

Cancers in Australia in 2010 attributable to infectious agents

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In its 2009 review of the carcinogenicity of infectious agents, the International Agency for Research on Cancer (IARC) found sufficient evidence to conclude that seven viruses (human papillomavirus [HPV], Epstein-Barr virus [EBV], hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus, type 1 [HIV-1], Kaposi's sarcoma herpes virus [KSHV] and human T-cell lymphotropic virus, type-1 [HTLV-1]) caused cancer in humans.¹ In addition, the bacterium *Helicobacter pylori* (*H. pylori*) and the parasites *Clonorchis sinensis*, *Opisthorchis viverrini* and *Schistosoma haematobium* were also declared Group 1 carcinogens by IARC.¹ The global cancer burden attributable to these infectious agents was estimated to be about 2 million cases in 2008 or 16.1% of new cancer cases.² The majority of these cancers occurred in less-developed regions of the world, where the population attributable fraction (PAF) was estimated to be 23%.² In more developed regions, such as North America and Australia/New Zealand, the estimated PAF was much lower at 4.0% and 3.3%, respectively.² The only Australasian PAFs calculated previously² were for Australia and New Zealand combined and they applied a PAF method for some infectious agents (*H. pylori*, Hepatitis B and C) that used world and Oceanic region prevalence of infectious agents in cases. Here, we present estimates for the fractions of cancer attributable to infectious agents solely for the Australian population using, for most agents but not all, prevalence of infection from Australian population-based surveys. We

Abstract

Objectives: To estimate the proportion and numbers of cancers in Australia in 2010 attributable to infectious agents.

Methods: The population attributable fraction (PAF) and number of cancers caused by hepatitis B and C viruses (HBV, HCV), *Helicobacter pylori* and human immunodeficiency virus (HIV) were calculated using standard formulae incorporating prevalence of infection in the Australian population, the relative risks associated with that infection and cancer incidence. For cancers with very strong associations to the infectious agent (Epstein-Barr virus [EBV], human papillomavirus [HPV] and HIV/Kaposi's sarcoma herpes virus [KSHV]), calculations were based on viral prevalence in the tumour.

Results: An estimated 3,421 cancers (2.9% of all cancers) in Australia in 2010 were attributable to infections. Infectious agents causing the largest numbers of cancers were HPV (n=1,706), *H. pylori* (n=793) and HBV/HCV (n=518). Cancer sites with the greatest number of cancers caused by infections were cervix (n=818), stomach (n=694) and liver (n=483). Cancers with highest proportions attributable to infectious agents were Kaposi's sarcoma (100%), cervix (100%), nasopharynx (87%), anus (84%) and vagina (70%).

Conclusions: Infectious agents cause more than 3,000 cancers annually in Australia.

Implications: Opportunities for cancer prevention through infection control are considerable, even in a 'first world' nation like Australia.

Key words: population attributable fraction, cancer, risk factor, infection

assessed all the infectious agents identified by IARC as Group 1 carcinogens, except *Clonorchis sinensis*, *Opisthorchis viverrini* and *Schistosoma haematobium*, which are not endemic to Australia.

Methods

Several approaches to calculating PAFs were used for these exposures, depending upon the nature of the infection, strength of association and presumed causal mechanism.

For EBV and HPV, where "... mechanistic knowledge strongly suggests that the

presence of infection in a cancer is sufficient to infer that infection caused the cancer"² the PAF was assumed to be equivalent to the prevalence of viral DNA in tumour cells. The number of excess cancers attributed to the infectious agent was calculated as follows:

$$\text{No. of excess cancers} = P_{\text{cases}} * I_x$$

where P_{cases} is the prevalence of the viral DNA (i.e. EBV or HPV) in tumour cells and I_x is the observed incidence of cancer.

Estimates of the prevalence of EBV and HPV DNA in tumour cells for specified cancer sites

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are presented in Table 1. We predominantly used estimates from meta-analyses as most individual studies, including those from Australia,³⁻⁵ were relatively small and not population-based. For cancers of the oral cavity and oropharynx (including tonsil), HPV was considered causal when both HPV DNA and p16 protein were present in the tumour cells using prevalence data from a systematic review and meta-analysis⁶ (Table 1). Sensitivity analysis for cancers of the oral cavity was also conducted using the prevalence of HPV DNA positive and E6/E7 mRNA positive cases.

