Chapter 3.7.

Gastric cancer prevention in China

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Summary

- Gastric cancer is a major health burden in China. Both incidence rates and mortality rates are higher in males and in rural areas, increasing substantially in people aged > 40 years.
- *H. pylori* infection is responsible for three quarters of gastric cancer cases in China, with prevalence rates of 40–50%. Infection rates vary by region, with the highest rates in north-western China, and rates have decreased during recent decades.
- Large-scale randomized trials in high-risk areas of China have demonstrated that *H. pylori* eradication significantly reduces gastric cancer incidence and mortality. The recent Mass Intervention Trial in Linqu, Shandong provides evidence supporting population-based *H. pylori* screening and treatment for gastric cancer prevention in high-risk community settings.
- China has implemented national gastric cancer screening programmes targeting high-risk regions, which have shown effectiveness in reducing incidence and mortality. However, challenges remain in expanding screening to populations in need across the country.
- Future directions include developing more targeted prevention strategies based on risk prediction and advancing a comprehensive tiered prevention system for gastric cancer in China.

3.7.1 Overview of gastric cancer and *H. pylori* infection in China

Epidemiological characteristics and disease burden of gastric cancer

Incidence, mortality, and survival rates

China accounts for the highest proportion of gastric cancer cases globally, with 37% of the worldwide cases. In China, gastric cancer ranks fifth among cancer types in terms of cancer incidence and third in terms of cancer mortality. In 2022, about 358 700 new gastric cancer cases occurred in China, of which 246 600 were in males and 112 100 in females [1]. The gastric cancer incidence rate has decreased in recent years [2–4]. The overall crude incidence rate is 25.4 per 100 000 person-years, and the age-standardized incidence rate is 13.7 per 100 000 person-years. The overall crude mortality rate is 18.4 per 100 000 person-years, and the age-standardized mortality rate is 9.4 per 100 000 person-years [1].

Both incidence rates and mortality rates are more than twice as high in males as in females and are correlated with age, remaining relatively low in people aged < 40 years and increasing substantially in people aged > 40 years [5]. For males, the highest age-specific incidence rate (244.2 per 100 000 person-years) and mortality rate (265.8 per 100 000 person-years) are at ages 80–84 years. For females, the highest age-specific incidence rate (122.1 per 100 000 person-years) is at ages 80–84 years and the highest age-specific mortality rate (117.3 per 100 000 person-years) is at ages > 85 years. Although there was a decreasing trend in the age-standardized incidence rate of gastric cancer in China from 2000 to 2018, it remains one of the top five causes of cancer death in both males and females.

Regional differences are noticeable. The age-standardized incidence and mortality rates for gastric cancer are highest in north-western China and lowest in southern China [6]. In general, both incidence rates and mortality rates are higher in rural areas than in urban areas. In people aged ≤ 55 years, there is no substantial difference, but in people aged > 55 years, both incidence rates and mortality rates in rural areas markedly exceed those in urban areas [5].

About 35.2% of patients with gastric cancer in China survive more than 5 years after diagnosis. There is no substantial difference in survival rates between males and females. The 5-year survival rates decrease with increasing age for both males and

females, and there is a trend of sharper decreases in the older age groups, particularly for people aged > 74 years [7].

Economic burden

Gastric cancer imposes a heavy economic burden in China, accounting for about 10% of the total costs for cancer inpatient care in 2017 [5]. Costs for gastric cancer increased from ¥ 5.5 billion in 2008 to ¥ 23.8 billion in 2017, and the expenses were highest for patients with gastric cancer treated in grade 3 general hospitals [8]. In a recent study, the average hospitalization cost per patient was US$ 19 876, and the out-of-pocket expenses were US$ 10 605. The major contributors to the cost were radiation therapy (US$ 2716) and chemotherapy (US$ 6518), and surgical fees averaged US$ 724 per case [9].

Burden of* H. pylori *infection

Prevalence

In China, the prevalence of *H. pylori* infection was estimated to be 40.7–49.4%, based on several reports in recent years [10–13]. The infection rate varies substantially by region. A systematic review of studies in China in 1990–2019 found the highest infection rates in north-western (51.8%), eastern (47.7%), and south-western (46.6%) China. The prevalence of *H. pylori* infection was > 50% in Xizang Autonomous Region (66.4%), Guizhou Province (60.5%), and Gansu Province (57.2%) [10]. A nationwide, multicentre cross-sectional survey conducted in 2023 found similar geographical variations in the prevalence of *H. pylori* infection, with southern provinces generally having lower infection rates than northern and eastern regions [14]. In China, the distribution of household-based (Spearman correlation coefficient $r = 0.46$; $P = 0.01$) and individual-based ($r = 0.49$; $P = 0.007$) prevalence of *H. pylori* infection in province-level administrative divisions is significantly correlated with the incidence of gastric cancer (Fig. 3.7.1).

In China, the overall prevalence of *H. pylori* infection has decreased significantly during the past few decades. The infection rate was higher in 1983–1994 (58.3%; 95% confidence interval [CI], 50.7–65.5%) compared with the periods 1995–1999 (48.0%; 95% CI, 36.5–59.6%), 2000–2004 (51.1%; 95% CI, 43.7–58.5%), and 2005–2009 (48.7%; 95% CI, 45.6–51.8%), and the infection rate decreased to about 40% in 2015–

2019 [10]. This downward trend was consistent with a large-scale nationwide survey conducted in 2021, which reported an average *H. pylori* infection rate of 40.7% [12], and was also observed when the data were stratified by geographical region and by the diagnostic method used, such as serology or the urea breath test [10].

