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The global health burden of infection-associated cancers in the year 2002

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Several infectious agents are considered to be causes of cancer in humans. The fraction of the different types of cancer, and of all cancers worldwide and in different regions, has been estimated using several methods; primarily by reviewing the evidence for the strength of the association (relative risk) and the prevalence of infection in different world areas. The estimated total of infection-attributable cancer in the year 2002 is 1.9 million cases, or 17.8% of the global cancer burden. The principal agents are the bacterium *Helicobacter pylori* (5.5% of all cancer), the human papilloma viruses (5.2%), the hepatitis B and C viruses (4.9%), Epstein-Barr virus (1%), human immunodeficiency virus (HIV) together with the human herpes virus 8 (0.9%). Relatively less important causes of cancer are the schistosomes (0.1%), human T-cell lymphotropic virus type I (0.03%) and the liver flukes (0.02%). There would be 26.3% fewer cancers in developing countries (1.5 million cases per year) and 7.7% in developed countries (390,000 cases) if these infectious diseases were prevented. The attributable fraction at the specific sites varies from 100% of cervix cancers attributable to the papilloma viruses to a tiny proportion (0.4%) of liver cancers (worldwide) caused by liver flukes.

Key words: infection; cancer; attributable fraction; estimates

In the last 30 years or so, considerable evidence has been found for a role for several infectious agents, particularly viruses, in human cancer. In this article, I summarise the evidence for 'causality' with respect to infectious agents linked with cancer, and for each one that meets the established criteria, estimate the fraction of the cancer concerned that is attributable to it. These estimates update that for 1990,[1] using new information on infection and cancer and the estimated global cancer burden in 2002.[2]

Those infectious agents that have been identified as causes of cancer (Groups 1 and 2A) in the IARC monographs series are included. They include hepatitis B and C viruses, human papilloma viruses (HPVs), human immunodeficiency virus (HIV), T-lymphotropic viruses, Epstein-Barr virus (EBV), human herpes virus 8, the bacterium *Helicobacter pylori* (HP), schistosomes and liver flukes (Table I).

Methods

Geographic divisions

The global estimates of numbers of cancer cases and the attributable fractions (AFs) for the different infectious agents are, for the most part, calculated for 20 world areas, as defined by the UN Population Division[153] (Fig. 1). Sometimes, these units are combined into larger groupings, for example, for 'developed countries', comprising those of areas 9,10b and 14–18 as shown in Figure 1 and 'developing countries' the remainder.

Cancer cases

The estimated numbers of new cancer cases in the year 2002 by country, age group and sex are available for 25 of the major cancers in GLOBOCAN 2002.[2] These estimates do not include certain cancers for which infectious agents apparently play a causative role: Burkitt lymphoma (in the case of EBV) and oro-pharyngeal and ano-genital cancers (vulva, vagina, penis and anus) in the case of HPV. The incidence of Kaposi sarcoma (KS) is provided only for Africa, and appears only within the overall totals for other world areas. Separate estimates have, therefore, been made for these cancer sites.

The estimates for oro-pharynx cancer have been derived from the numbers of cancers of the pharynx (from Globocan 2002) and, for each world area, the proportion of such cases that are located in the oro-pharynx, according to registry data in Cancer Incidence in Five Continents, volume VIII.[4] Worldwide, the percentage of pharyngeal cancers localised to the oropharynx was about 45%. The total cases of oral cavity cancers includes a small percentage of cancers of salivary gland, presumably unrelated to HPV, but the correction involved to the estimates would be very small (certainly within the margin of error).

For ICD-10 categories C51-52 (vulva and vagina) and C60 (penis), numbers of cases were estimated from cancer registry data (extracted from Cancer Incidence in Five continents, Volume VIII[4]) as the ratio of cases of cancer at these sites to cases of cervix cancer (C53) by age and area. The estimated numbers for 2002 are 40,000 annual cases of cancer of the external genitalia in females, and 26,300 cases of penile cancer worldwide. Anal cancers were estimated from recorded ratios of colo-rectal cancer to anal cancer (by age group, sex and area); the estimate is of 30,400 cases, about equally divided between males and females.

Burkitt lymphoma is predominantly a disease of children and young adults, with few cases occurring after the age of 45. Based on the cancer registry database, the proportion of non-Hodgkin lymphomas reported as Burkitt lymphoma at ages 0–14 and 15–44 in different areas of the world was estimated, and the corresponding number of cases were calculated (8,200 per year).

Estimating the number of KS cases outside the African continent is rather difficult; the most recent systematic data on cancer incidence[4] relate to cases occurring about 1995. With the advent of highly active antiretroviral therapy (HAART), however, the occurrence of clinical AIDS and its manifestations, including KS, has been much decreased.[5] The age–sex specific incidence of KS reported by the cancer registries of the US SEER programme in 2000–2001 (excluding San Francisco, with its atypically high rates)[6] have, therefore, been used to estimate the number of KS cases occurring in the United States in the year 2002. The estimate was of 1,525 cases in men and 60 cases in women. Using the ratio of KS cases to the number of HIV/AIDS cases in adults (by sex) in the USA at the end of 2001 as standard, the numbers of cases in other developed countries was estimated, based on number of HIV/AIDS cases by region in 2001.[7] The total is 2,500 cases in men and 110 in women.

This method is less applicable to other less affluent regions of the world where it is unlikely that antiretroviral therapy was widely available in 2002. KS remains very rare in Asian populations even in the presence of moderate population prevalence of HIV, presumably because infection with HHV-8 is rare.[8] The observed incidence of KS in Thailand in 1989–2001[8] and prevalence of HIV/AIDS in adults in other Asian regions[7] were used in an analogous method to that for developed countries to estimate the number of KS cases in 2002 as just 100 in men and 20 in

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women. For the other developing countries (and Eastern Europe), where the number of new AIDS cases will not greatly exceed the numbers of deaths from AIDS, the number of KS cases was estimated as 3.5% of AIDS deaths.[7] This probably gives a conservative estimate of the number of new cases (4,800 new cases in 2002).

The total estimate is 66,200 cases in the year 2002, and of which 88.7% (58,800) are in sub-Saharan Africa (Table VI).

Attributable fractions

For most infections, calculation of AF relies upon the classic formula for population attributable risk[9]:

$$\mathrm{AF} = \frac{p(r-1)}{1+p(r-1)} \tag{1}$$

where r represents the relative risk of exposure, and p is its prevalence in the population. The formula results in a proportion that is applied to the total number of incident cases in the target population to obtain the number of cases that can theoretically be attributed to the factor in that population (AF). Its application requires identification of data on the prevalence of the exposure to the 'causative' agents in different parts of the world, as well as the corresponding relative risks. The relative risk is assumed to be constant in different populations (representing a biological parameter), although some variation is possible if susceptibility differs between populations or the prevalence of other cofactors varies. This method was used to estimate the number of cancers due to HBV, HCV, HP, HIV (non-Hodgkin lymphoma) and schistosomes.

From formula (1), one can derive the expression for the number of attributable cases:

$$\mathrm{AC} = pI(r-1) \tag{2}$$

where p and r are as in Formula (1) and I is the incidence of the disease among nonexposed. This variant of the classic formula was used to estimate the number of Cholangiocarcinomas due to infection with the parasites *Clonorchis sinensis* and *Opistorchis viverrini*.

For EBV, the prevalence of relevant infection is hard to define, as the virus infects almost everyone in childhood or adolescence, and the virus persists in latent form in B-lymphocytes throughout the life. Clearly, agents other than EBV are essential cofactors in carcinogenesis, and EBV-attributable cancers are defined as those in which EBV-DNA can be demonstrated in tumour cells.

For the oncogenic HPVs, it is generally accepted that almost all cancers of the cervix uteri are the result of infection,[10] and so the AF is 100%. At other sites, the prevalence of infection in normal subjects is hard to define, and so use of the classic Cole-MacMahon formula is inappropriate; as for EBV, the HPV-attributable cancers are defined as those in which HPV-DNA can be demonstrated in tumour cells.

The numbers of cases of ATLL due to infection with HTLV-I were estimated based on the incidence of the malignancies in infected individuals. All cases of KS were attributed to HHV-8 infection (with or without coincident HIV).

