

# Cancers Attributable to Infectious Agents: an Ecological Study in Asia

*Zaher Khazaei*

Student Research Committee, Sabzevar University of Medical Sciences, Sabzevar, Iran

*Yousef Moradi*

Pars Advanced and Minimally Invasive Medical Manners Research Center, ParsHospital, Iran University of Medical Science, Tehran, Iran

*Hossein Ali Adineh*

Department of Epidemiology and Biostatistics, Iranshahr University of Medical Sciences, Iranshahr, Iran

*F Rezaei*

Department of Social Medicine, Jahrom University of Medical Sciences, Jahrom, Iran

*Malihe Sohrabivafa*

Department of Health and Community Medicine, Faculty of Medicine, Dezfoul University of Medical Sciences, Dezfoul, Iran

*Isan Darvishi*

MSc of Surgical Technology, Surgical Technology Department, School of Nursing and Midwifery, Shiraz University of Medical Sciences and Healthcare Services Behbahan Faculty of Medical Sciences, Behbahan, Iran

*Seyedeh Leila Dehghani*

Social Determinants of Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran

*Elham goodarzi*

Infections are a major contributor to cancer, especially in developing countries. Infections through the virus, bacteria and parasites are the most and most preventable causes of cancer in the world. The aim of the current study was to investigate the epidemiology of cancer-related infections in Asia. We considered 4 infectious agents classified as carcinogenic to human beings by the International Agency for Research on Cancer. We calculated the number of new cancer cases in 2012 attributable to infections by country, by combining cancer incidence estimates (from GLOBOCAN 2012) with the estimates of attributable fraction (AF) for the infectious agents. AF estimates were calculated from the prevalence of infection in cancer cases for the infection (for some sites). According to data registered in 2012, about 14 million new cases of cancer were detected worldwide of which 2.2 million people (15.4%) diagnosed with cancer due to infection. The highest incidence of infectious cancers related to the African continent with a prevalence of 27.6% followed by Asian continents (21.4%), America (7.9%), Europe (7.3%) and Oceania (4.8%), respectively. In the Asian continent, of all cancers associated with infection in males, 48.1% were related to *Helicobacter pylori* infection, 33.2% of hepatitis B virus, 8% of hepatitis C and 3.3% of HPV and in women 47.4% HPV, 28.7% *Helicobacter pylori*, 15.3% Hepatitis B and 4.5% Hepatitis C, respectively. India (230,000 cases) and Japan (140,000 cases) were the most affected, while Bahrain (86 cases) and Brunei (88 cases) had the least cases of infection-related cancer. In Asia, the most common cancer-related infection in males and females were reported for *Helicobacter pylori* and HPV, respectively. Therefore, with preventive interventions aimed at reducing these infections, the burden of cancers can be reduced.

## Introduction

Cancer is one of the most important Non-communicable diseases imposing a burden on society. Cancer is a multifactorial illness; these factors can cause cancer in various combinations. Infection is a known cancer-causing agent, especially in developing countries. One-sixth of reported cancers around the world were due to infectious pathogens [1]. Prevention and treatment of infectious

agents have a significant effect on cancer reduction [2, 3]. *Helicobacter pylori*, hepatitis B and C viruses and human viral papillomavirus (HPV) cause a major portion of cancers in the stomach, liver and cervix[3].

## **Hepatitis B and C**

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the main cause of chronic liver disease and hepatocellular carcinoma (HCC) and they were considered for one of the closest relationships between environmental factors and cancer that has been identified so far [4]. HCC is the fifth common type of tumor and the third leading cause of cancer-related death worldwide. The incidence of HCC is increasing; therefore, these infections are one of the most important public health problems. About 80% of HCC is due to HBV or HCV infection. In the United States, Europe, Egypt and Japan, more than 60% of HCC is associated with HCV, and about 20% is related to HBV. In Africa and Asia, in which HBV is endemic, 60% of HCC is related to HBV, 20% is related to HCV. Although no vaccine is available for HCV, new antiviral treatments may prevent chronic infections in developing countries in people with acute HCV infection. Antiviral treatment reduces the risk of developing liver cancer in people at risk for HBV and chronic HCV [5-8].

