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Cancers attributable to infection in the UK in 2010

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The infectious agents that have been identified as definitely or probably carcinogenic to humans (Groups 1 and 2A) in the International Agency for Research on Cancer (IARC) monograph series are shown in Table 1. They include hepatitis B (HBV) and C (HCV) viruses, human papillomaviruses (HPV), human immunodeficiency virus (HIV) and T-lymphotropic virus type-1 (HTLV-1), Epstein – Barr virus (EBV) and human herpesvirus 8 (HHV8), and the bacterium *Helicobacter pylori*.

In addition to these associations, there is substantial evidence for a causative relationship between chronic infection with hepatitis C virus (HCV) and non-Hodgkin lymphoma (NHL), an association that has been the subject of several recent systematic reviews (Gisbert *et al*, 2003; Matsuo *et al*, 2004; dal Maso and Franceschi, 2006).

METHODS

Attributable fractions

For most infections, calculation of the population-attributable fraction (PAF) relies on the classic formula for population-attributable risk (Cole and Macmahon, 1971):

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

where r represents the relative risk of exposure, and p its prevalence in the population. The formula results in a proportion that is applied to the total number of incident cases in the UK population, to obtain the number of cases that can theoretically be attributed to the factor in that population (PAF). Its application requires identification of data on the prevalence of the exposure to the 'causative' agents in the UK population, as well as the corresponding relative risks. This method is used to estimate the number of cancers due to HBV, HCV, *H. pylori* and HIV (NHL).

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

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For the oncogenic HPVs, it is generally accepted that almost all cancers of the cervix uteri are the result of infection (Walboomers *et al*, 1999), so the AF is 100%. At other sites, the prevalence of infection in normal subjects is hard to define, 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.

RESULTS

Human papillomavirus

IARC (2005) 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 (Walboomers *et al*, 1999).

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. In order to estimate attributable fractions, therefore, 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 (Daling *et al*, 2002; IARC, 2005); an overall HPV prevalence of 63% is assumed. About 20 – 50% of vulvar cancers contain oncogenic HPV DNA (Madeleine *et al*, 1997; Herrero and Munoz, 1999), 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 (Trimble *et al*, 1996); an overall HPV prevalence of 40% 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 (Frisch *et al*, 1999), and an AF of 90% is assumed. For penile cancer, HPV DNA was found in 30% of 71 cases of penile cancer from Brazil (Bezerra *et al*, 2001) and in 42% of 148 cases from the USA and Paraguay (Rubin *et al*, 2001); the AF is assumed to be 40%.

HPV has a role in the aetiology of a fraction of cancers of the oral cavity and pharynx (Shah, 1998), although the major risk factors are tobacco and alcohol. A review of more than 5000 tumours of the upper aerodigestive tract (Kreimer *et al*, 2005a) found that prevalence of HPV DNA in specimens from Europe was 16.0% (95% CI, 13.4–18.8) for oral cancers, 28.2% (95% CI, 24.4–32.2) for tumours of the oro-pharynx and 21.3% in squamous cell carcinomas (SCCs) of the larynx. However, HPV may not be of aetiological relevance in all such cases. Van Houten *et al* (2001) found that only 45% of DNA-positive cases showed E6 mRNA expression, indicative of viral activity. Kreimer *et al* (2005b) observed that about 50% of head and neck cancers had a high viral load of HPV, and serologic antibodies to HPV16 virus-like particles and HPV16 E6 and E7 proteins were detected in most of these cases. We assume therefore that 8% oral cancers, 14% oropharyngeal cancers and 10.6% laryngeal cancers are HPV-related.

HPV (any type) is estimated to be responsible for 5088 cancers occurring in the UK in 2010 (1.6% of all cancers), comprising 2691 cervix cancers, 1685 cases of ano-genital cancer and 712 cases of upper aerodigestive tract cancer (Table 2).

Table 1 Major human infection-associated malignancies

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

Abbreviations: EBV = Epstein–Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HHV8 = human herpesvirus 8; HPV = human papillomavirus; HTLV-I = human T-cell lymphotropic virus type I. From Mueller *et al* (2005).

