original article

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Population attributable fraction of infection-related cancers in Korea

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Background: A number of infectious agents have been classified as human carcinogens. The purpose of the current study was to provide an evidence-based assessment of the burden of infection-related cancers in the Korean population.

Materials and methods: The population attributable fraction was calculated using infection prevalence data from 1990 or earlier, relative risk estimates from meta-analyses using mainly Korean studies and national data on cancer incidence and mortality for the year 2007.

Results: The fractions of all cancers attributable to infection were 25.1% and 16.8% for cancer incidence in men and women, and 25.8% and 22.7% of cancer mortality in men and women, respectively. Among infection-related cancers, *Helicobacter pylori* was responsible for 56.5% of cases and 45.1% of deaths, followed by hepatitis B virus (HBV) (23.9% of cases and 37.5% of deaths) and human papillomavirus (HPV) (11.3% of cases and 6% of deaths) and then by hepatitis C virus (HCV) (6% of cases and 9% of deaths). Over 97% of infection-related cancers were attributable to infection with *H. pylori*, HBV, HCV and HPV.

Conclusion: Up to one-quarter of cancer cases and deaths would be preventable through appropriate control of infectious agents in Korea.

Key words: cancer burden, infection, population attributable fraction

introduction

A considerable number of infectious agents have been classified as human carcinogens. The International Agency for Research on Cancer (IARC) Monograph Working Group for Volume 100B reassessed the carcinogenicity of infectious agents with a comprehensive review of all the available published literature. Infections with *Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), *Clonorchis sinensis*, Epstein–Barr virus (EBV), HIV-1 and certain types of human papillomavirus (HPV) were classified as group 1 carcinogens by IARC based on 'sufficient evidence in humans' for some specific cancer sites [1]. Newly classified cancer sites for which sufficient evidence of an association in humans exists include non-Hodgkin's lymphoma for HCV, low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma for *H. pylori* and cholangiocarcinoma for *C. sinensis* (Table 1) [1].

In Korea, >25% of all deaths are due to cancer, and cancer has been the most common cause of death since 1983 [2]. Nationwide cancer incidence rates have been made available since 1999 [3] provided by the Korean Central Cancer Registry. In 2007, the age-standardized cancer incidence rates were 313.7 and 246.0 per 100 000 for males and females, respectively, which shows one of the highest incidence rates in Asia [4]. The age-standardized cancer mortality rates were 158.2 and 65.6 per 100 000 for males and females, respectively [2]. Observed mortality is relatively low compared with those in Asian countries.

Among the major cancers in the Korean population, cancers of the stomach, liver and uterine cervix have been classified as infection related [1]. It is important to quantify the proportion of the cancer burden that could be prevented by proper interventions to limit exposure to these etiologic infectious agents. The purpose of the current study was to estimate the number of infection-related cancer cases and deaths in the

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Table 1. List of group 1 carcinogenic biological agents and related cancer sites [1]

Cancers sufficient evidence in humans	Group 1 agent	Inclusion	Reason for exclusion
Oral cavity	HPV-16	Yes	
Oropharynx	HPV-16	Yes	
Nasopharynx	EBV	Yes	
Noncardia gastric cancer	*Helicobacter pylori*	Yes	
Anus	HIV-1	Yes	
	HPV-16	Yes	
Liver			
Hepatocellular carcinoma	HBV	Yes	
	HCV	Yes	
Cholangiocarcinoma	*Clonorchis sinensis*	Yes	
	HBV[a]	Yes	
	HCV[a]	Yes	
	Opisthorchis viverrini	No	No exposure in Korea
Vulva	HPV-16	Yes	
Vagina	HPV-16	Yes	
Cervix uteri	HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59/HIV-1	Yes	
Penis	HPV-16	Yes	
Hodgkin's lymphoma	EBV	Yes	
	HCV	Yes	
	HIV-1	Yes	
Non-Hodgkin's lymphoma	HIV-1	Yes	
Immune suppression-related non-Hodgkin's lymphoma	EBV	No	Lack of data on incidence and mortality
Burkitt's lymphoma	EBV	Yes	
Extranodal NK/T-cell lymphoma (nasal type)	EBV	No	Negligible number of cases
Adult T-cell leukemia and lymphoma	HTLV-1	No	Negligible number of cases and lack of prevalence data
Primary effusion lymphoma	KSHV	No	Negligible number of cases
Kaposi's sarcoma	KSHV/HIV-1	Yes	
Conjunctiva	HIV-1	No	Negligible number of cases
Low-grade B-cell MALT gastric lymphoma	*H. pylori*	Yes	
Urinary bladder cancer	*Schistosoma haematobium*	No	No exposure in Korea

[a]Cancer sites with limited evidence in humans.