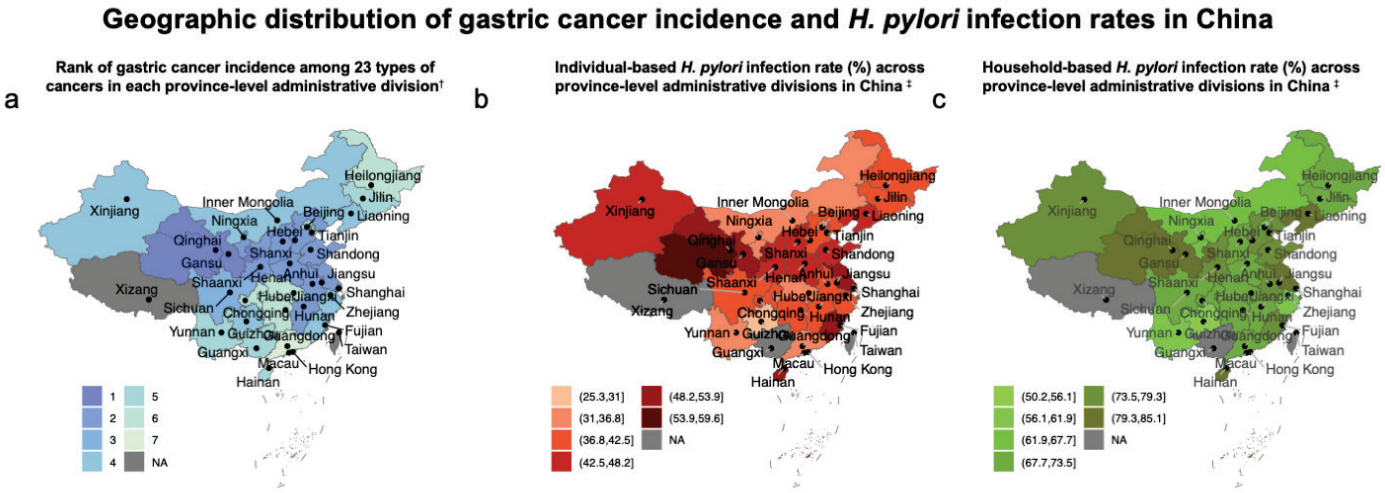

Fig. 3.7.1. Geographical distribution of gastric cancer incidence and *H. pylori* infection rates in China. The maps illustrate the geographical distribution of the rank of gastric cancer incidence among 23 types of cancer in province-level administrative divisions of China in 2018 (A) and the *H. pylori* infection rates in 2021 (B, C). The individual-based infection rate (B) and the household-based infection rate (C), defined as the percentage of households with *H. pylori* infection among all households, are derived from a large-scale national, family-based, cross-sectional survey conducted in 2021 across all 31 provinces of mainland China. The family-based *H. pylori* infection rates in China are significantly higher than the individual-based infection rates, with an average of 71.2% across 29 of 31 province-level administrative divisions (provinces, autonomous regions, or municipalities) in mainland China, ranging from 50.3% to 85.1%. Of these divisions, 26 had estimated family-based infection rates of > 60%, and 20 had rates of > 70%. Qinghai, Hainan, Gansu, Jiangsu, and Liaoning Provinces had family-based infection rates of > 80%. NA, not available. Compiled from (A) Zheng et al. (2022) [80] and from (B, C) Zhou et al. (2023) [12].

H. pylori infection rates also vary by age and sex. A nationwide survey reported a higher infection rate in adults (43.5%, aged ≥ 18 years) than in children and adolescents (20.6%, aged < 18 years) [12]. The average infection rate was slightly higher in males (44.9%; 95% CI, 43.6–46.2%) than in females (42.0%; 95% CI, 40.5–43.5%) [10]. The

difference in infection rates between males and females is seen in both children and adults.

Family cluster infection and intrafamilial transmission

In China, intrafamilial transmission of *H. pylori* infection is a frequent mode of transmission, especially in populations at high risk of gastric cancer [15, 16]. A family cluster infection, which is defined as a household with several family members with *H. pylori* infection, ranging from one to all family members, is a notable feature of *H. pylori* infection in both urban and rural China [12]. The risk factors for a family cluster infection of *H. pylori* are a large family size, multiple generations in a household, crowded conditions, having a large number of siblings, and poor household hygiene [12, 17–19]. The *H. pylori* infection rate in children is substantially influenced by the infection status of their parents [12]. In families in which both parents had *H. pylori* infection, the child infection rate was 34.3%, compared with 13.6% in families in which neither parent had *H. pylori* infection.

3.7.2 Primary prevention of gastric cancer in China

H. pylori infection was responsible for 340 000 new cancer cases in China (age-standardized incidence rate, 15.6 per 100 000 person-years) [20] and accounted for 74.5% of gastric cancer cases nationwide in 2018 [5]. Data from the China Kadoorie Biobank indicated that *H. pylori* infections were responsible for 78.5% of non-cardia gastric cancers and 62.1% of cardia gastric cancers in 2018 [21].

Since the 1990s, substantial efforts have been made to determine the efficacy and effectiveness of *H. pylori* treatment in preventing new cases of gastric cancer in several high-risk areas of China and globally [22, 23]. Nearly half of the available randomized trials were conducted in high-risk areas of mainland China, including Linqu County (Shandong Province; three trials) [24–28], Changle County (Fujian Province) [29, 30], and Yantai County (Shandong Province) [31, 32]. These trials have provided crucial evidence to support *H. pylori* eradication as a major primary prevention strategy for gastric cancer prevention (Table 3.7.1).

