

Gastric cancer: Epidemiology, risk factors and prevention strategies

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Abstract

Gastric cancer (GC) is a global health problem, with more than 1 million people newly diagnosed with GC worldwide each year. GC is more prevalent in less developed countries than in more developed countries. About half of all GC cases worldwide occur in East Asia, notably China. Globally, overall incidence rates of GC are declining, which is potentially attributed to a decrease in *Helicobacter pylori* (*H. pylori*) infection and the use of refrigeration to preserve foods rather than salt. GC is a multifactorial disease, and its occurrence and development were impacted by environmental and genetic factors. *H. pylori* infection is the primary risk factor for GC, especially for non-cardia. The prognosis of GC is poor due to stages at the first diagnosis. The 5-year survival rate is less than 10% when patients are diagnosed at an advanced stage, but the rate is as high as 85% if patients are detected at an earlier stage. Endoscopic screening can potentially prevent GC by early diagnosis and early treatment and has been widely adopted in screening programs in East Asian countries, such as Japan and Korea. This review summarizes updated epidemiological aspects, risk factors, and prevention strategies of GC in recent years to help researchers determine the most effective intervention strategies for reducing risk of GC.

Keywords: Gastric cancer; epidemiology; risk factor; prevention strategy

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Introduction

Although gastric cancer (GC) incidence and mortality rates continue to decrease, GC remains the fifth most commonly diagnosed cancer worldwide and the third most common cause of cancer-related death (1). GC has divided anatomically into two main subsites: cardia GC (arising in the area of gastro-esophageal-junction) and non-cardia GC

(arising from more distal regions of the stomach) (2). Risk factors for tumors arising from cardia and non-cardia locations were different (3). In recent decades, the incidence rate of non-cardia GC has been decreased, which might be explained by the increased standards of hygiene, a high intake of fresh fruits and vegetables, reduced consumption of salt-preserved foods, and *Helicobacter pylori* (*H. pylori*) eradication (2). Evidence from western

countries indicated that rates of cardia GC are increasing. This increase in incidence is not fully understood but is suspected to be related to obesity, smoking, and gastroesophageal reflux (3). Symptoms of GC often only appear at a late stage, which contributes to a poor prognosis. The overall 5-year relative survival of GC is about 20%–30% in most areas of the world, except in Japan and Korea (4). Such high survival in these two countries may be attributed to the effectiveness of mass screening programs launched in these countries, which confer a higher proportion of early stage of GC at diagnosis (5,6). However, as a malignancy with a high aggressiveness and heterogeneous nature, GC's survival with local advanced or metastasis disease has not shown significantly improved and remains a severe global health problem (7). In 2014, by integrating whole-genome sequencing, The Cancer Genome Atlas (TCGA) defined four molecular subtypes of GC to provide a roadmap for patient stratification and trials of targeted therapies (8). With the genome-wide association studies (GWAS) development, investigators try to stratify the high-risk individuals based on the genetic and environmental factors, which makes a hot topic in recent years (9,10). This article reviews the current progress of epidemiology, risk factors, and prevention strategies of GC in recent years to provide suggestions for further disease control.

Incidence and mortality

A total of 1,089,103 individuals are diagnosed with GC worldwide in 2020, of whom about 768,793 die from this disease, making it the third leading cause of cancer death. The highest incidence rates (1/100,000) around the world are in East Asian countries such as Mongolia (32.5), Japan (31.6) and Korea (27.9) and low incidence rates have been described in Africa and North America. Owing to a large population, about 44% of GC (478,508 cases) worldwide have occurred in China with an adjusted incidence rate of 20.6/100,000 in 2020 (11). The disease has occurred more frequently among males than females with a male to female ratio of 2.4 (12).

