Cancer can be prevented too
Protection against cancer-causing infections

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Introduction

Over the past three decades, infections have emerged as important risk factors for cancer. In 2006, I reported that an estimated 21% of the global cancer burden, was attributed to various infections and WHO estimates that infections are responsible for almost 22% of cancer deaths in the developing world and 6% in industrialised countries. For example, the third most common site for cancer mortality in women (Globocan 2002) after breast (410,712 deaths) and lung (330,786 deaths) cancer is cancer of the cervix (273,505 deaths), which is known to be caused by the human papillomavirus (HPV). Similarly, the bacterium Helicobacter pylori (H. pylori) and viral hepatitis infections are known contributors to the second and third of the top three sites for cancer mortality in men: stomach (446,052 deaths), and liver (416,882 deaths).

The pattern of cancer sites also varies substantially from region to region. For example, H. pylori and viral hepatitis infections contribute to the most and third most common cancer sites among individuals 15 years or older in East Asia - stomach (18.9%) and liver (14.3%)- however these cancers are not represented in the top three common cancer sites in North America.

Although recent research has significantly improved the understanding of infectious agents which cause cancer, there is a growing demand to multiply these research efforts to match the ever-increasing burden of cancer.

The identification of a number of infections linked to human cancers and, more so, the establishment of their causal role in the development of the respective tumours is a recent advancement in cancer control worldwide. Understanding the biological pathways of specific infectious agents has allowed for higher success in the prevention, detection and treatment of these infections in both high- and low-income countries. There is a broad range of infections that are now categorised as cancer-causing agents, which are covered in this report.

Thus, identification of infectious agents in human cancer, prevention, detection and treatment of these infections need to be the focus of current cancer research.

Globally, efforts to identify agents involved in human cancers and to study the mechanisms of how they lead to cancer are still remarkably underrepresented. In recent years, a large number of new virus types have been discovered in humans, many of them as yet without identified pathogenic effects (e.g. TT viruses and cryptogenic hepatitis). In addition, the existence of epidemiological hints for an involvement of yet unspecified infections in several human cancers (e.g. childhood leukaemia, Epstein-Barr virus-negative Hodgkin lymphomas, non-Hodgkin lymphomas, and others) emphasizes the need for further research.

Improvements in the methods for detection of infection have contributed to the definition of interruptions of biological pathways ultimately contributing to cancer. Early detection of lesions caused by infectious agents can greatly reduce their progression and can be achieved all around the world. Successful early detection has been witnessed especially in screening programmes for cervical cancer. Although early detection methods for other cancers have also been identified, such as for H. pylori and Burkitt’s lymphoma, implementation in low-income countries has been an enormous challenge due to limitations in disease awareness and public health infrastructures.

The identification of the role of infectious agents in human cancers not only paved the way for novel
approaches in the development of new diagnostic tools, but also contributed to primary cancer prevention i.e. prophylactic intervention. Within a brief period of time after the identification of infectious agents causing human cancers, such as with the Epstein-Barr virus (1965), dramatic new developments for cancer prevention took place: new vaccines became available, with the potential to protect efficiently against hepatitis B virus-linked liver cancer. This has been followed by the recent development of vaccines against cancer-causing human papillomavirus types 16 and 18. Furthermore, where prevention prior to infection (i.e. through vaccination) is not available or possible, other early interventions to treat the infections can be utilized. Antibiotics are known to prevent the progression of infections with the bacterium *H. pylori* to gastric cancer. Similarly, some cancer-causing parasites can be eliminated by a single tablet of chemotherapy. Unfortunately, however, the latter two types of treatment do not protect against subsequent re-infections by the same agent. Last, but not least, all these developments open the road to targeted chemotherapy, as beautifully exemplified in the present protocols for the treatment of human immunodeficiency virus infections.

This calls for an increased awareness of the contribution of infections to the global cancer burden, and, in turn, for actions for integrated cancer control plans to manage those infections, preferably by preventing their occurrence.

The present UICC campaign report aims at supporting cancer control professionals in their advocacy and awareness-building work related to cancer and infections and addresses current prevention strategies such as:

- **Primary prevention of the respective infections by vaccination (hepatitis B and high-risk papillomaviruses).**
- **Avoiding exposure to these infections, wherever possible (e.g. change in sexual behaviours, safe blood products, appropriate food preservation).**
- **Implementing effective early detection of major cancers via early diagnosis and screening (e.g. using established and new technologies for cervical cancer; test and treat policy for *H. pylori*; biopsy samples for Burkitt’s lymphoma and Kaposi’s sarcoma).**
- **Development of targeted treatment protocols, to optimize elimination of infection from both acute and chronically infected patients.**
- **Integrating cancer control with programmes for other chronic diseases and related problems.**

The International Union Against Cancer and I wish with this report to raise awareness of the large contribution infections make to the global cancer burden, to highlight the progress made so far and the options available to us all to take an active role in preventing, detecting or treating those infections before they cause cancer.

* 2008 Nobel Laureate in Medicine or Physiology for his discovery of human papillomaviruses causing cervical cancer
Hepatitis B virus: preventing liver disease with the first vaccine against cancer

Steven Wiersma

Key messages

• Hepatitis B virus infection is a major public health threat on a similar scale of magnitude as HIV, malaria and tuberculosis.
• Viral hepatitis diseases are a major cause of liver disease and liver cancer but are preventable through vaccination, safe healthcare and behaviour change. Global control of hepatitis B virus transmission is now a real possibility due to widespread use of vaccines as well as development and use of new effective treatments.
• Policies for the prevention of hepatitis B virus infection should be part of every comprehensive health policy and clear goals for the control of this disease are needed now to prevent hepatitis and liver cancer.

Hepatitis B virus infection and liver cancer

Hepatitis B virus (HBV) infection is a major cause of liver disease including cirrhosis and cancer. HBV is highly infectious through contact with blood or blood-derived body fluids of an infected person. Major modes of transmission include sexual, perinatal (from mother to infant at the time of birth) and percutaneous blood exposure through unsafe injection practices and needle stick injuries or transfusion with infected blood.

Initial infection with HBV can be symptomatic or asymptomatic. The likelihood of progression to chronic infection is the same whether an individual is symptomatic or asymptomatic. People with chronic HBV infection have a 15% to 25% risk of dying prematurely from HBV-related cirrhosis and liver cancer.

The age at which a person becomes infected with HBV is the main factor determining the outcome. Among children under 5 years of age who become infected, fewer than 10% are symptomatic whereas 80-90% of infants infected during the first year of life and 30-50% of children infected between one and four years of age develop the chronic condition. In adults however, 30-50% of adults are symptomatic when first infected but only 2-5% become chronically infected.

After the initial infection with HBV, some people clear the virus and become immune, while others develop chronic HBV infection, which can lead to the serious consequences of cirrhosis and liver cancer. Some of those infected develop a clinical syndrome referred to as acute hepatitis B.

Hepatitis B, coinfection and other exposures for the development of liver disease

Coinfection with hepatitis D in HBV-infected patients result in worse outcomes than infection with HBV alone; this includes a higher rate of liver failure in acute infections and a greater likelihood of developing liver cancer in chronic infections.

HBV and HIV coinfections are an increasing problem in countries with concentrated HIV epidemics and among injecting drug users. For those coinfected persons who are being treated with antiviral medicines, underlying viral hepatitis is becoming a major cause of death.
Several known exposures or underlying conditions contribute to the development of primary liver cancer, including aflatoxin (a fungal toxin which contaminates food), hemochromatosis (iron overload disease), alcohol abuse or liver cirrhosis of any cause, but the most common causes are infections with hepatitis viruses, specifically HBV and hepatitis C virus (HCV).

**Burden of hepatitis B virus infection**

Primary liver cancer causes an estimated 598,000 deaths worldwide every year. In some countries, primary liver cancer is among the three most common cancers among men, and an important cause of cancer among women. If discovered at a late stage, primary liver cancer is often fatal, with death occurring within a few months in untreated patients.

Hepatocellular carcinoma (HCC) is the major type of primary liver cancer (75-80%), usually preceded by liver cirrhosis. In a recent global study, 30% of cirrhosis was attributable to HBV and 53% of HCC was attributable to HBV.

It is estimated that two billion people have been infected with HBV, of which over 350 million have chronic HBV infection. Approximately 88% of the world’s population live in areas where the prevalence of chronic HBV infection is high (>8% HBsAg-positive) or moderate (2-7% HBsAg-positive). The Asian and African regions have a much higher burden of disease than other regions. The World Health Organization (WHO) estimates that 500,000 to 700,000 HBV-related deaths occur each year, approximately 93% of which are the result of chronic infection.
Opportunities for prevention
HBV vaccination

HBV infection is preventable with a vaccine—the first vaccine to prevent a major human cancer. As infection with HBV in infants is generally associated with the worst health outcomes, the WHO has since 1991 recommended that all infants receive hepatitis B vaccine through introduction into routine infant immunisation programmes.\(^6\)

Despite the global progress in immunisation of infants, coverage with hepatitis B vaccine has not yet reached the goal set by the WHO Global Immunisation Vision and Strategy\(^7\) (Figure 1 and 2) of 90% national vaccination coverage by 2010. Current global coverage levels for hepatitis B vaccination are well below those for diphtheria, tetanus and pertussis.\(^8\) Hepatitis B vaccination is an important element in strengthening health systems, especially as part of efforts to provide services to mother and child around the time of birth. Elimination of HBV transmission is feasible for future generations; however, prophylactic vaccination is unable to protect those 350 million who already have chronic HBV infections. Those chronically infected could benefit from an increasing number of effective treatments. Programmes to identify those who are chronically infected and provide treatment and monitoring are greatly needed.

Integration of hepatitis prevention efforts

Coordinating programmes for the prevention and control of hepatitis will contribute to building comprehensive health systems. Maximising existing networks of immunisation programmes and maternal and child health programmes are needed to ensure delivery of the first dose of hepatitis B vaccine within 24 hours of birth.\(^9\) Similarly, programme coordination is needed to ensure that vaccine is delivered to health workers, travellers, and in settings in which a high proportion of persons are likely to be at risk for HBV infection (e.g., those attending testing and treatment facilities for sexually transmitted diseases such as HIV, drug-abuse treatment and prevention settings, healthcare settings targeting services to injection drug users, healthcare settings targeting services to male homosexuals, and correctional facilities).
In addition to immunisation programmes, reduction of hepatitis B virus transmission could be achieved by applying the following practices:

- Recruiting only voluntary, unpaid blood donors to ensure safe blood supplies.
- Introducing effective blood donor selection and screening of all donated blood for markers of hepatitis B and C virus infection with highly sensitive and specific assays and following basic standardised procedures.
- Training of clinicians and nurses on safe injection practices and ensuring that sharps waste is properly managed through the sustainable procurement of sufficient quantities of syringes with safety functions.
- Improvement of food safety to prevent virus and toxin ingestion (especially aflatoxin) by implementation of international guidelines for the management of viruses and toxins in foods.
- Integration into services for the prevention, treatment and care of hepatitis B and C virus infections for injecting drug users, including access to sterile needles and syringes, hepatitis B vaccination and antiviral treatment.

These services and programmes can provide good entry points for both infected and most-at-risk people, and coordination can promote synergies for prevention, therapy and laboratory work.

Multiple health programmes could engage in comprehensive approaches to prevent infection and manage disease, and in particular create links with HIV diagnostic and treatment services and with national cancer control programmes. Behavioural change strategies for HCC risk reduction are not unique to HBV control and should be integrated in other disease control programmes.

**Conclusion**

The availability of the first vaccine against cancer to the majority of the world’s children through universal infant immunisation has protected millions of people from developing hepatocellular carcinoma. Countries that have implemented these strategies are documenting a dramatic reduction in chronic hepatitis B infection and mortality due to hepatocellular carcinoma. As global coverage reaches targets and other preventive behaviours are adopted, the incidence of hepatocellular carcinoma and consequent mortality can be expected to fall dramatically.