HPV-16, human papillomavirus type 16; EBV, Epstein–Barr virus; HIV-1, human immunodeficiency virus, type-1; HBV, hepatitis B virus; HCV, hepatitis C virus; NK, natural killer; HTLV-1, human T-cell lymphotrophic virus, type-1; KSHV, Kaposi's sarcoma herpes virus; MALT, mucosa-associated lymphoid tissue.

Korean population based on population-specific exposure prevalence of infectious agents and risk estimates between exposures and infection-related cancer.

materials and methods

infection-related cancer incidence and mortality data

The infectious agents and related cancer sites considered in the current study were based on the evaluations made by the IARC Monograph Working Group for Volume 100B (Table 1) [1]. The number of infection-related cancer cases and deaths in individuals aged 20 years and older for the year 2007 were obtained.

We reallocated the overall proportion of gastric cancers with an unspecified subsite [International Classification of Diseases for Oncology (ICD-O)-3 C169, 13.6% of all gastric cancer cases] into cardia and noncardia cases according to the site-specific proportion for each 5-year age- and gender-specific strata and then recalculated the total number of noncardia gastric cancer cases. The same proportion of noncardia cases to total gastric cancer cases was applied to the mortality data.

In order to obtain reliable numbers for hepatocellular carcinoma and intrahepatic cholangiocarcinoma, we reallocated primary liver cancer cases with unknown or unspecified histology (5.1% of the total), which exclude hepatocellular carcinoma diagnosed by the noninvasive methods [5]. According to the histologically verified proportion of liver cancer cases (ICD-O C22), cases with unknown or unspecified histology were reallocated pro-rata within each 5-year age group by gender to hepatocellular carcinoma (ICD-O 8170-8176), cholangiocarcinoma (all intrahepatic biliary ICD-O morphology codes 8050, 8140–8141, 8160, 8162, 8260, 8440, 8480–8500 and 8570–8572) and other subtypes of liver cancer, including hepatoblastoma (8970) and sarcoma. Extrahepatic

cholangiocarcinomas were defined by topography code C24.0 and by morphology codes 8000, 8010, 8020, 8041, 8070, 8140, 8144, 8160, 8161, 8162, 8260, 8310, 8480, 8490 and 8560. In the mortality data, the proportion of unspecified malignant neoplasms of the liver (C229) was 0.26%, and therefore, corrections were not made for hepatocellular carcinoma or cholangiocarcinoma deaths.

prevalence of infectious agents in Korea

Two nationwide cross-sectional studies of *H. pylori* seroprevalence were conducted in 1998 (66.9%) and in 2005 (59.6%) [6]. Using this information, we extrapolated prevalence estimates for 1990 of 83.1% for men and 75.5% for women. For HBV prevalence, we used pooled prevalence rates for HBsAg seropositivity from a review of 51 articles published between 1980 and 1989 [7] of 9.1% for men and 7.1% for women. Similarly, for HCV prevalence, we used pooled estimates for the Korean population for the time period between 1990 and 1994 [8] of 1.7% for men and 2.2% for women. Data from the third 'Prevalence of Intestinal Parasitic Infections in Korea' survey in 1981 were used to calculate the prevalence of *C. sinensis* infection at 2.6% [9].

Only three studies have been conducted to estimate HPV DNA prevalence among women with normal cervical cytology [10–12], which was found to be 8.5% [12]. Seroprevalence of HPV among Korean adult women and university students was 19.8% and 15%, respectively [12, 13]. No data were available for site-specific prevalences of HPV DNA for other organs, i.e., vulva, vagina, penis, anus, oral cavity or oropharynx in the general Korean population. We estimated HIV prevalence in the general Korean population in 2000 using data in the statistics on HIV/AIDS in Korea (0.03%) [14].