TABLE I – MAJOR HUMAN INFECTION-ASSOCIATED MALIGNANCIES[3]

Malignancy	Agent (group)
Carcinomas	
Bladder	*Schistosoma haematobium* (blood fluke)
Cervical	HPV (papillomavirus)
Hepatocellular	HBV (hepadnavirus)
	HCV (flavivirus)
Bile duct	*Opisthorchis viverrini* (liver fluke)
Nasopharynx	EBV (herpesvirus)
Stomach	*Helicobacter pylori* (bacterium)
Lymphomas	
Adult T-cell	HTLV-I (retrovirus)
Burkitt	EBV (herpesvirus)
Hodgkin	EBV (herpesvirus)
Sarcoma	
Kaposi	HHV8 (herpesvirus)

HPV, human papillomavirus; HBV, hepatitis B virus; HCV, hepatitis C virus; EBV, Epstein-Bar virus; HTLV-I, human T-cell lymphotropic virus type I; and HHV8: human herpesvirus 8.

Results

Helicobacter pylori

HP was classified as being carcinogenic for humans in 1994.[11] It is considered to be causally associated with both carcinoma of the stomach and gastric lymphoma.

Prevalence of HP varies in different regions of the world. In general, infection is acquired during childhood, and so the prevalence gradually increases (at a faster rate in developing than developed countries) to reach a maximum in middle age. Estimates of

FIGURE 1 – World Areas, as defined by the United Nations Population Division.[153]

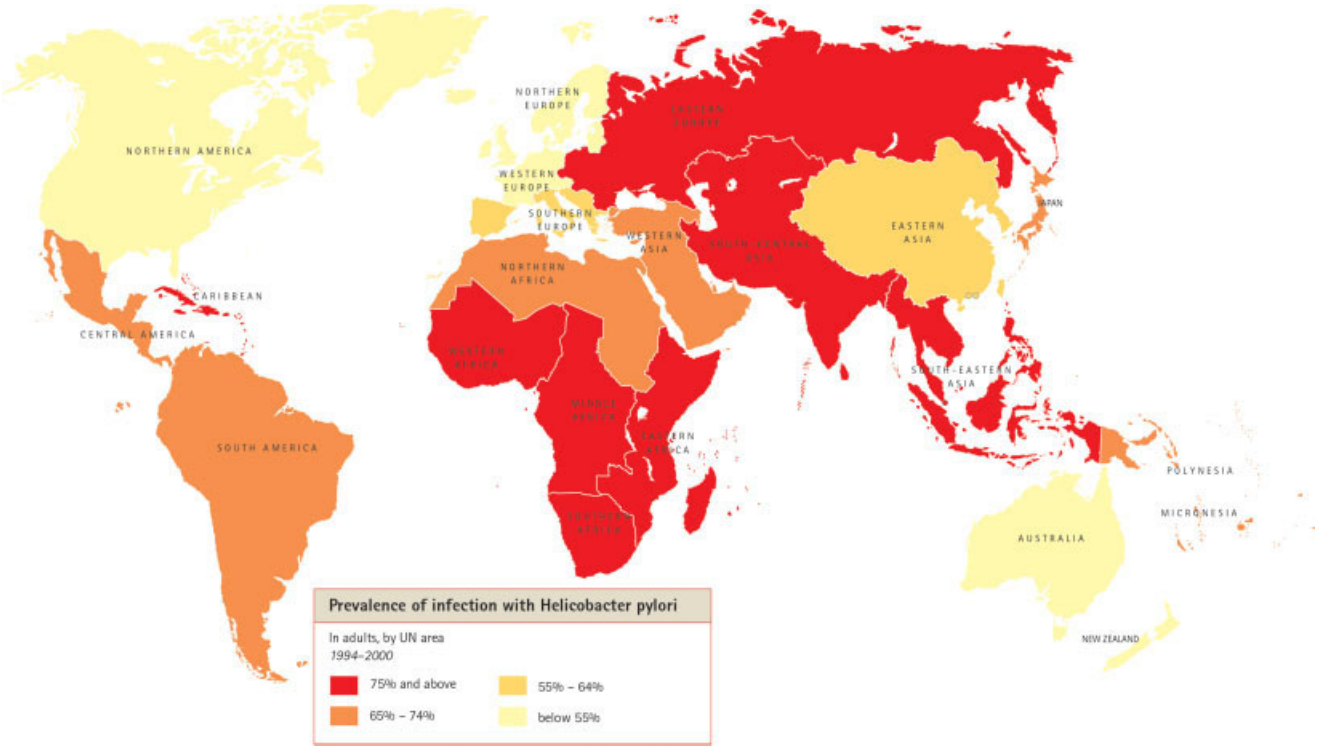

FIGURE 2 – Mean prevalence of infection with HP in adults, by World Area (source: see text) {Figure © Myriad Editions Ltd/www.Myriad Editions.com}.

prevalence of infection in adults (age range 45–64, centred upon 50–59) were taken from a review of the available literature, confining the data to those from population-based surveys of healthy adults, noncancer cases from prospective (cohort) studies or control series from case-control studies (subjects without gastrointestinal diseases). Estimates of prevalence based on biopsy or endoscopy, which are almost always performed on symptomatic subjects, have been excluded. The great majority of studies rely upon serology (detection of anti-HP antibody) to define presence of infection. Some studies provide data for several countries,[12–14] and certain reviews are useful sources of data.[11,15–17] The prevalence estimates from different studies within individual countries were averaged to provide a single figure, and the value for 20 world Areas (Fig. 2) obtained as the weighted (by population size) average of the values for the countries within the Area. Figure 2 shows that prevalence is, in general, higher in the 'developing' areas, although the values for China (58%) and Central America (62%) are lower than what might have been anticipated; however, prevalence in Eastern Europe (82%) and Japan (71%) is relatively high. As China accounts for a 38% of the world burden of gastric cancers, estimates of prevalence for this country will be important in determining the AF worldwide, and the result of a large pooled analysis of 89 studies[18] was used for this country.

The overall estimate is of prevalence of infection in middle-aged adults of 74% in developing countries and 58% in developed countries.

Gastric carcinoma

Cancer of the stomach still accounts for almost 10% of new cancers in the world, although incidence rates are steadily decreasing. The highest rates are observed in Eastern Asia, East Europe including the ex-USSR and central and tropical South America.[19]

The most satisfactory evidence on the magnitude of the risk is from prospective studies. Retrospective case-control studies are limited in observing HP infection after the development of cancer. HP tends to disappear as intestinal metaplasia and atrophy develop so that the prevalence of infection may be seriously underestimated in cases, even if anti-HP antibody is used as an indicator of infection. Several case-control studies nested within cohorts have now been published, in which infection is evaluated in cases and controls before the onset of disease. The results of these studies have been the subject of at least 4 metaanalyses.[14,20–22] In the most recent,[14] which included 12 prospective studies (which had yielded 1,228 gastric cancer cases, with 3,406 controls); overall, the OR for the association between HP infection and the subsequent development of gastric cancer was 2.36 (95% c.i. 1.98–2.81). There was no increase in risk for cancers of the gastric cardia (OR 0.99), risk for noncardia cancers was 2.97 (95% c.i. 2.34–3.77). The risk varied with the interval between sample collection and cancer diagnosis (as might be expected, if infection is progressively lost as gastric atrophy develops). The increase in risk was 5.9-fold (95% c.i. 3.4–10.3) for HP positivity 10 years or more prior to diagnosis. The associations were not related to histological type of gastric cancer (intestinal *vs*. diffuse) or sex.

The proportion of gastric cancer cases occurring at the cardia, compared to elsewhere in the stomach, certainly varies in different regions of the world. Cancers of the antrum and pylorus tend to be most common in high-risk countries, while cardia cancers are most common where overall rates are low. There are difficulties in clearly distinguishing between gastric cardia cancers and cancers of the lower third of the oesophagus.[23] Data from Cancer Incidence in Five Continents, Vol.VIII[4] were used to obtain the percentages of gastric cancer in different subsites of the stomach in cancer registries worldwide, and estimated the proportions of gastric cancers that are 'noncardia' in males and females in different world regions. The percentage of noncardia cancers is higher in females than in males, and higher in the developing world and Japan than in North American, North and West Europe and Australia/New Zealand. The total numbers of gastric cancer cases in these areas and the estimated number of noncardia cancers are shown in Table II.

