Original paper

Geographic particularities in incidence and etiopathogenesis of sporadic gastric cancer

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It is known that geographical differences in the prevalence and etiopathogenesis of gastric cancer exist across the world. Eastern Europe and East Asia are two of the largest endemic areas of gastric cancer in the world, yet there are few studies comparing its features in these two regions. Based on our experience and literature data, we performed a review that is mainly focused on the etiology and pathogenesis of sporadic gastric cancer and its geographic particularities. Geographic prevalence of specific *Helicobacter pylori* strains is also synthesized. The pathogenesis of gastric cancer in patients from countries of the authors, respectively Japan, Romania, Hungary and Poland, is particularly examined.

Key words: gastric cancer, Poland, Romania, Hungary, Japan.

Introduction

Although the incidence of gastric cancer (GC) has fallen significantly in the United States and across the world over the past few decades [1], it still remains the fifth most common malignancy and the third leading cause of cancer death [1, 2, 3]. There are approximately 900,000 new cases of GC per year and 723,000 registered deaths worldwide [4, 5]. In the United States, it was reported that the 5-year relative survival rates increased significantly from 1975 to 2009, from 15% during 1975-1977 to 20% during 1987-1989 and up to 29% during 2003-2009 [6]. In 2002, GC-related deaths were the 15th leading cause of mortality from all causes worldwide, and it is estimated that GC will be the 10th cause by the year 2030 [7].

The incidence of GC depends on demographic factors such as geographic region, patient's race, gender, and socioeconomic status [1]. In this review, we pay special attention to the home countries of the authors: Japan, representing East Asia, and Poland, Hungary, and Romania, representing Eastern Europe.

Asiatic versus European countries

In Europe, independently of the age of the patients, the diffuse type of GC (poorly cohesive adenocarcinomas and signet ring-cell adenocarcinomas) and also cardial location have increased in the last decades, compared with the intestinal-type adenocarcinomas (well/moderately differentiated and mucinous adenocarcinomas) and distal location [1]. Regarding the gastric body, it seems that the intestinal type predominates in this anatomic area. In East Asia, independent of the histological type, increasing incidence of non-cardia carcinomas was reported [1]. However, East Asia (Japan, Korea, China), Eastern Europe, and parts of Central and South America (especially Chile) seem to remain in the first places among countries with the highest risk of GC, while Australia, New Zealand, South Asia, North America, the United Kingdom, North Europe, and North and East Africa present the lowest rates of incidence [1, 4, 7].

Developing versus developed countries

Most of the published studies have revealed that low-economic level is associated with a predisposition for distally located tumors, their incidence especially increasing in developing countries such as Iran or India, while the number of diagnosed gastro-esophageal and cardia carcinomas rose in the past three decades by five- to sixfold in developed countries such as the UK, Norway, Denmark, and New Zealand [1, 8, 9, 10, 11]. On the other hand, the incidence of diffuse-type carcinomas increased independently of the geographic distribution, but intestinal-type carcinomas occur rather in countries such as those of East Asia, Eastern Europe, Iran, Central, North and South America [1, 4, 12]. However, up to 50% of the cases are diagnosed in developing countries, and half of the world's total occurs in Eastern Asia (mainly China), most of them in late stages, due to the absence of well-conducted screening programs. The geographic-related incidence of GC is also proved by a significantly higher number of cases diagnosed, for example, in South India when compared with North India [13].

GC remains the second or third leading cause of cancer death in most countries [1, 5], except the USA, where it seems to represent the 7th most common cancer death in the white (non-Hispanic) population [6].

White versus black races

Although intestinal-type carcinomas and location in the pyloric area of the stomach predominate in blacks and the proximally located tumors are increasing in incidence in whites [1, 14], it was proved that, independently of the patient's race, the geographical environmental factors and lifestyle modifications may play a role in the tumor location. For example, the incidence of GC decreased in Japanese people when they moved to low incidence regions [1], with the next generations presenting the same risk as the host country. In the US, the highest incidence was reported in Asian and Pacific islanders followed by blacks, Hispanic, American Indians, and whites [6].

Males versus females

Most of the published studies have revealed a male predominance of GC, the male-to-female ratio being about 2:1 for non-cardia carcinomas and 4-5:1 for the gastro-esophageal and cardia tumors, especially in the western countries [1, 13, 14]. In Asia, a 1 : 1 ratio was reported, with an increasing number of males for tumors located in the lower third of the stomach [1, 3]. Regarding the microscopic type, a male predominance is seen for intestinal type (M : F = 2 : 1), whereas the diffuse type is characterized by a more equal male-to-female ratio, especially in young patients, similar to the original description of Lauren from 1965 [1, 12, 14, 15].