Kaposi's Sarcoma Herpes Virus (KSHV) is recognised as a necessary cause of Kaposi's Sarcoma, and thus the population attributable fraction is 100%. However, HIV is a co-factor for many cases of Kaposi's sarcoma; to estimate the number of HIV-related Kaposi's sarcoma cases, we used historical incidence rates of Kaposi's sarcoma (i.e. prior to the HIV epidemic) to estimate the expected number of cases of Kaposi's Sarcoma in 2010 that would have occurred in the absence of HIV- infection. The difference between the observed and expected number of cases of Kaposi's sarcoma was considered attributable to HIV-infection.

For all other infectious agents considered here (HBV, HCV, HIV, *H. pylori*), we used the standard formula to estimate the PAF and number of cancers attributable to infection with these agents,⁷ as:

$$PAF = \frac{\sum(p_x \times ERR_x)}{1 + \sum(p_x \times ERR_x)}$$

where p_x is the proportion of the population in exposure level x and ERR_x the excess relative risk ($RR_x - 1$) associated with exposure level x .

Estimates of HBV, HCV, HIV and *H. pylori* prevalence in the Australian population, and the sources from which they were derived, are summarised in Table 2. Specific accounts of prevalence estimates, relative risks, sensitivity analyses and assumptions required to calculate particular PAFs are described in more detail in relevant sections of the Results.

Results

Summary results for the proportions and numbers of all cancers attributable to infectious agents are presented in Table 3. We estimated that 1,562 (2.4% of all cancers) in men and 1,859 (3.7% of all cancers) in women were caused by infections. The infectious agents with the largest contributions were HPV (1,706 cancers, 1.5% of all cancers),

Table 1: Cancers for which presence of viral infection is considered evidence of causation: prevalence of infection in cases.

Cancer (ICD-10 code)	Viral agent	Prevalence in cases (%)	Source of prevalence estimate
Oral Cavity (C02-C04)	HPV	6.8	Meta-analysis of 72 studies (5,478 cases) – overall HPV DNA prevalence of 24.2%. Four studies tested for p16, with 28.1% of cases (n=47) HPV DNA +ve/p16-positive. ⁶
Oropharynx (C01, C05, C09, C10)	HPV	39.7	Meta-analysis of 53 studies (3,496 cases) – overall HPV DNA prevalence of 45.8%. Eighteen studies tested for p16, with 86.7% of cases (n=738) HPV DNA +ve/p16-positive. ⁶
Anus (C21)	HPV	74.9 (M) 90.8 (F)	Meta-analysis of 29 studies (955 cases of anal carcinoma), stratified by sex ³⁷
Vulva (C51)	HPV	40.4	Meta-analysis of 63 studies (1,873 cases of vulval carcinoma) ³⁷
Vagina (C52)	HPV	69.9	Meta-analysis of 14 studies (136 cases of vaginal carcinoma) ³⁷
Cervix (C53)	HPV	100	Global investigation ³⁸
Penis (C60)	HPV	45.4	Meta-analysis of 30 studies (1,266 squamous cell carcinomas) ³⁹
Nasopharynx (C11)	EBV	87	Australian data series (87% of NPC were WHO Type 2 or 3) ⁸
Hodgkin's lymphoma (C81)	EBV	Varies by age group	Pooled data from four studies ⁹⁻¹² (see online supplementary file Table S1)
Burkitt's lymphoma (C83.7)	EBV	22.5	Review of EBV and Cancer ¹⁴
Kaposi's sarcoma (C46)	KSHV	100	IARC ¹

H. pylori (793 cancers, 0.7% of all cancers) and HBV/HCV (518 cancers, 0.4% of all cancers). The cancer sites with the greatest number of cancers caused by infections in 2010 were cervix (818 cases), stomach (694 cases) and liver (483 cases).