Helicobacter pylori

Helicobacter pylori was classified as being carcinogenic for humans in 1994 (IARC, 1994a). It is considered to be causally associated with both carcinoma of the stomach and gastric lymphoma.

Surveys of *H. pylori* show that prevalence gradually increases with age. Several studies have suggested that this represents a birth-cohort effect, with infection becoming progressively less common in recent generations (Banatvala *et al*, 1993; Kosunen *et al*, 1997; Roosendaal *et al*, 1997). In the UK the most comprehensive data on prevalence derive from the serological surveys of 10 000 serum samples collected in England and Wales in 1986 and 1996 (Vyse *et al*, 2002). Prevalence was related to decade of birth and increased from 4% in those born during the 1980s to 30% in those born before 1940; analysis by decade of birth showed no significant difference between samples collected in 1986 and 1996. Estimated prevalence of active infection varied by region and was highest in London.

We estimated prevalence in the UK population in 2000 from the data provided by Vyse *et al* (2002), assuming that prevalence in Scotland and Northern Ireland was the same as that observed in the North of England (Figure 1).

Gastric carcinoma The most satisfactory evidence on the magnitude of the risk is from prospective studies. Retrospective case–control studies are limited in observing *H. pylori* infection after the development of cancer. *H. pylori* tends to disappear as intestinal metaplasia and atrophy develop, so that prevalence of infection may be seriously under-estimated in cases, even if anti-*H. pylori* 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. In a meta-analysis by the Helicobacter and Cancer Collaborative Group (2001), including 12 prospective studies yielding 1228 gastric cancer cases, the OR for the association between *H. pylori* infection and the subsequent development of gastric cancer was 2.36 (95% CI 1.98–2.81). Analysing cancers of the gastric cardia, the most proximal portion of the stomach and non-cardia separately, they found no increase in risk for cardia cancers (OR 0.99), while the overall risk for non-cardia cancers was 2.97 (95% CI 2.34–3.77). The risk varied with the interval

Table 2 Estimated numbers of HPV-related cancers, UK (2010)

	Observed cases		HPV-related		
	Male	Female	Male	Female	Excess attributable cases (PAF)
Upper aerodigestive cancers					
Cervix uteri		2691		2691	2691 (100)
Oral cavity	2284	1421	183	114	296 (8.0)
Oropharynx	981	323	138	45	184 (14.1)
Larynx	1803	386	191	40	232 (10.6)
Anogenital cancers					
Anus	364	621	328	559	887 (90.0)
Vulva		1128		451	451 (40.0)
Vagina		251		157	157 (62.5)
Penis	475		190		190 (40.0)
Total (8 sites)	5907	6821	1030	4058	5088 (40.0)

Abbreviations: HPV = human papillomavirus; PAF = population-attributable fraction (%).

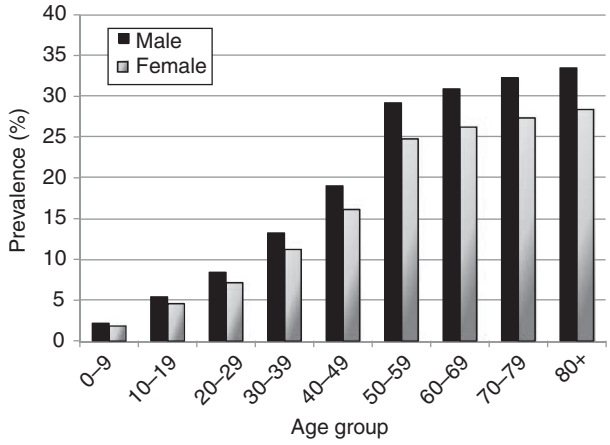

Figure 1 Estimated prevalence of *Helicobacter pylori* in the UK in 2000.