Rates also vary across races and neighborhood socioeconomic status. For example, in the United States, GC incidence rates are higher in Latinos than in non-Hispanic White populations (3). Similarly, in China, the incidence rate (1/100,000) was markedly higher in rural areas than in urban ones (22.82 vs. 17.29), and a similar result was seen in mortality rates (16.12 vs. 11.51) (12). The

higher incidence rate in impoverished populations may be associated with high exposure of GC carcinogens from dietary habits and environmental risk factors, especially *H. pylori* infection. GC incidence rates have been declining significantly in most parts of the world in recent decades. In China, the incidence rates decreased by 1.8% for males annually from 2003 to 2011 and 2.7% for females from 2000 to 2011 (13). For mortality rates, a 17.8% decrease was observed between 2006 and 2013 (14). The marked decrease of GC incidence and mortality rates in many countries was in line with the global decrease in *H. pylori* infection prevalence during that period (15,16). Take anatomical site into consideration, unlike for decreasing incidence trends of non-cardia GC, cardia GC rates have remained stable or increased around the world (17,18). Such contrasting trends for cardia and non-cardia GC may result from distinct etiologies. Studies indicate that obesity and gastroesophageal reflux seem to be risk factors for cardia GC (3), while *H. pylori* infection was most associated with non-cardia GC. However, another study from the US showed an increasing trend in incidence rates of non-cardia GC in non-Hispanic Whites younger than 50 years between 1995 and 2013, which manifested a more pronounced birth cohort effect on women born in 1983 and *H. pylori* seems unlikely to have played a role for this incidence increasing among the generations of American young women. One hypothesis is that GC in these individuals is the consequence of autoimmunity related to dysbiosis of gastric microbiome (19). The investigation of non-*H. Pylori* gastric microbiota composition inducing GC and the reason for the incidence increasing of GC in young generations will be crucial in the future.

Survival

Global variation in GC survival was extensive. Age-standardized 5-year net survival for GC was very high in South Korea (68.9%) and Japan (60.3%), which was similar to the average 1-year survival for all other countries, such as China, Austria, Germany, and the UK, ranging between 13% and 41% (4). GC survival was generally higher in women compared to men in most of the countries (20,21). Regardless of gender, survival was considerably lower for elderly patients, on average 40% lower than that of the youngest patients. Even though there was a large range of survival differences between countries, patients diagnosed with cardia tumors tend to have a worse prognosis than those with tumors arising from non-cardia locations (22).

Equally, patients diagnosed with the intestinal subtype showed higher survival than those diagnosed with diffuse tumors (23). The diagnosis of tumors may partially explain the very high survival for all GC patients combined in East Asian countries at earlier stages and with biological characteristics that confer a better prognosis (4). The proportion of patients diagnosed with cardiac tumors, depicting worse survival, ranged from 6% in South Korea to 72% in Finland for men, and from 4% in South Korea to 52% in Serbia for women (24). The two main histological subtypes of tumors occurring in the stomach: intestinal, and diffuse adenocarcinomas (25), have different etiologies and prognosis, with the intestinal type occurring more often in non-cardia locations, among older patients and depicting higher survival (23). The stage at diagnosis may also vary between countries, as mass screening programs exist in China, Japan, Korea, and Chile, although with different diagnostic methods, population coverage, and target groups (6,26-28). Marked increase in GC survival was observed in South Korea (from 48.6% to 68.9%) and China (from 30.2% to 35.9%) in recent years (4).

Risk factors or etiology

Several factors noted to have an increased risk of developing GC include *H. pylori* infection, Epstein-Barr virus (EBV) infection, genetic susceptibility, dietary habits, alcohol consumption, and smoking (2,15). Moreover, risk factors for tumors arising from cardia and non-cardia regions of the stomach or tumors of intestinal and diffuse histological type were different (29).

H. pylori

H. pylori have been classified as carcinogen to humans (Class 1) by the World Health Organization (WHO) in 1994 (30). Chronic infection with *H. pylori* is the most prominent cause of GC, accounting for approximately 90% of intestinal-type non-cardia cancer (15). Two main mechanisms have described the effect of *H. pylori* on the pathogenic process: an indirect inflammatory reaction to *H. pylori* infection on the gastric mucosa and a direct epigenetic outcome of *H. pylori* on gastric epithelial cells (31). Infection with *H. pylori* is a necessary but not sufficient cause; this explains why GC incidence does not mirror the prevalence of *H. pylori* infection (15). Studies demonstrated that people in East Asia harbor aggressive strains of *H. pylori*, have a diet that is high in salt, and may

