Cancer and Infectious Agents

An Overview of Effective Interventions

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Report Prepared For

By

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Executive Summary

> *At present, information concerning the role of viruses in the pathogenesis of human neoplasms is fragmented and incomplete. It is clear that their role is complex, and a complete understanding of the intricacies involved in viral interaction with the human genome may still take many years.*[1]

The International Agency for Research on Cancer has now confirmed 7 viral or bacterial agents as carcinogenic in humans. Cancers of the stomach, liver and cervix rank among the most prevalent ones with a viral or bacterial origin. These three cancers also represent some of the highest attribution rates with respect to a pathogen (see the table below); for instance, virtually every cervical cancer case is positive for the presence of one or more types of the human papillomavirus.

Agent	*Main associated cancer*	*Annual incidence of cancer (developed countries)*	*Proportion of specific cancer attributable to infection*
Human papillomavirus - various types	Cervix	100,000	90 to 100%
Hepatitis B / C virus	Liver	106,000	80%
Helicobacter pylori	Stomach	333,000	70%
Epstein-Barr virus	Hodgkin's disease; non-Hodgkin's lymphoma	264,000	30-90%
Human immuno-deficiency virus type 1 as co-factor	Kaposi sarcoma	8,600	
Human T cell lymphotrophic v. type I	Leukemia		1%
Human herpesvirus type 8 - probable	Kaposi sarcoma	8,600	

As reflected in the preceding table, the impact of infection-associated cancer is more substantial than sometimes realized by the general public. In fact, in the developed world, about 7% of total cancer incidence has been attributed to one or more infectious agent. After tobacco use, infections as a class may be the most important preventable cause of cancer, a fact of potentially tremendous significance for both individual and population health. Both an ageing population and the effect of disease latency means that cancers with an infectious cause will continue to be a significant burden in Canada for some time to come.

We examine each of the main pathogens seen in developed countries, in order to identify and evaluate the interventions available at various stages of exposure and disease development. These include:

[1] Phelan JA. Viruses and neoplastic growth. *Dental Clinics of North America.* 2003; 47(3): 533-43.

1. Early primary prevention: limiting exposure to the pathogen.
2. Primary prevention: stopping the establishment of infection (e.g., through prophylactic vaccination).
3. Secondary prevention: interrupting full cancer development once infection is present (including detecting and treating the infection or precancerous cells and lesions before cancer becomes established, e.g., using therapeutic vaccination).

While there have been success stories, such as a dramatic drop in cervical cancer incidence, much more progress is needed. The following table summarizes both the current and proposed strategies for the main pathogens discussed in this report.

Agent	*Transmission*	*Successful Prevention*	*Ineffective Approaches*	*Emerging or Debated Measures*
Human papillomavirus - various types	Sexual intercourse	Counselling; Screening & excision	Mass media & education; Condoms	HPV testing; Vaccine; Anti-virals
Hepatitis B / C virus	Contaminated blood; esp. via sexual activity (HBV) & injected drug use (HCV)	Counselling; Needle exchanges (mixed evidence); Protecting the blood supply; HBV vaccine; Anti-virals; Surgery	Mass media & education around sexual practices	Integrated injecting drug use programs; Combination therapies
Helicobacter pylori	Consuming, e.g., contamin-ated water	Combination therapy; Surgery		Universal screening & eradication
Epstein-Barr virus	Salivary contact			Immune system restoration; Anti-virals; Vaccine
Human immuno-deficiency virus type 1	Various body fluids, esp. in sexual contact	Programs integrating voluntary testing, counselling, and condom use; Programs re: injected drug use; Anti-virals, incl. in pregnancy	Single interventions to modify sexual practice	Vaccine; Prophylactic anti-virals
Human T cell lymphotrophic v. type I	Sexual contact & injected drug use			Preventing exposure
Human herpesvirus-8 - probable agent	Sexual contact, esp. homosexual men, commercial sex workers	Anti-virals		Preventing exposure

Several conclusions and recommendations emerged as we covered the terrain of infection-associated cancers.

Burden: Although some infection-related cancers are dropping in incidence, various factors are keeping the prevalence and mortality burden of these diseases at a high level in the Canadian population. Complacency is not an option.

Levels of Prevention: Intervening to limit the exposure to the pathogen in the first place, if practical, is certainly an ideal. If such early primary prevention is not

possible, then classic primary prevention must be pursued; with infections, the "gold standard" approach is prophylactic vaccines which prevent any exposure from becoming a serious problem. If infection does become established, then measures need to be taken to ensure that any detected precancerous or cancerous conditions do not progress any further.

Cost Considerations: A complicating factor is that some interventions are more cost-effective than others. For example, there is debate about whether testing for HPV (to prompt primary prevention, if possible) is worth the expense, especially in reference to highly effective cytological screening, which detects precancer or the early stages of cervical cancer and then prompts appropriate secondary prevention.

A Public Health Focus on Sexually Transmitted Infections: Since many of the pathogens covered in this report are sexually transmitted, much of the discussion of early primary prevention revolves around reducing the risk of sexual behaviours. This is a crucial area of public health, albeit a sensitive and challenging one. A program incorporating multiple interventions should be considered. To learn what a multi-faceted campaign would need to look like, we could closely examine the pilot projects set up in various jurisdictions to help, for example, injection drug users.

Ongoing Investment in Research: Greater insight into transmission, co-factors, and carcinogenesis will allow enhancements of the prevention armamentarium, ultimately allowing the disease burden of the various cancers to be reduced and possibly removed. The development and imminent launch of vaccines for HPV promises a brand new era for cervical cancer prevention, though many implementation questions remain unanswered. Continued study of other potential etiologic agents is vital in the overall battle against cancer; the potential for disease prevention represented by each of the candidate pathogens makes this a truly exciting area of medical research.

The Temptation of Technology: As captivating as new health technologies can be, it is also important to continue focusing on the classic "low-tech" public health options related to early primary prevention, including initiatives involving media advocacy, education and counselling. The modest record of progress in this regard, even with high-profile agents such as HIV, is very sobering. Planners also need to be wary of inappropriately supplanting old technologies with new. For instance, some authorities are suggesting that a new HPV vaccine should work alongside classic screening programs for up to 20 years.

It is clear that a strong coalition between researchers, clinicians, public health managers and funders will be required to navigate through the complex data and policy options and ultimately achieve the sort of prevention breakthroughs desired with the various infections and related cancers described in this report.

Introduction

The fact that viral infections can cause cancer has been suspected for over a 100 years, beginning with the observed connection between cervical cancer and multiple sexual partners.[2] By 1911, the *Journal of the American Medical Association* had reported on the association between viruses and cancer in animals. Proof of causality has proven more elusive, but slowly the research support for implicating specific pathogens has emerged.[3] The International Agency for Research on Cancer has now confirmed 7 viral or bacterial agents as carcinogenic in humans.[4] Cancers of the stomach, liver and cervix rank among the most prevalent ones with a viral or bacterial origin.

Several parasitical worms or flukes (known collectively as helminths) have been added to the list of proven or probable carcinogens. In fact, the blood fluke called *Schistosoma haematobium* was linked with bladder carcinoma as early as the middle of the 19th century.

The etiology and mechanisms of infection-based cancer have been important areas of study, generating several Nobel prizes in recent years.[5] Two features have spurred on the research:

- the study of viral carcinogenesis has offered a wealth of insight into the general cellular mechanisms of cancer.[6]
- an infectious origin for a particular cancer holds out the promise that such disease is actually *preventable*.

The impact of infection-associated cancer is more substantial than sometimes realized by the general public. Kuper and colleagues noted that "following tobacco use, infections as a group may be the most important preventable cause of cancer in humans."[7] Worldwide, the proportion of cancer attributable to infections with viruses, bacteria and parasites is estimated to be 15-16%, or 1.2 to 1.5 million new cases a year.[8,9,10] Some of these agents are less common in developed countries, so the proportion of cancers associated with infections may be half as much as the global rate.[11] For instance, in the US, about 7% of total cancer incidence has been

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[2] Moscicki AB, Palefsky J, Gonzales J et al. Human papillomavirus infection in sexually active adolescent females: prevalence and risk factors. *Pediatric Research.* 1990; 28(5): 507-13.
[3] Such agents are referred to as being carcinogenic or oncogenic.
[4] Herrera LA, Benitez-Bribiesca L, Mohar A et al. Role of infectious diseases in human carcinogenesis. *Environmental & Molecular Mutagenesis.* 2005; 45(2-3): 284-303. See Appendix A.
[5] Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. *Journal of Internal Medicine.* 2000; 248(3): 171-83.
[6] Butel JS. Viral carcinogenesis: revelation of molecular mechanisms and etiology of human disease. *Carcinogenesis.* 2000; 21(3): 405-26.
[7] Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. *Journal of Internal Medicine.* 2000; 248(3): 171-83.
[8] *Evidence-based Cancer Prevention Strategies for NGOs*. International Union Against Cancer; 2004.
[9] Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. *Journal of Internal Medicine.* 2000; 248(3): 171-83.
[10] Pisani P, Parkin DM, Munoz N et al. Cancer and infection: estimates of the attributable fraction in 1990. *Cancer Epidemiology, Biomarkers & Prevention.* 1997; 6(6): 387-400.
[11] Herrera LA, Benitez-Bribiesca L, Mohar A et al. Role of infectious diseases in human carcinogenesis. *Environmental & Molecular Mutagenesis.* 2005; 45(2-3): 284-303.

attributed to one or more infectious agent.[12] It is important to note that improved serological techniques may eventually reveal an even greater role for infection in the phenomenon of carcinogenesis.[13]

We will provide an overview of the pathogens associated with cancer, their disease mechanism and burden, before turning to a detailed presentation on each agent. The latter material will especially focus on the prevention and other management strategies that could be used to reduce the prevalence of infection-related cancer.

Overview of Agents and Disease Burden

As noted above, several viruses, bacteria and even microscopic parasites are involved in the development of cancer in humans. A couple of features are shared by these agents. First, they are often highly prevalent in populations, whereas malignancies in infected people are much rarer. For example, half the world's population harbours *Helicobacter pylori*, but only 1% develops gastric cancer.[14] Second, there is a prolonged latency period between initial infection and cancer development, during which time the agent persists in the host. Taken together, these facts suggest that cancers linked to infections follow the general pattern of most cancers, i.e., they are *multi-factorial*. In other words, infections are usually not sufficient for carcinogenesis; co-factors are required to promote both initiation and progression. One such factor, host genetic susceptibility, represents a particularly intense area of research.

Many synergies between infectious agents and other "environmental" factors are also being discovered; the latter include tobacco use, alcohol consumption and specific dietary components. Different infectious agents seem to interact with each other to create an additive or even multiplicative effect in terms of disease onset and progress. Human immunodeficiency virus type 1 (HIV-1) shows this effect with a number of other pathogens; another example is hepatitis B and C, which interact synergistically in the development of liver cancer.[15]

Some of these characteristics—prevalence in the general population, long latency, the role of other interacting factors—make the identification of causal relationships difficult. The etiology, or the causation, of disease is a notoriously complex area of medicine. When an agent is detected in tumours, there is no guarantee that it produced the cancer. Confirmation of an etiologic link requires a combination of epidemiological data, biological plausibility, and demonstrations of cellular proliferation in animal-based or *in vitro* studies. The ongoing work of confirming causation is reflected in the disparate inventories of cancer-linked infections provided in the appendices; because of political-legal implications, some government agencies are more "conservative" in adding agents to their list, as compared with the more

[12] Mueller NE. Cancers caused by infections: unequal burdens. *Cancer Epidemiology, Biomarkers & Prevention.* 2003; 12(3): 237s.
[13] Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. *Journal of Internal Medicine.* 2000; 248(3): 171-83.
[14] Herrera LA, Benitez-Bribiesca L, Mohar A et al. Role of infectious diseases in human carcinogenesis. *Environmental & Molecular Mutagenesis.* 2005; 45(2-3): 284-303.
[15] Donato F, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *International Journal of Cancer.* 1998; 75(3): 347-54.

expansive conclusions that may be drawn by academics and, especially, advocacy groups.

A final complicating factor in causation studies involves teasing apart the many subtypes of the carcinogenic viruses. For example, there are over 100 genotypes seen in human papillomavirus, but only a subset of these show a high risk for cancer development.[16]

The Cancers: Burden and Trends

The cancers with a significant infectious origin are not marginal. For example, stomach cancer, associated with the bacteria *Helicobacter pylori*, is the fourth most frequent cancer in the world, with 876,000 new cases in the year 2000. Liver cancer, with its strong association with the hepatitis viruses, is the fifth most common cancer globally and one of the leading causes of cancer death. Cervical cancer, with its well-known connection to the human papillomavirus, is the second most common type (after breast cancer) among women worldwide.[17] Augmenting the basic prevalence statistics is the fact that each of these cancers exhibit high rates of morbidity and mortality.

Although some key infection-linked cancers, such as Hodgkin's disease and gastric and cervical cancer, show continuing decline in incidence in Canada, we cannot afford to be complacent. The reality is that, often due to a growing and, mostly, ageing population,[18] the *absolute* numbers and / or mortality burdens of some relevant cancers (e.g., non-Hodgkin's lymphoma) continue to climb across the country and throughout the developed world. Disease latency also affects the trend-lines, increasing the impact over time of a disease such as cervical cancers (which tends to be diagnosed at a relatively young age); thus, even though cervical cancer rates are down, mortality attributable to this cancer is actually up in Canada.[19] In sum, the cancers associated with infections represent the loss of thousands of human lives. Thus, to quote international authorities, there is no question that "these specific oncogenic infections should be identified, monitored, and treated when indicated."[20]

Geographical Variation of Disease

A complicating feature of global public health policies related to infection-based cancers is the wide variation in prevalence of the agent and / or the cancer, especially comparing developed and developing countries. For example, almost two-thirds of stomach cancer cases occur in the developing world, and cervical cancer follows a similar pattern. Likewise, only about 20% of liver cancer cases occur in the industrialized world, and they account for only 1% of total cancer cases in, for

[16] Munoz N, Bosch FX, de Sanjose S et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine.* 2003; 348(6): 518-27.
[17] Parkin DM. International variation. *Oncogene.* 2004; 23(38): 6329-40.
[18] For example, stomach cancer is largely a disease of older age. Age-specific incidence and mortality rates do not begin to rise until age 40, and like many cancers, rates increase steeply only after age 50 (note: in Ireland, recent statistics showed that only about 1% of stomach cancer cases were in patients below age 35). These demographic factors explain why the incidence burden (total number of cases) of stomach cancer showed no percentage change for men in Canada over 1992-2001, even though the rate of stomach cancer has steadily declined.
[19] Canadian Cancer Society. *Canadian Cancer Statistics 2005.*
[20] Herrera LA, Benitez-Bribiesca L, Mohar A et al. Role of infectious diseases in human carcinogenesis. *Environmental & Molecular Mutagenesis.* 2005; 45(2-3): 284-303.

example, North America (compared to, for instance, 50% of cancer cases in China); however, the extremely high mortality rate with liver cancer somewhat mitigates any comfort among developed nations that may be derived from such statistics. Epidemiological studies confirm that the pattern of liver cancer can be largely explained by the worldwide distribution of chronic hepatitis infection, especially hepatitis B.[21]

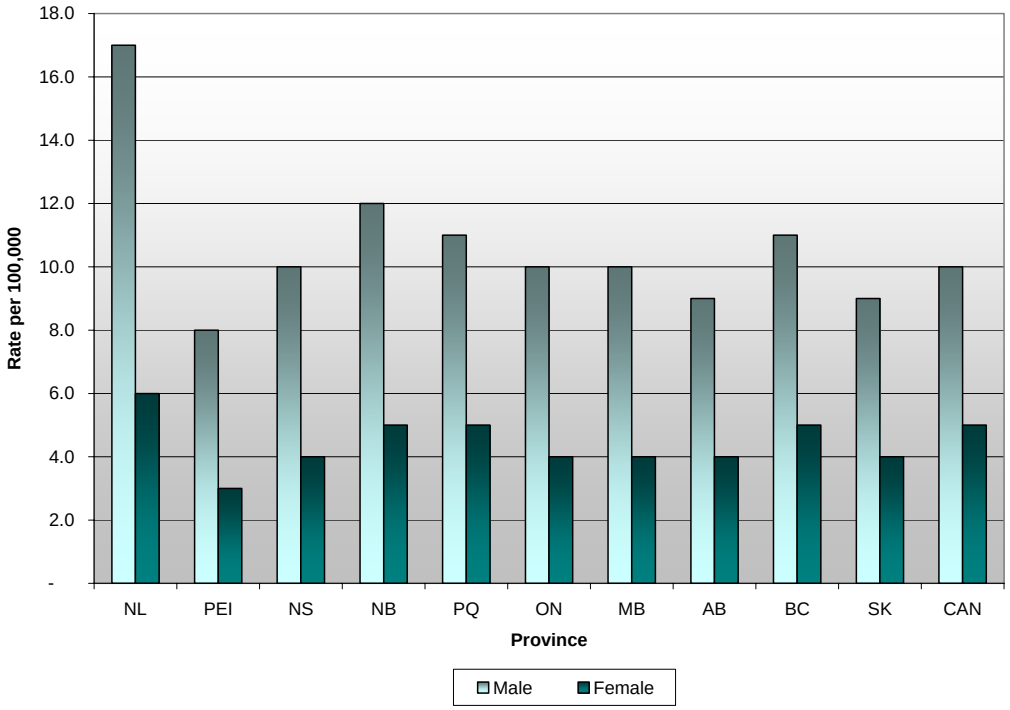
One of the most obvious geographical variations relates to the third class of infectious agent (alongside viruses and bacteria), namely, parasitic worms or flukes. These organisms are almost entirely restricted to areas outside of North America (see the fuller description in a later section).

There are more localized variations in cancer rates which are also significant; for instance, the rate of liver cancer is high in Japan compared to other developed countries. Somewhat rarer cancers also swing more towards developed countries. For reasons that are not entirely clear, the highest incidence rate for non-Hodgkin's lymphomas is observed in the developed areas of North America; the epidemiology cannot be entirely accounted for by the distribution of the major contributing agents, i.e., the Epstein-Barr and human immunodeficiency viruses.[22]Similarly, it is not yet clear if the somewhat higher leukemia rate in North America bears any connection to the pattern of infection with human T cell lymphotrophic virus type I.

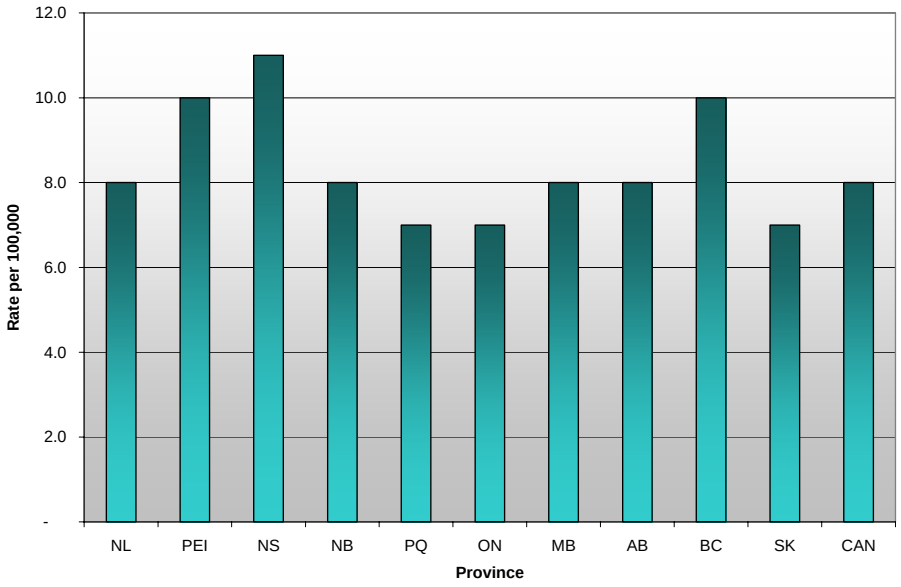
Rates also vary within countries and provinces. The following two charts show the different incidence rates across Canada for stomach and cervical cancers.[23]

[21] Bosch FX, Ribes J, Cleries R et al. Epidemiology of hepatocellular carcinoma. *Clinical Liver Diseases.* 2005; 9(2): 191-211.
[22] Parkin DM. International variation. *Oncogene.* 2004; 23(38): 6329-40.
[23] Canadian Cancer Society. *Canadian Cancer Statistics 2005.*

Stomach Cancer
Estimated Age-standardized Rates
Canadian Provinces 2005



Cervical Cancer
Estimated Age-standardized Rates
Canadian Provinces 2005



Epidemiology of the Main Infectious Agents in Developed Countries

The following table summarizes the major role of infection in carcinogenesis as seen in developed countries.

Agent	*Type*	*Prevalence of infection*	*Main associated cancer*	*Relative risk of infected person getting cancer*	*Annual incidence of cancer (developed countries)*[24]	*Proportion of specific cancer attributable to infection*
Human papillomavirus (HPV) - various types	Virus		Cervix		100,000	90 to 100%[25,26]
Hepatitis B / C virus (HBV, HCV)	Virus	• Chronic HBV 0.5 to 1.0%[27] • HCV 0.5 to 1.0%	Liver, esp. hepatocellular carcinoma (HCC)	• HBV: 13.7[28] • HCV: 11.5	106,000	80%[29] • HB: 40 to 60% • HC: 20 to 30%[30]
Helicobacter pylori	Bacter-ium	Up to 50% of population are carriers	Stomach	• Odds ratio about 2[31,32] • 1% of carriers[33]	333,000	70%[34]
Epstein-Barr virus (EBV)	Virus	90%[35]	Hodgkin's disease; non-Hodgkin's lymphoma		264,000	30-90%, depending on the disorder
Human immuno-deficiency virus type 1 (HIV-1) as co-factor	Virus		Kaposi sarcoma	• 0.1% females • 0.2% males	8,600	
Human T cell lymphotrophic v. type I (HTLV-I)	Virus		Leukemia			1%[36]
Human herpesvirus type 8 (HHV-8) - probable	Virus		Kaposi sarcoma		8,600	

[24] *Evidence-based Cancer Prevention Strategies for NGOs*. International Union Against Cancer; 2004.
[25] Pisani P, Parkin DM, Munoz N et al. Cancer and infection: estimates of the attributable fraction in 1990. *Cancer Epidemiology, Biomarkers & Prevention.* 1997; 6(6): 387-400.
[26] Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *Journal of Pathology.* 1999; 189(1): 12-9.
[27] Zhang J, Zou S, Giulivi A. Viral hepatitis and emerging blood borne pathogens in Canada: Hepatitis B in Canada.2002. Available at http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/01vol27/27s3/27s3e_e.html. Accessed May 2005.
[28] Colditz GA, Atwood KA, Emmons K et al. Harvard report on cancer prevention volume 4: Harvard Cancer Risk Index. Risk Index Working Group, Harvard Center for Cancer Prevention. *Cancer Causes & Control.* 2000; 11(6): 477-88.
[29] Bosch FX, Ribes J, Diaz M et al. Primary liver cancer: worldwide incidence and trends. *Gastroenterology.* 2004; 127(5 Suppl 1): S5-S16.
[30] *Targeting Cancer: An Action Plan for Cancer Prevention and Detection. Cancer 2020 Background Report*. Cancer Care Ontario; 2003.
[31] Huang JQ, Sridhar S, Chen Y et al. Meta-analysis of the relationship between Helicobacter pylori seropositivity and gastric cancer. *Gastroenterology.* 1998; 114(6): 1169-79.
[32] Parkin DM. International variation. *Oncogene.* 2004; 23(38): 6329-40.
[33] Herrera LA, Benitez-Bribiesca L, Mohar A et al. Role of infectious diseases in human carcinogenesis. *Environmental & Molecular Mutagenesis.* 2005; 45(2-3): 284-303.
[34] McLoughlin RM, Sebastian SS, O'Connor HJ et al. Review article: test and treat or test and scope for Helicobacter pylori infection. Any change in gastric cancer prevention? *Alimentary Pharmacology & Therapeutics.* 2003; 17 Suppl 2: 82-8.
[35] Rickinson AB, Callan MF, Annels NE. T-cell memory: lessons from Epstein-Barr virus infection in man. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences.* 2000; 355(1395): 391-400.
[36] Pisani P, Parkin DM, Munoz N et al. Cancer and infection: estimates of the attributable fraction in 1990. *Cancer Epidemiology, Biomarkers & Prevention.* 1997; 6(6): 387-400.

