through

examination of blood; based on the choice of virus marker, it is possible to distinguish between current, cleared, and chronic infection, along with absence of infection.[14,138] Acute and chronic HBV infections can be distinguished using various HBV antibody and antigen test results, combined with information from clinical examinations.[143] Current HBV infection is indicated by the presence of either HBV DNA or HBsAg (a serological marker with high levels during acute or chronic hepatitis).[14,143] The appearance of HBeAg (a marker of high HBV infectivity) three to six weeks post-infection indicates acute infection and severity of disease.[141] Should HBeAg presence persist eight to 10 weeks following symptom resolution, likelihood of becoming a Hepatitis B carrier and risk of progressing to chronic infection is increased.[141]

In 2004, the World Health Organization (WHO) estimated that over two billion individuals were infected with HBV, with approximately 360 million individuals chronically infected.[144] The **prevalence** of HBV is low (<2%) in the general population of North America, Western, Central, and Northern Europe, Australia and New Zealand, and parts of South America.[141,145]

In 2006, the **incidence** of Hepatitis B in Canada was approximately 2.0 cases for every 100,000 persons.[133] Although a study estimated a stable Canadian seroprevalence of 0.012% based on blood bank donations, other estimates place prevalence at 0.7% to 0.9%.[133,146] Differences in incidence and prevalence may occur as a result of disease notification, classification, or underreporting. Canadian seroprevalence will likely increase due to immigration from areas of high endemicity.

HBV and Cancer

Liver inflammation occurs following HBV infection. Among chronic carriers, inflammation can potentially lead to cirrhosis, liver failure or cancer, and death.[106,141] HCC is the most frequent subtype of liver cancer, representing over five percent of all cancers worldwide.[147,148] **Meta-analyses** have reported **odds ratios** of 15.6 to 20.4 of developing HCC in individuals with chronic HBV infection.[149,150] It is estimated that 54.4% of global liver cancer cases, or 340,000 cases, are due to HBV, with the fraction of cases attributable to HBV infection as high as 70% to 80% in **endemic** regions.[28,149] Studies have reported odds ratios as high as 48.0 (95% **Confidence Interval**: 25.1-92.0) for development of HCC in the presence of any HBV markers.[149,151] HBV may contribute to HCC development even in the absence of current infection, as evidenced by the presence of HBV DNA found in HCC in individuals with no positive serological markers.[151]

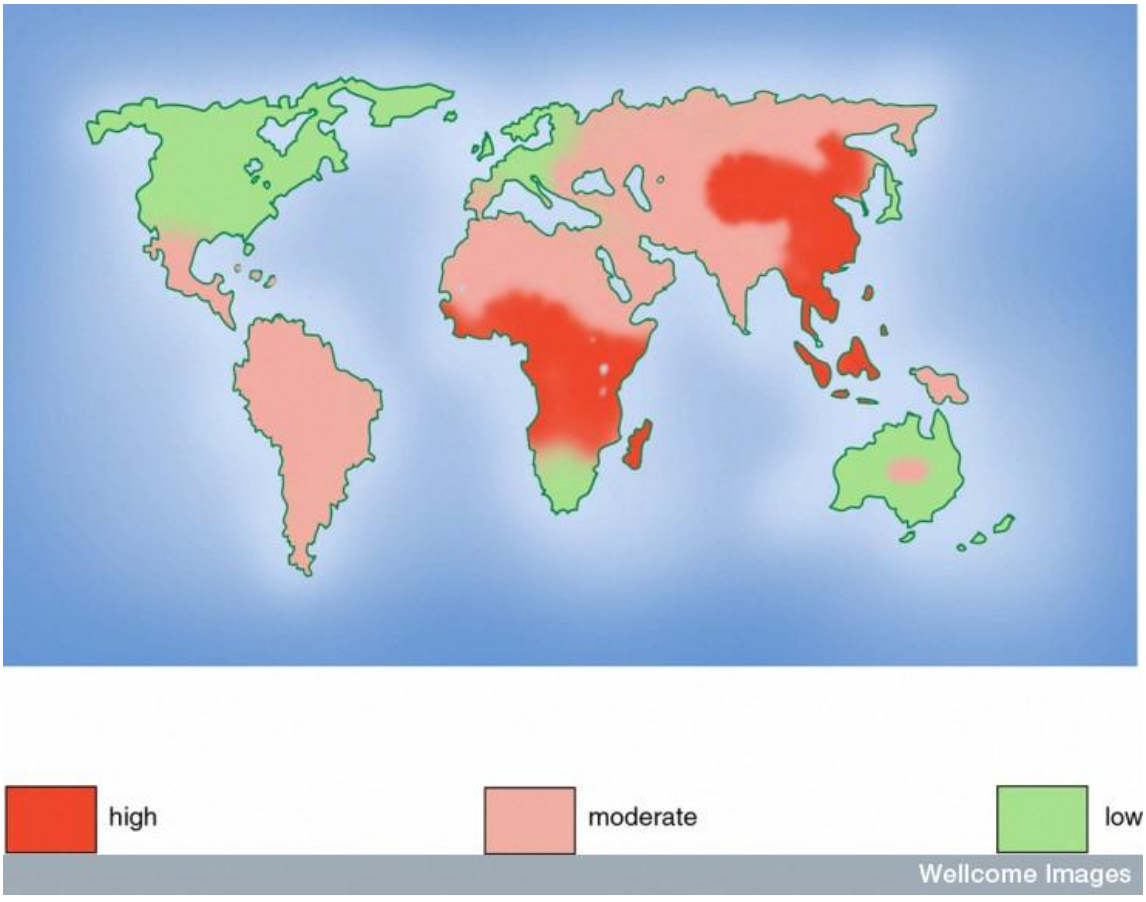
Since HBV does not contain a known **oncogene**, the general consensus is that HBV has no direct cancer-causing or **cytopathological** effect on infected liver cells.[14,15] Tumour development occurs, however, following a long period of chronic liver disease that is often accompanied by cirrhosis. The latency period between infection and development of HCC may range from 30 to 50 years.[106] This suggests that HBV induced **carcinogenesis** may be an indirect result of enhanced hepatocyte (liver cell) turnover that occurs as an immune response.[15] HCC may develop in the absence of cirrhosis and cirrhosis does not necessarily lead to HCC development.[152] HCC risk in the presence of HBV is thought to be influenced by viral load and genotype.[151]

Prevention, Treatment, and Control

Prevention of HBV is accomplished through immunization of infants and children; screening of pregnant women for HBsAg; pre-exposure immunization of high-risk groups; blood donor screening; and public education around risk behaviours.[106,140,153] Universal childhood vaccination is encouraged in Ontario; school-based programs are in place.[133,140] Although categorized as a low-risk group, health care workers are nevertheless recommended to take precautions, including the proper handling of contaminated materials, adequate disinfection of work areas, single-use needles and syringes, and Hepatitis B vaccination.[140,153]

There are two types of Hepatitis B vaccines.[144,154]. In Canada, only vaccines derived from cloning in yeast cells are employed as the initial vaccines (derived from the plasma of chronic HBV carriers) were not widely accepted due to concerns regarding possible contamination with other bloodborne **pathogens**.[144,154] Vaccination of infants and children is the most effective way to reduce HBV-related outcomes; there is some controversy, however, as to the best age to vaccinate.[106,140] In 1992, WHO recommended global vaccination of all children. By 2006, Hepatitis B vaccination was included in the national program of 164 countries.[137] Canada launched a nationwide school-based vaccination program in 1997, which is expected to

Figure 12: Prevalence of chronic Hepatitis B infection by Country, 2006



Source: Image copyright Wellcome Images

prevent 63% of acute Hepatitis B infections and 47% of chronic infections.[140,155] However, school-based vaccination will not prevent chronic Hepatitis B as a result of contracting HBV infection in infancy and childhood.[140] A few provinces and territories have universal infant Hepatitis B vaccination programs that, when compared to school-based programs, may prove to be more efficient and cost-effective in areas of low incidence over the long-term.[140] Children born to infected mothers should be given an initial dose of Hepatitis B immunoglobin and vaccine immediately following birth, with additional doses of the vaccine given for the first six months.[140,153] Any other individuals at high risk (e.g., homosexual/bisexual men, injection drug users, inmates of correctional facilities, etc.) should be vaccinated to prevent risk of chronic infection and development of HCC.[140]

Anti-viral treatment is aimed at eliminating or suppressing HBV, in addition to preventing disease progression and HBV transmission.[135,141] There are currently two standard treatments for HBV: one is a short-term treatment that, when successful, will allow the host to clear the virus, while the other may be used for long-term suppression.[133] Several drugs have been approved for the treatment of individuals with chronic HBV infection, however, there is an urgent need for the development of effective and affordable new drugs to reach large numbers of infected individuals located in countries where resources are slim.[141,156,157]

Future Directions

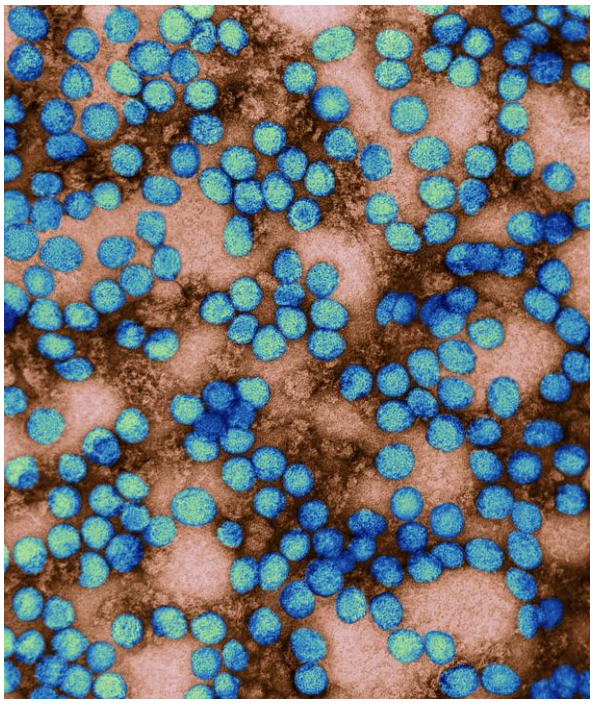
Researchers are investigating a potential synergy between HBV and Hepatitis C Virus (HCV) infections. It appears the co-infection of HBV-HCV may increase the severity of chronic Hepatitis B, particularly the risk of developing HCC.[140] The odds ratio for HBV-HCV co-infection is commonly found to be greater than the sum, and lower than the product, of the odds ratio for each infection.[150] Conclusive evidence about HBV-HCV co-infection and HCC risk is not available, as this combination of infections is quite rare.[28] Future research must continue to examine the roles of, and links between, HBV and HCV in the progression of cancer.

HCV

What is Hepatitis C Virus?