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% CI 3.4–10.3) for *H. pylori* 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 with elsewhere in the stomach, can be estimated from cancer registry data from England (2007), and from the results of 11 registries throughout the UK in 1998–2005 (Curado *et al*, 2007). In both sets, a variable proportion of gastric cancer cases (40–65%) are registered without specification of subsite. However, fitting a linear regression model of the proportion of cardia cancers *vs* the proportion of unspecified registrations suggests that mis-specification of site is more or less random. The predicted proportion of cardia cancers (with zero non-specification) is 51.9% in men and 38.9% in women. Age-specific proportions in the UK were estimated based on the distribution by age in England (2007).

With a relative risk of 5.9 and prevalence of infection in 2000 (10 years earlier) as shown in Figure 1, the attributable fraction of non-cardia gastric cancer cases in 2010 is 61% in men and 59% in women. This represents 2231 cases, 29.2% of all stomach cancers in men and 36.0% in women, or 0.7% of all cancers.

Gastric lymphoma One of the two large American cohort studies of *H. pylori* also examined the incidence of gastric NHL and found that these cases showed elevated titres of antibody to *H. pylori* (Parsonnet *et al*, 1994). The relative risk was 6.3 (95% CI 2.0–19.9). Gastric NHL is rather a rare tumour, comprising about 5% of all NHL (Newton *et al*, 1997).

Assuming that 5% of NHL cases in UK are localised to the stomach, there were about 580 new cases in 2010. With a relative risk of 6, and the estimated prevalence of infection in 2000 (Figure 1), 2.8% of NHL cases (327) would be attributable to *H. pylori*.

Epstein–Barr virus

EBV is considered to be a group I carcinogen by IARC (1997), with conclusive evidence with respect to carcinogenicity in Burkitt lymphoma, NHL 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 NHL *Burkitt lymphoma*: Burkitt lymphoma is a rare cancer in UK. There were an estimated 158 new cases in 2010. In North America and Europe, about one-fifth to one-third have demonstrable virus in tumour tissue, or elevated antibody titres to EBV (Lenoir *et al*, 1984; Gutierrez *et al*, 1992). The numbers of EBV-attributable Burkitt lymphoma cases in UK is therefore about 39.

Other NHL: EBV can cause lymphoproliferative diseases in individuals with immune dysfunction (Lenoir and Delecluse, 1989). Lymphomas arising in immunocompromised individuals are relatively rare, except in the case of AIDS, some of which are associated with EBV. The proportion of AIDS-related lymphomas is estimated in the context of HIV-related cancers (below). The proportion of NHLs that occur in immunocompromised individuals, excluding AIDS (hereditary, syndromes, iatrogenic), or are cases of the rare EBV-associated sino-nasal angiocentric T-cell lymphoma, is impossible to estimate. It must be a very small ($<1\%$) fraction of NHLs, 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 (Evans and Gutensohn, 1984). In a large prospective study, Mueller *et al* (1989) 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 acids in 25–50% of Hodgkin lymphomas, where it is located in the Reed–Sternberg cells (Weiss *et al*, 1989; Armstrong *et al*, 1992). The association with EBV appears to depend upon age. In the childhood age range about 80% of cases are EBV positive (Weinreb *et al*, 1996), whereas in young adults the proportion is about 15% (Jarrett *et al*, 1991). In older age groups, EBV positivity appears to be relatively high (70–75%) (Jarrett *et al*, 1991; Gledhill *et al*, 1991). In part, this pattern is determined by the frequency of different histological subtypes of Hodgkin lymphoma. The mixed cellularity subtype predominates in childhood, while the nodular sclerosing subtype accounts for the marked peak in young adults. The frequency of EBV positivity is much greater (5–15-fold) in mixed cellularity than in nodular sclerosing Hodgkin lymphoma. Nevertheless, it seems that, even allowing for cell type, age (more childhood cases are EBV positive) and level of socio-economic development are independent predictors of the association (Glaser *et al*, 1997). For the purposes of estimation, the attributable fraction at ages 0–14 is taken to be 80%, 20% at ages 15–44, and 70% at ages >45. Of the UK total of 1709 new cases in 2010, 773, or 45.2% of the total, are estimated to be EBV related.

