Preventing cancers by addressing infectious disease:

three case studies

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Introduction

By 2030 nearly one in five of all new cases of cancer in the world, and nearly one in six cancer deaths, will occur in Commonwealth member states (Ferley et al., 2010). Projections of the International Agency for Research on Cancer (IARC) indicate that the number of new cases of cancer in the Commonwealth will rise by more than 77 per cent – from 2,263,427 to 4,003,875 – and cancer deaths by more than 81 per cent – from 1,455,050 to 2,592,240 (ibid.). Low- and middle-income member states, particularly those in South Asia, will bear the brunt of this unfolding cancer pandemic where it is estimated that the number of new cancer cases will rise by 72 per cent and cancer deaths by more than 80 per cent (ibid.). Only effective prevention can reduce the incidence of cancer. A first step towards this is an understanding of the factors that predispose to cancer. These factors differ, often quite markedly, between the more and less developed countries and across different geographical regions. Geographical differences are particularly important with respect to the prevalence and types of chronic infection, some of which are known risk factors for cancer.

Infection as a causal factor of cancer

Tobacco consumption, overeating, excessive alcohol consumption and a sedentary lifestyle are the main risk factors for cancer in the more developed countries. Developing countries, on the other hand, bear a very high fraction of the global burden of cancers associated with infections (Table 1), including cervical cancer (approximately 80 per cent), liver cancer (85 per cent) and stomach cancer (70 per cent). The impact of the HIV epidemic has also led to marked changes in the cancer pattern. Overall, infections account for 22 per cent of new cases of cancer in the low- and middle-income countries compared to only 6 per cent in industrialised countries (WHO, 2012a). Tables 2 and 3 look at the accumulated incidence and age–standardised incidence of selected cancers linked to infection in selected Commonwealth countries.

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It is important to note at the outset that infectious agents are not necessarily associated with 100 per cent of a particular type of cancer and to acknowledge the concept of ‘attributable risk’ – the fraction of a given cancer (possibly in a given geographical region) that can be attributed to a specific carcinogen or infectious agent. For example, most hepatocellular carcinomas in Africa and China are related to hepatitis virus infection, but in Europe and the US over-consumption of alcohol is far more important as a causal factor. In Africa, Burkitt lymphoma (BL) is nearly always associated with the Epstein Barr (EB) virus, whereas in Europe only 10-20 per cent of BL cases are associated with the EB virus.

It is also important to recognise that there are many ways in which infectious agents may predispose to cancer; viruses act via their effect on cellular genes, while bacteria and parasites (or their ova) cause inflammation and often repeated cycles of hyperplasia and repair, increasing cell division and the likelihood of a genetic change relevant to carcinogenesis. At the same time, the multiple processes by which viral or parasitic infections facilitate the development of cancers are not yet fully understood. We do know that some infectious agents predisposing to cancer can remain latent in cells, organs or tissues for many years. Thus, vaccines that prevent infection must be given early in life before infection has occurred. Further research is needed to establish why cancer might develop in one infected person and not in another. Differences in the immune response, intensity of infection or genetic differences in the infectious agent are likely to be relevant.

National cancer control plans need to take these factors into account and to prepare multisectoral responses if countries are to enjoy the double advantage of cost-effective infection control that also results in a reduced incidence of specific cancers. In this article we explore in more depth three infections – two viral and one parasitic – that illustrate how knowledge of an infectious etiology can be of particular importance to the prevention of cancer and sometimes the early detection of cancer.