To date, comprehensive prevention and control efforts have been successful but fragmented. The time is right to create new opportunities for prevention, including establishing goals and strategies for disease control, increasing education and promoting healthy lifestyles and adequate treatment of the 500 million people already infected with hepatitis B and C viruses. The impact of these efforts on mortality and morbidity will be significant because of the tremendous burden of disease.
**SUMMARY**

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* Global disparities exist in availability and access to treatment

**GLOSSARY**

**Acute hepatitis B**
Acute hepatitis B is the period of illness that occurs during the first one to four months after acquiring the virus. Only 30% to 50% of adults develop significant symptoms during acute infection. Early symptoms may be non-specific, including fever, a flu-like illness, and joint pains. Symptoms of acute hepatitis may include: fatigue, loss of appetite, nausea, jaundice (yellowing of the skin and eyes), and pain in the upper right abdomen (due to the inflamed liver).

**Chronic hepatitis B**
Chronic hepatitis B infection is a long term hepatitis B liver inflammation that may never completely resolve itself.

**Cirrhosis**
Cirrhosis is a complication of many liver diseases including hepatitis infection. Cirrhosis is a slowly progressing disease in which healthy liver tissue is replaced with scar tissue, eventually preventing the liver from functioning properly.
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1 WHO Fact Sheet No 204, http://www.who.int/mediacentre/factsheets/fs204/en/


Hepatitis C virus: a growing threat to the fight against liver cancer

Silvia Franceschi

Key messages

- Liver cancer is frequent (half a million cases per year worldwide) and rarely curable.
- Globally, approximately 80% of liver cancer is caused by two viruses, hepatitis B virus (HBV) and hepatitis C virus (HCV).
- Acute HCV infection usually goes undetected, but ultimately leads to liver fibrosis, cirrhosis, and eventually liver failure or liver cancer.
- The frequency of HCV infection is severely underestimated worldwide and is increasing in developing countries.
- Prevention strategies for HCV infection are complicated due to the absence of a prophylactic vaccine. Prevention requires safe transfusions, safe injection practices and encouragement of oral treatment instead of injections whenever possible.

Liver cancer

Liver cancer is an important public health problem worldwide and a major example of inequality across different world populations. Nearly half a million new liver cancer cases are diagnosed every year, representing approximately 6% of all cancers.³ Less developed countries are hit especially hard by the disease: 80% of liver cancer worldwide occurs in less developed countries, and half of those in China. In more developed countries, there have been upward trends reported in the United States, Japan⁴, and in several European countries⁵ in the last two or three decades, although the majority of the burden remains in less developed countries.

Liver cancer is caused by the long-term consequences of infection with two viruses, hepatitis B (HBV) and hepatitis C (HCV), which are reported to account for 50% and 25%, respectively, of the disease burden. There is a 20-fold increased risk for liver cancer among carriers of either virus. The estimated fraction of liver cancer attributable to HBV and HCV in 2002 was 23% and 20% in more developed countries and 59% and 33% in less developed countries.¹ Liver cancer is one of the least curable malignancies and represents the third most frequent cause of cancer death among men worldwide.

Basic biology of the hepatitis C virus

HCV is a small RNA virus belonging to the same family as yellow fever, and was discovered in 1989. The virus is extremely capable of evading the immune response and as a result the majority of individuals exposed to HCV become chronically infected. HCV is similar to HIV with a fast viral replication. These characteristics provide the basis for its enormous genetic variability. Six major genotypes with different geographical distributions have been identified (Table 1).

Acute HCV infection and less-advanced stages of chronic infection usually go undetected, as they have no symptoms, but ultimately lead to liver fibrosis, cirrhosis, and eventually liver failure or liver cancer. The average time from infection to onset of cirrhosis is approximately 13 to 25 years, and time to onset of liver cancer 17 to 31 years.⁴
**Worldwide burden of HCV infection**

The World Health Organization (WHO) estimates that about 180 million people, some 3% of the world’s population, are infected with HCV, of which 130 million are chronic carriers at risk of developing liver cirrhosis and/or liver cancer. At least 3-4 million people are newly infected each year. The burden of HCV is, however, lower than the burden of HBV (i.e., 350 million people with chronic HBV infection). The proportion of liver cancer due to these viruses, however, varies enormously from country to country and there is evidence that the prevalence of HCV is currently substantially underestimated.5,6

Several factors contribute to the underestimation of HCV infection: 1) lack of country-specific data, even in more developed European countries8 2) poor sensitivity of HCV surveillance systems that focus on rarely symptomatic acute HCV infection and 3) tendency of available HCV prevalence surveys not to include highest prevalence populations (i.e., middle-aged and elderly people and, in more developed countries, intravenous drug users).

This last factor, in particular, is the most important reason for the more severe underestimation of HCV compared to HBV infection (Figure 1). Hepatitis prevalence surveys are mainly based on young age groups (e.g., blood donors or pregnant women). By young adulthood, the majority of HBV infections have already occurred because viral transmission, in populations where HBV vaccine has not yet been introduced, occurs at birth (e.g., China), during childhood (e.g., sub-Saharan Africa and India) or after becoming sexually active (e.g., more developed countries). In contrast, HCV is nearly exclusively transmitted through contact with blood and blood products. In countries where routine blood screening for HCV and safe injection practices are not available (or have been only recently introduced) iatrogenic transmission (induced inadvertently by a physician or surgeon, or by medical treatment or diagnostic procedures) of HCV continues into adulthood and old age. It is also worth noting that the late acquisition of HBV in adulthood is not only rare but also associated with substantially lower probability of becoming chronic than early acquisition. The risk of HCV becoming chronic, however, does not decline with age at infection.

**Prevention of HCV and treatment of liver cancer**

Only expensive and side effect-heavy multi-drug combinations can eradicate HCV, and accurate tests for its detection (second-generation tests) only became available in the early 1990s.7

The feasibility of treating liver cancer depends on disease stage at diagnosis, but also on the severity of liver impairment. Liver cancer most often arises within the framework of liver fibrosis and cirrhosis. Complete surgical resection and therapeutic liver transplantation are seldom possible, even in the most developed countries. In addition, radiotherapy and chemotherapy show a very low success rate among liver cancer patients.4 Although palliative treatments (local ethanol injection and radiofrequency ablation) offer some benefits and should be made increasingly available in less developed countries, it is clear that primary prevention is the best strategy to diminish the worldwide liver cancer burden. Implementation of a highly efficacious and cost-effective vaccine against HBV, which is now reaching two-thirds of the world’s children, is likely to diminish the liver cancer burden associated with HBV in the next generations.

<p>| Table 1: HCV genotypes in different parts of the world |</p>
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Country</th>
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<tr>
<td>1-3</td>
<td>Worldwide</td>
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<tr>
<td>4-5</td>
<td>Africa and Middle East</td>
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<td>6</td>
<td>Asia</td>
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With respect to HCV infection, however, prevention strategies are more complicated and, for the moment, sorely lacking in many less developed countries. No preventive vaccines against HCV yet exist.

HCV control measures – past and present
The rapid worldwide spread of HCV arose from its efficient transmission through contaminated blood and blood products, injections, and other invasive medical procedures. HCV epidemics have, therefore, accompanied the increasing availability of these medical procedures in different countries until safe blood supplies and safe injection practice were implemented. Injection, blood transfusions and medical procedures have been established and even increased at time of military conflicts around the world. By the end of the 1980s, one out of 50 blood units in more developed countries transmitted HCV. As a result, most chronic transfusion recipients and virtually all patients receiving clotting factor concentrates developed chronic hepatitis. However, the incidence of HCV infection greatly decreased within a few years because of the introduction of anti-HCV tests for blood donors, inactivation procedures for blood derivatives and disposable needles and syringes. The majority of new HCV infections in more developed countries in the last 15 years have been due to needle sharing by intravenous drug users.

Less developed countries: blood screening practices and injections
Approximately half of less developed countries do not systematically screen blood donations for HCV, although blood is generally screened for HBV and HIV. Most of the countries where blood donations are not screened for HCV are in Asia and Africa, but there are also a few in Latin America and the Caribbean. Blood safety in less developed countries is additionally threatened by lack of voluntary non-paid blood donors, inadequate supplies of instruments and laboratory reagents, and lack of infrastructure. Furthermore, although the greatest risk of HCV transmission is through contaminated blood transfusions, the use of contaminated injections concerns a much larger number of people of all ages and is therefore the main cause of unrecognised HCV transmission. More than 16 billion injections are administered annually in less developed countries and WHO estimates that they account for at least 2.3 million new HCV infections per year.

Re-use of needles and syringes and the administration of unnecessary injections are the main causes of iatrogenic transmission of HCV in less developed countries. Particularly high rates of injections have been reported in some countries of the former Soviet Union, Mongolia, Pakistan, and in some African countries. The most frequently injected medications include antibiotics, vitamins, and analgesics or treatments for non-specific symptoms, such as headache, fatigue, or fever that could be taken orally. The overuse of injections that led to major HCV epidemics in Japan and Southern Europe in the first part of the last century is now continuing in less developed countries due to various factors linked to poverty. A summary of approaches for the prevention of blood-borne infections including HCV is shown in Table 2.

In poorly funded healthcare systems avoidable injections represent an important source of revenue for the providers and are encouraged by the popular belief that injections are more effective than oral administration. However, injections in many instances only serve to increase transmission of infection. Insufficient hygiene, inappropriate use of multiple-dose medication vials, and sharing of bottles of intravenous solution for multiple patients also contribute to HCV spread in overcrowded hospitals in less developed countries. In addition, transmission also occurs through traditional medicine procedures (e.g., acupuncture and scarring) and outside healthcare settings (e.g., tattooing).

Conclusions
HCV has been rightly dubbed the “viral time bomb”. Many more developed countries are now facing the long-term consequences of past HCV epidemics, sustained by contaminated transfusions and unsafe injections in the last century and, more recently, intravenous drug use. HCV is, however, reaching worrying levels also in many less developed countries still fighting with a historically heavy burden of HBV infection. Many countries in Africa and Asia may see the benefits of HBV immunisation undermined by the spread of another powerful cause of liver cancer, HCV. In the absence of a vaccine, HCV prevention
Figure 1: Example of countries where HCV is more often found in liver cancer patients than HBV.

- **Japan** (n = 2715)
- **Pakistan** (n = 542)
- **Mongolia** (n = 363)
- **Egypt** (n = 938)
- **Spain** (n = 377)
- **Italy** (n = 981)
is more challenging than the prevention of HBV and requires integrated strategies. The systematic screening of blood donations and safe injection practices are essential but they need to be accompanied by campaigns to avoid unnecessary injections. The misperception that many treatments that can be given orally are “better” if injected is unfortunately still widespread among patients and even health workers in less developed countries, and represents a major obstacle to slow the incidence of blood-borne infection, including HCV, HBV and HIV.