Japan versus Poland, Hungary, and Romania

Similarly to other developing countries, most of the GCs diagnosed in Poland, Hungary, and Romania are in advanced stages, a tendency for proximal location and diffuse type of cancer being observed in the last 10 years. In **Romania**, a country with 18 million inhabitants, the GC incidence is about 16.66/100,000 (M : F = 2 : 1); 3000-4000 new cases are diagnosed every year, with an annual mortality rate of about 5.9% in females and 7.7% in males [16]. In Romania, GC incidence represents the 4th place in males and the 5th in females, being the second cause of cancer-related deaths. Between the years 2000 and 2004, GC average mortality was 16.75/100,000 in men and 6.27/100,000 in women [17], with a slightly decreasing rate during 2005-2009, in both genders (14.68/100,000 in men and 5.31/100,000 in women) [18]. In our department from Tirgu-Mures (central part of Romania, Transylvania), which is within a university hospital (150 beds in the Department of Surgery), about 100-120 new cases of GC are diagnosed annually; up to 70% of the cases are diagnosed in locally advanced stages, due to the absence of a national screening program. The 5-year survival rate in Romanian patients is below 15% (Gurzu *et al*. personal communication).

In **Hungary,** there are about 10 million inhabitants, and the 5-year mortality rate as a result of GC is about 15% (12.60/100,000 in men and 5.70/100,000 in women). Regarding the Hungarian incidence of GC, about 2200 new cases are diagnosed every year (M : F = 1.75 : 1), and GC is in the 4th place in males and the 5th place in females, from all cancers, similar to Romania. However, a tendency of decreasing incidence has been reported in the last years [17, 18].

There are 37 million inhabitants in **Poland** and about 5400 new cases of GC diagnosed annually with the incidence of 14.59/100,000 (M : F = 1.75 : 1) in 2011. More than 55% of GC patients are diagnosed in late stages. In an analysis of 15,066 cases of GC diagnosed in Poland in the last decade, the 5-year relative survival rate was 16.1% (12.94/100,000 in men and 4.68/100,000 in women) [19]. In men, a noticeable decrease of incidence was reported, from the 4th commonest malignancy in 2000 to the 6th position in 2011; a simultaneously rising number of deaths was observed, from the 3rd to the 4th position, respectively [5, 19].

In **Japan**, the country with the highest national incidence of GC worldwide, the age-adjusted inci-

dence rate of GC declined during 1975-1995, from 76.0/100,000 to 53.0 in men and from 38.4/100,000 to 21.3 in women, respectively. A few years later, in 2004, the reported incidence was 69.2/100,000 in men and 28.6/100,000 in women [1, 3, 20]. The distal location is predominant, but the incidence of tumors located in the upper third of the stomach is increasing among elderly males contrary to young people [21]. This profile of Japanese GCs, with high prevalence in the aged population [22], sheds light on another aspect when comparative pathological characteristics are discussed. It is estimated that 70% of GC cases in Japan occur in patients older than 65 years. Apart from the annual trend of increase of proximal cancers, Arai et al. focused on the particular population older than 65 years and found an age-dependent increase of cancer of the lower third of the stomach. In this population overall population, differentiated-type adenocarcinoma accounted for 89.6% in the early cancers and 50.3% in the advanced cancers. The proportion of cases involving differentiated-type carcinoma significantly increased with advancing age in early cancer and female advanced-cancer cases, whereas no significant change was found in male advanced-cancer patients [22].

Furthermore, the stages of GCs which Japanese patients have been pointed out for the first time in their life are quite different from those in the other country. In a single large clinical center, early GC represented 15% of all carcinomas in the 1960s and 50% at the beginning of this century [23]. However, Japan is the only country where mass screening for stomach cancer has been a national policy (encouraged since 1966) and has been included in the Health Services Law for the Aged since 1983 [20]. As a consequence, during 1975-1995, the age-adjusted mortality rate declined in Japan from 60.2% to 34.2% in men and 30.5% to 14.1% in women [20]. The 5-year survival rate, naturally, rose from 40% in the 1960s to 70% at the beginning of this century [23]. Putting it in a different way, free access and almost full coverage of the Japanese health insurance system influenced these observations, including detection bias.

