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REVIEW – GASTRIC MALIGNANCIES: PREVENTION & CLINICAL ASPECTS

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Abstract – Gastric cancer is the fifth most common type of cancer and the third most common cause of cancer related mortality worldwide. Although its incidence and prevalence continue to decrease in most countries, the absolute number of gastric cancers will continue to grow due to increasing lifespan and increasing in the world population. *Helicobacter pylori* is a type I carcinogen and is responsible for 89% of all gastric cancers except those from the cardia. Prospective and retrospective cohort studies have demonstrated that population based screening and *H. pylori* eradication therapy significantly reduced the risk of gastric cancer and provided significant economic benefits in China and Japan. Secondary prevention, that is in place in Japan and Korea, reduces the death rate from gastric cancer and costs for gastric cancer. Programs based on endoscopy are more successful than upper gastrointestinal series in early gastric cancer detection and patients enrolled in such programs have a better 5 year survival.

When the screen and treat approach is implemented, before preneoplastic changes develop in gastric mucosa due to *H. pylori* infection, up to a 63% reduction in gastric cancer can be achieved. Important cost savings, beside life savings, have been achieved in Japan since 2013 when *H. pylori* eradication was offered to all infected patients.

Without any prevention, the projected number of gastric cancer related deaths would be 124,000 in 2040, therefore 49,000 lives could be potentially saved in the optimal case of prevention strategies being implemented across Europe. In our opinion there are enough scientific data and results of cost benefit models to claim that the time has come for primary gastric cancer prevention programs to be implemented not only in Asia but also in other parts of the world, especially in those countries with medium to high gastric cancer incidence.

Keywords: *Helicobacter pylori*, Gastric malignancies, Primary prevention, Secondary prevention, Cost benefit.

INTRODUCTION

Helicobacter pylori is a type I carcinogen and is responsible for 89% of all gastric cancers (GC), not including those of the cardia. The cancerogenic cascade of chronic *H. pylori* infection occurs *via* a series of premalignant stages including atrophic gastritis, intestinal metaplasia and dysplasia and in 1%-3% GC is the final step. Who will develop GC cannot be predicted in advance, as the *H. pylori* strain, host immune response and environmental factors are important factors in this cancerogenic cascade.

Gastric cancer is the fifth most common cancer worldwide and the fourth most common cause of cancer related deaths in the world. Improved sanitation and hygiene has reduced the transmission of *H. pylori* and lowered the prevalence of infection in the younger generations. These data can explain the worldwide decline in the age-standardized incidence rate of GC[1]. Time-trend analyses based on global epidemiological data have predicted that, without active intervention, the number of GC cases will continuously grow along with the increase in elderly populations[2].

It has been estimated that, if all *H. pylori* infections were eradicated, approximately 89%, 29%, and 74% of the non-cardiac GC, cardiac GC, and gastric non-Hodgkin lymphoma would be prevented, respectively[3].

In this article, we have reviewed a selection of articles published over the previous twelve months and which we considered to represent some of the major advances in our understanding of the primary and secondary GC prevention and cost benefit analyses.

METHODS

A PubMed literature search was performed to obtain relevant English language publications associated with GC between April 2022 and March 2023. The search terms used included: "gastric cancer", "gastric adenocarcinoma", "prevention", "risk factors", "cost benefit analysis". The Boolean operator "AND" was subsequently used to derive relevant combinations and generate broad search results. Articles were screened according to their relevance, resulting in the refined selection of papers felt to be most pertinent to the review topic by the authors.

RISK FACTORS

Han et al[4] assessed the region-specific relative risk of cardia/non-cardia gastric cancer (CGC/NCGC) associated with *H. pylori* and quantified its contribution to the GC burden using population-attributable fractions. They included 108 studies in their meta-analysis. A significant association was observed between *H. pylori* infection and NCGC in East Asia (OR: 4.36; 95% CI: 3.54-5.37) and in West Asia (OR: 4.03; 95% CI: 2.59-6.27). Regarding CGC, a significant association was found only in East Asia (OR: 2.86; 95% CI: 2.26-3.63), and not in West Asia (OR: 0.80; 95% CI: 0.61-1.05). For studies with a follow-up time of ≥10 years, pooled ORs for NCGC and CGC in East Asia were 5.58 (95% CI: 4.08-7.64) and 3.86 (95% CI: 2.69-5.55), respectively. Pooled ORs for NCGC were 6.80 (95% CI: 3.78-12.25) in the West. The population-attributable fractions showed that *H. pylori* infection accounted for 71.2% of NCGC, 60.7% of CGC in East Asia, and 73.2% of NCGC in the West.