Human papillomavirus infection and cervical cancer

Human papillomavirus (HPV) infection is one of the most common sexually transmitted infections. HPV infects the epithelial cells of the skin or of the mucosal surfaces, usually transiently. Most types of HPVs are relatively harmless, causing benign lesions such as

Table 1 Infectious agents associated with cancer

Infectious agent	*Associated diseases*	*Probable contribution to carcinogenesis*
Viruses		
HIV	Kaposi sarcoma, lymphomas, cervical cancer, lung, liver, anus etc.	Inhibits immune responses to infectious agents or to the tumour cells themselves
HHV8	Kaposi sarcoma, primary effusion lymphoma	Effect on host cell genes
EBV	Burkitt lymphoma, nasopharyngeal carcinoma and other lymphoepitheliomas (stomach, oesophagus), T cell lymphomas, leiomysoarcoma in HIV+ individuals	Effect on host cell genes
HTLV1	Adult T-cell leukaemia/lymphoma	Effect on host cell genes
HPV	Squamous cervical cancer	Effect on host cell genes
HBV and HCV	Hepatocellular cancer	Inflammation, hyperplasia. Effect on host cell genome
Bacteria		
Helicobacter pylori response	Stomach MALT lymphoma	Inflammation and stimulation of a specific immune
Chlamydophila psittaci	Marginal lymphoma of ocular adnexi	Inflammation
Borrelia burgdorferi	Marginal lymphoma of skin	Inflammation
Campylobacter jejuni	Marginal lymphoma of small intestine	Inflammation
Parasites		
Plasmodium falciparum	Burkitt lymphoma	B cellular, immunosuppression, induction of chromosomal translocations
Schistosoma hematobium	Bladder cancer	Inflammation, hyperplasia (ova)
Schistosoma mansonii	Large bowel cancer	Inflammation, hyperplasia (ova)
Schistosoma japonicum	Hepatocellular cancer	Inflammation, hyperplasia (ova)
Clonorchis sinensis	Cholangiocarcinoma (bile duct)	Inflammation, hyperplasia
Opisthorchis viverini	Cholangiocarcinoma (bile duct) or gall bladder cancer	Inflammation, hyperplasia
Cryptosporidium parvum	Digestive tract cancers	Inflammation

Note: pathogenesis is only partially understood. All malignant neoplasms are associated with genetic disorders such that it is highly likely that the infectious agent provides only one element of pathogenesis. In some cases, inflammation and the production of free radicals could contribute to the genesis of genetic lesions. It should not be assumed that the organisms listed are associated with all cases of the relevant malignant neoplasm.

Table 2 Accumulated incidence

Accumulated incidence of selected cancers linked to infection and CDs in selected Commonwealth countries,* 2008–2030

	2008	*2010*	*2015*	*2020*	*2025*	*2030*
Bladder cancer	28472	30224	35222	41223	47889	55567
Cervical cancer	216369	228515	261000	297151	336529	378761
Liver cancer (HCC)	51972	55010	63376	72798	83434	95437
Cumulative total	296813	313749	359598	411172	467852	529765

*Bangladesh, Belize, Botswana, Cameroon, The Gambia, Ghana, Guyana, India, Jamaica, Kenya, Lesotho, Malawi, Malaysia, Maldives, Mauritius, Mozambique, Namibia, Nigeria, Pakistan, Papua New Guinea, Rwanda, Samoa, Sierra Leone, Solomon Islands, South African Republic, Sri Lanka, Swaziland, Uganda, United Republic of Tanzania, Vanuatu, Zambia.

Source: Ferlay et al., 2010.

common skin warts (HPV1, HPV2) or genital warts (HPV 6 or HPV 11). However, a small proportion of patients develop persistent infection (usually defined as infection in women over 30 years of age) with oncogenic subtypes of HPV, some of which progress to invasive and potentially fatal cancer. There are approximately 30 sub-types of HPV that are able to cause cancer. Foremost among these are HPV 16 and HPV 18, which together account for approximately 70 per cent of all cervical cancer (Muñoz et al., 2003).