Table 3.7.1. Randomized controlled trials of *H. pylori* treatment for gastric cancer prevention in mainland China

Trial	Location	Follow-up period (years)	*H. pylori* eradication therapy regimen used	Pre-neoplastic lesions at baseline (%)	Eradication rate (%)[a]	Mean age at baseline (years), (range)	Sample size (gastric cancer cases)		Effect estimates (95% CI)[b]
							Treatment	Placebo/control	
Changle Trial [29, 30]	7 villages in Changle County, Fujian Province	26.5	Omeprazole 20 mg, co-amoxiclav 750 mg, and metronidazole 400 mg b.i.d. for 2 weeks	37.7[c]	83.7	42.2 (35–65)	817 (21)	813 (35)	EE1: 0.60 (0.35–1.02) EE2: 0.57 (0.33–0.98)
Intervention trial on *H. pylori* eradication and COX-2 inhibition [28]	12 villages in Linqu County, Shandong Province	5	Omeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg b.i.d. for 1 week	100.0[c]	63.5	53.0 (35–64)	258 (3)	255 (1)	EE1: 3.04 (0.32–28.99)
Yantai Trial [31, 32]	11 villages in Yantai County, Shandong Province	10	Omeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg b.i.d. for 1 week	45.5[d]	55.6	52.0 (35–75)	276 (2)	276 (7)	EE1: 0.29 (0.06–1.36)
Shandong Intervention Trial [24–26]	13 villages in Linqu County, Shandong Province	22.3	Omeprazole 20 mg and amoxicillin 1000 mg b.i.d. for 2 weeks	98.5[c]	73.2	46.8 (35–64)	1130 (41)	1128 (78)	EE1: 0.52 (0.36–0.76) EE2: 0.48 (0.32–0.71)
Mass Intervention Trial in Linqu, Shandong [34, 77]	980 villages in all 10 townships of Linqu County, Shandong Province	11.8	Omeprazole 20 mg b.i.d., tetracycline 750 mg t.i.d., metronidazole 400 mg t.i.d., and bismuth citrate 300 mg b.i.d. for 10 days	NR	72.9	42.5 (25–54)	52 026 (354)	50 304 (399)	EE1: 0.86 (0.74–0.99) EE2: 0.87 (0.75–1.00)

b.i.d., 2 times a day; CI, confidence interval; EE1, effect estimate 1; EE2, effect estimate 2; NR, not reported; t.i.d., 3 times a day.

[a] True intention-to-treat analysis, with eradication therapy assumed to have failed in all dropouts.
[b] Effect estimates for the risk of gastric cancer are derived from univariate analyses (effect estimate 1) and, if applicable, from multivariate analyses (effect estimate 2).
[c] Defined as gastric atrophy, intestinal metaplasia, or dysplasia.
[d] Defined as gastric atrophy or intestinal metaplasia, calculated from Leung et al. (2004) [31] (n = 435).

H. pylori *eradication as a measure for primary prevention: evidence from Linqu, Shandong Province*

From 1973 to 1975, a national survey on cancer mortality patterns identified geographical clusters of major malignant tumours and established high-risk areas for gastric cancer, which included Linqu (Shandong Province), Zhuanghe (Liaoning Province), Wuwei (Gansu Province), and Changle (Fujian Province). Linqu County, a rural area in Shandong Province in northern China, has one of the highest gastric cancer mortality rates in the world. This makes it an ideal location to investigate the effects of *H. pylori* eradication on reducing the risk of gastric cancer.

Shandong Intervention Trial

The Shandong Intervention Trial (SIT) (ClinicalTrials.gov ID, NCT00339768), which started in 1995, was one of the first randomized trials in China to evaluate the effects of *H. pylori* eradication on reducing the risk of gastric cancer [24–27, 33]. The trial, which involved 2258 *H. pylori*-seropositive individuals, adopted a 2 × 2 × 2 factorial design to evaluate the effect of *H. pylori* treatment, vitamin supplementation, and garlic supplementation on the prevalence of advanced precancerous gastric lesions. *H. pylori* treatment resulted in statistically significant decreases in the combined prevalence of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer after 7.3 years (odds ratio [OR], 0.60; 95% CI, 0.47–0.75). By 2003, *H. pylori* treatment also had favourable effects on the average histopathological severity of gastric lesions and on the progression and regression of precancerous gastric lesions, but it did not reduce the combined prevalence of dysplasia or gastric cancer [24].

The SIT had an extended follow-up period and was the first study to report a statistically significant decrease in gastric cancer incidence after *H. pylori* treatment, at 14.7 years of follow-up (OR, 0.61; 95% CI, 0.38–0.96) [25]. Further follow-up substantiated the persistent benefits on gastric cancer incidence (OR, 0.48; 95% CI, 0.32–0.71) at 22.3 years of follow-up, and this study was the first to observe a marked reduction in gastric cancer mortality (hazard ratio [HR], 0.62; 95% CI, 0.39–0.99) [26]. Further evidence from the SIT has underlined the benefits of *H. pylori* eradication in the prevention of gastric cancer, even in people with severe gastric lesions [26].

Intervention trial on H. pylori *eradication and COX-2 inhibition*

Between 2002 and 2006, a randomized, placebo-controlled trial was conducted in Linqu to explore the effects of celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, and *H. pylori* eradication treatment on the progression of gastric lesions in a study with 1024 individuals and a 2 × 2 factorial design [28]. In this study, both *H. pylori* eradication (OR, 2.19; 95% CI, 1.32–3.64) and celecoxib treatment (OR, 1.72; 95% CI, 1.07–2.76) had beneficial effects on the regression of advanced gastric lesions, but there was no synergistic benefit when these two interventions were combined. During the 5-year follow-up period, neither *H. pylori* eradication nor celecoxib treatment was associated with the prevention of gastric cancer.

Community-based cluster-randomized trial of H. pylori *eradication with more than 180 000 participants*

Although previous randomized trials indicated that *H. pylori* treatment reduces gastric cancer incidence, those trials were conducted on a modest scale and accrued a limited number of events, leaving substantial knowledge gaps. In 2014, IARC noted that the currently available data were insufficient to precisely estimate the overall benefits and potential adverse consequences of *H. pylori* treatment and that large-scale, population-based *H. pylori* treatment programmes were needed. To address these uncertainties, in March 2011 research teams from China and Germany collaborated to initiate the Mass Intervention Trial in Linqu, Shandong (MITS) (Chinese Clinical Trials Registry ID, ChiCTR-TRC-10000979) [34, 35].