Other Agents Under Investigation

Before turning to our treatment of the confirmed infectious agents of interest in the developed world, it is important to note that this whole topic is a scientific "moving target." First, several additional suspect agents are under investigation from all three classes of infection. For example, people chronically infected with *Salmonella* (the bacterium that causes typhoid) are up to 8 times more likely to develop gallbladder cancer.[37,38] Various *Helicobacter* species have also garnered a lot of attention. For instance, *Helicobacter bilis* appears to play a role in biliary tract cancer.[39] Turning to the virus world, there is some evidence linking breast cancer to a human homologue of the mouse mammary tumour virus, as well as to cytomegalovirus.[40,41] As noted in the table above, human herpesvirus type 8 has been identified as a probable cause of Kaposi sarcoma.

Second, the list of cancers related to already well-known agents is being lengthened all the time. For example, mucosa-associated lymphoid tissue (MALT) and other lymphomas of the stomach have been associated with *Helicobacter pylori*.[42,43] This bacterium has also recently been connected to liver cancer[44] and biliary tract cancer.[45] As for viruses, hepatitis B and C also have been linked to biliary tract cancer,[46] and hepatitis C to non-Hodgkin's lymphoma.[47] Human papillomavirus has been connected to breast cancer, as has Epstein-Barr virus; the latter also has been associated with lung, gastric, colon and prostate cancers.[48,49] As will be described below, human papillomavirus has been detected in a spectrum of cancers as well.

The subtypes of specific viral agents being implicated in cancer development are steadily expanding as well. For example, the list of HPV subtypes demonstrated to cause cancer of the cervix gets longer and longer. Of the *known* subtypes of HPV, 15-20 have now been associated with cervical cancer.

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[37] Shukla VK, Singh H, Pandey M et al. Carcinoma of the gallbladder--is it a sequel of typhoid? *Digestive Diseases & Sciences.* 2000; 45(5): 900-3.
[38] Sheth S, Bedford A, Chopra S. Primary gallbladder cancer: recognition of risk factors and the role of prophylactic cholecystectomy. *American Journal of Gastroenterology.* 2000; 95(6): 1402-10.
[39] Murata H, Tsuji S, Tsujii M et al. Helicobacter bilis infection in biliary tract cancer. *Alimentary Pharmacology & Therapeutics.* 2004; 20 Suppl 1: 90-4.
[40] Levine PH, Pogo BG, Klouj A et al. Increasing evidence for a human breast carcinoma virus with geographic differences. *Cancer.* 2004; 101(4): 721-6.
[41] Richardson AK, Cox B, McCredie MR et al. Cytomegalovirus, Epstein-Barr virus and risk of breast cancer before age 40 years: a case-control study. *Brirish Journal of Cancer.* 2004; 90(11): 2149-52.
[42] Konturek PC, Konturek SJ, Starzyska T et al. Helicobacter pylori-gastrin link in MALT lymphoma. *Alimentary Pharmacology & Therapeutics.* 2000; 14(10): 1311-8.
[43] Parsonnet J, Hansen S, Rodriguez L et al. Helicobacter pylori infection and gastric lymphoma. *New England Journal of Medicine.* 1994; 330(18): 1267-71.
[44] Ito K, Nakamura M, Toda G et al. Potential role of Helicobacter pylori in hepatocarcinogenesis. *International Journal of Molecular Medicine.* 2004; 13(2): 221-7.
[45] Bulajic M, Maisonneuve P, Schneider-Brachert W et al. Helicobacter pylori and the risk of benign and malignant biliary tract disease. *Cancer.* 2002; 95(9): 1946-53.
[46] Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. *Seminars in Liver Disease.* 2004; 24(2): 115-25.
[47] Matsuo K, Kusano A, Sugumar A et al. Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: a meta-analysis of epidemiological studies. *Cancer Science.* 2004; 95(9): 745-52.
[48] Liu Y, Klimberg VS, Andrews NR et al. Human papillomavirus DNA is present in a subset of unselected breast cancers. *Journal of Human Virology.* 2001; 4(6): 329-34.
[49] Grinstein S, Preciado MV, Gattuso P et al. Demonstration of Epstein-Barr virus in carcinomas of various sites. *Cancer Research.* 2002; 62(17): 4876-8.

Mechanisms of Disease

There are three main mechanisms by which infections both initiate and promote carcinogenesis:[50]

1. When an agent becomes persistent in the host, it may induce a chronic inflammatory response, which in turn creates a chemical environment damaging to the DNA and to other elements within cells (such as systems which regulate cellular growth and death); the proliferation of cells, a common precursor to malignancy, can be a by-product of these processes. Bacterial toxins can also directly damage DNA.

2. Agents may directly transform cells by inserting active genes into the host DNA; this can result in an interruption of cellular controls which normally inhibit cancerous growth. The insertion of DNA in a sperm or egg cell creates the possibility of viruses essentially being inherited by offspring.

3. Agents such as the human immunodeficiency virus (HIV) act as immunosuppressors, which create a climate conducive to aggressive cancer development.

Prevention and Management

Focusing on the main pathogens in developed countries, we will look at each one in turn from the point of view of effective health care. The agenda is to identify and evaluate the interventions available at various stages of exposure and disease development, namely:

1. Preventing exposure to the pathogen in the first place.

2. Preventing establishment of infection (e.g., through prophylactic vaccination).

3. Preventing full cancer development once infection is present (including detecting and treating the infection or precancerous cells and lesions before cancer becomes completely established, e.g., through therapeutic vaccination).

The first category is a form of early primary prevention. Category 2 measures such as vaccinations are classic forms of primary prevention. Finally, screening for precancer or early cancer and other approaches covered under category 3 are species of secondary prevention. The ultimate aim of all these approaches is clear, namely, preventing cancer from fully developing.

Future Developments

As already noted, there are many potentially carcinogenic agents being investigated. Likewise, tremendous research energy is going into the development of therapies for current and emerging infectious agents related to cancer. The key factor in making real progress on prevention and treatments is a full understanding of the mechanisms of transmission, infection and disease progression. As will be seen for each of the

[50] Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. *Journal of Internal Medicine.* 2000; 248(3): 171-83.

main agents described in the balance of this report, there is still a long way to go in understanding the basic science. As one review summarized:

> *At present, information concerning the role of viruses in the pathogenesis of human neoplasms is fragmented and incomplete. It is clear that their role is complex, and a complete understanding of the intricacies involved in viral interaction with the human genome may still take many years. New virologic study techniques can be expected to emerge and epidemiologic studies will continue. With each new report, a bit more will be understood, new hypotheses stimulated, and additional studies undertaken.*[51]

[51] Phelan JA. Viruses and neoplastic growth. *Dental Clinics of North America.* 2003; 47(3): 533-43.

Human Papillomavirus

Globally, cervical cancer is the second most common female cancer (only exceeded in prevalence by breast cancer). As indicated in the table above, there is virtually a one-to-one connection between cervical cancer cases and the detection of HPV DNA. As Walboomers et al. concluded in 1999, "the presence of HPV in virtually all cervical cancers implies the highest worldwide attributable fraction so far reported for a specific cause of any major human cancer."[52] In short, HPV has been proposed as the first-ever necessary and sufficient cause of a human cancer identified by researchers.[53,54]

The human papillomavirus represents a bewildering array of types, subtypes and variants. Over 100 HPV types have been identified so far, with approximately 40 known to infect the human genital tract. Of these, about half are oncogenic, with the majority of cancer-causing forms related genetically to two main types, HPV-16 and HPV-18.[55,56] Indeed, the latter two types together account for about 70 to 75% of cervical cancer cases (an increase from earlier estimates of 50%).[57,58,59]

For completeness, it is important to note that HPV types have been implicated in a number of other cancers, including other anogenital carcinomas, e.g., of the vulva or penis,[60] and various nongenital mucosal and cutaneous diseases, e.g., oropharyngeal and lung carcinomas and certain skin cancers.[61,62,63,64] In the latter case, UV radiation

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[52] Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *Journal of Pathology.* 1999; 189(1): 12-9.
[53] Bosch FX, Munoz N. The viral etiology of cervical cancer. *Virus Research.* 2002; 89(2): 183-90.
[54] Bosch FX, Lorincz A, Munoz N et al. The causal relation between human papillomavirus and cervical cancer. *Journal of Clinical Pathology.* 2002; 55(4): 244-65.
[55] Munoz N, Bosch FX, de Sanjose S et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine.* 2003; 348(6): 518-27.
[56] Bosch FX, Manos MM, Munoz N et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. *Journal of the National Cancer Institute.* 1995; 87(11): 796-802.
[57] Clifford GM, Smith JS, Plummer M et al. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. *British Journal of Cancer.* 2003; 88(1): 63-73.
[58] Goldie SJ, Grima D, Kohli M et al. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. *International Journal of Cancer.* 2003; 106(6): 896-904.
[59] Harper DM, Franco EL, Wheeler C et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *The Lancet.* 2004; 364(9447): 1757-65.
[60] The attributable fraction of these cancers with respect to HPV infection is 40 to 50%. Dillner J, Meijer CJ, von Krogh G et al. Epidemiology of human papillomavirus infection. *Scandinavian Journal of Urology & Nephrology Supplement.* 2000; 34(205): 194-200.
[61] Mork J, Lie AK, Glattre E et al. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *New England Journal of Medicine.* 2001; 344(15): 1125-31.
[62] Gillison ML, Koch WM, Capone RB et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *Journal of the National Cancer Institute.* 2000; 92(9): 709-20.
[63] Cheng YW, Chiou HL, Sheu GT et al. The association of human papillomavirus 16/18 infection with lung cancer among nonsmoking Taiwanese women. *Cancer Research.* 2001; 61(7): 2799-803.
[64] Masini C, Fuchs PG, Gabrielli F et al. Evidence for the association of human papillomavirus infection and cutaneous squamous cell carcinoma in immunocompetent individuals. *Archives of Dermatology.* 2003; 139(7): 890-4.

is known to be a co-factor.[65] A particularly significant cancer related to HPV in high-risk male populations is squamous cell anal carcinoma.[66] Aside from lesions and full cancers, the other main disorders associated with HPV are different types of genital warts.

Taken as a group, anogenital HPV is the most common sexually transmitted infection.[67] The lifetime risk of contracting such an infection is about 80%.[68]

Transmission of the Agent

The primary mode of HPV transmission is sexual intercourse. Studies show that the number of recent sexual partners is significantly associated with the incidence of HPV infection.[69,70] Limited research has concluded that the virus can be passed through fomites (substances or articles that hold and convey infection, e.g., handkerchief) or skin contact, but this remains very debatable; no evidence of such transmission has been found in the case of genital lesions, the precursor to cancer.[71] A final transmission route implicated as plausible is non-penetrative sexual activity (including oral sex).[72] Although the whole area of transmission is subject to ongoing study, the basic understanding is that HPV infections are "easily transmitted."[73]

As Arena et al. have noted, "the data reported in the literature on the relationship between HPV and pregnancy are highly discordant."[74] Although earlier studies suggested the possibility of "vertical transmission" of HPV from mother to infant during delivery, more recent research has concluded that this route of viral spread is very low-risk.[75,76] Even when the virus is found in newborns, it often seems to clear

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[65] Pfister H. Chapter 8: Human papillomavirus and skin cancer. *Journal of the National Cancer Institute Monograph.* 2003; (31): 52-6.
[66] Xi LF, Critchlow CW, Wheeler CM et al. Risk of anal carcinoma in situ in relation to human papillomavirus type 16 variants. *Cancer Research.* 1998; 58(17): 3839-44.
[67] Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. *Journal of the National Cancer Institute Monograph.* 2003; (31): 14-9.
[68] Bekkers RL, Massuger LF, Bulten J et al. Epidemiological and clinical aspects of human papillomavirus detection in the prevention of cervical cancer. *Reviews in Medical Virology.* 2004; 14(2): 95-105.
[69] Sellors JW, Karwalajtys TL, Kaczorowski J et al. Incidence, clearance and predictors of human papillomavirus infection in women. *Canadian Medical Association Journal.* 2003; 168(4): 421-5.
[70] Kjaer SK, Chackerian B, van den Brule AJ et al. High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse). *Cancer Epidemiology, Biomarkers & Prevention.* 2001; 10(2): 101-6.
[71] Bruck LR, Zee S, Poulos B et al. Detection of cervical human papillomavirus infection by in situ hybridization in fetuses from women with squamous intraepithelial lesions. *Journal of Lower Genital Tract Disease.* 2005; 9(2): 114-7.
[72] Winer RL, Lee SK, Hughes JP et al. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *American Journal of Epidemiology.* 2003; 157(3): 218-26.
[73] Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. *Journal of the National Cancer Institute Monograph.* 2003; (31): 14-9.
[74] Arena S, Marconi M, Ubertosi M et al. HPV and pregnancy: diagnostic methods, transmission and evolution. *Minerva Ginecologica.* 2002; 54(3): 225-37.
[75] Smith EM, Ritchie JM, Yankowitz J et al. Human papillomavirus prevalence and types in newborns and parents: concordance and modes of transmission. *Sexually Transmitted Diseases.* 2004; 31(1): 57-62.

after a few months.[77] The first report has recently been made of fetal cervical HPV infection through *intrauterine* exposure.[78]

Co-factors and Correlates

HPV infection is very common, but mostly transient. The fact that, even in women with persistent HPV infection, only a certain fraction will eventually develop cervical cancer indicates that the virus, though necessary, is not always a sufficient cause. Co-factors seem to be involved in at least some cervical carcinogenesis.[79] For example, risk for cervical cancer developing with HPV infection increases twofold when the woman is or has been a smoker;[80] recently, evidence for the effect of passive smoking has also been reported.[81,82] In fact, some research suggests that exposure to cigarette smoke may be *required* as a carcinogen to advance HPV-infected cells toward high-grade neoplasms.[83] The crucial biological impact appears to be the oxidant load created through smoking, though this remains a matter of investigation.[84,85]

There is evidence that the presence of other sexually transmitted agents, cervical inflammation, multiple births (known as multiparity), and long-term oral contraceptive use all correlate with progression towards cervical cancer.[86,87,88,89] Although a causal relationship is unproven, herpes simplex virus-2 may act in conjunction with HPV to create cervical cancer (perhaps multiplying the risk of

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[76] Watts DH, Koutsky LA, Holmes KK et al. Low risk of perinatal transmission of human papillomavirus: results from a prospective cohort study. *American Journal of Obstetrics & Gynecology.* 1998; 178(2): 365-73.

[77] Arena S, Marconi M, Ubertosi M et al. HPV and pregnancy: diagnostic methods, transmission and evolution. *Minerva Ginecologica.* 2002; 54(3): 225-37.

[78] Bruck LR, Zee S, Poulos B et al. Detection of cervical human papillomavirus infection by in situ hybridization in fetuses from women with squamous intraepithelial lesions. *Journal of Lower Genital Tract Disease.* 2005; 9(2): 114-7.

[79] Munoz N. Human papillomavirus and cancer: the epidemiological evidence. *Journal of Clinical Virology.* 2000; 19(1-2): 1-5.

[80] Plummer M, Herrero R, Franceschi S et al. Smoking and cervical cancer: pooled analysis of the IARC multi-centric case--control study. *Cancer Causes Control.* 2003; 14(9): 805-14.

[81] Trimble CL, Genkinger JM, Burke AE et al. Active and passive cigarette smoking and the risk of cervical neoplasia. *Obstetrics & Gynecology.* 2005; 105(1): 174-81.

[82] Tay SK, Tay KJ. Passive cigarette smoking is a risk factor in cervical neoplasia. *Gynecologic Oncology.* 2004; 93(1): 116-20.

[83] Ho GY, Kadish AS, Burk RD et al. HPV 16 and cigarette smoking as risk factors for high-grade cervical intra-epithelial neoplasia. *International Journal of Cancer.* 1998; 78(3): 281-5.

[84] Giuliano A. Cervical carcinogenesis: the role of co-factors and generation of reactive oxygen species. *Salud Publica de Mexico.* 2003; 45 Suppl 3: S354-60.

[85] Moore TO, Moore AY, Carrasco D et al. Human papillomavirus, smoking, and cancer. *Journal of Cutaneous Medicine & Surgery.* 2001; 5(4): 323-8.

[86] Castellsague X, Bosch FX, Munoz N. Environmental co-factors in HPV carcinogenesis. *Virus Research.* 2002; 89(2): 191-9.

[87] Castellsague X, Munoz N. Chapter 3: Cofactors in human papillomavirus carcinogenesis--role of parity, oral contraceptives, and tobacco smoking. *Journal of the National Cancer Institute Monograph.* 2003; (31): 20-8.

[88] Munoz N, Franceschi S, Bosetti C et al. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. *The Lancet.* 2002; 359(9312): 1093-101.

[89] Moreno V, Bosch FX, Munoz N et al. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *The Lancet.* 2002; 359(9312): 1085-92.

developing the main types of cervical cancer up to 2 or 3 times).[90] HIV (with its associated immune suppression) and *Chlamydia trachomatis* are also on the list of potential co-factors.[91,92,93,94,95]

The most recent research has called into question how much birth and contraception experience actually influence cervical cancer rates.[96,97] A 2003 systematic review further concluded that "there was no evidence for a strong positive or negative association" between HPV infection and use of oral contraceptives.[98] In sum, it is probably best to say the connection between oral contraceptives, HPV and cervical cancer remains a fluid area of research.[99] As for the case of multiple births, if its association with cervical cancer risk holds up, then a general decline in parity might partly explain the decrease in cervical cancer in many industrialized countries.[100]

Finally, there is consistent evidence that higher intakes of fruit and vegetables are protective against cervical cancer, as well as weaker indications of a similar role for specific dietary ingredients (e.g., vitamins C and E, lycopene, and folate).[101,102,103,104]

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[90] Smith JS, Herrero R, Bosetti C et al. Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. *Journal of the National Cancer Institute.* 2002; 94(21): 1604-13.

[91] de Sanjose S, Palefsky J. Cervical and anal HPV infections in HIV positive women and men. *Virus Research.* 2002; 89(2): 201-11.

[92] La Ruche G, You B, Mensah-Ado I et al. Human papillomavirus and human immunodeficiency virus infections: relation with cervical dysplasia-neoplasia in African women. *International Journal of Cancer.* 1998; 76(4): 480-6.

[93] Weissenborn SJ, Funke AM, Hellmich M et al. Oncogenic human papillomavirus DNA loads in human immunodeficiency virus-positive women with high-grade cervical lesions are strongly elevated. *Journal of Clinical Microbiology.* 2003; 41(6): 2763-7.

[94] Palefsky JM, Holly EA. Chapter 6: Immunosuppression and co-infection with HIV. *Journal of the National Cancer Institute Monograph.* 2003; (31): 41-6.

[95] Smith JS, Munoz N, Herrero R et al. Evidence for Chlamydia trachomatis as a human papillomavirus cofactor in the etiology of invasive cervical cancer in Brazil and the Philippines. *Journal of Infectious Diseases.* 2002; 185(3): 324-31.

[96] Shields TS, Brinton LA, Burk RD et al. A case-control study of risk factors for invasive cervical cancer among U.S. women exposed to oncogenic types of human papillomavirus. *Cancer Epidemiology, Biomarkers & Prevention.* 2004; 13(10): 1574-82.

[97] Shields TS, Falk RT, Herrero R et al. A case-control study of endogenous hormones and cervical cancer. *British Journal of Cancer.* 2004; 90(1): 146-52.

[98] Green J, Berrington de Gonzalez A, Smith JS et al. Human papillomavirus infection and use of oral contraceptives. *British Journal of Cancer.* 2003; 88(11): 1713-20.

[99] Smith JS, Green J, Berrington de Gonzalez A et al. Cervical cancer and use of hormonal contraceptives: a systematic review. *The Lancet.* 2003; 361(9364): 1159-67.

[100] Munoz N, Franceschi S, Bosetti C et al. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. *The Lancet.* 2002; 359(9312): 1093-101.

[101] Castellsague X, Bosch FX, Munoz N. Environmental co-factors in HPV carcinogenesis. *Virus Research.* 2002; 89(2): 191-9.

[102] Ho GY, Palan PR, Basu J et al. Viral characteristics of human papillomavirus infection and antioxidant levels as risk factors for cervical dysplasia. *International Journal of Cancer.* 1998; 78(5): 594-9.

[103] Giuliano AR, Siegel EM, Roe DJ et al. Dietary intake and risk of persistent human papillomavirus (HPV) infection: the Ludwig-McGill HPV Natural History Study. *Journal of Infectious Diseases.* 2003; 188(10): 1508-16.

[104] Sedjo RL, Papenfuss MR, Craft NE et al. Effect of plasma micronutrients on clearance of oncogenic human papillomavirus (HPV) infection (United States). *Cancer Causes Control.* 2003; 14(4): 319-26.