The carcinogenic influence of interaction between environmental factors and *Helicobacter pylori*

It is well known that environmental factors influence the incidence of GC, being proved that *Helicobacter pylori (H. pylori)*, especially when carrying the cytotoxin-associated gene A (*cagA*+) [2], and dietary factors increase the risk for distal GC, while obesity, Barrett's esophagus, and gastro-esophageal reflux are the main predisposing factors of gastro-esophageal tumors [1, 4]. At the same time, non-atrophic pangastritis is the main premalignant status of diffuse type adenocarcinomas, while atrophic gastritis and intestinal metaplasia are rather related to intestinal type carcinomas of the pyloric area and gastric body [1]. However, cardia carcinomas seem to have a lower survival rate in comparison with the non-cardia ones [1]. It is observed that cagA disappears in metaplastic and tumor cells, being supposed that it plays an important role in the first steps of malignant transformation of gastric mucosa, through induced tyrosine phosphorylation [24, 25]. Moreover, the inflammatory tumor background increases the level of the proinflammatory cytokines such as interleukin-1 that could also induce genetic changes [26].

Regarding the lifestyle habits, the intake of salty, salt-preserved, smoked, or chemically preserved foods, pickled vegetables, chili peppers, as well as the nitrites from preserved meats, associated with low consumption of fresh fruits and vegetables [1, 4, 7] and decreased general fitness [2], are the main predisposing factors involved in pathogenesis of non-cardia GC, especially in association with infection with *H. pylori* [1, 27]. This bacillus favors synthesis of N-nitroso compounds and inhibits the activity of ascorbic acid that plays important roles in the formation of oxygen free radicals and degradation of N-nitroso compounds [1, 27]. At the same time, *H. pylori* induces detachment of E-cadherin and other junctional proteins [28], as a first step of carcinogenesis of diffuse type gastric carcinoma, with or without familial predisposition. It is interesting that red (e.g. beef) and processed meat consumption is associated with the risk of GC but not lamb or white meat [29].

Another predisposing factor for both cardia and non-cardia cancers is cigarette smoking [30], which seems to enhance the carcinogenic effect of *H. pylori* [4, 31]. The risk for GC increases by 60% in male and 20% in female smokers when compared with non-smokers [4, 32]. It is noticeable that nicotine increases tumor cell proliferation and promotes tumor angiogenesis in a COX-2/VEGF (vascular endothelial growth factor)-dependent manner [33]. At the same time, *H. pylori* promotes VEGF activity via the p38 MAPK-mediated COX-2-PGE2 pathway [34]. The nicotine-activated COX-2 stimulates ERK (extracellular signal-regulated kinases) phosphorylation and initiates the epithelial-mesenchymal transition via upregulation of adhesion proteins such as periostin inside the tumor cells [33, 34, 35]. On the other hand, the International Agency for Research on Cancer (IARC) revealed that the concentration of acetaldehyde, a group 1 human carcinogen and a water-soluble compound, is over 1000-fold in cigarette smoke; during active smoking, it dissolves in saliva and reaches high concentrations by modifying the oral flora to produce more of the compound from ethanol. Together, smoking and alcohol intake seem

to have a seven-fold effect in increasing exposure of the upper gastrointestinal tract to acetaldehyde [7, 36], although there are authors who even deny the carcinogenic role of alcohol in gastric carcinogenesis [37] or consider that the risk of non-cardia intestinal-type GC is higher in patients whose intake is ≥ 60 g alcohol/day, 2-7 days/week, for a medium period of 9-10 years [38]. Regarding the type of the ingested alcohol, heavy wine drinkers are more predisposed than consumers of beer or vodka [39].

Table I. Geographic distribution of *H. pylori* strains [24, 25, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50]

