

Retrospective Study

Geographical distribution of the incidence of gastric cancer in Bhutan

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Abstract

AIM: To estimate the prevalence of gastric cancer (GC) in a cohort of patients diagnosed with GC and to compare it with patients diagnosed with all other types of gastro-intestinal (GI) cancer during the same period.

METHODS: Between 2008 and 2013, five-year period, the medical records of all GI cancer patients who underwent medical care and confirm diagnosis of cancer were reviewed at the National Referral Hospital, Thimphu which is the only hospital in the country where surgical and cancer diagnosis can be made. Demographic information, type of cancer, and the year of diagnosis were collected.

RESULTS: There were a total of 767 GI related cancer records reviewed during the study period of which 354 (46%) patients were diagnosed with GC. There were 413 patients with other GI cancer including; esophagus, colon, liver, rectum, pancreas, gall bladder, cholangio-carcinoma and other GI tract cancers. The GC incidence rate is approximately 0.9/10000 per year (367 cases/5

years per 800000 people). The geographic distribution of GC was the lowest in the south region of Bhutan 0.3/10000 per year compared to the central region 1.4/10000 per year, Eastern region 1.2/10000 per year, and the Western region 1.1/10000 per year. Moreover, GC in the South part was significantly lower than the other GI cancer in the same region (8% *vs* 15%; OR = 1.8, 95%CI: 1.3-3.1, *P* = 0.05). Among GC patients, 38% were under the age of 60 years, mean age at diagnosis was 62.3 (\pm 12.1) years with male-to-female ratio 1:0.5. The mean age among patients with all other type GI cancer was 60 years (\pm 13.2) and male-to-female ratio of 1:0.7. At time of diagnosis of GC, 342 (93%) were at stage 3 and 4 of and by the year 2013; 80 (23%) GC patients died compared to 31% death among patients with the all other GI cancer (*P* = 0.08).

CONCLUSION: The incidence rate of GC in Bhutan is twice as high in the United States but is likely an underestimate rate because of unreported and undiagnosed cases in the villages. The high incidence of GC in Bhutan could be attributed to the high prevalence of *Helicobacter pylori* infection that we previously reported. The lowest incidence of GC in Southern part of the country could be due to the difference in the ethnicity as most of its population is of Indian and Nepal origin. Our current study emphasizes on the importance for developing surveillance and prevention strategies for GC in Bhutan.

Key words: Gastric cancer; Mortality; Epidemiology; Bhutan

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Core tip: The incidence rate of gastric cancer (GC) in Bhutan is twice as high in the United States but is likely an underestimate rate because of unreported and undiagnosed cases in the villages. The high incidence of GC in Bhutan could be attributed to the high prevalence of *Helicobacter pylori* infection that we previously reported. The lowest incidence of GC in Southern part of the country could be due to the difference in the ethnicity as most of its population is of Indian and Nepal origin. Our current study emphasizes on the importance for developing surveillance and prevention strategies for GC in Bhutan.

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INTRODUCTION

Gastric cancer (GC) is the second leading cause of cancer-related mortality and the fourth most common cancer globally^[1-3]. However, its incidence rates in different geographical regions are distinctly varied^[2]. It been reported that in East Asia, high-risk countries include South Korea, Japan and China, where the age-standardized incidence rate is higher than 20 cases of GC per 100000 inhabitants per year^[2]. The World Health Organization reports the incidence of GC in Bhutan to be very high^[4]; however there is no published data yet. Bhutan is a small mountainous country bordering India and China and consists of four geographical regions, west, east, central, and south with a population consists of 800000 citizens.

It has been established that a *Helicobacter pylori* (*H. pylori*) infection is an etiologic agent of chronic gastritis and peptic ulcer disease, GC and mucosal associated lymphoid tissue lymphoma (MALT) and it is listed as a number one carcinogen^[5-8]. We previously reported a very high prevalence of *H. pylori* in Bhutan^[9,10]. Childhood hygiene practices and family education determine the prevalence of *H. pylori* infection^[11,12]. The current study aimed to estimate the incidence of GC in Bhutan and to compare the geographic distribution of GC to our previously reported geographic distribution of *H. pylori* infection.