Kawai et al[5] aimed to estimate the cumulative incidence risks of developing GC from birth to 85 years among *H. pylori* infected and uninfected populations by using population-based cancer registry data and birth year-specific *H. pylori* infection prevalence rates in Japan. Death from GC and other causes were considered in the estimations of the adjusted cumulative incidence risks stratified by sex and *H. pylori* infection status. After performing 5,000 Monte Carlo simulations with repeated random sampling, they observed cancer incidence in three selected prefectures (Fukui, Nagasaki, Yamagata) of the prefectural population-based cancer registry in Japan, the mean adjusted cumulative incidence risk for GC was 17.0% for males and 7.7% for females in the *H. pylori*-infected population, and 1.0% for males and 0.5% for females in the uninfected population. These results calculated from the Japanese cancer registry data may be useful in considering and evaluating future prevention strategies for GC in Japan.

PRIMARY PREVENTION

Primary prevention means searching and treating for *H. pylori* infection in a younger asymptomatic population before the age of 35 years when gastric mucosa preneoplastic changes (atrophy and intestinal metaplasia) are usually not present. Eradication of *H. pylori* infection in the early thirties can also prevent vertical transmission of infection in families.

The office for prevention and treatment of *H. pylori* infection and GC was established in China in 2021, which aimed to launch the national or provincial or county demonstration center of the standard outpatient clinic of *H. pylori* diagnosis and treatment. Bismuth quadruple therapy, which was recommended as the first-line treatment for *H. pylori* infection, was effective and safe. High-dose dual therapy and vonaprazan-amoxicillin dual therapy were the alternative choice. Successful *H. pylori* eradication reduced the incidence of GC and prevented the progression of *H. pylori*-related diseases. The combination of primary (effective *H. pylori* eradication) and secondary prevention (increasing the rate of early GC diagnosis and treating them) was the effective way to decrease the incidence of GC and increase the survival rate of GC[6].

In Changle, Fujian province, China, 1,630 asymptomatic, *H. pylori*-infected subjects were randomly assigned to receive *H. pylori* eradication or placebo, and were then followed-up for 26.5 years (1994-2020). Subjects receiving *H. pylori* eradication had a lower incidence of GC than their placebo counterparts [hazard ratio (HR): 0.57; 95% CI: 0.33-0.98]. More evident risk reduction was observed among those without premalignant gastric lesions (HR: 0.37; 95% CI: 0.15-0.95) and those without dyspepsia symptoms at baseline (HR: 0.44; 95% CI: 0.21-0.94). Furthermore, compared with 32 cases of GC observed among 527 participants with persistent *H. pylori* infection in the placebo group, only 16 were identified in 625 subjects with successful eradication in the treatment group (HR: 0.46; 95% CI: 0.26-0.83)[7].

Kowada[8] studied which method would be the most cost effective to reduce GC in Japan. His conclusion was that *H. pylori* eradication strategy was more cost-effective than endoscopic screening at any interval in all age groups. Cost-effectiveness was dependent on the *H. pylori* infection rate. Cost-effective acceptability curves by Monte Carlo simulations for 10,000 trials demonstrated that *H. pylori* eradication strategy was 100% cost-effective at a willingness-to-pay threshold of US$50,000 per quality-adjusted life-years (QALY) gained in all age groups. Over a lifetime, *H. pylori* eradication strategy saves US$28.07 billion, increases QALY by 37.16 million, prevents 4.47 million GC cases and saves 319,870 human lives from GC. He concluded that population-based *H. pylori* eradication strategy is optimal and cost-effective for a national GC prevention program in Japan, replacing the current secondary prevention-focused biennial endoscopic screening.

