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Burden of cancer attributable to infection in Japan in 2015

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Abstract: Population attributable fraction (PAF) offers a means to quantify cancer burden that is attributable to a specific etiological factor. To better characterize the current cancer burden due to infection in the Japanese population, we estimated the PAF for cancer incidence and mortality in 2015 that could be attributable to infectious agents, including Helicobacter pylori (*H. pylori*), Hepatitis B and C (HBV/HCV), Human papillomavirus virus (HPV), Epstein-Barr virus, and human T-lymphotropic virus type 1. We estimated the PAFs for each infectious agent on the basis of representative data on prevalence and risk-outcome associations assuming a latency period of 10 years. Overall, 16.6% of cancer cases in 2015 in Japan were attributable to the infectious agents included in this analysis. The estimated PAF was slightly higher in men (18.1%) than in women (14.7%). The highest proportion of cancer deaths attributable to infectious agents was observed for *H. pylori* infection, followed by HBV/HCV, and HPV infection. Our findings corroborated with previous estimates that *H. pylori* and HBV/HCV infections were the two most important infectious agents in the Japanese population. Strategies focusing on eradication of infectious agents among infected individuals or primary prevention through vaccination could decrease the burden of infection-related cancers.

***Keywords*:** cancer, infection, population attributable fraction, Japan

Introduction

Cancer became the leading cause of death in Japan in 1981. The number of total cancer deaths increased continuously thereafter, in parallel with aging of the population, to reach 370,346 deaths in 2016. Lung, colorectal, stomach, pancreas, and liver cancers have constituted the five leading causes of cancer death in recent years (*1*). This mortality pattern reflects the high burden of cancers of the digestive system in the Japanese population.

Infectious agents are known to play a role in cancer etiology. The International Agency for Research on Cancer (IARC) has classified at least six viruses as Group 1, *ie.* carcinogenic in humans, namely Epstein-Barr virus (EBV), Kaposi sarcoma-associated herpesvirus/human herpesvirus 8 (KSHV/HHV8), Human papillomavirus (HPV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), human T-lymphotropic virus type 1 (HTLV-1) and *Helicobacter pylori* (*H. pylori*). Persistent infection with these pathogens is causally linked to several types of cancer, including liver, stomach, cervical cancers (*2*).

Population attributable fraction (PAF), which is calculated based on prevalence estimates and relative risk (RR) for exposure-outcome associations, provides a quantitative appraisal of the impact of etiological factors on cancer incidence and mortality (*3*). In the case of infectious agents, PAF indicates the proportion of cancer cases or deaths that would not have occurred if no one in the population had been infected. An estimated 13% of global cancer incidence was attributable to infectious agents in 2018, with PAFs varying according to geographic region and development status (*4*). In a 2005 PAF estimation in Japan, tobacco smoking had the highest PAF (30% for incidence and 35% for mortality) in men, followed by infectious agents (23% for incidence and 23% for mortality) (*5*), whereas infectious agents had the highest PAF (18% for incidence and 19% for mortality) in women.

The validity of PAF estimates depends on prevalence estimates and relative risk for exposure-outcome associations, which may change over time. In particular, the prevalence of *H. pylori* infection in asymptomatic individuals in Japan has markedly changed over a short

period of time (*6*). To better characterize the current cancer burden due to infection, we estimated the PAF of cancer incidence and mortality in 2015 that was attributable to selected infectious agents in the Japanese population.

Material and Methods

Cancers associated with infection

The target cancers and infectious agents were selected based on the assessment of the carcinogenicity of biological agents by the IARC Monograph Working Group (*2*). Cancers included in the present study were gastric, gastric non-Hodgkin lymphoma (NHL), liver, cervix uteri, penis, vulva, anus, oral cavity, oropharynx, nasopharynx, Birkitt lymphoma, and adult T-cell lymphoma (ATL). These were selected because they each had sufficient evidence of a supporting role of infectious agents in their causation. Parasitic agent (*Clonorchis sinensis, Opisthorchis viverrini, and Schistosoma haematobium*)- and human immunodeficiency (HIV)-related cancers were excluded because exposure to these pathogens in the Japanese population is rare.

Cancer incidence and mortality in Japan in 2015

Cancer incidence data in 2015 were estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan (MCIJ) (*7*), as determined by an age and period spline model. These models are used for short-term projection of cancer incidence in Japan (*8*). The sex- and age-specific incidence data for target cancers were coded in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), using the morphology code of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

The data on cancer mortality from 2015 were based on the vital statistics of Japan (*1*). We obtained sex- and age-specific mortality data by cause of death from an available data source provided by the Health, Labour, and Welfare Statistics Association (*9*). As with the cancer incidence data, 4-digit ICD-10 codes were used to classify cause of death.