Cancers attributable to human papillomavirus

In total, 1,706 cancers (436 in men, 1,270 in women) were attributable to HPV infection in Australia in 2010. The sites with the greatest numbers of HPV-caused cancers were cervix (n=818), anus (n=288), oropharynx (including tonsil) (n=304) and vulva (n=120). As above, we assumed that HPV infection was causal when HPV-infected tumour cells also over-expressed the p16 protein. A recent meta-analysis indicated that 28% of HPV-positive oral cavity cancers and 87% of HPV-infected

oropharyngeal cancers met this criterion,⁶ (Table 1). In a sensitivity analysis, we modelled the higher prevalence of HPV DNA positive and HPV E6/E7 mRNA positive cases in oral cavity cancers (67%),⁶ which resulted in an additional 108 cancers of the oral cavity attributable to HPV.

Cancers attributable to Epstein-Barr virus

EBV is causal for WHO type 2 and 3 nasopharyngeal carcinoma (NPC). The only Australian data series found 87% of NPC were WHO type 2 or 3;⁸ on this basis, we estimate 107 NPC in Australian in 2010 were caused by EBV.

To estimate the proportion of EBV-positive Hodgkin's lymphoma cases across different age groups, we pooled prevalence data from four studies (see supplementary file: Table

Table 2: Infectious agents defined by IARC as group 1 carcinogens: prevalence in Australia and relative risk of cancer.

Infectious Agent	Prevalence of infection in Australian population (%)	Cancer (ICD-10 code)	Relative risk
Hepatitis B virus (HBV)	1.0 (chronic infection) ¹⁵	Liver (C22)	20.4 (95%CI 11.3-36.5) ¹⁶
Hepatitis C virus (HCV)	1.0 (chronic infection) ¹⁵	Liver (C22)	23.8 (95%CI 16.9-33.6) ¹⁶
		Non-Hodgkin's lymphoma (C82-C85, C96)	1.78 (95%CI 1.40-2.25) ¹⁷
Human immunodeficiency virus, type 1 (HIV-1)	0.2 men ¹⁵ 0.02 women ¹⁵	Kaposi's Sarcoma (C46)	Not applicable
		Conjunctiva (C69.0)	~10 IARC ¹²⁸
		Non-Hodgkin's lymphoma (C82-C85, C96),	6.5 (95%CI 5.4-7.7) ¹⁹
<i>Helicobacter pylori</i>	15.4 ²³	Stomach (C16) [non-cardia]	5.9 (95%CI 3.4-10.3) ²⁵
		MALT gastric lymphoma	6.3 (95%CI 2.0-19.9) ²⁶

S1, available with the online version of this article).⁹⁻¹² Using those prevalence data, we estimated 188 of the 572 cases of Hodgkin's lymphoma that occurred in Australia in 2010 could be attributed to EBV infection (33% of all Hodgkin's lymphoma cases).

Between 1998 and 2002, 230 cases of Burkitt's lymphoma were diagnosed in Australia,¹³ from which we estimated that 53 cases of Burkitt's lymphoma were diagnosed in 2010 (38 in males and 15 in females). Virological

surveys indicate that 15–30% of the non-endemic Burkitt's lymphoma occurring in western populations is caused by EBV.¹⁴ We took the mid-point of this range (22.5%) and estimated that 12 of 53 Burkitt's lymphoma cases in 2010 were attributable to EBV; at the extremes of this range, the estimates were 8 and 16 cases.

EBV causes non-Hodgkin lymphoma (NHL) in people who are immunosuppressed.

The proportion of AIDS-related lymphomas was estimated in the context of HIV-related cancers. The proportion of NHLs that occur in people immunocompromised for other reasons, or are cases of the rare EBV-associated sino-nasal angiocentric T-cell lymphoma, cannot be estimated precisely due to insufficient data, but would be very small. We therefore did not calculate this separately.

Table 3: Population attributable fraction (PAF) and estimated numbers of cancers diagnosed in Australia in 2010 attributable to different infectious agents.