**Table 2: Prevention of blood-borne infections, including HCV, HBV, and HIV**

<table>
<thead>
<tr>
<th>Prevention of blood-borne infections, including HCV, HBV, and HIV</th>
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<tr>
<td>Increase awareness of the importance and possibility to prevent blood-borne infections including HCV among the population, health-care workers, and traditional healers</td>
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<tr>
<td>Use oral treatments to injections, whenever possible</td>
</tr>
<tr>
<td>Ensure that all injections (treatments and vaccination) are safe and that sharps waste is properly managed</td>
</tr>
<tr>
<td>Provide services to injecting drugs users, including access to sterile needles and syringes</td>
</tr>
<tr>
<td>Ensure safe blood supplies by recruiting voluntary donors and screening all donated blood for markers of HCV, HBV and HIV</td>
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**SUMMARY**

**Liver cancer (hepatocellular cancer)**

| Viral link | yes |
| HCV | Infectious agent | hepatitis C virus |
| Transmission/vector (as appropriate) | infected blood or blood products, contaminated hypodermic or tattooing needles |
| Treatment* | yes |
| Prevention strategies | avoid transmission of infection by blood contacts: safe medical and dental interventions; safe blood products; safe transfusions and injection practices; prefer oral therapy whenever possible; reduction of alcohol consumption; safe sexual practices; awareness and education activities |
| Vaccination | no |
| Early diagnosis | yes |
| Screening | no |

* Global disparities exist in availability and access to treatment
Other contributions to the development of liver disease

HCV is nearly exclusively transmitted through contact with blood and blood products. Heavy alcohol consumption, alone or in addition to hepatitis infection, is responsible for an important fraction of liver cancer especially in more developed countries where HBV and HCV infections are rare. Tobacco smoking has also been associated to increased liver cancer risk. Noteworthy contributions to liver cancer causation derive from aflatoxin contamination of food in less developed equatorial countries, and from dietary and metabolic factors (i.e., obesity, diabetes, and iron overload) in more developed countries.

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Human papillomavirus and cervical cancer: prevention and treatment with emphasis on low-resource settings

Lynette Denny, Neerja Bhatla and Scott Wittet

Key messages

- Persistent human papillomavirus infection is responsible for cervical cancer and other cancers including vaginal, penile, anal, oropharyngeal and oral cancers.
- At least 13 human papillomavirus types have high potential for causing cancer; two types in particular, HPV-16 and 18, are commonly found in cervical cancers worldwide.
- Although there is no cure for HPV infection, the majority of infections clear spontaneously. Progression of persistent infection to cancer, which is relatively uncommon, can be interrupted when pre-cancerous lesions are detected using cytology, visual inspection methods or HPV DNA tests.
- Recent developments in cervical cancer prevention (HPV vaccines) open new roads for cervical cancer control worldwide.
- The disparities in prevention, screening and treatment between developing and developed countries and between public and private sector markets remain the greatest challenge to potentially eliminating cervical cancer.

Human papillomavirus

Human papillomavirus (HPV) is easily transmissible and a common sexually transmitted infection (STI). Of more than 100 HPV types, there are at least 13 types of HPV which are known to be carcinogenic. The most important cancer-causing HPV type with regard to cervical cancer is HPV-16, followed by HPV-18.1 HPV types 16 and 18 are common around the world and account for about 70% of cervical cancer cases. HPV types 6 and 11 do not cause cancer, but are associated with 90% of genital warts. The disease burden of each particular HPV type varies somewhat by region, but HPV-16 and 18 dominate in all regions.2 Although cervical cancer is the most common malignancy caused by HPV infection, HPV infection is also associated with vaginal, vulvar, penile, anal, oropharyngeal and oral cancers.

Cervical Cancer

Due to the success of pre-cancer screening (primarily using cytology, the “Pap test”, and adequate management of positive cases) and improved treatment of advanced cancer in industrialised countries, cervical cancer is now a disease primarily of the developing world, where it is the leading cancer killer of women. Nearly 500,000 women develop new cases and about 270,000 women die from cervical cancer each year. Globally, cervical cancer is among the major cancer causes of female mortality and 80 to 85% of these deaths occur in middle- and low-resource countries (Figure 1).3 Families and communities are severely impacted as they lose mothers, daughters and grandmothers, women who often are primary caretakers or providers. This is particularly important in areas also devastated by HIV/AIDS, as risk of developing cervical cancer is increased in HIV-positive women.
Case Study

HPV and cancer of the oropharynx

Johan Fagan

Smoking and alcohol have long been known to be the major risk factors for oropharyngeal cancer. Infection with human papillomavirus (HPV) infection is now also recognised as an important risk factor in cancers of the oropharynx (oral cavity or throat), such as the tonsils, soft palate and the base of tongue.1,2

Certain HPV types are known to be cancer-causing, specifically HPV type-16 (HPV-16). In the case of oropharyngeal cancers, HPV-16 infection is strongly associated with these cancers, in addition to oral infection with any of 37 types of HPV.

Transmission of the HPV virus occurs easily through skin-to-skin contact. This mode of transmission is known for other HPV-related cancers such as cervical, vaginal and penile cancers. Oral HPV infection may be sexually acquired and could partially explain the increased incidence of oropharyngeal cancer worldwide.

Determining the HPV status of patients with oropharyngeal cancer may become the standard because of its prognostic implications. How to utilize this information in practical terms other than counselling sexual partners of HPV-positive patients with oropharyngeal cancer, however, requires further research. Since approximately 90% of oropharyngeal cancers are caused by HPV-16, vaccination could potentially reduce HPV-related oropharyngeal cancer.

References

Natural History of HPV and Cervical Cancer

HPV spreads through skin-to-skin contact, not in body fluids. It is most commonly spread through any type of sexual contact (penetrative sex4 as well as any genital, anogenital or orogenital contact). Up to 80% of women are infected with HPV at least once in their lifetime.5,6 Usually in their teens, 20s, and early 30s. Adolescents who initiate sex at an early age are at especially high risk of infection and for developing persistent infection, because the virus can more easily penetrate an immature cervical epithelium (cell lining of the cervix).

Individuals with multiple sexual partners, or whose partners have many partners, are also at higher risk of infection. While condoms provide protection against other STIs, they are less effective for protection against HPV infection.7 Therefore, interventions that have proven effective against HIV likely will prove less effective against HPV, and additional protective measures, such as vaccination, are necessary.

Infection with HPV does not always result in cancer. In fact, the majority of infections clear spontaneously within 3 – 24 months, and in the majority of cases the infection is entirely asymptomatic. In about 10% of women, however, the infection persists. Persistent infection with the cancer-causing types of HPV is strongly correlated with the development of precancerous cervical lesions (pre-cancer), known as low- or high-grade cervical intraepithelial neoplasia, or CIN and also known as squamous intra-epithelial lesions or SIL.
These precancerous lesions can develop into cancer unless detected and removed. Progression from HPV infection to invasive cancer generally takes 20 to 30 years, so cervical cancer is most often diagnosed in women age 40 to 60 years.8

HPV infection is a necessary, but not sufficient, cause of cervical cancer. Factors contributing to the development of cervical cancer after HPV infection include early age at first intercourse, multiparity, early age at first delivery, cigarette smoking, long-term hormonal contraceptive use, immune suppression and infection with other STIs such as Chlamydia trachomatis and herpes simplex virus 2,9,10,11

Screening, diagnosis and treatment of cervical lesions
Cervical cancer is the most preventable of all cancers because the disease develops slowly and treatment of precancerous lesions can be both effective and inexpensive. In high-resource settings, organised cytology-based screening with systematic call, recall, follow-up and surveillance systems have shown the greatest impact on cervical cancer incidence, while using fewer resources than less organised programmes. However, most developing countries have not been able to initiate or sustain Pap-based screening programmes and most women in the world currently have no access to cervical screening. This failure has been due to the demands of competing health needs as well as the challenges of providing cytology services. These challenges include a lack of quality assurance, poor coverage of women at risk, and the failure to follow up women with abnormal Pap smears.12 The most effective and cost-effective strategies for cervical screening are those requiring the fewest patient visits as this improves treatment compliance, follow-up and minimizes cost.13, 14 Even screening a woman once in her lifetime, after age 30, and providing treatment as needed, would significantly reduce her risk of cervical cancer.15

Large numbers of studies conducted in developing countries (e.g. India, Africa and South America) have shown that alternative strategies to cytology for the prevention of cervical cancer are feasible, effective and relatively easily implemented. Two of the most

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**Figure 1: Age-specific cervical cancer mortality rates per 100,000 women**

Many more women die of cervical cancer in the developing world than in wealthier countries. In the industrialised world, effective screening programmes help to identify pre-cancerous lesions at a stage when they can easily be treated. But lack of screening programmes in poorer countries means that the disease is not identified until it is too late, resulting in higher mortality.
studied alternatives are visual inspection with acetic acid (known as VIA) and HPV DNA testing. VIA is a simple low-cost screening method that can give an immediate result and can be linked to rapid treatment. HPV DNA testing has also been studied as a screening test in India and Latin America, can also be linked to rapid treatment, and has been shown to work well in research settings. A low cost, ‘field friendly’ HPV test may become available as early as 2011.

**HPV Vaccination**

Currently two vaccines against HPV are available on the global market. Both prevent infection with the two most common cancer-causing types, HPV-16 and 18. And both vaccines are produced from DNA-free “virus-like particles” (VLPs), which cannot cause HPV infection.

The World Health Organization recommends that routine HPV vaccination be included in national immunisation programmes when:

*...prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost-effectiveness of vaccination strategies in the country or region is considered. HPV vaccines are most efficacious in females who are naive to vaccine-related HPV types; therefore, the primary target population should be selected based on data on the age of initiation of sexual activity and the feasibility of reaching young adolescent girls through schools, health-care facilities or community-based settings. The primary target population is likely to be girls within the age range of nine or ten years through 13 years.*

The vaccines provide no therapeutic benefit to those already infected with relevant HPV types or those with pre-cancerous lesions or invasive cancer. Because the vaccines are most effective when given prior to infection, it is recommended that girls are vaccinated beginning at age nine-ten years, when most will not yet have been exposed to HPV infection through sexual activity.

It should be emphasised that while the vaccines represent a major breakthrough in the fight against cancer, up to 30% of cases are the result of other cancer-causing HPV types that are not covered by the current vaccines, though there may be some crossprotection against related HPV types. For this reason, vaccination cannot completely replace screening.

**Vaccination – boys and men**

Computer modelling of the impact on cervical cancer when vaccinating boys along with girls suggests that the strategy is not cost-effective, except in scenarios of very low vaccine coverage among girls. Furthermore, vaccine efficacy against HPV-16/18-specific pre-cancerous lesions has not yet been demonstrated in men, although protection has been shown against noncancerous genital warts.

**Ensuring access to HPV vaccination, cervical screening and treatment programmes**

Awareness and coordination of cervical cancer prevention options must be increased globally in order for policy-makers to appropriately prioritise adoption of new cervical cancer prevention interventions. For low-resource countries, vaccination with currently available vaccines will be possible only with substantial vaccine subsidies. The HPV vaccine is one of four vaccines that the GAVI Alliance is considering for subsidised provision to the poorest countries in the world.

Community acceptance of HPV vaccine could be an issue in some places as a result of the stigma around cancer in general, or the nature of how HPV is acquired (i.e. with onset of sexual activity). That said, recent experience of high acceptance of HPV vaccination in Africa, Asia and Latin America suggests that parental concern about cancer, and the desire to protect their daughters against it, outweigh other considerations.

Young adolescents do not routinely interact with health systems in most developing countries, and ensuring access to vaccination will be a challenge. Within and among cancer control programmes, traditional efforts have been designed to focus on screening rather than interventions like vaccination. And most other immunization programmes target infants and toddlers, not adolescents. One promising suggestion for reaching eligible girls is to strengthen school health programmes, especially because of the increase in primary school attendance over the past decade. Where many young girls drop out of school at an early age, community programmes might help to...
fill the gap. The role of the Ministry of Education as well as the importance of culturally appropriate sexual education for all children and adolescents cannot be overstated. Once effective strategies have been developed to reach these girls, additional health interventions appropriate for older children also can be provided that include tetanus, rubella, hepatitis B, measles, and eventually HIV immunisation; deworming; vitamin A supplementation; malaria intermittent preventive treatment; provision of bed nets; treatment of schistosomiasis, filariasis, and trachoma; iron and/or iodine supplementation; nutritional supplementation; and education about hand washing, tobacco, drugs, body awareness, and life-choice decision-making. Using one system to deliver multiple interventions—at the same time as HPV vaccination or at different times—could increase the cost-effectiveness of all the interventions.