H. pylori prevalent type/strain	*H. pylori* genotype	Prevalent countries (*H. pylori* incidence)	Predominant ethnicity in the same country	Associated lesions
East Asian type *cagA*	*m1*	Japan (100%), China (65%)	NS	Virulent genotype -frequent GC
		Thailand	Chinese ethnicity	
Western type *cagA*	NS	Europe (50% – overall incidence; Portugal – 75%), Africa, South Asia (India)	NS	Rare GC
		Thailand	Thai ethnicity	
vacA s1	*s1a*	South Asia, Turkey, Northern Europe	NS	High-grade gastritis
	s1b	Portugal, Spain	NS	
	s1c	East Asia (Japan, China)	NS	
	s1m1	Brazil, Eastern Europe (Slovenia), Midwestern USA, Asia (Japan, Korea, China [19%]))	NS	High-grade gastritis
	s1m2	Turkey (57%), Poland (84%), Asia (Vietnam, Hong Kong, China [40%])	NS	Rare GC
	s2m2	Spain	NS	NS
vacA m1+	NS	NS	NS	High-grade gastritis
iceA1	NS	Asia (Korea [76%], China [63%]), Slovenia (62%), North America (44%), Israel (37%), Brazil (20-30%), Turkey (2-30%)	NS	NS
iceA2	NS	Midwestern USA (84%), Brazil (55%), Turkey (55%), Israel (52%), China (19%)	NS	NS
cagE	NS	Canada (59%), Bulgaria (42%), Israel (25%), Turkey (22%)	NS	NS
babA2	NS	Brazil (84%), Bulgaria (67%), Turkey (41%), Midwestern USA (36%), Portugal (17%) [no differences in East Asia vs. Western countries]	NS	NS

bab – blood group antigen binding adhesion; cag – cytotoxin-associated gene; GC – gastric cancer; NS – non-specific

Coffee consumption does not seem to influence the occurrence of GC [37], whereas green tea has a protective role due to high antioxidant content [40].

It is unclear why East Asian patients with *H. pylori* infection present a high risk for GC while patients from Africa, Thailand, South Asia (e.g. India), and Western patients do not have such a high risk. One explanation could be the geographical prevalence of some *H. pylori* type/strains; data from the literature reports in the field are synthesized in Table I [24, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50].

Regarding hereditary diffuse gastric cancer (HDGC), infection with *H. pylori* was denied in eligible families from North America and Europe, except one family from Portugal and two families from New Zealand [41, 48]. At the same time, in the first-degree relatives of early-onset GC patients from Portugal (diffuse, intestinal, and mixed-type), gastric atrophy was detected in 70% of the cases, compared with 34% of controls, and *H. pylori vacA* prevalence was similar in the two groups [42, 49]. Dysplasia was seen in 19% of these cases, especially in people homozygous for *IL1B-511*T*, being negative in controls, while intestinal metaplasia was observed in 43% of the cases, compared with 25% of controls [42]. While *H. pylori* and intestinal metaplasia are not characteristic for HDGC, this study highlights, in line with other published data, the fact that the familial clustering is related not only to the genetic heritage but also to family alimentary habits and lifestyle, and the exposure to an ethnicity-specific type of *H. pylori* can also influence the inheritance [42, 50].

A pertinent and valuable observation is that disorders of the genetic information predispose to early-onset carcinoma while environmental factors contribute to GC of older age, which can also have a genetic component [42]. This observation is also sustained by the recently reported African enigma in which a higher incidence of GC was identified in Okinawa-Japan (a small island with a US population) when compared with mainland Japan, in patients infected with similar *H. pylori* strains [41]. At the same time, natives from Japan and China immigrating to Singapore have a higher risk for GC than those living in Hawaii [43].

From all GCs, 0.4-5.4% of patients present *H. pylori* negative carcinomas (HpNGC). They are diagnosed based on the following minor criteria proposed in 2015 by Yamamoto *et al.* [51]: negativity for *H. pylori* proved by endoscopic and/or pathological examinations, negative UBT or serum IgG test, negative serum pepsinogen test, and no *H. pylori* eradication history. These tumors are mostly early onset flat or depressed poorly cohesive (predominately signet ring cell type) carcinomas located in the lower third stomach. The intestinal-type HpNGCs are more frequently diagnosed in elderly patients and involve the gastric body [51].

Summary and perspectives

For GC, screening programs and clinical surveillance should be performed based on a large spectrum of clinicopathological factors including geographic particularities. Because *H. pylori* remains one of the commonest factors with a possible carcinogenic influence, the screening and eradication should be performed taking into account identification of its prevalent subtype for a specific geographic region. Moreover, as COX-2 overexpression seems to influence gastric carcinogenesis, long-time consumption of anti-COX-2 substances, combined with cessation of alcohol and smoking and decreasing ingestion of processed and red meat, could lead to decreasing incidence of sporadic GC worldwide.