GLOBOCAN[2] data show there were 216,369 new cases of cervical cancer in low- and middle-income Commonwealth countries in 2008. Estimates based on demographic growth alone project a 75 per cent increase in new cases by 2030, leading to an annual incidence of 378,761 new cases by that year (Ferley et al., 2010). Knowledge of the association of HPV with cervical cancer has led to the development of objective early detection tests based on the presence of HPV in cervical secretions and prophylactic vaccines that offer effective protection against HPV 16 and HPV 18

Table 3 Age standardised rates

Age standardised incidence rates in selected low- and middle-income Commonwealth countries

Cervical cancer *Rate per 100,000 (all ages)*		***Bladder cancer*** *Rate per 100,000 (both sexes)*		***Liver cancer*** *Rate per 100,000 (both sexes)*	
Sri Lanka	11.82	Maldives	0	Maldives	0
Mauritius	12.92	Botswana	0.39	Sri Lanka	1.58
Maldives	13.26	Cameroon	0.68	Namibia	1.69
Namibia	15.77	Lesotho	0.77	Mauritius	2.11
Vanuatu	17.01	Solomon Islands	0.82	India	2.19
Solomon Islands	17.62	Samoa	0.87	Pakistan	2.5
Malaysia	17.9	The Gambia	1	Tanzania	2.73
Pakistan	19.46	Sierra Leone	1.2	Botswana	2.78
Samoa	20.19	Swaziland	1.25	Jamaica	3.79
Botswana	22.22	Sri Lanka	1.33	Bangladesh	3.8
Papua New Guinea	23.25	Papua New Guinea	1.4	Zambia	4.22
Kenya	23.38	Namibia	1.46	Malawi	4.26
Cameroon	23.96	Vanuatu	1.61	Samoa	4.3
South Africa	26.56	Uganda	1.63	Mozambique	4.62
India	26.96	India	1.67	Guyana	4.79
Belize	29.62	Guyana	1.91	Lesotho	5.6
Bangladesh	29.83	Tanzania	1.98	Malaysia	5.65
Togo	29.99	Kenya	2.13	Kenya	6.61
The Gambia	32.45	Bangladesh	2.2	Belize	6.9
Nigeria	32.95	Ghana	2.34	Solomon Islands	7.29
Rwanda	34.46	Nigeria	2.52	Uganda	8.61
Lesotho	34.97	Belize	2.56	Cameroon	9.28
Ghana	39.51	Zambia	3.04	Papua New Guinea	9.43
Guyana	44.68	Malaysia	3.29	South Africa	9.54
Jamaica	45.69	Mauritius	3.33	Swaziland	9.83
Uganda	47.53	Pakistan	3.49	Nigeria	9.95
Swaziland	49.99	Rwanda	3.68	Rwanda	13.14
Mozambique	50.64	Mozambique	4.16	Vanuatu	14.66
Malawi	50.77	South Africa	4.57	Sierra Leone	15.79
Tanzania	50.86	Jamaica	4.89	Ghana	17.38
Zambia	52.77	Malawi	6.23	The Gambia	36.06

Source: Ferlay, et al., 2010.

infection. A new vaccine directed at nine sub-types of HPV is under development (Ma et al., 2010).

The authors of a meta-analysis of nine studies conducted in India, involving 3,723 patients, concluded that HPV 16 and HPV 18 vaccines would provide over 75 per cent protection against invasive cervical cancer in South Asia (Batla et al., 2008; Ma et al., 2010). These vaccines are most effective when administered at a young age (e.g., 9-12 years), before the onset of sexual activity. The recommendation of vaccinating males, who may also be infected with HPV and are at risk for a number of HPV associated cancers, as well as providing a potential reservoir from which women could be re-infected once vaccine-induced immunity has waned, remains controversial. Despite the resources that have been dedicated to global reproductive health, these vaccines are still not available in a number of countries with limited resources. Even though the price of vaccines has been reduced in some of the poorer countries , affordabilty remains an issue. In addition, the logistics of vaccine delivery, especially to rural areas, raises other challenges that would have to be addressed in the context of national programmes. Since only a few per cent of women are at risk, even in populations where cervical cancer is common, toxicity should also be carefully followed with each new vaccine.