## **Helicobacter Pylori**

Gastric cancer is a major threat to global health and is the third leading cause of cancer death worldwide [9]. *Helicobacter pylori* is the leading cause of gastric cancer it is estimated that 89% of non-cardia gastric cancers, accounting for 78% of gastric cancer cases, are associated with *Helicobacter pylori* infection. *H. pylori* causes chronic stomach inflammation that can progress to the pre-cancerous changes in atrophic gastritis and intestinal metaplasia. The risk of gastric cancer increases with the severity and extent of these pre-cancerous changes[10, 11].

## **Human Papilloma Virus (HPV)**

Human papillomavirus (HPV) is a major cause of cervical cancer. It also causes a significant proportion of cancers of the mouth and vagina, as well as penis. HPV vaccines have a very effective effect on the prevention of cancers associated with this virus [12, 13]. The prevalence of HPV infection is ranged from 5% in North America to 21% in Africa , In 2006, vaccines protecting the two types of HPV reduced the majority (70%) of cervical cancer and a new vaccine in 2014 protected all types of HPV cancers by about 90%[14, 15]. The high cost of HPV vaccines has prevented large-scale vaccination in countries[16]. The study of cancers would be incomplete without considering and addressing infectious agents. Based on epidemiological studies, it is anticipated that, over the next few decades, identifying the nature of infectious agents will be more useful tools for the prevention and treatment of related cancers[17]. Therefore, the detection of carcinogenic infections and their carcinogenesis can be used to reduce their prevalence. The aim of this study was to investigate cancer-related infections in Asia.

## **Methods**

The Cancers Attributable to Infections website presents estimates of the burden of cancer in 184 countries or territories of the world. The geographical designations used on this website follow the definitions of the United Nations (World Population Prospects: The 2010 Revision), except for Cyprus, which for the purposes of this website is considered to be located in southern Europe rather than in western Asia. Because of the low number of cases, estimates in Oceania excluding Australia and New Zealand were grouped into "Other Oceanian regions". Results were also grouped by the 2012 Human Development Index (HDI), a composite indicator of life expectancy, education, and gross domestic product per person. As per the methodology for HDI grouping in 2012, the 184 countries were divided by quartiles of their 2012 HDI distribution into four groups, each with an equal number of countries (although with substantially different population sizes) and

labelled as low, medium, high, and very high HDI (Human Development Report 2013: The Rise of the South: Human Progress in a Diverse World. New York: United Nations Development Programme, 2013. ).

## Infectious Agents

Ten infectious agents that have been classified as well-established (Group 1) carcinogenic agents in humans by the International Agency for Research on Cancer (IARC) were considered, namely: *Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV; types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 — known collectively as high-risk types), Epstein-Barr virus (EBV), human herpes virus type 8 (HHV-8; also known as Kaposi sarcoma-associated herpes virus), human T-cell lymphotropic virus type 1 (HTLV-1), *Opisthorchis viverrini*, *Clonorchis sinensis*, and *Schistosoma haematobium*.

## Population Attributable Fraction (PAF) of cancer incidence attributable to infections

The PAF for carcinogenic infections is an estimate of the proportion of new cancer cases that would have been prevented in a population if all infections had been avoided or successfully treated before they caused cancer. The number of cancer cases that would have been prevented in a population if all infections had been avoided or successfully treated was calculated by multiplying the PAF by the total cancer burden (i.e. the total number of all cancers in the population).

## Infection-related Cancers

Cancers for which there is well-established evidence of a causal link with the above-mentioned infectious agents; these include carcinoma of the oral cavity, oropharynx including tonsil and base of tongue, larynx, anus, cervix, vulva, vagina, and penis (HPV); adult T-cell leukemia and lymphoma (HTLV-1); Kaposi sarcoma (HHV-8); Hodgkin lymphoma, Burkitt lymphoma, and nasopharyngeal carcinoma (EBV); non-cardia and cardia gastric carcinoma, and gastric non-Hodgkin lymphoma (*H. pylori*); liver cancer (HBV); liver cancer and non-Hodgkin lymphomas (HCV); bile duct cancer (*Opisthorchis viverrini* and *Clonorchis sinensis*); and bladder carcinoma (*Schistosoma haematobium*).

## Results

Of the estimated 14 million new cancer cases worldwide in 2012, 2.2 million (15.4%) were attributable to infection (Fig. 1).

**Fig. 1** Proportion (%) (Worldwide) of all cancer cases among both sexes in 2012 attributable to infection (all infection agents), by country [extracted from Globocan 2018].

