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## Characteristics of gastric cancer in Asia

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## Abstract

Gastric cancer (GC) is the fourth most common cancer in the world with more than 70% of cases occur in the developing world. More than 50% of cases occur in Eastern Asia. GC is the second leading cause of cancer death in both sexes worldwide. In Asia, GC is the third most common cancer after breast and lung and is the second most common cause of cancer death after lung cancer. Although the incidence and mortality rates are slowly declining in many countries of Asia, GC still remains a significant public health problem. The incidence and mortality varies according to the geographic area in Asia. These variations are closely related to the prevalence of GC risk factors; especially *Helicobacter pylori* (*H. pylori*) and its molecular virulent characteristics. The gradual and consistent improvements in socioeconomic conditions in Asia have lowered the *H. pylori* seroprevalence rates leading to a reduction in the GC incidence. However, GC remains a significant public health and an economic burden in Asia. There has been no recent systemic review of GC incidence, mortality, and *H. pylori* molecular epidemiology in Asia. The aim of this report is to review the GC incidence, mortality,

and linkage to *H. pylori* in Asia.

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**Key words:** Gastric cancer; Asia; Epidemiology; Gastric cancer incidence; Gastric cancer mortality

**Core tip:** Gastric cancer (GC) is the third most common cancer and the second most common cause of cancer death in Asia. Highest incidence rates are observed in Eastern Asia and varies in other parts of Asia. Mortality rates are slowly declining but remain a significant public health problem. The seroprevalence of *Helicobacter pylori* is very closely related to the incidence of GC in Asia. In contrast to Western world, management of GC is focused on prevention and early detection in Eastern Asia.

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## INTRODUCTION

Gastric cancer (GC) is a heterogeneous, multi factorial disease. It endangers human physical and psychosocial wellbeing, causing a significant public health and economic burden both in the developed and developing countries<sup>[1,2]</sup>. According to International Agency for Research on Cancer, the global and regional burden of GC is enormous<sup>[3]</sup>. The incidence and mortality vary widely according to geographic areas, socio-cultural and economic entities. GLOBOCAN 2008 data revealed that about one million new cases of GC were estimated to have diagnosed in 2008, making it the fourth most common malignancy in the world, after lung, breast, and

**Table 1 Gastric cancer incidence, mortality and prevalence in the world as reported in GLOBOCAN 2008<sup>[3]</sup>**

	Total incidence (in 1000s)	Incidence rate per 100000	Total mortality (in 1000s)	Mortality rate per 100000	5-yr prevalence (in 1000s)	Prevalence
World	988	14.0	737	10.3	1598	5.5%
Asia	727	18.5	530	13.4	1216	10.4%
Europe	145	10.3	116	7.9	201	2.4%
Northern America	24	4.2	12	2.1	37	0.8%
Africa	22	4.0	21	3.8	30	2.1%

**Table 2 Male gastric cancer incidence, mortality and prevalence in the world as reported in GLOBOCAN 2008<sup>[3]</sup>**

	Total incidence (in 1000s)	Incidence rate per 100000	Total mortality (in 1000s)	Mortality rate per 100000	5-yr prevalence (in 1000s)	Prevalence
World	640	19.7	463	14.2	1050	7.8%
Asia	484	25.9	342	18.3	819	15.7%
Europe	86	14.5	68	11.3	121	2.9%
Northern America	15	5.8	7	2.8	23	1.0%
Africa	12	4.7	11	4.5	16	3.0%

**Table 3 Female gastric cancer incidence, mortality and prevalence in the world as reported in GLOBOCAN 2008<sup>[3]</sup>**

	Total incidence (in 1000s)	Incidence rate per 100000	Total mortality (in 1000s)	Mortality rate per 100000	5-yr prevalence (in 1000s)	Prevalence
World	348	9.1	273	6.9	548	3.6%
Asia	243	11.7	188	8.9	396	6.2%
Europe	59	7.0	47	5.3	79	1.9%
Northern America	9	2.8	5	1.5	13	0.6%
Africa	10	3.3	9	3.2	13	1.5%