meta-analysis

To obtain the pooled odds ratios (ORs), meta-analyses were conducted using risk estimates from epidemiological studies. The studies reporting risk estimate of infectious agents and cancer published before May 2009 were identified using databases, including PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and KoreaMed (http://www.koreamed.org/SearchBasic.php). The search keywords were 'Korea', 'cancer' and each of infectious agents. We also reviewed the references cited in the articles to identify additional studies for inclusion (supplemental Table 1, available at *Annals of Oncology* online). For associations between HBV, HCV and hepatocellular carcinomas, *H. pylori* and noncardia gastric cancer and *C. sinensis* and cholangiocarcinomas, our meta-analyses included risk estimates from Korean studies only. For the association between HBV, HCV and cholangiocarcinomas, we expanded our search to the studies from other countries to be included in the meta-analysis. Pooled ORs and 95% confidence intervals (CIs) based on both fixed effect and random effect models were estimated. Heterogeneity was assessed to test whether significant differences existed between studies. In the case of significant heterogeneity, a random effect model was used [15]. Specifically, fixed effect models were used for HBV and hepatocellular carcinomas (for both men and women) and for HCV and cholangiocarcinomas. All other meta-analyses were carried out based on random effect models. The 'Meta' command in Stata version 10.0 (StataCorp, College Station, TX) and Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ) were used to carry the meta-analyses.

relative risk of cancers and infectious agents

The relative risks (RRs) by cancer site and infectious agent applied in this study are summarized in Table 3.

gastric cancer. We adopted the RR of 5.9 from the international meta-analysis of nested case–control studies for the current analysis [16] because four Korean studies had a case–control design [17–20] (supplemental Table 2 and Figure 1a and 1b, available at *Annals of Oncology* online). In addition, a matched OR of 6.3 from a nested case–control study of the association between *H. pylori* and gastric MALT lymphoma within an American cohort was adopted for the current analysis [21].

hepatocellular carcinoma. Six studies on the association between HBV infection and liver cancer risk have been conducted in the Korean population [22–27]. Two studies were excluded due to unusually lower or higher prevalences of HBsAg in the control groups than that in the general population [22, 26]. Separate summary measures were estimated by meta-analysis for men and women using risk measures derived from two case–control studies, which provided combined risk measures for men and women [24, 25], and RRs from Jee et al. [27] due to the most recent follow-up information and a larger study population. We estimated the RRs for HBV for hepatocellular carcinoma to be 24.4 in men and 33.7 in women (supplemental Tables 3 and 4 and Figures 2a and 3b, available at *Annals of Oncology* online). Three case–control studies assessed the association between anti-HCV antibody positivity and liver cancer risk [22, 25, 26], and the pooled OR was estimated to be 11.5 (supplemental Table 5 and Figure 4a and b, available at *Annals of Oncology* online).

cholangiocarcinoma. The pooled OR was 4.6 from five case–control studies for the association between *C. sinensis* egg positivity in stool samples and cholangiocarcinoma risk [25, 28–31] (supplemental Table 6 and Figure 5a and b, available at *Annals of Oncology* online).

For HBV and cholangiocarcinoma, four Korean studies and six studies conducted in other countries were included in the meta-analysis [25, 30–38]. For HCV and cholangiocarcinoma, four Korean studies and seven studies conducted in other countries were included in the meta-analysis [25, 30–34, 36–40]. The results of our meta-analysis of HBV and HCV were previously published [41]. The pooled ORs for HBV and HCV for cholangiocarcinomas were 2.6 and 1.8, respectively.

other cancers. Pooled ORs from a meta-analysis of 15 case–control studies and three cohort studies of associations between HCV and the risk of lymphoma were used for the population attributable fraction (PAF) for non-Hodgkin's lymphoma [42]. The standardized incidence rate for cancers of the anus and uterine cervix and for Hodgkin's lymphoma, non-Hodgkin's lymphoma and Kaposi's sarcoma among HIV carriers were derived from the scientific literature [43]. Since Kaposi's sarcoma herpes virus infection is an etiologic risk factor for development of Kaposi's sarcoma, a PAF of 100% was applied in analyses of this disease [44].