Hepatitis C Virus (HCV) (Figure 13) belongs to the flavivirus family, which is a group of viruses (including the dengue and yellow fever viruses) that cause a wide range of diseases in animals and humans.[35] First identified in 1989, HCV has six major **genotypes** and more than 50 subtypes. Genotype 1 is predominant in Canada (approximately 60% of cases) followed by type 2 (11% to 16%), and type 3 (6% to 14%), with types 4 to 6 each accounting for less than 5% of cases.[158]

Figure 13: Hepatitis C Virus



Source: Image copyright Dennis Kunkel

HCV is spread through contact with infected blood. The results of several studies conducted in the last 15 years suggest that injection drug use is the transmission route for 70% to 80% of newly acquired cases in Canada. HCV acquisition is possibly associated with sharing contaminated intranasal cocaine equipment.[158]

Among residents of larger Canadian cities, the next most important risk factor is travel to, or spending time as a resident in countries where HCV infection is **endemic**. In many countries, health care-related injections are delivered by reusing syringes, resulting in an increased risk of transmitting blood borne **pathogens**. Epidemiologic data indicate that such injections account for high **seroprevalence** in areas such as Egypt, Pakistan, and (in the past) southern Italy and Japan.[158]

Tattoos, body piercing, and acupuncture with HCV-contaminated equipment also increase the risk of HCV acquisition. Infection resulting from sharing personal items contaminated with blood (e.g. razors, nail clippers, toothbrushes) is possible. Accidentally being pricked by a needle with contaminated blood is a risk for health care workers in particular. Children born to a mother with HCV infection are also at increased risk.[159]

The risk of transmission through sexual intercourse is low, with greater risk among those with multiple sexual partners.[158,160] Traumatic sex that results in tearing of the mucus membranes may increase the risk of transmission.[158]

In Canada, while blood products previously represented a major route of transmission, risk is now estimated to be one per thirteen million blood donations.[161,162] Transmission from organ transplants has also been virtually eliminated. The reduction in risk can be attributed to the exclusion of high-risk

donors and the introduction of new viral inactivation procedures after 1990.[158]

Symptoms of acute infection are often absent, but, when present, are similar to those from infection from Hepatitis B Virus (HBV) and include fatigue and jaundice. Most (80%) cases of acute infection are asymptomatic.[35] The virus becomes persistent in 75% or more of those acutely infected.[35]

HCV infection is diagnosed in some during a diagnostic medical exam for clinical manifestations or abnormal liver enzyme levels. Most people, however, are asymptomatic and can be identified only by screening for risk factors. Additional laboratory testing can then be performed to identify infected individuals.[158]

Globally, 120 to 170 million people (2% to 3% of the world population), are chronically infected with HCV, and 3 to 4 million people are newly infected each year.[132,163] High **prevalence** (>10%) is seen in some countries (e.g., Egypt, Mongolia).[132] In 2007 it was estimated that 242,500 Canadians were infected with HCV (<1% of the population), with 7,900 of these newly infected.[162] It is also estimated that over 21% of infected Canadians are unaware of their infection, and that 58% of prevalent cases were among those who use injection drugs.[164] In Ontario, it is estimated that over 110,000 people are infected (<1% of the population), with about one third undiagnosed.[165]

In Canada, reported acute and chronic HCV infection rates increased rapidly in the early 1990s, however, this reflected both incident and prevalent cases (HCV was not characterized until the late 1980s).[148,158] A U.S. study examined the prevalence of HCV infection among different age groups and estimated the **incidence** of HCV prior to its discovery in 1989. The results indicated that incidence of infection increased in the U.S. from the 1960s to the 1980s, followed by a decrease beginning in the late 1980s.[166] Although recent Canadian data (1998 to 2004. Early rates are unavailable for Canada) suggest a decline in the rate of newly acquired HCV infection, the virus remains an important health threat to Canadians.[167]

HCV and Cancer

The International Agency for Research on Cancer (IARC) has concluded that chronic infection with HCV is **carcinogenic** to humans and that HCV is a Group 1 carcinogen.[80,168] Although some patients (15% to 50%) clear HCV infection, in the rest it becomes chronic, resulting in ongoing inflammation of the liver, leading to **fibrosis** and then **cirrhosis.**[158]

Regardless of the agent (HCV or some other factor), the transformation of hepatocytes (the principal cell in the liver) into malignant cells occurs most often when there is a history of chronic liver injury, regeneration, and cirrhosis, with increased cell turnover in the context of chronic inflammation and oxidative DNA damage ultimately leading to cancer. Whether HCV plays a role in directly influencing molecular pathways leading to cancer development is an active area of research.[169]

Several host factors increase the risk of fibrosis progressing to cirrhosis, including sex and age. Males and those who acquire infection at an older age have a greater rate of progression, as do those with hemochromatosis (uncontrolled iron absorption), and co-infections with Human Immunodeficiency Virus (HIV), HBV or schistosomiasis.[170] Risk of progression is also increased by long-

term infection (the risk is 2% to 20% in those infected for 20 to 30 years), moderate to heavy alcohol use, smoking, and obesity. Progression appears to be slower for African Americans.[170] Following the development of cirrhosis, the risk of Hepatocellular Carcinoma (HCC) is 1% to 4% per year.[158] Almost all HCC associated with chronic HCV occur in the cirrhotic liver.[132]

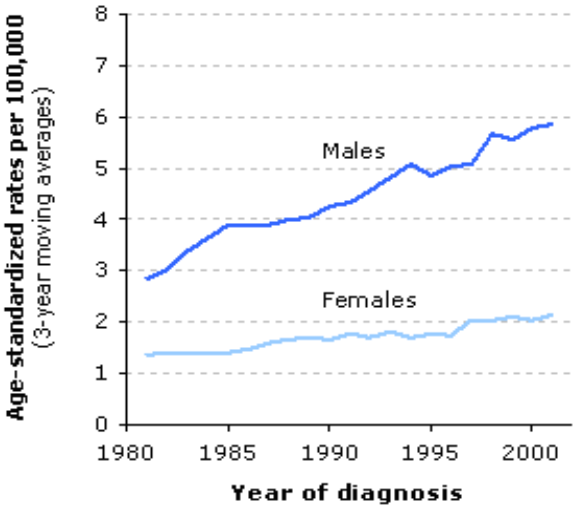
HCC accounts for 75% to 90% of all liver cancers. Reliable data for the geographic distribution of HCC are not available, but extensive data are available for liver cancer. Although common in sub-Saharan Africa and Eastern Asia, liver cancer incidence is generally low in North and South America, Northern Europe, and Australia. Canada is among the countries with the lowest rates in the world.[132] In Canada, it was estimated that there were 1,700 diagnoses of liver cancer in 2009, 1,300 of which were in males.[30] Globally, 70% of liver cancers are diagnosed in males.[171] In Ontario, liver cancer rates have increased since at least 1980, particularly in males (Figure 14).

HCV was characterized in 1989 and subsequent **case-control** studies have indicated a greatly increased risk for HCC in HCV-positive subjects. A **meta-analysis** conducted in 1997 indicated an increased risk of 17.3 (95% **Confidence Interval**: 13.9-21.6). As more sensitive tests were used, risks estimates increased: a **relative risk** of 20 is now assumed.[28] Follow up studies have also provided evidence that HCC is associated with long-term HCV infection.[132]

Much greater risk estimates for HCC have been reported in those with both HCV and HBV infection. These estimates, however, vary greatly among populations. For example, in one meta-analysis, a combined risk of 165 (95% Confidence Interval: 81.2-374) was reported, while in a second study using populations from China, the risk estimate was 35.7 (95% Confidence Interval: 28.2-48.5). It is not clear whether the presence of both viruses results in a **synergistic** effect, or if the higher risk is simply due to having an added risk of developing cancer when a second infection is contracted.[28]

It has been suggested that increasing liver cancer rates may be the result of the increasing number of people with HCV infection. A U.S. study using linked databases[172] found that for those with HCC, HCV presence increased from 11% in 1993-1996 to 21% in 1996-1999. The same study also found an increased

Figure 14. Liver and intrahepatic bile duct (ICD9 155) cancer incidence rates in Ontario, 1980-2002



Source: Cancer Care Ontario, Ontario Cancer Registry, 2006

presence of HBV, from 6% in 1993-1996 to 11% in 1996-1999. Cases related to alcoholic liver disease and non-specific cirrhosis (also risk factors), changed little over the same time period. Two other studies, one using linked databases and the other examining cases in a single health care centre in the U.S., also implicate HCV infection as contributing to increasing liver cancer rates.[173,174]

In Ontario and in most countries, **cholangiocarcinoma** is the next most common form of liver cancer after HCC.[132,175] Recent studies suggest that HCV may be a risk factor for this cancer.[176-181] IARC has determined that there is some limited evidence in humans for a link between HCV and cholangiocarcinoma.[80]

Among other cancers, studies examining the role of HCV in thyroid cancer have not produced consistent results.[182-186] In contrast, results from most case-control studies and **cohort studies** indicate that HCV infection increases the risk of non-Hodgkin lymphoma,[112,185,187,188] especially **B-cell** lymphoma.[80] Risk estimates have, however, varied substantially between studies. It is not clear how risk varies for different non-Hodgkin lymphoma subtypes.[112] An intervention study found that HCV infected patients with splenic lymphoma, given interferon (**anti-viral**) showed regression of the lymphoma.[80] Additional research is needed before a causal relationship can be established.[189]

Prevention, Treatment, and Control

There is currently no HCV vaccine, and there are a number of challenges to developing one: 1) HCV is characterized by the continuous emergence of different forms of the virus, making it a moving target for vaccine design.[190]; 2) the only animal model available is chimpanzees, the use of which is costly, controversial and restricted; and 3) the antibodies generated by HCV seem incapable of resolving infection.[190]

Another approach to preventing HCV-related pathologies is to screen for and treat the infection. While there are no long-term data available on the **efficacy** of HCV screening and treatment on the development of liver cancer and other HCV-related diseases, the Canadian Consensus Conference on Viral Hepatitis Management recommends testing for antibodies in people at increased risk of infection, with HCV-positive patients undergoing evaluation to determine if treatment is appropriate. This recommendation is based on the success of combinations of anti-viral drugs that can clear the virus in 45% to 80% of cases, with improvement to **hepatic** inflammation, and on evidence that other interventions (e.g. counseling against alcohol use, Hepatitis A and B Virus immunization) reduce disease progression.[158] The best treatment results have been achieved with a combination of the drugs pegylated interferon and ribavirin. The side effects from treatment of HCV are common, but rarely life threatening.[191] Occasionally, deaths have occurred due to liver failure or blood infection, mostly in those with cirrhosis. Because of anemia from treatment, those with certain types of heart disease combined with marginal liver function cannot be treated with the current standard of care.[192] Depression is a common adverse event associated with alfa-interferon treatment, and suicides have been reported.[193]

Prevention of infection is the most desirable method of control, and personal preventive measures can be adopted to help reduce risk of exposure. Risk of infection can be reduced among drug

users by instructing them not to share drug use equipment, and addiction counseling. Safe injection sites and needle exchange programs are extensions of this. Individuals at risk of coming in contact with blood through occupational exposure should practice 'universal precautions'. Only reputable licensed individuals should be chosen for acupuncture treatment or for providing tattoos or body piercing. Consumers should protect themselves by ensuring all equipment is sterile, for example by not allowing use of homemade materials or previously used equipment. Individuals should learn about safe sex practices and discuss them with their partner(s). Women who are pregnant or are planning to become pregnant should speak to their health care providers about being tested for hepatitis viruses.[159]

An important initiative is the Public Health Agency of Canada's Hepatitis C Prevention, Support, and Research Program, established in 1998 by the government of Canada.[159] In 2008, the federal Minister of Health announced a renewed Hepatitis C Program, funded annually ($10.6 million per year), with a focus on: knowledge development, policy and program development, community capacity-building, education (public and professional), collaboration across sectors and disciplines, and information synthesis and exchange.[164] The Program recently prepared a set of priorities, and has among its goals: infection prevention, support for the infected, the provision of evidence for policy/program decisions, and strengthening capacity to address HCV in Canada.[164]

Future Directions

The U.S. National Institutes of Health 2002 consensus statement on management of HCV, and the Public Health Agency of Canada have outlined several priorities for HCV research.[194,195] Recommendations relate to preventing and understanding disease transmission and progression. Research that assesses infection control strategies is needed, including the evaluation of interventions to reduce infection risk among injection drug users.[164,194,195] **Randomized controlled trials** that involve special populations are needed to determine the best approaches to treating HCV in a number of groups, including: children, patients with acute hepatitis, patients in drug treatment programs, active drinkers, and patients co-infected with HIV.[195] A better understanding of factors that might predict transmission, such as phase of infection, risk associated with specific sexual practices, and effectiveness of risk reduction counseling are also required.[195]

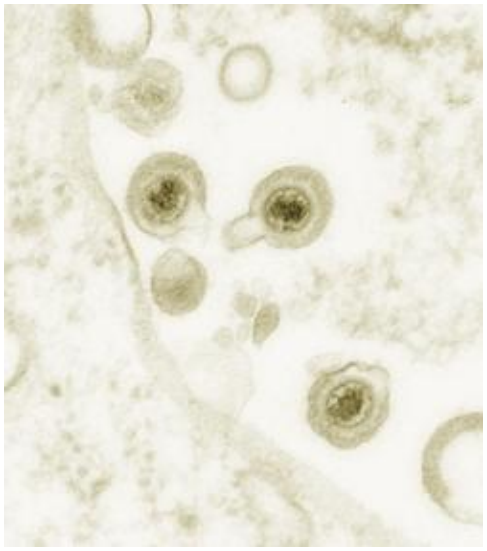
The role of genetics in the natural history of HCV infection has recently been identified. The role of specific genetic polymorphisms in cancer development and immune response should also be investigated.[195,196] Efforts that improve the monitoring and surveillance of HCV are required.[164,194] Finally, more research is needed to explore the relationship between HCV and cholangiocarcinoma of the **intrahepatic bile ducts**, non-Hodgkin lymphoma and thyroid cancer.