colorectal cancers. More than 70% of GC cases occur in developing countries with half the world's total cases occurring in Eastern Asia<sup>[1,2]</sup>. Overall, GC incidence and mortality have fallen dramatically over the past 70 years. Despite its recent decline, GC is the second leading cause of cancer death in both sexes worldwide. The highest mortality rates occur in Eastern Asia while the lowest occur in Northern America. In Asia, GC is the third most common cancer after breast and lung. But is the second most cause of cancer death in Asia after lung cancer<sup>[2,3]</sup>. Although the incidence and mortality rates of GC are slowly declining in Asia, it still remains a significant health problem. Asia is the world's largest and most populous continent. With approximately 4.3 billion people, it accounts for 60% of the world's current human population. Asia's growth rate is very high for the modern era and has quadrupled during the last 100 years. It is estimated that Asia's growth rate will remain high<sup>[3,4]</sup>. There has been no recent systemic review of GC incidence, mortality and *Helicobacter pylori* (*H. pylori*) molecular epidemiology in Asia.

**CURRENT EPIDEMIOLOGY OF GC**

More than 727000 cases of GC were diagnosed in Asia in

2008, accounting for 11.9% of all the cancers diagnosed. It is the third most common cancer in Asia after breast and lung cancer<sup>[3]</sup>. Table 1 shows that the age-standardized rate (ASR) of incidence is highest in Asia (18.5%) compared to other continents. The ASR of mortality is also highest (13.4%) and it is second only to lung cancer (19.15) in Asia. It is the third most prevalent cancer in Asia after breast and colorectal cancers<sup>[3]</sup>. The incidence and mortality rates of GC are also the highest in both males and females in Asia compared to other continents (Tables 2 and 3)<sup>[3,5]</sup>.

The incidence and mortality rates are also higher in Eastern Asia compared to other regions in Asia. This region includes China, Japan and South Korea, the three countries with the highest GC incidence and mortality rates, while the lowest rates occur in South-Central Asia<sup>[1,3,5,6]</sup>. The age adjusted GC incidence, mortality, and prevalence rates in the various regions in Asia are summarized in Table 4. In all the four parts of Asia, the rates are lower in females than males as shown in Tables 5 and 6<sup>[1-5]</sup>.

**CURRENT INCIDENCE TREND OF GC IN ASIA**

More than half of the world's population live in Asia<sup>[2]</sup>



**Table 4 Gastric cancer incidence, mortality and prevalence in Asia as reported in GLOBOCAN 2008<sup>[3]</sup>**

	Total incidence (in 1000s)	Incidence rate per 100000	Total mortality (in 1000s)	Mortality rate per 100000	5-yr prevalence (in 1000s)	Prevalence
Eastern Asia	601	30.2	418	20.3	1071	15.2%
South-Eastern Asia	43	8.6	35	7.1	56	3.9%
South-Central Asia	68	4.8	63	6.5	68	2.6%
Western Asia	14	9.4	13	8.3	19	4.2%

**Table 5 Male gastric cancer incidence, mortality and prevalence in Asia as reported in GLOBOCAN 2008<sup>[3]</sup>**

	Total incidence (in 1000s)	Incidence rate per 100000	Total mortality (in 1000s)	Mortality rate per 100000	5-yr prevalence (in 1000s)	Prevalence
Eastern Asia	408	42.4	274	28.1	732	21.0%
South-Eastern Asia	24	10.9	20	8.9	32	6.2%
South-Central Asia	42	6.7	39	6.3	42	4.3%
Western Asia	9	12.6	8	11.2	12	5.8%

**Table 6 Female gastric cancer incidence, mortality and prevalence in Asia as reported in GLOBOCAN 2008<sup>[3]</sup>**

	Total incidence (in 1000s)	Incidence rate per 100000	Total mortality (in 1000s)	Mortality rate per 100000	5-yr prevalence (in 1000s)	Prevalence
Eastern Asia	193	18.3	144	13.0	338	9.5%
South-Eastern Asia	18	6.7	15	5.6	23	2.6%
South-Central Asia	26	3.9	23	3.6	26	1.6%
Western Asia	5	6.7	4	5.9	7	3.0%