TABLE II – ESTIMATED NUMBERS OF STOMACH CANCER CASES, AND NUMBERS ATTRIBUTABLE TO HP INFECTION IN DEVELOPING AND DEVELOPED COUNTRIES, 2002

	Stomach cancer cases (2002)		Noncardia cases (%)		Stomach cancer: noncardia cases		HP[1]	AF[2] (r.r. = 5.9)	Cases attributable to HP			% of all stomach cancer
	Male	Female	Male	Female	Male	Female			Male	Female	Both	
Developed countries	196,600	115,800	80	88	158,000	101,000	58%	0.74	117,000	75,000	192,000	61.4
Developing countries	406,800	214,700	80	87	324,000	187,000	74%	0.78	254,000	146,000	400,000	64.4
World	603,400	330,500	80	87	482,000	288,000			371,000	221,000	592,000	63.4

[1]Prevalence of antibody to H. pylori in adults (45–64).–[2]Attributable Fraction.

With a relative risk of 5.9 (accepting that gastric cancer is unlikely to develop in subjects who have not been infected for at least 10 years), the AF of noncardia gastric cancer cases is 74% in developed countries and 78% in developing countries. This represents 592,000 cases 63.4% of all stomach cancers worldwide (Table II) and 5.5% of all cancers.

Gastric lymphoma

One of the two large American cohort studies of HP also examined the incidence of gastric non-Hodgkin lymphomas and found that these cases showed elevated titres of antibody to HP.[24] The relative risk was 6.3 (95% c.i. 2.0–19.9), statistically significant. Gastric NHL is rather a rare tumour. It comprises about 5% of all NHL, with rather higher percentages in southern Europe and Western Asia.[25]

Assuming that 5% of NHL cases are localised to the stomach, there are about 15,000 new cases worldwide per year (7,500 in developed countries and the same number in developing countries). With a relative risk of 6 and the prevalence of infection assumed earlier, 79% of cases in developing countries (5,900) and 74% in developed countries (5,600) would be attributable to HP.

Human papilloma virus

IARC[26] considers that there is convincing evidence that infection with HPV 16,18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 or 66 can lead to cervical cancer. For HPV 16, the evidence further supports a causal role in cancer of the vulva, vagina, penis, anus, oral cavity and oropharynx and a limited association with cancer of the larynx and periungual skin. HPV 18 also shows a limited association with cancer at most of these sites. Evidence for associations of HPV types of genus beta with squamous cell carcinoma of the skin is limited for the general population. There is some evidence that HPVs are involved in squamous cell carcinoma of the conjunctiva, but inadequate evidence for a role of HPVs in cancer of the esophagus, lung, colon, ovary, breast, prostate, urinary bladder and nasal and sinonasal cavities.

With respect to cancer of the cervix, oncogenic HPV may be detected by PCR in virtually all cases of cervix cancer, and it is generally accepted that the virus is necessary for development of cancer, and that all cases of this cancer can be 'attributed' to infection.[10]

With respect to squamous cell cancers of the vulva and vagina, carcinoma of the penis and anal cancer, published studies do not allow quantification of relative risk and infection prevalence, because they are generally small in size and usually do not include comparable measurement of prevalence of infection at these sites in normal subjects. To estimate AFs, approximate estimates of the proportion of cancer cases infected with HPV in various series are used.

The prevalence of HPV in vaginal cancer is about 60–65% in studies using PCR methodology.[26,27] About 20–50% of vulvar cancers contain oncogenic HPV DNA,[28,29] but only the basaloid and warty type that tends to be associated with vulvar intraepithelial neoplasia is caused by HPV infection (prevalence 75–100%), and only 2–23% of the keratinizing carcinomas harbour HPV.[30] HPV-related vulvar cancer occurs in younger women than the typical keratinizing squamous histology related to chronic inflammatory precursors. Vulvar carcinomas are generally rather more frequent than cancers of the vagina; an overall HPV prevalence of about 40% in cancers of the lower genital tract in women is assumed. For anal cancer, in a large series of cases from Denmark and Sweden 95% and 83% of cancers involving the anal canal in women and men, respectively, were positive for oncogenic HPV[31]; the AF is taken to be 90% worldwide. For penile cancer, HPV DNA was found in 30% of 71 cases of penile cancer from Brazil[32] and in 42% of 148 cases from the USA and Paraguay;[33] the AF is assumed to be 40%.

HPV probably plays a role in the aetiology of a fraction of cancers of the oral cavity and pharynx,[34] although the major risk factors are, of course, tobacco and alcohol. Several studies have investigated prevalence of HPV in cancers of the mouth and pharynx.[35,36] On average ~40% of tumours were HPV-positive, but the prevalence varied widely with the population studied, subsites, type of specimen and detection method. HPV was detected most commonly in oropharynx and tonsil, but at every subsite, HPV 16 was the predominant type.[37] The largest study so far is a multicentre case-control study in 9 countries, including more than 1,600 cases of cancers of the mouth and oropharynx and 1,700 controls.[38] HPV DNA was detected in tumour specimens (cases) by PCR, and presence of antibodies against HPV 16 L1 and HPV 16 E6 and E7 was tested for by ELISA methods in cases and controls. HPV DNA was detected in 4 and 18% of cancers of the mouth and oropharynx, respectively (HPV 16 was found in 95% of the positive cases). As HPV DNA cannot be evaluated in controls, and there was a good correlation between HPV DNA in cancer biopsies and serum anti-E6/E7 antibodies, a comparison was made between HPV-positive cases who were positive for HPV DNA or E6/E7 antibody (6.4% mouth cancers, 15.3% oropharyngeal cancers), and HPV-positive control subjects positive for anti E6 or anti-E7 antibody (1.6%). The AFs, based on these figures, would be 5% for mouth cancers and 16% for cancers of the oropharynx. However, assessment of HPV DNA presence by PCR assay may lead to an overestimation of cases in which the virus is etiologically involved, as suggested by the lower proportion of cases with E6/E7 expression[39]—4.6% of oral cancers and 12% of oro-pharyngeal cancers in the IARC multinational study.[38] The corresponding OR's and AFs would be 2.9 and 3% for mouth cancers and 9.2 and 12% for oropharynx cancers. For the purpose of estimation, it is assumed that 3% of oral cavity cancers and 12% of cancers of the oropharynx are attributable to HPV.

The results are shown in Table III (by site; developed *vs*. developing countries).

HPV (any type) is responsible for all of the cervix cancers occurring in the world (492,800) for 53,900 cases of ano-genital cancer and 14,500 cases of oro-phayngeal cancer. This means that HPV is one of the most important infectious agents in cancer causation, responsible for 5.2% of the world cancer burden. The distribution is very different between developing and developed countries: the AF is 2.2 in developed countries and 7.7% in developing countries.

Hepatitis viruses

Hepatitis B virus. The role of chronic infection with hepatitis B virus in the aetiology of hepatocellular carcinoma is well estab-

TABLE III – CANCERS ATTRIBUTABLE TO INFECTION WITH ONCOGENIC TYPES OF HPV

Site	Developed countries				Developing countries				World			
	Total cancers	AF (%)	Attributable cancers	% all cancer	Total cancers	AF (%)	Attributable cancers	% all cancer	Total cancers	AF (%)	Attributable cancers	% all cancer
Cervix	83,400	100	83,400	1.7	409,400	100	409,400	7.0	492,800	100	492,800	4.5
Penis	5,200	40	2,100	0.04	21,100	40	8,400	0.14	26,300	40	10,500	0.1
Vulva, vagina	18,300	40	7,300	0.2	21,700	40	8,700	0.2	40,000	40	16,000	0.2
Anus	14,500	90	13,100	0.3	15,900	90	14,300	0.2	30,400	90	27,400	0.2
Mouth	91,100	3	2,700	0.1	183,000	3	5,500	0.1	274,100	3	8,200	0.1
Oro pharynx	24,400	12	2,900	0.1	27,700	12	3,300	0.1	52,100	12	6,300	0.1
All sites	5,016,100		111,500	2.2	5,827,500		449,600	7.7	10,843,600		561,200	5.2