New screening initiatives in places where cytology (Pap test) is not feasible may initially train providers to use visual inspection for primary screening among women aged 30 and older, followed by cryotherapy or other treatment options as indicated. And once a low cost HPV test becomes available, it is possible that it will be used for primary screening, and visual inspection will be employed for treatment triage of women who test positive for the virus. Countries will need to assess and allocate resources for staff training in screening methods and for procurement of cryotherapy equipment and, eventually, HPV tests. This may be a challenge, but advocates may cite mathematical modelling results which clearly show screening to be a cost-effective intervention, especially in countries currently paying for treatment of advanced cancer. Palliative care to avoid unnecessary physical and emotional suffering is a crucial element of cervical cancer control, one that unfortunately is often lacking in developing world settings. Freedom from pain is especially important, but is vastly underutilised, even though pain control can be relatively inexpensive and effective in 90% of cases. In addition, palliative care can be received at home when patients, family and other caregivers receive adequate support, training and supplies.

Lack of appropriately trained professionals extends across the treatment spectrum: the best outcome for women with any cancer is when management is agreed upon by a multidisciplinary team of gynaecological oncologists, radiation oncologists, oncology nurses, pathologists and, of course, the patient and her family. The availability of such comprehensive treatment and qualified personnel almost always decreases when a country has fewer resources overall. This highlights the critical need for adequate and universally available cancer prevention to pre-empt the need for treatment.

**Conclusion**

There are tremendous disparities in access to cervical cancer prevention between women in industrialised and developing nations. However, innovative technologies to detect HPV and screen for pre-cancer, along with new HPV vaccines, provide exciting new options and aspirations.

Visual inspection and HPV DNA approaches to screening, coupled with simple, and effective treatment methods, make screening every woman at least once in her lifetime a feasible goal.

The overall assessment from the global scientific community is that HPV vaccines are safe and effective and, ideally they should be offered to girls no matter where they live. There also is consensus that expansion of cervical cancer screening and treatment programmes could result in dramatic declines in mortality in the developing world, just as they already have in wealthier nations.

It is therefore imperative that where cervical cancer is a public health concern, national authorities allocate adequate resources to bring under control this ultimately preventable disease.

**Cervical cancer treatment**

Cervical cancer is treated according to the stage of the disease; however not all women with cervical cancer are symptomatic. In the developing world, 75-80% of women with cervical cancer present with late, invasive stages of the disease. The optimal treatment is primary, radical chemoradiation, however access to this treatment is limited in many developing countries. Only about 20 countries in sub-Saharan Africa have radiation facilities. When surgery is required, there are few hospitals with the proper facilities and fewer still with the appropriately trained staff to perform the procedure.
**HPV-related cancers**

<table>
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<tr>
<td>Cervix¹</td>
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<tr>
<td>Penis²</td>
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</tr>
<tr>
<td>Anus²</td>
<td>0.1-2.8 (males)</td>
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<td>0.0-2.2 (females)</td>
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<tr>
<td>Oropharynx and tonsils²</td>
<td>0.3-21.5 (males)</td>
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<td>0.0-2.8 (females)</td>
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**SUMMARY**

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<th>Cervical, oropharyngeal, anal, penile cancer</th>
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<td><strong>HPV</strong></td>
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<td>Transmission/vector (as appropriate)</td>
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<tr>
<td>Treatment*</td>
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<tr>
<td>Prevention strategies</td>
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<td>vaccination</td>
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<tr>
<td>early diagnosis screening</td>
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<tr>
<td>screening</td>
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</tbody>
</table>

* Global disparities exist in availability and access to treatment
REFERENCES


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Burkitt's lymphoma: an African view

**Key messages**

- Burkitt's lymphoma is a cancer of the lymphatic system and is associated with infection with the Epstein-Barr virus.
- Endemic Burkitt's lymphoma has an especially high incidence in equatorial Africa among children 3 to 16 years of age.
- Burkitt's lymphoma is more common in areas where malaria is endemic and is often associated with other forms of immunesuppression such as HIV.
- Burkitt's lymphoma is highly aggressive, but a readily treatable and curable form of cancer if detected early.

**Burkitt's lymphoma is a cancer of the lymphatic system**

Burkitt's lymphoma (BL) is a cancer of the lymphatic system and in most persons afflicted there is an associated infection with the Epstein-Barr virus (EBV). The Epstein-Barr virus is a type of herpesvirus, which well over 90% of all adults worldwide are exposed to at some point in their lives. EBV is transmitted by saliva, is an infectious, very widespread viral disease more commonly known by its more colloquial names of “kissing disease”, “glandular fever” or “mono”.

Most people are exposed to the virus as children, when the disease produces no noticeable symptoms or only flu-like symptoms. In less developed countries, people are exposed to the virus in early childhood more often than in developed countries. Since it is most common among adolescents and young adults, BL is also more common in this age group. It is to be noted that BL is occasionally seen in areas of the world where it is not associated with the EBV. On the other hand, EBV has been associated with other cancers such as nasopharyngeal cancers (cancers of the uppermost region of the pharynx or «throat», where the nasal passages and auditory tubes join the remainder of the upper respiratory tract) in Asian populations.

BL is an aggressive cancer type. There are several forms, or variants, of BL:

1. **Endemic Burkitt's lymphoma** (eBL) occurs more readily in persons who have been weakened by malaria and has an especially high incidence in equatorial Africa among children three to 16 years of age (Figure 1). The disease is characterized by tumours of the jaw bones and is named after Denis Burkitt, who mapped its peculiar geographic distribution across Africa in the 1950s.

2. **Sporadic Burkitt's lymphoma** (sBL) is the form subsequently described outside the African region. The tumour cells have a similar appearance to eBL but the jaw is less commonly involved than the endemic variant. Sporadic BL commonly involves the abdominal region and can be detected at any age and no specific co-factor has been described, although impaired immunity is believed to provide an opening for the development of EBV.

3. **Immunodeficiency-associated Burkitt's lymphoma** is most commonly associated with HIV infection and AIDS but can also occur in the post-transplant setting in patients receiving immuno-suppressive medication.
Causes of Burkitt’s lymphoma

Epstein-Barr virus and low immunity

In 1975 Zech and colleagues discovered a chromosome translocation (small changes in the position of pieces of the chromosome) characteristic of BL. Subsequent studies demonstrated that this influenced the activity of genes responsible for the production of antibodies and controlling cell growth. After many years of research this is considered to be the principal cause of the rapid growth associated with BL.

The EBV has been identified as having a strong association with eBL whereas the association of EBV is less clear for sBL. The association of EBV and BL has been based on the fact that lymphocytes (type of white blood cells) have receptors for the EBV and are its specific target after infection. In eBL, the hosts are believed to be unable to mount an appropriate immune response to primary EBV infection, possibly because of coexistent malaria or another infection that is immunosuppressive such as HIV. Months to years later, excessive B cell (type of white blood cell) proliferation occurs. This also results in an increase in the proportion of circulating B cells infected by EBV and the total burden of EBV. This increases the likelihood of the specific chromosome translocations described by Zech that are the cause of BL.

Similar mechanisms are considered likely in patients with HIV-associated BL which can be identified in any geographical area and at all ages. This disease is of great importance especially in sub-Saharan Africa.

Distribution of Burkitt’s lymphoma

The geographical distribution of BL can be derived from the general pattern of incidence and mortality of non-Hodgkin lymphoma (NHL). BL is the single most common entity contributing to NHL in Africa. BL is more common in Eastern Africa as compared to other African countries where malaria is endemic. Eastern Africa shows the highest NHL incidence and mortality rates with estimated incidence rates over 7.5 per 100,000 and mortality rates over 5.7 per 100,000. Incidence and mortality show exactly the same regional pattern (Figure 2). For example, data provided by the African cancer registries illustrate that incidence of BL is highest in the cancer registry from the Kyaddondo County, Uganda, with an age-standardised incidence rate (ASR)
per 100,000 of 4.7 for boys and 3.0 for girls (in all 90 cases reported in a five-year period of registration). The second ranking registry is Malawi with ASR per 100,000 of 2.8 for boys and 0.6 for girls. Incidence rates of BL in Mali, Nigeria, Congo and The Gambia are lower than those reported in Uganda but substantially higher than those observed in other African regions.

African countries in the lower range of incidence show values around one case per million, which are lower than those observed in France (eight cases per million) or in the Netherlands (seven cases per million).

In the recent decades there has been an increase in incidence rates of many malignancies, some of which can be related to changes in lifestyle and the HIV epidemic. Among the HIV-related malignancies, NHL and Burkitt’s lymphoma have been most affected. In Uganda, Burkitt’s lymphoma incidence rates have been reported to increase from 9.5 per million in 1960–71, to 34.3 per million during 1991–97. The mean age at diagnosis for both periods was 6.6 years. Although part of the increase could be explained by better case ascertainment, HIV is likely to have largely contributed to this increase.

**Early diagnosis and treatment of Burkitt’s lymphoma**

Surgery is rarely a treatment option: even on the rare occasions when a tumour could be entirely removed, regrowth occurred. Radiotherapy could be an option, however today there are very few radiotherapy facilities in the Sub-Saharan region. A number of simple and relatively cheap chemotherapies are nevertheless available and several are particularly active in BL. Therefore, BL is a readily treatable and curable form of cancer. Unfortunately, because there is low disease awareness among the general public and health care workers alike, more than 80% African children with BL present at the hospital with advanced disease and in a poor general condition. Thus in most instances, chances of survival with BL is greatly reduced. In addition, as a result of poor referral systems and health infrastructure, more
than 50% of BL patients have no access to hospital services and, therefore, receive no treatment at all. If the patient does access medical services, delays in diagnostic procedures contribute to the low treatment and survival rates.

**SUMMARY**

<table>
<thead>
<tr>
<th>Burkit’s Lymphoma (BL)</th>
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<tbody>
<tr>
<td><strong>Viral link</strong></td>
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<td><strong>EBV</strong></td>
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<tr>
<td><strong>Transmission/vector (as appropriate)</strong></td>
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<td><strong>Treatment</strong>*</td>
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<tr>
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<tr>
<td>screening</td>
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</table>

* Global disparities exist in availability and access to treatment

**REFERENCES**


Case Study

Improving outcomes for Burkitt’s lymphoma patients in Tanzania through international collaboration

**Identifying the problem - Tanzania**

The population of Tanzania, 40 million people, includes ten million children under 14 years of age – the peak age for Burkitt’s lymphoma (BL) not associated with HIV infection. The estimated average annual incidence of BL in Tanzania is seven children per 100,000. It is thus projected that approximately 700 new cases of BL in Tanzania occur every year.

In 2005, it was estimated that only 145 of these children were treated in various hospitals scattered throughout the country, most of which did not have expertise in the management of this rapidly progressive disease. There were no national guidelines for referral or treatment and cyclophosphamide, as a single agent, was the most commonly administered therapy in the district hospitals in Tanzania.

**International collaboration helps addressing the problem**

In August 2004, the Ocean Road Cancer Institute (ORCI) joined a multi-institutional study group coordinated by the International Network for Cancer Treatment and Research (INCTR) to work together on the treatment and characterisation of Burkitt’s lymphoma in Africa. As a result of using a standardised treatment protocol and a high compliance to this protocol, five years later great improvement was seen in the clinical care of Burkitt’s lymphoma children. The survival rate is now 70% at ORCI.

In 2005, the UICC and Sanofi-Aventis launched the “My Child Matters” project designed to improve the care and support of children with cancer in developing countries. ORCI presented and was awarded support for a project whose primary objective is to expand effective care to as many children with BL as possible in Tanzania. This is to be achieved through a coordinated programme of public and professional education; the identification of appropriately distributed hospitals capable of treating patients effectively and provision of assistance to establish an effective programme; and the development of an effective triage system for patients with suspected Burkitt’s lymphoma – critically important because of the known higher incidence of this disease in rural regions. Furthermore, a National Burkitt’s Lymphoma Working Group has been established, which developed treatment guidelines subsequently endorsed by the Ministry of Health and Social Welfare.