China, Japan and South Korea have reported the highest GC incidence rate both in males and females in the world. More than half of the total cases of GC are diagnosed in East Asia each year<sup>[1,2,5,6]</sup>. Overall, the incidence rate trend of GC in Asia is declining in the last two decades. Although the incidence rate of GC remains somewhat unchanged in some countries of Asia, the overall incidence rate of GC in East Asia is declining<sup>[7]</sup>. In China, the incidence rate of GC in males declined from 41.9 per 100000 in 2000 to 37.1 per 100000 in 2005<sup>[8,9]</sup>. While from 2000 to 2005, GC incidence rate decreased from 19.5 to 17.4 per 100000, respectively in females<sup>[1,8,9]</sup>. In Japan, the incidence rate of GC declined from about 80 to 60 per 100000 from 1980 to 2000. In 2008, the incidence rate of GC in Japan was 31.1 per 100000 both in males and females<sup>[5,10,11]</sup>. In South Korea, the incidence rate of GC also declined to 65.6 per 100000 in males and 25.8 per 100000 in females<sup>[2,6,12]</sup>. Many countries of South-East Asia (Singapore, Thailand, and Malaysia) have also observed a slow decline of GC incidence rate over the last few decades<sup>[2,3]</sup>.

The overall incidence rate of GC in South-Central Asia is low in comparison to the other parts of Asia. The incidence of GC in India (3.8 per 100000) is overall less than the worldwide incidence. The age-adjusted rate of GC among urban registries in India is 3.0-13.2 per 100000<sup>[2,3]</sup>. Overall, the incidence rate of GC in India is decreasing. However, this declining trend has not been seen in certain parts of India. Among the major population-based cancer registries in India, only Mumbai

and Chennai have reported a decline in incidence. The incidence rate of GC in other parts of South-Central Asia like Pakistan, Bangladesh and Sri Lanka is also decreasing slowly<sup>[2-4,13,14]</sup>.

Western Asia is the land of multiple ethnic groups, principally from three main backgrounds: Semitic (Arabs and Jews), Indo-European (Persians and Kurdish) and Turkic (Turkish and Turkmens). Its geographic location, which has been under continuous influences from Asia, Europe and Africa, has variable incidence rates of GC. The GC rate differs in this region from very high in Iran (26.1 per 100000) to low in Israel (12.5 per 100000)<sup>[3,15,16]</sup>. GC occurs nearly 7 times more frequently in Iran than in Iraq<sup>[17]</sup>. In Jordan, the overall incidence rate is 4.8 per 100000 (males 5.6 and females 4.1)<sup>[3,15,16]</sup>. The incidence rate of GC and its trend remains stable or improving slowly in most of the countries in Western Asia<sup>[3,15-17]</sup>.

## GC MORTALITY IN ASIA

The overall GC mortality rate and its variations according to geographic areas closely follow the distribution of the GC incidence rate in the world as well as in Asia. In Asia, the mortality rate is higher in males than females<sup>[3]</sup>. Similar to the incidence rate, GC mortality rate is the highest in Eastern Asia (Table 4)<sup>[3]</sup>. Mortality rates also vary in different countries in Asia (Table 7). China has the highest mortality rate from GC (30.1 per 100000) followed by Japan (20.5 per 100000) and South Korea (13.8 per 100000). The mortality rate is moderate to low in South-

**Table 7** Incidence, mortality and prevalence of gastric cancer in selected countries in Asia as reported in GLOBOCAN 2008<sup>[3]</sup>

Country	Incidence rate per 100000	Mortality rate per 100000	Prevalence
China	29.9	22.3	5.6%
Japan	31.1	13.5	18.1%
South Korea	12.1	9.8	7.0%
Indonesia	9.4	8.8	4.8%
Malaysia	8.4	7.4	3.3%
Thailand	3.5	2.5	1.5%
India	3.8	3.6	1.5%
Bangladesh	5.2	5.0	2.8%
Pakistan	6.3	5.9	3.0%
Iran	15.6	14.1	8.8%
Iraq	3.6	3.5	1.9%
Jordan	4.8	4.5	2.2%
Saudi Arabia	3.3	3.0	2.0%
Israel	8.6	4.7	2.4%

Eastern Asia (Malaysia 8.5 per 100000), while relatively low in South-Central Asia (India 4.6 and Bangladesh 5.7 per 100000). The mortality rates vary in Western Asia (Iran 19.9, Israel 6.7, Jordan 5.2 and Iraq 3.7 per 100000)<sup>[1,3,5,6,8,15]</sup>.