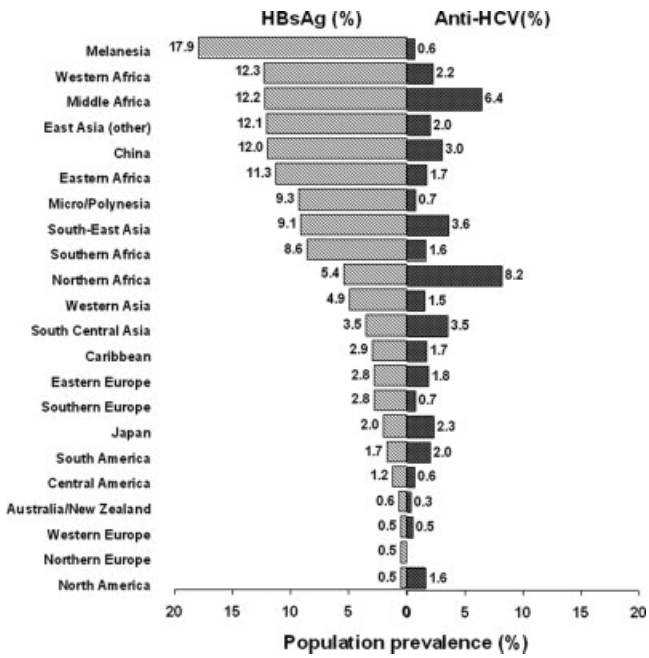

FIGURE 3 – Prevalence of chronic infection by hepatitis B (carriers of HbsAg) and hepatitis C (seropositive for anti-HCV) by World Area.

lished. The IARC Monograph[40] summarises the results of some 15 cohort studies and 65 case control studies worldwide, examining the association between seropositivity for hepatitis B surface antigen (HBsAg), indicating chronic infection and the risk of hepatocellular carcinoma. The cohort studies yield relative risk estimates of 5.3–148, while the majority of case-control studies yield relative risk estimates between 3 and 30. Some of these studies were able to address potential confounding by aflatoxin, hepatitis C infection, alcohol drinking and tobacco consumption, and the IARC overall evaluation assessed HBV as carcinogenic to humans.[40] Information on the prevalence of hepatitis B infection is available from surveys of carriage rates of HBsAg. WHO produces country specific estimates and somewhat more recent data have been compiled by Custer *et al.*[41] from which the average prevalence by world area has been estimated (Fig. 3). Using these prevalence figures and assuming a relative risk of 20, the fraction of cases attributable to chronic infection with hepatitis B can be estimated.

Overall, some 340,000 cases of liver cancer are attributable to hepatitis B infection or 54.4% of the world total (Table IV).

Hepatitis C virus. The role of hepatitis C virus (HCV) in the aetiology of liver cancer was clarified after specific tests to detect HCV antibodies became available in 1989. By 1993, several case control studies had been reported, and the IARC classified HCV as definitely carcinogenic to humans.[40] The magnitude of the risk associated with chronic 'infection' became evident as the results of studies using second and third generation anti-HCV ELISA tests or detection of HCV RNA (by reverse transcription polymerase chain reaction) became available. In a metaanalysis of studies reported prior to July, 1997,[42] the relative risk was estimated as 17.3 in HBsAg negative subjects, while a similar combined analysis of Chinese studies[43] found a relative risk of 8.7. In recent studies in Greece,[44] Taiwan[45] and Gambia,[46] the relative risks for HCV alone were 23.2, 21.5 and 16.7, respectively. In fact, as only some 85% of HCV antibody-positive subjects have a chronic infection (as determined by the presence of circulating viral RNA), the true relative risk of chronic infection with the virus would be rather higher. But as the estimate is based upon anti-HCV prevalence, a relative risk of 20 is assumed.

Prevalence of HCV antibodies in serum has been studied in various groups of subjects—community-based studies, blood donors and in pregnant women. The results of these, by country, have been compiled by WHO[47] and for Africa by Madhava *et al.*[48] The regional prevalence figures (in Fig. 3) are calculated from these data. Prevalence of HCV infection is strongly related to birth-cohort; for example in Japan, prevalence is much lower in recent generations than earlier ones, where individuals were more likely to have been exposed to infection through injections or transfusions. Thus, prevalence should really be estimated for the same age groups as those experiencing liver cancer. However, in the absence of such precise information, general population prevalence has been used. This varies from 8.2% in North Africa to less than 0.1% in northern Europe, with a world average of about 2.4%. With a relative risk of 20, the total numbers of cases due to HCV are 195,000 or 31% of the world total (Table IV).

Combined HBV and HCV infection

Estimation of the joint effects of HBV and HCV is difficult because of the rarity of combined infections in the general population (and hence in the control series of case control studies). In their metaanalysis, Donato *et al.*[42] found a relative risk for combined infection of 165 (95% c.i. 80–374), suggesting a less than multiplicative, but more than additive, effect on risk. The metaanalysis of Chinese studies[43] gave a similar but less marked result (relative risk of combined infection ~35). If this were so and if the probability of infection with both viruses were independent, the AF due to hepatitis viruses (one or both) would be rather greater than the sum of the individual AFs.[49] However, in the other studies cited earlier, the effect of combined infection was additive at most. A conservative assumption is that the effect is additive, and the AFs for the two viruses have been simply added (noting that, for several cancers, particularly in developing countries, the total is anyway close to 100%).

Based on the aforementioned assumptions, 340,000 + 195,000 = 535,000 liver cancer cases, or 85.5% of the world total, are attributable to infection with hepatitis C or hepatitis B (with a small proportion the result of joint infections). The AFs are 42.5% for developed countries and 92% for developing countries.

Epstein-Barr virus

EBV is considered to be a group I carcinogen by IARC,[50] with conclusive evidence with respect to carcinogenicity in Burkitt

TABLE IV – ESTIMATED CASES OF LIVER CANCER IN DEVELOPING AND DEVELOPED COUNTRIES IN 2002, AND NUMBERS ATTRIBUTABLE TO INFECTION WITH VIRUSES OF HEPATITIS B (HBV) OR HEPATITIS C (HCV)

	Liver cancer cases	HBV			HCV			Cases attributable to HBV or HCV
		Prevalence[1] (%)	Attributable fraction (%)	Attributable cases	Prevalence[2] (%)	Attributable fraction (%)	Attributable cases	
Developed countries	110,800	1.6	23.3	26,000	1.3	19.9	22,000	48,000
Developing countries	515,300	7.5	58.8	303,000	2.64	33.4	172,000	475,000
World	626,100	6.3	54.4	340,000	2.4	31.1	195,000	535,000

[1]Percentage of the general population positive for Hepatitis B surface antigen (HbsAg).–[2]Percentage of the general population positive for anti Hepatitis C antibody (anti-HCV).

TABLE V – CANCERS ATTRIBUTABLE TO INFECTION WITH EBV

	Non-Hodgkin lymphoma									
	All NHL		Burkitt lymphoma		Hodgkin Lymphoma				NPC	
	Ages 0–14	Ages 15–44	Total cases	Attributable to EBV	Ages 0–14	Ages 15–44	Ages 45+	Attributable to EBV	Total cases	Attributable to EBV
Sub-Saharan Africa	6,300	8,900	5,700	5,400	1,300	2,400	1,400	2,500	5,300	4,800
N. Africa and W. Asia	2,000	4,100	900	800	900	2,700	1,800	2,600	4,500	4,500
Latin America and Caribbean	1,900	6,400	400	200	1,200	2,500	2,200	3,000	800	750
East/SE Asia	3,600	15,600	500	100	500	2,500	2,600	2,700	56,200	56,200
Other	4,600	28,800	700	200	3,600	21,000	8,100	17,900	13,200	11,800
World	18,400	63,800	8,200	6,700	7,500	31,100	23,800	28,600	80,000	78,100
More developed countries	2,100	19,100	400	100	1,200	16,000	10,800	11,500	7,200	6,500
Less developed countries	16,300	44,700	7,800	6,600	6,200	15,100	13,000	17,100	72,600	71,600

lymphoma, non-Hodgkin lymphoma in immunosuppressed subjects, sino-nasal angiocentric T-cell lymphoma, Hodgkin lymphoma and nasopharyngeal carcinoma. The evidence concerning other cancers for which an association with EBV has been demonstrated (lymphoepithelial carcinomas, gastric adenocarcinoma and smooth muscle tumours in immunosuppressed subjects) was considered to be inconclusive.

EBV and non-Hodgkin lymphoma

Burkitt lymphoma (BL). Table V shows the estimated numbers of BL cases worldwide (see methods).

African BL has a clear and strong association with EBV. This has been shown in several sero-epidemiological studies and most convincingly in a cohort study in Uganda[51] where the level of antibodies to EBV was considerably higher in children who subsequently developed of BL than in normal children.