Hepatitis B and hepatocellular carcinomas (liver cancers)

Hepatitis B virus (HBV) infection remains a major health problem worldwide, with an estimated 400 million chronic carriers of the HBV surface antigen (HBsAg) (Pollicino et al., 2011). HBV is commonly transmitted either 'vertically' (i.e., perinatally from carrier mothers) or 'horizontally' through contact with an infected person, contaminated surfaces or unsafe injections and other medical procedures (Gonzalez et al., 2012; Kane, 2012). HBV infection is the most prevalent risk factor for hepatocellular carcinoma (HCC), which is the most frequent form of liver cancer. Liver cancer is the third most common cause of death from cancer worldwide (Ferley et al., 2010). There were 51,972 new cases of liver cancer in low- and middle-income Commonwealth member states in 2008. Estimates based on demographic growth project an increase in the annual incidence of HCC in these countries of 84 per cent (to 95, 437 new cases) over the period 2008–2030.

Chronic HBV infection accounts for 55 per cent of global HCC cases and 89 per cent of HCC cases in those regions (Asia-Pacific and sub-Saharan Africa) where HBV infection is endemic (Kew, 2010). The global distribution of Hepatitis B virus (HBV) vaccine, supported in part by the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunisation) and the GAVI Fund, has been successful, with more than 90 per cent of countries now including it as a routine intervention for children in their national immunisation programmes (Kane, 2012). Uncontrolled maternal infection, leading to a high risk of vertical transmission, is a key factor in the failure to prevent HCC (Chang et al., 2009). National vaccination programmes in Asia have proved effective in reducing HBV prevalence and HCC incidence (ibid; Gwack et al., 2011). Data from a 20-year follow-up study in Taiwan indicates that HCC incidence was statistically significantly lower among children and young people (aged 6–19 years) who had been vaccinated at birth compared with unvaccinated birth cohorts (age- and sex-adjusted relative risk: 0.31, $P < .001$ vaccination at birth) (Chang et al., 2009).

Comprehensive national programmes of HBV vaccination at birth with follow up 'booster' vaccinations should ultimately have a major impact on the reduction of HCC incidence, and thus the overall burden of liver cancer, in those Commonwealth countries where chronic HBV infection is currently endemic.

Schistosomiasis and bladder cancer

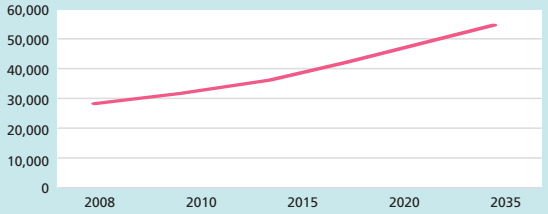
Schistosomiasis is a neglected tropical disease caused by trematode worms (blood flukes) of schistosoma haematobium that live in fresh water snails (Botelho, 2009; Salem et al., 2011; WHO, 2012b). Infection begins when larval forms of the parasite penetrate the skin during contact with infested water (WHO, 2012b). The larvae develop into adult worms (schistosomes), which live in the blood vessels of the body, particularly the venous plexuses around the bladder. When the female worms release their eggs, some of the eggs pass out of the body in the faeces or urine but others remain in the body tissues, causing inflammation and progressive organ damage (ibid.). Schistosomiasis is prevalent in tropical and sub-tropical areas such as countries in Africa and the Middle East, especially in poor communities without access to safe drinking water and adequate sanitation. Populations particularly at risk are agricultural workers in regions where irrigation is essential (hence the high incidence of this disease in Egypt), fishing communities, women doing domestic chores (e.g. washing clothes) in infested water and children playing in infested streams or lakes (ibid.). At least 230 million people require treatment every year, of which 90 per cent live in Africa (ibid.). In children, schistosomiasis can cause anaemia, stunting and a reduced ability to learn, although the effects are usually reversible with treatment (ibid.).