## CURRENT MORTALITY TREND OF GC IN ASIA

In the new millennium, there have been some distinct and progressive changes in the pattern of gastrointestinal cancer - especially in GC in Asia. Despite all the recent changes in screening, diagnosis, treatment and surveillance, GC still remains the second most common cause of cancer mortality in Asia<sup>[3]</sup>. The mortality rate of GC remains statistically unchanged in some countries of Asia, however, a significant decline in the mortality rate of GC in Eastern Asia led to an overall decline in the mortality rate in Asia<sup>[7]</sup>. In China, the highest mortality rate was observed in rural areas, especially in Gansu, Henan, Hebei, Shanxi and Shaanxi Provinces in the middle-western part of China<sup>[8,9]</sup>. Although there was a slight increase from the 1970s to early 1990s, a significant decline in GC mortality was noticed in almost the entire population during the last decade in China. Between 2000 and 2005, Mortality from GC declined in males, while the number slightly increased in females, despite the significant declining trend in mortality rates among all age groups in China. In 2008, the mortality rates of GC in China were 30.1 in males and 14.6 in females per 100000<sup>[1,7,8]</sup>.

There has been a significant change in the mortality trend of GC in Japan. This country has had a significant decline in the mortality rate of GC from 1980 to 2010. In 2008, the overall mortality rate was 14.7 per 100000 (20.5 and 12.6 per 100000 in males and females, respectively)<sup>[2,3,11]</sup>. Similar decline was also observed in South Korea<sup>[2,3,12]</sup>. The mortality rate also declined in most of the countries in Eastern and South-Eastern Asia<sup>[2,3,7,18]</sup>.

There was a decline in the mortality rates of GC in

urban areas of India (overall 3.6, male 4.6, and female 2.7 per 100000 in 2008). But in many rural areas, the mortality rate still remains high and unchanged. The mortality rates in other countries in South-Central Asia remain low and unchanged. Iran has the highest mortality rate of GC in South-Central and Western Asia. The overall mortality rate is 14.1 per 100000 (male 19.9 and female 8.2) and is slowly declining. The mortality rate remains low and improving slowly in Jordan (overall 4.5, male 5.2 and female 3.8 per 100000) and Israel (overall 4.7, male 6.7 and female 3.0 per 100000)<sup>[3,13-15]</sup>.

## EPIDEMIOLOGY OF *HELICOBACTER PYLORI* INFECTION IN ASIA

It is well postulated that the seroprevalence of *H. pylori* is very closely related to the incidence of GC. There is a difference in the seroprevalence of *H. pylori* infection between countries and within specific regions and communities of individual countries, not only in Asia but also in other countries of the world. In tandem with the socioeconomic development in many countries, a temporal decrease in the seroprevalence rate has been reported<sup>[2]</sup>.

The seroprevalence rates of *H. pylori* infection in under-developed or developing countries are higher than in developed countries. The highest seroprevalence rate is reported in Bangladesh (92%) followed by Kuwait (84%) and India (79%)<sup>[2,19,20]</sup>. On the other hand, the seroprevalence rates in developed countries are reported to be lower. Among East Asian countries, the overall seroprevalence rate is 58.07% in China, 39.3% in Japan, 59.6% in South Korea and 54.5% in Taiwan<sup>[21-24]</sup>. Among South-east Asian countries, the reported seroprevalence rate was 35.9% in Malaysia, 31% in Singapore, 75% in Vietnam and 57% in Thailand<sup>[2,7,18,25-27]</sup>. The seroprevalence rates are also high in many countries of the South-Central and Western Asia - 78% in Jordan, 77% in Iran, 78% in Iraq, 75% in Saudi Arabia and 72% in Israel<sup>[15,28]</sup>. In addition, a temporal effect was also evident with the younger population having low prevalence rates similar to developed Western countries<sup>[2]</sup>.