EBV genome is regularly demonstrated in tumour cells from over 95% of BL cases from sub-Saharan Africa. In North America and Europe, BL is much rarer and generally comprises about 20–30% of childhood NHL, with a different clinical presentation. These 'sporadic' BL cases do not show such a close association with EBV—maybe only one-fifth to one-third have demonstrable virus in tumour tissue or elevated antibody titres to EBV.[52,53] In North Africa, BL occurs with clinical features resembling the 'sporadic' pattern, but despite this, about 85% of cases are associated with EBV.[54] There is some evidence that the proportion of EBV-associated tumours in Latin America may be intermediate between that in Africa and Europe/N America.[55] These proportions are used to estimate the numbers of EBV-attributable BL cases in different regions (Table V). The result is an estimated 5,400 EBV-associated cases in sub-Saharan Africa in 2002 and 1,300 cases elsewhere—an annual total of 6,700 cases (Table V).

Other non-Hodgkin lymphomas. EBV can cause lymphoproliferative diseases in individuals with immune dysfunction, most of which are polyclonal B-cell proliferations classified as diffuse lymphomas.[56] Lymphomas arising in immunocompromised individuals are relatively rare, except in the case of AIDS. In San Francisco, where AIDS is particularly common, more than one quarter of NHL cases occurred in persons with AIDS by 1989.[57] The proportion of AIDS-related lymphomas is estimated in the context of HIV-related cancers. Not all of these are associated with EBV, and the proportion of tumours containing EBV genome appears to vary between the different subtypes—almost all CNS lymphomas, about 90% immunoblastic lymphomas, but about half of the Burkitt-type lymphomas.[50]

It is almost impossible to estimate what proportion of non-Hodgkin lymphomas worldwide occur in immunocompromised individuals, excluding AIDS (hereditary syndromes and iatrogenic), or are cases of the rare sino-nasal angiocentric T-cell lymphoma, but it must be very small (<1%), and so there is no numerical allowance for these cases in the estimates.

EBV and Hodgkin lymphoma

Case-control studies generally demonstrate higher titres of anti-EBV antibodies in cases of Hodgkin lymphoma than in controls.[58] In a large prospective study, Mueller *et al.*[59] found that elevated antibody titres precede diagnosis by several years—the actual relative risks (2.6 and 3.7 for IgG and IgA capsid antigens, 4.0 for EBNA and 2.6 for Early Antigen (diffuse)) and prevalence of raised titres correspond to attributable risks of 30–45%.

Sensitive techniques are able to detect EBV nucleic acid in 25–50% of Hodgkin lymphomas, where it is located in the Reed-Sternberg cells.[60,61] The association with EBV appears to depend upon age. In the childhood age range, about 70% of cases are EBV-positive (with rather higher proportions in developing countries and lower in developed countries[62]), whereas in young adults, the proportion is about 15%.[63] In older age groups, EBV positivity appears to be relatively high (70–75%).[63,64] In part, this pattern is determined by the frequency of different histological subtypes of Hodgkin lymphoma. The mixed cellularity subtype predominates in childhood and in developing countries, while the nodular sclerosing subtype accounts for the marked peak in young adults in developed countries. The frequency of EBV positively is much greater (5- to 15-fold) in mixed cellularity than nodular sclerosing Hodgkin lymphoma. Nevertheless, it seems that, even allowing for cell type, age (more childhood cases EBV-positive) and level of socioeconomic development (more childhood cases in developing countries are EBV-positive) are independent predictors of the association.[65]

For the purposes of estimation, the AF at ages 0–14 is taken to be 60% in developed countries and 80% in developing countries, 20% at ages 15–44, and 70% at ages 45+ (Table V).

Of the world total of 62,300 new cases in 2002, 28,600, or 46% of the total, are estimated to be EBV related (Table V).

EBV and nasopharyngeal carcinoma

Nasopharyngeal cancer (NPC) is relatively rare on a world scale (80,000 new cases per year, 0.7% of all cancers), but it has a very distinctive geographic distribution. Thus, the age-standardised incidence rate is generally less than 1 per 100,000, with the exception of populations living in, or originating from, southern China (in whom the rates are very high), and in populations elsewhere in China, south-east Asia, north-east India, North Africa and Inuits (Eskimos) of Canada and Alaska, all of whom have moderately elevated rates. Males are more often affected than females (sex ratio 2–3:1), and in most populations, there is a progressive increase in risk with age. In moderate risk populations, however, most notably in North Africa, there is a peak in incidence in adolescence.

Genetic and environmental (particularly dietary) factors are certainly important in aetiology.[66] In addition, antibodies to various components of the EBV are raised in NPC cases, and increase in titre as the disease progresses.[67] Case control studies in Chinese populations have been able to control for other risk factors, particularly diet.[68,69] A cohort study involving 9,699 men in Taiwan with follow-up for up to 16 years identified 22 new cases of NPC.[70] The relative risk of NPC in men positive at enrolment for both anti-VCA-IgA and anti-EBV Dnase was 32.8, and with only one of these markers positive was 4.0. Molecular genetic data linking EBV to NPC also provide compelling evidence for causality. EBV-DNA is never found in normal epithelial cells of the nasopharynx, but can be detected in every single case of undifferentiated nasopharynx carcinoma. Furthermore, the DNA is present in the tumour cells, rather than the stroma, and it is monoclonal and various latent genes (EBNA-1, EBER, LMPs) are expressed in the carcinoma cells. Clonal EBV infection has been found in dysplastic (premalignant) lesions of the nasopharynx in individuals with elevated anti-EBV titres in studies in China,[71] consistent with involvement of EBV in the premalignant phase of disease.

The involvement of EBV appears to be with undifferentiated carcinomas of the nasopharynx—these comprise the vast majority of cancers in populations at high and medium risk. In low risk areas, about 10–25% of NPC is of type 1 (keratinising), which is less often infected. For estimation purposes, it has been assumed that 100% of NPC in medium and high-risk areas (ASR > 2.0 in men, 1.0 in women) are EBV-related, and 90% of cases elsewhere (low risk areas), a total of 78,100 cases or almost 98% of all NPC (Table V).

HIV and human herpes virus 8 (HHV-8)

In 1996, an IARC working group concluded that HIV was carcinogenic to humans, an assessment based upon the strong link between infection with the virus and two cancers: KS and non-Hodgkin lymphoma.[72] These two diseases, along with cancer of the cervix, are considered to be 'AIDS-defining conditions'—that is, a HIV-positive subject with these cancers is considered to have AIDS.[73] Subsequently, increased risks for several other cancers have been reported. The most convincing data come from follow-up of cohorts of HIV-positive subjects, comparing the occurrence of cancers with the number expected in the general population. Such studies suggest increased risks of several cancers, especially Hodgkin disease, anal cancer, seminoma, myeloma, and, less certainly, cancers of the lip, brain and lung.[74–76] Although the vast majority of the research into the link between AIDS and cancer has been carried out in 'western' populations (mainly in one country, the USA, and to a lesser extent in Europe and Australia), these account for only a minority of the cases of AIDS occurring in the world today, or the numbers of individuals who are carriers of HIV. Sub-Saharan Africa accounted for about 70% of all such persons in the world at the beginning of the 21st century.

The evaluation by IARC[50] considered that the evidence for a role of KSHV/HHV8 in the causation of KS was 'compelling, but as yet limited'. However, it is now generally accepted to be the principal cause of the disease.[77] In general, HHV8 seroprevalence rates in 'normal' populations *i.e.* blood donors, patients without KS and population samples, appears to be highest in Africa, (prevalences varying from 10 to 100%, depending on the assay) intermediate in the middle east and Mediterranean littoral, lower in the west and lowest in Asia.[78,79] The effect of HIV is probably through immunosuppression—allowing HHV-8 to escape control and thereby increasing viral load, for example. The epidemiology of this virus probably explains the geography of KS pre-AIDS, and the relative rarity of the cancer in West and South Africa, despite the increasing prevalence of HIV.