have genetic elements that favor the development of GC (32,33), whereas people in Africa harbor less aggressive strains of *H. pylori* and generally have a diet that includes less salt (15). Studies indicate that seropositivity for *H. pylori* antigens such as CagA and VacA is related to a higher risk of developing both premalignant and malignant lesions in the non-cardia stomach and could be used as markers for risk stratification (34). In China, a well-characterized cohort study indicated that *H. pylori* seropositivity had been associated with increased risks for both cardia GC and non-cardia GC (35). Typically, during the chronic inflammation process induced by *H. pylori* infection, altered cell proliferation, apoptosis, and some epigenetic modifications to the tumor suppressor genes might occur, which could eventually lead to inflammation-associated oncogenesis. Consistent with its causal role, eradication of *H. pylori* results in healing of inflammation and halts the progression of *H. pylori*-associated mucosal and genetic damage. The effectiveness of *H. pylori* eradication for GC and precancerous lesion prevention among high-risk individuals has been proven in different populations. In studies of precancerous lesions or gastric atrophy, eradication of *H. pylori* promoted regression of these precursors (36). In a well-characterized Chinese cohort established in 1995 (37), after a 22.3-year follow-up, 41 GC cases occurred in the *H. pylori* group, compared with 78 in the placebo group, supporting the hypothesis that *H. pylori* eradication may reduce GC incidence and mortality (38). This finding was further confirmed by another cohort of Chinese patients from Matsu Islands, after six rounds of mass screening and eradication, the prevalence rates of *H. pylori* fell from 64.2% to 15.0%, the incidence and mortality of GC during the chemoprevention period have been reduced 53% [95% confidence interval (95% CI), 30%–69%, $P < 0.001$] and 25% (95% CI, 14%–51%, $P = 0.18$), respectively (39). Moreover, a recent study suggested that the overall *H. pylori* eradication rate is a key factor for evaluating effectiveness of *H. pylori* eradication intervention program (30). Except for direct or indirect inflammation, *H. pylori* infection contributes significantly to gastric microbial dysbiosis that may be involved in carcinogenesis (40). Since the development of new molecular methods studying the microbiota, it has been shown that *H. pylori* are not the only bacterium that is found in the stomach, and the question of the newly recognized role of the microbiota in gastric carcinogenesis has emerged (40-42). A study in Singapore and Malaysia compared GC cases and controls

with functional dyspepsia and found that patients with GC had higher relative abundance of bacterial species that are commonly found in the oral cavity (43). A study in Taiwan, China compared patients with gastritis, intestinal metaplasia and GC, respectively and found a GC-specific bacterial signature consisting of *Clostridium*, *Fusobacterium*, and *Lactobacillus* (44). The main limitation of these studies is that they are cross-sectional and cannot reveal whether the gastric microbiota described corresponds to bacteria that are resident or only transitory. Studies reported that successful *H. pylori* eradication potentially restores gastric microbiota to a similar status as found in uninfected individuals, and shows beneficial effects on gut microbiota (40). Therefore, *H. pylori* eradication was recommended by WHO-International Agency for Research on Cancer as a prevention strategy (45).

EBV

In 1990, EBV was first detected via polymerase chain reaction (PCR) in gastric tumors and it is now known that approximately 10% of GC is the consequence of EBV infection worldwide (46,47). EBV is a ubiquitous infectious factor and it is estimated that 95% of the world's population has an asymptomatic life-long infection (48). EBV infection is associated with more than 18 times increase in the risk of GC. Although the prevalence of EBV was higher in male patients than in female patients with GC, compared with males, females are more likely to develop EBV-associated GC (49). EBV-induced hypermethylation silences key tumor suppressor genes, cell cycle genes, and cellular differentiation factors to promote a highly proliferative and poorly differentiated cell population (50). However, even with a number of studies that have been completed, there is still insufficient epidemiologic evidence of an exact etiologic role for EBV in gastric carcinogenesis (51).