HHV-8

What is Human Herpesvirus 8?

Human Herpesvirus 8 (HHV-8) (Figure 15) is a member of the **herpesvirus** family, closely related to Epstein-Barr Virus (EBV).[197,198] Although HHV-8 fragments were discovered through Acquired Immunodeficiency Syndrome (AIDS) research, the virus was present in Europe and Africa long before the AIDS epidemic.[199,200] Also known as Kaposi's Sarcoma-Associated Herpesvirus (KSHV), HHV-8 was discovered in 1994.[197,198] HHV-8 has been commonly accepted as the primary cause of Kaposi's Sarcoma (KS) which was highly prevalent worldwide in the early stages of the AIDS epidemic.[28]

Figure 15: Human Herpesvirus 8



Source: Cynthia Goldsmith

HHV-8 is thought to be transmitted through semen, blood, and saliva.[201] The role of breast milk and the risk of transmission from mother-to-child and sibling-to-sibling is still uncertain.[202] It is thought that HHV-8 is primarily transmitted through sexual contact, but the exact modes of transmission are not fully understood. It is known that HHV-8 is more frequently detected in saliva than in semen.[201-203] The risk of acquiring HHV-8 infection is increased among **immunocompromised** individuals, including individuals with end-stage renal disease, transplant recipients, and individuals with Human Immunodeficiency Virus (HIV)/AIDS.[204] Of the various HIV/AIDS risk groups, HHV-8 is most **prevalent** in homosexual men.[205] The results of one study found HHV-8 antibodies in 100% of homosexual men, 23% of injection drug users, and 21% of women.[205] Among homosexual and bisexual men, HHV-8 infection has been correlated with homosexual activity, number of homosexual partners, and previous history of sexually transmitted infections.[206] Regardless of HIV infection status, men who have sex with men have a higher **seroprevalence** of HHV-8.[207]

Symptomatic disease will only develop in a small number of healthy individuals who contract HHV-8, but there have been some indications of symptoms upon initial infection.[206,208] These symptoms include diarrhea, fatigue, localized rash, and lymph node inflammation.[206]

Three methods are available to detect HHV-8: molecular methods, immunohistochemical staining, and serologic assays.[203] HHV-8 expresses proteins differently at different stages of infection and may be **latent** following initial infection; thus, tests must be able to detect antibodies throughout the replicative cycle.[198,209] Currently, there are no recommendations for routine screening for HHV-8 in HIV-infected individuals, despite high frequency of coinfection of the viruses.[207]

The distribution of HHV-8 infection varies geographically. Estimates of **prevalence** among healthy individuals of non-**endemic** areas, including North America, range up to five percent, whereas in Southern Europe the prevalence is much higher (up to 35%).[198,204,205] Currently, HHV-8 prevalence data are unavailable for the Canadian population.

HHV-8 and Cancer

HHV-8 infection has been associated with development of all four types of KS: sporadic (classic), endemic (African), epidemic (AIDS-associated), and **iatrogenic**.[111,210] Different types of KS have specific epidemiologic profiles, but identical histopathology.[111,210] Generally, it is more likely that immunocompromised individuals, particularly HIV-positive individuals, will develop KS.[210] Among homosexual and bisexual men with AIDS, AIDS-associated KS is the most common tumour, and in approximately 25% of AIDS patients, it is the first clinical manifestation.[203] Considering all cancers worldwide, an estimated 0.9% (66,200 KS cases) can be attributed to HHV-8/HIV co-infection, with the majority occurring in sub-Saharan Africa.[28] Classic KS occurs primarily in older Mediterranean, eastern European, and Jewish men, with comparatively high **incidence** rates in Italy, Greece, Turkey, and Israel.[203,212] Endemic KS occurs primarily in adult males of African countries, although occasionally children also develop the cancer.[111] The majority of iatrogenic cases occur in individuals who have received chronic immunosuppressive therapy or who are organ transplant recipients.[203]

Although the role of HHV-8 in the pathogenesis of KS is not clearly understood, in the majority of cases, HHV-8 is thought to precede tumour development.[111] Immunosuppression can lead to an increase in HHV-8 infected cells and subsequent development of HHV-8-related tumours.[202] Although HHV-8 is found in more than 95% of all KS tissues, HHV-8 infection appears to be essential but not adequate to develop KS.[35,213,214] The International Agency for Research on Cancer (IARC) recently reclassified HHV-8 as **carcinogenic** to humans.[80,111]

HHV-8 has also been associated with Multicentric Castleman's Disease (MCD) (a rare malignant disease, resembling a lymphoma, in which lymphatic cells proliferate) and Primary Effusion Lymphoma (PEL) (non-Hodgkin lymphoma).[203,207,211] The majority of individuals with PEL or MCD have severely suppressed immune systems.[202,211] PEL is seen more commonly among homosexual men than among other HIV risk groups.[202] It is possible for individuals with MCD to also develop KS, and HHV-8 is found in many individuals with MCD.[211]

Prevention, Treatment, and Control

It is difficult to propose a comprehensive strategy to prevent infection, as there is inadequate knowledge of the routes of HHV-8 transmission. The increased risk of developing KS when co-infected with HIV and HHV-8 highlights the importance of preventing HHV-8 acquisition among HIV-positive individuals.[201] As a precaution, HHV-8 uninfected individuals should avoid deep kissing and sexual intercourse with KS patients, HIV-infected individuals, or others who are at high risk of being infected with HHV-8.[201] Use of a condom will aid in minimizing risk during sexual intercourse.[201]

HHV-8 replication is inhibited by certain drugs, although these drugs present

some challenges.[201] Some are associated with bone marrow suppression and reproductive toxicity, while others are available only by injection.[215] DNA synthesis **inhibitors** are thought to be capable of inhibiting HHV-8 replication, but study results are inconsistent in those with HHV-8 related infections.[215] Since the introduction of highly active antiretroviral therapy (HAART), a treatment that improves compromised immune responses, the incidence and mortality of KS have been greatly decreased.[201,202,216-218]

Future Directions

An effective HHV-8 vaccine is not currently available, yet prevention of infection and associated diseases may only be achieved by vaccination of risk groups.[203] Continued examination of the role of **anti-viral** medication in treatment and prevention is vital.[215] The current options for treatment of HHV-8-related infections are ineffective as most tumour cells are latently infected; current treatments require lytic replication (i.e., proteins expressed when infection has completed a full cycle including reproduction).[208,215]

HIV

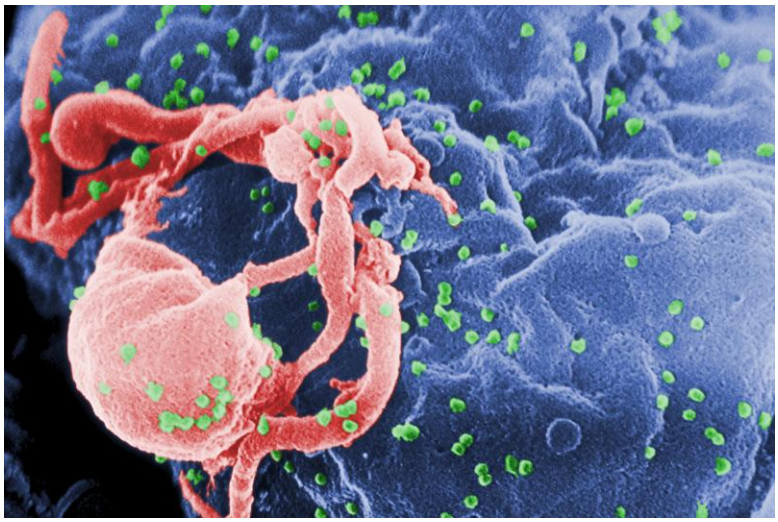
What is Human Immunodeficiency Virus?

Human Immunodeficiency Virus (HIV) (Figure 16) attacks the immune system and leads to chronic, progressive illness that leaves those infected vulnerable to **opportunistic infections** and cancer.[219] Over time, the immune system becomes unable to fight off infections, indicating that the illness has progressed to advanced HIV disease known as Acquired Immunodeficiency Syndrome (AIDS).[219] There are two major strains of HIV: HIV-1 is largely responsible for most infections worldwide, including North America, while HIV-2, present primarily in West Africa, has few diagnoses in North America.[220,224]

In 1981, a rare pneumonia and other unusual infections were noted in five Los Angeles men.[221] Following isolation in 1983, a virus was associated with these cases.[222,223] Initially known by a few names, the virus was officially named HIV in 1986 and renamed HIV-1 when a second virus, HIV-2, was discovered in West Africa.[222,223] Although there are genetic differences of up to 40%, HIV-1 and HIV-2 share the same immunological and clinical spectrum of disease, modes of transmission, and development of AIDS and opportunistic infections in the advanced stages of the disease.[223,224] Compared to HIV-1, HIV-2 is less infectious in early stages; immunodeficiency develops more slowly and is milder in HIV-2.[224] HIV-2 is relatively rare in North America, generally only seen in individuals from West Africa or their sexual partners.[222] Thus, this chapter refers to HIV-1 as HIV unless otherwise stated.

There are three primary routes of HIV transmission: through unprotected vaginal, anal, or oral sexual activity; mother-to-child transmission during pregnancy, childbirth, and breastfeeding; and blood contact by transfusion of infected blood products, penetrating injuries of health care workers, or injection drug users, particularly through the re-use of needles and drug equipment.[17,220,221] HIV can be found in blood, seminal fluid, pre-ejaculate, vaginal secretions, cerebrospinal fluid, saliva, tears, and breast milk.[17,220,221] Among Canadians reporting an exposure category, men who have sex with men account for the majority of diagnoses (45.1%), with heterosexual contact (30.8%) and injection drug use (19.1%) rounding out the top reported risk categories.[225] The proportion of Canadian infants confirmed to be HIV infected by perinatal transmission decreased to 1.7% in 2008 from 33% in 1996.[225,226]

Figure 16: Human Immunodeficiency Virus



Source: Cynthia Goldsmith

Following infection, HIV attaches to the Cluster of Differentiation 4 (CD4) surface proteins present on a Helper **T-cell**.[220] In healthy individuals, CD4 counts would number between 500 and 1,500 cells/mm^3, but infected individuals have much lower counts due to destruction by HIV.[220] This reduced CD4 count leaves infected individuals unable to fight off a variety of opportunistic infections and complications.[221] The progression of HIV to AIDS follows four stages (Table 3).