**Positive outcomes of focused, evidence-based projects**

Good planning and seed funding can enable low-resource countries to provide good quality treatment to more children and improve their survival outcomes. The use of standardised treatment guidelines has shown to improve cure rates at ORCI. In Tanzania, the treatment of Burkitt’s lymphoma can serve as a public health model that can be applied to other cancers and expanded to other countries. The project has also increased awareness of the significant role clinical trials play in the improvement of public health issues in developing countries.
Human immunodeficiency virus, Kaposi’s sarcoma and AIDS-related lymphomas: an African view

Zainab Mohamed

Key messages

- Kaposi’s sarcoma is the most common malignancy occurring in the HIV-infected population.
- Kaposi’s sarcoma is caused by a virus, the human herpesvirus 8 (HHV-8).
- Kaposi’s sarcoma, aggressive B-cell non-Hodgkin lymphoma and invasive cervical cancer are “AIDS-defining” malignancies.
- It is estimated that in sub-Saharan Africa, 30% of approximately seven million people who required treatment for HIV were receiving antiretroviral therapy by December 2007. With improved access to antiretroviral therapy, the incidence and severity of AIDS-related malignancies should decline in Africa.

Human immunodeficiency virus (HIV) is the greatest challenge facing clinicians and politicians in Africa today. Among HIV-infected patients, there is an increased risk for the development of Kaposi’s sarcoma (KS), non-Hodgkin lymphoma, and other cancers such as vulvar and cervical cancer.\(^1\) The World Health Organization (WHO) clinical staging system denotes the presence of KS, aggressive B-cell non-Hodgkin lymphoma, primary central nervous system lymphoma, and invasive cervical cancer to be diagnostic of AIDS or Stage 4 HIV infection.

Kaposi’s sarcoma - background

Prior to the advent of HIV, KS was an unusual, painless vascular tumour found in elderly males of Jewish or Mediterranean ancestry known as classic KS. Endemic KS occurs in children in Africa and is most likely due to mother-to-child transmission of the causative organism. Immunosuppression-related KS is seen in organ transplant patients. AIDS-associated KS is aptly termed epidemic KS.

KS is a cancer now known to be associated with the human herpesvirus 8 (HHV-8) in patients with or without human immunodeficiency virus (HIV). In HIV-infected patients, uncontrolled HIV-1 replication causes deregulation of the HHV-8 replication process, leading to the formation of KS lesions as the HIV progresses and patients become more immunosuppressed.

Distribution of Kaposi’s sarcoma

HHV-8 is endemic among adults in Africa with a prevalence rate in excess of 50% in Central and Southern Africa, in comparison to a 1-5% prevalence rate in Northern Europe, Asia and North America.\(^2\)

A large study conducted in the United States found the risk of KS to be 22,100 times greater (1990 to 1995) in HIV-infected individuals than in the general population. From 1996 to 2002, the risk fell to 3,460 times with the use of antiretrovirals.\(^3\) According to the WHO and the United Nations Joint Programme on HIV/AIDS (UNAIDS), there were 33 million people worldwide living with HIV in 2007 of whom 22 million reside in sub-Saharan Africa. Two million deaths occurred due to HIV during that year worldwide,
1.5 million of those living in sub-Saharan Africa. In Africa, KS has reached epidemic proportions among men and women alike: it is the one of the most common malignancies in Uganda and Zimbabwe and the commonest AIDS-defining malignancy worldwide (Figures 1 and 2).

Basic pathophysiological and clinical features of Kaposi’s sarcoma
KS is a vascular tumour originating from the lymphatic vessels. It is characterised by spindle-shaped cells, slit-like vascular channels, extravasated red blood cells and an inflammatory infiltrate generally occurring in the dermis of the skin.

KS lesions (or tumours) have a wide spectrum of clinical features ranging from minimal to extensive disease and generally involves the skin, most commonly the lower extremities, face and genitalia. KS occurring on the skin consists of a purple-red multifocal rash, which in the early stage of the disease is flat (patch stage). These can progress to thick elevated lesions (plaque stage), which may develop further into tumours (nodular stage) that may ulcerate, bleed and become infected. It is commonly associated with significant swelling (lymphoedema), particularly of the lower extremities, genitalia and face. “Visceral” KS may involve other organs, most commonly the gastrointestinal tract, lungs, lymph nodes, eyes, and the mucosa of the oral cavity. Disease involving the bone marrow, heart, liver, pancreas and testes is rarer.

Treatment of Kaposi’s sarcoma
Initial management, and generally the only treatment required for KS, is highly active antiretroviral therapy (HAART). HAART reduces the number and size of lesions and prevents new lesions from developing. In Africa, however, with poor access to antiretroviral therapy, KS can be a rapidly progressive fatal disease with some patients surviving less than six months.

HAART alone can induce remission by restoring immune function and reducing viral load; however it may take two-14 months to see an improvement, depending on tumour bulk and immune reconstitution. KS rates have declined rapidly in Europe and the US since the introduction of HAART. The Eurosida study, conducted in Europe, demonstrated a 39% annual reduction between 1994 and 2003. This result is echoed by the large Swiss HIV Cohort study showing that the hazard ratio for developing KS was reduced by 76% after just five months of HAART use.

According to UNAIDS estimates, only 30% of approximately seven million people who required treatment for HIV in sub-Saharan Africa were receiving antiretroviral therapy by December 2007. It is thus imperative to improve access to HAART to ensure that the incidence and severity of AIDS-related malignancies decline in Africa.

Further treatment is given for symptomatic, visceral or cosmetically unacceptable disease. Symptomatic and visceral or disseminated KS is treated with chemotherapy in combination with antiretroviral therapy. Combining HAART and chemotherapy is more effective than HAART alone. However, there is the problem of overlapping toxicities to be considered when using these drugs in combination.

Internationally available chemotherapies are unfortunately not available in most of Africa, including the state sector in South Africa due to cost constraints and cheaper alternatives are used, either as single agents or in various combinations. Radiotherapy is used to treat localised disease, particularly the lower leg involvement commonly seen in these patients.

AIDS-related lymphomas
Lymphomas are cancers that affect the white blood cells of the lymph system, part of the body’s immune system. Lymphomas are grouped by the way their cells look under a microscope. They may be indolent (slow-growing) or aggressive (fast-growing). AIDS-related lymphoma is usually aggressive. The WHO has subdivided AIDS-related lymphomas (ARLs) into three groups:

1. Lymphomas also occurring in immunocompetent patients like Burkitt’s lymphoma and diffuse large B-cell lymphomas (90% of ARLs).

2. Lymphomas occurring more specifically in HIV-infected individuals like primary effusion lymphomas which tend to occur in the lining of body cavities such as the pericardium and peritoneum.
and plasmablastic lymphoma, often found in the oral cavity).

3. Those also occurring in other immunodeficiency states such as post-transplant lymphoproliferative disorder.

Patients with ARL usually present at a more advanced stage and generally with a large tumour burden. Since the introduction of HAART the incidence of ARLs, particularly primary central nervous system lymphoma (PCNSL), has decreased significantly in Europe and the US. However it has increased as an AIDS-defining illness due to a decrease in opportunistic infections and KS.

During the pre-HAART era, non-Hodgkin lymphoma (NHL) occurred 60-200 times more frequently in the HIV-infected population than in the general population.12 The incidence of AIDS-related lymphomas has decreased significantly since the advent of HAART but is still 20 times more common in the HIV-positive group.13 Diffuse large B-cell lymphoma (DLBC) is the commonest histology, seen in two thirds of ARLs. Burkitt’s lymphoma is accountable for 25% of ARLs. Plasmablastic and primary effusion lymphomas (PEL) occur less frequently. Plasmablastic lymphoma is an aggressive lymphoma typically seen in the oral cavity of HIV-infected individuals, but can be found at any site. PEL is characterised by malignant effusions without nodal disease and has a very poor prognosis with a median survival of three-six months despite HAART.

In terms of other viruses which contribute to these lymphomas, the Epstein-Barr virus (EBV) is largely accountable for 80% of DLBC, 30-50% of Burkitt’s lymphoma and 100% of primary CNS lymphoma. PEL is associated with both EBV and HHV-8.14

**Treatment of AIDS-related lymphomas**

Currently patients are treated with HAART and standard dose chemotherapy which has resulted in response rates approaching those seen in non-HIV-infected individuals. Adverse effects of chemotherapy include opportunistic infections and negative drug interactions between chemotherapeutic agents and antiretrovirals. Radiotherapy is used for palliation in patients who do not respond to chemotherapy; or has involved field radiotherapy in some patients with early stage disease who have achieved a complete response to chemotherapy. Anti-CD20 antibody therapy has shown promising results and stem cell transplant is currently being investigated for relapsed or refractory ARLs.15

**Conclusion**

Managing Kaposi’s sarcoma or AIDS-related lymphomas in Africa is extremely challenging. Patients tend to present very late and often the diagnosis is delayed due to the heavy burden of disease and resource constraints. In the case of the treatment of lymphomas, many African countries do not have access to the expensive chemotherapy agents required to cure these patients. Radiotherapy is also not widely accessible in Africa. Poverty, poor living conditions and poor nutrition contribute to the development of neutropenic sepsis during treatment. In addition, there is a lack of locally conducted randomised controlled trials to guide clinicians in their management of these patients.

KS has become a disease that is easily managed and rarely fatal (91% overall survival at five years) with the early use of HAART.16 Non-Hodgkin’s lymphoma is less common but is the AIDS-defining event that has the worse prognosis despite antiretrovirals.17 In resource-rich countries the survival rate approaches that of the HIV-negative population18 but in Africa, it is inevitably fatal. However, it is possible to reduce the incidence of AIDS-related malignancies with the early implementation of HAART.

Governments and NGOs involved in the care of persons afflicted with HIV should ensure that antiretroviral treatment is initiated early in the disease. The latest WHO recommendations are to initiate antiretrovirals at a CD4 count of less than 350. This will bring Africa in line with the developed world, although it follows that the need for antiretrovirals will increase.
### SUMMARY

#### Kaposi sarcoma (KS)

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<td>Treatment*</td>
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<tr>
<td>Prevention strategies</td>
<td>based on the prevention of HIV infection: safe blood products; safe medical and injection practices; safe sexual practices; awareness and education activities</td>
</tr>
</tbody>
</table>

* Global disparities exist in availability and access to treatment

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**Figure 1: Kaposi sarcoma, females, age-standardized incidence rate per 100,000**

![Map of Africa showing incidence rates for females with Kaposi sarcoma]

- < 0.2
- < 1.0
- < 3.4
- < 8.9
- < 28.8

Source: Globocan 2002, IARC

**Figure 2: Kaposi sarcoma, males, age-standardized incidence rate per 100,000**

![Map of Africa showing incidence rates for males with Kaposi sarcoma]

- < 0.6
- < 3.7
- < 10.1
- < 22.0
- < 74.8

Source: Globocan 2002, IARC
REFERENCES


11 Swerdlow SH, Campo E, Harris NL et al. WHO Classification of Tumours, Volume 2; IARC WHO Classification of Tumours, No 2 2008.


Helicobacter pylori: a bacterium that can lead to cancer of the stomach

Meinhard Classen, Christian Prinz and Wei-cheng You

Key messages

- *Helicobacter pylori*, a bacterium that colonizes the mucus layer of the stomach, has a known association with stomach cancer.
- *Helicobacter pylori* is acquired early in life and in the absence of antibiotic therapy it generally persists for life.
- Stomach cancer is one of the leading cancer-related causes of death in China and Japan.
- Lifestyle choices, early detection and treatment can reduce stomach cancer rates and potentially eliminate peptic ulcer disease and its complications.

What causes stomach cancer?