Mizukami et al[9] tried to analyze disease trends in their *H. pylori* eradicated population in a retrospective cohort study. They used a Japanese nationwide health claims database (April 2009-March 2020), developed by the Japanese Ministry of Health, Labour and Welfare. The database contained almost all health insurance claims data issued in Japan, and specific health check-up data for individuals who took the check-ups. Descriptive statistics were used for the analyses. Patients who received primary eradication therapy were defined as those prescribed medication for *H. pylori* eradication. New diagnoses, defined as incidence of upper gastrointestinal diseases, inflammatory bowel disease (IBD) and prevalence of allergic diseases were compared before and after eradication. The incidence and prevalence of each disease were also compared between the 3-year period before eradication (from the 4th to the 2nd year prior to the year of eradication) and the 3-year period after eradication (from the 1st to the 3rd year after the year of eradication) based on the age category and calendar year and month. Changes in body mass index and proportion of patients with metabolic syndrome were examined before and after eradication. They identified 5,219,731 patients who received primary eradication therapy. The 65-69 year age group had the greatest number of patients in both sexes. There was no significant increase in the incidence of gastroesophageal reflux disease after eradication when considering the effects of aging and the reporting period. However, the incidence of Barrett's esophagus was higher in the 3-year period after eradication than in the 3-year period before eradication for all age categories (0.02%-0.10% *vs.* < 0.01%-0.05%). The incidence of IBD and prevalence of allergic diseases was also higher after eradication. In contrast, the incidence of gastric and duodenal ulcers and gastritis was reduced after eradication. In patients with at least one entry of health check-up data (1,701,111 patients), the percentage of patients with metabolic syndrome showed a slight increase following eradication (11.0% in the year of eradication and 12.2% after 5 years).

Two EU research project-implementation studies have started: EUROHELICAN (Grant Agreement Number 101079944)[10] at the end of 2022 and TOGAS at the beginning of 2023 (EU4H-2022-PJ-01)[11]. The EUROHELICAN screen and treat implementation study started in Slovenia. A retrospective analysis of the GISTAR study population will be performed to fill the gaps of knowledge related to the potential adverse/beneficial effects of the test-and-treat strategy over the long-term and IARC/WHO Working Group Report recommendations for the screen and treat approach will be prepared. In the work package 4 of Study 1 of TOGAS, the screen and treat approach will be tested in implementation studies in six EU member states. Different aspects of secondary GC prevention will also be part of the TOGAS project.

SECONDARY PREVENTION

The aim of the secondary prevention for GC is to find patients in the population with preneoplastic changes of gastric mucosa and to implement surveillance programs for those at risk. Two approaches have been tested: pepsinogen testing or endoscopy. *H. pylori* infection should be eradicated in all infected and surveillance should be implemented in OLGA / OLGIM III-IV stages.

In a population-based prospective study Li et al[12] in China included 375,800 individuals, 14,670 of them underwent an endoscopic screening (2012-2018). Receiving endoscopic screening significantly decreased the risk of invasive GC (age- and sex-adjusted relative risk [RR]: 0.69, 95% CI: 0.52-0.92) and GC-specific mortality (RR: 0.33, 95%CI 0.20-0.56), particularly for NCGC. Repeated screening strengthened the beneficial effect on invasive GC-specific mortality of one-time screening. Among invasive GCs, screening-detected individuals had significantly better overall survival (RR: 0.18, 95%CI: 0.13-0.25) and disease-specific survival (RR: 0.18, 95%CI: 0.13-0.25) than unscreened individuals, particularly for those receiving repeated endoscopy. For individuals with intestinal metaplasia or low-grade intraepithelial neoplasia, repeated endoscopy at an interval of <2 years, particularly within 1 year, significantly enhanced the detection of early GC, compared with repeated screening after 2 years (p-trend=0.02). Endoscopic screening prevented GC occurrence and death, and improved its prognosis in a population-based study. Repeated endoscopy enhanced the effectiveness. Screening interval should be based on gastric lesion severity.

The effectiveness of endoscopic screening in reducing mortality from GC in Japan has been studied by Narii et al[13]. A nationwide endoscopic screening program was introduced in Japan in 2016, providing biennial endoscopic screening for people aged 50 years and older. In a large prospective population-based cohort study including 80,272 participants, the authors compared the risk of mortality and incidence of GC among participants who underwent endoscopic or radiographic screening compared with those who did not undergo any screening, using multivariable Cox proportional hazards models. In the 1,023,364 person-year observation period (median 13.0 years), 1977 cases of GC were diagnosed, and 783 of them died. In the endoscopic screening group, the GC mortality and GC incidence of advanced GC were reduced by 61% (HR: 0.39, 95% CI: 0.30-0.51) and 22% (HR: 0.78, 95% CI: 0.67-0.90), respectively. The radiographic screening reduced the mortality from GC (HR: 0.63, 95% CI:0.54-0.73), but its effectiveness was lower than that of endoscopic screening. Endoscopic screening reduced the mortality and incidence of GC by 61% and 12%, respectively.