EBV and nasopharyngeal carcinoma The involvement of EBV in nasopharyngeal cancer (NPC) appears to be with undifferentiated carcinomas of the nasopharynx. In low-risk areas, about 10–25% of NPC is of type 1 (keratinising), which is less often infected. It is assumed that 90% of cases of the estimated 446 NPC cases occurring in the UK in 2010 are infected, a total of 401 cases, or 5.8% of all cancers or of the oral cavity and pharynx.

Summary: EBV EBV is the third most important cancer-causing infection in the UK, responsible for an estimated 1213 cases in 2010 (0.4% of cancers), comprising 773 cases of Hodgkin disease, 401 nasopharyngeal cancers and 39 Burkitt lymphoma cases.

Hepatitis viruses

The role of chronic infection with the viruses of hepatitis B and C in the aetiology of liver cancer is well established (IARC, 1994b). More recently, on the basis of a substantial number of case–control and cohort studies, an association between HCV and NHL

has been demonstrated (Gisbert *et al*, 2003; Matsuo *et al*, 2004; dal Maso and Franceschi, 2006).

Prevalence of hepatitis B surface antigen (HBsAg) positivity and HCV antibodies in the serum of the general population of UK is unknown, as no true random survey results exist. Age-specific prevalence is published for first-time blood donors (subjects found to be positive are obviously excluded from becoming repeat donors), although these are healthy individuals, with a prevalence much lower than the average in the population. An estimate of the prevalence of hepatitis C in adults (aged 15–59), based on a model incorporating all relevant samples, was made for England in 2003 (HPA, 2006); this estimate had not been updated by the end of 2010. These data were assumed for UK, with an estimate of prevalence at ages >60 based on sero-surveys of laboratory samples in England and Wales in the 1990s (Balogun *et al*, 2002).

For hepatitis B, the estimated population prevalence, based on sero-surveys of laboratory samples in England and Wales in 1996 (Gay *et al*, 1999), was used to adjust the observed age–sex-specific prevalence data from blood donors in England in 1995–2008 (HPA, 2009), and further adjusted upwards, to allow for the rather higher prevalence in blood donors in UK, compared with those in England (HPA, 2009).

The estimated prevalences are shown in Figure 2.

HBV and HCV and liver cancer The IARC Monograph (1994b) summarises the results of some 15 cohort studies and 65 case–control studies worldwide, examining the association between seropositivity for HBsAg, indicating chronic infection with HBV, 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 Monograph (1994b) overall evaluation assessed HBV as carcinogenic to humans. A recent meta-analysis by Cho *et al* (2011) found an odds ratio for mono-infection with a HBV of 13.5 for all 47 studies included, and 20.3 for the four studies in low-prevalence areas (such as UK). A relative risk of 20 is assumed in the current analysis.

The magnitude of the risk of liver cancer associated with chronic 'infection' with HCV 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 meta-analysis of studies, Donato *et al* (1998) estimated the relative risk in HCV antibody-positive subjects who were HBsAg negative as 17.3. The more recent meta-analysis by Cho *et al* (2011) found an odds ratio of 23.8 in seven studies from low-prevalence countries. We assume a relative risk of 20 for HCV infection.

Assuming relative risks of chronic infection by these viruses of 20, and that joint infection by both HBV and HCV is very rare, we estimate the fraction of liver cancers attributable to the two viruses to be just 15.9% (567 of 3568 cases). This represents 0.18% of cancers in the UK in 2010.

HCV and NHL At least three meta-analyses (Gisbert *et al*, 2003; Matsuo *et al*, 2004; dal Maso and Franceschi, 2006) have been conducted to evaluate the strength of the relationship between HCV and NHL. The most recent of these (dal Maso and Franceschi, 2006) gives a rather lower estimate for the relative risk (2.5) than the earlier studies. However, as it considered all NHL (not just B-cell neoplasms) and took into account differences in age between cases and controls, it is probably the most valid estimate. A recent report pooling the results of seven case–control studies (de Sanjose *et al*, 2008) gave a similar result (odds ratio of 1.8). Using the value of 2.5, and the estimated prevalence of HCV infection in the UK in 2010 (Figure 2), one can estimate the fraction of NHL attributable to HCV as just 0.5% (53 of 11 602 cases).