For HPV infection, PAFs from published paper on cancers of the oral cavity, oropharynx, anus, cervix, vulva, vagina and penis were used [45]. PAFs for EBV for cancer of the nasopharynx, Hodgkin's lymphoma and Burkitt's lymphoma were also adopted from Parkin [45] due to a lack of data on relevant exposure prevalence in a Korean population.

estimation of PAFs

The PAF can be calculated as a function of the RR of cancer associated with exposure to a particular risk factor and the prevalence of the exposure to that risk factor in the population. The PAF was calculated by using the formula, which was modified from Levin's formula for multiple categories, as proposed by Hanley [46, 47]. The counterfactual exposure for all considered infectious agents was that of no infection.

sensitivity analysis and CIs

Sensitivity analyses were carried out for the PAF for *H. pylori*, HBV and HCV by using exposure prevalence at different time points as alternative exposure scenarios. To account for uncertainty in the estimation of PAFs arising from the estimation of RRs and the exposure prevalence of risk factors, a delta method based on Taylor-series expansion was used to estimate the variance of the PAF. Based on the variance of the PAF, the 95%

CI of the PAF was computed by using the standard formula approximated by delta method.

coinfection with HBV, HCV and *C. sinensis*

Interaction between HBV, HCV and *C. sinensis* was also considered when estimating overall cancer cases and deaths attributable to all infectious agents. We took into account the potential joint effect as follows, by assuming independency of infection with HBV and HCV. When considering the three agents, HBC, HCV and *C. sinensis* simultaneously, an extended version of the formula was used to account for the joint effect among all three [48, 49].

results

The number of infection-related cancer cases and deaths among individuals aged 20 years and older for the year 2007 are presented in Table 2 [2, 50]. These cancers comprised ~31.3% of cancer cases and 37.5% of cancer deaths.

The RRs or ORs, prevalence of exposure to the infectious agents in the year 1990, and PAF values adopted from the scientific literature are summarized in Table 3. The PAF due to infectious agents by cancer site are summarized in Table 4. Using the RRs and exposure prevalence, *H. pylori* infection was responsible for 80.3% of noncardia gastric cancers in men and 78.7% in women. HBV and HCV infections were associated with 68.1% and 15.2% of hepatocellular carcinoma cases in men and 69.9% and 18.8% in women, respectively. *Clonorchis sinensis* was related to 11.9% of cholangiocarcinoma cases in men and 5.5% in women. Additionally, HBV was responsible for 12.8% of cholangiocarcinoma in men and 10.3% in women, and HCV accounted for 1.4% of cholangiocarcinoma in men and 1.8% in women. Because all uterine cervical cancers were regarded as a consequence of HPV infection, 100% of cervical cancer incidence was attributed to HPV infection.

Table 2. Total number of cases and deaths considered when a population attributable fraction of an infectious agent-related cancer was estimated in the Korean adult population aged 20 years and older, 2007 [4]

ICD-10 code	Cancer sites	Men		Women	
		Cases	Deaths	Cases	Deaths
C00–C09	Oral cavity	1002	377	456	140
C10	Oropharynx	74	33	4	0
C11	Nasopharynx	253	120	94	45
C161–C168	Noncardia gastric cancer	16 149	6406	7966	3 543
C21	Anus	83	22	90	20
C220	Hepatocellular carcinoma	8851	7131	2450	1976
C221 + C24.0	Cholangiocarcinoma	2491	1823	1537	1213
C51	Vulva			87	13
C52	Vagina			57	19
C53	Cervix uteri			3575	987
C60	Penis	75	15		
C81	Hodgkin's lymphoma	107	21	60	13
C82–85, 96	Non-Hodgkin's lymphoma	1748	768	1283	487
C837 9687/3	Burkitt's lymphoma	33	–	17	–
9699/3	Gastric MALT lymphoma	103		134	
9140/3	Kaposi's sarcoma	32	–	8	–
	Infection-related cancer	31 001	16 716	17 818	8456
	All cancer	82 121	42 521	73 650	24 591

ICD, International Classification of Diseases; MALT, mucosa-associated lymphoid tissue.

The numbers of cancer cases and deaths due to infectious agents are listed in Table 4. In summary, 25.1% of all cancer incidence in men and 16.8% in women in Korea were attributable to chronic infection. The PAF for cancer mortality was 25.8% in men and 22.7% in women. Overall, we estimated that 21.2% of all cancer incidence and 24.7% of all cancer deaths in Korea in the year 2007 were attributable to chronic infection in the current study. Among infection-related cancers, *H. pylori* was responsible for 56.5% of cases and 45.1% of deaths, followed by HBV (23.9% of cases and 37.5% of deaths) and HPV (11.3% of cases and 6% of deaths) (Figure 1).

discussion

Overall, we found that 21.2% of all cancer incidence and 24.7% of all cancer deaths were attributable to infection in Korea in 2007. Because the PAFs in our study were estimated using Korea-wide cancer incidence and mortality data that included detailed information on subtypes and subsites, our study is the most accurate estimation to date of the burden of infection-related cancers available when compared with previously conducted studies [51–53].