A systematic review and meta-analysis on GC screening has been published by Fari et al[14]. GC screening was offered to healthy asymptomatic individuals in three Far East countries. In Japan, upper gastrointestinal series (UGIS) or Esophagogastroduodenoscopy (EGD) are both first-line options for asymptomatic individuals > 40 years old. The National Cancer Screening Program for GC in Korea offers biennial UGIS or EGD to individuals > 40 years old. In China, screening through EGD is available in high-risk areas for individuals aged 40-69 years old. In contrast, in Western countries, there are no population-based GC screening programs ongoing.

Studies by UGIS demonstrated that GC screening was associated with significantly lower GC mortality rates (OR: 0.63, 95% CI: 0.55-0.73). Benefits on mortality were also found in EGD and serum pepsinogen (PG) studies. EGD was associated with significantly higher GC (0.55%, 95% CI: 0.39-0.75%) and early-GC (EGC) detection rates (0.48%, 95% CI: 0.34-0.65%) when compared to UGIS (GC: 0.19%, 95% CI: 0.10-0.31%; EGC: 0.08%, 95% CI: 0.04-0.13%) and PG (GC: 0.10%, 95% CI: 0.05-0.16%; EGC: 0.10%, 95% CI: 0.04-0.19%). Non-invasive methods tended to get higher adherence rates when compared to EGD. Regardless of the screening method, individualized recruitment performed better. Screening positively impacted GC mortality rates. EGD was associated with higher diagnostic yield, while UGIS and PG tended to obtain higher adherence rates. Screening uptake was predominantly impacted by recruitment strategies independently of the adopted method.

Individual factors also impact the adherence to GC screening programs. Higher household income and education level were associated with higher adherence rates. Similarly, family history of GC and past medical history of gastric ulcer, led to higher adherence rates. Also, non-smokers were more likely to undergo GC screening.

COST BENEFIT ANALYSIS

Without any prevention, the projected number of GC-related deaths would be 124,000 in 2040, while 49,000 lives could be potentially saved in the optimal case of prevention strategies being implemented across Europe. However, the estimated impact depends also on other factors, such as the prevalence of *H. pylori* infection and precancerous lesions, the age of asymptomatic individuals to be included, the participation rate, the treatment acceptance, and the frequency of related adverse events, as well as the effectiveness of the treatment. Furthermore, cost implications are also important since the choice of the most appropriate strategy will not be based only on efficacy but also on the related costs[15].

A novel family-based *H. pylori* infection control and management (FBCM) strategy was introduced for *H. pylori* infection prevention and control in China. If either or both of the parents was infected by *H. pylori*, their children from 18 year of age were screened by ^{13}C-UBT for *H. pylori* infection, and those positive children and parents received an eradication treatment. However, its cost-effectiveness has not been evaluated. Ma et al[16] conducted a health economic evaluation to investigate the cost-effectiveness of FBCM, screen-and-treat, and no-screen strategies in the Chinese population. Cost-effectiveness analysis was performed using the decision tree and Markov model. Parameters required for the model were from published literature and public databases, including health state utility, screening characteristics, treatment effectiveness, and medical costs for the three strategies. Outcomes were cost, QALY and incremental cost-effectiveness ratio (ICER). To prevent GC in a cohort of 1 million asymptomatic Chinese families, FBCM and screen-and-treat strategies prevented 1,010 and 1,201 new GC cases, reduced 2809 and 3339 GC-related deaths, and saved 956,971 and 1,137,549 QALYs, respectively, when compared with no-screen strategy. Cost-effectiveness analysis showed that the FBCM strategy cost was $9.18/QALY, and the screen and-treat strategy cost $12.08/QALY for GC prevention when compared with no-screen strategy. One-way sensitivity analysis revealed that screening at younger age by both strategies is more cost-effective. When compared with FBCM strategy, screen-and-treat strategy saved 5.98% GC cases and 5.78% of GC deaths, but costed $9348 to reduce a GC case. Results are not sensitive to any variables, and sensitivity analysis confirmed the robustness of the results. Both FBCM and screen-and-treat strategies are cost-effective for GC prevention compared with no-screen strategy.