HIV and HHV8

In 1996, an IARC working group concluded that HIV was carcinogenic to humans, an assessment based on the strong link between infection with the virus and two cancers: Kaposi sarcoma (KS) and NHL (IARC, 1996). 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 (CDC, 1992). Subsequently, increased risks for several other cancers have been reported. The most convincing data come from a 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 (Goedert *et al*, 1998; Frisch *et al*, 2001; Grulich *et al*, 2002).

The evaluation by IARC (1997) 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 (Boshoff and Weiss, 2001). The effect of HIV is probably through immunosuppression – allowing HHV-8 to escape control and thereby increasing viral load, for example.

HIV/HHV8 and KS Prior to the epidemic of HIV/AIDS, KS was a very rare cancer in the UK. Grulich *et al* (1992) calculated the incidence in England and Wales in 1971–80 as 0.14 per million (same in males and females).

Because of the enormous increase in risk in subjects infected with HIV (1000–5000 times the risk in the general population (Serraino *et al*, 1997)), the increasing incidence of KS was the first obvious manifestation of the AIDS epidemic. Before 1990, up to a third of AIDS cases developed KS at some point (Hoover *et al*, 1993; Lundgren *et al*, 1995). The introduction of antiretroviral therapy (HAART) for treating HIV in adults has caused a decline in the incidence of KS in Western countries (International Collaboration on HIV and Cancer, 2000); 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 1990–1 to 2.4 in 2000–2001 (Ries *et al*, 2004).

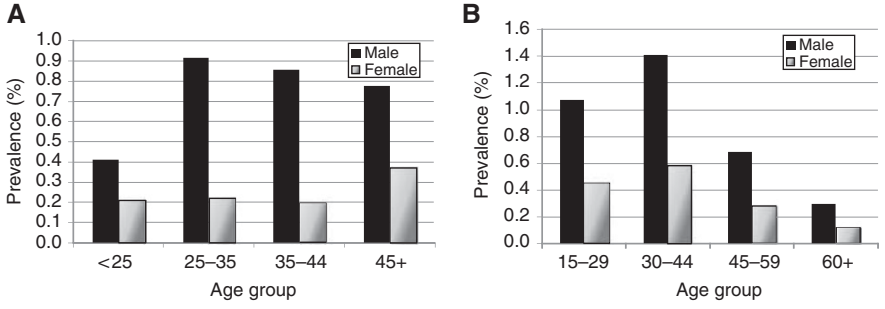

Figure 2 Estimated age- and sex-specific prevalence of carriers of (**A**) HBsAG and (**B**) anti-HCV antibodies in the UK.

The estimated number of KS cases in UK in 2010 is 172. All might be ascribed to infection with HHV-8. Based on the rates in the pre-AIDS era (Grulich *et al*, 1992), the number of cases expected was 10. The difference (162 cases) is considered to be attributable to HIV infection, while all cases of KS are attributable to infection with HHV-8.

HIV and NHL The increased frequency of NHL in AIDS was noted in 1982 (Ziegler *et al*, 1982). Since then, the elevated risk has been confirmed in studies in the United States and Europe (Casabona *et al*, 1991; Beral *et al*, 1991). 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*. (1997) estimated the excess risk in AIDS to be about 160 times that in HIV-negative subjects. Risk is highest for high-grade lymphomas; especially diffuse immunoblastic (relative risk = 630) and undifferentiated Burkitt lymphomas (relative risk = 220). Extra nodal lymphomas are more common in AIDS than usual (Beral *et al*, 1991), although it is probably because of the great excess of CNS lymphomas (15-fold increase); other extra nodal lymphomas are not in excess (Coté *et al*. 1997). Males are more commonly affected – but it could be that this is simply because of risk-group differences.