Based on estimates from different continents, the results showed that the highest percentages of infections associated with the African continent were found to be 27.6% followed by Asian continents (21.4%), America (7.9%), Europe (7.3%) and Oceania (4.8%) respectively (Fig. 2).

**Fig. 2** Cancer cases (Per population) among both sexes attributable to infection in 2012 (by continent)

Results from continental isolation and infections revealed that the highest incidence of cancers in the Americas (48%), Oceania (42.4%) and Africa (45.2%) were related to HPV and in continental



Europe (5% 39%) and Asia (35.9%) is related to *Helicobacter pylori* (Fig 3).

**Fig. 3** Proportions of cancer cases among both sexes attributable to infection in 2012 (by continent) (globocan.iarc).

The results of the study on the Asian continent showed that of all cancers associated with infection in males, 48.1% were related to *Helicobacter pylori*, 33.2% to Hepatitis B, 8% to Hepatitis C and 3.3% to HPV while in women, 47.4% were HPV-related, 28.7% *Helicobacter pylori*, 15.3% hepatitis B and 4.5% hepatitis C (Fig. 4).

**Fig. 4** Proportions of cancer cases attributable to infection in Asia in 2012(globocan.iarc).

Based on the findings from all Asia-Pacific regions of all cancer-related infections, in East Asia, *Helicobacter pylori*-associated cancers were 51% in men and 42% in women with the highest cancer-related infection. In South-East Asia, 39 percent of the cancers associated with infection in men were related to hepatitis B and in women 59 percent were HPV. In South-Central Asia, about 80 percent of the cancers associated with infection in women associated with HPV and in males are 55 percent related to *Helicobacter Pylori*. In West Asia, about 39% of the cancers associated with infection in women associated with HPV and 51% of males are *Helicobacter pylori* affected (Tab. 1).

Frequency Cancer case attributable to infection (%)	
Human papillomavirus	Hepatitis C virus
Both	Female
94000 (10)	
54000 (32)	
170000 (59)	
5500 (18)	

**Tab. 1** Cancer case attributable to infection in Asia, shown by infectious agents (globocan.iarc).

The results of the registration of cancers associated with infection in some Asian countries showed that India (210,000 cases) and Japan (140,000 cases) had the highest number of recorded cancers associated with the infection and Bahrain (86 cases) and Brunei (88 cases) had the lowest incidence of infection-related cancers (Tab. 2, [Fig. 5](#)).

Cancer case(all infection agents) attributable to infection	Region	Cancer case(all infection agents) attributable to infection	Region
Both	Female	Male	
1800	---	920	Israel
3200	1700	1500	Afghanistan
3700	2900	870	Nepal
7300	3800	3500	Malaysia
160	67	95	Kuwait
86	43	43	Bahrain
17000	10000	6900	Philippines
200	90	110	Oman
15000	8600	6300	Myanmar
220000	150000	64000	India
---	2400	1600	Cambodia
2100	870	1200	Saudi Arabia

1500	660	850	Yemen
56000	20700	35300	Korea
2000	820	1200	Singapore
4800	3000	1800	Uzbekistan
1500	910	620	Georgia
---	4300	6300	Iran
140	69	68	Bhutan
140000	52000	87000	Japan

**Tab. 2** Cancer case (all infection agents) attributable to infection, shown by region (globocan.iarc).

**Fig. 5** Proportion (%) (In Asia) of all cancer cases among both sexes in 2012 attributable to infection (all infection agents), by country [extracted from Globocan 2012] \*Proportion (%) (In Asia) of all cancer cases among both sexes in 2012 attributable to infection (all infection agents), by country [extracted from Globocan 2012]\*

## Discussion

Identifying cancer-related infections helps to understand, prevent and treating the cancer. An infection-related study identifies many of the key concepts in key carcinogenesis mechanisms. A recent study found that of the 12.7 million new cancer cases that occurred in 2008 around the world, about 2 million of these new cases (16.1%) have been related to infectious agents [2, 18-20]. In less developed regions, 22.9% and developed regions, 7.4% of the cancers were infection-related, and this is from 3.3% in Australia and New Zealand to 32.7% in sub-Saharan Africa in which H pylori, HBV, HCV and HPV were responsible for it and the cause of about 1.9 million cases was gastric cancer, HCC, and cervical cancer [21]. According to data recorded in 2012, about 14 million new cases of cancer worldwide were 2.2 million (15.4%) cases related to infection. The highest frequencies of infection-related cancers were related to the African continent with 27.6%, followed by Asia (21.4%), America (9.9%), and Europe (7.3%) and the Oceania (8.4%). In the Asian continent, all of the cancers associated with infection in males were 48.1% for *Helicobacter pylori*, 33.2% for hepatitis B, 8% for hepatitis C and 3.3% for HPV and for females 47.4% for HPV, 28.7% for *Helicobacter pylori*, 15.3% for Hepatitis B and 4.5% for Hepatitis C virus. The highest frequencies of infection-related cancer were reported for India and Japan with 220,000 and 140,000 cases as compared to Bahrain with 86 and Brunei with 88 cases as the countries with lowest