HIV/HHV8 and KS

Prior to the epidemic of HIV/AIDS, KS was a rare cancer in western countries (annual incidence in the US and Europe was $\leq$0.5 per 100,000, comprising about 0.3% of male and 0.1% of female cancers). It was seen mainly among immigrants from the Mediterranean littoral and African regions, and immunosuppressed transplant recipients. In Africa, endemic KS had a quite distinct geographic distribution: rare in Northern and Southern Africa, it comprised up to 10% of cancers in men in some case series from certain parts of central and eastern Africa.[80,81] Because of the enormous increase in risk in subjects infected with HIV (1,000–5,000 times the risk in the general population[82]), the increasing incidence of KS was the first obvious manifestation of the AIDS epidemic. Before 1990, 15% of AIDS patients in the USA had presented with KS[83] and 17% of cases in Europe.[84] The proportion with KS was very different by risk group—about 21% in homosexuals, compared with 2–3% in heterosexuals and IV drug users[83]—(the figures for 1988 in Europe were 26% and 3.6%[84]). These refer to initial diagnoses of KS, although it is clear from follow-up of cohorts of HIV-positive homosexual/bisexual men that additional cases will occur after the diagnosis of AIDS, and so up to a third of AIDS cases will develop KS at some point.[85,86] The proportion of AIDS cases presenting with KS has declined with time, both because of a decline in the proportion of cases of AIDS in the homosexual risk group, as well as a secular decline within risk groups. The introduction of antiretroviral therapy (HAART) for treating HIV in adults has caused a decline in the incidence of KS in western countries;[5] in the USA, for example, the incidence of KS in men aged 20–54 in the cancer registries of the SEER program fell from 17.2 per 10^5 in 1990–1991 to 2.4 in 2000–2001.[6]

In Africa, KS has become the most common cancer of men in several countries where the epidemic of HIV/AIDS is severe, *e.g.* Uganda[87] and Zimbabwe.[88] The proportion of AIDS cases presenting with, or developing KS, is not well known, not least because most AIDS cases are unreported. Early studies in Central Africa (Zaire, Rwanda) suggested that KS occurred in about 13–18% of AIDS cases[89–91]—this might be an overestimate, however, as the probability of a correct clinical diagnosis of AIDS is enhanced in the presence of such an obvious lesion as KS. The estimated ratio of AIDS cases to KS cases in Kampala was about 15:1, implying that about 7% of AIDS cases have KS.[92]

All cases of KS are attributed to infection with HHV-8/HIV; the estimated number of KS cases occurring in 2002 (see Methods) is 66,200 (Table VI).

HIV and non-Hodgkin lymphoma

The increased frequency of NHL in AIDS was noted in1982.[93] Since then, the elevated risk has been confirmed in studies in the United States and Europe.[84,94] About 3% of AIDS cases present with a lymphoma, but lymphomas may occur in up to 10% of AIDS cases at some point. Almost all lymphomas in AIDS cases are of B-cell type. The cohort study of Coté *et al.*[57] provides the most accurate estimate of excess risk in AIDS, about 160 times

TABLE VI – CANCERS ATTRIBUTABLE INFECTION WITH TO HIV OR HHV-8

	Kaposi sarcoma			Non-Hodgkin lymphoma		
	Male	Female	Both	Male	Female	Both
Developing countries	42,500	19,900	62,500	18,800	8,000	26,800
Sub-Saharan Africa	40,200	18,600	58,800	3,000	2,700	5,700
Asia	100	<100	100	11,500	2,900	14,400
Latin America and Caribbean	2,000	1,300	3,300	3,600	1,700	5,300
Other developing countries[1]	200	100	300	700	700	1,400
Developed countries	3,200	500	3,700	7,000	2,300	9,300
Eastern Europe	700	300	1,100	2,600	1,200	3,800
Other developed countries	2,500	200	2,700	4,300	1,200	5,500
Total	45,800	20,500	66,200	25,700	10,300	36,100

[1]Central and Western Asia, North Africa, Oceania excl Australia and New Zealand.

that in HIV negative subjects. Risk is highest for high-grade lymphomas, especially for diffuse immunoblastic (×630) and undifferentiated Burkitt lymphomas (×220). Extra nodal lymphomas are more common in AIDS than usual,[94] although it is probably because of the great excess of CNS lymphomas (15-fold increase); other extra nodal lymphomas are not in excess.[57] Males are more commonly affected, but it could be that this is simply because of risk-group differences. Thus, the risk in females is 1.2 times that in males in heterosexually acquired cases of AIDS.[95]

In Africa, case-control studies estimating the risk of NHL (all histological subtypes) in HIV-positive compared with HIV negative subjects yield risk ratios in the range of 2–12.[96–99] A record-linkage (prospective) study[100] yielded a RR of 6.7. These are very low excess risks compared with observations in Europe and the United States. Probably this relates to the poor prognosis of AIDS cases in Africa, with other causes of death—particularly from infectious diseases—supervening in AIDS patients with relatively low levels of immunosuppression. NHL was present undiagnosed at autopsy in 2.8% of HIV-positive subjects in Cote d'Ivoire (4% of subjects with AIDS),[101] a figure not very different from the cumulative probability of developing a lymphoma observed in cohorts of AIDS patients in the USA.[57]

EBV is present in two-thirds of AIDS-related lymphomas[102] and may play an important role in lymphomagenesis.[50,72] The frequency varies by lymphoma type—it is found in almost all CNS lymphomas, 70–80% of immunoblastic lymphomas and 30–40% of small cell/BL type lymphomas.

The formula $[p(r-1)/1+p(r-1)]$ was used to estimate the number of NHL cases attributable to HIV based on the prevalence of HIV-AIDS at the end of 2001,[7] a relative risk of 100 (50 in developing countries and 5 in sub-Saharan Africa), and the number of NHL cases, by region. HIV-related case numbers appear reasonable for developing countries, including Eastern Europe (3,810) where the prevalence of HIV/AIDS is substantial (about 0.4%). However, for developed countries, the numbers estimated in this way are very high; for example, it would result in an estimated 21,000 cases of NHL attributable to HIV-AIDS in the USA (37% of all NHL) in the year 2002, while there were only some 14,000 AIDS deaths in total in 2001. This probably reflects availability of HAART in recent years: NHL incidence in HIV-infected people fell from 0.62% per year in the pre-HAART era (1992–1996) to 0.36% when HAART regimens were widely available (1996–1999).[5] Estimating HIV related NHL cases as 0.36% of the estimated HIV/AIDS cases at the end of 2001[7] give an estimated 3,420 cases in North America (5.5% of all NHL). The number of HIV related cases estimated for Eastern Europe (3,204) is a little lower than obtained using the first method of estimation.

The total estimate is for 36,000 cases in the year 2002 (Table VI).

HIV and other cancers

Hodgkin lymphoma. Several prospective studies suggest that the risk of Hodgkin lymphoma is increased some 10-fold in HIV-infected subjects.[74,76,100,103] Case series document unusually aggressive disease, including a higher frequency of the unfavourable histological subtypes (mixed cellularity and lymphocyte depleted), advanced stages and poor therapeutic response compared with the behaviour of HD outside of the HIV setting. It is not clear whether most or all of these cases of Hodgkin lymphoma are related to EBV, all of which cases have already been attributed to infection with this virus. A separate calculation of HIV-attributable cases has not been carried out.

HPV-associated cancers. HPV associated malignancies, most notably cancer of the cervix uteri and anal cancers, occur frequently in patients with HIV infection and AIDS.[104] In part, this may simply reflect the lifestyle factors associated with both infections—HIV-positive individuals are more likely to be infected by HPV. On the other hand, HIV may alter the natural history of HPV-associated oncogenesis through loss of immune control, facilitating infection with HPV or enhancing its persistence in cells and therefore increasing the development of squamous intraepithelial lesions (SIL). These cancers have already been attributed to infection with HPV.

HIV infection is associated with a 10-fold increase in the risk of conjunctival squamous cell carcinoma (SCC) in Africa. Several case-control studies have been completed in Africa, comparing prevalence of HIV infection in cases of SCC of the conjunctiva with that in control subjects.[105] All suggest a strong association with the estimated OR between 8 and 13. The association is confirmed in follow-up of cohorts of HIV-positive subjects in the USA.[75,106] High ambient solar ultraviolet radiation may act synergistically with HIV or potentiate the effects of the virus in promoting neoplastic transformation.

Summary: HIV-related cancer

Table VI suggests that some 102,000 cases of KS and NHL (0.9% of the world cancer burden) were caused by HIV or HHV-8 in 2002, and all but a few cases of endemic KS can be attributed to HIV.

Schistosomiasis

Schistosoma haematobium is considered to be carcinogenic to humans, with sufficient evidence for its role in causing carcinoma of the bladder.[11] The role of other schistosomes in human carcinogenesis is less clear. *S. japonicum* has been associated with an increased risk of liver cancer and of colo-rectal cancer, but most studies are flawed, and the IARC[11] appraisal was such that the evidence was 'limited'.