The main proposal for the function of dietary co-factors is an antioxidant protective mechanism.[105]

Natural History and Carcinogenesis

This section will focus on the main HPV-related cancer of interest to public health, namely, cervical cancer. This type of cancer arises through three carcinogenic steps. First, HPV infection of the cervix occurs, primarily as a result of sexual intercourse. The effect of infection on cervical cells is quite variable. Whatever the impact, most infections tend to resolve over a one- to two-year period.[106] The next step, progression to a precancerous state, happens in a small percentage of cases. The crucial factor is the persistence of HPV as opposed to clearance of the virus. Persistence is due mostly to some capability of the virus to suppress or evade the body's natural immune system.[107,108]

The modal time between HPV infection (most often in late teens or early 20s) and the peak of precancer development is 7 to 10 years. This places the typical age of women with precancerous lesions at about 30 years. The final step is full-blown, invasive cancer, which may take another 10 years to develop; between one third and two-thirds of women with precancer will move on to this end-point. In sum, this generic, prolonged natural history confirms the basic understanding that rapidly invasive cancers among young women are rare events.[109]

Preventive Interventions

As outlined above, there are three approaches to preventing cancer with an infectious origin: limiting exposure to the pathogen in the first place; interrupting the establishment of infection; and stopping full cancer development once infection is present. We will look at each of these approaches in turn.

Early Primary Prevention

The most "full-proof" way to eliminate the risk for future genital HPV infections is to refrain from genital contact with another person. The next most certain approach is to only be sexually active within a long-term, mutually monogamous relationship with an uninfected partner.[110] Indeed, reducing the number of potentially risky sexual partners by any means is clearly a preventive measure. These sort of proactive "partner management" interventions become important in light of the fact that

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[105] Castle PE, Giuliano AR. Chapter 4: Genital tract infections, cervical inflammation, and antioxidant nutrients--assessing their roles as human papillomavirus cofactors. *Journal of the National Cancer Institute Monograph.* 2003; (31): 29-34.

[106] Schiffman MH, Castle P. Epidemiologic studies of a necessary causal risk factor: human papillomavirus infection and cervical neoplasia. *Journal of the National Cancer Institute.* 2003; 95(6): E2.

[107] Frazer IH, Thomas R, Zhou J et al. Potential strategies utilised by papillomavirus to evade host immunity. *Immunological Reviews.* 1999; 168: 131-42.

[108] Padilla-Paz LA. Human papillomavirus vaccine: history, immunology, current status, and future prospects. *Clinical Obstetrics & Gynecology.* 2005; 48(1): 226-40.

[109] Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. *Journal of the National Cancer Institute Monograph.* 2003; (31): 14-9.

[110] *Report to Congress: Prevention of Genital Human Papillomavirus Infection.* Centers for Disease Control and Prevention; 2004. Available at http://www.cdc.gov/std/HPV/2004HPV%20Report.pdf. Accessed May 2005.

preventing transmission through condom use has not been demonstrated (though condoms may protect against the development of genital warts and lesions).[111,112]

The literature related to the prevention of sexually transmitted infections (STIs) is extensive. To avoid an overly lengthy document, we will confine our description of this sort of early primary prevention to a few notable programs.

Population-Based Interventions to Reduce Sexually Transmitted Infection (STI). The relevant review by the Cochrane group restricted itself to randomized controlled trials where, by definition, the unit of randomization was either a community or treatment facility (not individuals). These stringent criteria yielded only 5 qualifying studies, *all based in developing countries* and none focusing on HPV per se. The interventions in population-based programs include: education and media campaigns aimed at promoting safer sexual behaviour; improved STI treatment services; integration of case-finding into routine health care; and mass treatment of persons in at-risk communities, even if they are asymptomatic. The programs reviewed, which may have limited applicability in developed countries anyway, were for the most part unsuccessful in reducing STI incidence rates. Only one study showed a significant decrease in gonorrhoea and syphilis (which, for our purposes, will be taken as proxies for HPV infection) and an increase in condom use (with the latter being of limited application to HPV prevention anyway, given current information).[113] A 2005 systematic review of interventions to prevent STIs examined three of the same community-based studies identified by Cochrane, including the one trial that showed some success. All the included population-level studies were based in the same African communities covered by Cochrane.[114] There apparently has been no population-level experimental research in developed countries, even though it is acknowledged that, to have maximum impact, STI interventions will likely need to be applied to whole populations.[115]

Individual and Group Approaches to STI Control. The bulk of the 41 studies identified in the 2005 review noted above dealt with individual approaches; a smaller number looked at group-based programs. A large percentage of the projects showed significant success. [116] For instance, a third of the 9 group-based programs in the review involved counselling and skills building that led to significant decreases in STI transmission. One study showed counselling focused on skills training (8.6%

[111] Giles S. Transmission of HPV. *Canadian Medical Association Journal.* 2003; 168(11): 1391; author reply.
[112] Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sexually Transmitted Diseases.* 2002; 29(11): 725-35.
[113] Sangani P, Rutherford G, Wilkinson D. Population-based interventions for reducing sexually transmitted infections, including HIV infection. *Cochrane Database of Systematic Reviews.* 2004; (2): CD001220.
[114] Manhart LE, Holmes KK. Randomized controlled trials of individual-level, population-level, and multilevel interventions for preventing sexually transmitted infections: what has worked? *Journal of Infectious Diseases.* 2005; 191 Suppl 1: S7-24.
[115] Sangani P, Rutherford G, Wilkinson D. Population-based interventions for reducing sexually transmitted infections, including HIV infection. *Cochrane Database of Systematic Reviews.* 2004; (2): CD001220.
[116] Kamb ML, Fishbein M, Douglas JM, Jr. et al. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. *Journal of the American Medical Association.* 1998; 280(13): 1161-7.

incidence over 12 months) was superior to a health education model (15.4%).[117] The most recent literature has supported the efficacy of cognitive-behavioural group interventions for STI control.[118]

Another review from 2002 found 8 interventions designed to reduce STI incidence; 5 of them showed significant success, including individual counselling, mass communications regarding risk reduction, and multiple-component motivation and skills education.[119]

A Cochrane review originally completed in 2000 confirmed that health promotion directed at women can reduce sexual risk behaviours, especially with respect to increased use of condoms for vaginal intercourse.[120] However, we have already noted the limited protection of condoms against HPV. In fact, none of the studies included in the review focused on the control of cervical cancer as an end-point.

Summing up STI prevention, it was acknowledged in 2002 that "the evidence based for many interventions is sparse and randomised trials of interventions are in their early days."[121]

Despite the fact that not contacting and subsequently contracting HPV would be 100% effective in preventing cervical cancer, it is possible that the advent of an HPV vaccine will create some complacency around such behavioural interventions, as well as other approaches to controlling cervical cancer. This would possibly be a backwards step, especially given the Centers for Disease Control's 2004 position statement; they maintained that an effective HPV vaccine should not replace other prevention strategies.[122]

Primary Prevention

The one-to-one association of cervical cancer and HPV infection has two practical implications: the development of a vaccine and enhanced screening programs based on HPV testing.[123] The development of a vaccine has had a clearer rationale and, in fact, has progressed further at this point. The vaccine story, though chronologically a later development than conventional cervical cancer screening, must logically come

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[117] Baker SA, Beadnell B, Stoner S et al. Skills training versus health education to prevent STDs/HIV in heterosexual women: a randomized controlled trial utilizing biological outcomes. *AIDS Education & Prevention.* 2003; 15(1): 1-14.

[118] Boyer CB, Shafer MA, Shaffer RA et al. Evaluation of a cognitive-behavioral, group, randomized controlled intervention trial to prevent sexually transmitted infections and unintended pregnancies in young women. *Preventive Medicine.* 2005; 40(4): 420-31.

[119] Elwy AR, Hart GJ, Hawkes S et al. Effectiveness of interventions to prevent sexually transmitted infections and human immunodeficiency virus in heterosexual men: a systematic review. *Archives of Internal Medicine.* 2002; 162(16): 1818-30.

[120] Shepherd J, Weston R, Peersman G et al. Interventions for encouraging sexual lifestyles and behaviours intended to prevent cervical cancer. *Cochrane Database of Systematic Reviews*. 2000.

[121] Johnson AM, Fenton KA, Mercer C. Phase specific strategies for the prevention, control, and elimination of sexually transmitted diseases: background country profile, England and Wales. *Sexually Transmitted Infections.* 2002; 78 Suppl 1: i125-32.

[122] *Report to Congress: Prevention of Genital Human Papillomavirus Infection.* Centers for Disease Control and Prevention; 2004. Available at http://www.cdc.gov/std/HPV/2004HPV%20Report.pdf. Accessed May 2005.

[123] Bosch FX, Munoz N. The viral etiology of cervical cancer. *Virus Research.* 2002; 89(2): 183-90.

first; it represents a primary approach to prevention, whereas detecting the presence of cancer is already part of a secondary strategy.

HPV Vaccine. Vaccination can either be prophylactic (preventing contact with a virus from becoming an active infection) or therapeutic (clearing an existing infection). There has been a great deal of excitement and energy around creating and testing a vaccine targeting HPV. This has been a special focus in the context of developing countries, for two reasons: the bulk of the annual 200,000 deaths related to cervical cancer occur there (making it the most prevalent cause of female cancer mortality), and less than 5% of these women currently participate in the other major public health strategy, namely, screening.[124]

Many challenges exist in the development of a vaccine. Because of the multiplicity of HPV types which are oncogenic, there is motivation to make any vaccine polyvalent. However, this adds development and manufacturing expense, so the balancing act becomes one of targeting those viral types which cause the greatest proportion of cancer. Once a strategy has been set, there still must be vigilance against the "potential epidemiological shift of HPV disease to currently less frequent types and variants."[125]

There have been several studies exploring either preventive or therapeutic HPV vaccines in humans. The trial by Koutsky et al. has provided the most conclusive evidence to date that HPV vaccination will be both safe and effective.[126] The main objectives of this double-blind, placebo-controlled, randomized trial were:[127]

- determine whether an HPV-16 vaccine would prevent persistent infection.
- estimate the impact of the vaccine on the incidence of cervical neoplasia.[128]
- assess the immunogenicity (i.e., ability to create an immune response) and tolerability of the vaccine.

The observed efficacy rate against cancer development was 100%. These encouraging results were matched by a very low rate of adverse events with the vaccine (less than 1%). As well, the vaccine not only prevented the development of disease, but also seems to prevent "its causative agent from residing in the genital tract where it can infect new sexual partners."[129] The main caveat emerging from this study was evidence that vaccination against one type of HPV will not protect against infection by another. Another limitation is that the vaccine does not appear to reverse infection or cervical neoplasia once it is present.

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[124] Goldie SJ, Grima D, Kohli M et al. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. *International Journal of Cancer.* 2003; 106(6): 896-904.
[125] Padilla-Paz LA. Human papillomavirus vaccine: history, immunology, current status, and future prospects. *Clinical Obstetrics & Gynecology.* 2005; 48(1): 226-40.
[126] Koutsky LA, Ault KA, Wheeler CM et al. A controlled trial of a human papillomavirus type 16 vaccine. *New England Journal of Medicine.* 2002; 347(21): 1645-51.
[127] Padilla-Paz LA. Human papillomavirus vaccine: history, immunology, current status, and future prospects. *Clinical Obstetrics & Gynecology.* 2005; 48(1): 226-40.
[128] An abnormal cell growth that may progress to cancer.
[129] Crum CP. The beginning of the end for cervical cancer? *New England Journal of Medicine.* 2002; 347(21): 1703-5.

The results of the only other phase III trial were reported in November, 2004. It studied the effect of a bivalent vaccine protecting against HPV-16 and HPV-18; adding HPV-18 has the potential for eliminating another 10% of total cervical cancer cases.[130] On an intention-to-treat basis, the vaccine was 95% efficacious against persistent infection and 93% against cytological abnormalities and lesions. In addition to these results, the vaccine was shown to be safe, well-tolerated and highly immunogenic.

Several other studies have reported on earlier stages of vaccine testing. The phase II data from a quadrivalent vaccine published in May, 2005, were very promising.[131] Over two and a half years of follow-up, the vaccine reduced the combined incidence of persistent infection from HPV-6, HPV-11, HPV-16, or HPV-18—as well as related genital disease including new cervical pre-cancers and genital warts—by 90%. The phase III trial of this vaccine is now under way. Several other vaccines are in the pipeline that will be targeting even higher numbers of HPV subtypes.

As one or more of these vaccines move towards licensing in the next few years, several questions remain open:

- Who should be vaccinated, and when? Some argue that the key population should be girls before they are sexually active, but since HPV causes a variety of cancers in men and women, a case can be made to vaccinate everyone.[132,133]
- How long does the protection last?
- How polyvalent should a widely-used public health vaccine be? For example, if women were vaccinated against five HPV types (16, 18, 31, 33, and 45), it would reduce cervical cancer risk by 85%.[134] Another consideration is mortality; one study showed that cervical cancer patients with HPV-18 or -45 are more likely to die from their disease.[135]
- How effective and cost-effective would a vaccination program be over the long-term, especially compared to current screening strategies?

There are two routes to answering the last question. The first is to compare the results from highly successful hepatitis B vaccination programs (see the next major section of this report). The second is mathematical modeling of disease progression and the impact of a vaccine. An example of the latter is offered by Taira et al.[136] Their model

[130] Harper DM, Franco EL, Wheeler C et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *The Lancet.* 2004; 364(9447): 1757-65.
[131] Villa LL, Costa RL, Petta CA et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncology.* 2005; 6(5): 271-8.
[132] Winer RL, Koutsky LA. Human papillomavirus through the ages. *Journal of Infectious Diseases.* 2005; 191(11): 1787-9.
[133] Crum CP. The beginning of the end for cervical cancer? *New England Journal of Medicine.* 2002; 347(21): 1703-5.
[134] Crum CP. The beginning of the end for cervical cancer? *New England Journal of Medicine.* 2002; 347(21): 1703-5.
[135] Wright JD, Li J, Gerhard DS et al. Human papillomavirus type and tobacco use as predictors of survival in early stage cervical carcinoma. *Gynecologic Oncology.* 2005; in press: 8 pp.
[136] Taira AV. Evaluating human papillomavirus vaccination programs. *Emerging Infectious Diseases.* 2004; 10(11): 1915-23.

estimated HPV prevalence and infection rates for the population overall, by age group, by level of sexual activity and by gender. The conclusion was that administering an HPV-16/18 vaccine to 12 year old girls would reduce cervical cancer cases by almost 62%, with a cost-effectiveness ratio of $14,583 per QALY.[137]

HPV Testing. There is a lot of debate concerning the potential usefulness of augmenting (or even replacing) conventional cytological screening (see under secondary prevention below) for cervical cancer with an HPV DNA test. As one study noted, "the extreme rarity of HPV-negative cancers reinforces the rationale for HPV testing in addition to, or even instead of, cervical cytology in routine cervical screening."[138] Additional pressure to consider alternatives comes from the challenges and deficiencies of current routine screening methods (see below). However, the extra cost of HPV testing is viewed by some as being prohibitive.

In April, 2005, the American College of Obstetricians and Gynecologists released a practice bulletin that acknowledges the high sensitivity of detecting HPV DNA in terms of ruling out cervical cancer.[139] If HPV is not present, women can be reassured with a high level of certainty that they are cancer-free. Using the test in the opposite direction is where the problems begin, i.e., deciding whether a detected HPV infection (even high risk types) but *without* cervical abnormality should be followed and treated (and, if so, when and how).[140] The cost of any additional surveillance (in about 4 to 6% of the screened population) adds to the already higher expense of HPV testing.[141] On the other hand, women with normal cytology and negative for high-risk HPV types can be screened less frequently; cost-effectiveness and modeling studies suggest that this fact could offset increased costs with HPV testing and thus make the procedure attractive from a public health perspective.[142] A comprehensive review of the literature up to 2005 confirmed that adding HPV testing to conventional screening would "likely" be cost-effective, though it also acknowledged that "further research is needed into the practicalities of implementing such a policy."[143]

Another potential area of usefulness for HPV testing is rapid intermediate evaluation of precancer treatments (see under secondary prevention below).[144,145,146] An alternate

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[137] Quality-adjusted life-year, a standard measure of improved health which takes into consideration delayed mortality as well as reduced morbidity.

[138] Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *Journal of Pathology.* 1999; 189(1): 12-9.

[139] Summary available at http://investor.digene.com/phoenix.zhtml?c=82439&p=irol-newsArticle_Print&ID=695453&highlight=. Accessed June 2005.

[140] Franceschi S, Mahe C. Human papillomavirus testing in cervical cancer screening. *British Journal of Cancer.* 2005; 92(9): 1591-2.

[141] Cuzick J, Szarewski A, Cubie H et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. *The Lancet.* 2003; 362(9399): 1871-6.

[142] Brink AA, Zielinski GD, Steenbergen RD et al. Clinical relevance of human papillomavirus testing in cytopathology. *Cytopathology.* 2005; 16(1): 7-12.

[143] Holmes J, Hemmett L, Garfield S. The cost-effectiveness of human papillomavirus screening for cervical cancer. A review of recent modelling studies. *European Journal of Health Economics.* 2005; 6(1): 30-7.

[144] Elfgren K, Jacobs M, Walboomers JM et al. Rate of human papillomavirus clearance after treatment of cervical intraepithelial neoplasia. *Obstetrics & Gynecology.* 2002; 100(5 Pt 1): 965-71.

[145] Paraskevaidis E, Arbyn M, Sotiriadis A et al. The role of HPV DNA testing in the follow-up period after treatment for CIN: a systematic review of the literature. *Cancer Treatment Reviews.* 2004; 30(2): 205-11.

approach to tracking the development of disease and the effectiveness of therapy is surveillance of molecular biomarkers associated with the natural history of HPV-related carcinogenesis.[147]

Avoiding Co-factors. Women who smoke do not seem to clear an HPV infection as quickly as non-smokers. Smoking is a risk co-factor for cervical cancer (as well as many other cancers, of course); but, in the case if cervical cancer, it is possible that this relationship is not necessarily a causative one (e.g., smokers perhaps having more sexual partners, on average). For this reason, it cannot be assumed that not smoking (or cessation) will automatically reduce the risk of HPV infection developing into cancer. While no specific studies were found which evaluated that particular issue, it is of significance in terms of secondary prevention that smoking does seem to decrease the effectiveness of precancer treatments.[148]

Exposure to other sexually transmitted infections should also be avoided to reduce cervical cancer risk, but the same behavioural changes already "prescribed" for preventing HPV infection would automatically be protective against some of the other agents anyway.

Conservative Treatment. The therapeutic approaches to a detected HPV infection are limited, though some new directions are being explored. In fact, in the absence of coexistent cellular changes, treatment is generally not recommended for subclinical genital HPV infection diagnosed by colposcopy,[149] biopsy, acetic acid application, or the detection of HPV by laboratory tests. The diagnosis of subclinical genital HPV infection is often not definitive, and no therapy has yet been identified that can eliminate infection.[150,151] This was confirmed in the only systematic review located, which dates back to 2000 and was not published in a top-tier journal.[152] Nonetheless, the results there (which mainly looked at laser therapy) can be added to earlier conclusions that effective antiviral therapies for subclinical HPV infection are not yet available.[153]

Research continues in this area. Reversing the assessment of earlier studies,[154] recombinant human interferon gamma has shown good results in effecting regression

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[146] Bodner K, Bodner-Adler B, Wierrani F et al. Is therapeutic conization sufficient to eliminate a high-risk HPV infection of the uterine cervix? A clinicopathological analysis. *Anticancer Research.* 2002; 22(6B): 3733-6.

[147] Padilla-Paz LA. Emerging technology in cervical cancer screening: status of molecular markers. *Clinical Obstetrics & Gynecology.* 2005; 48(1): 218-25.

[148] Acladious NN, Sutton C, Mandal D et al. Persistent human papillomavirus infection and smoking increase risk of failure of treatment of cervical intraepithelial neoplasia (CIN). *International Journal of Cancer.* 2002; 98(3): 435-9.

[149] Visual examination of the cervix and vagina using a lighted magnifying instrument.

[150] See the CDC website at http://www.cdc.gov/STD/treatment/6-2002TG.htm#SubclinicalGenitalHPV Infection. Accessed June 2005.

[151] Stanley M. Chapter 17: Genital human papillomavirus infections--current and prospective therapies. *Journal of the National Cancer Institute Monograph.* 2003; (31): 117-24.

[152] Russomano F, Reis A, de Camargo MJ et al. Efficacy in treatment of subclinical cervical HPV infection without intraepithelial neoplasia: systematic review. *Sao Paulo Medical Journal.* 2000; 118(4): 109-15.

[153] Phelps WC, Alexander KA. Antiviral therapy for human papillomaviruses: rational and prospects. *Annals of Internal Medicine.* 1995; 123(5): 368-82.

[154] Stanley M. Chapter 17: Genital human papillomavirus infections--current and prospective therapies. *Journal of the National Cancer Institute Monograph.* 2003; (31): 117-24.

of precancer cells and sometimes complete remission of HPV infection.[155] As well, one study suggested that the highly active antiretroviral therapy used with human immunodeficiency viral infection and AIDS can have a positive effect on cervical precancer regression (the impact on HPV clearance was not reported).[156] The quest is for a targeted antiviral, rather than simply the induction of non-specific inflammation which in turn generates a "bystander immune response."[157] Antivirals for HPV are especially important for the large population of immunosuppressed individuals who will mostly likely not benefit from immunotherapies.

A new approach is the potential use of therapeutic vaccines to control HPV infection or associated lesions. The main targets shaping vaccine development have been the key oncoproteins responsible for malignant transformation.[158] Mostly, results from small phase I trials have been variable.[159] If the promise seen in some early results is eventually fulfilled, then these therapeutic agents may play a role in both primary and secondary prevention of cervical cancer.

The last statement underlines the fact that therapies for HPV often overlap with those for the various precancer and early cancer stages which may lead to full invasive cervical cancer. The object of therapy is a "moving target" throughout the natural history of HPV disease. Somewhere we pass from primary prevention related to controlling HPV infection per se, through intermediate stages of precancerous development, and finally to a point where advanced precancer or early cancer is clearly in place. For our purposes, we will treat the latter stages as cases requiring secondary prevention; once detected through screening, the transformed cells and lesions become candidates for treatment, which usually is some form of ablation[160] through surgery or other means (see below).