MATERIALS AND METHODS

Data source and case identification

Between 2008 and 2013, five-year period, the medical records of all Gastro-Intestinal Cancer patients who underwent medical care and confirm diagnosis of cancer were reviewed at the National Referral Hospital, Thimphu which is the only hospital in the country where surgical and cancer diagnosis can be made. Diagnosis and ascertainment of the GC cases was based on endoscopic and pathological examination. There is only one surgeon in the country (TD) who operates on most/all the oncology cases in the country and there not yet established GC registry in Bhutan. Demographic information, *e.g.*, age, gender, place of residence, and date of diagnosis were collected. For each patient, type of gastro-intestinal cancer was retrieved.

Geography, population, and climate of Bhutan

Bhutan is a remote Himalayan country between India and Tibet (China) with a population consists of only 800000 citizens residing in 18147 sq mi (47000 sq km) (Figure 1). Seventy percent of country is rural and agriculture based and the literacy rate is 47% (2011



Figure 1 Geographic of the map of Bhutan.

Census). More than 30% of Bhutan populations live below poverty level. The climate in Bhutan varies with elevation, from subtropical in the south to temperate in the highlands and polar-type climate, with year-round snow in the north.

Bhutan is demographically divided into four main regions, Southern, Western, Eastern, and central regions. The Southern region shares border with India and ethnically they are of Indian and Nepal origin. The Western region is mostly on higher altitudes and socioeconomic standard is higher than Southern region. The normal water supply is through rural water scheme that is supported by the government and most people use local streams, rivers and piped water supply. The Central region shares similarity with the Western region both socioeconomically and geographically though it is little warmer. The Eastern region is lower in altitude than the Western region and have similar rural water supply scheme as the Western region.

Statistical analysis

Calculation of the crude incidence rate was based on the number of recorded cases divided by the overall population by the number of years. The estimated Bhutan population in 2005 was 800000.

RESULTS

There were a total of 767 GI related cancer records reviewed during the years of 2008 and 2013. There were 354 (46%) patients diagnosed with GC and 413 patients with diagnosed with esophagus, colon, liver, rectum, pancreas, gall bladder, cholangio-carcinoma

and other types of GI cancers. The GC incidence rate was approximately 0.9/10000 per year (354 cases/5 years/800000 people). Among GC patients, 38% were under the age of 60 years, mean age at diagnosis was 62.3 (SD \pm 12.1) years and the male-to-female ratio 1:0.5. The mean age among patients with all other type GI cancer was 60 years (\pm 13.2) and male-to-female ratio of 1:0.7. GC in the South part was significantly lower than the other GI cancer in the same region (8% vs 15%, OR = 1.8, 95%CI: 1.3-3.1, P = 0.05).

The geographic distribution of the overall number of GC cases by each city is presented in Figure 1. We calculated the incidence rate of GC by each region; we found that the geographic distribution of GC was the lowest in the Southern region of Bhutan 0.3/10000 per year compared to the central region 1.4/100000 per year, Eastern region 1.2/10000 per year, and the Western region 1.1/10000 per year (Figure 2). As we previously reported, the geographic distribution of *H. pylori* infection was the lowest in the south region of the country (Figure 3).

At time of diagnosis of GC, 10 (3%) of the patients were at stage 1, 15 (4%) at stage 2, 211 (60%) at stage 3 and 118 (33%) stage 4. By the year 2013; 79 GC patients (22%) died.

DISCUSSION

The latest estimate of the global incidence rates of GC was updated by the International Agency for Research on Cancer in 2008 report estimated that there were 989000 new cases of GC or (7.8% of all reported cancer cases)^[1-3]. We found that the incidence rate