One of the earliest extensive efforts to estimate avoidable causes of cancer was conducted by Doll and Peto [52] in 1981 for the USA population. They estimated that the fraction of cancers attributable to infection was 10%. Subsequently, a study in the UK attributed 5% of cancer deaths to chronic infection in an estimation published in 2003 [53]. In the French population, chronic infection was responsible for only 3.6% of cancer deaths [51]. Parkin [45] estimated that 17.8% of the worldwide cancer cases were attributable to infectious agents in 2002, 26.3% in developing countries and 7.7% in developed countries. Ours is one of the first comprehensive reports to use population-specific cancer incidence and death and exposure data in Asian countries. Our results support the global estimates of infection-associated cancers provided by Parkin [45] and more in general, the notion that infectious agents are a major cause of cancer in East Asia.

In our study, the fractions of stomach and liver cancer attributable to chronic infection were much higher than in other populations. The reason for the higher attributable fractions for infectious agents found in our study is the high prevalence of cancer-causing infectious agents, i.e., *H. pylori*, HBV, HCV and *C. sinensis* in the Korean population. However, a significant decrease in the prevalence of *H. pylori* seropositivity occurred between 1998 (66.9%) and 2005 (59.6%) [6]. Seroprevalence was 81% in a control group recruited between 1993 and 1999 from a nested case–control study conducted in rural areas of Korea [20]. Additionally, the introduction of HBV vaccination and HCV screening for blood donors contributed to a decrease in chronic viral carriers. According to the Korea National Health and Nutrition Examination Survey, the prevalence of HBV in the 20–29 age group decreased from 6.9% (1998) to 4.9% (2005) in men and from 4.1% (1998) to 2.9% (2005) in women [54]. The pooled prevalences of HCV in 1990–1994 were 1.69% for men and

Table 3. RR or ORs, prevalence of exposure in 1990 to infectious agents, and PAFs due to infectious agents in Korea

Cancer sites	Agents	Exposure prevalence (%)		Pooled RR (OR)	PAF	Sources for pooled RR (OR) or PAF
		Men	Women			
Oral cavity	HPV				3	[45]
Oropharynx	HPV				12	[45]
Nasopharynx	EBV				90	[45]
Noncardia gastric	*Helicobacter pylori*	83.1	75.5	5.9		[16]
Gastric MALT lymphoma	*H. pylori*	83.1	75.5	6.3		[21]
Anus	HPV				90	[45]
	HIV	0.03	0.03	Men: 3.3, women: 3.0		[43]
Hepatocellular carcinoma	HBV	9.1	7.1	Men: 24.45, women: 33.73		Meta-analysis of Korean data [24, 25, 27]
	HCV	1.7	2.2	11.54		Meta-analysis of Korean data [22, 25, 26]
Cholangiocarcinoma	*Clonorchis sinensis*	3.7	1.6	4.65		Meta-analysis of Korean data [25, 28–31]
	HBV	9.1	7.1	2.62		Meta-analysis of all published data [25, 30–38]
	HCV	1.7	2.2	1.83		Meta-analysis of all published data [25, 30–34, 36–40]
Vulva	HPV	–	–	–	40	[45]
Vagina	HPV	–	–	–	40	[45]
Uterine cervix	HPV		8.5		100[a]	[45]
	HIV		0.03	9.1		[43]
Penis	HPV				40	[45]
Hodgkin's lymphoma	EBV				46	[45]
	HIV	0.03	0.03	Men: 8.0, women: 6.4		[43]
Non-Hodgkin's lymphoma	HCV	1.7	2.2	2.5	2.5	[42]
	HIV	0.03	0.03	Men: 37.4, women: 54.6		[42]
Burkitt's lymphoma	EBV				25	[45]
Kaposi's sarcoma	KSHV/HIV				100[a]	[43]

[a]A PAF of 100% was applied regardless of exposure prevalence and pooled OR.