Rounding out the conservative approaches to HPV infection, both dietary nutrients (e.g., retinoids, related to vitamin A, and beta-carotenes) and a topical medication called cidofovir have been investigated, with mixed-to-promising results.[161,162] Nonsteroidal anti-inflammatories and gene therapies are also in an early stage of

[155] Sikorski M, Zrubek H. Recombinant human interferon gamma in the treatment of cervical intraepithelial neoplasia (CIN) associated with human papillomavirus (HPV) infection. *European Journal of Gynaecology & Oncology.* 2003; 24(2): 147-50.
[156] Heard I, Tassie JM, Kazatchkine MD et al. Highly active antiretroviral therapy enhances regression of cervical intraepithelial neoplasia in HIV-seropositive women. *Aids.* 2002; 16(13): 1799-802.
[157] Stanley M. Chapter 17: Genital human papillomavirus infections--current and prospective therapies. *Journal of the National Cancer Institute Monograph.* 2003; (31): 117-24.
[158] Peng S, Ji H, Trimble C et al. Development of a DNA vaccine targeting human papillomavirus type 16 oncoprotein E6. *Journal of Virology.* 2004; 78(16): 8468-76.
[159] Stanley M. Chapter 17: Genital human papillomavirus infections--current and prospective therapies. *Journal of the National Cancer Institute Monograph.* 2003; (31): 117-24.
[160] The removal or destruction of a body part or tissue or its function. Ablation may be performed by surgery, hormones, drugs, lasers, radiofrequency, heat, freezing, or other methods.
[161] Stanley M. Chapter 17: Genital human papillomavirus infections--current and prospective therapies. *Journal of the National Cancer Institute Monograph.* 2003; (31): 117-24.
[162] Manetta A, Schubbert T, Chapman J et al. beta-Carotene treatment of cervical intraepithelial neoplasia: a phase II study. *Cancer Epidemiology, Biomarkers & Prevention.* 1996; 5(11): 929-32.

investigation.[163,164] Finally, an experimental treatment of HPV infection, photodynamic therapy, has shown variable efficacy.[165]

Secondary Prevention

Screening. Chronologically, conventional cervical cancer screening (the backdrop for future decisions about HPV tests) has a longer history than the development of vaccines or HPV DNA testing, but *logically* it belongs at this point in the discussion. Cancer screening is designed to detect the presence of precancerous cells or lesions and then prompt preventive measures. By identifying the precursor lesions associated with HPV infection, screening programs based on cytology[166] have reduced the incidence of invasive cervical cancer. One case study, a report in the UK, concluded that cervical cancer screening has prevented an epidemic that would have killed about 1 in 65 British women born since 1950, or about 6,000 deaths per year. In sum, at least 100,000 women born between 1951 and 1970 have been spared premature death in that country.[167] Even with such dramatic statistics, cost-effectiveness analyses of such programs have produced variable results. In countries where an abnormal test result can lead to substantial resources being invested in management, the cost per life year saved may run into many thousands of dollars.[168]

The most common screening test that goes beyond a regular gynecologic examination is the so-called Pap smear, the name being a shortened form of its originator, GN Papanicolaou.[169] He published results concerning the correlation between abnormalities in scraped cells and cervical cancer in a cornerstone paper in 1941. The aim, and the eventual result, of a simple screening test were to save "millions of women who would otherwise discovered their cancer of the cervix uteri at a non-curable stage."[170] As described earlier, precursor lesions usually appear a considerable length of time before a carcinoma; thus early detection and prompt management can lead to effective prevention of the disease.

The Pap smear is a screening rather than a diagnostic test. This means that any abnormal cells (so-called cervical intraepithelial neoplasia, or CIN) need to be followed up, starting with further examinations or tests (e.g., via colposcopy) to evaluate whether cancer itself is present or threatening.

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[163] Helm CW, Meyer NJ. Anti-inflammatory agents for preventing the progression of cervical intraepithelial neoplasia. Cochrane Gynaecological Cancer Group *Cochrane Database of Systematic Reviews.* 2005.

[164] Sethi N, Palefsky J. Treatment of human papillomavirus (HPV) type 16-infected cells using herpes simplex virus type 1 thymidine kinase-mediated gene therapy transcriptionally regulated by the HPV E2 protein. *Human Gene Therapy.* 2003; 14(1): 45-57.

[165] Stanley M. Chapter 17: Genital human papillomavirus infections--current and prospective therapies. *Journal of the National Cancer Institute Monograph.* 2003; (31): 117-24.

[166] The examination of cellular structure.

[167] Peto J, Gilham C, Fletcher O et al. The cervical cancer epidemic that screening has prevented in the UK. *The Lancet.* 2004; 364(9430): 249-56.

[168] Crum CP. The beginning of the end for cervical cancer? *New England Journal of Medicine.* 2002; 347(21): 1703-5.

[169] Alternate terminology includes PAP Test, Papanicolaou smear, cervical smear, cervical/vaginal cytology.

[170] Michalas SP. The Pap test: George N. Papanicolaou (1883-1962). A screening test for the prevention of cancer of uterine cervix. *European Journal of Obstetrics & Gynecology & Reproductive Biology.* 2000; 90(2): 135-8.

An abnormal Pap smear can be treated in a variety of ways, from conservative monitoring over a period of months to see if it returns to normal, to cryosurgery that freezes and destroys infected cells, to other procedures that excise problem tissue (see below).

The main strategic issues with Pap smears are:

- Identifying the most efficient age cut-offs and frequency of routine testing.
- Focusing on organized or opportunistic screening.[171]
- Introducing automatic scanning devices.[172]
- As noted earlier, how and when to integrate HPV DNA testing. The most common proposal is a primary Pap test with an adjunctive HPV test, especially if the cytological examination provides equivocal results.[173]
- Establishing the best protocol for monitoring tissue status after precancer intervention. A meta-analysis of the literature suggested that a double negative (i.e., no abnormality in Pap smear or HPV DNA test) at 6 months and then again at 24 months is sufficient to allow the person to return to a routine testing protocol.[174]

Despite the amazing track record of Pap smears, the motivation to also move towards HPV testing and / or vaccinations has emerged due to the high false-negatives seen in conventional testing. The false-negative rate with Pap smears ranges from 5 to 30%.[175] This results in, for example, about half of the cervical cancer cases in the US (representing about 7,000 women per year) occurring in those who are routinely screened. Cervical adenocarcinomas[176] in younger women are especially hard to prevent.[177] All of this uncertainty has prompted a large amount of litigation and huge awards. False positives are also a concern, given that the vast majority of HPV infections resolve spontaneously; of course, this challenge would also apply to the newer HPV tests.

We may be at the limit of human ability to derive appropriate and consistent information from the microscopic examination of Pap specimens. Thus efforts to increase the sensitivity of the test have focused more on the collection, handling and processing of specimens. So called thin layer (or liquid-based) technology involves collecting material with a soft brush and then rinsing it into a special fluid

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[171] Gustafsson L, Ponten J, Zack M et al. International incidence rates of invasive cervical cancer after introduction of cytological screening. *Cancer Causes Control.* 1997; 8(5): 755-63.

[172] Nieminen P, Vuorma S, Viikki M et al. Comparison of HPV test versus conventional and automation-assisted Pap screening as potential screening tools for preventing cervical cancer. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2004; 111(8): 842-8.

[173] Vassilakos P, de Marval F, Munoz M et al. Human papillomavirus (HPV) DNA assay as an adjunct to liquid-based Pap test in the diagnostic triage of women with an abnormal Pap smear. *International Journal of Gynecology & Obstetrics.* 1998; 61(1): 45-50.

[174] Zielinski GD, Bais AG, Helmerhorst TJ et al. HPV testing and monitoring of women after treatment of CIN 3: review of the literature and meta-analysis. *Obstetrical & Gynecological Survey.* 2004; 59(7): 543-53.

[175] Foulks MJ. The Papanicolaou smear: its impact on the promotion of women's health. *Journal of Obstetric, Gynecologic & Neonatal Nursing.* 1998; 27(4): 367-73.

[176] A cancer that develops in the lining or inner surface of an organ. As opposed to, for instance, cancer in squamous epithelial cells.

[177] Crum CP. The beginning of the end for cervical cancer? *New England Journal of Medicine.* 2002; 347(21): 1703-5.

preservative; from there, a thin-layer slide can be prepared which offers several improvements in terms of the quality of the cytological examination. This method has the advantage of providing material for any subsequent HPV DNA test as well.[178]

Resisting Critics / Increasing the Use of Screening. Whatever the risk, inconvenience and cost of false negatives, there is a tragic irony developing around looking for a "perfect" Pap smear: it may become too good to be affordable. The cost of more specialized specimen collection and preparation, computerized rescreening and malpractice insurance could mean the loss of an inexpensive, widely available Pap smear, which "will undoubtedly lead to increased cervical carcinoma."[179] The fact is that more women experience the development of cancer because of the failure to have a regular Pap smear than because of errors in cytodiagnosis.[180]

The Cochrane review of interventions to encourage cervical screening identified the following approaches:[181]

- invitations to women who are not overdue (letters, telephone calls, etc.)
- reminders to those overdue
- education (materials, home visits, etc.)
- counselling
- risk factor assessment
- improvements in screening methods
- economic incentives.

In all, 35 studies were identified in the review (27 being randomized controlled trials). The only extensive and strong evidence was for invitation letters; there was limited support for educational interventions.

Surgery and Other Forms of Ablation. It becomes a matter of judgment as to when to categorize surgery and other means of dealing with precancerous situations as interventions which truly have left behind the "world of prevention" and entered the arena of full cancer management. One way to enable a categorization of required interventions is the grading system that has been adopted to describe a Pap smear diagnosis. In the US, two levels of CIN (more generally known as squamous intraepithelial lesions, or SILs) are recognized: low-grade and high-grade; in contrast, the Europeans distinguish 3 levels of precancerous development.[182] High-grade SILs of the cervix require treatment because of their potential to progress to invasive cancer. One of the "advantages" of such cervical lesions is that they are localized, allowing for excision or other ablative therapies to be highly effective. Once we have entered this level of response, we are no longer treating HPV infection per se, though

[178] Michalas SP. The Pap test: George N. Papanicolaou (1883-1962). A screening test for the prevention of cancer of uterine cervix. *European Journal of Obstetrics & Gynecology & Reproductive Biology.* 2000; 90(2): 135-8.
[179] DeMay RM. Common problems in Papanicolaou smear interpretation. *Archives of Pathology & Laboratory Medicine.* 1997; 121(3): 229-38.
[180] Boronow RC. Death of the Papanicolaou smear? A tale of three reasons. *American Journal of Obstetrics & Gynecology.* 1998; 179(2): 391-6.
[181] Forbes C, Jepson R, Martin-Hirsch P. Interventions targeted at women to encourage the uptake of cervical screening. *Cochrane Database of Systematic Reviews.* 2002.
[182] Stanley M. Chapter 17: Genital human papillomavirus infections--current and prospective therapies. *Journal of the National Cancer Institute Monograph.* 2003; (31): 117-24.

effective treatment of CIN usually means that HPV is also cleared from the site.[183] Targeted antiviral therapies need to be developed in order to reduce the risk of recurrence after ablation.

Types of local destruction or excision used with high-grade SILs include:[184]

- cryotherapy
- cold coagulation
- electrodiathermy
- CO_2 laser
- cone biopsy (laser or knife)
- loop diathermy, or loop electrosurgical excision procedure (LEEP).

The Cochrane review of these approaches noted that there is "no obviously superior surgical technique" for treating CIN. The LEEP did seem to offer the least morbidity and the most reliable specimens for evaluating success of the treatment.[185] A very recent study of the cold-knife section technique showed it was very effective, with low morbidity and little adverse consequences for childbearing.[186] This is in stark contrast to the most invasive treatment for high-grade CIN or full cancer, namely, hysterectomy.

Much like subclinical infection (discussed above under primary prevention), the treatment of low-grade SILs is a complex matter, and varies widely across jurisdictions.[187] The approaches fall into three categories: surveillance (but this misses the small number of women who are at risk for disease progression); routine ablation (this tends to overtreat, for most infections and associated lesions are self-limiting); and selective ablation (this depends on triage through something like the new HPV DNA test). In the near term, the best improvement in any management protocol would be the clinical adoption of proven immunotherapies, such as a vaccine.[188] As noted earlier, interferon has shown some effectiveness against low-grades SILs, though it still offers inferior results compared to surgery.[189]

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[183] Elfgren K, Jacobs M, Walboomers JM et al. Rate of human papillomavirus clearance after treatment of cervical intraepithelial neoplasia. *Obstetrics & Gynecology.* 2002; 100(5 Pt 1): 965-71.
[184] Stanley M. Chapter 17: Genital human papillomavirus infections--current and prospective therapies. *Journal of the National Cancer Institute Monograph.* 2003; (31): 117-24.
[185] Martin-Hirsch PL, Paraskevaidis E, Kitchener, H. Surgery for cervical intraepithelial neoplasia. Cochrane Gynaecological Cancer Group. *Cochrane Database of Systematic Reviews.* 2005.
[186] Mazouni C, Porcu G, Haddad O et al. Conservative treatment of cervical intraepithelial neoplasia using a cold-knife section technique. *European Journal of Obstetrics & Gynecology & Reproductive Biology.* 2005:
[187] Scheungraber C, Kleekamp N, Schneider A. Management of low-grade squamous intraepithelial lesions of the uterine cervix. *British Journal of Cancer.* 2004; 90(5): 975-8.
[188] Stanley M. Chapter 17: Genital human papillomavirus infections--current and prospective therapies. *Journal of the National Cancer Institute Monograph.* 2003; (31): 117-24.
[189] Sikorski M, Zrubek H. Long-term follow-up of patients treated with recombinant human interferon gamma for cervical intraepithelial neoplasia. *International Journal of Gynaecology & Obstetrics.* 2003; 82(2): 179-85.

Hepatitis Viruses

The term "hepatitis virus" has traditionally been reserved for viruses that are hepatotropic, i.e., having a special affinity for or exerting a specific effect on the liver. Hepatitus B and C qualify, as they are strongly associated with liver infection, as well as liver cancer. The history of grouping such viruses together according to disease rather than virological properties means that at least four different virus families are represented by hepatitis viruses. Thus hepatitis B virus (HBV) belongs to the *Hepadnaviridae* family, and hepatitis C virus (HCV) to the *Flaviviridae*.[190] Neither of these viruses are singular agents; they each exhibit multiple genotypes, which may in turn represent variation in natural history and response to treatment (though the current evidence for variable disease expression with HCV subtypes is mixed).[191,192,193,194] A further complication is the fact that several viruses can be implicated in a particular case of liver disease, including hepatitis B and C interacting together, as well as Epstein Barr virus and HIV.[195,196,197,198,199]

Transmission of the Agent

As summarized in the epidemiological overview table above, there is a high risk of chronic HBV and / or HCV infection leading to liver cancer. Naturally, this is especially a concern in areas with an elevated infection rate in the first place. For example, more than 8% of the population in Africa and Asia are chronic carriers of HBV. This contrasts with the less than 2% prevalence in Western Europe, North America and Australia.[200] The prevalence of hepatitis C is also under 2% in developed countries, though in this case the mean worldwide rate is not much higher (i.e., the average global prevalence of HCV is 3%—about half that of chronic

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[190] Howard CR. Hepatitis viruses: a pandora's box? *Journal of Gastroenterology & Hepatology.* 2002; 17 Suppl: S464-7.

[191] Schaefer S. Hepatitis B virus: significance of genotypes. *Journal of Viral Hepatology.* 2005; 12(2): 111-24.

[192] Chen DS. Viral hepatitis: from A to E, and beyond? *Journal of the Formosa Medical Association.* 2003; 102(10): 671-9.

[193] Howard CR. Hepatitis C virus: clades and properties. *Journal of Gastroenterology & Hepatology.* 2002; 17 Suppl: S468-70.

[194] Alexopoulou A, Dourakis SP. Genetic heterogeneity of hepatitis viruses and its clinical significance. *Current Drug Targets--Inflammation & Allergy.* 2005; 4(1): 47-55.

[195] Shi J, Zhu L, Liu S et al. A meta-analysis of case-control studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma in China. *British Journal of Cancer.* 2005; 92(3): 607-12.

[196] Santolamazza M, Marinelli RM, Bacosi M et al. What kind of hepatitis? *Journal of International Medical Research.* 2001; 29(5): 441-4.

[197] McCarron B, Main J, Thomas HC. HIV and hepatotropic viruses: interactions and treatments. *International Journal of STD & AIDS.* 1997; 8(12): 739-45; quiz 45-6.

[198] Alberti A, Pontisso P, Chemello L et al. The interaction between hepatitis B virus and hepatitis C virus in acute and chronic liver disease. *Journal of Hepatology.* 1995; 22(1 Suppl): 38-41.

[199] Kottilil S, Jackson JO, Polis MA. Hepatitis B & hepatitis C in HIV-infection. *Indian Journal of Medical Research.* 2005; 121(4): 424-50.

[200] Maddrey WC. Hepatitis B--an important public health issue. *Clinical Laboratory.* 2001; 47(1-2): 51-5.

HBV).[201] This means that HCV is a widespread problem, not isolated geographically. It is, for instance, the most common bloodborne infection in the US.[202]

Hepatitis B is transmitted primarily by contact with contaminated blood or blood products—though saliva, semen, vaginal fluids, tears, breast milk and urine also can contain the virus.[203] Infection occurs in several ways:

- direct injection of infected blood or serums through transfusions, treatment with blood products, or accidental needlesticks
- haemodialysis
- transmission through skin openings such as burns or scratches
- direct introduction of saliva or blood into inner body surfaces (i.e., mucosa)
- breathing microscopic blood droplets or aerosols
- indirect transfer of blood or other secretions from obviously soiled surfaces or objects.

In endemic areas such as Asia, perinatal (or so-called vertical) transmission from mother to child during or soon after delivery is the most common means of spreading HBV. A related topic is the risk of infection through normal breastfeeding; the evidence to date strongly suggests "that any risk of transmission associated with breast milk is negligible compared to the high risk of exposure to maternal blood and body fluids at birth."[204] Any risks that do exist can be virtually eliminated through routine vaccination of infants.

In regions like North America where endemicity is low, the predominant means of hepatitis B transmission is horizontal, especially sexual activity and intravenous drug use.[205] The risk of HBV infection is notably high in homosexual men with multiple partners. For health care workers, being stuck with contaminated needles and syringes or being splattered with blood are also important ways of becoming infected with HBV.

Prior to the implementation of new policies surrounding therapeutic blood supplies in the early 1990s, receiving a transfusion during an operation was a risk factor for contracting hepatitis B and C; organ transplantation also fell into this category before new precautions were instituted. Today, the risk of new infection by these means in developed countries is approaching zero for several viruses,[206,207] though further

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[201] Yen T, Keeffe EB, Ahmed A. The epidemiology of hepatitis C virus infection. *Journal of Clinical Gastroenterology.* 2003; 36(1): 47-53.
[202] Rose VL. CDC issues new recommendations for the prevention and control of hepatitis C virus infection. *American Family Physician.* 1999; 59(5): 1321-3.
[203] Atkins M, Nolan M. Sexual transmission of hepatitis B. *Current Opinions in Infectious Diseases.* 2005; 18(1): 67-72.
[204] Hepatitis B and breastfeeding. World Health Organization Update. 1996. Available at http://www.who.int/child-adolescent-health/New_Publications/NUTRITION/updt-22.htm. Accessed May 2005.
[205] Maddrey WC. Hepatitis B--an important public health issue. *Clinical Laboratory.* 2001; 47(1-2): 51-5.
[206] Dodd RY. Current safety of the blood supply in the United States. *International Journal of Hematology.* 2004; 80(4): 301-5.
[207] Soldan K, Barbara JA, Ramsay ME et al. Estimation of the risk of hepatitis B virus, hepatitis C virus and human immunodeficiency virus infectious donations entering the blood supply in England, 1993-2001. *Vox Sanguinis.* 2003; 84(4): 274-86.

progress needs to be made with HBV detection specifically,[208] as well as screening tissue grafts.[209] Unfortunately, with its long latency period, chronic hepatitis originally derived through transfusions and transplants will continue to manifest itself for some decades.

Hepatitis C is transmitted by blood to blood contact only. This means that blood infected with hepatitis C must come into direct contact with the bloodstream of another person. Even the smallest amounts of blood can transmit hepatitis C. Transmission occurs through:

- sharing of equipment used to inject drugs
- unsterile tattooing, body piercing and skin penetration procedures
- household practices (such as sharing razor blades and toothbrushes)
- occupational procedures (e.g., needlestick and sharps injuries)
- haemodialysis
- certain sexual activities
- mother to baby.

In the setting of developed countries, intravenous drug use stands out as the predominant behavioural risk factor, accounting for over 40% of HCV cases (or 3 times the proportion due to sexual activities).[210,211] Almost 80% of injecting-drug users in the US are known to be infected with HCV.[212]

By contrast, the risk of either sexual or perinatal transmission of HCV is estimated to be only about 5%.[213,214] A 2005 study revealed that one third to one half of children infected with HCV acquired the virus in utero.[215] Again, breastfeeding is a matter of some interest; as with hepatitis B, the current conclusion is that it is safe for mothers with hepatitis C to breastfeed.[216]

Co-factors and Correlates

Other than hepatitis infection, the main modifiable risk factors for liver cancer in developed countries are excessive alcohol consumption and cirrhosis. In fact, these

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[208] Chiavetta JA, Escobar M, Newman A et al. Incidence and estimated rates of residual risk for HIV, hepatitis C, hepatitis B and human T-cell lymphotropic viruses in blood donors in Canada, 1990-2000. *Canadian Medical Association Journal.* 2003; 169(8): 767-73.

[209] Zou S, Dodd RY, Stramer SL et al. Probability of viremia with HBV, HCV, HIV, and HTLV among tissue donors in the United States. *New England Journal of Medicine.* 2004; 351(8): 751-9.

[210] Alter MJ. Epidemiology of hepatitis C. *Hepatology.* 1997; 26(3 Suppl 1): 62S-5S.

[211] Perez CM, Suarez E, Torres EA et al. Seroprevalence of hepatitis C virus and associated risk behaviours: a population-based study in San Juan, Puerto Rico. *International Journal of Epidemiology.* 2005; 34(3): 593-9.

[212] Data available at http://www.cdc.gov/ncidod/diseases/hepatitis/c_training/edu/1/default.htm. Accessed May 2005.

[213] Dienstag JL. Sexual and perinatal transmission of hepatitis C. *Hepatology.* 1997; 26(3 Suppl 1): 66S-70S.

[214] Newell ML, Pembrey L. Mother-to-child transmission of hepatitis C virus infection. *Drugs Today.* 2002; 38(5): 321-37.

[215] Mok J, Pembrey L, Tovo PA et al. When does mother to child transmission of hepatitis C virus occur? *Archives of Disease in Childhood Fetal & Neonatal Edition.* 2005; 90(2): F156-60.

[216] Mast EE. Mother-to-infant hepatitis C virus transmission and breastfeeding. *Advances in Experimental Medicine & Biology.* 2004; 554: 211-6.

factors, as well as diabetes (and perhaps obesity), interact synergistically with viral infection to increase the rate of cancer development.[217] The same multiplicative effect applies with exposure to aflatoxin in poorly stored grains, though this mainly affects populations in sub-Saharan Africa and Asia.[218]

Co-infections are an especially difficult problem. Combined hepatitis virus infections account for 5 to 10% of all HCV cases; such patients, infected with HCV and HBV (and sometimes hepatitis D), are often associated with more severe forms of liver disease and less responsiveness to interferon (see below). HCV is a common co-infection with HIV; a unique challenge is the fact that HIV drug treatments can themselves be hepatotoxic.[219]

Natural History and Carcinogenesis

Understanding the disease course in hepatitis B and C is a complex task, partly impeded by incomplete epidemiological data.