HIV infection is diagnosed using antibody tests. A two-step process is used to confirm the presence of HIV antibodies in blood.[221] As detectable levels may not be present initially, testing should occur three to six months following the most recent suspected HIV exposure.[220] Guidelines for health care providers in the United States recommend routine HIV testing for patients aged 13 to 64 years.[220] As viral loads and CD4 counts aid in disease staging and are correlated with risk of opportunistic conditions, CD4 and viral load testing are recommended every three to six months for all HIV-infected individuals.[221]

The following statistics are quoted for HIV-1 and HIV-2 combined. With continuous long-term interventions to promote safer sexual behaviour, **prevalence** is high but appears to be stabilizing in many parts of the world.[227,228] In 2008, an estimated 33.4 million people were living with HIV, 2.7 million of whom were newly infected with the virus.[227] Sub-Saharan Africa is home to 68% of newly infected adults and 91% of newly infected children.[227]

Based on surveillance data from 1985 to 2008, there have been a total of 67,442 HIV diagnoses in Canada.[225,229] The vast majority of Canadian diagnoses came from three provinces, Ontario, Quebec,

Table 3:
The stages of progression from HIV to AIDS[17,210,221]

Stage	Name	Time	Details	CD4 counts	HIV Test
1	Acute or Primary Infection	Lasts 2 to 6 weeks	Begins as the virus starts multiplying in cells; some individuals experience flu-like symptoms often mistaken for **mononucleosis**		Antibody test generally negative (other tests can be positive)
2	Asymptomatic stage	Varies from 1 to 15 years	HIV present in the lymph nodes, spleen, and other organs and tissues; no symptoms of disease	Fall quite low	Positive
3	Early symptomatic stage		Mild health problems may speed the progression of HIV but not serious enough to qualify as AIDS	Further decrease	Positive
4	Advanced HIV or AIDS	Averages 10 years to develop with considerable variation (longer period for HIV-2)	Immune function seriously impaired; serious opportunistic condition (major infection or cancer) occurs	Drops below 200 cells/mm^3	Positive

and British Columbia.[225] In 2008, Ontario accounted for 42.7% of new diagnoses and 44.2% (29,785 cases) of all cases.[225] The estimated range of new HIV-positive diagnoses Canada-wide was 2,300 to 4,300 in 2008.[229] Among new diagnoses, the proportion of women (26.2%) was unchanged from previous estimates and much lower than the global estimate (46.4%).[225,226,229-231] Approximately 26% of HIV-infected individuals are estimated to be unaware of their infection.[229] It should be noted that there are some limitations to using surveillance data and estimates are subject to underreporting. Comprehensive estimates of prevalence and **incidence** are produced every three years by the Public Health Agency of Canada and were last published for 2008.[229]

HIV and Cancer

Despite great advances in knowledge and treatment, AIDS-defining cancers remain a leading cause of death in HIV-infected individuals; recent studies have indicated that immune deficiency, rather than other factors commonly associated with HIV infection, is responsible for this excess risk.[217,232-234] During the course of HIV infection, approximately 30% to 40% of individuals will develop a malignancy.[233] Specific AIDS-defining cancers identified thus far are Kaposi's sarcoma (KS), non-Hodgkin lymphoma (NHL), and Invasive Cervical Cancer (ICC).[220,233] In addition, Hodgkin lymphoma, cancers of the anus and conjunctiva have newly identified links to HIV.[80] HIV-infected individuals are also more likely to develop Hepatocellular Carcinoma (HCC), cancers of the vulva, vagina, penis, lung, mouth, testes, and skin including non-melanoma skin cancer.[80,220,233]

The aptly termed AIDS-related KS is one of four types of KS.[210] Immune deficiency, generally caused by HIV infection, is the primary risk factor.[210] In the HIV uninfected population, KS is a rare cancer, affecting older people predominantly of Mediterranean descent or those receiving immunosuppressants following an organ transplant.[233] Individuals infected with HIV are 100 to over 300 times more likely to have KS than the general population.[218,233] Since the introduction of highly active antiretroviral therapy (HAART), KS incidence and mortality has greatly decreased, likely a result of immune reconstitution.[216-218] KS in HIV-positive individuals is related to another sexually transmitted agent, Human Herpesvirus Type 8 (HHV-8).[210,217,220] In 2002, 66,200 global cases of KS were attributed to HIV and HHV-8.[28] For further information, refer to the chapter on HHV-8.

NHL has been linked to HIV as an AIDS-defining condition since 1985; it develops in up to 30% of those infected and is the most frequently fatal AIDS-defining condition.[217,235] The risk of developing NHL is increased as immune competence declines over the duration of infection; risk is 100 to 200 times greater in HIV-infected individuals than in the general population.[218,233] NHL is the initial AIDS-defining condition in approximately 3% of cases.[28] It was estimated that 5.5% of NHL cases in North America in 2002 could be attributed to AIDS.[28] While the risk of developing NHL is 1.2 times greater in females than males in heterosexually acquired AIDS cases, the overall number of males affected is greater, primarily due to risk-group differences.[28] As with KS, the incidence of HIV-related NHL has declined dramatically in the HAART era, although less than most other AIDS-defining conditions.[216,217] In HIV-infected individuals, NHL is most often of **B-cell** derivation.[28,236,237] The two most common

histologic patterns in HIV-associated NHL are large-cell lymphoma and Burkitt's lymphoma.[236] Extranodal disease is observed in almost 90% of NHL cases associated with AIDS, with involvement of the central nervous system (CNS) (20%), bone marrow, or digestive tract (25%).[233]

Newly identified links between HIV and cancer have been found for ICC, Hodgkin lymphoma, and cancers of the anus and conjunctiva.[80] Compared to uninfected women, the risk of developing ICC is five to 10 times greater in HIV-positive women, with ICC progressing faster, treatment being less effective, and risk of recurrence higher.[217,218,220] Although a formal relationship between Human Papillomavirus (HPV) and HIV has not been established, in conjunction, they may increase the risk of ICC development since HPV is involved in the majority of cervical cancers and is strongly associated with precursors to ICC.[217,218]. The introduction of HAART led to an unexpected increase in the incidence of Hodgkin lymphoma.[238] HIV-positive individuals have up to a 10-fold greater risk of developing Hodgkin lymphoma than uninfected individuals.[238] Co-infection with Epstein-Barr Virus (EBV) is found in 80% to 100% of HIV Hodgkin lymphoma cases.[238] At the time of diagnosis in HIV-infected individuals, 74% to 92% of cases are in the advanced stages of the disease.[238]

Although frequency varies widely by cancer type and sex, many additional non AIDS-defining malignancies appear two- to three-fold more frequently on average in HIV-infected individuals compared to uninfected individuals.[217] Since the introduction of HAART has decreased the risk of developing AIDS-related malignancies, the incidence of other cancers has been increasing; deaths due to cancers have risen from an estimated 10% to 28%.[217,238,239] While prolonged survival, aging, and a decrease in fatality due to opportunistic infections may be contributing factors to the increased amount of non-AIDS defining cancers, the excess risk that cannot be explained by improved survival alone is thought to result from immunosuppression due to HIV infection.[217,232] Recent data indicate that increasing an individual's CD4 count by 100 results in a risk reduction of 19% for developing a non-AIDS defining cancer.[232] Practitioners should be aware of the increased risk of developing non-AIDS defining cancers and should screen HIV-positive individuals accordingly.[239]

Prevention, Treatment, and Control

Currently, there is no cure or vaccine for HIV. Research into the development of an AIDS vaccine is ongoing.[220] In Canada, the goal of creating a globally accessible, safe, affordable, and effective vaccine has resulted in a collaborative effort between the Government of Canada and the Bill and Melinda Gates Foundation.[240] Termed the Canadian HIV Vaccine Initiative, this program will provide Canadian scientists with funding to broaden the scope of research on vaccine candidates.[240] To date, the Canadian government has pledged $111 million towards the Canadian HIV Vaccine Initiative.[240]

As there is no cure for HIV, treatment for HIV/AIDS aims to rebuild and preserve immune capability, while controlling viral levels and preventing or minimizing the impact of opportunistic infections.[220] There are numerous antiretroviral drugs which, given in combination, inhibit steps in the viral replication cycle of HIV and form the basis of HAART.[220,221] HAART inhibits HIV replication, diminishes production of **Tat protein**, and promotes

protective immune activity within the body.[216] Antiretroviral treatment increases the lifespan of HIV-infected individuals and may have protective effects, preventing some forms of cancer; there are concerns of cancer vulnerability, however, in individuals living longer with subtle but persistent immunodeficiency.[216,241]

To reduce the risk of infection, individuals can abstain from sexual activity or reduce their number of sexual partners, consistently and correctly use condoms when engaging in sexual activity with a partner whose HIV status is uncertain, or abstain from unprotected sexual activity with infected individuals.[220] Injection drug users can abstain from injection drug use or use sterile equipment.[220] Drug-dependence treatment programs and supplied sterile needle programs help reduce the risk of HIV infection among injection drug users.[17,220] HIV screening of all blood donors helps minimize the transmission of HIV through blood products.[220] In Canada, the risk of infection is estimated to be less than one out of every million units transfused.[146]

Future Directions

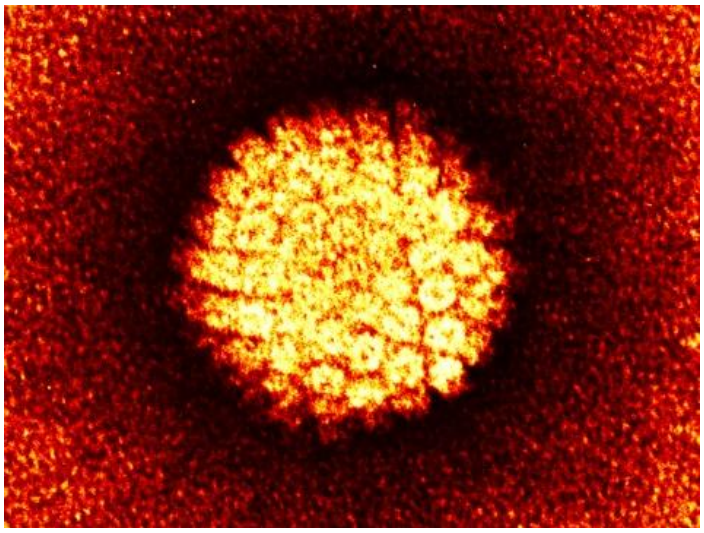
Current research is focused on the development of a vaccine, improvement of existing drugs, and development of new treatment options.[220] In Canada, a federal initiative is working towards: 1) reducing the social and economic concerns that threaten health; 2) preventing spread of infection; 3) providing diagnosis, care, treatment, and support that are timely, safe, and effective ; and 4) contributing to the global effort to reduce the spread of HIV and mitigate the impact of the disease.[242,243] To accomplish these goals, the initiative will focus on five areas: coordination, planning, evaluation, and reporting; program and policy interventions; knowledge development; communications, and social marketing; and global engagement. This initiative brings together all levels of Canadian government, in addition to non-governmental organizations, researchers, health care providers, and infected or vulnerable individuals.[243]

HPV

What is Human Papillomavirus?