*Helicobacter pylori* (*H. pylori*) is a spiral-shaped bacterium that can inhabit various areas of the stomach and duodenum. Over 80% of individuals infected with the bacterium are asymptomatic. *H. pylori* has co-existed with humans for thousands of years, however this bacterium was not discovered until the 1980s.

The stomach is the main habitat for *H. pylori* colonization. The bacterium is acquired early in life. While the exact mode of transmission is not known, it seems to be spread from person to person by saliva or fecal contamination and in the absence of antibiotic therapy it generally persists for life (Figure 1).1 *H. pylori* is present in about half of the human population. Actual infection rates vary from nation to nation. The higher prevalence among the elderly reflects higher infection rates when they were children rather than infection at later ages.2

To colonize the stomach *H. pylori* must survive the acidic pH and burrow into the mucus to reach its niche, close to the stomach’s epithelial cell layer. The bacterium has flagella (hairlike structures projecting from the cell that move the cell through their movement) and moves through the stomach and drills into the lining of the stomach.

Figure 1: The prevalence of *H. pylori* infection in more developed countries is low in children but higher in people over the age of 50. In lesser developed countries childhood infection is common and the majority of adults are infected1.

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1 Meinhard Classen, Christian Prinz and Wei-cheng You

2 Meinhard Classen, Christian Prinz and Wei-cheng You
*H. pylori* produces large amounts of urea which are secreted into the stomach and converted to ammonia. The ammonia that is produced along with the other products of *H. pylori* are toxic to the epithelial cells and damages those cells.\(^3\)

Colonization of the stomach by *H. pylori* results in chronic gastritis, an inflammation of the stomach lining. Duodenal and stomach ulcers result when the consequences of inflammation allow the acid in the stomach to overwhelm the mechanisms that protect the stomach and duodenal lining from these caustic substances. It has been estimated that between two to 20\% of people infected with *H. pylori* will develop ulcers. Although *H. pylori* has been linked to chronic inflammation (gastritis) which progresses to atrophy of the gastric mucous membrane layer of the stomach. It is about 1mm thick and its surface is smooth, soft, and velvety. \(^4\)

**Figure 2: *H. pylori* types that produce greater degrees of inflammation result in a greater risk of stomach cancer**

<table>
<thead>
<tr>
<th><strong>Cellular and disease state</strong></th>
<th><strong>What's happening</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal gastric mucosa</td>
<td>The gastric mucous membrane layer of the stomach. It is about 1mm thick and its surface is smooth, soft, and velvety</td>
</tr>
<tr>
<td>Chronic active gastritis</td>
<td>Chronic inflammatory response in the mucosa caused by <em>H. pylori</em></td>
</tr>
<tr>
<td>Gastric atrophy</td>
<td>A condition in which the stomach muscles shrink and become weak</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>Cells change from one type into another that are better suited to the new environment as a result of a stimulus (<em>H. pylori</em>) is removed or stops, tissues return to their normal pattern of differentiation. Metaplasia is not the same as dysplasia and is not directly considered carcinogenic</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Abnormal mature cells in the epithelial lining of the stomach. These abnormalities are generally the precursor to the cells proliferating abnormally (pre-cancer)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Cancer cells which infiltrate into the glands and the epithelial lining of the stomach</td>
</tr>
</tbody>
</table>

\(^3\) Helicobacter pylori infection. What's happening. Cellular and disease state.

\(^4\) Intestinal metaplasia and gastric atrophy.
(wasting or decrease in size) of the stomach lining and subsequently to cancer, the actual mechanisms by which \textit{H. pylori} promotes cancer are still under investigation. Indirect evidence of a causal link is that in recent years, the number of \textit{H. pylori} infections in developed countries have decreased, most likely due to changes in diet, refrigeration, better hygiene, and increased antibiotic use. The decline in \textit{H. pylori} infection in developed countries has coincided with a decline in rates of stomach cancer.

**Worldwide geographical distribution of stomach cancer**

Stomach cancer (also called gastric cancer) is the second leading cause of cancer-related deaths worldwide. Stomach cancer occurs twice as often in men and it is more common in people over the age of 55.

Stomach cancer is a leading cause of cancer death in China and Japan. Each year about 300,000 adults in China die from stomach cancer and 400,000 new cases are diagnosed. In Africa, stomach cancer seems to be less common: it accounted for an estimated 28,000 new cases in the year 2000. However, there was certainly considerable underreporting and lack of diagnostic facilities. In addition, the incidence rate has increased in the last years to 14/100,000 for the continent with highest rates in Mali, La Réunion and a particular population of South Africa (Figure 3).

Even though the incidence of stomach cancer is declining, in particular in the more developed countries, the absolute burden is predicted to increase due to demographic changes: in less developed countries where the risk for the disease remains high more people will live to an elderly age with an increasing cancer risk.

**Prevention: lifestyle and intervention**

Elimination of \textit{H. pylori} before the onset of stomach tissue atrophy would be the best strategy to prevent subsequent cancer. Unfortunately clinical study results addressing the question whether or not \textit{H. pylori} can be eliminated effectively will not be available for several years. It is still unknown if this eradication of infection would significantly reduce...
Lifestyle choices can help prevent stomach cancer
Adopting a healthy lifestyle including a diet containing vegetables and fruits (Vitamin C uptake), regular physical exercise, appropriate body weight and avoiding a risk-associated behaviour are able to reduce the risk of stomach cancer. Tobacco product dependency has also shown to increase stomach cancer risk. Certain ways of preparing food (smoking, excess of salt) are also contributing factors to stomach cancer. Recent studies in Scandinavia also suggest that regular ingestion of red meat and, thereby, increased iron uptake may be associated with increased risk of gastrointestinal cancer.

Intervention and reduction of symptoms caused by H. pylori
Diagnosis of infection is usually made by checking for dyspeptic symptoms and by tests which can indicate H. pylori infection. Noninvasive tests for H. pylori infection include a blood or stool test as well as a carbon urea breath test. However, the most reliable method for detecting H. pylori infection is a biopsy check during endoscopy.

Universal screening preventing the serious side effects of H. pylori infection cannot be recommended at the present time. It is, however, possible to identify high-risk persons for whom a “test and treat” policy should be considered (Table 1). Such a policy offers the potential of preventing a lethal cancer with a relatively inexpensive intervention, although actual costs of the “test and treat” policy are extremely variable between countries.

The “test and treat” policy in action
Clinical considerations
H. pylori can be detected by histology, gastric urease and by culture from biopsies of the gastric mucosa. Urea breath test is an excellent tool for demonstrating the presence and disappearance of H. Pylori after eradication therapy. Gastroscopy is the diagnostic gold standard.

Treatment of the H. pylori infection
Treatment usually includes two antibiotics that help to kill the bacteria and one proton pump inhibitor which causes the stomach to make less acid and help the ulcer to heal – known as triple therapy. A fourth compound such as a bismuth salt may be added in quadruple therapy. Most compounds are now available as inexpensive generics.

Most people are cured after finishing one to two weeks of treatment. Some people may need to extend treatment for another two weeks. A breath or stool test is usually conducted after completion of treatment to be sure that the bacteria has been eradicated. It is expected that H. pylori eradication will prevent gastric cancer in 20 – 40% of those treated.

Table 1 High-risk persons for whom a “test and treat” policy should be considered

<table>
<thead>
<tr>
<th>High-risk persons for whom a “test and treat” policy should be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ulcer disease of stomach or duodenum</td>
</tr>
<tr>
<td>First degree relatives of patients with gastric cancer</td>
</tr>
<tr>
<td>Gastric cancer patients after resection of gastric cancer</td>
</tr>
<tr>
<td>Patients in whom long-term Non Steroidal Anti Inflammatory Drugs (NSAID) therapy (including low-dose aspirin) is planned</td>
</tr>
<tr>
<td>Patients who desire testing</td>
</tr>
<tr>
<td>Patients with dyspepsia (optional)</td>
</tr>
</tbody>
</table>
### SUMMARY

#### Stomach cancer

<table>
<thead>
<tr>
<th>Viral link</th>
<th>no</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H. pylori</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Infectious agent</strong></td>
<td><em>Helicobacter pylori (H. pylori)</em> / bacterium</td>
</tr>
<tr>
<td><strong>Transmission/vector (as appropriate)</strong></td>
<td>while the exact mode of transmission of <em>H. pylori</em> is not known, it seems to be spread from person to person by saliva, and most people who are infected become infected as children. It also has the potential to be spread by fecal contamination</td>
</tr>
<tr>
<td><strong>Treatment</strong>*</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Prevention strategies</strong></td>
<td>improve food conservation; education on a balanced diet and hygienic practices in preparing food</td>
</tr>
<tr>
<td>vaccination</td>
<td>no</td>
</tr>
<tr>
<td>early diagnosis</td>
<td>yes</td>
</tr>
<tr>
<td>screening</td>
<td>no</td>
</tr>
</tbody>
</table>

* Global disparities exist in availability and access to treatment

### REFERENCES


Liver flukes and cancer of the bile ducts (cholangiocarcinoma)

Key messages

- *Opisthorchis viverrini, Opisthorchis felineus,* and *Clonorchis sinensis* are foodborne trematodes or liver flukes that infect the human liver. *Opisthorchis viverrini* is carcinogenic to humans.
- Cholangiocarcinoma is a glandular cancer caused by liver fluke infection – resulting from chronic inflammation or obstruction of the bile duct.
- Infection occurs by eating raw or undercooked freshwater fish.
- In East Asia and Eastern Europe, liver fluke infection is endemic in many regions. Approximately 600 million people are estimated to be infected.
- There is no cure for cholangiocarcinoma.
- Prevention and control of infection can be achieved through behavioural changes in diet and health education.

Liver fluke infection by the flat worms trematodes *Opisthorchis viverrini, Opisthorchis felineus,* and *Clonorchis sinensis* is known to result in cholangiocarcinoma, a glandular cancer in the liver. This type of cancer affects the bile ducts, generally producing tumours that inhibit bile from draining from the liver into the small intestine.1 *O. viverrini* is cancer-causing in humans whereas *O. felineus* and *C. sinensis* have not been identified as cancer-causing although there is an established link to the development of cholangiocarcinoma.2

Liver flukes and cholangiocarcinoma

More than 600 million people are at risk of liver fluke infection, and the prevalence worldwide has increased over several decades. An estimated nine million people living in Thailand and Laos are infected with *O. viverrini,* 1.5 million people in Russia with *O. felineus* and *C. sinensis* is estimated to infect seven million people in Korea, China, Hong Kong, Macau and Vietnam.2 In geographical areas where undercooked, salted, pickled, or smoked freshwater fish are a staple of the diet, there is high prevalence of infection with food-borne parasites.

An increasing incidence of cholangiocarcinoma has been observed in East Asia and Eastern Europe.3 The western world has also seen a rise in the incidence of cholangiocarcinoma, however these figures remain substantially lower than those observed elsewhere3 (Figure 1).

Causation and life cycle

Due to poor sanitation or inadequate sewage infrastructure, parasite eggs in human faeces are passed into natural water reservoirs. The eggs are eaten by intermediate host aquatic snails, after which the hatched free swimming parasites encyst in the scales, fins and muscles of cyprinoid fishes. These are infectious to humans who consume the fish either raw or undercooked (Figure 2).

How can liver flukes cause cancer?

Mechanical injury from the activities of feeding and migrating flukes contributes to bile duct damage in the human host. Both oral and ventral suckers of the fluke hook onto the biliary epithelium (lining of the bile duct) resulting in tissue damage, even at the early stages of infection. As the parasite matures, the lesion becomes more pronounced and ulcerates.
Regional differences in the mean estimated annual percent change in age-adjusted (1970 World Standard population) gender-specific mortality rates from intrahepatic biliary tract tumours (top) and gall-bladder and extra-hepatic biliary tract tumours (bottom).¹

Figure 1: Regional differences in the mean estimated annual percent change
The liver fluke secretes or excretes metabolic products, some of which are highly immunogenic, into the bile. Apart from inducing host immune responses, the metabolic products themselves may be toxic to or interact with the biliary epithelium. Long-term or repeated infections can lead to a number of liver problems including swelling of the liver, jaundice, bile stones and cholangiocarcinoma. Chronic inflammation and obstruction of the bile flow caused by liver fluke infection is suggested to play a key role leading to the progression of cholangiocarcinoma.