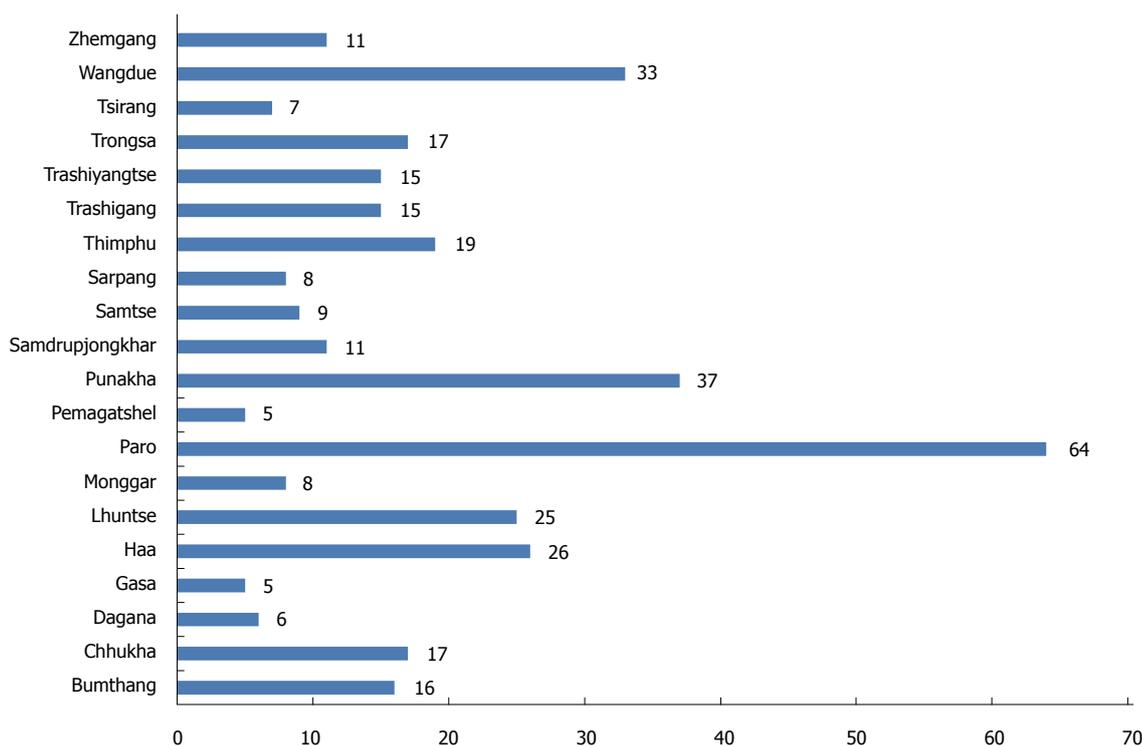


Figure 2 Gastric cancer cases distribution by area in Bhutan.

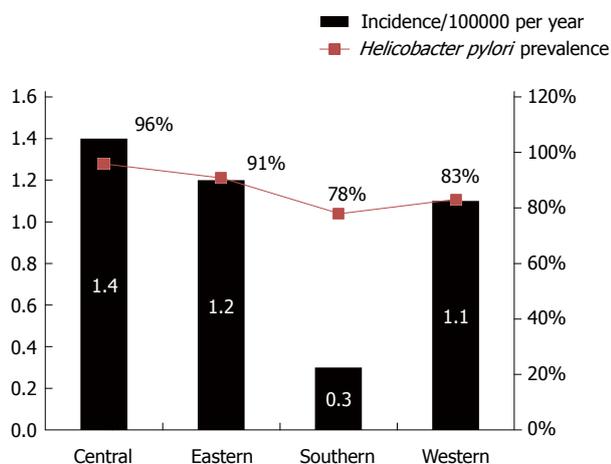


Figure 3 Geographic distribution of the incidence of gastric cancer and *Helicobacter pylori* infection.

of GC in Bhutan is high as it is second higher rate of cancer in the country after the incidence of cervical cancer (Unpublished data). The results of the current study add more emphasis to literature of the high GC incidence rate in South Asia, as the current study is the first report of the incidence of GC in Bhutan. In our previous study in Bhutan when we assessed subjects for gastric mucosal atrophy, we found that PG I/II ratio was significantly inversely correlated with the atrophy score in the antrum and the corpus. Furthermore, we found that the PG status was significantly associated with the presence of atrophy in the corpus and the prevalence of the PG-positive

status was significantly higher among *H. pylori*-positive subjects than among *H. pylori*-negative subjects. We concluded that the high incidence of GC in Bhutan can be attributed to the high prevalence of *H. pylori* infection and gastric mucosal atrophy^[13].

Geographic variations in GC incidence have been reported in both the West and the East^[14-16]. Of interest our results revealed the lowest GC rate was found in south Bhutan than the rest of the country. This variation is consistent with our previous published results of the finding of the lowest *H. pylori* prevalence in the south part Bhutan^[9]. The marked lower prevalence in the Southern region could be due is the different of the ethnicity in the region as they are of Indian and Nepal origin and they have different food habits than the original Bhutanese. It is known that Bhutanese are broadly from three ethnic backgrounds. The first ethnic group is from Tibetan descent that mainly from the Western parts of the country while the second is the Indo-Burmese ethnic group where mostly from the population in the Eastern parts of the country, the Southern Bhutanese, the third group, is of the Nepali origin and mainly Aryan descent. Migration studies have shown that first-generation migrants from countries with a high incidence of *H. pylori* infection relocating to countries of low incidence rates had similar risks as that of the country of origin, but the incidence rate tended toward that of the host country in subsequent generations, suggesting the important role of environmental risk factors^[17-20]. Moreover, various biological strains could be present in different

parts of the country and within individuals. A study published that Indian *H. pylori* isolates have been shown to have European origins and are widely held to be only mildly pathogenic^[21].