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References

1. Crew KD, Neugut AI. Epidemiology of gastric cancer. World J Gastroenterol 2006; 2: 354-362.
2. Guilford P, Blair V, More H, Humar B. A short guide to hereditary diffuse gastric cancer. Hered Cancer Clin Pract 2007; 54: 183-194.
3. Parkin DM. International variation. Oncogene 2004; 23: 6329-6340.
4. Vogelaar IP, van der Post RS, Bisseling TM, et al. Familial gastric cancer: detection of a hereditary cause helps to understand its etiology. Hered Cancer Clin Pract 2012; 10: 18.
5. International Agency for Research. Stomach cancer. Estimated incidence, mortality and prevalence worldwide in 2012. Globocan 2012: Estimated cancer incidence and prevalence worldwide in 2012. Available from: URL: www.globocan.iarc.fr.
6. Siegel R, Ma J, Zou Z, Jemal A. Cancer Statistics 2014. Ca Cancer J Clin 2014; 64: 9-29.
7. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PloS Med 2006; 3: e442.
8. Lynch HT, Grady W, Suriano G, Huntsman D. Gastric cancer: new genetic developments. J Surg Oncol 2005; 90: 114-133.
9. Hansen S, Wiig JN, Giercksky KE, Tretli S. Esophageal and gastric carcinoma in Norway 1958-1992: incidence time trend variability according to morphological subtypes and organ subsites. Int J Cancer 1997; 71: 340-344.
10. Møller H. Incidence of cancer of oesophagus, cardia and stomach in Denmark. Eur J Cancer Prev 1992; 1: 159-164.
11. Armstrong RW, Borman B. Trends in incidence rates of adenocarcinoma of the oesophagus and gastric cardia in New Zealand, 1978-1992. Int J Epidemiol 1996; 25: 941-947.
12. Guilford P, Hopkins J, Harraway J, et al. E-cadherin germline mutations in familial gastric cancer. Nature 1998; 392: 402-405.
13. Sharma A, Radhakrishnan V. Gastric cancer in India. Indian J Med Paediatr Oncol 2011; 32: 12-16.