Five case-control studies of bladder cancer in which controls were properly matched to the cases with respect to age and sex allow the magnitude of the risk conferred by infection by *S. haematobium* to be estimated.[107–111] The estimated relative risk ranges between 1.8[111] and 23.5,[109] the consequence of imprecision of the estimates of infection, and the different type of exposure measures: from questionnaires, detection of eggs in urine and bladder wall calcification. As the available data on prevalence of Schistosomiasis relate to current infection (see later), a relative

TABLE VII – BLADDER CANCER CASES ATTRIBUTABLE TO INFECTION WITH *SCHISTOSOMA HAEMATOBIUM*

Area	Prevalence of *S. haematobium* (%)	Attributable fraction[1] (%)	Total cases	Attributable cases
East Africa	29.2	53.9	5,400	2,900
Middle Africa	30.3	54.8	600	300
Northern Africa	11.3	31.1	14,200	4,400
Southern Africa	10.2	29.0	1,980	600
Western Africa	32.6	56.6	3,400	1,900
Western Asia	1.2	4.6	10,300	500
Total				10,600

[1]Assuming RR = 5.

TABLE VIII – ESTIMATED NUMBERS OF CASES OF ATLL IN 2002

Area/country	Carriers (% of population)	Population (2002) age 40–79 (thousands)		Expected cases*		
		Male	Female	Male	Female	Both Sexes
Eastern Africa	1.5	19,957	21,816	300	160	460
Middle Africa	2.5	7,640	8,495	190	110	300
Northern Africa	0.1–0.5	19,524	20,423	60	40	100
Western Africa	2	18,986	19,989	380	200	580
East Asia: Taiwan	1.5	4,123	4,028	60	30	90
East Asia: Japan	1.2	29,567	31,677	360	190	550
Latin America	?1	60,190	66,363	600	330	930
Caribbean	3.5	5,207	5,730	180	100	280
Melanesia	5	660	652	30	20	50
World total		165,855	179,173	2,160	1,180	3,340

*Ages 40–79, assuming annual incidence in carriers of 0.1% in men 0.05% in women.

risk of 5 indicated by studies based on markers of current infection, such as eggs in urine, is assumed for the AF.

The average prevalence of *S. haematobium* infection in the world areas affected was calculated from country-specific data (mainly from population surveys in the early 1980s)[112] (Table VII). Using these prevalences and an estimated relative risk of 5, the percentage of bladder cancer cases and the absolute number attributable to Schistosomiasis can be estimated as 10,600, or about 3% of all bladder cancer cases (Table VII).

HTLV I and acute T-cell leukaemia/lymphoma (ATL)

Acute T-cell leukaemia/lymphoma (ATL) was first recognised as a distinct clinico-pathological entity in Japan in the 1970s.[113] The evidence for the causal role of Human T-cell leukaemia virus type I (HTLV-I) is compelling.[72] There is a close association of cases of the disease with presence of antibodies to HTLV-I, both geographically (with striking clustering in southern Japan) and in individuals (almost all cases are antibody-positive). All antibody-positive cases of ATL have monoclonally integrated HTLV provirus in the malignant cells.[114] The related syndrome, lymphosarcoma T-cell leukaemia in Caribbean patients is similarly linked to HTLV-I, as are a few cases of T-cell lymphomas in the US and elsewhere.[115]

Tajima and Hinuma[116] have reviewed information on the prevalence and epidemiology of HTLV worldwide and Verdier *et al.*[117] for Africa. After the initial observations of high prevalence of infection in southern Japan, it became evident that the virus could be detected in other areas, notably the Caribbean, West and Central Africa, in American Indian populations and in Melanesian populations of Australia and the Pacific. Table VIII shows the approximate prevalence of HTLV-I carriers in different regions.

Studies in Japan[118–121] suggest that the incidence of ATL in HTLV-I carriers is about 0.75–1.0 per 1,000 per year at ages 40–69 (the rate in men is about double that in women). In the Caribbean, where most of the cases present as lymphomas, incidence in carriers is estimated at 0.4–0.8 per 1,000 in men, and 0.2–0.8 per 1,000 in women.[122,123] ATL has been rarely identified in Africa, although this may be due to lack of diagnostic facilities, and there is presumably a similarly raised risk of ATL in HTLV-I carriers. The disease is rare in HTLV-I negative subjects, although it does occur.[124] Assuming that the incidence is 1 per 1,000 carriers in males and 0.5 per 1,000 carriers in females worldwide, the estimated number of cases (HTLV-I attributable cases of non-Hodgkin lymphoma) is 3,340 (Table VIII).

Liver flukes (opisthorchis and clonorchis)

The evidence for an association between chronic infection with liver flukes and the risk of cholangiocarcinoma of the liver (CCA) was evaluated by IARC in 1994.[11] *Opisthorchis viverrini* (OV), endemic in South East Asia, was considered definitely carcinogenic. Three studies (in Thailand) allow estimates of the relative risk associated with infection,[125–127] although the estimates are probably conservative, because of misclassification arising from nonspecificity of the antibodies for OV infection. For estimation purposes, the mean of the three observations (12) is taken as the relative risk of infection.

The evidence for the carcinogenicity of *Opisthorchis felineus* was considered insufficient for an evaluation, although there is clearly an increased incidence of cholangiocarcinoma in the endemic areas of Siberia, and a relative risk the same as for *O. viverrini* is assumed.

The epidemiological evidence relating infection with *Clonorchis sinensis* was judged limited by IARC;[11] it depends mainly upon autopsy series from Hong Kong and two case-control studies from Korea,[128,129] showing OR's of 6.0 and 2.7. For simplicity, the same figure as that for OV (12) is assumed.

The incidence of CCA in nonendemic areas of the world is rather low—the age-standardised rates generally lie between 1 and 2 in Asian populations.[130] Age specific rates for Japan were estimated using registry data for 1993–1997[4] and applied to the populations of countries where liver flukes were endemic in 1995[131] to estimate the crude incidence of CCA in the absence of infection (Table IX). Using the estimated infected populations in these countries,[131] the corresponding annual attributable cases can be calculated using formula (2) described in the Methods (population infected × rate in uninfected × excess relative risk in infected individuals (12 − 1 = 11).

TABLE IX – CASES OF CHOLANGIOCARCINOMA ATTRIBUTABLE TO LIVER FLUKE INFECTION

	Sex	Rate in uninfected (per 100,000)	Number infected (×100,000)	Annual attributable cases
Clonorchiasis				
China (incl Hong Kong, Macao)	Male	1.6	25	450
	Female	1.2	25	330
Korea	Male	1.6	5	90
	Female	1.4	5	80
Vietnam	Male	1.2	5	70
	Female	0.9	5	50
Opisthorchiasis				
Laos	Male	0.9	9	90
	Female	0.6	9	60
Thailand	Male	1.3	35	520
	Female	1.0	35	380
Ex-USSR	Male	2.2	8	190
	Female	2.2	8	200
Total				2,490

TABLE X – TOTAL INFECTION ATTRIBUTABLE CANCERS WORLDWIDE IN 2002: BY INFECTIOUS AGENT

Agent	Cancer	Number of cases	% of all cancers
H. pylori	Stomach	592,000	5.5
	Lymphoma	11,500	
HPV	Cervix	492,800	5.2
	Ano-genital	53,880	
	Mouth, pharynx	14,500	
HBV and HCV	Liver	535,000	4.9
EBV	Nasopharynx	78,100	1.0
	Hodgkin lymphoma	28,600	
	Burkitt lymphoma	6,700	
HIV/HHV-8	Kaposi sarcoma	66,200	0.9
	Non-Hodgkin lymphoma	36,100	
Schistosomes	Bladder	10,600	0.1
HTLV-I	ATL	3,300	0.03
Liver flukes	Liver	2,500	0.02
Total		1,932,800	17.8

The small total number (2,500 attributable cases of liver cancer) reflects the conservative estimates of relative risk. The estimated incidence of liver cancer in Thailand[2] is 50–100% higher than in other countries in South East Asia without infection by liver flukes, but with similar, or higher, prevalence of infection with hepatitis viruses (Philippines, southern Vietnam and Singapore). So, at least 5,000 of the estimated 15,000 annual cases of liver cancer in Thailand may be cholangiocarcinomas, related to fluke infestation, rather than the 900 or so suggested in Table IX.