Cancer site (ICD-10 code)	Estimated number of cancer cases by infectious agent							Total	
	HPV	H pylori	EBV	HBV	HCV	HIV	KSHV	No. of cancers	PAF
Males									
Oral cavity (C02-C04)	53							53	6.8
Oropharynx (C01, C05, C09, C10)	237							237	39.7
Nasopharynx (C11)			74					74	87.0
Stomach (C16)		431						431	32.9
Anus (C21)	108					**		108	74.9
Liver (C22)				162	190			352	34.4
Kaposi Sarcoma (C46)						**	58	58	100.0
Penis (C60)	38							38	45.4
Hodgkin's lymphoma (C81)			110			**		110	31.5
Non-Hodgkin's lymphoma (C82-C85, C96)		56	9		20	16		101	3.9
Total	436	487	193	162	210	16	58	1562	
% of all cancers ^a	0.7%	0.7%	0.3%	0.2%	0.3%	0.02%	0.1%		2.4%
Females									
Oral cavity (C02-C04)	24							24	6.8
Oropharynx (C01, C05, C09, C10)	67							67	39.8
Nasopharynx (C11)			33					33	87.0
Stomach (C16)		263						263	38.5
Anus (C21)	180					**		180	90.8
Liver (C22)				60	71			131	34.4
Kaposi Sarcoma (C46)						**	22	22	100.0
Vulva (C51)	120							120	40.4
Vagina (C52)	61							61	69.9
Uterine Cervix (C53)	818					**		818	100.0
Hodgkin's lymphoma (C81)			78					78	31.5
Non-Hodgkin's lymphoma (C82-C85, C96)		43	3		15	1		62	3.2
Total	1270	306	114	60	86	1	22	1859	
% of all cancers ^a	2.5%	0.6%	0.2%	0.1%	0.2%	0.0%	0.04%		3.7%
Persons									
Oral cavity (C02-C04)	77							77	6.8
Oropharynx (C01, C05, C09, C10)	304							304	39.8
Nasopharynx (C11)			107					107	87.0
Stomach (C16)		694						694	34.8
Anus (C21)	288							288	84.1
Liver (C22)				222	261			483	34.4
Kaposi Sarcoma (C46)							80	80	100.0
Vulva (C51)	120							120	40.4
Vagina (C52)	61							61	69.9
Uterine Cervix (C53)	818							818	100.0
Penis (C60)	38							38	45.4
Hodgkin's lymphoma (C81)			188					188	32.9
Non-Hodgkin's lymphoma (C82-C85, C96)		99	12		35	17		163	3.6
Total	1706	793	307	222	296	17	80	3421	
% of all cancers ^a	1.5%	0.7%	0.3%	0.2%	0.3%	0.01%	0.1%		2.9%

Abbreviations: HPV = human papillomavirus; H pylori = Helicobacter pylori; EBV = Epstein-Barr virus; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; KSHV = Kaposi's sarcoma herpes virus; PAF = population attributable fraction (expressed as a percentage)

a: % of all cancers diagnosed in 2010 excluding basal cell carcinoma and squamous cell carcinoma of the skin

** Numbers not calculated separately as HIV is not necessary or sufficient

Cancers attributable to hepatitis B and C viruses

The prevalence of chronic HBV infection in Australia in 2011 was about 1% (209,000; plausible range: 184,000–241,000).¹⁵ The prevalence of HCV infection in Australia in 2011 was about 1.4% (304,000; plausible range: 231,000–376,000),¹⁵ of which 74% were estimated to have chronic HCV infection (1.0% of the Australian population).¹⁵

Summary relative risks for liver cancer associated with HBV and HCV mono-infection from countries that have low prevalences of infections¹⁶ (e.g. US and Australia) were 20.4 (95%CI 11.3–36.5; 4 studies) and 23.8 (95%CI 16.9–33.6; 7 studies), respectively. In addition, a pooled analysis of seven case-control studies conducted in the US, Canada, Europe and Australia,¹⁷ using data from 4,784 cases and 6,269 controls, derived a summary odds ratio for HCV infection and NHL of 1.78 (95%CI 1.40–2.25).¹⁷

Based on these estimates of prevalence and risk, we estimate that 221 liver cancers diagnosed in 2010 were attributable to HBV infection (16% of liver cancers) and a further 262 cases to HCV infection (19%). In total, 34% of liver cancers were attributable to infections with these viruses. At the lower and upper end of plausible prevalence ranges, the estimated cases were 190 and 239 for HBV and 208 and 310 for HCV. In addition, we estimated that 35 cases of NHL diagnosed in 2010 (20 men and 15 women) were attributable to HCV infection (0.8% of all NHL cases).