Papillomaviruses are small (52 to 55 nm), double stranded DNA viruses that lead to abnormal tissue growth. These viruses occur across the animal kingdom, yet they are species- and tissue-specific and, with a few exceptions, only infect squamous **epithelial** cells.[244] Human Papillomaviruses (HPVs) (Figure 17) are ancient viruses that co-evolved with their hosts, and infect humans only.[244]

Figure 17: Human Papilllomavirus



Source: Image copyright Pasieka/SPL/Science Photo Library/ Getty Images

Over 120 different types of HPV exist. HPV can infect many areas of the body, including the face, feet, hands, and mucosal areas of the genital and upper aero-digestive tract. More than 40 HPV types can infect the mucosal epithelial lining of the anogenital tract and other areas,[35,245] and this applies to both sexes. Among genital HPVs, the terms 'high-risk' and 'low-risk' differentiate the types frequently found in cervical cancers from those rarely or never found in cervical cancers.[244] Cervical cancer is caused by HPV types of the mucosotropic alpha **genus**.[246]

The sexually transmitted nature of cervical cancer was theorized as early as 1842, and papillomas (warts) were linked to viruses in 1907. In the 1970s scientists who specialize in viruses began to explore the relationship between HPV and cervical cancer, followed up with research by epidemiologists. In 1995, a group of international scientists concluded that cervical cancer stems from sexually transmitted HPV.[247] It is now accepted that infection with certain types of HPV is a necessary, although not sufficient, cause of cervical cancer.[3]

Because sexually transmitted HPV is typically found on the moist mucosa and adjacent skin of the human genitalia, genital HPV infections are common. The virus is transmitted frequently, largely due to the following reasons:

- HPV infections, per se, are common and frequently asympomatic;
- the virus is easy to transmit via skin-to-skin sexual contact (cervical, vaginal, vulvar, penile, anal, or oral), and non-sexual transmission (e.g., open mouth kissing) is possible, though uncommon; and
- the infection may also be transmitted from infected mothers to their newborn children during passage through the birth canal, and by spreading infection from one part of the body to another.[244]

HPV infection is not blood borne and does not enter the circulation, therefore the body's immune response is confined to the site of the infection.[248] The infectious cycle of HPV occurs within fully developed squamous epithelial cells. It is not known how long the virus can persist in humans. After one to two years, most HPV infections are not detectable by HPV testing; high-risk types persist somewhat longer than low-risk types.[244,249] While most type-specific HPV infection 'clears' in this two year time frame, it has been reported that women can experience a reactivation of the infection, or can be infected with a new HPV **genotype**.[249] An estimated 3% to 10% of infected women do not clear the infection.[250] Persistent infection is a prerequisite for the development of cervical cancer.[35] A recent **meta-analysis** confirmed that persistence of HPV infection is consistently and strongly associated with cellular changes of concern, and that persistence is a clinical marker and endpoint.[251] Research on HPV infection in non-genital sites, and in men, is accumulating.[252] It is unclear if an infection confers a reduced risk for subsequent infection with related types.[253]

HPV infection can result in a range of morphological manifestations. While severe lesions may be due to accumulated events, some severe lesions can develop rapidly. Viral clearance is associated with lesion regression.[244]

Low-risk HPV type infections can result in benign anogenital warts and Low-Grade Squamous Intraepithelial Lesions (LSIL). Some genital warts regress spontaneously, and most self-limited LSILs resolve in 12 to 24 months. HPV types 6 and 11 (not believed to be **carcinogenic**) are estimated to cause 90% of genital warts.[254] Recurrent respiratory papillomatosis, a rare condition characterized by recurrent warts or papillomas in the upper respiratory tract, is also linked to types 6 and 11. This condition sometimes (3% to 5% of cases) undergoes malignant transformation, associated with the presence of HPV types 16 and 18.[254]

The risk of infection is associated with a high number of sexual partners (for both the woman and her sexual partners),[28] and sex with a new partner.[255] Other risk factors include early age at sexual debut, and sexual partners who are high-risk, i.e., those who are more likely to have an HPV infection, such as sex workers, and others with multiple sexual partners.[256] A high proportion of Human Immunodeficiency Virus (HIV)-positive women have multiple HPV infections, and these infections are more likely to persist than those among HIV-negative women.[244]

With respect to diagnosis of infection, warty lesions (associated with non-cancerous HPV types) are diagnosed visually. Due to the subclinical presentation and asymptomatic nature of cancer precursor lesions, they are diagnosed on the basis of an abnormal **Pap test**, or high-risk **HPV DNA testing** (these are both discussed later). Serostatus is not used to detect active infection. While the presence of antibodies indicates HPV exposure, the infection itself may have cleared. Only 50% to 60% of women develop serum antibodies following infection.[248,257]

Prevalence estimates vary according to age, research method, site sampled, and country of residence. Among Canadian women, the overall prevalence of any type of HPV ranges from 11% to 29%, with great variation among age groups (3% to 42%).[258] Within Canada,

prevalence varies by age, place of residence, and ethnicity, although these differences may reflect laboratory detection methods.[258] Regarding the acquisition of new infections, one Ontario study of women 15 to 49 years old found that in a mean interval of 14 months, new infections occurred in 11.1% of previously HPV-negative women, with the highest **incidence** (25%) found in those 15 to 19 years old.[259] In another study in Montreal (Quebec), prevalence of HPV was 56% in new heterosexual couples. This prevalence was higher (85%) among those with infected partners, and much lower in those with HPV-negative partners (19%).[255] It is estimated that high-risk HPV types have a prevalence of 11% to 25% in the Canadian female population.[260] Prevalence most often peaks in early adulthood, with another pattern (U-shaped) common in Latin America, and another (flat) in countries such as Nigeria, India and China.[261] A significant percentage of women infected (20% to 30%) have more than one type of HPV.[254]

HPV and Cancer

High **oncogenic** risk HPV types are Group 1 carcinogens, i.e., they cause cancer in humans. The DNA of oncogenic HPV types is found in virtually all cervical cancer cases. The major steps to cervical cancer are: 1) infection with high-risk (carcinogenic) HPV; 2) persistent infection; 3) precancerous lesions; and 4) invasion. This process frequently reverses (prior to invasion) when the infection is cleared and the pre-cancer regresses.[244] Prognosis is linked to HPV type; in comparison to the other high-risk types, HPV 16 and 18 show a clearer pattern to progression versus regression.[262]

HPV may or may not be incorporated into the chromosomes of the host cell, but integration of the viral **genome** of a cancer-causing HPV type occurs before cancer development. The virus produces proteins which allow for disordered cell replication, and leave the host cell unable to effectively block the accumulation of genetic mutations during replication.[254] If abnormal cervical tissue (cervical dysplasia) or cancer do occur, it is likely that the immune function did not work properly, and the **Helper T-cells** were unable to clear the infection.[254] Oncogenic HPV is implicated in other types of cancer, but the association is not as strong as for cervical cancer.[263]

Epidemiologic evidence shows that some HPV types are carcinogenic. The most potent type of HPV is 16, known to cause cancer in several sites (alpha, mucosatropic, type 1 carcinogen). Other alpha type 1 HPV types linked to cervical cancer are 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. For HPV type 68, there is limited evidence in humans, but strong mechanistic evidence for its relationship to cervical cancer. Group 2B HPV types (possibly carcinogenic to humans) are 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, and 97. Beta (cutaneous-tropic) HPV types that are Group 2B and are 5 and 8.[80]

Over half (54%) of invasive cervical cancers are caused by HPV 16, while another 17% can be attributed to HPV 18.[28] The relatively easy access of HPV to the rapidly replicating basal cells of the cervical transformation zone is thought to make this area particularly susceptible to HPV infection.[254] HPV 16 (and HPV 18, to a limited extent), also plays a causal role in cancers of the vulva, vagina, penis, anus, oral cavity, and oropharynx, with some association with cancers of the larynx and the skin around the nails.[244] In vaginal cancer, HPV is prevalent in 60% to 65% of cases; oncogenic HPV

DNA is present in 20% to 50% of vulvar cancers, and the worldwide attributable fraction (proportion of the disease due to HPV infection) for anal cancer is 90%.[28] A recent review by zur Hausen (2009) concluded that the same HPV types associated with cervical cancer are associated with 25% to 30% of head and neck cancers.[264] HPV types of genus beta are associated with **squamous-cell carcinoma** of the skin. HPVs are also involved in squamous-cell carcinoma of the conjunctiva. The evidence is inadequate for the role of HPV in cancer of the esophagus, lung, colon, ovary, breast, prostate, bladder, and nasal and sinonasal cavities.[244]

HPV types 6 and 11 are classified by the International Agency for Research on Cancer (IARC) as Group 3 in their carcinogenic classification system, based on the fact that molecular studies do not show carcinogenic potential, and because there is inadequate epidemiologic evidence.[80]

It is estimated that HPV (any type) is responsible for 5.2% of the world cancer burden, with the attributable fraction in developed countries lower than that of developing countries (2.2% and 7.7% respectively).[28] Of the cancers associated with HPV, cervical cancer receives the largest share of research attention, due to the strength of its association. Globally, HPV is responsible for all cervical cancer cases (approximately 500,000), 53,900 ano-genital cancers, and 14,500 oropharyngeal cancers annually.[28]

In Canada, approximately 1,300 women were diagnosed with cervical cancer in 2009, and 380 women died from the disease. With respect to Ontario, it is estimated that approximately 500 women were diagnosed with and 140 women died from cervical cancer in 2009.[30] As in other parts of the world, the cancer burden associated with HPV in Canada is mainly due to the strong association of the virus with cervical cancer.

Epidemiologic and laboratory-based studies have concluded that infection with a high-risk strain of HPV is a necessary, although not sufficient, cause of cervical cancer.[265] While it is unknown why HPV infection leads to cervical cancer in some but not others, factors thought to play a role include: immune status and poor diet (particularly low **antioxidant** intake), individual susceptibility, hormones (endogenous and exogenous), smoking tobacco, parity, co-infection with another sexually transmitted agents that cause erosive or ulcerative infections of the cervix (e.g., HIV, herpes simplex virus type 2, *Chlamydia trachomatis*), viral characteristics (e.g., HPV type), concomitant infection with other HPV types, viral integration, and viral load.[245,266,267]

Prevention, Treatment, and Control

HPV infection is prevented by limiting the number of sexual partners. With respect to condoms, a recent study reported that they exert a stronger protective effect on males than females.[255] Because the virus is so widely present in the population, infection is difficult to prevent, especially in the young and sexually active.

Historically, HPV screening focused on cervical testing, which identifies cellular changes/abnormalities which are removed in order to prevent cancer from developing. Following the introduction of the Pap test in 1949, there was a dramatic decrease in the incidence of cervical cancer, and in the mid-1970s, a slowing of this decline.[266] Conventionally,

cervical cells are smeared onto a slide and sent to a lab for analysis (conventional cytology). Conventional Pap testing dramatically reduced cervical cancer rates, yet the test has low **sensitivity** (it 'finds' existing lesions about half of the time), thus screening must be frequent.[250] Low sensitivity, error, and the under-screening of some populations has resulted in a leveling off of the decline in cervical cancer rates.[266]

Liquid-based cytology (LBC), another screening technique, is thought to offer a higher rate of satisfactory specimens than conventional cytology.[268] In LBC, samples are immediately rinsed into a vial containing fixative. Samples are uniformly fixed, prepared in a lab, and are said to have improved cell presentation over conventional Pap testing.[268] Despite this, some studies have shown that LBC does not offer improved sensitivity.[269]

More recently, HPV DNA tests have been introduced. If a woman tests positive for a DNA test, viral DNA has been detected along her lower genital tract (cervix/vagina), and she is diagnosed as having an HPV infection.[248] HPV DNA tests are 25% to 35% more sensitive than cytology-based screening (both conventional and liquid-based), but they are 8% to 12% less **specific**.[270] **Specificity** is improved when testing is restricted to women age 30 years or over, who are less likely to have a transient infection.[266,271] Although one recent **randomized controlled trial** found that co-testing (using conventional cytology and HPV DNA testing) reached 100% sensitivity (with specificity of 92.5%), the authors note the need to evaluate the cost effectiveness of co-testing.[272]

In Ontario, LBC is currently recommended for screening, with conventional cytology used as an adequate alternative. HPV DNA testing is used to triage women 30 years or older with equivocal cytology results into **colposcopy** (if HPV-positive) or repeat cytology in twelve months (if HPV-negative).[268] Some studies found this combination to yield sensitivity and specificity approaching 100%.[266]

HPV testing is currently of high cost because it is not part of standard screening, and current practice (testing used for triage) contributes to this problem.[271] It has been suggested that HPV DNA tests be used as the first-line screen, with cytology used as the second-line screen to triage the women who test positive for HPV DNA. This strategy could allow for longer screening intervals, and be used in post-vaccination surveillance. This strategy has not been adopted because data on the safety of extending screening intervals are needed.[271]

New HPV DNA tests, developed and currently in clinical trials, have included HPV 66 among the targeted genotypes. HPV 66 (previously thought to be a probable carcinogen) has recently been reclassified to possibly carcinogenic, a change that will slightly lower the specificity of these newer tests.[246]

While there is no cure for HPV infection, lesion treatment includes cryosurgery, laser therapy, Loop Electrical Excision Procedures (LEEP) (the removal of lesions with a hot wire loop), and surgery.[273] While low-grade lesions are ablated, excision of high grade lesions is preferred. For benign warts caused by HPV, similar treatments can be used, in addition to drugs.[273] Recent literature suggests that out-patient treatment of

precancerous cervical lesions leads to clearance of HPV infection.[274] **Anti-viral** agents are not currently available.