The course of hepatitis B from a clinical perspective can be categorized into four stages of varying duration: [220]

I. Active viral replication / immune system tolerance.
II. Initial immune response, inflammation and hepatic tissue injury.
III. Clearance of virus-infected cells.
IV. Full immunity.

If a person does not proceed beyond stage II, they become by definition chronic carriers of HBV. Cirrhosis and hepatocellular carcinoma (HCC) are common sequelae of a (usually) prolonged experience of chronic HBV; these diseases occur in 25-30% of carriers.[221]

This general progression needs to be modified according to the age when the infection occurs. In the perinatal type of transmission experienced in endemic areas, a large percentage of the infected infants become carriers; in contrast, a smaller proportion of those infected as children or adults develop chronic forms of the disease. Of HBV carriers, 1 to 2% develop cirrhosis each year (some studies put the rate as high as 10 to 12%). The presence of cirrhosis is a major risk factor for hepatocellular carcinoma. Cancer develops in 1.5 to 4% of cirrhotic hepatitis B patients each year, usually decades after they had first become infected.[222] As indicated in the table above, this progression to HCC eventually accounts for 40 to 60% of liver cancers worldwide.

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[217] Yuan JM, Govindarajan S, Arakawa K et al. Synergism of alcohol, diabetes, and viral hepatitis on the risk of hepatocellular carcinoma in blacks and whites in the U.S. *Cancer.* 2004; 101(5): 1009-17.
[218] Yu MC, Yuan JM. Environmental factors and risk for hepatocellular carcinoma. *Gastroenterology.* 2004; 127(5 Suppl 1): S72-8.
[219] Teoh NC, Farrell GC. Management of chronic hepatitis C virus infection: a new era of disease control. *Internal Medicine Journal.* 2004; 34(6): 324-37.
[220] Custer B, Sullivan SD, Hazlet TK et al. Global epidemiology of hepatitis B virus. *Journal of Clinical Gastroenterology.* 2004; 38(10 Suppl): S158-68.
[221] Maddrey WC. Hepatitis B--an important public health issue. *Clinical Laboratory.* 2001; 47(1-2): 51-5.
[222] See the summary at http://www.hepnet.com/update6.html. Accessed May 2005.

The natural history and epidemiology of hepatitis C infection is still being elucidated, which is not surprising given that the virus was only identified 15 years ago.[223] Some facts have become clearer; for instance, research has shown that fully 75% of persons with HCV will develop chronic infection.[224] Beyond that, it seems that HCV progresses less intensely than HBV. A systematic review of the literature in 2001 suggested that for persons infected with HCV in young adulthood, less than 10% will develop cirrhosis within 20 years.[225] A Markov modelling exercise from 2002 pegged the rate more precisely at 7% after 20 years, and only 20% after 40 years of infection.[226] However, the risks are double or more for people infected after age 40.[227] The annual incidence of hepatocellular carcinoma among cirrhotic HCV patients is similar to that with HBC, 1.5 to 2.5%.[228] Putting it differently, the total risk for developing liver cancer among viral cirrhosis patients is approximately 7%.[229]

As indicated earlier, this end-point for HCV infection accounts for 20 to 30% of the global burden of liver cancer. Although creating less cancer than HBV, the sobering fact remains that liver carcinoma derived from any source is deadly; the annual death rate is about 80% in industrialized countries.[230]

Preventive Interventions

The urgency for preventive measures around the hepatitis viruses arises not just from current rate of liver cancer and its high mortality, but from the impact of other serious diseases such as cirrhosis and the risks related to the vast "reservoirs" of viral carriers around the world. Exacerbating this scenario is that fact that HBV, HCV and HIV have similar transmission routes, leading to high co-infection rates; the conditions caused by these viruses interact synergistically, with the potential for "a major health care catastrophe in the coming years."[231] This "perfect storm" of conditions and circumstances ought to motivate a concerted effort to control if not eradicate these viral threats.

We will now examine each of the categories of prevention in reference to HBV and HCV, and, where possible, review their effectiveness in reducing the burden of cancer.

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[223] Freeman AJ, Marinos G, Ffrench RA et al. Immunopathogenesis of hepatitis C virus infection. *Immunology & Cell Biology.* 2001; 79(6): 515-36.
[224] Global burden of disease (GBD) for hepatitis C. *Journal of Clinical Pharmacology.* 2004; 44(1): 20-9.
[225] Freeman AJ, Dore GJ, Law MG et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology.* 2001; 34(4 Pt 1): 809-16.
[226] Dore GJ, Freeman AJ, Law M et al. Is severe liver disease a common outcome for people with chronic hepatitis C? *Journal of Gastroenterology & Hepatology.* 2002; 17(4): 423-30.
[227] Global burden of disease (GBD) for hepatitis C. *Journal of Clinical Pharmacology.* 2004; 44(1): 20-9.
[228] Global burden of disease (GBD) for hepatitis C. *Journal of Clinical Pharmacology.* 2004; 44(1): 20-9.
[229] Moriwaki H. Prevention of liver cancer: basic and clinical aspects. *Experimental & Molecular Medicine.* 2002; 34(5): 319-25.
[230] El-Serag HB, Mason AC, Key C. Trends in survival of patients with hepatocellular carcinoma between 1977 and 1996 in the United States. *Hepatology.* 2001; 33(1): 62-5.
[231] Kottilil S, Jackson JO, Polis MA. Hepatitis B & hepatitis C in HIV-infection. *Indian Journal of Medical Research.* 2005; 121(4): 424-50.

Early Primary Prevention

Because the relative importance of various modes of transmission differs from country to country, the most relevant control strategies for each setting need to be carefully selected.[232] Another consideration in setting priorities is that while HCV has a lower global prevalence than HBV, HCV causes the most hepatocellular carcinoma in economically developed regions.[233] A final factor to note is that the ranking of interventions is a moving target. For example, now that the blood supply has been made almost completely risk-free, this is no longer a preventive area where substantial new gains can be made (though the robust maintenance of safety programs remains an issue).

As for HBV in a context like Canada, the first focus for preventing exposure to the virus should be public health education and other interventions around high-risk sexual practices and intravenous drug use. These measures to prevent transmission are also important for HCV (and HIV—see below); this is especially true for the area of drug injection. Assuming that Canada parallels the US, we can conclude that "prevention of illegal drug injecting will eliminate the greatest risk factor for HCV infection."[234]

Obstacles. The control of hepatitis infection can be seen as a paradigm for the challenges encountered with regard to many of the agents in this report. The obstacles to developing preventive strategies include: asymptomatic carriers; limitations in testing procedures; long latency before cancer development; the fact that addictions are difficult to overcome; surveillance difficulties; socioeconomic forces influencing prosecution; the complication of psychological problems and full mental illness; lack of trust of authorities; concerns about privacy and discrimination (regarding test results and participation in public programs); insufficient political capital for more controversial "harm reduction" or legal measures; and (as always) limited resources.

Effectiveness of Programs. It is outside the scope of this chapter to systematically describe and evaluate the multitude of drug and sexually-transmitted infection (STI) programs in use around the world. Aside from the sheer volume of information to consider, there is the fact that it is rare for the interventions, if they have been evaluated at all, to be tied to the specific end-point of reduced hepatitis prevalence and / or lower cancer rates. With regard to STI programs, in particular, we would need to depend on evaluations related to other viruses to serve as a proxy for hepatitis control. Whatever the obstacles, based on the assumption of favourable impacts on disease when risky behaviours are eliminated or mitigated, a few notable drug use prevention programs will be described, as well as studies related to individual- or group-based approaches. With respect to STI prevention, we refer the reader to the description of approaches under the human papillomavirus section above.

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[232] Mast EE, Alter MJ, Margolis HS. Strategies to prevent and control hepatitis B and C virus infections: a global perspective. *Vaccine.* 1999; 17(13-14): 1730-3.
[233] Monto A, Wright TL. The epidemiology and prevention of hepatocellular carcinoma. *Seminars in Oncology.* 2001; 28(5): 441-9.
[234] Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. *MMWR Recommendations & Reports.* 1998; 47(RR-19): 1-39.

Syringe and Needle Exchange Programs. The centrepiece of many harm reduction initiatives for injection drug users (IDUs) is the prescription or distribution of sterile injection equipment to prevent re-use by a single person and (more pertinent to our topic) sharing between users. The Centers for Disease Control and Prevention (CDC) in the US officially recommended community-based syringe and needle-exchange programs in 1998, though the calls for such an approach and the first pilot projects go back to the 1980s.[235,236] As of 2002, 180 needle-exchange programs were operating in the US.[237] The CDC report noted that several studies up to 1998 had produced two crucial conclusions: such measures can be effective in reducing the incidence of bloodborne virus transmission; and they do not lead to the negative side effect of increased drug use. An example of a study from that era was conducted in Tacoma; non-use of the exchange program was associated with a sixfold greater risk of hepatitis B and a sevenfold greater risk of hepatitis C.[238] Subsequent research has confirmed that equipment exchange programs can reduce syringe sharing among IDUs[239] and decrease HCV prevalence in this at-risk population.[240] However, other results suggest that an exchange program alone may not be enough to produce positive results; the same lead researcher from the Tacoma study found contrary results in a Seattle-based syringe exchange program.[241] Likewise, after almost a decade of operation, the needle exchange initiative in Vancouver (the largest in North America) had failed to have much impact on needle-sharing behaviour or HCV rates.[242] Other studies confirm that, while prevention efforts among IDUs have managed to control HBV and HIV rates, the transmission of HCV has continued at very high levels.[243] One fact put forward to explain this is the high efficiency of bloodborne transmission with HCV.[244] As well, the special vulnerability of and

[235] Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. *MMWR Recommendations & Reports.* 1998; 47(RR-19): 1-39.

[236] Vlahov D, Des Jarlais DC, Goosby E et al. Needle exchange programs for the prevention of human immunodeficiency virus infection: epidemiology and policy. *American Journal of Epidemiology.* 2001; 154(12 Suppl): S70-7.

[237] Data available from AIDS Alert at http://www.ahcpub.com/ahc_root_html/hot/archive/aa062002.html. Accessed May 2005.

[238] Hagan H, Jarlais DC, Friedman SR et al. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. *American Journal of Public Health.* 1995; 85(11): 1531-7.

[239] Bluthenthal RN, Kral AH, Gee L et al. The effect of syringe exchange use on high-risk injection drug users: a cohort study. *AIDS.* 2000; 14(5): 605-11.

[240] MacDonald MA, Wodak AD, Dolan KA et al. Hepatitis C virus antibody prevalence among injecting drug users at selected needle and syringe programs in Australia, 1995-1997. Collaboration of Australian NSPs. *Medical Journal of Australia.* 2000; 172(2): 57-61.

[241] Hagan H, McGough JP, Thiede H et al. Syringe exchange and risk of infection with hepatitis B and C viruses. *American Journal of Epidemiology.* 1999; 149(3): 203-13.

[242] Strathdee SA, Patrick DM, Currie SL et al. Needle exchange is not enough: lessons from the Vancouver injecting drug use study. *AIDS.* 1997; 11(8): F59-65.

[243] van Beek I, Dwyer R, Dore GJ et al. Infection with HIV and hepatitis C virus among injecting drug users in a prevention setting: retrospective cohort study. *British Medical Journal.* 1998; 317(7156): 433-7.

[244] Coutinho RA. HIV and hepatitis C among injecting drug users. *British Medical Journal.* 1998; 317(7156): 424-5.

expanding cohort of newer (usually younger) IDUs has suggested the need to target them with prevention messages and measures.[245]

The most comprehensive analysis of equipment exchange programs was carried out by Australian researchers in 2002, though some of the methodology has been questioned.[246] They evaluated their own country's 16-year old exchange effort very positively; an estimated 21,000 HCV infections and 90 deaths had been averted. The cost of the various programs, at $122 million, was more than made up by $2.4 billion in avoided government costs related to treatment of HCV and HIV.[247] Nonetheless, the study acknowledged that overall HCV rates in Australia had continued to rise over the 1990s, reinforcing the fact that an integrated approach using several interventions is probably going to be more effective than a needle exchange program alone (see below).

At the same time, the exchange programs themselves may need enhancement. Different authorities have advocated offering a variety of options for syringe access by relevant populations, including prescriptions and syringe deregulation.[248,249] In addition, given the efficiency of HCV transmission by blood, it may be important to focus on modifying more than needle-sharing behaviours in IDUs.[250,251,252] As one review concluded, "control of HCV may necessitate the use of practices that guarantee elimination of exposure to equipment contaminated with even small amounts of blood."[253]

Integrated Approaches with Injecting Drug Users. Although there has been circumstantial evidence that comprehensive harm reduction approaches may have a positive impact on HCV rates, notably in the UK, more recent data has called this conclusion into question.[254,255] Nonetheless, there is a sound face-value rationale for multi-intervention strategies, such as The City of Vancouver's well-known Four Pillars program, as well as its pilot project involving a safer injection site.

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[245] Thorpe LE, Ouellet LJ, Levy JR et al. Hepatitis C virus infection: prevalence, risk factors, and prevention opportunities among young injection drug users in Chicago, 1997-1999. *Journal of Infectious Diseases.* 2000; 182(6): 1588-94.
[246] Copeman M. Injecting drug use in Australia: needle/syringe programs prove their worth, but hepatitis C still on the increase. *Medical Journal of Australia.* 2003; 179(2): 119; author reply.
[247] Law MG, Batey RG. Injecting drug use in Australia: needle/syringe programs prove their worth, but hepatitis C still on the increase. *Medical Journal of Australia.* 2003; 178(5): 197-8.
[248] Rich JD, Wolf FA, Macalino G. Strategies to improve access to sterile syringes for injection drug users. *AIDS Reader.* 2002; 12(12): 527-35.
[249] Stancliff S, Agins B, Rich JD et al. Syringe access for the prevention of blood borne infections among injection drug users. *BMC Public Health.* 2003; 3(1): 37.
[250] Hagan H, Thiede H. Changes in injection risk behavior associated with participation in the Seattle needle-exchange program. *Journal of Urban Health.* 2000; 77(3): 369-82.
[251] Thorpe L, Ouellet L, Hershow R et al. The multiperson use of non-syringe injection equipment and risk of hepatitis c infection in a cohort of young adult injection drug users, chicago 1997-1999. *Annals of Epidemiology.* 2000; 10(7): 472-3.
[252] Crofts N, Caruana S, Bowden S et al. Minimising harm from hepatitis C virus needs better strategies. *British Medical Journal.* 2000; 321(7265): 899.
[253] Hagan H, Des Jarlais DC. HIV and HCV infection among injecting drug users. *Mount Sinai Journal of Medicine.* 2000; 67(5-6): 423-8.
[254] Hope VD, Judd A, Hickman M et al. Prevalence of hepatitis C among injection drug users in England and Wales: is harm reduction working? *American Journal of Public Health.* 2001; 91(1): 38-42.
[255] Judd A, Hickman M, Jones S et al. Incidence of hepatitis C virus and HIV among new injecting drug users in London: prospective cohort study. *British Medical Journal.* 2005; 330(7481): 24-5.

Other Interventions. Having identified the priority "front-line" approaches to controlling exposure, it is also important to maintain vigilance around well-established areas. This includes continuing high standards around screening for HCV in donated blood supplies. The latency period means that improvements in screening introduced in the 1990s should result in a decreased incidence of HCV-positive liver cancer in 2010 to 2015.[256]

Primary Prevention

Vaccination. Both adults and children can be protected by an HBV vaccine developed over 20 years ago. It is considered to be one of the great public health achievements.[257] A special instance is vertical (from mother to newborn) transmission; this can be avoided by vaccinating infants born to HBV-positive women. The case for universal vaccination of children is more controversial, though such a policy is in place in many countries.[258] For example, in Taiwan, where HBV-related childhood liver cancer was once endemic, the effect of universal HBV vaccination has almost eradicated this form of paediatric cancer.[259]

HCV vaccine development remains at an early stage, and progress is characterized as being "agonisingly slow"[260,261]

Co-factors. Any of the many programs to reduce excessive drinking would theoretically reduce the rate of liver cancer, even in people with existing hepatitis infections.[262] However, the health effects of reduced drinking in infected patients have not yet been quantified; the same gap exists in research around obesity, though one study of weight reduction did show a reversal of hepatic fibrosis.[263]

Testing & Treatment. Information on the effect of virus eradication from *asymptomatic* carriers on the subsequent risk of liver cancer is not available. This makes the benefit of routine testing for hepatitis virus infection rather questionable, at least from the perspective of cancer control. The usual indication for antiviral treatment (at least that which will be covered by government or third party payers) is the presence of symptoms, i.e., detection of a certain stage of fibrosis development,

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[256] Moriwaki H. Prevention of liver cancer: basic and clinical aspects. *Experimental & Molecular Medicine.* 2002; 34(5): 319-25.
[257] Achievements in public health: hepatitis B vaccination—United States, 1982-2002. *M & Meekly Report.* 2002; 51(25): 549-52.
[258] Boxall EH, Jefferson TO, Pratt M et al. Vaccines for preventing hepatitis B in high risk newborn infants. Cochrane Hepato-Biliary Group. *Cochrane Database of Systematic Reviews.* 1997.
[259] Chang MH, Chen CJ, Lai MS et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *New England Journal of Medicine.* 1997; 336(26): 1855-9.
[260] Krahn MD, John-Baptiste A, Yi Q et al. Potential cost-effectiveness of a preventive hepatitis C vaccine in high risk and average risk populations in Canada. *Vaccine.* 2005; 23(13): 1549-58.
[261] Koff RS. Hepatitis vaccines: recent advances. *International Journal for Parasitology.* 2003; 33(5-6): 517-23.
[262] See the information from the *Alcohol and Cancer Working Group* of the Toronto Cancer Prevention Coalition at http://www.apolnet.org/resources/apu0003.pdf. Accessed June 2005.
[263] Teoh NC, Farrell GC. Management of chronic hepatitis C virus infection: a new era of disease control. *Internal Medicine Journal.* 2004; 34(6): 324-37.

as assessed by a liver biopsy. Developing *non-invasive* methods to predict disease severity is an active area of research.[264]

There is good evidence that removing HCV from chronic hepatitis patients significantly reduces the risk of liver cancer.[265,266,267] A sustained HCV response after antiviral therapy for hepatitis can lead to more than a 90% reduction in the risk of primary liver cancer, though some studies demonstrate a more modest 50% reduction.[268,269] The same type of effect is seen in patients with full cirrhosis, though the reduction in risk is less dramatic. The main issue at hand is: exactly how much of a sustained viral response can be achieved?

The traditional drug of choice to clear hepatitis viruses has been interferon, a protein that modulates biological responses. As demonstrated in a Cochrane review, interferon is effective in clearing acute HCV infections in about a third of patients.[270] The results with chronic infection with hepatitis viruses are more modest.

In addition to interferon, lamivudine is approved for HBV. Neither have been particularly effective in clearing a chronic infection, and few studies support the use of such chemotherapy for actually preventing HBV-associated liver cancer.[271,272,273]

Combination therapy with ribavirin improves the HCV response rate to interferon (as much as doubling it), as does altering the interferon molecule in a process called pegylation.[274] The latter technology is more expensive than conventional interferon combined with ribavirin, but the improved response rates (i.e., 40 to 85% for HCV, depending on the genotype) probably make it cost-effective.[275] The improvement rates using interferon are much lower for relapsing and cirrhotic patients (i.e., those

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[264] Teoh NC, Farrell GC. Management of chronic hepatitis C virus infection: a new era of disease control. *Internal Medicine Journal.* 2004; 34(6): 324-37.
[265] Moriwaki H. Prevention of liver cancer: basic and clinical aspects. *Experimental & Molecular Medicine.* 2002; 34(5): 319-25.
[266] Moriwaki H. Prevention of liver cancer: current strategies and future perspectives. *International Journal of Clinical Oncology.* 2002; 7(1): 27-31.
[267] Tabor E. Interferon for preventing and treating hepatocellular carcinoma associated with the hepatitis B and C viruses. *Digestive & Liver Diseases.* 2003; 35(5): 297-305.
[268] Teoh NC, Farrell GC. Management of chronic hepatitis C virus infection: a new era of disease control. *Internal Medicine Journal.* 2004; 34(6): 324-37.
[269] Yoshida H, Shiratori Y, Moriyama M et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Annals of Internal Medicine.* 1999; 131(3): 174-81.
[270] Myers RP, Regimbeau C, Thevenot T et al. Interferon for acute hepatitis C. Cochrane Hepato-Biliary Group. *Cochrane Database of Systematic Reviews.* 2001.
[271] Tabor E. Interferon for preventing and treating hepatocellular carcinoma associated with the hepatitis B and C viruses. *Digestive & Liver Diseases.* 2003; 35(5): 297-305.
[272] Rasi G, Pierimarchi P, Sinibaldi Vallebona P et al. Combination therapy in the treatment of chronic viral hepatitis and prevention of hepatocellular carcinoma. *International Immunopharmacology.* 2003; 3(8): 1169-76.
[273] Wong JB, Koff RS, Tine F et al. Cost-effectiveness of interferon-alpha 2b treatment for hepatitis B e antigen-positive chronic hepatitis B. *Annals of Internal Medicine.* 1995; 122(9): 664-75.
[274] Teoh NC, Farrell GC. Management of chronic hepatitis C virus infection: a new era of disease control. *Internal Medicine Journal.* 2004; 34(6): 324-37.
[275] Siebert U, Sroczynski G, Rossol S et al. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut.* 2003; 52(3): 425-32.

with severe liver disease, most need of treatment—many of whom are infected with HCV of genotype 1).[276]

Several novel therapies for hepatitis virus infections have entered phase I trials in the last two years.[277] The relatively poor response to current HBV therapies is motivating adoption of combination treatments that make use of nucleoside analogues and immunomodulators alongside interferon. This approach is also proving useful for the significant proportion of the HCV-infected population that does not respond to interferon therapy.[278]

In addition to the universal use in children and adolescents, HBV vaccination is recommended for those with chronic liver disease. The increased risk with co-infection also suggests the routine use of hepatitis A vaccine with such patients.[279]

Secondary Prevention

Screening. Patients who do not respond to antiviral treatment may progress to full cirrhosis. They may be screened for the emergence of early cancer lesions, though the efficacy and the cost-effectiveness of such protocols have not been proven.[280] Lesions that are detected can prompt treatments that may cure the cancer, from surgical resection and other ablative procedures to full liver transplantation.[281] The use of interferon as a conservative measure to treat liver cancer has shown enough promise to warrant further research.[282]

Treatment. A specialized form of prevention with liver cancer involves protecting against recurrence or a new primary cancer after a patient has received surgery, ablation or other therapies for their initial liver cancer. Successful interventions in this regard have included the use of retinoids (compounds related to vitamin A) and interferon.[283,284,285]

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[276] Rasi G, Pierimarchi P, Sinibaldi Vallebona P et al. Combination therapy in the treatment of chronic viral hepatitis and prevention of hepatocellular carcinoma. *International Immunopharmacology.* 2003; 3(8): 1169-76.
[277] Teoh NC, Farrell GC. Management of chronic hepatitis C virus infection: a new era of disease control. *Internal Medicine Journal.* 2004; 34(6): 324-37.
[278] Rasi G, Pierimarchi P, Sinibaldi Vallebona P et al. Combination therapy in the treatment of chronic viral hepatitis and prevention of hepatocellular carcinoma. *International Immunopharmacology.* 2003; 3(8): 1169-76.
[279] Reiss G, Keeffe EB. Review article: hepatitis vaccination in patients with chronic liver disease. *Alimentary Pharmacology & Therapeutics.* 2004; 19(7): 715-27.
[280] McHutchison JG, Manns M, Patel K et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology.* 2002; 123(4): 1061-9.
[281] Teoh NC, Farrell GC. Management of chronic hepatitis C virus infection: a new era of disease control. *Internal Medicine Journal.* 2004; 34(6): 324-37.
[282] Tabor E. Interferon for preventing and treating hepatocellular carcinoma associated with the hepatitis B and C viruses. *Digestive & Liver Diseases.* 2003; 35(5): 297-305.
[283] Muto Y, Moriwaki H, Saito A. Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma. *New England Journal of Medicine.* 1999; 340(13): 1046-7.
[284] Ikeda K, Arase Y, Saitoh S et al. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor-A prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology.* 2000; 32(2): 228-32.