A temporal effect in *H. pylori* seroprevalence rate has also been noted in Asia<sup>[29,30]</sup>. In a study from Guangzhou province in China, it was found that the overall *H. pylori* seroprevalence rate had decreased from 62.5% in 1993 to 47% in 2003. Among children aged 1-5 years, the seroprevalence rate was 19.4% and this rose to 63.2% among subjects aged 40-50 years. In Japan, the overall seroprevalence rate was 72.7% in 1974, decreased to 54.6% in 1984 and was 39.3% in 1994. In South Korea, the seroprevalence rate decreased from 66.9% in 1998 to 59.6% in 2005<sup>[31]</sup>. In addition to a temporal decline in the overall seroprevalence rate over time, the younger population generally has a lower seroprevalence rate. Current evidence suggests that most *H. pylori* infection is acquired in childhood. The data from Asia also indicates that the rate of *H. pylori* infection has been decreasing over the last 40-50 years, with an overall decline in *H. py-*



*lori* seroprevalence, similar to that of Western developed countries<sup>[2,32-34]</sup>. Evidence related to the survival of *H. pylori* outside the gastric niche is limited. Principal route of transmission yet to be confirmed. There is strong evidence that indicates the prevalence of *H. pylori* infection has a strong correlation with access to clean water, suggesting a transmission route to the host<sup>[35,36]</sup>.

The Indian enigma is a subset of the Asian enigma, which refers to the observations that there are regions where *H. pylori* infection is high yet the GC incidence is relatively low. The term was coined based on the epidemiological observation. The regions where these observations are made are India, Bangladesh, Pakistan and Thailand<sup>[2,4,5]</sup>. It is to be acknowledged that there are still gaps in our appreciation of the process of gastric carcinogenesis. There is also a lack of data documenting the precise gastric histology in these populations with low GC but high *H. pylori* seroprevalence rates<sup>[37,38]</sup>.

## MOLECULAR EPIDEMIOLOGY OF *H. PYLORI* IN ASIA

Different *H. pylori* strains transpire across diverse geographic regions, and the differences in these strains have been correlated with the variation in GC epidemiology. Six main geographic strains were identified, the hpEastAsia is the strain from East Asian countries<sup>[39]</sup>. It has been perceived that populations with high GC rates correspond almost exactly to populations with the hpEastAsia strain. In South Asian countries where *H. pylori* seroprevalence rates are high but GC prevalence rates are low, the strains were predominantly hpAsia<sup>[29,39-41]</sup>.

In the milieu of GC carcinogenesis, bacterial virulence factors that have been implicated include the cytotoxin-associated gene A antigen (CagA), vacuolating cytotoxin (VacA), and outer membrane proteins (OMP)<sup>[41]</sup>. Huang *et al.*<sup>[42]</sup> performed a meta-analysis of 16 studies with 2284 cases and 2770 controls to scrutinize the relationship between CagA seropositivity and the risk of GC and indicated that infection with cagA-positive strains of *H. pylori* amplified the risk for GC over the risk associated with *H. pylori* infection alone. CagA protein has been classified into Western and Eastern types. The East Asian strain has been documented to be more virulent than the Western CagA with respect to clinical outcomes<sup>[42,43]</sup>. Azuma *et al.*<sup>[44]</sup> validated that in the grades of inflammation and mucosal atrophy were significantly higher in patients infected with Eastern CagA-positive strains than in those infected with Western CagA-positive strains. Satomi *et al.*<sup>[45]</sup> revealed that in Okinawa, Japan, where both Western and East Asian CagA were present, the prevalence of East Asian CagA-positive strains was significantly higher in patients with GC (84.6%) than in patients with duodenal ulcer (27.3%). There are increased frequencies of GC in individuals with type O blood and in secretors [expressing Le (b) antigen], but other studies have not found any relationship between blood groups and this infection<sup>[46,47]</sup>. The prevalence of *H. pylori* infec-

tion in intestinal-type GC is higher than in the diffuse type and in the control group. An association was found between *H. pylori* infection and GC located distally (antrum/pylorus)<sup>[48]</sup>.

## MANAGEMENT AND OUTCOME OF GC IN ASIA

GC management has been principally focused on the management of advanced GC in western populations, where the risk of GC tends to fall into the low-risk category. But this statement does not hold true for the highest-risk continent - Asia, where resources have focused on preventive strategies as well as management of early stage GC<sup>[49]</sup>. It is widely accepted that GC, like many other malignancies, progresses through a cancer cascade<sup>[50]</sup>. However, why certain individuals and families have a greater propensity to move along the cascade towards GC, is most certainly a multi-factorial process, and arises from complex and multifaceted interactions between host factors, *H. pylori* and environmental factors. Diets high in salt and nitrates carry the highest risks, with salt in particular demonstrating an ability to augment the effects of carcinogens. Fresh fruits and vegetables are associated with a reduced risk of GC. But fortification of the diet with ascorbic acid or use of multivitamins does not appear to confer the same protection. Studies focusing on sustained measurable alterations in diet sufficient to affect GC incidence and prevalence are underway<sup>[51-53]</sup>.