Prevalence of exposures

Assuming a latency period of 10 years between infection and cancer occurrence, we extracted the best-available data on the prevalence of infectious agents in the Japanese population in 2005. Because of a clear cohort effect observed for the prevalence of *H. pylori* infection, we previously estimated prevalence by birth year from 1908 to 2003 in a systematic review and meta-regression analysis of studies conducted in Japan (*6*). Based on these results, we obtained the corresponding prevalence data by sex and 5-year age group for the year 2005. To capture representative data on the prevalence of HBV and HCV in the general population, we referred to the pooled prevalences of HBsAg and anti-HCV by sex and birth year that were estimated by combining three large cohorts in Japan: first-time blood donors, participants in screening programs initiated by local governments, and individuals who underwent a comprehensive medical checkup (Ningen dock) (*10*). Estimated prevalence by birth year was converted to prevalence of HBV or HCV by 5-year age group in 2005. Because prevalence data were not available for individuals born before 1930 or after 1986, we assumed that these individuals had the same estimated prevalence as the next or preceding birth cohort (1931-1935 and 1981-1985), respectively. As with previous studies, the prevalence of HPV infection was assumed to be 100%, based on the fact that HPV DNA virus can be detected in all cervical cancer cases (*4,11*). For EBV and HTLV, we quoted the prevalence data from previously published literature (*4*), because very few data were available for Japanese subjects.

Estimation of relative risk

The majority of previous PAF studies used an RR of 5.9 for the association between *H. pylori* and non-cardia gastric cancer, as determined by a previous meta-analysis involving 12 case-control studies on this topic (*12*). However, this risk estimate might be an underestimation given that several studies using more sensitive measurement methods, such as western blot, demonstrated much stronger associations, with odds ratios (ORs) ranging from 10.6 to 21.4 (*13*). Furthermore, in a 2015 meta-analysis of the *H. pylori*-stomach cancer association in Japanese subjects, the RR for individuals who had both *H. pylori* infection and gastric atrophy was 15-fold greater than that of those with neither *H. pylori* infection nor gastric atrophy (*14*). Therefore, we used an RR of 15 for the calculation of PAF for both men and women. For gastric cardia cancer, we adopted an RR of 2.0, obtained from a meta-analysis of studies conducted in Asian countries, including Japan (*15*).

Concerning the RR of liver cancer associated with HBV or HCV infection, no data from meta-analyses of studies involving Japanese are yet available. We therefore adopted results from the Japan Public Health Center-based Prospective Study, a nationally representative cohort study. RR was 35.8 (95% CI: 20.4-62.7) for HCV-infected subjects and 16.1 (95% CI: 7.6-33.9) for HBV-infected subjects. These estimates were comparable to those reported in a 2015 meta-analysis which showed an OR of 45.3 (95% CI: 25.4-80.6) for HCV infection and 38.9 (95% CI: 19.8-38.4) for HBV infection (*16*).

With respect to RR estimates for EBV and HTLV-1, we adopted the corresponding data from a synthesis

analysis of the global burden of cancer attributable to infections in 2012 (*4*).

Estimation of PAF

For *H. pylori*, HBV, and HCV, PAF was calculated using Levin's formula (*4*):

$$\mathrm{PAF} = \frac{P \times (RR - 1)}{P \times (RR - 1) + 1}$$

where *RR* is relative risk and *P* indicates the prevalence of infectious agents in the general population.

Regarding the contribution of HTLV-1 to adult T-cell lymphoma and the contribution of HPV to cervical cancer, infection is thought to be necessary for carcinogenesis, and thus the PAF was assumed to be 100%; all of these cancers could be attributed to persistent infections among exposed subjects (*4*). For other HPV-related cancer sites and EBV-related cancers, PAF was calculated using the prevalence of each infectious agent in cases only and RRs associated with the infection (*4*):

$$PAF = Pc \times \frac{RR - 1}{RR}$$

where *Pc* is prevalence among cases.

The number of cancer incidence or mortality in 2015 attributable to a single infectious agent was calculated by multiplying total cancer incidence or mortality in that year by PAF.