The MITS is a cluster-randomized, blinded mass intervention trial that enrolled all 980 villages in all 10 townships of Linqu and included 180 284 eligible people aged 25–54 years [34]. Individuals who were *H. pylori*-positive, as determined using the ^{13}C-urea breath test, received either 10-day quadruple anti-*H. pylori* treatment (in 493 villages; 20 mg of omeprazole 2 times a day, 750 mg of tetracycline 3 times a day, 400 mg of metronidazole 3 times a day, and 300 mg of bismuth citrate 2 times a day) or symptom alleviation treatment (in 487 villages; a single dosage of 20 mg of omeprazole and 300 mg of bismuth citrate). In a pilot study in the Linqu population, the combined resistance rate to tetracycline and metronidazole was only 5.3%. *H. pylori*-negative individuals did not receive any treatment.

The overall successful eradication rate was 72.9% (32 325 of 44 329 participants with known results from a second ^{13}C-urea breath test) in the participants who had received anti-*H. pylori* treatment, and 15.1% of the participants who had received symptom alleviation treatment were *H. pylori*-negative after treatment. Moderate adverse effects were reported in 1345 participants during the 10-day treatment. Severe intolerable events were not observed during the treatment, and no related adverse events were reported during the follow-up. During the 11.8 years of follow-up (2011–2022) of the 180 284 participants, 1035 incident gastric cancer cases were documented, including 354 cases in people who had received anti-*H. pylori* treatment, 399 cases in people who had received symptom alleviation treatment, and 282 cases in the *H. pylori*-negative group. Most of the gastric cancer cases occurred in non-cardia stomach sites (90.3%; 714 of 791 site-specified cases).

Based on the intention-to-treat analyses, individuals who received anti-*H. pylori* therapy had a statistically significant reduction in gastric cancer incidence compared with individuals who received symptom alleviation treatment (HR, 0.86; 95% CI, 0.74–0.99). Stronger effects were observed in individuals in whom *H. pylori* infection had been successfully eradicated (HR, 0.81; 95% CI, 0.69–0.96) than in individuals in whom the treatment had failed (HR, 1.02; 95% CI, 0.83–1.26). The beneficial effect of successful eradication was particularly noteworthy for individuals aged 25–45 years. Neither anti-*H. pylori* treatment (HR, 0.89; 95% CI, 0.72–1.11) nor successful eradication (HR, 0.81; 95% CI, 0.63–1.05) was associated with significantly decreased gastric cancer mortality rates during the 11.8 years of follow-up, although the effect estimates appeared similar to those for gastric cancer incidence rates. *H. pylori* eradication did not alter overall mortality or the risk of other individual cancers.

In the subgroup analysis, successful *H. pylori* eradication modestly reduced the cumulative risk of non-cardia gastric cancer (142 cases in 32 325 participants for successful treatment versus 284 cases in 50 304 participants for symptom alleviation treatment; HR, 0.80; 95% CI, 0.66–0.98) but did not reduce the risk of cardia gastric cancer (17 cases in 32 325 participants versus 25 cases in 50 304 participants; HR, 1.11; 95% CI, 0.60–2.05). In the MITS, in individuals aged < 45 years at baseline in whom *H. pylori* infection had been successfully eradicated, there was a reduction of 35% in gastric cancer incidence and a reduction of 43% in gastric cancer mortality.

As a large-scale community-based trial, the MITS confirmed the effect of *H. pylori* eradication with anti-*H. pylori* treatment. The comparatively modest protective effect of *H. pylori* treatment may be explained partly by the use of omeprazole and bismuth citrate in the comparison group instead of a pure placebo, the suboptimal (but still relatively successful) eradication rate in the individuals who received anti-*H. pylori* treatment (72.9%), and the relatively short follow-up period. Even so, the MITS provides evidence for implementing gastric cancer prevention by *H. pylori* eradication in the wider population, especially in regions or countries with a high burden of gastric cancer. The MITS strengthens the evidence base supporting the implementation of mass *H. pylori* screening and treatment from early adulthood as a public health policy and clinical practice for gastric cancer prevention in high-risk community settings.

H. pylori *eradication as a measure for primary prevention: evidence from other trials*

Beyond the findings from Linqu, other randomized trials have been conducted in China to examine the effects of *H. pylori* eradication on the evolution of gastric lesions and the risk of gastric cancer.

Yantai Trial

A randomized trial in Yantai (Shandong Province) investigated the effects of *H. pylori* eradication on the progression of intestinal metaplasia towards gastric cancer [31]. This study involved 587 individuals with *H. pylori* infection. Progression of intestinal metaplasia, which was defined as worsening severity of intestinal metaplasia at 5 years in either the antrum or the corpus or the development of neoplasia, was found in 52.9% of participants, and the progression rate was highest in individuals aged > 45 years with persistent *H. pylori* infection (62.8%) [31]. These findings highlight the protective role of *H. pylori* eradication against the progression of premalignant gastric lesions.

Changle Trial

The Changle Trial was initiated in 1994 and involved 1630 asymptomatic people with *H. pylori* infection. The primary outcome of this trial was the incidence of gastric cancer. Like with the SIT, in the initial 7.5-year follow-up of the Changle Trial no significant difference in gastric cancer incidence was observed between the treatment group and the placebo group, although a significant reduction in gastric cancer incidence was

observed in individuals without premalignant gastric lesions [29]. After 26.5 years of follow-up (1994–2020), the study reported that *H. pylori* eradication treatment did reduce the risk of gastric cancer (HR, 0.57; 95% CI, 0.33–0.98). Unlike the SIT, the Changle Trial only reported beneficial effects of *H. pylori* eradication for individuals without severe gastric mucosal lesions, and it did not observe a significant reduction in gastric cancer mortality risk from *H. pylori* eradication at 26.5 years of follow-up (HR, 0.76; 95% CI, 0.38–1.53) [30].