Family history and genetic susceptibility

Hereditary GC makes up about 1%–3% of GC cases (52). Historically, family studies have long been used to assess the heritability of diseases, as underlying genetic components of variability are expected to determine, to a large extent, the correlation among disease statuses in related individuals. Hereditary diffuse gastric cancer (HDGC) is the most recognizable familial GC, which is caused by the *cadherin 1* gene (*CDH1*) alterations. The risk of gastric carcinoma in patients with a family history is

around three-fold higher than in individuals without such a history (53). In whole-exome sequencing studies, germline mutations in the tumor suppressor genes *CTNNA1*, *STK11*, and *SDHB* and the DNA repair-related genes *PALB2*, *BRCA2*, and *ATM* were identified in HDGC without *CDH1* mutation (54). Hereditary GC always develops in patients with Lynch syndrome (mutations in the mismatch repair genes *MSH2*, *MSH6*, *PMS2*, or *MLH1*) and, more rarely, in patients with Li-Fraumeni syndrome (TP53 germline mutation), Peutz-Jeghers syndrome (*STK11* mutation), and familial adenomatous polyposis (*APC* mutation) (55).

Recent studies have clearly shown that common single-nucleotide polymorphisms (SNPs) have important roles in genetic susceptibility in defining the development process of GC (56). An example of this was in a meta-analysis, carried out by Yan *et al.* that identified 12 loci to be associated with GC risk in Chinese populations and deciphered the mechanisms of PRKAA1 at 5p13.1 and NOC3L at 10q23.33 in gastric tumorigenesis (57). That said, genetic susceptibility for complex conditions should not be viewed in isolation but be considered along with lifestyle and environmental factors in the multivariate evaluation of disease risk (10).

Dietary habits and social behavior

High-salt foods and salt-preserved foods, including pickled vegetables and salted or dried fish, as traditionally prepared in East Asia, increases the risk of GC (2). According to a large cohort study of 2,476 Japanese subjects, high dietary salt intake is a significant risk factor for GC and its association might be stronger in the presence of *H. pylori* infection with atrophic gastritis (2). The evidence that consumption of broiled or barbecued (charbroiled) meat and fish will increase the risk of GC is still limited (15). Most studies suggest an inverse association between vegetables and citrus fruits and GC risk, especially lower the risk of non-cardia GC. Fresh fruit and vegetables are rich sources of folate, carotenoids, vitamin C, and phytochemicals, which have antioxidant effects and might have a protective role in the carcinogenesis process. A pooled analysis of studies in China, Japan, and Korea suggested that increasing fruit intake was associated with decreasing risk of non-cardia GC [odds ratio (OR)=0.71; 95% CI, 0.52–0.95; P-trend=0.02]. Even among individuals infected with CagA-positive *H. pylori*, high fruit consumers still show potential protective effects (OR=0.82; 95% CI, 0.66–1.03), compared to low-fruit consumers (58). A recent cohort study using SNPs confirmed this inverse

association. The study demonstrated that even among individuals at high genetic risk, those who adopt a healthy lifestyle (i.e., a high intake of fruits, vegetables, and soy foods, and a low intake of processed or red meat) could substantially reduce their risk of incident GC (10). A double-blind, randomized, placebo-controlled trial initiated in Linqu County, China showed that consumption of high-proanthocyanidin juice twice daily (44 mg proanthocyanidin/240 mL serving) for 8 weeks resulted in decreased *H. pylori* infection rate by 20% as compared with other dosages and placebo ($P < 0.05$) (59). Regarding smoking and GC, both current and former smokers have an increased risk of GC compared with people who have never smoked, with estimates of increased risk ranging from 1.5 to 2.5 times that of never-smokers. The risk increase is larger in men than in women, but a dose-response relationship is apparent in both genders (60). Greater consumption of alcoholic drinks (from 45 grams per day) is probably a cause of GC, especially for men indicated by Asian studies (2). However, new evidence shows that the association between tobacco smoking, alcohol consumption and GC was at a lower magnitude than previously established (15). Gastroesophageal reflux disease (GERD) has shown to be significantly associated with cardia GC and some study results show a 2-4-fold increased risk. Obesity can promote GERD and then the risk of cardia GC has been linked to obesity and GERD (61). A study indicated that those with a body mass index (BMI) 30–35 kg/m² had a two-fold risk of cardia GC, whereas those with a BMI greater than 40 kg/m² had a three-fold risk of cardia GC. However, the evidence does not show an association between these risk factors and non-cardia GC (3).