However, *H. pylori* infection has proven to be an interesting target and multiple studies have indicated that *H. pylori* infection is a necessary, but not a sufficient causal factor in the development of GC<sup>[51]</sup>. Unfortunately, four randomized placebo-controlled trials evaluating the impact of *H. pylori* screening and eradication on GC prevalence did not show a significant reduction in GC development; however, there was a non-significant trend towards risk reduction for GC with *H. pylori* eradication. The strategy of population screening and treatment of *H. pylori* infection appears to be the strategy of choice in high GC risk populations in Eastern Asia<sup>[54-57]</sup>.

China, Japan and South Korea are the in champions in the management of early GC, and this has primarily been driven by need. Given that these countries have some of the highest GC, screening is done through barium meal (Japan), gastroscopy (Japan and South Korea) and serum pepsinogen/gastroscopy (China)<sup>[55-57]</sup>. Studies from the eastern Asia examining the techniques of endoscopic mucosal resection and endoscopic submucosal dissection for early stage GC have proven that with improving technical expertise and careful surveillance, the outcome is excellent with high 5-year survival<sup>[58]</sup>. However, the detection of early GC is difficult and only systematic population screening has been shown to increase early detection and confer a survival advantage<sup>[59,60]</sup>. Health economics modeling indicates that population endoscopic screening for early GC is cost effective in moderate- to high-risk populations and may not be economically prudent for other

part of Asia<sup>[59,61]</sup>.

In the management and outcome of advanced GC, the majority of the studies have been carried out in the Western world, as most of the cases of GC are diagnosed at advanced stages<sup>[62]</sup>. The backbone of the management of advanced GC is chemotherapy, which is comparable between Western world and Asia<sup>[63]</sup>. The S1-cisplatin doublet remains the standard chemotherapy regimen for advanced GC in Japan, replacing 5FU-cisplatin. S1-cisplatin is also available in South Korea, Singapore, Taiwan, Philippines and China for this indication, but is not approved in North America<sup>[64,65]</sup>. Fluoro-pyrimidines show less toxicity in Asian populations, possibly secondary to polymorphisms in genes encoding drug-metabolizing enzymes, translating into more options for advanced GC treatments in Asian populations. Better survival differences after gastrectomy for GC favoring Asians patients may be explained by different disease patterns, the related need for fewer extensive procedures, and fewer patient risk factors in Eastern Asia. In other parts of Asia, the outcomes after surgery are variable<sup>[9,58,66]</sup>. The overall 1 and 5-year survivals are comparable between Asia, Europe, and North America according to gender and stage. There are slight variations of outcomes among different regions of Asia, depending on socioeconomic condition and access to medical care<sup>[9,65,67]</sup>.

## CONCLUSION

GC is exerting a significant health and economic burden in many countries of Asia<sup>[3]</sup>. The gradual and consistent improvement in socioeconomic condition in Asia has brought about an overall decrease in *H. pylori* seroprevalence rates and thus improvement of GC incidence<sup>[2,7]</sup>. Nonetheless, differences still exist between developed and less developed countries of Asia<sup>[7,68]</sup>. There is now better understanding of the process of gastric carcinogenesis, and the role of bacterial virulence factors interrelating with host immune factors. In order to address the high clinical burden of GC, a recent Asia-Pacific Gastric Cancer Consensus meeting has strongly recommended a strategy for *H. pylori* screening and eradication in high-risk populations to reduce GC incidence. On the other hand, there have been continuous efforts to improve the screening, early diagnosis, surgical and medical management and surveillance of GC<sup>[7]</sup>.

Similar to the Western world, the incidence and prevalence of *H. pylori* infection and GC in Asia has decreased over the past few decades. Multiple factors have played interactive roles in this regard. With a better understanding of the molecular epidemiology of *H. pylori* infection, GC carcinogenesis and overall improved management of GC, the clinical outcome is slowly improving<sup>[69,70]</sup>. However, more elaborative and circumferential steps have to be taken for primary, secondary and tertiary prevention of GC in Asia which in turn will eventually decrease the global burden of GC.

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