Discussion

Worldwide an estimated 1.9 million cancer cases were attributable to infectious agents in 2002, representing 17.8% of all cancers (Table X). Most of this burden was related to viral infections (12.1%) with 5.6% related to infection with HP, and a very small proportion (about 0.1%) to the parasitic infections. The percentage of infection-attributable cancer is higher in developing countries (26.3%) than in developed countries (7.7%), reflecting the higher prevalence of infection with the major causative agents (hepatitis viruses, HPV, HP and HIV) (Table XI).

The results are dependent upon the assumptions made about relative risk, and prevalence of infection in the general population. Clearly, prevalence of infection with the main infectious agents is unknown in most of the world, and even when data are available—for example, for the hepatitis viruses—the samples in which prevalence was measured may not be entirely representative of the population from which the cancer cases are derived. A basic assumption is that a given infectious agent will impose the same relative risk on infected individuals worldwide (ignoring possible differences in the virulence of different strains, cofactors and genetic susceptibility). For some of the associations, especially in relation to HPV and ano-genital cancers, the estimate of AF was based upon the proportion of tumours in which the virus (as viral DNA) could be detected. The reason is mainly that prevalence of infection in the same tissues of normal individuals is usually unknown. This may overestimate AFs by including some cancer cases in which the presence of the virus was coincidental, without, for example, expressing viral oncoproteins. The estimate of HPV attributable cancers of the oral cavity and pharynx, on the other hand, makes use of data from the IARC multinational study[38] on prevalence of HPV16 E6 or E7 antibody in controls as well as cases, and the resulting AFs (3% for oral cancer, 12% for oropharynx) are, therefore, rather lower than the percentage of tumours with detectable HPV DNA (4 and 18%, respectively).

The estimate of 17.8% updates the previous one of 14.8% cancer attributable to infection in 1990.[1] The increased fraction results from the availability of more recent information on prevalence of infection with hepatitis viruses and HIV in different countries, as provided by WHO and UN AIDS, an assumption that the fraction of cervix cancer cases attributed to HPV is 100% rather than 88%. The risk associated with chronic infection with HP, previously assumed to be 2-fold, has also been set substantially higher (5.9). The infectious agents evaluated by IARC as definite or probable causes of human cancer (Groups I and 2A in the Monographs series) have remained more or less the same since that earlier estimate, with the exception that HHV-8 (KSHV) is now considered to be the probable cause of KS;[50] previously, epidemic KS cases had been ascribed to HIV infection.

The estimate of infection-attributable cancer is a conservative one. Several other associations between infections and human cancers, for which there is reasonable evidence for causality, have not been taken into account. EBV has been detected in several types of cancer, other than those attributed to it in this article,[132] with the

TABLE XI – TOTAL INFECTION ATTRIBUTABLE CANCERS IN DEVELOPING AND DEVELOPED COUNTRIES IN 2002: BY TYPE OF CANCER

Site	Developed countries				Developing countries			
	Total cancers	Agent	Attributable cancers	% cancer	Total cancers	Agent	Attributable cancers	% cancer
Liver	110,400	HBV, HCV	48,000	1.0	513,100	HBV, HCV	475,000	8.2
		Flukes	0			Flukes	2,500	
Cervix	83,400	HPV	83,400	1.7	409,400	HPV	409,400	7.0
Stomach	311,200	H. pylori	192,000	3.8	619,200	H. pylori	400,000	6.9
Kaposi sarcoma		HIV/HHV8	3,700	0.1		HIV/HHV8	62,500	1.1
Non-Hodgkin		H.pylori	5,600			H.pylori	5,900	
lymphoma	151,100	EBV(B.L.)	100	0.2	149,200	EBV(B.L.)	6,600	0.7
		HIV	9,300			HIV	26,800	
		HTLV-I	550			HTLV-I	2,790	
Ano-genital cancer	38,000	HPV	22,450	0.4	58,700	HPV	31,430	0.5
Nasopharynx cancer	7,200	EBV	6,500	0.1	72,600	EBV	71,600	1.2
Mouth and oropharynx	115,500	HPV	5,600	0.1	210,700	HPV	8,800	0.2
Hodgkin lymphoma	28,000	EBV	11,500	0.2	34,300	EBV	17,100	0.3
Bladder	225,200	Schistosomes	0	0.0	131,000	Schistosomes	10,600	0.2
All cancer	5,016,000		389,000	7.7	5,828,000		1,527,000	26.3

most suggestive evidence implicating it in the aetiology of gastric cancer. EBV can be detected in the tissue of about 10% of gastric carcinoma cases throughout the world, and in these cases, 100% of carcinoma cells are infected with EBV and the viral genome is monoclonal;[133] antibody titres to EBV are significantly higher in subjects who later develop EBV-associated gastric cancer than in control subjects (or those subsequently developing non-EBV-associated gastric cancer).[134] A link between infection with HCV and B-cell non-Hodgkin lymphoma has been observed in many retrospective case control studies, although there is some inconsistency in results from different countries.[135,136] It does seem likely that *Chlamydia trachomatis* infection increases the risk of developing squamous cell carcinoma of the cervix.[137] In any case, no case of cancer has been attributed to more than one infectious agent, and so the numbers of infection-attributable cases can be calculated for different populations. Thus, for example, the risk of cancer of the cervix uteri may be increased by HIV infection[73] as well as *C. trachomatis*, but as all cases are attributed to HPV, none are included as HIV-related cancers. In addition, the estimates of relative risk for those associations accepted as causal that have been used in the calculations are deliberately modest. For example, the relative risk of liver cancer due to infection with hepatitis B is based on measurement of serum HBsAg. However, viral DNA can be found in many liver cancers without evidence of infection based on HBs antigenaemia or antibody to HCV.[138] It is possible that the relative risk of noncardia gastric cancer in relation to infection with HP that was used (5.9) may be too modest; some authors consider that the infection may be responsible for all noncardia gastric cancers, possibly by a 'hit and run' mechanism.[139] Accepting that all noncardia gastric cancers are caused by infection (HP or EBV) as well as 10% of NHL caused by HCV (independent of HIV)[136] would not, however, greatly change the overall estimate (19.7% of cancer due to infectious agents worldwide).

The AF is a measure that provides an indication of the proportion of a particular cancer that would be avoided if the responsible agent were eliminated (or the human organism was no longer susceptible to it). So far, there is little direct evidence for the effect of eliminating infection on cancer incidence. Effective vaccines are available against hepatitis B infection, and two trials to quantify the effectiveness of vaccination against hepatitis B in preventing liver cancer have been established;[140,141] so far they have shown that vaccination effectively prevents the chronic carrier state. Vaccination against HBV has been introduced in many countries.[142] A reduction of the incidence of hepatocellular carcinoma in children was observed in Taiwan 8 years after the introduction of mass vaccination of new-borns against HBV.[143]

Vaccines against other viral infections are currently under development. Phase II studies of vaccines against the oncogenic HPV types 16 and 18 have demonstrated a high degree of efficacy in preventing infection with these viruses and the development of cervical neoplasia.[144–146] The first results of one of the ongoing large phase III efficacy trials[147] have confirmed these optimistic preliminary results. As HPV 16 and 18 are the dominant types involved in cervical cancer aetiology in all parts of the world, a vaccine against these two types should, in theory, be able to prevent some 70% of cases of cancer.[148]

In theory, eradication of HP is possible by combinations of antibiotic treatment. Although there is some evidence that this could be a cost-effective strategy for prevention of gastric cancer and other HP-related disease,[149,150] the reduction in gastric cancer incidence in the one randomised trial so far reported[151] was nonsignificant. Other trials currently under way, as well as additional cost-effectiveness studies, are needed before decisions about the desirability of embarking on large-scale medication of the population becomes clearer.[152] In the meantime, the challenge of producing a satisfactory vaccine may have provided a more acceptable solution. It seems clear that we shall probably see quite rapid progress in the primary prevention of these important cancers.

Summary

An estimated 17.8% (1.9 million cases) of the worldwide incidence of cancer in 2002 can be attributed to infection with the bacterium HP, several viruses (hepatitis B and C viruses, the Human Papillomaviruses, EBV, HIV, HHV-8 and HTLV-I), schistosomes or liver flukes. There would be 26.3% fewer cancers in developing countries (1.5 million cases per year) and 7.7% in developed countries (390,000 cases) if these infectious diseases were prevented. The AF at the specific sites varies from 100% of cervix cancers attributable to the papilloma viruses to a tiny proportion (0.4%) of liver cancers (worldwide) caused by liver flukes.

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