Prevention strategies

GC prevention has focused on primary and secondary prevention strategies. Primary prevention strategies include better diet and lifestyle habits such as decreasing the intake of salty foods, increasing the intake of fruits and vegetables, smoking cessation and avoiding high alcohol drinks, improving sanitation and hygiene, and refrigeration or *H. Pylori* eradication. Secondary prevention usually referred to detecting and treating GC at its early stages using available resources, mainly the endoscopic method.

Primary prevention

The World Cancer Research Fund (WCRF)'s ongoing

program, the Continuous Update Project (CUP), recommended that maintaining a healthy weight, being physically active, and eating a healthy diet should be general primary prevention strategies for preventing GC (2). *H. pylori* eradication is another primary prevention approach for GC development. In 2013, the Japanese government approved insurance coverage for a GC prevention program which includes *H. pylori* screening and treatment (62).

Secondary prevention-endoscopic screening

GC screening has played a significant role in reducing GC mortality, while only Korea and Japan have a national program for GC screening worldwide (5,6). In Japan, GC screening was conducted regionally around the 1960s, and since 1983, it has expanded nationwide following the Health Law for the Aged (63). Although radiographic screening with barium meal and endoscopic examinations have been the primary methods for GC screening in Japan, it was not until 2018 that endoscopic screening has been recommended for population-based opportunistic screening by the updated version of the guidelines for GC screening in Japan (6). Moreover, the screening is recommended to individuals aged 50 years and older. In Korea, mass screenings of GC have been introduced since 2000 and recommend biennial GC screening for individuals older than 40 years, with direct upper-gastrointestinal series or endoscopy (or both) (5). Studies from East Asian countries demonstrated that screening using endoscopy among high-risk individuals is associated with a substantial reduction in GC mortality (64). A multi-center population-based cohort study conducted in six areas in China suggested that one-time endoscopic screening is useful in the prevention of upper gastrointestinal cancer in individuals aged 40–69 years in high-risk areas in China, with incidence and mortality of upper gastrointestinal cancer decreased by 23% [relative risk (RR)=0.77; 95% CI, 0.74–0.81] and 57% (RR=0.43; 95% CI, 0.40–0.47) in the screened group, respectively (65). However, in the United States, with a relatively low incidence of the diseases, there are no population-based mass screening programs to reduce the incidence of GC (51). Equally, endoscopic and radiographic screenings were not recommended because no reduction of GC mortality was observed in the United States (66). Considering cost-effectiveness, a cost-utility study from Portugal suggested that GC screening using endoscopy alone in Europe can be

cost-effective only if in countries with a GC risk >25 per 100,000 (67). Therefore, to identify individuals at high GC risk (e.g., patients with advanced precancerous lesions) precisely before referred to upper endoscopy is critical for the potential mortality reduction of GC. Measurement of serum pepsinogen combined with *H. pylori* antibody test had been a popular non-invasive serological screening test to identify those at high risk, particularly in Japan (6,68). However, no study evaluated the mortality reduction from GC using the combined method of *H. pylori* antibody and serum pepsinogen tests or serum pepsinogen tests alone. There are several limitations to the serum pepsinogen test. First, it detects only the presence of atrophic gastritis and is, therefore, more applicable to intestinal-type GC only. Moreover, different cut-offs used in different studies might affect the sensitivity and specificity of results (28). Yanaoka *et al.* reported that sensitivity of the serum pepsinogen test was 58.7% (95% CI, 45.6–70.8) and its specificity was 73.4% (95% CI, 72.1–74.6) when the cut-off value was defined as PG I ≤70 ng/mL and PG I/II ≤3.0 (69). Furthermore, the serum concentrations may strongly be affected by individual conditions such as age, *H. pylori* infection status (28). A prospective, multicenter study launched in a low GC incidence area using the Pepsinogens I and II, Gastrin-17, and *H. pylori* serology combined shows the sensitivity and specificity for detecting atrophic gastritis were only 39.9% and 93.4%, respectively (70). Therefore, in the new version of the guideline for GC screening in Japan, the *H. pylori* antibody and serum pepsinogen tests used alone or in combination are not recommended for population-based screening (6).