EBV is present in two-thirds of AIDS-related lymphomas (Hamilton–Dutoit *et al*, 1993) and may have an important role in lymphomagenesis (IARC, 1996, 1997). 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/Burkitt-type lymphomas.

The availability of HAART in recent years has resulted in a decline in the risk of NHL in HIV-infected individuals; it fell from 0.62% per year in the pre-HAART era (1992–1996) to 0.36% when HAART regimens were widely available (1996–1999) (International Collaboration on HIV and Cancer, 2000). In the USA, cohort studies suggest that the relative risk of NHL in HIV-positive subjects since the introduction of HAART is about 6.5 (Hessol *et al*, 2004; Engels *et al*, 2008), and this figure is used to estimate the attributable fraction.

The overall prevalence of HIV infection in the UK in 2009 was estimated to be 2.89 per 1000 in men aged 15–59 and 1.46 per 1000 in women (HPA, 2010). Prevalence in childhood and those over 60 is much lower: 0.09 and 0.46 per 1000, respectively (HPA, 2010; UK CGHSS, 2006).

Based on these estimated prevalences, and a relative risk of 6.5, only 52 cases of NHL in men and 16 in women (69 total) would have been attributable to HIV in 2010. The numbers seem small, but they are broadly in line with the numbers of cases expected based on observed incidence rates of NHL in HIV-positive subjects in recent years – for example, 1.8 per 1000 in the Swiss cohort in 2002–6 (Polesel *et al*, 2008) and 0.97 in three US states in 1996–2002 (Engels *et al*, 2008). With these rates, 120 cases of NHL would have occurred in HIV-positive subjects in the UK, compared with 11 expected, an excess of 109.

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 (Goedert *et al*, 1998; dal Maso *et al*, 2001; Grulich *et al*, 2002). 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 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 (Frisch *et al*, 2000). 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 has been found to be associated with an increased risk of conjunctival SCC in follow-up of cohorts of HIV-positive subjects in the USA (Goedert and Coté, 1995; Frisch *et al*, 2001). With a relative risk of 10, about 1% of cases might be attributable to HIV, given the prevalence of infection in the UK. As only 23 cases of conjunctival cancer were registered in England in 2007, the number of attributable cases is ignored.

Summary: HIV-related cancer In all, 172 cases of KS and 69 cases of NHL were caused by HIV and/or HHV-8 in 2010. Of the KS cases, 162 are attributed to infection with HIV.

Human T lymphotropic virus

The evidence for the causal role of HTLV-1 in acute T-cell leukaemia/lymphoma (ATL) is compelling (IARC, 1996). Prevalence of HTLV infection in UK is available for first-time blood donors (HPA, 2009). Overall, it is 4.7 per 100 000 in men and 10.7 per 100 000 in women, strongly increasing with age. Based on the recorded incidence of ATL (ICD 91.5) in England in 2007, 25 cases would have been expected in the UK population.

Summary

Table 3 summarises the quantification of cancers attributable to infections in the UK in 2010. The estimate is 3925 (2.5% of all cancers) in men and 5820 (3.7% of all cancers) in women. Of the total of 9745, the infectious agents making the largest contribution are HPV (5088 cases, 1.6% of all cancers), *H. pylori* (2559 cases, 0.8%) and EBV (1213 cases, 0.4%).

The cancers for which an infectious aetiology is most important are cervix uteri (2691 cases in 2010), stomach (2231) and the upper aerodigestive tract (mouth, pharynx and larynx – 1113 cases).

DISCUSSION

Worldwide, 17.8% of all cancers are attributable to infections (Parkin, 2006), with a higher percentage in developing countries (26.3%), and an average of 7.7% in developed countries reflecting the higher prevalence of infection with the major causative agents (hepatitis viruses, HPV, *H. pylori*, HIV). The proportion in the UK is around half of the average for developed countries, and very similar to the estimate (3.5%) for the Netherlands (van Lier *et al*, 2008).