Cancers attributable to human immunodeficiency virus (HIV)

The prevalence of HIV in the Australian population in 2010 was estimated to be 0.2% in men and 0.02% in women (19,407 and 1,984 cases, respectively).¹⁵ The number of new diagnoses of HIV infection differs by sex (~90% of HIV infections occurred in men) and age group (~90% of infections occurred in the 20–59 year age group; see online supplementary file: Table S2).¹⁵ We assumed that the age and sex distributions of new diagnoses of HIV infections also applied to prevalent infections and estimated the proportion of males and females living with HIV infection in 2010 by age group (online supplementary file: Table S2).

The number of cases of Kaposi's sarcoma diagnosed in Australia in 2010 was 80, all of which were attributable to KSHV. To estimate the proportion of Kaposi's sarcoma attributable to co-infection with HIV, we

subtracted the number cases expected in the population in the absence of HIV infection from the number of cases actually observed. The pre-AIDS incidence of Kaposi's sarcoma in New South Wales (1972–1982) was 0.47 per million.¹⁸ The expected number in 2010 in the absence of HIV infection was 10 cases. The difference of 70 cases (out of a total of 80 cases) was attributed to co-infection with HIV. HIV is also thought to cause non-Hodgkin lymphoma (NHL) through depletion of CD4-positive T-lymphocytes and dysregulation of B cells, resulting in loss of immunological control of lymphotropic viral replication.¹⁹ The introduction of Highly Active Antiretroviral Therapy (HAART) for people infected with HIV was associated with a decrease in incidence of NHL in HIV-infected people,²⁰ although an elevated risk still remains. Assuming that the relative risk of NHL in people infected with HIV in the HAART-era was 6.5,^{19,21,22} and assuming the HIV-prevalence distributions above, we estimate that 17 cases of NHL diagnosed in 2010 (16 in men and 1 in women) were attributable to HIV infection (0.4% of all NHL cases).

We did not perform separate calculations for HIV-attributable cases of Hodgkin's lymphoma, cervical and anal cancers, as it is assumed that most or all of the HIV-attributable cases are due to co-infection with EBV (Hodgkin's lymphoma) or HPV (cervix and anus).

The number of cases of conjunctival SCC diagnosed in 2010 was not available, but it was reported for 1998 to 2002.¹³ We applied the average incidence for that time period to the Australian population and estimated that 62 cases of conjunctival SCC were diagnosed in 2010 (50 men and 12 women). The relative risk of conjunctival SCC associated with HIV infection is about 10.¹ The estimated attributable fraction of conjunctival SCC was 0.7%, equating to less than one case in 2010.

Cancers attributable to *H. pylori*

Prevalence data on *H. pylori* infection in the Australian population (online supplementary file: Table S3) were sourced from two studies. For ages 15–59, estimates were obtained from a random sample of 2,413 sera from 37 diagnostic laboratories across Australia.²³ For those 60 years and over, estimates were sourced from an analysis of 1,355 community controls in a nationwide case-control study in Australia conducted between 2002 and 2005.²⁴ Prevalence was lowest in younger age categories and steadily increased with age to 32% in those aged 70 years and over.

We used relative risks for the association between *H. pylori* infection and non-cardia stomach cancer from a pooled analysis of 12 case-control studies nested within prospective cohort studies.²⁵ When stratified by length of follow-up, the strength of association was greater for cases diagnosed 10 or more years after recruitment (OR=5.93, 95%CI 3.41–10.3) than those diagnosed earlier (OR=2.93, 95%CI 1.82–3.12). In our primary analysis, we assumed a latent period of 10 years between age at exposure and age at cancer diagnosis, and used the effect estimates for cases diagnosed 10 or more years after recruitment.