Helicobacter pylori

The bacterium *Helicobacter pylori* is able to invade and colonize the human stomach. There it can interact with gastric epithelial cells, leading to a number of tissue changes and disease conditions, including: inflammation, loss of mucosa (i.e., an ulcer), and development of masses from benign polyps to full cancers.[286] The latter include gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. Generally, the association between *H. pylori* and gastric cancer is well-accepted, though the debate is not completely concluded. As an example of supporting data, infected individuals appear to have a 6-fold increased risk of developing an adenocarcinoma compared to the uninfected population. Overall, it is proposed that about 70% of gastric cancers can be attributed to *H. pylori*.[287]

H. pylori was first cultured in 1982, and classified as a carcinogen over 10 years ago; an entire scientific journal devoted to the biology of this one bacterium accounts for some of the thousands of articles published on *H. pylori* and related conditions each year.

As noted in the table in the introduction of this report, *H. pylori* exists in up to 50% of the global population, making it the most common chronic bacterial infection in humans. In developing countries, the dominant means of transmission is consumption of sewage-contaminated water or food. Oral-to-oral transmission is also possible (e.g., by kissing), as well as via contaminated secretions (such as vomit). Generally, the bacterium is harder to contract in developed countries, but there, as in other parts of the world, transmission typically occurs in early childhood within a family context.[288,289] Studies show, however, that mother-to-child transmission is rare, though it may occur through breastfeeding.[290]

It is known that only certain strains are highly pathogenic, so only a subset of the population carrying the bacteria actually experience disease. A larger proportion develops some sort of pre-neoplasias, but ultimately only 2% of infected people will get a malignancy. The infected pool is large, however, resulting in stomach cancer being the second most common cancer in the world. Of related significance is the survival rate, i.e., less than 20% after 5 years. In sum, this represents an enormous disease burden.

Smoking is an important co-factor; among patients carrying the most dangerous strain of bacteria, the risk of developing some form of cancer is almost three times

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[285] Kubo S, Nishiguchi S, Hirohashi K et al. Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized, controlled trial. *Annals of Internal Medicine.* 2001; 134(10): 963-7.

[286] de Luca A, Iaquinto G. Helicobacter pylori and gastric diseases: a dangerous association. *Cancer Letters.* 2004; 213(1): 1-10.

[287] McLoughlin RM, Sebastian SS, O'Connor HJ et al. Review article: test and treat or test and scope for Helicobacter pylori infection. Any change in gastric cancer prevention? *Alimentary Pharmacology & Therapeutics.* 2003; 17 Suppl 2: 82-8.

[288] Herrera AG. Helicobacter pylori and food products: a public health problem. *Methods in Molecular Biology.* 2004; 268: 297-301.

[289] Moss SF, Sood S. Helicobacter pylori. *Current Opinions in Infectious Diseases.* 2003; 16(5): 445-51.

[290] Kitagawa M, Natori M, Katoh M et al. Maternal transmission of Helicobacter pylori in the perinatal period. *Journal of Obstetrics & Gynaecology Research.* 2001; 27(4): 225-30.

higher in those who smoke.[291] Diet can hurt or help; excessive salt and (perhaps) alcohol are risk factors, whereas the antioxidants in regularly consumed vegetables and fruit are thought to decrease the risk of gastric cancer by up to a third.[292,293,294]

Two primary pathways are thought to be involved with gastric carcinogenesis: proliferation of epithelial cells in the gut and oxidative stress of stomach mucosa.[295] The precise molecular mechanisms at work in these processes are still being worked out, including the defences which protect the bacterium in unstable, often hostile microenvironment of the stomach.[296] Recently, a major advance occurred in our understanding of why certain patients develop serious disease; apparently, there can be a 90-fold difference in the risk of gastric cancer depending on particular mixtures of *H. pylori* virulence and host genetics.[297,298]

The disease induced by *H. pylori* is not limited to the stomach. Infection with the bacteria has been linked to squamous cell cancer in the larynx,[299] and esophagus[300] (though it is actually thought to be *protective* against esophageal adenocarcinoma).[301]

Preventive Interventions

Given the ubiquity of the bacterium and its ease of transmission, it seems unlikely that early primary prevention will ever be the cornerstone of a public health strategy, at least not in the developed world. The measures promoted in developing countries do not really apply in North America.[302]

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[291] Brenner H, Arndt V, Bode G et al. Risk of gastric cancer among smokers infected with *Helicobacter pylori*. *International Journal of Cancer.* 2002; 98(3): 446-9.
[292] Tsugane S. Salt, salted food intake, and risk of gastric cancer: epidemiologic evidence. *Cancer Science.* 2005; 96(1): 1-6.
[293] Correa P. Helicobacter pylori infection and gastric cancer. *Cancer Epidemiology, Biomarkers & Prevention.* 2003; 12(3): 238s-41s.
[294] Lunet N, Barros H. Helicobacter pylori infection and gastric cancer: facing the enigmas. *International Journal of Cancer.* 2003; 106(6): 953-60.
[295] Mucosa refers to the moist tissue that lines some organs and body cavities (such as the nose, mouth, lungs and stomach).
[296] de Luca A, Iaquinto G. Helicobacter pylori and gastric diseases: a dangerous association. *Cancer Letters.* 2004; 213(1): 1-10.
[297] Figueiredo C, Machado JC, Pharoah P et al. Helicobacter pylori and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. *Journal of the National Cancer Institute.* 2002; 94(22): 1680-7.
[298] Rad R, Prinz C, Neu B et al. Synergistic effect of Helicobacter pylori virulence factors and interleukin-1 polymorphisms for the development of severe histological changes in the gastric mucosa. *Journal of Infectious Diseases.* 2003; 188(2): 272-81.
[299] Aygenc E, Selcuk A, Celikkanat S et al. The role of Helicobacter pylori infection in the cause of squamous cell carcinoma of the larynx. *Otolaryngology - Head & Neck Surgery.* 2001; 125(5): 520-1.
[300] Ye W, Held M, Lagergren J et al. Helicobacter pylori infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *Journal of the National Cancer Institute.* 2004; 96(5): 388-96.
[301] de Martel C, Llosa AE, Farr SM et al. Helicobacter pylori infection and the risk of development of esophageal adenocarcinoma. *Journal of Infectious Diseases.* 2005; 191(5): 761-7.
[302] Plummer M, Franceschi S, Munoz N. Epidemiology of gastric cancer. *IARC Scientific Publications.* 2004; (157): 311-26.

With the synergistically added risk represented by tobacco use, the one clear primary prevention method is smoking cessation (or encouragements to not take up the habit).[303] Controlling the intake of salted foods may also help.

Both endoscopic biopsies and non-invasive tests are used to establish whether a gastric disease process has begun, but neither of these approaches are considered cost-effective at a population level.[304] However, the potential benefits of surveillance may propel this approach onto the high priority list in the next few years.[305]

When disease is detected, combination therapies involving a proton-pump inhibitor[306] and two to three antibiotics are effective in eradicating *H. pylori*, with good tolerance by the patient; a one-week regimen is curative in 80 to 90% of cases.[307] This type of treatment has been shown to accomplish regression of precancerous lesions and low-grade MALT lymphomas.[308,309] Supplementation with ascorbic acid or beta-carotene also has resulted in a smaller but still significant likelihood of regression in at least one study.[310] However, the Cochrane review of antioxidants in the prevention of gastric cancer cast grave doubts on their effectiveness.[311] Anti-inflammatories are also being investigated as a means to slow disease progression.[312] When disease is not detected and / or conservative therapies fail, then surgery is the best solution for any early cancer that develops. The techniques for resection increase in levels of invasiveness: endoscopic, laparocscopic and, finally, open surgery.[313]

The Cochrane review of *H. pylori* eradication methods is still at the protocol stage. The reality is that there has been little recent advance in therapies for *H. pylori*, though many long term intervention trials (with gastric cancer as the end-point) are now underway in the US and Europe.[314] Many compounds can kill the bacterium *in*

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[303] Brenner H, Arndt V, Bode G et al. Risk of gastric cancer among smokers infected with *Helicobacter pylori*. *International Journal of Cancer.* 2002; 98(3): 446-9.
[304] Correa P. Helicobacter pylori infection and gastric cancer. *Cancer Epidemiology, Biomarkers & Prevention.* 2003; 12(3): 238s-41s.
[305] Whiting JL, Sigurdsson A, Rowlands DC et al. The long term results of endoscopic surveillance of premalignant gastric lesions. *Gut.* 2002; 50(3): 378-81.
[306] A proton pump inhibitor is a drug that reduces the amount of gastric acid produced by stomach cells.
[307] Axon A. Review article: gastric cancer and Helicobacter pylori. *Alimentary Pharmacology & Therapeutics.* 2002; 16 Suppl 4: 83-8.
[308] Correa P. Helicobacter pylori infection and gastric cancer. *Cancer Epidemiology, Biomarkers & Prevention.* 2003; 12(3): 238s-41s.
[309] Moss SF, Sood S. Helicobacter pylori. *Current Opinions in Infectious Diseases.* 2003; 16(5): 445-51.
[310] Correa P, Fontham ET, Bravo JC et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. *Journal of the National Cancer Institute.* 2000; 92(23): 1881-8.
[311] Bjelakovic G, Nikolova D, Simonetti et al. Antioxidant supplements for preventing gastrointestinal cancers. Cochrane Hepato-Biliary Group. *Cochrane Database of Systematic Reviews.* 2004.
[312] Juhasz M, Herszenyi L, Tulassay Z et al. Helicobacter pylori and molecular mechanisms of gastric carcinogenesis: targets for prevention and therapy. *Expert Review of Anticancer Therapy.* 2004; 4(1): 97-103.
[313] Kitajima M. Strategies for gastric cancer treatment in the twenty-first century: minimally invasive and tailored approaches integrating basic science and clinical medicine. *Gastric Cancer.* 2005; 8(2): 55-8.
[314] Hasham-Jiwa N, Kasakura Y, Ajani JA. Brief review of advances in the treatment of gastric carcinoma in North America and Europe, 1995-2001. *International Journal of Clinical Oncology.* 2002; 7(4): 219-24.

vitro, but reproducing such effects in live bodies is more elusive. Animal models are helping in the development of vaccines; there has been some success, but no clear strategy has emerged.[315,316] One cost-effectiveness analysis suggested that resource allocation for vaccine development and implementation only made sense in developed countries.[317]

At this point, anti-*H. pylori* therapies remain the best option, one that is recommended for all symptomatic infected individuals according to recent professional consensus statements.[318] Using such an approach with the entire infected population would hardly seem to be feasible.[319] Nonetheless, one modeling study demonstrated that a program of universal screening (plus treatment for those who test positive) would generate an incremental cost of only US$26 per case.[320] Many uncertainties remain, including the effect of total eradication of *H. pylori* on gastric cancer risk, and the fact that infection actually seems to be protective against certain cancers.[321,322] One Canadian review has called for a major demonstration project to help answer some of the scientific and pragmatic questions.[323]

[315] Moss SF, Sood S. Helicobacter pylori. *Current Opinions in Infectious Diseases.* 2003; 16(5): 445-51.
[316] Moran AP, Svennerholm AM, Penn CW. Pathogenesis and host response of Helicobacter pylori. *Trends in Microbiology.* 2002; 10(12): 545-7.
[317] Rupnow MF, Owens DK, Shachter R et al. Helicobacter pylori vaccine development and use: a cost-effectiveness analysis using the Institute of Medicine Methodology. *Helicobacter.* 1999; 4(4): 272-80.
[318] Coelho LG, Leon-Barua R, Quigley EM. Latin-American Consensus Conference on Helicobacter pylori infection. Latin-American National Gastroenterological Societies affiliated with the Inter-American Association of Gastroenterology (AIGE). *American Journal of Gastroenterology.* 2000; 95(10): 2688-91.
[319] Li H, Stoicov C, Cai X et al. Helicobacter and gastric cancer disease mechanisms: host response and disease susceptibility. *Current Gastroenterology Reports.* 2003; 5(6): 459-67.
[320] Leivo T, Salomaa A, Kosunen TU et al. Cost-benefit analysis of Helicobacter pylori screening. *Health Policy.* 2004; 70(1): 85-96.
[321] Roderick P, Davies R, Raftery J et al. The cost-effectiveness of screening for Helicobacter pylori to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model. *Health Technology Assessment.* 2003; 7(6): 1-86.
[322] Fendrick AM, Chernew ME, Hirth RA et al. Clinical and economic effects of population-based Helicobacter pylori screening to prevent gastric cancer. *Archives of Internal Medicine.* 1999; 159(2): 142-8.
[323] Sullivan T, Ashbury FD, Fallone CA et al. Helicobacter pylori and the prevention of gastric cancer. *Canadian Journal of Gastroenterology.* 2004; 18(5): 295-302.

Epstein Barr Virus

About 100 herpesviruses have been isolated, but it seems that only 8 infect humans. The best known of these are the herpes simplex viruses, types 1 and 2. The herpesviruses are widely separated in genetic make-up, but share a similar complex structure.

Epstein Barr virus (EBV) is also a human herpesvirus (HHV), specifically HHV-4. Apart from EBV, the only other type which has been significantly associated with cancer is human herpesvirus-8 (see below).

EBV infects more than 90% of adults in the world; two subtypes are found in humans, with EBV-1 being the most prevalent. Once infected, an individual is a lifelong carrier.[324,325,326] The means of transmission is salivary contact; this is because EBV primarily infects the squamous epithelium and the lymphoid organs (specifically, the B cells) of the oropharynx. Virus can continue to be shed into the saliva for years after primary infection.[327] Most EBV carriers are asymptomatic, though infection in adolescence frequently results in infectious mononucleosis (so-called "kissing disease"). The mechanisms which trigger a small proportion to develop a malignancy remain unclear, though, driven by the hope of discovering therapeutic strategies, they remain an intense focus of theory and research.[328,329]

EBV was the first human tumour virus identified. It was isolated in 1964 from a common lymphoma in African children first described by Burkitt (after whom the cancer is named). Since that time, EBV has been implicated in a wide variety of cancers, most of which can emerge years after the primary infection.[330] However, the very functioning of EBV, which involves "strategies to minimize or eliminate its pathogenic potential, in the interest of maintaining infection and the survival of the host," means that causal connections between the virus and disease are difficult to prove.[331] After more than 40 years of research, the picture regarding EBV and oncogenesis remains complex.[332] An inventory of likely EBV-influenced cancers is offered in the next section.

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[324] Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. *Clinical Cancer Research.* 2004; 10(3): 803-21.
[325] Rickinson AB, Callan MF, Annels NE. T-cell memory: lessons from Epstein-Barr virus infection in man. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences.* 2000; 355(1395): 391-400.
[326] Dolcetti R, Guidoboni M, Gloghini A et al. EBV-associated tumors: pathogenetic insights for improved disease monitoring and treatment. *Current Cancer Therapy Reviews.* 2005; 1: 27-44.
[327] Murray PG, Young LS. The Role of the Epstein-Barr virus in human disease. *Frontiers in Bioscience.* 2002; 7: d519-40.
[328] Niller HH, Salamon D, Ilg K et al. EBV-associated neoplasms: alternative pathogenetic pathways. *Medical Hypotheses.* 2004; 62(3): 387-91.
[329] Ambinder RF. Epstein-Barr virus-associated lymphoproliferative disorders. *Reviews in Clinical & Experimental Hematology.* 2003; 7(4): 362-74.
[330] Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. *Clinical Cancer Research.* 2004; 10(3): 803-21.
[331] Thorley-Lawson DA, Gross A. Persistence of the Epstein-Barr virus and the origins of associated lymphomas. *New England Journal of Medicine.* 2004; 350(13): 1328-37.
[332] Niedobitek G, Meru N, Delecluse HJ. Epstein-Barr virus infection and human malignancies. *International Journal of Experimental Pathology.* 2001; 82(3): 149-70.

Associated Cancers

As noted, the list of cancers linked to EBV seems to be ever expanding. As Hsu and Glaser noted: "Given that the complexity and duration of EBV-host interaction provides numerous possibilities for a malignant outcome, the heterogeneity of the cancers associated with EBV is not surprising."[333]

We begin with where the EBV story started, the disease identified by Burkitt. So-called nonendemic Burkitt's lymphoma is the version of the disorder seen most often in western countries. It has been a rare disorder, though incidence has increased recently because of its association with the immunosuppression due to AIDS. Compared to the endemic version of Burkitt's lymphoma found in Africa, the nonendemic, AIDS-related form is not as closely associated with EBV; only 15-30% of cases demonstrate the presence of the virus.[334,335]

EBV is involved with Hodgkin's disease, though positivity for the virus varies with the subtype of Hodgkin's (from 10% to more than 95% infection rate). About half the Hodgkin's cases in the US demonstrate the presence of EBV. However, this rate goes up to 95% in HIV- associated cases.[336] Although not considered an AIDS-defining condition, in developed areas of the world Hodgkin's lymphoma competes with Kaposi sarcoma as the cancer most diagnosed alongside HIV infection.[337]

Undifferentiated nasopharyngeal carcinoma is strongly associated with EBV.[338,339] Although mostly rare in the west (the exception being the Inuit), it is common in Canton, Hong Kong, and Taiwan.[340,341] The latter geographic connection may have something to do with the consumption of salted fish.[342] However, as incidence is high in people of Chinese descent regardless of where they live, immigration may make this disease more of a concern for western countries in the future.[343]

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[333] Hsu JL, Glaser SL. Epstein-barr virus-associated malignancies: epidemiologic patterns and etiologic implications. *Critical Reviews of Oncology/Hematology.* 2000; 34(1): 27-53.
[334] Dolcetti R, Guidoboni M, Gloghini A et al. EBV-associated tumors: pathogenetic insights for improved disease monitoring and treatment. *Current Cancer Therapy Reviews.* 2005; 1: 27-44.
[335] Subar M, Neri A, Inghirami G et al. Frequent c-myc oncogene activation and infrequent presence of Epstein-Barr virus genome in AIDS-associated lymphoma. *Blood.* 1988; 72(2): 667-71.
[336] Gandhi MK, Tellam JT, Khanna R. Epstein-Barr virus-associated Hodgkin's lymphoma. *British Journal of Haematology.* 2004; 125(3): 267-81.
[337] Dolcetti R, Boiocchi M, Gloghini A et al. Pathogenetic and histogenetic features of HIV-associated Hodgkin's disease. *European Journal of Cancer.* 2001; 37(10): 1276-87.
[338] Niedobitek G, Agathanggelou A, Nicholls JM. Epstein-Barr virus infection and the pathogenesis of nasopharyngeal carcinoma: viral gene expression, tumour cell phenotype, and the role of the lymphoid stroma. *Seminars in Cancer Biology.* 1996; 7(4): 165-74.
[339] Dolcetti R, Menezes J. Epstein-Barr virus and undifferentiated nasopharyngeal carcinoma: new immunobiological and molecular insights on a long-standing etiopathogenic association. *Advanced Cancer Research.* 2003; 87: 127-57.
[340] Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. *Clinical Cancer Research.* 2004; 10(3): 803-21.
[341] Busson P, Keryer C, Ooka T et al. EBV-associated nasopharyngeal carcinomas: from epidemiology to virus-targeting strategies. *Trends in Microbiology.* 2004; 12(8): 356-60.
[342] Hsu JL, Glaser SL. Epstein-barr virus-associated malignancies: epidemiologic patterns and etiologic implications. *Critical Reviews of Oncology/Hematology.* 2000; 34(1): 27-53.
[343] Young LS, Murray PG. Epstein-Barr virus and oncogenesis: from latent genes to tumours. *Oncogene.* 2003; 22(33): 5108-21.

There are several AIDS-related lymphomas which have been linked to EBV.[344] Other routes of becoming immunocompromised (e.g., inherited disorders, transplantation drugs) also can lead to the lymphoproliferative conditions. The AIDS-related versions are either systemic (e.g., Burkitt's) or target the central nervous system; they tend to be aggressive. The systemic lymphomas demonstrate EBV positivity in 30 to 90% of cases. Finally, there are effusion lymphomas of the visceral cavity that sometimes demonstrate the presence of EBV; these conditions are also associated with human herpesvirus-8 (see below).

Although mainly infecting immune system B cells, EBV also can infect other cells.[345] For example, certain T cell non-Hodgkin's lymphomas have been associated with the virus. One type, localized in the nasal area, demonstrates a remarkable 90% EBV-positivity.

In addition to the preceding conditions, EBV is also being investigated in the context of breast cancer, certain gastric cancers, salivary gland tumours, hepatocellular carcinomas, and smooth muscle tumours known as leiomyosarcomas (the latter only occurring in immunosuppressed patients).[346,347,348,349,350] Whatever the theoretical interest in these investigations, it must be admitted that at present any indication of EBV-association does not have prognostic or therapeutic implications.[351]

Preventive Interventions

With such a massive prevalance of EBV infection and its routine oral transmission, it is difficult to hold out much hope for early primary prevention, that is, eliminating exposure to and contracting of the infection. As well, given the limited understanding of oncogenetic triggers and mechanisms in the many types of cancer influenced by EBV, effective primary prevention also remains elusive. Recalling the role that immunosuppression plays in the development of certain EBV-associated malignancies (see above), some of the most promising research involves therapies designed to reestablish immunocompetence.[352,353] This approach can theoretically be used prophylactically or to eradicate existing disease. One research focus has been

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[344] Cesarman E. Epstein-Barr virus (EBV) and lymphomagenesis. *Frontiers in Bioscience.* 2002; 7: e58-65.