RR, relative risks; ORs, odds ratios; PAF, population attributable fraction; HPV, human papillomavirus; EBV, Epstein–Barr virus; MALT, mucosa-associated lymphoid tissue; HBV, hepatitis B virus; HCV, hepatitis C virus; KSHV, Kaposi's sarcoma herpes virus.

2.2% for women. However, those prevalences decreased dramatically to 0.65% for men and 0.85% for women in 1995–2000 [8]. Therefore, we anticipate that the PAF due to infection in the Korean population and incidence and mortality rates for infection-related cancers will decrease in the future.

When the RR from a pooled analysis of 12 cohort studies (RR: 5.9) was applied [16], *H. pylori* infection explained 78%–80% of noncardia gastric cancer incidence. This PAF is very similar to that reported by Parkin [45]. For the sensitivity analysis, a meta-analysis was conducted for the summary risk measures from four case–control studies conducted in the Korean population with regard to the association between *H. pylori* and gastric cancer risk [17–20]. When the pooled RR of 1.69 from the Korean studies was applied, the PAFs due to *H. pylori* were 36.44% in men and 34.25% in women. The reason for the relatively small effect size from the Korean studies is the higher seroprevalence of anti-*H. pylori* antibody in the control population and limitation of case–control design.

When the effects of HBV, HCV and *C. sinensis* coinfection were considered, infectious agents explained 72.9% of hepatocellular carcinoma and 24.3% of cholangiocarcinoma. In a study conducted at the National Cancer Center, Korea, 0.4% of HBV carriers were coinfected with HCV, which is higher than the coinfection rate with an assumption of independency in our joint effect calculation [55]. Therefore, the overall PAFs of infection for hepatocellular carcinoma and cholangiocarcinoma may be slightly overestimated in the current study. A possible association between chronic infection with HBV and HCV, which is known to cause hepatocellular carcinoma and cholangiocarcinoma was noted by IARC, as human evidence assessed for this cancer was classified as 'limited'. Because the meta-analyses from the published literature revealed significant risk associated with HBV or HCV infection in the development of cholangiocarcinoma [41], we included these two viral infections as risk factors for cholangiocarcinoma.

Because we restricted our exercise to infectious agents that were classified as group 1 carcinogens by IARC, with the exception of HBV and HCV for cholangiocarcinoma, it is possible that the PAF may have been underestimated due to the lack of consideration of cancer sites for which there is limited evidence of a causal association with infectious agents. In contrast, the PAF may have been overestimated because the attributable fraction of other risk factors was not considered

Table 4. Number of cancer cases and deaths attributable to infection in Korea, 2007

Agents	Cancer sites	Men			Women			Both sexes	
		PAF % (95% CI)[a]	Cases	Deaths	PAF % (95% CI)[a]	Cases	Deaths	Cases	Deaths
Helicobacter pylori	Noncardia gastric	80.3 (66.7–88.5)	12 965	5143	78.7 (64.5–87.5)	6271	2789	19 236	7932
	MALT gastric lymphoma	81.5 (45.4–94.0)	84	–	80.0 (43.0–93.4)	107	–	191	–
HBV[b]	Hepatocellular carcinoma	68.1 (65.8–70.3)	6027	4856	69.9 (60.2–78.0)	1713	1382	7740	6238
	Cholangiocarcinoma	12.8 (4.3–24.6)	320	234	10.3 (3.4–20.3)	159	125	479	359
HCV[b]	Hepatocellular carcinoma	15.2 (3.1–43.2)	1345	1084	18.8 (4.0–49.6)	461	372	1806	1456
	Cholangiocarcinoma	1.4 (0.7–2.4)	35	25	1.8 (0.8–3.0)	28	22	63	47
	Non-Hodgkin's lymphoma	2.5 (1.8–3.3)	43	19	3.2 (2.3–4.2)	41	16	84	35
HPV	Uterine cervix	–			100	3575	987	3575	987
	Vulva	–			40	35	5	35	5
	Vagina	–			40	23	8	23	8
	Penis	40	30	6	–			30	6
	Oral cavity	3	30	11	3	14	4	44	15
	Oropharynx	12	9	4	12	0	0	9	4
	Anus	90	75	20	90	81	18	156	38
Clonorchis sinensis[b]	Cholangiocarcinoma	11.9 (4.3–24.5)	296	217	5.5 (1.9–12.3)	85	67	381	284
EBV	Nasopharynx	90	228	108	90	85	41	313	149
	Hodgkin's lymphoma	46	49	10	46	28	6	77	16
	Burkitt's lymphoma	25	8	–	25	4	–	12	–
HIV	Anus	0.07	0	0	0.06	0	0	0	0
	Uterine cervix				0.24	0	0	0	0
	Hodgkin's lymphoma	0.21	0	0	0.16	0	0	0	0
	Non-Hodgkin's lymphoma	1.08	19	8	1.58	20	8	39	16
KSHV/HIV	Kaposi's sarcoma	100	32	–	100	8	–	40	–
	Total[a]		20 633	10 973		12 402	5580	33 035	16 553
	PAF for all cancers, %[a]		25.1	25.8		16.8	22.7	21.2	24.7