Health economics of H. pylori *screening and eradication*

Evidence from China has shown that the screen-and-treat strategy for *H. pylori* eradication reduces gastric cancer incidence and costs, which benefits high-risk populations. Zheng et al. identified that treating *H. pylori* infection was a cost-saving measure, which increased the number of quality-adjusted life years (QALYs) compared with no eradication treatment, particularly for close relatives of patients with gastric cancer [36]. Han et al. demonstrated that *H. pylori* screening followed by eradication treatment significantly decreased both the occurrence of gastric cancer and its associated expenses in asymptomatic individuals [37]. Chen et al. demonstrated that a population-wide approach in China involving screening and treating *H. pylori* infection was more cost-effective and efficient in preventing gastric cancer in the general asymptomatic population (individuals who tested positive for *H. pylori* but who were otherwise healthy) than a strategy without screening [38].

The optimal settings for implementing a screen-and-treat strategy in China have been explored. For example, one study reported that starting eradication treatment at age 20 years could enhance both health outcomes and economic savings [39].

Healthy lifestyles and nutrition supplementation as preventive tactics against gastric cancer

Regional studies in high-risk areas for gastric cancer in China have highlighted the potential role of healthy lifestyles and nutrition supplementation in primary prevention of gastric cancer. Findings from studies in Linqu (Shandong Province), Changle (Fujian Province), and Zhuanghe (Liaoning Province) have shown that dietary factors closely related to gastric cancer risk include high salt intake and consumption of acid-fried pancakes, fish sauce, and salty pork. Dietary habits such as consuming overheated

food and eating too quickly can also increase the risk of gastric cancer by causing physical irritation to the digestive tract mucosa, which promotes carcinogenesis. Cohort studies in Linqu found that a high-salt diet, low intake of fresh vegetables and fruits, and lower serum vitamin C levels were significantly associated with an increased risk of gastric cancer [40–42]. Conversely, consumption of allium vegetables (garlic, onion, leek, etc.) was inversely associated with the risk of gastric cancer, indicating a significant protective effect [43–45]. The 22.3-year extended follow-up of the SIT showed that gastric cancer incidence decreased significantly with vitamin supplementation (OR, 0.64; 95% CI, 0.46–0.91) but not with garlic supplementation (OR, 0.81; 95% CI, 0.57–1.13) [26]. Vitamin supplementation (HR, 0.48; 95% CI, 0.31–0.75) and garlic supplementation (HR, 0.66; 95% CI, 0.43–1.00) also significantly reduced gastric cancer mortality [26]. Lifestyle factors may also modify the effects of nutrition supplementation on gastric cancer risk [25, 46].

The Nutrition Intervention Trial in Linxian County (Henan Province), which is a high-risk area for oesophageal cancer, showed that supplementation with the antioxidant combination of selenium, vitamin E, and β-carotene significantly reduced gastric cancer mortality (relative risk [RR], 0.79; 95% CI, 0.64–0.99) [47]. A 10-year post-trial follow-up confirmed that these beneficial effects persisted for up to a decade (HR, 0.89; 95% CI, 0.79–1.00) [48].

3.7.3 Secondary prevention of gastric cancer in China

Major population-based national gastric cancer screening programmes

Since the 1980s, there have been sporadic gastric cancer screening programmes in China, led by various research teams. For example, endoscopic screening in Linqu (Shandong Province) in 1989–1990, which involved 3433 individuals, revealed the pervasive presence of precancerous gastric lesions and provided prospective follow-up data that substantiated the progression of these lesions to gastric cancer [49–52]. The Chinese government has promoted nationwide-level secondary prevention of gastric cancer, beginning with the Outline of Chinese Cancer Program (2004–2010). Subsequently, three major national programmes for gastric cancer screening have been conducted, which provide free gastric cancer screening for eligible residents: the Upper Gastrointestinal Cancer Early Detection (UGCED) programme for rural residents [53],

the Cancer Screening Program in Urban China (CanSPUC), and the Huai River Basin Cancer Early Diagnosis and Treatment Project (Table 3.7.2) [54, 55].

Table 3.7.2. Major population-based national gastric cancer screening programmes in China

Programme	Initiation year	Target population	Coverage	Achievements
Upper Gastrointestinal Cancer Early Detection programme for rural residents	2005	Individuals aged 40–69 years in selected high-risk rural areas	Organized screening in 249 counties or districts in 31 provinces, autonomous regions, or municipalities in mainland China, and opportunistic screening in 748 hospitals in 31 provinces, autonomous regions, or municipalities in mainland China	• Screened more than 2.6 million people; early diagnosis rate of 80% • Decreased gastric cancer incidence rates by 31% and mortality rates by 67% (based on evidence from Linqu, Shandong)
Huai River Basin Cancer Early Diagnosis and Treatment Project	2007	High-risk individuals aged 45–74 years, identified by questionnaire-based risk assessment	38 counties or districts in Henan, Jiangsu, Anhui, and Shandong Provinces in China	• Achieved high early diagnosis rates (70.33–76.55%) and treatment rates (87.89–96.41%) for upper gastrointestinal cancers • Decreased age-standardized gastric cancer mortality rates from 32.1 to 16.5 per 100 000 (2008–2018)
Cancer Screening Programme in Urban China	2012	High-risk individuals aged 45–74 years, identified by questionnaire-based risk assessment or pre-screening rapid test for *H. pylori*	75 cities in 30 provinces, autonomous regions, or municipalities in mainland China	• Completed risk assessments for nearly 4.5 million people and clinical screening for 1 million people • Included 143 000 people undergoing endoscopic screening by 2020, and detected 8953 cases (6.27%) of precancerous lesions and 290 cases (0.20%) of upper gastrointestinal cancers

Source: Adapted from Xia et al. (2023) [54].