Schistosoma haematobium infestation is present in approximately 107 million people (Mutapi et al., 2011). There is compelling epidemiological evidence linking schistosoma haematobium with the development of bladder cancer (Mostafa et al., 1999). Although the mechanisms underlying the association remain ill-defined, repeated rounds of hyperplasia and repair of the bladder mucosa is likely to be a major factor, and a carcinogenic role for parasite antigens has been postulated (Botelho, 2009). N-nitroso compounds, found at high levels in the urine of patients with schistosomiasis-associated bladder cancer, may also be significant (Mostafa et al., 1999).

There were 28,472 new cases of bladder cancer in low- and middle-income Commonwealth countries in 2008. Estimates based on demographic growth project an increase in incidence of 95 per cent over the period 2008–2030, leading to an annual incidence of 55,567 per year by 2030 (Ferley et al., 2010). Control of schistosome infections is through treatment of infected people with a single dose of the anti-helminth drug, praziquantel (one tablet per 15 kg of body mass). Praziquantel is safe, highly efficacious and cheap – average tablet costs are 20 cents per child and 24–32 cents per adult (WHO, 2012b). Annual mass drug administration (MDA) praziquantel treatment programmes, largely school based, have been shown to improve child growth and development and to reverse the anaemia and some of the end-organ pathologies linked to the parasitic infection (Hotez, Fenwick and Kjetland, 2009). These MDA programmes generally exclude children aged 5

Figure 1

Projected increase in cases of selected cancers linked to infection and communicable diseases in low- and middle-income Commonwealth countries



Source: Ferlay et al., 2010.

years and below, although there is evidence that these younger children would benefit from treatment (Mutapi et al., 2011), with little harmful effect.

The economic and health effects of schistosomiasis are considerable, yet despite the availability of a cheap and efficacious treatment less than 5 per cent of the infected population is currently receiving praziquantel (ibid.). This situation that has been described as 'one of the first great failures of the global health decade' (Hotez and Fenwick, 2009) Priority programmes to combat schistosomiasis should include the provision of clean drinking water and adequate sanitation (as well as the teaching of hygienic practices) to reduce contamination of water sources (WHO, 2012b), the scaling up of praziquantel manufacture and distribution to populations at risk (Hotez, Fenwick and Kjetland, 2009).

Conclusion

Infection-related cancers represent a prime target for preventative approaches, whether by vaccination, treatment or strategic multisectoral initiatives. In Egypt co-ordinated environmental health strategies in the battle against schistosomal infection have already led to a significant decline of the relative frequency of bladder cancer (Salem et al., 2010; Gouda et al., 2007).

Box 1

Recommendations for cancer prevention through infection control programmes

HPV infection and cervical cancer
- Extend HPV vaccination programmes
- Research second-generation vaccinations

Hepatitis B and hepatocellular carcinomas
- Support national HBV vaccination at birth

Schistosomiasis and bladder cancers
- Scale up of manufacture of praziquantel and annual delivery to populations at risk
- Accelerate research on the causative agents operating in schistosome-associated bladder carcinogenesis
- Provide clean drinking water and adequate sanitation

The future, as represented by the steeply climbing curve in Figure 1, is based on predicted demographic growth and on the situation remaining unchanged. It need not be our future if we choose to make the change now. The additional burden to the health services of low- and middle-income Commonwealth member states of the three cancers described above could be measurably reduced by effective infection control programmes (Box 1). Initiating a Commonwealth-wide response to infectious disease related cancers at this year's World Health Assembly in Geneva would be an appropriate place to start.

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Endnote

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[2] The GLOBOCAN Project of the World Health Organization International Agency for Research on Cancer aims to provide contemporary estimates of the incidence and prevalence of and mortality from major types of cancers for 184 countries. See http://globocan.iarc.fr/

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