[a]CIs were calculated by sensitivity analysis using 95% CIs for relative risks.

[b]Joint effect of coinfections of HBV and HCV on hepatocellular carcinoma and HBV, HCV and *Clonorchis sinensis* on cholangiocarcinoma were taken into account.

PAF, population attributable fraction; CI, confidence interval; MALT, mucosa-associated lymphoid tissue; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; EBV, Epstein–Barr virus; KSHV, Kaposi's sarcoma herpes virus.

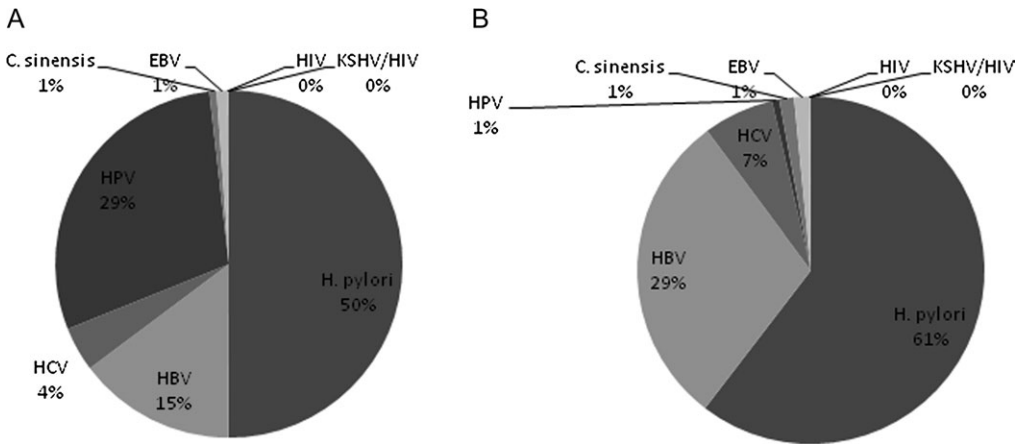

Figure 1. Attributable fraction due to infection-related cancer incidence by each infectious agent (25.1% for men and 16.8% for women for all cancer incidence) in 2007. (A) men (B) women. EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; KSHV, Kaposi's sarcoma herpes virus.

in the current report. However, the fact that some hepatocellular carcinoma (HCC) attributable to HBV or HCV are also attributable to other risk factors such as alcohol or tobacco does not affect the PAF for HBV/HCV, as they represent the proportion of HCC that would be prevented if the infections were eliminated.

The strengths of the current analysis include the use of observed numbers for cancer incidence and mortality for

each cancer site by subsite and subtype if needed. Because stomach and liver cancers are major cancers in Korea, it is important to estimate PAF separately for HBV, HCV and liver fluke to hepatocellular carcinoma and/or cholangiocarcinoma and properly PAF of *H. pylori* to noncardia gastric cancer only. The prevalence of infectious agents in 1990 or earlier was used in consideration of a 15-year induction period between exposure to infectious agents and cancer development. Furthermore, risk estimates for the most common infection-related cancers in Korea, such as hepatocellular carcinoma and cholangiocarcinoma, were derived from meta-analyses of studies conducted within the Korean population. A limitation of our study was the lack of available Korean exposure prevalence data for EBV, HPV and HIV.

In summary, our results represent a systematic assessment of chronic infection-related cancer risk and showed that approximately one-quarter of total incidence and mortality from cancer in the Korean population can be attributed to infection, taking into consideration ~20-year induction period for such infections. Since infections are—at least in theory—preventable risk factors, appropriate control of cancer-causing infectious agents is an important strategy for reduction of the cancer burden in Korea.

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disclosure

The authors declare no conflict of interest.

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