Following natural infection, only half of women develop detectible serum antibodies against HPV, and at levels that may not be protective.[248] Merck and GlaxoSmithKline have developed prophylactic HPV vaccines. Merck's quadrivalent vaccine, Gardasil®, targets types 16, 18, 6 and 11, while GlaxoSmithKline's vaccine, Ceravix™, is effective against types 16 and 18 alone.[275] Types 16 and 18 account for about 70% of cervical cancers, and types 6 and 11 account for 90% of genital warts.[275]

In July 2006, Health Canada approved the use of Gardasil® for females 9 through 26 years old for the prevention of cancers and pre-cancers of the lower genital tract, as well as genital warts.[276] This vaccine is effective when given to females prior to exposure to HPV infection, i.e., before the onset of sexual activity. Since the fall of 2007, this voluntary, three-dose (at 0, 2, and 6 months) vaccine has been offered in Ontario in a school-based vaccination program to grade eight girls, administered by public health nurses, with federal funding.[277]

Public acceptance of the HPV vaccine is high; studies conducted in 2006 to 2007 found that 74% to 89% of parents were likely to have their daughters vaccinated.[278] Women who are in the approved age range, but do not qualify for the school-based program must pay $400 to $500 for this vaccine.[279] Recently, this vaccine has been approved by Health Canada for use in males. Major vaccine makers plan to extend the vaccines to more carcinogenic types.[267]

Implementation issues remain. Concern has been raised that vaccination may be viewed as providing full protection from all HPV types.[275] Screening programs must include vaccinated women. Furthermore, although most of the reported side effects of vaccination are minor, more serious side effects, such as headache with hypertension, gastroenteritis, bronchospasm, vaginal hemorrhage, and injection site pain have been reported.[280] The three-dose inoculation schedule also presents some difficulty for hard-to-reach populations. Vaccine implementation and its impact on cervical cancer is fertile ground for research investigation.

Future Directions

While HPV vaccines are good news, there are still many issues to be explored. The duration of protection is unknown (evidence suggests protection for up to 6 years),[35] and the **efficacy** in women over age 26,[270] and the effect of immunization on cervical screening participation warrant further study. Vaccine safety and immunogenicity when administered with other vaccines, general safety and pregnancy outcomes, and economic implications[280] also require additional study. Further, it is not known if women at risk for the development of cervical cancer, i.e., the under-screened, will participate in an inoculation program, or receive booster shots.[266]

It is unknown whether vaccination will lead to increased cervical cancer rates (if the immunized forego cervical screening altogether). Cross-protection against related HPV strains has been observed with vaccines; the extent and duration of this needs further exploration.[253] The role of HPV testing in organized screening programs still needs further exploration, as does the link between HPV and other cancers. Further, expert consensus is

needed regarding the acceptable tradeoff in sensitivity versus specificity with respect to which HPV types to include in testing.[246] Future challenges in vaccination include encompassing more HPV types, decreasing the cost and complexity of vaccine production, and determining whether vaccination protects women who have cleared infection against re-infection.[35,281] Finally, it has been suggested that in order to achieve maximal coverage, a more compact dosing schedule, given at birth, or in childhood would be desirable.[35] This idea requires exploration.

HTLV-1

What is HTLV-1?

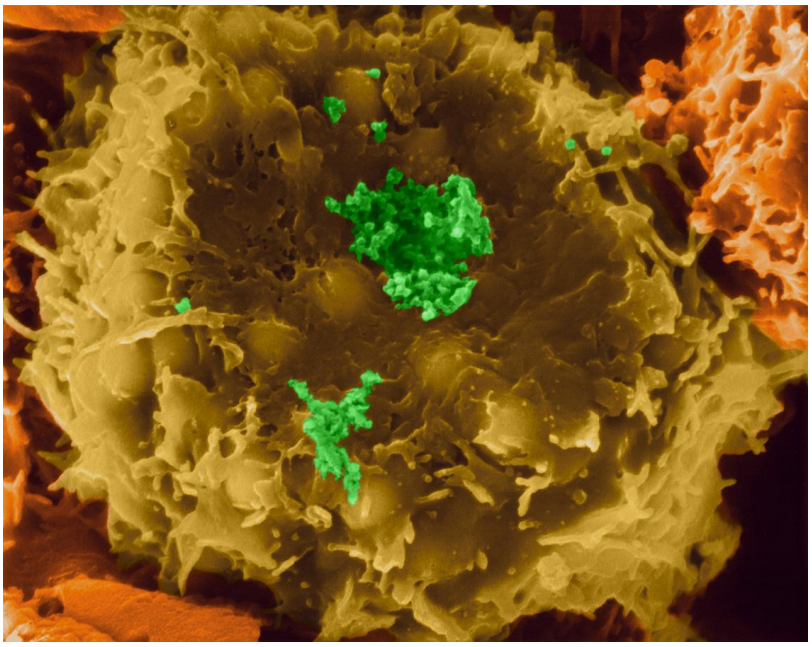
Human T-cell Lymphotrophic/Leukemia viruses (HTLV) are **retroviruses**, in the same class as Human Immunodeficiency Virus (HIV) but with a slower replication rate.[282] Type 1 (HTLV-1) has been classified by the International Agency for Research on Cancer (IARC) as a Group 1 **carcinogen** in the development of Adult T-cell Lymphoma/Leukemia (ATL) (Figure 18).[17] Type 2 (HTLV-2), present in North America primarily among intravenous drug users, has thus far not been classified as carcinogenic.[17, 283] HTLV are the only viruses known to initiate both mammalian and avian tumours.[17]

There are six different subtypes of HTLV-1. Subtype A, commonly referred to as the Cosmopolitan subtype, was the first strain of HTLV-1 identified. Subtype A is found in **endemic** areas such as the Caribbean basin and sub-Saharan Africa.[284] Subtypes B, D, E, and F are primarily located in Central Africa. Subtype E is also found in South Africa. Subtype C is localized to Melanesia.[284]

ATL was identified in Japan in 1977.[285] The associated retrovirus, subsequently named Human T-cell Lymphotrophic Virus Type 1 or Human T-cell Leukemia Virus Type 1, was isolated from ATL cells by two separate teams of researchers.[285,286] This was the first proof of the existence of human retroviruses and of their possible connection with human malignancies.[287]

There are three modes of HTLV-1 transmission: mother-to-child, sexual contact, and parenteral transmission (injection or bood transfusion).[17,284] In endemic areas, transmission occurs primarily through breastfeeding and sexual contact. Conversely, transmission through sexual contact or blood via infection or blood transfusion are the principal means of contracting HTLV-1 in the Western world.[283]

Figure 18: T-cell infected with HTLV-1 (green)



Source: Image copyright Dennis Kunkel

The most effective transmission mode is injection.[284] Various studies have estimated the risk of seroconversion (development of antibodies in the blood as a result of infection) after transfusion of infected blood at 40% to 60%, with a time interval of 51 to 65 days following exposure.[284] Packed red blood cells, whole blood, and platelets are more likely to transmit the virus

than blood plasma.[284] In Canada, screening of blood donors has been in place since 1990 to reduce the risk of transmission during transfusion.[146] Cold storage of blood products can also reduce the risk of transmission.[284] Sharing needles (e.g., between injection drug users) increases transmission risk.[284]

Less than five percent of children of infected mothers contract HTLV-1 infection while in utero or during childbirth; the majority of mother-to-child transmission occurs through breastfeeding, particularly breastfeeding for longer than six months.[17,287] The probability of infection via breastfeeding in children of infected mothers is approximately 10% to 30%, with higher percentages reported among subgroups of children who experienced prolonged periods of breastfeeding.[285,287] Other significant risk factors include the amount of virus in the mother's blood and the antibody titres.[284]

Risk of transmission resulting from sexual contact is associated with unprotected sex, the presence of sores, a high number of lifetime sexual partners, and paying or receiving payment for sex.[284] Some **cross-sectional studies** report a greater risk of females acquiring HTLV-1 from infected males than vice versa, but prospective studies following participants over time have found mixed results.[17,284,287]

The majority of individuals infected with HTLV-1 will remain asymptomatic; as many as 10% of infected individuals, however, are at risk of developing a serious associated disease over the course of their lifetime.[287] Inflammation of the anterior chamber of the eye (uveitis), chronic and **opportunistic** lung infections, inflammation of the thyroid gland, and chronic kidney failure have all been linked with HTLV-1 infection, although definitive epidemiological proof is lacking for some conditions.[284,285] Diagnosis of HTLV-1 infection may also commonly lead to conditions that are psychosocial in nature, such as depression and increased anxiety.[284]

Another related condition, HTLV-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP), is prevalent in all endemic areas and carries a lifetime risk of 0.3% to approximately 4% in HTLV-1 carriers.[287] Affected individuals experience loss of function in the nerves that serve the limbs and organs, as well as weakness, extremity spasms, and urinary and bowel incontinence.[286] In Canada, HAM/TSP has been documented in British Columbia First Nations where HTLV-1 has a know presence.[288]

The presence of HTLV-1 can be determined through screening of blood using various methods. These methods have known limitations, including occasional indeterminate results or the inability to distinguish between HTLV-1 and HTLV-2.[287] In these cases, further tests using **polymerase chain reaction** will allow for viral subtyping, in addition to providing a clear picture of prognosis and disease progression.[284,287]

The **prevalence** of HTLV-1 infection in the general population is not well defined. The vast majority of studies have focused on determining the prevalence of infection in high-risk groups or geographic areas.[284] These studies indicate a greater prevalence of infection in women, particularly those over 50 years of age living in endemic areas.[17,289] Current estimates of worldwide infection range from 10 to 25 million individuals.[17,283,286] HTLV-1 is endemic in southwestern Japan, the Caribbean Basin countries, and sub-

Saharan Africa, and in indigenous peoples or localized areas of Melanesia, Papua New Guinea, the Solomon Islands, Iran, the Philippines, and Australia.[282,284,286] Measured **seroprevalence** is high in South American at-risk groups, but a lack of general population studies precludes conclusive determination of endemic infection across the continent.[284] Studies of indigenous peoples in the Americas have found that HTLV-2 is endemic in many tribes, however, HTLV-1 infection is more rare.[282,288,290,291] HTLV-1 infection is present among British Columbian First Nations and Nunavut Nunavummiut.[282,288,290,291]