Current parameters and procedures of gastric cancer screening programmes

Unlike Japan and the Republic of Korea, which have established nationwide screening for gastric cancer, China's national programmes have primarily targeted high-risk regions, with population selection typically relying on cluster sampling in each region.

Recent guidelines from the National Cancer Center of China recommend a starting age of 45 years and a stopping age of 74 years for gastric cancer screening [56]. Although the CanSPUC and Huai River programmes follow these age recommendations, the UGCED programme empirically targets individuals aged 40–69 years in most areas.

The Technical Plan for Early Diagnosis and Treatment of Cancer, published in 2011 [57], recommends two screening approaches for gastric cancer in China. The first approach, used before 2012, involved preliminary screening using serum pepsinogen testing and questionnaire surveys, followed by endoscopic screening for high-risk individuals aged 40–69 years. The second approach, adopted after 2012, involves direct gastro-endoscopy screening and tissue biopsy for residents aged 40–69 years in selected high-risk areas. The CanSPUC and Huai River programmes also use questionnaire surveys for risk assessments, which incorporated an individual's residential history in high-risk areas, personal history of precancerous lesions, family history, exposure to related risk factors, and *H. pylori* infection status.

Recommendations for screening frequency have evolved over time. According to the Technical Plan published in 2011, individuals with chronic atrophic gastritis, severe intestinal metaplasia, and low-grade intraepithelial neoplasia (LGIN) should be followed up with annual gastro-endoscopy. The Technical Plan for Screening and Early Diagnosis and Treatment of Upper Gastrointestinal Cancer (trial version 2020) [58] suggests that individuals with severe chronic atrophic gastritis, severe intestinal metaplasia, and LGIN identified during endoscopy screenings should have follow-up endoscopy at least once every 3 years. The latest guideline issued by the National Health Commission in 2024 [59] recommends endoscopy every 3 years for patients with atrophic gastritis or intestinal metaplasia that is limited to the gastric antrum or body, and annually if atrophy involves the gastric fundus or the entire stomach. For LGIN, endoscopy is recommended annually, and for high-grade intraepithelial neoplasia it is recommended every 3–6 months.

Assessment of endoscopic screening for gastric cancer: benefits and cost–effectiveness

Gastric cancer screening programmes in China have been demonstrated to be effective in reducing gastric cancer incidence and mortality. A 10-year follow-up study showed that endoscopic screening significantly reduced the incidence of non-cardia invasive

gastric cancer (RR, 0.66; 95% CI, 0.59–0.73) and the mortality from non-cardia gastric cancer (RR, 0.38; 95% CI, 0.33–0.45) and cardia invasive gastric cancer (RR, 0.58; 95% CI, 0.49–0.68) [60]. Another prospective study, in Linqu, also reported significant decreases in the incidence of and mortality from invasive gastric cancer, and it indicated that repeated endoscopy further reduced gastric cancer-specific mortality, with 5-year survival rates of 31.9% in the unscreened group, 73.4% in the group with single screening, and 90.2% in the group with repeated screening [61].

Balancing the costs and benefits of gastric cancer screening is essential to guide future government actions and policy-making. In high-risk areas of China, the incremental cost–effectiveness ratio (ICER) for various upper gastrointestinal cancer screening strategies ranged from US$ 1343 to US$ 3035 per QALY, compared with no screening over a lifetime [62]. A personalized screening strategy has been shown to be cost-effective for high-risk population subgroups [63]. The low uptake rate of upper gastrointestinal cancer screening can substantially reduce the benefits of endoscopic screening [64], and switching to endoscopy with sedation may increase participation [65].

3.7.4 Challenges and future directions

China still faces major challenges in prevention of gastric cancer, which remains one of the major threats to public health. Because *H. pylori* infection is the most established risk factor for gastric cancer, the efficacy and effectiveness of *H. pylori* eradication have been proven for the primary prevention of gastric cancer based on data from large intervention trials in high-risk areas. Secondary prevention for early detection and early diagnosis is widely accepted as the primary focus of current gastric cancer prevention efforts of both the local and central governments in China. Despite the progress that has been made in both primary and secondary prevention of gastric cancer, there are still knowledge gaps and challenges that need to be addressed. These challenges present opportunities for further advancement in these areas.

Primary prevention

Despite the recognized beneficial effect of *H. pylori* treatment for gastric cancer prevention, the implementation of the *H. pylori* screen-and-treat strategy, which focuses on detecting the presence of *H. pylori* infection and subsequently eradicating it when

detected, is mostly limited to certain symptomatic individuals or those with personal health concerns. There has been international interest in using *H. pylori* testing to screen asymptomatic individuals for gastric cancer prevention, but these practices are still relatively infrequent.

Systemic consequences after H. pylori *eradication treatment*

Although *H. pylori* eradication is proven to prevent gastric cancer and may benefit dyspepsia, peptic ulcer disease, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma, the broader health implications remain unclear. Reports from the SIT and the MITS have addressed concerns about *H. pylori* eradication inducing major individual cancers. Further studies are needed to understand its effect on oesophageal adenocarcinoma, Barrett oesophagus, and gastro-oesophageal reflux, although a recent population-based multinational cohort study did not lend support to the possibility of an increased risk of oesophageal adenocarcinoma after *H. pylori* eradication treatment [66]. In addition, potential benefits of *H. pylori* eradication, such as colorectal cancer prevention and improvements in the condition of children with hypochlorhydria, require investigation. *H. pylori* treatment has also been shown to alter gut microbiota and metabolomic profiles, with complex implications. Despite potential benefits, unaddressed concerns about adverse effects hinder the broader application of *H. pylori* eradication treatment, highlighting the need for a balanced approach to consider the unintended consequences of this treatment [67].