[345] Jones JF, Shurin S, Abramowsky C et al. T-cell lymphomas containing Epstein-Barr viral DNA in patients with chronic Epstein-Barr virus infections. *New England Journal of Medicine.* 1988; 318(12): 733-41.

[346] Wu MS, Shun CT, Wu CC et al. Epstein-Barr virus-associated gastric carcinomas: relation to H. pylori infection and genetic alterations. *Gastroenterology.* 2000; 118(6): 1031-8.

[347] Wang CP, Chang YL, Ko JY et al. Lymphoepithelial carcinoma versus large cell undifferentiated carcinoma of the major salivary glands. *Cancer.* 2004; 101(9): 2020-7.

[348] McClain KL, Leach CT, Jenson HB et al. Association of Epstein-Barr virus with leiomyosarcomas in children with AIDS. *New England Journal of Medicine.* 1995; 332(1): 12-8.

[349] Macsween KF, Crawford DH. Epstein-Barr virus-recent advances. *Lancet Infectious Diseases.* 2003; 3(3): 131-40.

[350] Herrmann K, Niedobitek G. Epstein-Barr virus-associated carcinomas: facts and fiction. *Journal of Pathology.* 2003; 199(2): 140-5.

[351] Herrmann K, Niedobitek G. Epstein-Barr virus-associated carcinomas: facts and fiction. *Journal of Pathology.* 2003; 199(2): 140-5.

[352] Khanna R, Tellam J, Duraiswamy J et al. Immunotherapeutic strategies for EBV-associated malignancies. *Trends in Molecular Medicine.* 2001; 7(6): 270-6.

[353] Taylor GS. T cell-based therapies for EBV-associated malignancies. *Expert Opinion in Biological Therapy.* 2004; 4(1): 11-21.

infusion with cytotoxic T lymphocytes from donors, though this treatment carries its own danger of graft-versus-host disease.[354,355,356] Clearly, another approach which can be useful in reducing the incidence of this class of tumours is prevention of HIV infection either through changes in sexual behaviour or by vaccination.[357] Efforts are also underway to create an EBV vaccine to prevent initial infection or boost immunity in the face of EBV-associated tumours.[358,359,360,361] There are now two candidate vaccines ready for trial.[362] Rounding out the discussion in terms of secondary prevention, broad-spectrum antiherpesvirus agents already in use clinically may have an effect on EBV diseases, though to date "reports of tumour regression remain anecdotal."[363,364] Novel EBV-focused treatments are also under investigation. As one study noted, "the consistent presence of…EBV in particular tumor types offers the potential for the development of highly specific, viral-targeted therapies."[365]

Summing up the progress to date, it must be acknowledged that, whatever the promise of immunotherapies and antivirals, the prevention and management of EBV-related morbidity remains in the "nascent stages."[366]

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[354] Comito MA, Sun Q, Lucas KG. Immunotherapy for Epstein-Barr virus-associated tumors. *Leukemia & Lymphoma.* 2004; 45(10): 1981-7.
[355] Murray PG, Young LS. Epstein-Barr virus infection: basis of malignancy and potential for therapy. *Expert Reviews in Molecular Medicine.* 2001; 2001: 1-20.
[356] Gottschalk S, Heslop HE, Roon CM. Treatment of Epstein-Barr virus-associated malignancies with specific T cells. *Advanced Cancer Research.* 2002; 84: 175-201.
[357] Mueller N. Overview: viral agents and cancer. *Environmental Health Perspectives.* 1995; 103 Suppl 8: 259-61.
[358] Moss DJ, Khanna R, Bharadwaj M. Will a vaccine to nasopharyngeal carcinoma retain orphan status? *Developments in Biologicals.* 2002; 110: 67-71.
[359] Lopes V, Young LS, Murray PG. Epstein-Barr virus-associated cancers: aetiology and treatment. *Herpes.* 2003; 10(3): 78-82.
[360] Bharadwaj M, Moss DJ. Epstein-Barr virus vaccine: a cytotoxic T-cell-based approach. *Expert Reviews of Vaccines.* 2002; 1(4): 467-76.
[361] Taylor GS. T cell-based therapies for EBV-associated malignancies. *Expert Opinion in Biological Therapy.* 2004; 4(1): 11-21.
[362] Macsween KF, Crawford DH. Epstein-Barr virus-recent advances. *Lancet Infectious Diseases.* 2003; 3(3): 131-40.
[363] Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. *Clinical Cancer Research.* 2004; 10(3): 803-21.
[364] Abdulkarim B, Bourhis J. Antiviral approaches for cancers related to Epstein-Barr virus and human papillomavirus. *Lancet Oncology.* 2001; 2(10): 622-30.
[365] Israel BF, Kenney SC. Virally targeted therapies for EBV-associated malignancies. *Oncogene.* 2003; 22(33): 5122-30.
[366] Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. *Clinical Cancer Research.* 2004; 10(3): 803-21.

Human Immunodeficiency Virus

The human immunodeficiency virus (HIV) infects cells of the immune system. One of the sequelae of HIV infection is the well-known acquired immune deficiency syndrome (AIDS). Although not the greatest direct or even indirect cause of human cancers, the medical and sociopolitical realities around HIV infection (as well as associated AIDS) means that it has been a major driver of advances in the area of sexually transmitted infections such as HPV and blood-borne diseases such as HCV (the latter also related to injecting drug use).

HIV transmission can occur when blood, semen and pre-seminal fluid, vaginal fluid, or breast milk from an infected person enters the body of an uninfected person. Access can be gained through a vein (e.g., through an injection), the lining of the anus or rectum, the lining of the vagina or cervix, the opening to the penis, the mouth, other mucous membranes (e.g., eyes or inside of the nose), or cuts and sores. Contact with saliva, tears, or sweat has never been shown to result in transmission of HIV. Health care workers could come into contact with the virus through fluids surrounding the brain, spinal chord, and joints, as well as amniotic fluid.

Although spreading in heterosexual populations, men who have sex with men still account for over 50% of HIV transmission in the US.[367] Drug users also play a significant role in HIV incidence. Although opioid users represent a small proportion of the population, the predominant means of delivery of such drugs is by injection; thus there is a disproportionate contribution of this risky behaviour to HIV transmission, accounting for perhaps 5 to 10% of HIV infections. More precisely the risk arises through sharing injection equipment, which promotes blood-to-blood contact. The most efficient transmission of HIV occurs in blood transfusions and vertically from mother to child in pregnancy and delivery. Transmission through sexual encounters and drug injecting is not particularly efficient, but multiple exposures increase the risk to the point where these routes of HIV infection end up dominating the landscape.

Associated Cancers

As has already been noted in this report, HIV co-infection alongside other carcinogens such as HPV increases the risk of the associated cancers (e.g., in the case of HPV, it is true for certain types of cervical cancer). This relationship is also true for nonviral carcinogens such as tobacco smoke. For example, one study showed that lung cancer occurred at twice the rate in HIV-infected women as in non-infected women.[368]

Cancer development in HIV infection is promoted through a combination of immunosuppression and activation of inflammation.[369] The cancers associated with HIV, rather than being directly caused by the virus, are “opportunistic,” more or less exploiting the biological environment produced by HIV infection and AIDS.[370] It is

[367] Johnson WD, Hedges LV, Diaz RM. Interventions to modify sexual risk behaviors for preventing HIV infection in men who have sex with men. Cochrane HIV/AIDS Group. *Cochrane Database of Systematic Reviews.* 2002.
[368] Phelps RM, Smith DK, Heilig CM et al. Cancer incidence in women with or at risk for HIV. *International Journal of Cancer.* 2001; 94(5): 753-7.
[369] Boshoff C, Weiss R. AIDS-related malignancies. *Nature Reviews Cancer.* 2002; 2(5): 373-82.
[370] Scadden DT. AIDS-related malignancies. *Annual Reviews of Medicine.* 2003; 54: 285-303.

not clear exactly what impact the improved survival of immunosuppressed patients may have on future rates of cancers associated with HIV.[371] Some believe that the incidence of Kaposi sarcoma and AIDS-related lymphomas is certain to increase.[372]

The most common virally-associated cancers and / or those with the highest relative risk with HIV co-infection are noted in the following table:[373]

Cancer	Etiologic or Contributing Agent	Relative Risk in Men with HIV	Relative Risk in Women with HIV
Kaposi sarcoma	Herpesvirus-8	98	203
Non-Hodgkin's lymphoma	EBV / HHV-8	37	55
Cervical (non-invasive)	HPV		9
Hodgkin's disease	Epstein Barr virus	8	6
Tongue	HPV / EBV	2	7
Rectal / anal	HPV	3	3
Liver	HCV	5	
Central nervous system	EBV	3	3
Skin	HPV	21	8

Preventive Interventions

Sexual behaviour is the major factor determining the incidence of HIV infection, and a major target for early primary prevention. In this regard, the trends are not encouraging. UK surveys showed, for example, that since 1990, people have, on average, a greater number of lifetime partners, lower age at first intercourse, and more partners who do not use a condom consistently (especially among male homosexuals).[374,375] Motivated and informed by this reality, UK authorities recently developed a conceptual framework for comprehensively reviewing evidence related to early primary intervention strategies.[376] The framework, which is useful in other developed settings such as Canada, included these features:

- The priority at-risk (or risky) populations involved in the strategy should be men who have sex with men, commercial sex workers, certain immigrant (especially African-origin) communities, and people with HIV.

[371] Beral V, Newton R. Overview of the epidemiology of immunodeficiency-associated cancers. *Journal of the National Cancer Institute Monograph.* 1998; (23): 1-6.
[372] Marco M. Acquired immunodeficiency syndrome-related cancers: the community perspective. *Journal of the National Cancer Institute Monograph.* 1998; (23): 21-2.
[373] Boshoff C, Weiss R. AIDS-related malignancies. *Nature Reviews Cancer*. 2002; 2(5): 373-82.
[374] Johnson AM, Fenton KA, Mercer C. Phase specific strategies for the prevention, control, and elimination of sexually transmitted diseases: background country profile, England and Wales. *Sexually Transmitted Infections.* 2002; 78 Suppl 1: i125-32.
[375] Hickson F, Nutland W, Doyle T et al. *Making it Count: a Collaborative Planning Framework ot Reduce the Incidence of HIV Infection During Sex Between Men.* London: Sigma Research; 2000.
[376] Ellis S, Barnett-Page E, Morgan A et al. HIV Prevention: a review of reviews assessing the effectiveness of interventions to reduce the risk of sexual transmission. *NHS Health Development Agency.*2003. Available at http://194.83.94.67/uhtbin/hyperion_image.exe/EBBD_HIV_pdf_ft. Accessed June 2005.

- Interventions need to focus on influencing behaviours, e.g., increasing use of condoms, reducing the number of different partners, and encouraging only people with the same HIV status to have sex.

- Interventions need to address the underlying factors that give rise to risky behaviours, e.g., lack of knowledge and skills, availability of resources, discrimination, and substance abuse.[377]

- Interventions can be delivered at different levels, from individual (counseling, helplines) to groups (sex education) to whole communities (campaigns, professional development of healthcare personnel). A special topic of interest is peer-based and other approaches to preventing the exposure of women to HIV.[378,379,380]

- Behavioural change will probably require a large-scale program involving multiple components and levels.

The conclusion of the resulting UK literature review were sobering: there was very little or no evidence concerning the impact of interventions on any underlying factors or actual behaviours / health outcomes among any of the target populations. It is important to note that "no evidence" is not the same as evidence of ineffectiveness; it does, however, point to glaring research gaps. A Cochrane review from 2002, which looked at men who have sex with men, came up with a similar assessment: the evidence for behavioural interventions to reduce risky behaviours and HIV infection rates, though promising, is very limited; a meta-analysis of results suggested that the proportion of men engaging in unprotected sex was reduced by almost a quarter.[381] Another review from that year identified the following best practices for community-based programs dealing with sexually transmitted infections and HIV transmission:[382]

- establish community partnerships
- use opinion leaders and role models
- delivery by peer educators
- involvement of target groups in design of messages
- diffusion of interventions through existing social networks.

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[377] Semaan S, Des Jarlais D, Sogolow E et al. Interventions to modify sexual risk behaviors for preventing HIV infection in drug users. Cochrane HIV/AIDS Group. *Cochrane Database of Systematic Reviews.*1998.

[378] Tholandi M, Kennedy G, Wilkinson, D. Female condom for preventing heterosexually transmitted HIV infection in women. Cochrane HIV/AIDS Group. *Cochrane Database of Systematic Reviews.*2002.

[379] Doull M, O'Conner A, Robinson V et al. Peer-based interventions for reducing morbidity and mortality in HIV-infected women. Cochrane HIV/AIDS Group. *Cochrane Database of Systematic Reviews.*2004.

[380] Ehrhardt AA, Exner TM. Prevention of sexual risk behavior for HIV infection with women. *Aids.* 2000; 14 Suppl 2: S53-8.

[381] Johnson WD, Hedges LV, Diaz RM. Interventions to modify sexual risk behaviors for preventing HIV infection in men who have sex with men. Cochrane HIV/AIDS Group. *Cochrane Database of Systematic Reviews.* 2002.

[382] Ross MW, Williams ML. Effective targeted and community HIV/STD prevention programs. *Journal of Sex Research.* 2002; 39(1): 58-62.

To this list, we can add two general points that emerged from the reviews noted earlier: multi-component interventions work best; and voluntary testing and counselling are more effective in combination with other interventions. The Cochrane review on the efficacy of counselling and testing is still in the protocol stage.

The most high profile method of HIV prevention is consistent and correct use of condoms. The efficacy of this approach has been proven, but the uptake is still low in many parts of the world. There are many interventions to promote condom use. The great majority of these have been behavioural interventions targeting individual-level barriers to employing condoms, and most have been conducted in a specific high-risk context (e.g., commercial sex work, drug use, homelessness, prisons).[383] While there have been acknowledged successes in these as well as population-wide settings, there have been no recent systematic reviews of intervention effectiveness, and no assessment of group or population approaches (even the Cochrane work is still at the protocol stage). The closest comprehensive Cochrane review to this topic noted that consistent use of condoms could reduce heterosexual HIV transmission by 80%.[384]

Structural approaches to promoting condom use may prove to be the most useful, though evidence remains to be gathered. The options include:[385]

- legislation of condom use among commercial sex workers
- improving the visibility, availability and accessibility of condoms
- free condom distribution.

Since sharing syringes and needles is a very efficient way of spreading HIV, interventions related to reducing drug use or making it safer become important in controlling infection and associated diseases. While this topic has already been introduced earlier in the context of hepatitis C prevention, it is significant to note at this point that many studies of so-called structural interventions (e.g., syringe exchange programs) have demonstrated reductions in those behaviours that increase the risk of HIV transmission.[386] At least one recent systematic review has been published in the context of HIV per se. The Cochrane group looked at oral substitution treatment to reduce high-risk drug behaviours, concluding that there was clear, though limited, support for this approach as a means to reduce HIV infection.[387] Another study of almost 3,000 injection drug users suggested that targeting "incremental risk reduction" may be more successful than promoting abstinence.[388]

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[383] Myer L. Morroni C, Mathews, C et al. Structural and community-level interventions for increasing condom use to prevent HIV and other sexually transmitted infections. Cochrane HIV/AIDS Group. *Cochrane Database of Systematic Reviews.*2001.

[384] Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane HIV/AIDS Group. *Cochrane Database of Systematic Reviews.*2005.

[385] Myer L. Morroni C, Mathews, C et al. Structural and community-level interventions for increasing condom use to prevent HIV and other sexually transmitted infections. Cochrane HIV/AIDS Group. *Cochrane Database of Systematic Reviews.*2001.

[386] Des Jarlais DC. Structural interventions to reduce HIV transmission among injecting drug users. *Aids.* 2000; 14 Suppl 1: S41-6.

[387] Gowing L, Farrell M, Bornemann R et al. Substitution treatment of injecting opioid users for prevention of HIV infection. Cochrane Drugs and Alcohol Group *Cochrane Database of Systematic Reviews.*2004.

[388] Celentano DD, Munoz A, Cohn S et al. Dynamics of behavioral risk factors for HIV/AIDS: a 6-year prospective study of injection drug users. *Drug and Alcohol Dependence.* 2001; 61(3): 315-22.

Some specialized populations and topics deserve mention. A Cochrane review of methods to prevent transmission of HIV from mother to child in pregnancy or delivery showed that two antiretroviral drugs were effective in risk reduction. One agent, nevirapine, was useful during labour itself; this drug is not indicated for long term monotherapy because of the potential for resistant viruses to emerge. A final method which reduced HIV transmission to the child was birth by elective caesarean section.[389] The related topic of breastfeeding is being examined by the Cochrane group, but their assessment is in process. The possible interventions to prevent HIV transmission include formula feeding, early weaning, treatment of breast milk and antiretroviral prophylaxis in child and / or mother.[390]

Employees in healthcare have a definite risk for inadvertent exposure to HIV. Procedures and protocols like those recommended by the World Health Organization[391] need to be in place to minimize the danger.

Heterosexual transmission of HIV is increasing globally. This reality prompted a 2002 review of interventions directed to heterosexual men. Elwy et al. found 8 studies designed to reduce sexually transmitted infection (including HIV) rates.[392] There were 5 successful programs, which included on-site individual counselling and HIV testing, mass communications regarding risk reduction and motivation and skills education. Another 2002 review confirmed that interventions can have a positive effect on risky behaviours and HIV rates.[393] Most of the included studies took place in healthcare settings, and included the following features: information on HIV and risk behaviours, along with technical and personal skills.

According to the Centers for Disease Control, people under 25 account for 50% of new HIV infections in the US. This has created a great deal of urgency around creating effective prevention programs. A 2003 review of sexual risk reduction among youth found positive results in just over half of the 23 studies identified.[394]

Of course, many of the early primary prevention methods related to HIV are based on the knowledge that an infection is in place, and then limiting the spread of that infection. Thus, interventions aimed at promoting voluntary testing is theoretically very important. While the Cochrane work on this area is just starting, an earlier review suggested that testing still remains to be proven as useful in early primary

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[389] Brocklehurst P. Interventions for reducing the risk of mother-to-child transmission of HIV infection. Cochrane HIV/AIDS Group. *Cochrane Database of Systematic Reviews.*2001.

[390] Tholandi M, Wilkinson D, Dabis F et al. Interventions to decrease the risk of mother-to-child transmission of HIV-1 through breast milk. Cochrane HIV/AIDS Group *Cochrane Database of Systematic Reviews.*2003.

[391] See http://www.avert.org/needlestick.htm. Accessed June 2005.

[392] Elwy AR, Hart GJ, Hawkes S et al. Effectiveness of interventions to prevent sexually transmitted infections and human immunodeficiency virus in heterosexual men: a systematic review. *Archives of Internal Medicine.* 2002; 162(16): 1818-30.

[393] Neumann MS, Johnson WD, Semaan S et al. Review and meta-analysis of HIV prevention intervention research for heterosexual adult populations in the United States. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology.* 2002; 30 Suppl 1: S106-17.

[394] Pedlow CT, Carey MP. HIV sexual risk-reduction interventions for youth: a review and methodological critique of randomized controlled trials. *Behavior Modification.* 2003; 27(2): 135-90.

prevention; on the other hand, its role in preventing disease development among the already infected has been demonstrated.[395]

There is evidence that the "cocktail" of antiretroviral drugs taken by HIV-positive patients can be preventive against cancer development. The incidence of Kaposi sarcoma and AIDS-related lymphoma have dropped as the drugs have come into routine use.[396] Secondary prevention also comes into play, in the sense that antiretroviral therapy seems to actually resolve established Kaposi sarcoma lesions. Information on treatments targeted to specific HIV-influenced cancers is provided in the sections of this report dealing with the relevant etiologic factor. The sort of immunity-boosting therapies being considered for some of these cancers may in turn be used to treat HIV infection.[397]

Primary prevention after voluntary exposure to HIV (e.g., through sexual intercourse, intravenous drug needle sharing), which usually means the use of antiretroviral drugs in a prophylactic way, is a controversial topic. It is an expensive proposition, and there are no controlled trials supporting its efficacy. Nevertheless, the demand for such an intervention is great, prompting a Cochrane review of the limited evidence available; so far, only the protocol has been published.[398] A specialized application for prophylactic treatment is in healthcare workers who experience a needle-stick or some other accidental form of exposure; again, the investigation of this type of intervention has only just begun at the Cochrane group.

HIV vaccine development remains an intense area of focus. Since 1987, more than 30 candidate vaccines have been tested in approximately 60 Phase I/II trails, involving more than 10,000 healthy volunteers. Most of these trials have been conducted in the US and Europe, but several have also been conducted in developing countries. The results have confirmed the safety of the vaccines. Currently, there are only two candidate vaccines being evaluated in Phase III trials.[399]

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[395] Weinhardt LS, Carey MP, Johnson BT et al. Effects of HIV counseling and testing on sexual risk behavior: a meta-analytic review of published research, 1985-1997. *American Journal of Public Health.* 1999; 89(9): 1397-405.

[396] Boshoff C, Weiss R. AIDS-related malignancies. *Nature Reviews Cancer.* 2002; 2(5): 373-82.

[397] Kieff E. Current perspectives on the molecular pathogenesis of virus-induced cancers in human immunodeficiency virus infection and acquired immunodeficiency syndrome. *Journal of Nationall Cancer Institute Monograph.* 1998; (23): 7-14.

[398] Martin NV, Almeda J, Casabona J. Effectiveness and safety of HIV post-exposure prophylaxis after sexual, injecting-drug-use or other non-occupational exposure. Cochrane HIV/AIDS Group. *Cochrane Database of Systematic Reviews.* 2005.

[399] See the World Health Organization website at http://www.who.int/hiv/topics/vaccines/Vaccines/en/. Accessed June 2005.

Human T Cell Lymphotrophic Virus

An estimated 10 to 20 million people worldwide are infected with human T cell leukemia virus type I (HTLV-I).[400] Most of these carriers are asymptomatic (though capable of transmitting the infection), but 5 to 10% develop either adult T cell leukemia or a particular myelopathy, a neurologic disease characterized by demyelinating lesions in the brain and spinal chord.[401] Interestingly, these two conditions are very different, and rarely occur together in the same individual.[402] The fact that most infected people do not develop disease naturally raises questions about the factors and processes which prompt movement towards one or other of the symptomatic states.