For the association between *H. pylori* infection and low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma (hereafter 'gastric lymphoma'), we assumed a relative risk of 6.3 (95%CI 2.0–19.9).²⁶ We further assumed that distribution of NHL in Australia was similar to the UK and US, in which 4% of NHL cases arise in the stomach.²⁷

Using these data, the estimated attributable fraction of non-cardia stomach cancer cases in 2010 was 56% in both men and women. This equates to 694 cases; 35% of all stomach cancers. In a sensitivity analysis, we repeated the PAF calculations using the overall relative risk for non-cardia gastric carcinoma (OR 2.97) and estimated that 419 cases (21%) were due to *H. pylori* infection. We also estimated 99 cases of NHL in the stomach (54% of gastric NHL cases; 2.2% of all NHL cases) in 2010 were due to *H. pylori* infection.

Discussion

We estimated that more than 3,000 cases of cancer occurring in the Australian population in 2010 could be attributed to infections with viruses (HPV, EBV, HBV, HCV, KSHV and HIV) and *H. pylori*. This represents 2.9% of all cancers diagnosed in 2010, excluding basal cell and squamous cell carcinomas of the skin. The PAF was 100% for cancer of the uterine cervix and Kaposi's sarcoma, where the infectious agents (HPV and KSHV respectively) are considered necessary causal factors. The PAFs for cancers of the nasopharynx, anus and vagina were all higher than 50% (87% due to EBV, 84% due to HPV and 70% due to HPV, respectively). In absolute terms, the cancer sites with the greatest number of cancers attributable to infectious agents were uterine cervix, stomach and liver.

Our overall estimate (2.9%) is marginally lower than the PAF of 3.3% for Australia and New Zealand previously estimated

in a study of the global burden of cancers attributable to infections in 2008² and the PAF of 3.1% estimated for the UK.²⁸ Several methodological differences may explain the variations in risk estimates across populations. First, prevalence data for *H. pylori* were available by age and sex for the UK population, and prevalence was higher than in Australia for the older male age groups.²⁸ Second, we used different sources of prevalence data that were more recent than those used in the PAF studies above. For example, we derived a pooled prevalence estimate for EBV in Hodgkin's lymphoma that included more recent data than was used in the UK analyses. Third, we calculated PAFs separately for HBV and HCV to estimate the fraction of liver cancers attributable to infectious agents. Finally, we did not calculate a PAF for the association between laryngeal cancer and HPV, as IARC noted only a positive (and not a causal) association between HPV and this cancer.¹ All of these methodological factors would contribute to some of the differences in PAFs between studies.

Several limitations in our analyses should be acknowledged. For cancers caused by EBV and HPV, we used the prevalence of the infectious agent identified in the tumour tissues among cases. This approach makes the assumption that the presence of the infectious agent has caused the cancer in all cases.² However, it is possible that an infectious agent may be present but not causal. This is particularly likely to be the case for HPV and cancers of the oral cavity and oropharynx (including tonsil), where the oncogenic genes are not always expressed in HPV-infected tumour cells. Two approaches have been used to identify the proportion of tumours where the HPV infection was pathogenic: over-expression of p16; and expression of E6/E7 mRNA. The definition of p16-positive varies across studies, which influences the proportion classified as having over-expression. For oropharyngeal cancers, the proportion of p16 positive and E6/E7 positive was very similar in the most recent meta-analysis,⁶ but there were considerable differences for cancers of the oral cavity, resulting in attributable fractions ranging from 6.8% to 16.3%. Prevalence of HPV is also likely to vary by country, age and time. There are limited Australian data available, but studies from Australia have observed an HPV-positive prevalence of about 50%^{4,5} in cancers of the oropharynx, which is similar to the proportion we used (46%). There is some evidence that HPV-positive prevalence in cancers of the oropharynx has increased