Although HTLV-1 infection is not a reportable disease in most jurisdictions, Canadian seroprevalence has been estimated at 0.0014% to 0.0018%.[146,291] The Canadian Blood Services began screening blood donors for HTLV-1 in 1990. On average, 10 to 12 positive tests per 800,000 donations occur annually.[291] In Nunavut, the small population results in a higher prevalence of infection, despite the low number of infected individuals.[291] A study to determine HTLV-1 prevalence with greater precision was conducted by the Nunavut Department of Health and Social Services and the Public Health Agency of Canada. To date, the full report has not been made public, however, news outlets report HTLV-1 infection prevalence of 0.37% in the territory and three known cases of associated-ATL.[292,293]

A 1994 study that was extended in 2002, tested First Nations individuals entering drug and alcohol treatment centres for HTLV infections.[282,288] The prevalence of HTLV-1 infection was 5.6 per 1000 (95% **Confidence Interval**: 2.3-9.0).[282] This rate was much higher than that measured in Canadian blood donors but much lower than the 15% valence found in some endemic areas.[282] Women had higher prevalence (8.3/1000) than men (3.1/1000). The vast majority of infected individuals were residents of Vancouver Island.[282]

In the case of families immigrating from endemic to non-endemic areas, there is a marked decrease of prevalence in subsequent generations.[284] Regardless, measured seroprevalence in non-endemic areas is primarily a result of the emigration of HTLV-1 carriers from endemic areas.[17] Chiavetta et al. (1992) compared blood samples among 853 Toronto (Ontario) residents. While none of the individuals of Canadian origin tested positive for HTLV-1, serum from 2.3% of immigrants from the Caribbean, an endemic area, tested positive.[289]

HTLV-1 and Cancer

ATL was first reported in Kyoto, Japan. Additional reports of patients in southwestern Japan, Caribbean immigrants in the United Kingdom, and patients from other endemic regions followed.[284] Initially, the observation of clustering within certain age groups led to the consideration that this new disease was related to a virus.[284] Geographical, immunological, molecular, genetic, and serological findings have established a causal link between ATL and HTLV-1.[285]

There are four different types of ATL: acute, chronic, smoldering, and lymphoma type. The majority of ATL cases (55% to 75%) are acute.[284] Without treatment, acute ATL is rapidly and invariably fatal. The principal causes of death, in addition to impairment of **T-cell** function and immunodeficiency, are pulmonary complications, opportunistic infections, sepsis (presence of bacteria or their toxins in blood or tissues), and

hypercalcemia (abnormally high level of calcium in the blood).[284,286]

The data regarding **incidence** and prevalence of ATL are scarce. Given the rapid disease course and difficulties with correct diagnostic classification, reported ATL rates are likely an underestimation, especially in developing countries where there is particular difficulty confirming ATL.[284] In Canada, there are documented cases of ATL in First Nations individuals of British Columbia and Nunavut.[288,292,293] Since 2005, three individuals in Nunavut have died of ATL attributed to HTLV-1 infection.[292,293]

From the data available, high levels of ATL incidence correspond with reported high prevalence of HTLV-1 infection.[285] In HTLV-1 carriers, the cumulative ATL incidence is estimated at 1% to 5%.[17,284] HTLV-1 infection acquired during childhood may carry higher risk of ATL.[284] While more females than males are HTLV-1 carriers in the general population, the ratio of male to female ATL incidence is 1.4:1.0.[285] In 2002, the expected ATL incidence among carriers was 1,302 per 100,000 male carriers and 659 per 100,000 female carriers.[28] Familial clustering suggests the influence of genetic background in ATL development.[294]

ATL occurs primarily in areas where HTLV-1 infection is endemic. Cases in other areas, including the United States and Europe, mostly involve immigrants from endemic areas and their children.[17] In Japan, an estimated 1.2 million individuals are HTLV-1 seropositive and more than 800 cases of ATL are diagnosed per year.[286] The cumulative risk of developing ATL in the presence of HTLV-1 in Japan is 6.6% in men and 2.1% in women.[286]

Multiple studies have established a relationship between HTLV-1 infection and ATL development based on geographic correspondence, similarities among leukemic cells, tumour development in animal models, the presence of infection in 80% to 90% of ATL cases in endemic regions, and the ability to culture HTLV-1 from ATL cells.[17,284] **Case-control studies** have also implicated HTLV-1 infection in tumours of the vagina, cervix, and liver; nevertheless, these associations are inconclusive.[17]

Prevention, Treatment, and Control

Effective prevention of HTLV-1 infection requires a multi-faceted approach. Important initiatives include counseling and education to implement safe sexual behaviour and harm reduction practices among injection drug users.[282,284] Screening for HTLV antibodies in pregnant women and blood donors is an essential transmission prevention practice.[284] In Canada, screening and storage procedures have virtually eliminated the risk of contracting HTLV via transfusion.[295] Prenatal screening for maternal infection to prevent mother-to-child transmission via breastfeeding is vital, as avoiding breastfeeding can decrease mother-to-child transmission rates by 80%.[294] Breastfeeding for less than seven months may limit transmission while retaining the benefits of breastfeeding, and freezing breast milk prior to consumption may also reduce transmission.[292] In developing countries, however, when breastfeeding is discouraged, some studies have suggested the possibility of increased malnutrition and infant mortality when additional nutritional resources were not supplied to infected mothers.[284,287]

To aid prevention efforts, work is continuing towards development of a HTLV-1 vaccine. Although animals have been successfully immunized against HTLV-1 infection, a preventive vaccine for humans is not yet available.[283,284]

Currently, there are no recommended treatments for HTLV-1 carriers. Precautions regarding routes of transmission are given to individuals who test positive. Recommendations include condom use, bottle-feeding for infants of infected mothers, and education on safe needle use. Aside from practices to prevent transmission to others, little can be done.[282] Any treatment given is primarily for relief of the symptoms of HTLV-1 associated diseases.[287]

Future Directions

Development of a vaccine and other preventive measures are important research goals. While work continues on a cheap and preferably oral human vaccine, other methods to prevent HTLV-1 transmission and to stem the growing numbers of infected individuals should not be ignored.[283] Several promising studies are working towards the goal of improving therapeutic outcome. There is a need for novel therapeutic strategies based on the mechanisms of ATL.[294]

CONCLUSION

Over the last 30 years, there has been growth in the number of cancer cases and cancer deaths in Canada. Because these rate increases are mainly due to population growth and aging, these trends are expected to continue.[30] In 2009, it was estimated that over 65,000 Ontarians would be diagnosed with cancer, and that 27,900 would die from the disease.[30] While demographic trends cannot be controlled, a substantial proportion of cancers can be prevented. Cancer prevention results in a reduction in cancer mortality, by way of reduced cancer **incidence**. Because cancer is an important issue in Ontario that affects many residents, prevention efforts that can reduce the impact of cancer should be explored.

The epidemiologic term 'attributable fraction' refers to the proportion of a disease that could be eliminated if an exposure were eliminated.[35] Although likely an underestimate (due to data limitations), approximately 18% of all cancers can be attributed to infectious agents. Viral infections are responsible for the bulk of these cancers (12%), the bacterium *Helicobacter pylori* is responsible for another 5.6% of cancers, and parasitic agents account for an additional, small proportion of global cancer incidence.[28] Infectious agents are responsible for 26% of cancers in developing nations, and 8% of cancers in industrialized nations.[28] To put these numbers into perspective, with respect to some other well-known causes of cancer, it has been estimated that: inherited cancer syndromes account for up to 4% of all cancers; up to 30% of cancers are likely to be related to diet and nutrition; and, in most industrialized nations, tobacco consumption accounts for up to 30% of all malignant tumours.[296] Among the causes of cancer, **carcinogenic** infections are important.

Carcinogenic infections are preventable

Unlike cancers caused by genetics, or by lifestyle factors such as smoking, an infection is a definite, specific event that can, theoretically, be prevented.[297] The discovery of an infectious etiology for many cancers raises hope for prevention and treatment, particularly with respect to cancers of the cervix, stomach, and liver.[296]

Preventing carcinogenic infections requires political will, resources, and a shared strategy between government and non-government organizations.[296] As this document has demonstrated, a number of approaches are being used that reduce the impact of carcinogenic infections, including:

- avoidance of exposure, e.g., through safer sex practices, the use of disposable medical equipment, and improvements in hygiene and sanitation;
- behavioural change, e.g., avoiding co-infection;
- medications, e.g., praziquantel for liver fluke infections, antibiotics for *H. pylori* infection, and **anti-viral** drugs for Hepatitis C infection;
- prophylactic vaccinations, e.g. against HPV and HBV;
- screening, e.g., HPV DNA tests and **Pap tests** for cervical lesions; and
- early treatment of cancer pre-cursors, e.g., surgical excision.

Future directions

Future directions in the area of infectious agents and cancer are wide ranging. There is a need for:

- accurate infection **prevalence** estimates;
- greater understanding of the role of co-infections and other co-factors that lead to cancer (i.e., what leads to **carcinogenesis** in some but not all of those infected);
- accessible, effective vaccines with known duration of protection (prophylactic, therapeutic);
- affordable, effective treatments (anti-viral, antibiotic) with minimal side effects;
- monitoring of the impact of prevention efforts, including process measures (e.g., percent of population vaccinated, screened);
- a public health focus on transmission prevention, screening, and treatment;
- research into emerging infectious agents, and exploration into other cancers with an infectious etiology;
- understanding of the implications of vaccine development and infection treatment; and
- public and physician education about all carcinogenic infectious agents, including those that are less common, and likely to become more common over time.

There is a need for mass screening that is affordable, sensitive, and specific, but screening must only be for those agents where there is: demonstrated screening effectiveness, sufficient resources, significant prevalence, effective treatments, and capacity for follow-up.[296]

The list of infectious agents associated with cancer, either proven or theoretical, is growing, as is the list of cancers being studied for an infectious etiology. Attributing a cancer to a particular infectious agent shows a clear path to prevention through elimination of the exposure (infection or its carcinogenic actions). This has understandably led to scientific and government attention, with definite public health implications.[297]

Sensitive detection methods are increasingly available, as are effective treatments and vaccines, but, as this document has shown, there are major gaps in our knowledge,[35] and there is a need for a concerted effort with respect to these agents. If carcinogenic infectious agents became a focus of research and public health, there is the potential for a substantial reduction in the burden of cancer in Ontario.

GLOSSARY

Antigen
A substance (e.g., protein, polysaccharide, glycolipid, tissue transplant) capable of inducing a specific immune response. The introduction of an antigen may be by invasion of infectious organisms, immunization, inhalation, ingestion, etc.

Antioxidant
A substance that protects cells from the damage caused by free radicals (unstable molecules made by the process of oxidation during normal metabolism). Free radicals may play a part in cancer, heart disease, stroke, and other diseases of aging. Antioxidants include beta-carotene, lycopene, vitamins A, C, and E, and other natural and manufactured substances.

Anti-viral
A drug used to treat infections caused by viruses.

Arthropod
A member of a large group of animals that possess a hard external skeleton and jointed legs and other appendages. Many arthropods are of medical importance, including mites, ticks, and insects.

Atrophic gastritis
Chronic gastritis with thinning of the mucous membrane and destruction of the pepsin secreting glands, sometimes associated with pernicious anemia (caused by deformed red blood cells) or gastric cancer. The term is also applied to gastric atrophy without inflammatory changes.

B-cell (B-lymphocyte)
A white blood cell from bone marrow. As part of the immune system, B-lymphocytes make antibodies and help fight infections.

Carcinogen (Carcinogenic)
An agent that can cause cancer.

Carcinogenesis
The process by which cancer develops.

Case-control study
The observational epidemiologic study of persons with the disease (or other outcome variable) of interest and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently the attribute is present or, if quantitative, the levels of the attribute, in each of the groups. In short, the past history of exposure to a suspected risk factor is compared between 'cases' and 'controls'.