Results

Table 1 lists the prevalence of *H. pylori* and HBV/HCV infections by sex and 5-year age group in the general population in 2005. Notably, prevalence increased with age for both infections.

Table 2 shows the PAFs of cancer incidence and mortality attributable to infectious agents. HIV was not included in the present study because of a lack of relevant data. Overall, we estimated that 16.6% of cancer incidence and 17.7% of cancer mortality in 2015 in Japan were attributable to infectious agents. The PAF estimates were slightly higher in men than in women for both cancer incidence (18.1% *vs.* 14.7%) and mortality (18.5% *vs.* 16.5%). Among infection-induced cancers, the PAF estimates for cancer incidence ranged from 4.3-100% in men, with the highest PAF noted for HTLV-1 (100% for ATL), followed by *H. pylori* (89% for stomach non-cardia cancer), HPV (88% for anal cancer), and EBV (80% for nasopharynx cancer). In women, the PAF estimates ranged from 4.3-100%, with the highest PAFs observed for HPV (100% for cervical cancer and 88% for anal cancer), followed by *H. pylori* (90% for stomach non-cardia cancer) and EBV (80% for nasopharynx cancer) (Table 2) (Table S1 and S3, online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=35*). Similar PAF estimates were obtained for cancer mortality (Tables 2), (Table S2 and S4, online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=35*).

For site-specific cancers, the number of cancer incidence attributable to infection was highest for stomach cancer, followed by liver cancer. Among infectious agents, *H. pylori* contributed the largest proportion of attributable cancer incidence, accounting for approximately 12.0% (14.3% in men and 8.9% in women) of all incident cases in Japan in 2015 (Table S1, online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=35*). HBV and HCV contributed 2.8% (3.1% in men and 2.4% in women) of attributable cancer incident cases (Table S3, online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=35*). HPV contributed 1.5% of cancer cases in

Table 1. Estimated prevalence for major infectious agents by sex and 5-year age group in the Japanese population in 2005

Age at exposure (2005)	*H. pylori*	HBV	HCV
Men			
0 - 4	5.7	0.3	0.1
5 - 9	8.0	0.3	0.1
10 - 14	13.0	0.3	0.1
15 - 19	17.4	0.3	0.1
20 - 24	22.0	0.3	0.1
25 - 29	26.4	0.5	0.2
30 - 34	31.4	0.7	0.3
35 - 39	37.6	0.9	0.5
40 - 44	44.7	1.1	1.0
45 - 49	51.7	1.3	1.2
50 - 54	56.6	1.4	1.2
55 - 59	59.9	1.5	1.5
60 - 64	62.5	1.5	1.9
65 - 69	65.0	1.2	2.7
70 - 74	66.8	1.0	4.9
≥ 75	67.5	1.0	4.9
Women			
0 - 4	5.7	0.2	0.2
5 - 9	8.0	0.2	0.2
10 - 14	13.0	0.2	0.2
15 - 19	17.4	0.2	0.2
20 - 24	22.0	0.2	0.2
25 - 29	26.4	0.4	0.2
30 - 34	31.4	0.6	0.3
35 - 39	37.6	0.6	0.5
40 - 44	44.7	0.7	0.8
45 - 49	51.7	0.9	1.0
50 - 54	56.6	1.1	1.2
55 - 59	59.9	1.3	1.5
60 - 64	62.5	1.3	2.0
65 - 69	65.0	1.1	2.9
70 - 74	66.8	1.2	4.5
≥ 75	67.5	1.2	4.5

Abbreviations: *H. pylori* = *helicobacter pylori*; HBV = hepatitis B virus; HCV = hepatitis C virus.

Table 2. PAF of cancer incidence and mortality attributable to infectious agents in Japan in 2015