In China, with the heaviest disease burden of GC worldwide (1), population-based endoscopic screening has been adopted as one of the national screening programs in some high-risk areas since 2005 (71). For cancer screening programs in Huai River and cancer screening programs in urban areas, launched in 2007 and 2012, respectively by the Chinese government (72), subjects are first evaluated with a questionnaire and those who are certified as high-risk individuals will be further screened by endoscopy (73). Population-based programs of endoscopic screening launched in high-risk areas or among high-risk individuals hold the greatest promise for reducing GC's burden. High-quality evidence to support the efficacy and cost effectiveness of endoscopy screening is still lacking in China (74). A recent multi-center population-based cohort study in China indicated that one-time endoscopic screening is effective for all types of upper gastrointestinal

cancers in individuals aged 40–69 years in high-risk areas in China (65). Another multi-center cluster randomized controlled trial of GC screening initiated in 2015 in China reported that compared with low-risk areas, the detection rate and early-detection rate of GC in high-risk areas were higher, with a detection rate of 0.9% vs. 0.3% and an early-detection rate of 81.5% vs. 33.3%, respectively, which provides important clues for evaluating and improving the effectiveness of upper-endoscopic screening in China (75,76). Despite promising data, the technique depends heavily on the endoscopist's skills and the availability of a gastroscope (48).

The Healthy China Program (2019-30) released by the State Council of China in 2019 set a national target of improving the early detection rate of cancers by 15% by 2022 and continuous improvement by 2030, and set the goal of 5-year survival of all cancers combined improving to 43.3% by 2022 and 46.6% by 2030, respectively (77). In line with those policies of cancer control, the population-based mass screening programs of cancer funded by the government expanded to all provinces of mainland China in 2019, and abundant promising results were reported by Chinese researchers (73,75). However, in terms of massive population-based GC screening, several issues should still be noted in China. First, there is still a lack of experienced endoscopists for GC endoscopic screening, especially in China's rural areas. One study showed that less experienced and trained endoscopists for GC screening might be attributed to the lower early-detection rate and higher complication rate (75). Moreover, standardized endoscopic therapy or surgery by trained endoscopists is effective and curative in early GC. Second, the compliance rate to participate in endoscopic screening show significant variation in different areas (rural and urban), even if the screening is provided free of charge. Many people fear physical discomfort from the invasive endoscopy procedure. Therefore, public education on the benefit of endoscopic screening is also a key factor for the success of the early detection strategy of GC (78). Finally, identifying individuals accurately at a high risk of GC for endoscopic screening is a key public health need in China. Besides enhancing cost-effective utilization of endoscopy, risk stratification will also eliminate unnecessary endoscopy procedures and related complications for participants. However, there is no optimal risk stratification model to identify high-risk individuals who need to receive endoscopic screening in China. The Cancer Screening Program in Urban China used the questionnaire as a risk

assessment tool, which might not be accurate enough to identify high-risk participants. Recently, with the development of gene sequencing technology, a dozen genetic variants for GC risk have been identified (57). A recent nationwide, prospective cohort study: the China Kadoorie Biobank indicated that using polygenic risk score derived from several risk-predictive SNPs identified in GWAS, independent of lifestyle factors, could identify Chinese individuals who are at a high risk of incident GC (10). A polygenic risk score, generated by aggregating multiple common genetic variants with a small effect on a risk model can efficiently predict cancer risk. It will provide a roadmap for the precision prevention of GC in China.

Conclusions

GC is a multifactorial, multi-stage complex disease with marked heterogeneity. There are apparent differences in the epidemiological characteristics of GC between the East and the West. Although knowledge about GC risk has dramatically increased, future research is warranted to evaluate GC epidemiology by subsite and explore the interactions between *H. pylori* infection, genetics, and environmental factors.

For endoscopic screening, in countries with a high incidence of GC, endoscopic screening can reduce the incidence and mortality of GC, especially in recent high-level evidence from China. However, the definition and stratification of high-risk groups are essential for cost-effective screening programs. With the development of the Human Genome Project and protein genomics, more genetic molecular biomarkers with risk prediction functions will be recognized and hold great promise for precise prevention of GC. Except for that, more attention should be paid to the inequality of endoscopy resources within countries that have already launched mass population-based screening programs, especially in less developed countries such as China. After all, endoscopic participation rate, experienced endoscopists who can provide standardized treatment, and health-care insurance schemes were three essential factors for acquiring cost benefit in GC prevention strategy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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