Antibiotic resistance

Antibiotic resistance is a burden for health care in China and is a major cause of *H. pylori* eradication failure. A multiregion study in China found high resistance rates to metronidazole (67.2%), clarithromycin (37.5%), levofloxacin (33.5%), rifampicin (14.2%), amoxicillin (6.8%), and tetracycline (3.5%) [68]. Resistance ranged from mono-resistance (34.2%) to sextuple resistance (0.3%) and was influenced by factors such as sex, age, and the presence of peptic ulcer [68]. A recent nationwide survey showed resistance rates of 50.8% to clarithromycin and of 47.2% to levofloxacin, with higher rates in women and people aged 40–60 years [14]. The high resistance rates to metronidazole, clarithromycin, and levofloxacin could be due to the increasing consumption of these antibiotics and cross-resistance to the corresponding antibiotics. In China, macrolides ranked third and quinolones ranked fourth for use of antibiotics

during 2018–2020 [69]. Although there are no definitive data on imidazole use, the long-term use of metronidazole since its introduction to China in the 1960s for treating anaerobic infections may have contributed to the high resistance rates observed today [70]. This extensive use has made metronidazole resistance particularly prevalent in China. Despite these challenges, the MITS reported a 72.9% elimination rate using tetracycline and metronidazole, with a combined resistance rate of 5.3%.

There are notable geographical variations in resistance rates in China. Northern provinces, such as Heilongjiang and Jilin, have high clarithromycin resistance rates (> 77.0%), and southern provinces, such as Hunan, have lower rates (27.8%) [14]. Levofloxacin resistance rates are higher in eastern coastal provinces and lower in southern regions [14]. These regional variations may be linked to differences in socioeconomic conditions, hygiene, availability of health care, and use of antibiotics [14].

Expert consensus and national guidelines on H. pylori *treatment for gastric cancer prevention*

Since 2017, there have been several expert consensus reports on *H. pylori* infection control in China, which generally highlight that the *H. pylori* screen-and-treat strategy is effective in reducing gastric cancer risk by slowing progression of inflammation. Key guidelines and initiatives from 2021–2023 have made recommendations for *H. pylori* screening and population intervention strategies (Table 3.7.3). A consensus report in 2021 introduced a novel family-based *H. pylori* infection control and management strategy [11]. In July 2023, the Chinese Center for Disease Control and Prevention issued a white paper on the prevention and control of *H. pylori* infection in China [71], which emphasizes population intervention strategies as the most effective national approach to reduce the disease burden of *H. pylori* infection and suggests an *H. pylori* screen-and-treat strategy in high-risk areas and a test-and-treat strategy in low-risk areas. The *H. pylori* screen-and-treat strategy involves proactively screening the predominantly healthy general population for *H. pylori* infection, followed by offering eradication treatment to individuals who test positive. In contrast, the test-and-treat approach is more targeted, involving testing individuals for the presence of *H. pylori* based on clinical suspicion or symptoms, and then providing eradication therapy only when *H. pylori* is detected. The white paper also advocates for establishing national

public health insurance funds to support population interventions for *H. pylori* infection as a primary preventive measure against gastric cancer.

Table 3.7.3. Recent expert consensus and national guidelines on *H. pylori* treatment for gastric cancer prevention in China

Year	Guidelines or consensus report [reference]	Lead organization	Key points
2023	White paper on the prevention and control of *H. pylori* infection in China [71]	Institute of Infectious Disease Control and Prevention, Chinese Center for Disease Control and Prevention	Advocates for population intervention strategies, including a screen-and-treat strategy in high-risk areas and a test-and-treat strategy in low-risk areas, with a focus on national public health insurance support and integration into the Healthy China 2030 initiative
2022	Chinese guideline for the screening, early detection, and early treatment of gastric cancer [56]	National Cancer Center	Recommends screening for *H. pylori* infection in high-prevalence areas using the urea breath test as the primary method, supplemented by serum antibody and stool antigen testing
2021	Chinese consensus report on family-based *H. pylori* infection control and management [11]	Changhai Hospital of Naval Medical University	Introduces family-based *H. pylori* infection control to prevent intrafamilial transmission and reduce medical expenses
2019	Consensus report on eradication of *H. pylori* and prevention and control of gastric cancer in China [13]	Changhai Hospital of Naval Medical University	Supports the *H. pylori* eradication strategy for gastric cancer prevention
2017	Consensus report on chronic gastritis in China [78]	Shanghai Institute of Digestive Disease	Highlights the importance of managing chronic gastritis to prevent progression to gastric cancer
2017	Fifth Chinese national consensus report on the management of *H. pylori* infection [79]	Chinese Study Group on *Helicobacter pylori* and Peptic Ulcer, Chinese Society of Gastroenterology	Emphasizes the effectiveness of an *H. pylori* screen-and-treat strategy to reduce gastric cancer risk by slowing progression of inflammation

Advancing precision primary prevention

The development of gastric cancer involves complex interactions between genetic susceptibility, environmental factors, and *H. pylori* infection. Most individuals with *H. pylori* infection do not develop gastric cancer, and even with successful eradication, some individuals develop cancer later [26]. This highlights the need for a targeted test-and-treat approach that focuses on populations at higher risk who may benefit most from early intervention. Cohort studies in high-risk areas of China have identified several risk factors for gastric cancer, such as *H. pylori* infection, poor dietary habits, and

unhealthy lifestyles. However, these findings have not yet been fully integrated into a comprehensive risk prediction framework. A nationwide, multicentre research initiative is needed to standardize information collection and follow-up, provide large-scale data to track the progression of gastric lesions, and identify target populations for primary prevention. Host characteristics, including genetic factors, should be considered to improve risk prediction and the effectiveness of prevention. Genetic factors have shown interactions with environmental factors and influence the efficacy of prevention. Jin et al. developed a polygenic risk score for gastric cancer in more than 21 000 Han Chinese individuals and showed that a healthy lifestyle significantly reduced cancer risk for individuals with high genetic risk [72]. A recent study further demonstrated that *H. pylori* treatment particularly benefited individuals with high genetic risk, suggesting that primary prevention be tailored for more effective outcomes [73].