Agent	Cancer site	ICD-10	Prevalence in cases (PAF)	Obs. cases	Attrib. cases	Obs. deaths	Attrib. deaths
Men							
H. pylori	Stomach cancer	C16	-	91,883	78,078	30,809	27,009
	Gastric NHL	5% of C82-C85, C96	74	760	561	328	243
HBV/HCV	Liver cancer	C22	-	28,222	16,823	19,008	11,922
HPV	Penis	C60	51	412	210	141	72
	Anus	C21	88	521	458	209	183
	Oral cavity	C02-C06	4.3	6,409	276	1,844	79
	Oropharynx	C01, C09-C10	46	2,688	1,236	824	379
EBV	Nasopharynx	C11	80	581	465	224	179
	Birkitt Lymphoma	C837	30	170	51	36	11
	Hodgkin Lymphoma	C81	56	805	444	102	57
HTLV-1	ATL	C915	100	912	879	446	446
Total				549,241	99,481	219,508	40,580
% of cancers					18.1		18.5
Women							
H. pylori	Stomach cancer	C16	-	42,203	35,822	15,870	14,050
	Gastric NHL	5% of C82-C85, C96	74	629	464	257	190
HBV/HCV	Liver cancer	C22	-	15,087	9,663	9,881	6,714
HPV	Cervix uteri	C53	100	11,253	11,253	2813	2,813
	Vulva	C51	48	867	416	262	126
	Vagina	C52	78	363	279	151	118
	Anus	C21	88	472	415	202	178
	Oral cavity	C02-C06	4.3	4,544	195	1,467	63
	Oropharynx	C01, C09-C10	46	514	236	169	78
EBV	Nasopharynx	C11	80	277	222	75	60
	Birkitt Lymphoma	C837	30	138	41	19	6
	Hodgkin Lymphoma	C81	56	446	249	58	32
HTLV-1	ATL	C915	100	663	638	506	506
Total				408,572	59,893	150,838	24,935
% of all cancers					14.7		16.5
Both sexes							
Total				957,813	159,374	370,346	65,515
% of all cancers					16.6		17.7

women, while other infectious agents, such as EBV and HTLV, contributed less than 1% of attributable cancer incident cases.

Discussion

Based on the best available data, we estimated that 16.6% of cancer incident cases were attributable to six infectious agents in Japan in 2015. Unlike other developed countries, in which infection contributes to only a small proportion of cancer etiology (*3,4,17*), infectious agents, particularly *H. pylori* and HBV/HCV, are still responsible for a high proportion of cancer burden among some Eastern Asian countries, including Japan (*18*).

The overall PAF estimate in the present study was slightly lower than that reported for 2005 in an earlier study (*5*). One possible reason is the difference in prevalence data used to estimate PAF. The earlier study used the prevalence of *H. pylori* and HBV/HCV infections in cases. However, given the dynamic changes in *H. pylori* and HBV/HCV infections across various age groups, we used prevalence data by 5-year age group in the general population extracted from our previous systematic review and meta-regression of studies targeting Japanese populations (*6,10*). Another difference is that the RR used to calculate PAF was higher in the present study than in our previous study (15.0 *vs.* 5.9). Methodological differences aside, our slightly lower PAF estimates suggest a relatively decrease in the contribution of infectious agents to cancer, albeit that confirmation of this finding awaits further study.

We estimated that approximately 90% of non-cardia gastric cancers were attributed to *H. pylori* infection in the Japanese population. This result is similar to the updated IARC PAF estimate. Recognizing the possible underestimation of PAF in their previous study, in which prevalence data were obtained from serologic antibody tests, the IARC group presented an updated PAF of 89.0% for gastric cancer associated with *H. pylori* infection based on prevalence data from immunoblot (western blot) assay, which provides greater sensitivity in detecting anti-*H. pylori* antibodies than ELISA (*13*). Collectively, these findings reinforce the dominant role of *H. pylori* in the etiology of non-cardia gastric cancer. Less consistent, however, is the role of *H. pylori* in proximal and gastrointestinal junction gastric adenocarcinomas, which share a common pathogenesis with distal cancers but are distinct

from them (*19*). While *H. pylori* has been shown to be positively associated with both distal gastric cancer and proximal and gastroesophageal junction cancers in East Asian countries, including China and Japan (*20,21*), no significant associations have been observed in Western populations (*22*). Here, to our knowledge for the first time, we estimated that 38% of gastric cardia cancers were attributable to *H. pylori* infection in the Japanese population. However, cautious interpretation is warranted because of the inconsistent definition of gastric cardia cancer across studies, and quality of population-based cancer registry data.

Chronic infection with HBV or HCV is a major risk factor for liver cancer worldwide. Overall, our study showed that 59.6% of incident cases and 62.7% of deaths were attributed to either HBV or HCV infection in 2015. This estimate is comparable to the worldwide estimate of 60%, but is much higher than that in other developed countries (*23*). Interestingly, the prevalence of HBV and HCV infections and their contributions to liver cancer etiology exhibit remarkable geographical variation (*23*). HBV infection is the dominant cause of liver cancer in the majority of Asian countries, including China and Korea (*22*), whereas only 16% of liver cancer cases and deaths were attributable to HBV infection in Japan, as shown in our study. On the other hand, our data showed that HCV is a predominant cause of liver cancer in Japan, with approximately 46% of cases attributable to it. One striking feature is that the prevalence of anti-HCV peaked in individuals born between 1931 and 1935, who also showed high mortality rates of live cancer (*10*). Unsafe healthcare-related injections and blood transfusion were thought to have contributed to the wide transmission of HCV in this birth cohort (*10*). With the improvement in medical care since the 1950s, the prevalence of HCV has continuously decreased in successive younger generations, and was estimated to be 0.13% in the 1981-1985 birth cohort (*10*).