The results are dependent on the assumptions made about relative risk, and accuracy of the estimates of prevalence of infection in the general population. For some of the associations – especially in relation to HPV and anogenital cancers – the estimate of attributable fraction was based on 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 attributable fractions, 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, pharynx and larynx attempts

Table 3 Estimated numbers of cancers attributable to different infectious agents, UK 2010

	Estimated number of cancer cases by infectious agent						
Cancer site	**HPV**	***H. pylori***	**EBV**	**HBV and HCV**	**HIV and KSHV**	**HTLV**	**Excess attributable cases (PAF)**
Males							
Oral cavity and pharynx	321		241				562 (0.35)
Larynx	191						191 (0.12)
Stomach		1304					1304 (0.82)
Anus	328						328 (0.21)
Liver				446			446 (0.28)
Kaposi					147		147 (0.09)
External genitalia	190						190 (0.12)
Non-Hodgkin lymphoma		182	31	38	52	12	316 (0.20)
Hodgkin lymphoma			442				442 (0.28)
Total	1030	1486	713	484	200	12	3925
% of all cancer[a]	0.65	0.94	0.45	0.31	0.13	0.01	2.5%
Females							
Oral cavity and pharynx	159		160				319 (0.21)
Larynx	40						40 (0.03)
Stomach		927					927 (0.60)
Anus	559						559 (0.36)
Liver				121			121 (0.08)
Kaposi					25		25 (0.02)
Cervix uteri	2691						2691 (1.73)
External genitalia	608						608 (0.39)
Non-Hodgkin lymphoma		145	9	14	16	13	197 (0.13)
Hodgkin lymphoma			331				331 (0.21)
Total	4058	1072	501	135	41	13	5820
% of all cancers[a]	2.61	0.69	0.32	0.09	0.03	0.01	3.7%
Persons							
Oral cavity and pharynx	480		401				881 (0.28)
Larynx	232						232 (0.07)
Stomach		2231					2231 (0.71)
Anus	887						887 (0.28)
Liver				567			567 (0.18)
Kaposi					172		172 (0.05)
Cervix uteri	2691						2691 (0.86)
External genitalia	798						798 (0.25)
Non-Hodgkin lymphoma		327	39	53	69	24	513 (0.16)
Hodgkin disease			773				773 (0.25)
Total	5088	2559	1213	619	241	24	9745
% of all cancers[a]	1.62	0.81	0.39	0.20	0.08	0.01	3.1%

Abbreviations: EBV = Epstein–Barr virus; *H. pylori* = *Helicobacter pylori*; HBV and HCV = hepatitis B and C viruses; HIV and KSHV = human immunodeficiency virus and human herpesvirus 8/Kaposi sarcoma; HPV = human papillomaviruses; HTLV = human T lymphotropic virus type 1; PAF = population-attributable fraction. [a]Excluding non-melanoma skin cancer.

to compensate for this, by estimating the number of aetiologically relevant infections (expressing E6 and E7 proteins, for example).

The estimate of infection-attributable cancer is a conservative one. Some 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 analysis, with the most suggestive evidence implicating it in the aetiology of gastric cancer (Takada, 2002; Herrmann and Niedobitek, 2003). *Chlamydia trachomatis* infection has been shown to increase the risk of developing SCC of the cervix (Smith *et al*, 2004). In any case, no case of cancer has been attributed to more than one infectious agent, so that 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 (Frisch *et al*, 2001) 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 (Paterlini *et al*, 1990). The relative risk of non-cardia gastric cancer in relation to infection with *H. pylori* that was used (5.9) may also be too modest; more sensitive techniques for estimating the presence of *H. pylori* (for example, by detecting bacterial DNA) have much higher relative risks (Mitchell *et al*, 2008), but as the prevalence estimates are based on the presence of anti-*H. pylori* antibody, we use the relative risk estimates based on the same techniques. Accepting that all non-cardia gastric cancers are caused by infection (*H. pylori* and/or EBV) as well as 10% of NHL are caused by HCV (independent of HIV) would not, however, greatly change the overall estimate.

See acknowledgements on page Si.

Conflict of interest

The author declares no conflict of interest.

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