frequency of infection-related cancer. The results of the infection-related cancers in 2012 revealed that the highest infection associated with cancers in Asian men is related to *Helicobacter pylori* infection. The global prevalence of *Helicobacter pylori* infection has been reported to be over 50%. This rate was higher in developing countries and in the countries with younger age groups are more common[22]. In the occurrence of gastric adenocarcinoma, several factors are effective, but in recent years the role of *Helicobacter pylori* is more prominent and more widely known; also, in various studies of *Helicobacter pylori*, it has increased the incidence of gastric adenocarcinoma 2 to 3 times and is one of the important factors in the gastric adenocarcinoma[23]. Various studies have shown that eradication of *Helicobacter pylori* can reduce the incidence of gastric adenocarcinoma[24, 25]. *Helicobacter pylori* treatment in low-risk cases can prevent 20%-30% of gastric adenocarcinoma[26]. The incidence of stomach cancer and mortality has consistently declined since the mid-20th century in many North American and European countries and recently in many other countries, including Asia and Latin America. The process of reducing gastric cancer is due to a reduction in the prevalence of *H. pylori* infection as well as the high level of sanitary and antibiotic used[16]. According to the results of the infection-related cancer registry in 2012, HBV was identified as the second most common cancer-related infection in men with the incidence of 33.2%. According to studies, about 70% to 90% of liver cancers around the world are hepatocellular carcinoma (HCC) mostly due to chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). The risk of infection in people with chronic HBs is 7 to 100 times higher than those who did not have the infection. These factors account for 80% of cases of cancer. HBV now accounts for 2.3% of liver cancer in less developed countries and 1.4% in developed countries while HCV is a relatively low-level cause of liver cancer in less developed countries (1.8 cases)[6]. Liver cancer can be prevented through a variety of public health measures. Vaccination for HBV has been available since 1982 and has now been introduced in 181 countries. Although no vaccine for HCV is available, new antiviral treatments may prevent chronic infections in people with acute HCV infection[16]. By developing rapid and sensitive screening tests, these viruses have been eliminated as a cause of hepatitis after a blood transfusion. However, they are still widely transmitted by drug abuse, and are transmitted to a small extent in a sexual manner. In 2012, the results of the incidence of infection-related cancers in Asia showed that the highest rate of cancer-related infection in women (47.4%) is related to HPV infection. Cervical cancer is the third leading cause of death from cancer in women in developing countries[13]. The incidence of cervical cancer and mortality is higher in most sub-Saharan Africa, Southeast Asia, Latin America and the Caribbean, and Central and Eastern Europe. Various studies have shown the sustained association of human HPV infection with the spread of cervical cancer. Infection with the HPV virus can infect cells on the skin, the genital area, anus, the mouth, and the pharynx. More than two thirds of cervical cancers are caused by chronic infection with HPV types 16 and 18[27]. Information from extensive studies on HPV has shown that sexually active young women are at the highest risk of HPV infection [28]. One of the most important progresses in cancer prevention over the last decade was the development and implementation of HPV vaccination to prevent cervical cancer. The priority should be to ensure that the vaccine reaches populations with the highest incidence of HPV infection and cervical cancer[19].

## Conclusion

The global burden of infection-related cancer in the less developed areas is significant. Identifying and detecting carcinogenic biological agents and their transmission pathways can be a means to prevent and control the incidence of infectious cancers. With the help of the HBV and HPV vaccine and preventive measures other than vaccination, we can help reduce the burden of the disease in the future. Therefore, further studies and evaluations of other carcinogenic environmental factors are needed.

## Suggestion

The necessary education for the community, especially in developing countries, the timely



identification of life-threatening cancer-related infections and timely treatment, can largely overcome the burden of cancer in the world.

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## Conflict of Interest

The authors declare that there is no conflict of interest

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