14. Lauren P. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol 1965; 64: 31-49.
15. El-Serag HB, Mason AX, Petersen N, Key CR. Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. Gut 2002; 50: 368-372.
16. Globocan (n.d.). Fact Sheets by Population. Retreived May 17, 2014, from http://globocan.iarc.fr/Pages/fact_sheets_population.aspx?country=642.
17. La Vecchia C, Bosetti C, Lucchini F, et al. Cancer mortality in Europe, 2000-2004, and an overview of trends since 1975. Ann Oncol 2010; 21: 1323-1360.
18. Bosetti C, Bertuccio C, Malvezzi M, et al. Cancer mortality in Europe, 2005-2009, and an overview of trends since 1980. Ann Oncol 2013; 24: 2657-2671.
19. Wojciechowska U, Didkowska J, Zatonski W. Cancer in Poland – five-year survival rates by regions. The Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology. Warsaw Poland 2010; 15.
20. Lambert R, Guilloux A, Oshima A, et al. Incidence and mortality from stomach cancer in Japan, Slovenia and the USA. Int J Cancer 2002; 97: 811-818.
21. Liu Y, Kaneko S, Sobue T. Trends in reported incidences of gastric cancer by tumour location, from 1975 to 1989 in Japan. Int J Epidemiol 2014; 33: 808-815.
22. Arai T, Esaki Y, Inoshita N, et al. Pathologic characteristics of gastric cancer in the elderly: a retrospective study of 994 surgical patients. Gastric Cancer 2004; 7: 154-159.
23. Suzuki H, Gotoda T, Sasako M, Saito D. Detection of early gastric cancer: misunderstanding the role of mass screening. Gastric Cancer 2006; 9: 315-319.
24. Yamakawa A, Yamazaki S, Fukuta K, et al. Correlation between variation of the 3' region of the cagA gene in Helicobacter pylori and disease outcome in Japan. J Infect Dis 2002; 186: 1621-1630.
25. Yamazaki S, Yamakawa A, Ito Y, et al. The CagA protein of Helicobacter pylori is translocated into epithelial cells and binds to SHP-2 in human gastric mucosa. J Infect Dis 2003; 187: 334-337.
26. El-Omar EM, Rabkin CS, Gammon MD, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology 2003; 124: 1193-1201.
27. O'Connor HJ, Schorah CJ, Habibzedah N, et al. Vitamin C in the human stomach: relation to gastric pH, gastroduodenal disease, and possible sources. Gut 1989; 30: 436-442.
28. Humar B, Fukuzawa R, Blair V, et al. Destabilized adhesion in the gastric proliferative zone and c-Src kinase activation mark the development of early diffuse gastric cancer. Cancer Res 2007; 67: 2480-2489.
29. Zamani N, Hajifaraji M, Malekshah AF, et al. A Case-control Study of the Relationship between Gastric Cancer and Meat Consumption in Iran. Arch Iran Med 2013; 16: 324-329.
30. Koizumi Y, Tsubono Y, Nakaya N, et al. Cigarette smoking and the risk of gastric cancer: a pooled analysis of two prospective studies in Japan. Int J Cancer 2004; 112: 1049-1055.
31. Gonzales CA, Lopez-Carillo L. Helicobacter pylori, nutrition and smoking interactions: their impact in gastric carcinogenesis. Scand J Gastroenterol 2010; 45: 6-14.
32. Ladeiras-Lopez R, Pereira AK, Nogueira A, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Causes Control 2008; 19: 689-701.
33. Shin VY, Wu WK, Ye YN, et al. Nicotine promotes gastric tumor growth and neovascularization by activating extracellular signal-regulated kinase and cyclooxygenase-2. Carcinogenesis 2004; 25: 2487-2495.
34. Liu N, Wu Q, Wang Y, et al. Helicobacter pylori promotes VEGF expression via the p38 MAPK-mediated COX-2-PGE2 pathway in MKN45 cells. Mol Med Rep 2014; 10: 2123-2129.
35. Liu Y, Liu BA. Enhanced proliferation, invasion, and epithelial-mesenchimal transition of nicotine-promoted gastric cancer by periostin. World J Gastroenterol 2011; 17: 2674-2680.
36. Salaspuro M. Acetaldehyde and gastric cancer. J Dig Dis 2011; 12: 51-59.
37. Franceschi S, La Vecchia C. Alcohol and the risk of cancers of the stomach and colon-rectum. Dig Dis 1994; 12: 276-289.
38. Duell EJ, Travier N, Lujan-Barosso L, et al. Alcohol consumption and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Am J Clin Nutr 2011; 94: 1266-1275.
39. Everatt R, Tamosiunas A, Kuzmickiene I, et al. Alcohol consumption and risk of gastric cancer: a cohort study of men in Kaunas, Lithuania, with up to 30 years follow-up. BMC Cancer 2012; 12: 475.
40. Setiawan VW, Zhang ZF, Yu GP, et al. Protective effect of green tea on the risks of chronic gastritis and stomach cancer. Int J Cancer 2001; 92: 600-604.
41. Yamaoka Y, Kato M, Asaka M. Geographic differences in gastric cancer incidence can be explained by differences between Helicobacter pylori strains. Intern Med 2008; 47: 1077-1083.
42. Marcos-Pinto R, Dinis-Ribeiro M, Carneiro F, et al. First-degree relatives of early-onset gastric cancer patients show a high risk for gastric cancer: phenotype and genotype profile. Virchows Arch 2013; 463: 391-399.
43. Nagini S. Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World J Gastrointest Oncol 2012; 4: 156-169.
44. Ozbey G, Dogan Y, Demiroren K. Prevalence of Helicobacter pylori virulence genotypes among children in Eastern Turkey. World J Gastroenterol 2013; 19: 6585-6589.
45. van Doorn LJ, Figueiredo C, Megraud F, et al. Geographic distribution of vacA allelic types of Helicobacter pylori. Gastroenterology 1999; 116: 823-830.
46. Maciorkowska E, Roszko I, Kowalczuk O, et al. The evaluation of vacA gene alleles frequency in Helicobacter pylori strains in children and adults in Podlaskie region. Folia Histochem Cytobiol 2007; 45: 215-219.
47. Zhou Y, Huang Y, Shao CH, et al. CagA, vacA and iceA genotypes of Helicobacter pylori isolated from children in Shanghai. Zhongguo Dang Dai Er Ke Za Zhi 2010; 12: 267-271.
48. Caldas C, Carneiro F, Lynch HT, et al. Familial gastric cancer: overview and guidelines for management. J Med Genet 1999; 36: 873-880.
49. Charlton A, Blair V, Shaw D, et al. Hereditary diffuse gastric cancer: predominance of multiple foci of signet ring cell carcinoma in distal stomach and transitional zone. Gut 2004; 53: 814-820.
50. Yamada H, Shinmura K, Ito H, et al. Germline alterations in the CDH1 gene in familial gastric cancer in the Japanese population. Cancer Sci 2011; 102: 1782-1788.
51. Yamamoto Y, Fujisaki J, Omae M, et al. Helicobacter pylori negative gastric cancer: characteristics and endoscopic findings. Dig Endosc 2015; 27: 551-556.

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