over time;^{4,6,29} if so, then the incidence of cancers of the oropharynx and the proportion attributable to HPV may also increase. For those cancers caused by other infectious agents (*H. pylori*, HBV, HCV, HIV), we used the traditional PAF formula that incorporates measures of exposure prevalence in the general population and measures of effect from epidemiological studies. Where possible, we sourced data from several different surveys to try to obtain representative estimates for the Australian population. For *H. pylori* we combined prevalence data from two surveys to cover all adult age groups; however, the representativeness of the samples is open to question. For HBV, HCV and HIV, published prevalence data by age were not available, which may lead to over- or under-estimation of the prevalence of these infections in the overall population. For HBV and HCV, we used data from published surveys. The prevalence estimate for HBV in Australia was higher than figures for New Zealand and the UK, but substantially lower than prevalence figures in countries such as Vietnam, China, Greece and Italy, where many Australian immigrants were born and were therefore at risk of perinatal transmission of HBV. Indeed, HBV prevalence estimates for people born in high-risk countries (Vietnam, Cambodia, China, Taiwan and Afghanistan) now living in Australia was estimated to be 10%.¹⁵ Among people attending needle and syringe programs, prevalence of HCV infection was about 50% in 2011.¹⁵ For both HBV and HCV, incidence rates are more than three times higher in Aboriginal and Torres Strait Islander populations than in non-Indigenous populations.¹⁵ Moreover, we did not consider the burden of cases due to co-infection of HBV and HCV, as accurate prevalence data for co-infections were not available; therefore, there are likely to be groups within the Australian population where the fractions of cancer attributable to HBV and HCV are higher than we have estimated here. Thus, while we have used the best available prevalence estimates, there is considerable uncertainty around their precision. Our results for HBV are identical to those generated in a record linkage study in NSW, but our HCV PAF is somewhat higher (19% vs. 13%).³⁰ Given the uncertainty around these estimates, we conducted sensitivity analyses around estimates for common infections, or those contributing large numbers of cases, but – again – our results must be interpreted cautiously.

We were able to explore the effects of latency only for cancers caused by *H. pylori*, for which

separate summary risk estimates have been derived according to duration of infection. Analogous risk estimates have not been published for other common infections such as HBV and HCV, but would clearly be informative.

We did not estimate cancers attributable to *Clonorchis sinensis*, *Opisthorchis viverrini* and *Schistosoma haematobium*. While these parasites are not endemic to Australia, they may have caused a small proportion of cases of cholangiocarcinoma and bladder cancer in Australia due to immigration from endemic parts of south-east Asia and Africa. Prevalence estimates to perform these calculations were not available.

IARC has declared that HTLV-1 causes acute T-cell leukaemia/ lymphoma (ATLL),¹ but we were not able to estimate PAFs because the prevalence of HTLV-1 in the broader Australian population is unknown. Prevalence in the Australian blood donor population is estimated at between 0.0032%³¹ and 0.001%,³² but this is likely an underestimate of the true prevalence due to stringent donor selection criteria.³¹ HTLV-1 is endemic in Aboriginal populations in Central Australia, where prevalence may be as high as 14% in some communities.^{32,33} Moreover, national incidence data for ATLL are not reported routinely, since ATLL is rare. Thus, the total number of cancers attributable to HTLV-1 would be small. The numbers of cases may rise in the future, as overall life expectancy among at-risk groups rises and those with infections survive to older ages, at which leukaemia and lymphomas arise.

The attributable burden of cancer due to infection is subject to change over time. New treatments can increase the population prevalence of previously fatal infection (e.g. people infected with HIV are able to live longer with the disease) and it is not entirely clear how this will alter cancer risk. In addition, anti-viral therapies for HCV may have an impact on future rates of liver cancer.^{34,35} With the introduction of HPV vaccines, the numbers of cancers are expected to decrease as vaccinated cohorts advance to adulthood. Indeed, there are early Australian data suggesting that the vaccine is able to reduce the risk of developing precancerous cervical abnormalities.³⁶ In contrast to these expected decreases in cancer incidence, there is the prospect for some infectious agents to become more prevalent in Australia due to changing immigration patterns (e.g. HBV, *H. pylori*), with consequent implications for cancer incidence.

Monitoring trends in infections within age and sex categories would provide important information for projecting changes in cancer incidence into the future.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary Table 1: EBV prevalence in Hodgkin's Lymphoma by age groups: summary of published studies and pooled results.

Supplementary Table 2: Distribution (%) of new diagnoses of HIV infection, cumulative to 2011 and estimated proportion and number of people living with HIV in 2010, Australia, by age and sex.

Supplementary Table 3: Estimated *H. pylori* prevalence, Australia.