The high incidence of GC in Bhutan could be attributed to the high prevalence of *H. pylori* infection that we previously reported. Moreover, it was also reported that host genetic have an impact on host responses to gastric inflammation and acid secretion, thereby interacting with *H. pylori* infection in gastric carcinogenesis. Therefore, host genetic factors may determine why some individuals infected with *H. pylori* develop GC, while others do not^[22].

It has been established that a *H. pylori* infection is an etiologic agent of chronic gastritis and peptic ulcer disease, GC and MALT and it is listed as a number one carcinogen^[1-4]. Several studies and randomized controlled trials showed that *H. pylori* eradication reduce GC incidence by at least 35%^[23-28]. Current consensus is that *H. pylori* screening and treatment is effective only in high-risk populations^[29-32]. However, up till today such screening/surveillance had not taken place yet in Bhutan in spite the high prevalence of *H. pylori* infection and high GC rate among all age groups.

The current study revealed that 95% of GC patients were diagnosed at stages 3 and 4 and accordingly this could result in a higher mortality than early diagnosis. Early cancer detection is important because countries that perform GC surveillance, such as Japan and Korea, have lower mortality rates^[3]. The Asian-Pacific Consensus Group recommended the screening and treatment of *H. pylori* as an evidenced-based and reasonable strategy for primary prevention of GC in selected communities where the burden of GC is high^[32].

It has been well documented that treatment of *H. pylori* infection has an impact on the precursors of GC. A study from Colombia, a region with high GC risk, assessed the effect of *H. pylori* eradication therapy on intestinal metaplasia, multifocal atrophy and dysplasia in reported significant regression in histopathology score after treatment^[33-36]. A recent study from Taiwan reported that mass eradication of *H. pylori* infection resulted in significant reduction in incidence of gastric atrophy resulting from chemoprevention^[37]. Adopting the 2008 Asia-Pacific guidelines for a low threshold for treatment of symptomatic patients, as well as low cost follow-up testing could significantly lower the prevalence of peptic ulcer disease, GC. Therefore, there it is a great need for developing surveillance and prevention strategies for GC in Bhutan.

The utilization of the current data for constructing our study has some shortcomings that should be addressed. The main limitation is that we relied on the hospital records and not GC registry to identify the cancer cases. However, up till today, there is no cancer registry in Bhutan and the Timphu National hospital is the only hospital that diagnoses all cancer cases in

the country, so our data is valid as representative GC cases in Bhutan. The second limitation of the study that we did not have enough data to calculate the overall mortality rate due GC and further studies are highly needed to address that topic.

In conclusion, this study demonstrates clear evidence of the high GC incidence in Bhutan that could be attributed to the high prevalence of *H. pylori* infection that we previously reported. The lowest incidence of GC in Southern part of the country could be due to the difference in the ethnicity as most of its population is of Indian and Nepal origin. Our current study emphasizes on the importance for developing surveillance and prevention strategies for GC in Bhutan.

COMMENTS

Background

The World Health Organization reports the incidence of gastric cancer (GC) in Bhutan to be very high; however there is no published data yet. GC is the second leading cause of cancer-related mortality and the fourth most common cancer globally. However, its incidence rates in different geographical regions are distinctly varied. It has been established that a *Helicobacter pylori* (*H. pylori*) infection is an etiologic agent of chronic gastritis and peptic ulcer disease, GC and mucosal associated lymphoid tissue lymphoma and it is listed as a number one carcinogen.

Research frontiers

The authors performed a retrospective study on a cohort of patients estimate the incidence of GC in Bhutan and to compare the geographic distribution of GC to our previously reported geographic distribution of *H. pylori* infection.

Innovations and breakthroughs

The incidence rate of GC in Bhutan is twice as high in the United States but is likely an underestimate rate because of unreported and undiagnosed cases in the villages.

Applications

The high incidence of GC in Bhutan could be attributed to the high prevalence of *H. pylori* infection that the authors previously reported. The lowest incidence of GC in Southern part of the country could be due to the difference in the ethnicity as most of its population is of Indian and Nepal origin. It is of importance for developing surveillance and prevention strategies for GC in Bhutan.

Peer-review

This is an interesting and well written paper.

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