Clinical signs of liver fluke infection and cancer
The majority of primary malignant liver cancers are of two main histologic types distinguished by their cellular origin. Hepatocellular cancer derives from hepatocytes, the cells found specifically in the liver, and is the most common form of liver cancer. Cholangiocarcinoma is derived from cholangiocytes, which form the epithelial lining of both intrahepatic (inside the liver) and extrahepatic (outside the liver) bile ducts, except for those of the gallbladder. There are generally no symptoms of the disease. Only 5-10% of infected people have non-specific symptoms like abdominal pain, flatulence or fatigue and these tend to occur only when the bile ducts are blocked by the tumour.

Cholangiocarcinoma is a lethal and rapidly progressing disease with no cure. The only primary treatment currently available is to surgically remove the tumours. Cholangiocarcinoma has less chance of being removed surgically than other forms of liver cancer and most cases are currently untreatable except for complete liver transplantation. In patients where surgery is not an option, palliative chemotherapy may be considered.

Preventative measures
With a combination of health education and improved sanitation, control of liver fluke infection may be achieved by the following:

- Treatment to reduce the excretion of eggs.
- Prevention of eggs reaching the water source.
- Preventing untreated sewage from being discharged into freshwater reservoirs and ponds can reduce the infection in fish populations.
- Change eating habits (eliminate eating raw foods in endemic areas). Thorough cooking of freshwater fish will kill the parasites and prevent infection when consumed.
- Effective short-term infection control can be focused on health education.
- Effective long-term infection control would target health education programmes to young age groups.
- Build and strengthen effective communication campaigns and partnerships with Ministries of Health focusing on health education, prevention and treatment.
Embryonated eggs are discharged in the biliary ducts and in the stool ①. Eggs are ingested by a suitable snail intermediate host ②. Each egg releases a miracidia ②a, which go through several developmental stages (sporocysts ②b, rediae ②c, and cercariae ②d). The cercariae are released from the snail and after a short period of free-swimming time in water, they come in contact and penetrate the flesh of freshwater fish, where they encyst as metacercariae ③. Infection of humans occurs by ingestion of undercooked, salted, pickled, or smoked freshwater fish ④. After ingestion, the metacercariae exists in the duodenum ⑤ and ascend the biliary tract through the ampulla of Vater ⑥. Maturation takes approximately 1 month. The adult flukes (measuring 10 to 25 mm by 3 to 5 mm) reside in small and medium sized biliary ducts. In addition to humans, carnivorous animals can serve as reservoir hosts.
### SUMMARY

<table>
<thead>
<tr>
<th>Stomach cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral link</strong></td>
</tr>
<tr>
<td><strong>Opisthorchis viverrini</strong></td>
</tr>
<tr>
<td><strong>Infectious agent</strong></td>
</tr>
<tr>
<td><strong>Transmission/vector (as appropriate)</strong></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
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<tr>
<td>early diagnosis</td>
</tr>
<tr>
<td>screening</td>
</tr>
</tbody>
</table>

* Global disparities exist in availability and access to treatment

### REFERENCES


2. IARC. Summaries and Evaluations: Infection with liver flukes; 1994; 61: 121.


Schistosomiasis and bladder cancer

Serigne Magueye Gueye, Lamine Niang and Mohamed Jalloh

Key messages

- Schistosomiasis (Bilharziasis) is a parasitic disease borne by the flat worm Schistosoma haematobium.
- Bladder cancer is associated with chronic infection with Schistosoma.
- Infection occurs by exposure to Schistosoma-infected water, i.e. any waterway supporting the secondary host, a snail of the Bulinus species.
- Approximately 200 million people are estimated to be infected, mostly in Africa but also in other areas such as the Middle East, Saudi Arabia and sub-Saharan Africa.
- Several regions around the globe have demonstrated that a combination of appropriate therapy and an efficient communication campaign can result in a significant decrease in the morbidity and prevalence of schistosomiasis and thus reduce the burden of bladder cancer.

Schistosomiasis is caused by three different fluke (flat worm) species, one of which (Schistosoma haematobium) is responsible for urinary bilharziasis, a parasitic infection of the urinary tract.

There is still uncertainty if the relationship between bilharziasis and bladder cancer is causal or only an association but clinical observations and studies support the existence of a link.1-6 It has been confirmed that schistosomiasis contributes to 27.6% of bladder cancer cases7 and that a particular bladder cancer sub-type (squamous cell carcinoma) predominates.

Bladder cancer and Schistosoma haematobium

Schistosomiasis (also known as bilharzias or bilharziasis) is a major public health problem affecting millions of people. Estimates suggest that 200 million people worldwide are infected of whom 120 million are asymptomatic and 20 million have severe disease. In addition, 600 million people are at risk of infection.7,8

The parasitic cycle is well described.9 The eggs of the adult worm of Schistosoma haematobium are released when infected people urinate or defecate in water, where the eggs develop into mobile embryos which can only live in water for 48 hours. During this time, a host such as an amphibian snail is entered and the embryo duplicates into many flukes or worms with a forked tail (approximately 500 μm in size). The worms infect humans by breaking through the skin and entering the blood vessels. Exposure to the worms generally occurs when people are in contact with infected water while swimming, wading, washing, etc. Any waterway supporting the secondary host, the snail, is a potential source of infection.

Once the worms have entered the skin, the ‘immature schistosoma’ move passively via the circulation system to reach the liver, then the intrahepatic portal veins. Only worms that reach these veins mature and reproduce. The female worms then move toward their final destination, the urinary tract, to lay eggs and complete the cycle.

Schistosomiasis has been identified in Egyptian mummies dating back to as early as 1200 B.C. Theodor Bilharz, a German pathologist working in Cairo in 1852, was the first to describe the worm infection, associated cystitis and the main symptom, haematuria (blood in the urine). Infection with
Schistosoma haematobium is prevalent throughout Africa and increases the risk of bladder cancer approximately 2- to 4-fold.\textsuperscript{1,2,10} Infection with Schistosoma haematobium is responsible for an estimated 50\% of bladder cancer cases in some parts of Africa, and about 3\% of cases overall.\textsuperscript{3,11-13} The peak age of infection is between 30 and 50 years.\textsuperscript{7}

The prevalence of Schistosoma haematobium infection used to be particularly high in areas irrigated by the Nile and in regions watered by the Tigris and Euphrates rivers. Infection is also found in other areas such as the Middle East, Saudi Arabia and sub-Saharan Africa.\textsuperscript{10} Where both prevalence and intensity of infestation is high, there is also a high prevalence of the squamous cell carcinoma sub-type of bladder cancer.

In contrast, in industrialised countries, the main risk factors for cancer of the bladder are cigarette smoking and occupational exposures.

**Clinical signs of bladder cancer**

How schistosomiasis infection causes cancer is not well understood, although it is suggested that nitrogen-containing metabolites (nitrites and N-nitroso compounds) formed in the bladder, by parasitic or microbial metabolism of normal urinary constituents, may play a role.\textsuperscript{14} In addition, some studies have identified frequent gene mutations in schistosomiasis-associated bladder-cancers.\textsuperscript{15-18}

Generally, bladder cancer patients have a long history of irritation and inflammation of the bladder mucus membrane due to chronic bacterial infection as well as fluke activity.

There is often associated benign proliferation of the lining of the urinary bladder,\textsuperscript{19} but bladder cancer with urinary bilharziasis has a distinct clinicopathological pattern. The only curative treatment in this case is radical cystectomy - surgical removal of all or part of the urinary bladder.

Patients usually present with symptoms of cystitis, painful urination, increased frequency and haematuria (blood in the urine) in the early stages. In areas with endemic schistosomiasis, haematuria is common from a young age and is often considered a sign of virility, so recurring haematuria neither raises concerns nor lead to seeking of medical advice even in adulthood. In some cultures, where infection rates are high, children not having haematuria are often considered “abnormal”.

**Control programmes and treatment options**

The treatment of patients with confirmed bilharziasis targets reduction of egg production by the adult worms, using chemotherapy. Although chemotherapy is effective, transmission rates are high and the treatment does not protect against reinfection. Thus successful public health control measures are also necessary and methods range from environmental modification to elimination of the snail vector together with public information campaigns. For low-income countries, the challenge is great as along with the political support and resource, there is need for a public health infrastructure to undertake and maintain sustainable programmes.

If a patient has a long term infection, the major concern is the chronic inflammation caused by the presence of eggs and dead worms. At this stage the treatment is no longer specific, but rather addresses the consequences of the inflammation. Early surgery to remove part of the bladder or a benign tumour, in some cases with reconstructive surgery, can be undertaken. Most of the bilharziasis-related bladder cancers are invasive into the deeper layers of the bladder. In Africa particularly, patients often present at late stages of infection with advanced cancer usually invading the surrounding tissues and metastatic (spread to other parts of the body). In such cases it is rarely appropriate to perform radical surgery with bladder replacement. External urinary diversion is often not acceptable to the patient or appropriate due to the lack of drainage bags in low income countries. Ureterosigmoidostomy – a surgical procedure where the ureters which carry urine from the kidneys, are diverted into the sigmoid colon - is a good palliative procedure in carefully selected cases.
**Conclusion**

Bladder cancer associated with bilharziasis is a preventable disease through public health measures to provide safe water environments and public education to encourage early treatment of infection. The relationship between the two diseases remains controversial. However, the significant decrease in the morbidity and prevalence of schistosomiasis in some countries such as Egypt that have successfully implemented such measures reinforces the hypothesis of a causative link between the two diseases. This change is associated with an increase in presentation of bladder cancers of the sub-type not associated with infection, an increase in the average age at presentation and a decreased prevalence of infection in males. If these changes continue at the current rate, the features of bladder cancer in Egypt will become identical to those of Western countries in the near future. Therefore, proven efficient schistosomiasis control programmes should be extended particularly to sub-Saharan Africa.

**SUMMARY**

<table>
<thead>
<tr>
<th>Schistosoma haematobium</th>
<th>Bladder cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral link</strong></td>
<td>no</td>
</tr>
<tr>
<td><strong>Infectious agent</strong></td>
<td>Schistosoma haematobium / blood fluke</td>
</tr>
<tr>
<td><strong>Transmission/vector (as appropriate)</strong></td>
<td>contact with contaminated fresh water</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>yes</td>
</tr>
<tr>
<td><strong>Prevention strategies</strong></td>
<td>provision and use of safe water supplies; improvement of environmental sanitation, sanitation and hygiene habits; awareness and education activities</td>
</tr>
<tr>
<td><strong>vaccination</strong></td>
<td>no</td>
</tr>
<tr>
<td><strong>early diagnosis</strong></td>
<td>yes</td>
</tr>
<tr>
<td><strong>screening</strong></td>
<td>no</td>
</tr>
</tbody>
</table>

* Global disparities exist in availability and access to treatment
REFERENCES


3 IARC monographs on the evolution of carcinogenic risks to human, Volume 61, Schistosomes, liver flukes and helicobacter pylori, Lyon, France. International Agency for Cancer Research.


Case Study

- Adult T-cell leukaemia (ATL) is a cancer known to be associated with human T-cell leukaemia virus type 1 (HTLV-1).¹ This is a cancer of the immune system caused by viral infection of the T cells (white blood cells). ATL is an aggressive non-Hodgkin’s lymphoma and affects one in 500 people infected by HTLV-1. Most patients die within one year of diagnosis.