HPV is one of the most important infectious agents for a wide range of cancers, accounting for 4.6% of new cancer cases in 2012 (*4*). According to National Cancer Registry data, 11,283 women were newly diagnosed with cervical cancer in 2016. HPV infection would have contributed to all these incident cases if we assume a PAF of 100%. Notably, cervical cancer is the second leading cause of cancer-related deaths for women between the ages of 20 and 39 (*24*), suggesting that early detection is important in reducing the burden for this age group. In addition to cervical cancer, high-risk HPV also contributes to a varying fraction of head and neck, anal, penile, vulvar and vaginal cancers in men and women, with the PAF estimates ranging from 4.3% to 100%.

One strength of our study is that we used the best available, nationwide representative data to estimate PAFs due to infectious agents for Japanese subjects. In particular, by using population data by sex and 5-year age group, we were able to capture the dynamic changes occurring in the prevalence of *H. pylori* and hepatitis infection, two key etiologic factors responsible for a high proportion of cancer incidence and mortality in the Japanese population. We also highlight several methodological weaknesses that should be addressed to allow better interpretation and application of our PAF estimates. First, uncertainties remain concerning PAF estimates for EBV and HPV, because prevalence or risk factor data mostly came from studies involving Western populations. Second, given the varied latent periods between exposure and outcome used to estimate PAFs in the previous studies, we assumed it to be 10 years in the present study. In the case of *H. pylori*-induced gastric cancer, a cascade of carcinogenic processes for intestinal-type gastric cancer has been established; the process - starting from *H. pylori*-induced gastritis, then moving to gastric atrophy, intestinal metaplasia, dysplasia, and finally to malignant tumor - may take more than 10 years (*25*). Although the latency of 10 years adopted in our study may be too short, analysis using a latency of 15 years yielded similar results (data not shown). Third, assuming independent causes of mortality, we did not take possible interactions between infectious agents into account. However, the proportion of co-infections with HBV and HCV was 0.1% in a previous population-based cohort study (*16*), and the PAF estimate was 1.8% for co-infections with HBV and HCV in our earlier study (*5*). These findings suggest that the exclusion of coinfection with HBV and HCV in the present study might not have introduced serious bias.

From a practical point of view, PAF estimates are most useful in informing public health interventions when the exposure-disease association is recognized as causal and the exposure can be avoided through primary prevention. This notion fits well with pathogen-related cancers. Elimination of pathogens or vaccination could theoretically result in a marked decrease in disease outcomes. For example, the HBV vaccination program introduced in 1986 contributed to a decrease in age-adjusted mortality rates of liver cancer in childhood in Japan (*26*). For *H. pylori* infection, a population-wide "test-and-treat" strategy may be cost-effective and worthy of implementation in a country like Japan, which has both a high incidence of gastric cancer and high prevalence of *H. pylori* (*27*). The success of this implementation might also expedite a reduction in gastric cancer incidence/mortality, eventually making it a rare cancer. Despite the demonstrated safety and effectiveness of HPV vaccine, vaccination uptake plummeted in Japan shortly after it was introduced in 2013 due to anecdotal reports of adverse effects, such as complex regional pain and postural orthostatic tachycardia syndrome (POTS), in a small proportion of girls who had been vaccinated (28). Concerns have

been raised about a possible increase in the incidence of HPV-related diseases, including cervical cancer, if the current suspension of the vaccination program continues.

Conclusion

An estimated 16.6% of cancer incidence and 17.7% of cancer mortality were attributable to infection in Japan in 2015. Our findings corroborate the previous estimate that *H. pylori* and HBV/HCV still remain the two most important infectious agents in the Japanese population. Strategies focusing on the eradication of infectious agents among infected individuals or primary prevention through vaccination could decrease the burden of infection-related cancers. As dynamic changes in exposure prevalence occur over time, continued efforts to estimate the PAF due to infection is important for public health regulation.

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