Cholangiocarcinoma
A rare type of cancer that develops in cells that line the bile ducts in the liver.

Cohort study
The analytic method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of a cohort study is the observation of large numbers of individuals over a long period (commonly years) with comparison of incidence rates in groups that differ in exposure levels.

Colposcopy
The examination of the vagina and cervix with a low-power stereoscopic binocular field microscope and a powerful light source.

Confidence Interval
Measurement of confidence in the accuracy of a rate. 95% Confidence Interval implies there is 95% confidence that the rate falls between the two limits.

Cross-sectional study
A study that examines the relationship between diseases (or other health-related characteristics) and other variables of interest in a defined population at one time. The presence or absence of disease and the presence or absence of the other variables (or, if they are quantitative, their level) are determined in each member of the study population or in a representative sample at one particular time.

Cytopathological
A term that denotes cellular changes in disease. The term relates to cytopathology.

Disability-adjusted life years (DALYs)
A measure of the burden of disease in a defined population, and a measure of intervention effectiveness. DALYs are claimed to be a valid indicator of population health, and are based on the adjustment of life expectancy in order to allow for long-term disability, as estimated from official statistics. DALYs are calculated using a 'disability weight' (a proportion less than one) multiplied by chronologic age to reflect the burden of the disability.

DNA repair genes
A gene engaged in damaged DNA repair. When a DNA repair gene is altered, mutations accumulate throughout the DNA.

Efficacy
In clinical epidemiology, indicates the extent to which a specific intervention, procedure, regimen, or service produces a beneficial result, under ideal conditions. Also refers to the benefit or utility to the individual or the population of the service, treatment regimen, or intervention.

Endemic
Denotes a temporal pattern of disease occurrence in a population in which the disease occurs with predictable regularity with only relatively minor fluctuations in its frequency over time.

Episome
A closed circular nuclear molecule of viral DNA that associates with chromosomal material.

Epithelium
A thin layer of cells that covers the organs, glands, and other structures within the body.

Epithelial
Refers to the cells that line the internal and external surfaces of the body.

Fibrosis
The growth of fibrous tissue.

Gastritis
Inflammation of the lining of the stomach.

Genome
The array of genes carried by an individual.

Genotype
The genetic constitution inherited by an organism or a person, as distinct from physical characteristics and appearance that emerge with development, i.e., phenotype.

Genus
A taxonomic category that ranks below a family and above a species and generally consisting of a group of species exhibiting similar characteristics. In taxonomic nomenclature, the genus name is used, either alone or followed by a Latin adjective or epithet, to form the name of a species.

Gram-negative bacteria
Bacteria which fail to stain with crystal violet that are stained pink when treated by Gram's method. The other type of bacteria is Gram-positive.

Hemodialysis
Dialysis of soluble substances and water from the blood by diffusion through a semi-permeable membrane. Separation of cellular elements and colloids from soluble substances is achieved by pore size in the membrane and rates of diffusion.

Hemophiliac
A person suffering from hemophilia (a group of hereditary disorders in which affected individuals fail to make enough of the proteins needed to form blood clots).

Hepatic
Refers to the liver.

Herpesvirus
A member of the herpes family of viruses.

Holoendemic
A disease for which a high prevalent level of infection begins early in life and affects most of the child population, leading to a state of equilibrium such that the adult population shows evidence of the disease much less commonly than the children. Malaria in many communities is holoendemic.

HPV DNA testing
Machine-read laboratory procedure that searches/detects HPV DNA in cellular samples obtained from the cervix or other squamous epithelial membranes.

Iatrogenic
Denoting a response to medical or surgical treatment that is usually unfavorable.

Immortalization
Normal cells cultured in the lab with an infinite lifespan, from spontaneous mutation, exposure to chemical carcinogens, or viral infection. Immortalization of primary cells in culture is the first of several steps in the expression of transforming genes of DNA tumour viruses, of retrovirus oncogenes, and cellular oncogenes derived from human cancer cells.

Immunocompromised
Having a weakened immune system caused by certain diseases or treatments.

Immunodeficient (Immunosuppressed)
Lacking in some essential function of the immune system. People are said to be immunosuppressed when they have an immunodeficiency disorder.

Immunodiagnostic
The process of determining specified immunologic characteristics of individuals or of cells, sera, or other biologic specimens.

in vitro
Occurring in the laboratory (outside the body). The opposite of *in vivo* (in the body).

Incidence
The number of instances of illness commencing, or of persons falling ill, during a given period in a specified, previously disease-free population. More generally, incidence refers to the number of new events, i.e., new cases of a disease in a defined population, within a specified period of time.

Inhibitor
An agent that restrains or retards physiologic, chemical, or enzymatic action.

Intrahepatic bile duct
A bile duct that passes through and drains bile from the liver.

Latent (infection)
Indicates the persistence of an infectious agent within the host without symptoms (often without demonstrable presence in blood, tissues, or bodily secretions of host). When an infection is latent, the host is not infectious to others.

Liquid-based cytology (LBC)
A relatively new technology intended to improve the detection of cytological abnormalities. LBC involves the collection and placement of cervical cells into vials containing fixative solution, automated processing, and transfer of cells onto glass slides and their staining. LBC provides a thin layer of uniform cellular preparations, free of blood and inflammatory cells, which are easier to screen than conventional Pap tests. This test is expensive in terms of equipment, capital costs, maintenance, consumables, training, technical preparation time, transportation, and disposal of liquid media.

Liver cirrhosis
A condition in which the liver responds to injury or death of some of its cells by producing interlacing strands of fibrous tissue between which are nodules of regenerating cells. Causes include alcoholism, viral hepatitis, chronic obstruction of the common bile duct, autoimmune diseases, and chronic heart failure. In at least half of cirrhosis cases no cause is found. Cirrhosis cannot be cured, but its progress may be stopped if the cause can be removed or if it can be treated by liver transplantation.

Lymphocyte
Lymphocytes are a type of white blood cell. Lymphocytes have a number of roles in the immune system, including the production of antibodies and other substances that fight infections and other diseases.

Meta-analysis
A statistical synthesis of pooled data from separate but similar, i.e., comparable, studies, leading to a quantitative summary of results. In the biomedical sciences, the systematic, organized, and structured evaluation of a problem of interest, using information (commonly in the form of statistical tables or other data) from a number of independent studies of the problem.

Mononucleosis
Infectious mononucleosis is an acute febrile illness of young adults, caused by the Epstein-Barr Virus, frequently spread by saliva transfer. Symptoms include fever, fatigue, sore throat, and swollen lymph nodes. Mononucleosis is also called 'mono'.

Odds Ratio
A measure of the odds of an event happening in one group compared to the odds of it happening in another group. In cancer research odds ratios greater than one mean the exposure may increase the risk of cancer, and an odds ratio of less than one means the exposure may reduce the risk of cancer.

Oncogene
A gene that can cause the abnormal transformation of a cell. Oncogenes are slightly transformed equivalents of normal genes.

Oncogenic
A substance, organism, or environment known to be a causal factor in tumour production. Some viruses are considered to be oncogenic, including papillomaviruses, retroviruses, certain adenoviruses and herpesviruses, and the Epstein-Barr virus.

Opportunistic Infection
Infection with organism(s) that are normally innocuous, but become pathogenic when the body's immunologic defenses are compromised, e.g., in Acquired Immunodeficiency Syndrome (AIDS).

Pap test
A procedure in which cells are scraped from the cervix and examined under a microscope. The Pap test is used to detect cancer and cellular changes that may lead to cancer. A Pap test can also show non-cancerous conditions, such as infection or inflammation. These tests are also called Pap smears. The test was named after its inventor, Dr. Papanicolaou.

Pathogen
An organism capable of causing disease (literally, causing a pathological process).

Polymerase chain reaction
A laboratory method used to make many copies of a specific DNA sequence. Also called PCR.

Prevalence
The number of new and old cases of disease in a given population at a designated time. The term usually refers to the situation at a specified point in time (point prevalence), but may refer to a duration of time (period prevalence).

Randomized controlled trials
An epidemiologic experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental, preventive, or therapeutic procedure, maneuver, or intervention. Results are assessed by rigorous comparison of rates of disease, death, recovery, or another appropriate outcome in the study and control groups. Randomized controlled trials are generally regarded as the most scientifically rigorous method for hypothesis testing available in epidemiology.

Relative Risk
The ratio of risk (disease or death) among the exposed versus the unexposed. This is synonymous with risk ratio.

Retrovirus
This name is given to a family of RNA viruses characterized by the presence of an enzyme (reverse transcriptase) enabling transcription of RNA to DNA inside an affected cell. Thus, retroviruses can make copies of themselves in host cells. The most important retrovirus is the Human Immunodeficiency Virus (HIV); which makes copies of itself in host cells such as T4 'helper' lymphocytes, responsible for immune competence.

Sensitivity
The proportion of truly diseased persons in the screened population identified as diseased by a screening test. Sensitivity is a measure of the probability of correctly diagnosing a case, or the probability that any given case will be identified by the test. It indirectly measures the false-negative rate.

Seroprevalence
The fraction of a population with antibodies against a specific pathogen, as measured by serologic testing.

Serotypes
The categories into which material is placed, based on its serological activity, particularly in terms of the antigens it contains or the antibodies that may be produced against it. Thus, bacteria of the same species may be subdivided into serotypes that produce slightly different antigens. The serotype of an infective organism is important when treatment or prophylaxis with a vaccine is being considered.

Specificity
The proportion of non-diseased persons who are so identified by a screening test. Measures the probability of correctly identifying a non-diseased person with screening. It indirectly measures the false-positive rate.

Squamous-cell carcinoma
Cancer that begins in squamous cells, which are thin, flat cells that look like fish scales. Squamous cells are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the passages of the respiratory and digestive tracts.

Superoxide Radical
A highly reactive compound produced when oxygen is reduced by one electron.

Synergistic (synergy)
Under an additive model, a situation in which the combined effect of two or more factors is greater than the sum of their solitary effects. Any joint effect that is more than additive is synergistic.

T-cell (helpers)
A type of white blood cell (called a lymphocyte) that helps stimulate immune reactions.

Tat protein
A small protein produced by a lentivirus (as HIV) within infected cells. This protein greatly increases viral transcription and replication, and is also secreted extra-cellularly, which plays a role in increasing the viral replication of newly infected cells, and in enhancing the susceptibility of T-cells to infection.

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ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
ATL	Adult T-Cell Lymphoma/Leukemia
CCA	Cholangiocarcinoma
CCO	Cancer Care Ontario
CD4	Cluster of Differentiation 4
DNA	Deoxyribonucleic Acid
EBV	Epstein-Barr Virus
HAART	Highly Active Antiretroviral Therapy
HAM/TSP	HTLV-Associated Myelopathy/Tropical Spastic Paraparesis
HBsAg	Hepatitis B Surface Antigen
HBeAg	Hepatitis B Antigen that indicates high HBV infectivity
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HHV-8	Human Herpesvirus 8
HIV	Human Immunodeficity Virus
HPV	Human Papillomavirus
HTLV-1	Human T-Cell Lymphotropic/Leukemia Virus Type 1
IARC	International Agency for Research on Cancer
ICC	Invasive Cervical Cancer
KS	Kaposi's Sarcoma
KSHV	Kaposi's Sarcoma Associated Herpervirus
LBC	Liquid-Based Cytology
LEEP	Loop Electrical Excision Procedures
LSIL	Low-Grade Squamous Intraepithelial Lesions
MALT	Mucosa-Associated Lymphoid Tissue
MCD	Multicentric Castleman Disease
NHL	Non-Hodgkin Lymphoma
PEL	Primary Effusion Lymphoma
RNA	Ribonucleic Acid
WHO	World Health Organization

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