- HTLV-1 is spread by sharing syringes or needles, through blood transfusions or sexual contact, and from mother to child during birth or breast-feeding. In particular, mother-to-child transmission is associated with prolonged breast-feeding in the postnatal period.²,³ Transmission through breast milk is implicated as a major route for the maintenance of infection in high prevalence areas.

- HTLV-1 infection occurs in clusters in certain geographic locations around the world. It is endemic in Southern Japan (15-30%), the Caribbean (3-6%), Papua New Guinea, South America, the Southern part of North America, Eastern Europe and in some parts of Africa.³

- Seroprevalence of HTLV-1 increases with age and is twice as high in females as in males. This gender difference usually emerges after 30 years and probably reflects more efficient transmission from males to females during sexually active years.⁴

Prevention strategies for HTLV-1 infections

HTLV-1 carriers remain for the most part asymptomatic, therefore those infected are often undetected until a more serious disease develops, such as ATL or other inflammatory syndromes. There are few treatment options, although research is being carried out on the development of a vaccine against HTLV-1.

Prevention strategies to reduce the likelihood of transmission are currently being used in several countries with a high prevalence of infection. Screening blood donations for HTLV-1 is now routinely carried out in Japan and in low prevalence areas there is also a trend towards screening blood donors who originate from high prevalence areas. In Japan, antenatal screening for HTLV-1 antibody is carried out for pregnant women. Those who are positive are advised not to breastfeed their infants.

Evidence for reduction of transmission of infection – refraining from breastfeeding in highly endemic areas

There is evidence which shows that the transmission of infection between mother and child can be greatly reduced in highly endemic areas of HTLV-1. One study in Japan demonstrated that when mothers who were known to be HTLV-1 positive refrained from breastfeeding, and children were bottle fed instead, there was a significantly lower number who became infected (3%) compared to breastfed children (18%). These findings clearly support that prevention can be achieved through straightforward public health measures to reduce new infections, and ultimately, cancer.²

Acronyms

**AIDS**
Acquired immune deficiency syndrome

**ARLs**
AIDS-related lymphomas

**ATL**
Adult T-cell lymphoma

**BL**
Burkitt's lymphoma

**CD4**
Cluster of differentiation 4

**CIN**
Cervical intraepithelial neoplasia

**CNS**
Central nervous system

**DNA**
Deoxyribonucleic acid

**DLBC**
Diffuse large B-cell lymphoma

**EAPC**
Estimated annual percent change

**eBL**
Endemic Burkitt's lymphoma

**EBV**
Epstein-Barr virus

**GAVI**
Global Alliance for Vaccine and Immunization

**HAART**
Highly active antiretroviral therapy

**HBsAg**
Hepatitis B surface antigen

**HBV**
Hepatitis B virus

**HCC**
Hepatocellular carcinoma

**HCV**
Hepatitis C virus

**HHV-8**
Human herpesvirus 8

**HIV**
Human immunodeficiency virus

**HPV**
Human papillomavirus

**HTLV-1**
Human T-cell leukemia virus type 1

**IARC**
International Agency for Research on Cancer

**KS**
Kaposi's sarcoma

**NHL**
Non-Hodgkin lymphoma

**NSAID**
Non steroidal anti inflammatory drugs

**ORCI**
Ocean Road Cancer Institute

**PCNSL**
Primary central nervous system lymphoma
**PEL**
Primary effusion lymphoma

**RNA**
Ribonucleic acid

**sBL**
Sporadic Burkitt’s lymphoma

**STI**
Sexually transmitted infection

**UICC**
International Union Against Cancer

**UNAIDS**
United Nations Joint Programme on HIV/AIDS

**VIA**
Visual inspection with acetic acid

**VLPs**
Virus-like particles

**WHO**
World Health Organization
Glossary

Adenocarcinoma
A malignant epithelial tumour arising from glandular structures, which are constituent parts of most of the organs of the body.

Age-standardized rate (ASR)
A summary measure of a rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because age has such a powerful influence on the risk of cancer. The most frequently used standard population is the World Standard Population. The calculated incidence rate is then called the World Standardized Incidence Rate. It is also expressed per 100,000.

Basal cell carcinoma (BCC)
The commonest form of skin cancer. BCC usually occurs on the central area of the face, especially in fair-skinned people; the prevalence increases greatly with exposure to sunlight.

Chlamydia trachomatis
Chlamydiae are bacteria that are intracellular parasites in humans and other animals in which they cause disease. Some strains of Chlamydia, especially trachomatis, are common cause of sexually transmitted infections (STI).

Crude rate
Data on incidence or mortality are often presented as rates. For a specific tumour and population, a crude rate is calculated simply by dividing the number of new cancers observed during a given time period by the corresponding number of people in the population at risk. For cancer, the result is usually expressed as an annual rate per 100,000 persons at risk.

Dysplasia
Abnormal development of the skin, bone, or other tissues.

Effusion
The escape of pus, serum, blood, lymph, or other fluid into a body cavity as a result of inflammation or the presence of excess blood or tissue fluid in an organ or tissue; fluid that has escaped into a body cavity.

Endoscopic view
View of the interior of the body, generally obtained by inserting a tube with a light at the end and an optical system or miniature video camera for transmitting an image to the examiner’s eye.

Epithelium
The tissue that covers the external surface of the body and lines hollow structures (except blood and lymphatic vessels).

Gastroscopy
Inspection of the interior of the stomach using an illuminated optical instrument.

HAART
Highly Active Antiretroviral Therapy, a combination of three or more anti-HIV drugs.

Haemochromatosis
Hereditary disorder in which there is excessive absorption and storage of iron. This leads to damage and functional impairment of many organs, including the liver, pancreas, and endocrine glands.

Histology
The study of the structure of tissues by means of special staining techniques combined with light and electron microscopy.

Hodgkin’s disease
A malignant disease of lymphatic tissue - a form of lymphoma - usually characterised by painless enlargement of one or more groups of lymph nodes in the neck, armpits, groin, chest, or abdomen; the spleen, liver, bone marrow, and bones may also be involved. Apart from enlarging nodes, there may also be weight loss, fever, pain, profuse sweating at night and itching.
**Immunocompetent**
Able to develop an immune response. Able to recognize antigens and respond to them.

**Immunocompromised**
Having an immune system that has been impaired by disease or treatment. Immunocompromised patients are vulnerable to opportunistic infections.

**Immunogenicity**
The property that enables a substance to provoke an immune response.

**Incidence**
Incidence is the number of new cases arising in a given period in a specified population. This information is collected routinely by cancer registries. It can be expressed as an absolute number of cases per year or as a rate per 100,000 persons per year. The latter provides an approximation to the average risk of developing a cancer.

**Lithiasis**
Formation of stones in an internal organ, such as the bladder, urinary system, pancreas or appendix.

**Lymph nodes**
Small swellings found at intervals along the lymphatic system, which act as filters for the lymph, preventing foreign particles from entering the bloodstream; lymph nodes also produce lymphocytes.

**Lymphocytes**
White blood cells which are responsible for immune responses. There are two main types of lymphocytes: B cells, which make antibodies that attack bacteria and toxins; and T cells, which attack body cells themselves when they have been taken over by viruses or have become cancerous.

**Lymphoma**
A malignant tumour of the lymph nodes.

**Metaplasia**
An abnormal change in the nature of a tissue, which may be an early sign of malignant change.

**Morbidity**
The state of being diseased. The morbidity rate is the number of cases of disease found to occur in a stated number of the population, usually given as cases per 100,000 or per million.

**Mortality**
Mortality is the number of deaths occurring in a given period in a specified population. It can be expressed as an absolute number of deaths per year or as a rate per 100,000 persons per year.

**Neutropenic sepsis**
Also called neutropenia. Is an abnormally low level of neutrophils, which are white blood cells produced in the bone marrow that ingest bacteria in the blood.

**Non-Hodgkin lymphoma (NHL)**
Any of a large group of cancers of lymphocytes (white blood cells). Non-Hodgkin lymphomas can occur at any age and are often marked by lymph nodes that are larger than normal, fever, and weight loss. There are many different types of non-Hodgkin lymphoma. These types can be divided into aggressive (fast-growing) and indolent (slow-growing) types, and they can be formed from either B-cells or T-cells. Prognosis and treatment depend on the stage and type of disease.

**NSAID**
Non Steroidal Anti-Inflammatory Drugs, referred to any one of the large group of drugs used for pain relief.

**Oropharyngeal airway**
Curved tube designed to be placed in the mouth of an unconscious patient, behind the tongue, to create a patent airway.

**Palliative**
A medicine that gives temporary relief from the symptoms of a disease but does not actually cure the disease.

**Pap smear/test**
The collection of cells from the cervix for examination under a microscope. It is used to detect changes that may be cancer or may lead to cancer and can show noncancerous conditions, such as infection or inflammation.
Pathogenesis
The origin of a disease and the chain of events leading to that disease.

Pathophysiological
The functional changes associated with or resulting from disease or injury.

Plasmablastic lymphoma (PBL)
Recently characterised as an aggressive subtype of non-Hodgkin lymphoma, most frequently arising in the oral cavity of HIV-infected patients.

Population at risk
The part of a population which is susceptible to have a specific cancer. It is defined on the basis of demographic data, such as place of residence, sex, age group and (where appropriate) ethnicity.

Post-transplant lymphoproliferative disorder (PTLD)
A condition in which a group of B-cells grow out of control after an organ transplant in patients with weakened immune systems. This usually happens if the patient has also been infected with Epstein-Barr virus. Post-transplant lymphoproliferative disorder may progress to non-Hodgkin lymphoma.

Prevalence
The prevalence of a particular cancer can be defined as the number of persons in a defined population who have been diagnosed with that type of cancer, and who are still alive at a given point in time. Patients who are still alive five years after diagnosis are usually considered cured since the death rates of such patients are similar to those in the general population. There are exceptions, particularly breast cancer.

Primary central nervous system lymphoma (PCNSL)
A primary intracranial tumor appearing primarily in patients with severe immunosuppression. Primary CNS lymphoma is highly associated with Epstein-Barr virus (EBV) infection in immunodeficient patients regardless of age group.

Primary effusion lymphoma (PEL)
A human herpesvirus-8 (HHV8)-associated large-cell non-Hodgkin lymphoma localized in body cavities. It typically affects immunocompromised patients and usually involves only one body site.

Prophylactic
An agent that prevents the development of a condition or disease.

Proton-pump inhibitor
A drug that reduces gastric acid secretion by blocking the proton-pump within the parietal cells.

Risk factors
Factors that increase the probability that a disease will occur. Risk factors can be environmental, behavioral/lifestyle, genetic.

Squamous cell carcinoma (SCC)
The second most common form of skin cancer after basal cell carcinoma. SCC is mainly found on areas exposed to the light. It spreads locally at first but later may spread to sites distant from its origin.

Survival
It is defined as the probability of survival, expressed as time elapsed since diagnosis (1, 3, 5-year survival). This observed survival probability is influenced by mortality both from the cancer of interest and from other causes.

Transition cell carcinoma (TCC)
The most common type of bladder cancer. It is a form of cancer that affects the urothelium, which lines the urinary collecting system of the kidney, ureters, bladder, and most of the urethra.

Vaccination coverage
Percentage of people in the target population that have been fully vaccinated against a specific disease out of all people in the target group.

Essential sources: Concise medical dictionary, Oxford paperback reference, 6th edition; NCI dictionary of cancer terms (online); IARC glossary of statistical terms (online)
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The International Union Against Cancer (UICC) is the leading international non-governmental organization dedicated to the global prevention and control of cancer. UICC’s mission is to connect, mobilize and support organizations, leading experts, key stakeholders and volunteers in a dynamic community working together to eliminate cancer as a life-threatening disease for future generations.

UICC works closely with its member organizations and partners to implement a comprehensive strategy that includes:

- Promoting the World Cancer Declaration
- Organizing the World Cancer Congress
- Raising awareness through coordinating World Cancer Day annually, on 4 February

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Protection against cancer-causing infections