For our purposes, it is useful to know that the 1 to 5% of infected individuals who develop leukemia demonstrate mucosal exposure to the virus as the route of transmission (as opposed to progression to myelopathy, a disease which favours infection via blood).[403] After transmission by whatever route, "the differential immune response mounted by the host…likely plays a key role in determining the outcome of HTLV-I infection."[404]

Unfortunately, HTLV-induced malignancies do not respond to conventional chemotherapy; disease progression is often rapid, potentially leading to death within 2 years.[405]

The specific mechanisms by which leukemogenesis is initiated following HTLV-I infection remains a matter of intense investigation. The hope is that gaining understanding about disease pathways will lead to proven prevention or therapeutic measures, neither of which currently exists.[406] This makes early primary prevention all the more important. That is to say, modifying activity to eliminate viral exposure is the recommended course for individuals to follow. The main behavioural risk factors for contracting HTLV are intravenous drug use and multiple sexual contacts. Family members of HTLV-positive people also show a higher rate of infection.[407]

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[400] Edlich RF, Arnette JA, Williams FM. Global epidemic of human T-cell lymphotropic virus type-I (HTLV-I). *Journal of Emergency Medicine.* 2000; 18(1): 109-19.
[401] Barmak K, Harhaj E, Grant C et al. Human T cell leukemia virus type I-induced disease: pathways to cancer and neurodegeneration. *Virology.* 2003; 308(1): 1-12.
[402] Yao J, Wigdahl B. Human T cell lymphotropic virus type I genomic expression and impact on intracellular signaling pathways during neurodegenerative disease and leukemia. *Frontiers in Bioscience.* 2000; 5: D138-68.
[403] Kannagi M, Harashima N, Kurihara K et al. Tumor immunity against adult T-cell leukemia. *Cancer Science.* 2005; 96(5): 249-55.
[404] Barmak K, Harhaj E, Grant C et al. Human T cell leukemia virus type I-induced disease: pathways to cancer and neurodegeneration. *Virology.* 2003; 308(1): 1-12.
[405] Poiesz BJ, Poiesz MJ, Choi D. The human T-cell lymphoma/leukemia viruses. *Cancer Investigation.* 2003; 21(2): 253-77.
[406] Barmak K, Harhaj E, Grant C et al. Human T cell leukemia virus type I-induced disease: pathways to cancer and neurodegeneration. *Virology.* 2003; 308(1): 1-12.
[407] Poiesz BJ, Papsidero LD, Ehrlich G et al. Prevalence of HTLV-I-associated T-cell lymphoma. *American Journal of Hematology.* 2001; 66(1): 32-8.

Herpesvirus Type 8

HHV-8 appears to have a causal role in several diseases, including certain lymphomas and Kaposi sarcoma. The latter connection lends the virus it's alternate name, Kaposi sarcoma-associated herpesvirus (KSHV). The virus is detected infrequently in people at low risk for Kaposi sarcoma (KS).[408]

HHV-8 has been isolated in a number of body tissues and fluids, prompting investigation of multiple potential routes of transmission. There is a strong link with HIV infection, as noted earlier. In fact, the predominant means of transmitting HHV-8 appears to be male homosexual sex. About 1 out of 5 men who have sex with men and who have HIV, also show HHV-8 in their blood.[409] The virus is also present in the saliva of 75% of HIV-infected patients who have KS.[410] In contrast, there is no evidence that monogamous heterosexual sex is a usual mode of transmission.[411] Beyond men having sex with men, the only other sexual activity that has been clearly shown to be a risk factor is female prostitution. Studies have shown that the behaviours related to injection-drug use (such as needle sharing) may lead to HHV-8 infection, though less efficiently than HBV, HCV or HIV.[412] This suggests the need to be vigilant about transmission through blood transfusions, though there is no evidence of this risk so far; for instance, haemophiliacs do not acquire KS.[413,414,415] Finally, the high rate of HHV-8 among African preadolescent children suggests that nonsexual routes of transmission may be in operation, but these are not well understood.[416]

Associated Cancers

HHV-8 is best known for its connection to KS. A relatively rare condition until 25 years ago, it has become a "sentinel diagnosis" for AIDS, along with a characteristic pneumonia. Prior to the emergence of AIDS, an endemic form of KS has been noted for centuries among elderly males in southern Europe and both adults and children in equatorial Africa.

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[408] Whitby D, Howard MR, Tenant-Flowers M et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. *The Lancet.* 1995; 346(8978): 799-802.

[409] Whitby D, Boshoff C. Kaposi's sarcoma herpesvirus as a new paradigm for virus-induced oncogenesis. *Current Opinion in Oncology.* 1998; 10(5): 405-12.

[410] Koelle DM, Huang ML, Chandran B et al. Frequent detection of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) DNA in saliva of human immunodeficiency virus-infected men: clinical and immunologic correlates. *Journal of Infectious Diseases.* 1997; 176(1): 94-102.

[411] Smith NA, Sabin CA, Gopal R et al. Serologic evidence of human herpesvirus 8 transmission by homosexual but not heterosexual sex. *Journal of Infectious Diseases.* 1999; 180(3): 600-6.

[412] Cannon MJ, Dollard SC, Smith DK et al. Blood-borne and sexual transmission of human herpesvirus 8 in women with or at risk for human immunodeficiency virus infection. *New England Journal of Medicine.* 2001; 344(9): 637-43.

[413] Engels EA, Eastman H, Ablashi DV et al. Risk of transfusion-associated transmission of human herpesvirus 8. *Journal of National Cancer Institute.* 1999; 91(20): 1773-5.

[414] Boshoff C, Chang Y. Kaposi's sarcoma-associated herpesvirus: a new DNA tumor virus. *Annual Review of Medicine.* 2001; 52: 453-70.

[415] Whitby D, Howard MR, Tenant-Flowers M et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. *The Lancet.* 1995; 346(8978): 799-802.

[416] Gessain A, Mauclere P, van Beveren M et al. Human herpesvirus 8 primary infection occurs during childhood in Cameroon, Central Africa. *International Journal of Cancer.* 1999; 81(2): 189-92.

KS has also long been known as a complication among transplant patients undergoing immunosuppressive therapy.[417] It seems that that a compromised immune system is an essential milieu for the development of KS; the fact is that only a small fraction of *immunocompetent* people infected with HHV-8 end up with a malignancy.[418]

The more recent form of KS is the epidemic version related to HIV infection. It still requires the presence of HHV-8, with HIV supplying the necessary immunosuppressive component.

KS begins with a few skin lesions, but without treatment it can eventually affect multiple organs, including the lung, liver, digestive tract and spleen.[419] The clinical course of KS is highly variable, ranging from minimal disease to explosive growth, with significant morbidity and mortality.

There are certain rare lymphomas that are closely related to both HIV infection and KS in men who have sex with men. These malignancies have been connected to HHV-8. They are distinguished from other non-Hodgkin's lymphomas (NHLs) by their presentation as effusions in the visceral cavity; they do not exhibit a significant tumour mass. [420] Only a few cases of this type of lymphoma have been reported in HIV-negative individuals.[421]

Preventive Interventions

In the absence of specific vaccines or treatments in the rather complex world of KS and lymphomas related to HHV-8, it becomes all the more important to follow preventive strategies.[422] The main early primary prevention measures are the same as for HIV, namely, "safe sex" education and practices, especially among male homosexuals (see the earlier section).

There are no specific KS secondary prevention methods. The classic treatments used for KS involve different types of cancer management, and thus are not preventive per se.

The best primary prevention results for HHV-8 diseases are emerging as a by-product of the HIV / AIDS battle. The introduction of effective antiretroviral therapies for HIV infection seems to be having an impact on both KS and AIDS-related NHLs, at least in developed countries.[423] After a rapid rise over a 20 year period, the incidence

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[417] Boshoff C, Chang Y. Kaposi's sarcoma-associated herpesvirus: a new DNA tumor virus. *Annual Review of Medicine.* 2001; 52: 453-70.
[418] Boshoff C. Kaposi's sarcoma. Coupling herpesvirus to angiogenesis. *Nature.* 1998; 391(6662): 24-5.
[419] Boshoff C, Chang Y. Kaposi's sarcoma-associated herpesvirus: a new DNA tumor virus. *Annual Review of Medicine.* 2001; 52: 453-70.
[420] Boshoff C, Chang Y. Kaposi's sarcoma-associated herpesvirus: a new DNA tumor virus. *Annual Review of Medicine.* 2001; 52: 453-70.
[421] Baris D, Zahm SH. Epidemiology of lymphomas. *Current Opinion in Oncology.* 2000; 12(5): 383-94.
[422] Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. *Oncogene.* 2004; 23(38): 6524-34.
[423] Baris D, Zahm SH. Epidemiology of lymphomas. *Current Opinion in Oncology.* 2000; 12(5): 383-94.

of these diseases has decreased in the US since the mid-1990s. By contrast, non-AIDS-associated NHL rates have continued to climb.[424,425]

An unexpected result of successful treatment of immunocompromised individuals, where they then live longer, is the possible development of more NHL in the future.[426]

[424] Eltom MA, Jemal A, Mbulaiteye SM et al. Trends in Kaposi's sarcoma and non-Hodgkin's lymphoma incidence in the United States from 1973 through 1998. *Journal of National Cancer Institute.* 2002; 94(16): 1204-10.
[425] Chiu BC, Weisenburger DD. An update of the epidemiology of non-Hodgkin's lymphoma. *Clinical Lymphoma.* 2003; 4(3): 161-8.
[426] Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. *Oncogene.* 2004; 23(38): 6524-34.

Helminths

We have already referred to parasitic worms or flukes as another category of infection linked cancer. These animals are sometimes known as helminths, after the Greek word for worm. Of the 72 known species of parasites that can infect humans by food or water,[427] only two have been definitely identified as carcinogenic: the blood fluke *Schistosoma haematobium* and the liver fluke *Opisthorchis viverrini*. Neither of these occurs naturally in North America.

S. haematobium and related species are endemic in 74 countries of Africa and the eastern Mediterranean. More than 200 million people suffer from schistosomiasis, a condition which accounts for an astounding 1 million annual deaths. *S. haematobium*, whose eggs end up in the urine, also can create an inflammatory reaction in the bladder; in addition to its normal parasitical morbidity, the worm has been associated with bladder cancer in several case-control studies.[428]

O. viverrini is common in Thailand, Laos and Cambodia, infecting an estimated 9 to 10 million people.[429] There is strong evidence connecting this liver fluke to cholangiocarcinoma, a rare malignancy situated in the biliary duct system.[430]

Although the lifecycle of these parasites prevents them from being prevalent in North America, with the growing volume of international travel, migration and smuggling, the infections are increasingly being seen in countries where the disease is not endemic. A recent outbreak of opisthorchiasis in Israel, derived from illegally imported Siberian carp, provided the sort of wake-up call that is needed in our ever more globalized society.[431] Another consideration is that people in industrialized settings who happen to pick up the relevant parasite in uncommon ways may live longer than if they resided in other countries, increasing the chance of cancer developing.[432]

As with the other infectious agents, the helminths also represent a fluid area of research in terms of carcinogenesis.[433] The liver flukes *O. felineus* and *Clonorchis sinensis* have also been implicated in cancer of the biliary ducts, though the evidence is more limited than for their close cousin, *O. viverrini*. Likewise, various *Schistosoma* species have been associated with hepatocellular carcinoma (liver cancer) and colorectal cancer.[434,435] Finally, concerns about the carcinogenicity of *S. haematobium* have been extended beyond the bladder to the urinary tract.[436]

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[427] Pozio E. Foodborne and waterborne parasites. *Acta Microbiologica Polonica.* 2003; 52 Suppl: 83-96.
[428] Herrera LA, Benitez-Bribiesca L, Mohar A et al. Role of infectious diseases in human carcinogenesis. *Environmental & Molecular Mutagenesis.* 2005; 45(2-3): 284-303.
[429] Sithithaworn P, Haswell-Elkins M. Epidemiology of Opisthorchis viverrini. *Acta Tropica.* 2003; 88(3): 187-94.
[430] Herrera LA, Benitez-Bribiesca L, Mohar A et al. Role of infectious diseases in human carcinogenesis. *Environmental & Molecular Mutagenesis.* 2005; 45(2-3): 284-303.
[431] Yossepowitch O, Gotesman T, Assous M et al. Opisthorchiasis from imported raw fish. *Emerging Infectious Diseases.* 2004; 10(12): 2122-6.
[432] Herrera LA, Ostrosky-Wegman P. Do helminths play a role in carcinogenesis? *Trends in Parasitology.* 2001; 17(4): 172-5.
[433] Herrera LA, Ostrosky-Wegman P. Do helminths play a role in carcinogenesis? *Trends in Parasitology.* 2001; 17(4): 172-5.
[434] Abdel-Rahim AY. Parasitic infections and hepatic neoplasia. *Digestive Diseases.* 2001; 19(4): 288-91.

Conclusions and Recommendations

A number of key insights and conclusions offered throughout the report will be collected here for convenience; some the comments may serve as recommendations for policy-makers and planners.

Burden and Trends

Although some infection-related cancers are dropping in incidence, various factors are keeping the prevalence and mortality burden of these diseases at a high level in the Canadian population. Complacency is not an option. Some have suggested that, following tobacco use, infections as a group may be the most significant arena for preventive measures in cancer control.

Uncertainty and Action

The complexity of working out disease mechanisms and interpreting epidemiological data means that confirmed causality relationships between infectious agents and cancer emerge very slowly. As some of the cancers implicated represent such a serious burden for patients and the health care system, however, planners may need to act in the face of uncertain data.

Levels of Prevention

Emphasising the foundation or base of the prevention hierarchy is important. This means intervening to limit the exposure to the pathogen in the first place. If such early primary prevention is not practical or successful, then classic primary prevention must be pursued; with infections, the "gold standard" approach is prophylactic vaccines which prevent any exposure from becoming a serious problem. Finally, if infection does become established and is not expected to resolve spontaneously, then measures need to be taken to ensure that cancer does not develop; sometimes detecting precancerous cells and lesions through screening programs is the beginning of such secondary prevention.

Cost Considerations

A concerted attack across the prevention levels may be required to ultimately control a disease within a population. A complicating factor is that some interventions are more cost-effective than others. For example, there is debate about whether testing for HPV (to prompt primary prevention, if possible) is worth the expense, especially in reference to highly effective cytological screening, which detects precancer or the early stages of cervical cancer and then prompts appropriate secondary prevention. Likewise, though early intervention at the level of transmission is probably preferable, effective vaccines may be as effective as and less costly than preventing exposures to what are sometimes ubiquitous and easily transmitted organisms.

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[435] Matsuda K, Masaki T, Ishii S et al. Possible associations of rectal carcinoma with Schistosoma japonicum infection and membranous nephropathy: a case report with a review. *Japanese Journal of Clinical Oncology.* 1999; 29(11): 576-81.

[436] Hodder SL, Mahmoud AA, Sorenson K et al. Predisposition to urinary tract epithelial metaplasia in Schistosoma haematobium infection. *American Journal of Tropical Medicine & Hygiene.* 2000; 63(3-4): 133-8.

A Key Focus: Sexually Transmitted Infections

The strategies at each of the prevention levels just described should be as comprehensive and aggressive as necessary. Since many of the pathogens covered in this report are sexually transmitted, much of the discussion of early primary prevention revolved around reducing risky behaviours related to sexual activity. This is a crucial area of public health, albeit a sensitive one.

As a framework for the specific programs noted in the report, the list below provides the typical behavioural intervention categories. Understanding the "landscape" of potential interventions provides a context for particular initiatives that have been tried and tested for the various agents. This taxonomy of measures also might suggest some new directions for a jurisdiction to consider if they are aiming towards a truly comprehensive strategy.

Measures Directed at High Risk Populations

1. Community-wide risk reduction education.
   - · prevent initiation or promote cessation of risky behaviour.
   - · reduce risk for getting infection or transmitting to others.
2. Screening for risky behaviour through routine history-taking in medical settings.
3. Recruiting for programs (see nos. 4-6 below) among high-risk populations.

Measures Directed at High Risk Individuals

4. Targeted counselling / education among high-risk individuals not yet infected (e.g., newer, younger, drug users).
   - · prevent initiation or promote cessation of risky behaviour (this includes relapse prevention measures).
   - · reduce risk for getting infection (e.g., diversion to non-injecting routes of drug administration).
5. Substance-abuse treatment.
6. Provide other services among high-risk-individuals ("harm reduction")
   - · vaccinations for those engaging in risky behaviours and / or in contact with infected or potentially infected persons.
   - · syringe / needle exchange.
   - · safer injection sites.
   - · condom distribution.

Measures Directed at Infected Individuals

7. Screening for presence of the virus by testing high-risk individuals (i.e., those injecting drugs or having sex with multiple partners and / or partners who are themselves at risk).
8. Targeted counselling / education among infected individuals.
   - · promote cessation of risky behaviour.
   - · otherwise reduce risk for transmitting to others.
9. Treatment of infection.
10. Provide other services among infected individuals related to stopping transmission ("harm reduction"); see under no. 6 above.
11. Quarantine / prosecution to prevent acts which endanger others.

Overarching Strategies

12. Thorough education for health care professionals in all of the above.
13. Integration of multiple public health and clinical strategies.
14. Surveillance to evaluate effectiveness and guide the development of new programs.

Ongoing Investment in Research and Pilot Projects

It is clear that more needs to be known about the transmission of the various pathogens, the co-factors which may be part of initiating and maintaining carcinogenesis, and the overall course of disease. Greater insight into any of these areas will allow enhancements of the prevention armamentarium, ultimately allowing the disease burden to be reduced and, perhaps, eradicated. The dramatic drop in cervical cancer rates, primarily as a result of screening programs, spurs on public health efforts and holds out hope for similar results with other diseases. The development and imminent launch of vaccines for HPV promises a brand new era for cervical cancer prevention, though many implementation questions remain unanswered. Intense resources will be required to encourage other research frontiers, including a vaccine for HIV.

Finally, continued study of other potential etiologic agents is vital in the overall battle against cancer; the potential for disease prevention represented by each of the candidate pathogens makes this a truly exciting area of medical research.

The Temptation of Technology

As captivating as new health technologies can be, it is also important to continue focusing on the classic “low-tech” public health options related to early primary prevention, including initiatives involving media advocacy, education and counselling. The modest record of progress in this regard, even with high-profile agents such as HIV, is very sobering. Much more needs to be done.

Planners also need to be wary of inappropriately supplanting old technologies with new. For instance, some authorities are suggesting that a new HPV vaccine should work alongside rather than replace screening programs, at least until the backlog of potential cervical cancer cases is cleared. The latency period involved can be up to 20 years.

It is clear that a strong coalition between researchers, clinicians, public health managers and funders will be required to navigate through the complex data and policy options and see the sort of breakthroughs desired with the significant cancers described in this report.

Appendix A: ARC List of Infectious Causes of Cancer

From *IARC Monographs* Volumes 1-88 (a total of 900 agents, mixtures and exposures). In 1969, the International Agency for Research on Cancer (IARC) initiated a program to evaluate the carcinogenic risk of chemicals to humans and to produce monographs containing the evidence and other details. The program has since been expanded to include exposures to mixtures of chemicals and to other agents, such as radiation and viruses.[437]

- **Group 1:** Carcinogenic to humans (out of a total of 95 agents currently recognized)

Epstein-Barr virus (Vol. 70; 1997)
Helicobacter pylori (infection with) (Vol. 61; 1994)
Hepatitis B virus (chronic infection with) (Vol. 59; 1994)
Hepatitis C virus (chronic infection with) (Vol. 59; 1994)
Human immunodeficiency virus type 1 (infection with) (Vol. 67;1996)
Human papillomavirus types 16 and 18 (Vol. 64; 1995)
Human T-cell lymphotropic virus type I (Vol. 67; 1996)
Opisthorchis viverrini (infection with) (Vol. 61; 1994)
Schistosoma haematobium (infection with) (Vol. 61; 1994)

- **Group 2A:** Probably carcinogenic to humans (out of 66)

Clonorchis sinensis (infection with) (Vol. 61; 1994)
Human papillomavirus types 31 and 33 (Vol. 64; 1995)
Kaposi sarcoma herpesvirus / human herpesvirus 8 (Vol. 70; 1997)

- **Group 2B:** Possibly carcinogenic to humans (out of 241)

Human immunodeficiency virus type 2 (infection with) (Vol. 67;1996)
Human papillomavirus: some types other than 16, 18, 31 and 33 (Vol. 64; 1995)
Schistosoma japonicum (infection with) (Vol. 61; 1994)

- **Group 3:** Not classifiable as to human carcinogenicity (out of 497)

Hepatitis D virus (Vol. 59; 1994)
Human T-cell lymphotropic virus type II (Vol. 67; 1996)
Opisthorchis felineus (infection with) (Vol. 61; 1994)

[437] From the preamble to the Monograph series. Available at http://www-cie.iarc.fr/monoeval/preamble.html. Accessed July 2005.

Appendix B: NTP List of Infectious Causes of Cancer

From *The Report on Carcinogens, 11th Edition* (2004). Published by the National Toxicology Program (NTP), US Dept. of Health & Human Services (Public Health Service). The NTP is formed from parts of several different US government agencies, including the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA).

Known to be Human Carcinogens.

Hepatitis B Virus
Hepatitis C Virus
Human Papillomas Viruses: Some Genital-Mucosal Types

Note: all of these agents were added as of this edition of the Report.

Reasonably Anticipated to be Human Carcinogens.

None

Appendix C: ACS List of Infectious Causes of Cancer

From American Cancer Society (ACS) *Cancer Facts & Figures 2005.*

Hepatitis B virus
Hepatitis C virus
Human papillomavirus
Helicobacter pylori
Human herpesvirus type 8
Human immunodeficiency virus
Epstein-Barr virus
Human T cell lymphotrophic virus

Appendix D: Dr. J. Goldie's List of Cancers and Infectious Causes

Dr. James Goldie, University of British Columbia

Source: **Is there a case for infectious agents playing a significant role in causing cancers?** *Presentation to BC Cancer Agency Conference 2003*
Available at http://www.bccancer.bc.ca/RS/CommunitiesOncologyNetwork/EducationandPlanningConferences/ACC2003/MSS/default.htm. Accessed July 2005.

Proven

Gastric carcinoma	*H. pylori*
Gatric MALT lymphoma	*H. pylori*
Hepatocellular carcinoma	Hepatitis B, C
Cervical and other anogenital carcinoma	Human papillomavirus
Posttransplantation lymphoproliferative disorder	Epstein-Barr virus
Burkitts' lymphoma	Epstein-Barr virus
Nasopharyngeal carcinoma	Epstein-Barr virus
Kaposi sarcoma	Herpesvirus type 8
Primary effusion lymphoma	Epstein-Barr virus
Adult T-cell leukemia	Human T cell lymphotrophic virus-1

Strongly Suggested

Bladder carcinoma	*S. haematobium*
Squamous skin and oral mucosa	Human papillomavirus
Hodgkin's disease	Epstein-Barr virus
Non-Hodgkin's lymphoma	Epstein-Barr virus; Hepatitis C

Tentative Association

Gall bladder carcinoma	*S. typhi*
Breast cancer	Human mammary tumour virus
Primary CNS tumours / mesothelioma	Polyomaviruses
Ovarian carcinoma	*Chlamydia*
Ocular MALT lymphoma	*Chlamydia*
Primary CNS lymphoma	Epstein-Barr virus
Childhood acute lymphoblastic leukemia	???