Family-based H. pylori *infection control*

It is important to clarify whether *H. pylori* eradication, the most important measure for the primary prevention of gastric cancer, would be particularly effective in specific environmentally exposed subgroups [46]. Population-level research in China has demonstrated the effectiveness and efficacy of *H. pylori* eradication in preventing gastric cancer in high-risk areas. Families with shared lifestyles should be studied when defining exposed subgroups for intervention, because family cluster infection and intrafamilial transmission are features of *H. pylori* infection [74]. The novel concept of whole family-based *H. pylori* infection control and management has been reported as being effective and convenient in clinical practice because of better engagement of family members, higher eradication rates, lower reinfection rates, and cost–effectiveness [16, 74]. This approach has been recommended by the Chinese Study Group on *Helicobacter pylori* and Peptic Ulcer of the Chinese Society of Gastroenterology [11].

Secondary prevention

The Chinese government has made substantial efforts to implement nationwide cancer screening. However, endoscopic screening for the entire eligible population in China is unrealistic because of the large population size, lack of trained endoscopists and pathologists, inadequate facilities, socioeconomic disparities, and high costs. Although government-organized gastric cancer screening programmes are free, the current

annual investment of less than US$ 0.1 billion for five cancer screening programmes (for lung cancer, liver cancer, gastric cancer, colorectal cancer, and oesophageal cancer) is insufficient to cover the entire population. In addition, disparities in health-care access and the invasiveness of endoscopic examinations lead to low uptake rates and non-compliance, reducing the effectiveness of these programmes [53]. Efforts are needed to make screening programmes more affordable and accessible to underserved populations and to improve the quality of screening services. Incorporating evidence from well-designed studies for regular updates of screening programmes, including area selection, optimal ages, and screening intervals, is essential. This evidence-based approach will ensure better resource allocation and maximize the social and economic benefits. Currently, national organized gastric cancer screening covers only a fraction of eligible individuals in high-risk areas, with suboptimal early detection rates and substantial disparities in diagnosis and treatment. Opportunistic screening, conducted primarily by primary medical institutions, can complement current population-based programmes in high-risk rural and urban settings. Opportunistic screening is key to align with the goals of the Healthy China 2030 framework, which emphasizes reducing premature mortality from major chronic diseases through enhanced early diagnosis rates. Given the current constraints of insufficient resources and professional capacity, opportunistic screening presents a sustainable way of expanding gastric cancer screening to a wider population in China [75]. This approach, which is already part of the UGCED programme for rural residents, involves recommendations by health-care providers during routine consultations or self-referral by individuals. In 2021, opportunistic screening led to the detection of 56 677 cases of upper gastrointestinal cancer in 2.6 million screened individuals, with a detection rate of 2.2% [53].

The recent funding announcement by the National Health Commission encourages exploring sequential screening strategies for gastric cancer. This involves identifying new biomarkers for gastric mucosal lesion progression and integrating these with existing risk assessments to prioritize screening resources effectively [53, 72, 73, 76]. Translating these findings into practical screening tools, large-scale prospective studies, and cost–effectiveness evaluations is essential.

A comprehensive tiered prevention and control system for gastric cancer

The crucial roles of primary and secondary prevention for gastric cancer necessitate future efforts to establish a tiered prevention framework that is tailored to China's national context and is amenable to broad application. By targeting high-risk populations and subgroups who may benefit most from primary prevention, the framework would be able to delineate individual risk profiles subsequent to primary interventions. For people who would not evidently benefit from primary prevention, a refined secondary prevention strategy, informed by early diagnosis models for gastric cancer, would be provided. To further optimize the key components of the framework, an in-depth health economic evaluation combined with risk prediction and intervention efficacy assessment is needed. The framework is expected to serve as a cornerstone for enhancing government-led precision gastric cancer prevention protocols, informing health policy formulation and rational allocation of health-care resources. Such endeavours would pave the way for a scientifically grounded, advanced approach to gastric cancer prevention, thereby elevating the national response to this public health challenge.

3.7.5 Conclusions

Gastric cancer remains a major public health challenge in China, and *H. pylori* infection is a causal factor. Although *H. pylori* eradication has shown promising results in reducing gastric cancer incidence and mortality, its implementation at the national level should be scientifically devised, efficiently allocating medical resources, and pursued in a phased manner, starting with high-incidence areas before expanding to lower-incidence populations. Establishing national public health insurance funds for *H. pylori* interventions in high-risk areas embodies a governmental tactic to nurture gastric cancer prevention efforts. National cancer screening programmes in China have also been effective in early detection and reducing risks. However, challenges remain in fully implementing cancer prevention strategies nationwide, such as mobilizing investment, enhancing health awareness, boosting participation rates, and ensuring quality to prevent harms and overdiagnosis. Future directions for gastric cancer prevention in China should focus on addressing these knowledge gaps and improving implementation. This may encompass expanding research within the complex interplay of gastric cancer etiology, refining risk prediction models, and harnessing digital health technologies for more personalized and accessible prevention strategies.

China is committed to combating cancer, as outlined in the Healthy China Action – Implementation Plan for Cancer Prevention and Control (2023–2030). This plan, developed under the Healthy China Initiative and the Healthy China 2030 framework, emphasizes multidepartment collaboration, proactive prevention, and innovative cancer control models. Future endeavours encompass controlling cancer risk factors, enhancing prevention services, and improving access to anti-cancer medications, with the aim of reducing cancer incidence and mortality rates and increasing the 5-year cancer survival rate to 46.6% by 2030. Through multicentre and multidisciplinary efforts, China strives to achieve these goals and contribute to the global fight against cancer, ensuring better health outcomes for future generations.

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