Zheng et al[17] performed a cost-effectiveness analysis of *H. pylori* and New Gastric Cancer Screening Scoring System for screening and prevention of gastric cancer. This study aimed to evaluate the cost-effectiveness of *H. pylori* eradication and of a New GC screening scoring system (NGCS: age, sex, *H. pylori,* PG, G17) in areas with a high incidence of GC in China using the Markov model. In the NGCS screening arm, *H. pylori* was eradicated and surveilance endoscopy was performed according to NGCS score. The high-risk GC group was examined using a magnifying endoscopy and monitored by gastroscopy annually. The moderate-risk GC group was examined using magnifying endoscopy and monitored by gastroscopy every two years. Gastroscopy was performed every three years in the low-risk GC group. The results of the cost-effectiveness analysis revealed that the application of the NGCS had the highest cost-effectiveness compared to *H. pylori* eradication alone or no screening. Wang et al[18] performed a decision analysis on effect, affordability and cost-effectiveness optimisation of a Nationwide GC prevention in China, 2021-2035. The aim of the analysis was to project future trajectories of the GC burden in China under different scenarios of GC prevention and identify strategies to improve affordability and cost-effectiveness. They included a cohort of Chinese men and women born during the 1951-1980 period and assumed that different prevention strategies were conducted, including eradication of *H. pylori* and endoscopy screening (one-time, annual, biennial, triennial or stratified according to personal risk). They performed a literature search to identify up-to-date data and populate a Markov model to project the number of new GC cases and deaths during 2021-2035, as well as resource requirements and QALYs. They examined the impacts of general (among the whole population) and targeted (high-risk population) prevention. During 2021-2035, 10.0 million new GC cases and 5.6 million GC deaths would occur, with 7.6%-35.5% and 6.9%-44.5%, respectively, being avoidable through various prevention strategies. Relative to the status quo, *H. pylori* eradication was a cost-saving strategy. General annual screening dominated other screening strategies, but cost more than CNY 70 000 per QALY gained (willingness-to-pay) compared with *H. pylori* eradication. Among endoscopy strategies, targeted screening resulted in 44%-49% lower cost per QALY gained over the status quo than general screening. Among high-risk population, tailoring the screening frequency according to personal risk could reduce endoscopy-related resources by 22% compared with biennial screening and by 55% compared with annual screening.

Their results showed that general eradication of *H. pylori* would be a cost-saving intervention and would significantly modify the GC burden in the long run. Therefore, this strategy should be considered for inclusion in national health plans. Nationwide endoscopy screening is not cost-effective but the balance of costs and effects could be improved when risk subgroups (eg, family history, smoking) are targeted or integrated with *H. pylori* eradication. By incorporating blood test results, tailoring the screening frequency according to individual risk level could further help reduce the endoscopy-related resources.

Sarmasti et al[19] performed a systematic review on cost-effectiveness of screening *H. pylori* for GC prevention. The purpose of their study was to evaluate *H. pylori* screening techniques and to specify the efficient technique from a cost-effectiveness perspective. They reported the incremental cost-effectiveness ratio (ICER) screening compared to non-screening and different screening strategies. Eight studies were identified and retained for the final analysis. When screening techniques were compared to no-screening, serology screening techniques showed to be cost-effective. The lowest ICER calculated was US$1,230 cost per life-year gained and US$1,500 cost per QALY. However, determining the optimal strategy compared to other strategies was depended on parameters such as context-specific, type of cost, threshold, and perspective, and also, it is influenced by the framework of the cost-effectiveness analysis.

GC Trends and MALT Lymphoma

Rustgi et al[20] analyzed the Surveillance, Epidemiology and End Results-18 cancer registry (2000-2018) to determine age-standardized incidence rates (ASIR) and annual percentage change (APC) trends for histologically-confirmed GCs, stratified by anatomic location (noncardia vs cardia), age group (20-49 *vs.* ≥50 years), sex, race, and ethnicity in the USA. Joinpoint regression modeling estimated the statistical significance of trend comparisons. Of 74,520 individuals with NCGC, most (66.2%) were gastric adenocarcinome (GA), with the next largest categories being non-mucosa-associated lymphoid tissue (non-MALT) lymphomas (6.9%), gastro-intestinal stromal tumours (GIST) (6.7%), neuro-endocrine tumours (NET) (6.4%), and MALT lymphoma (5.6%). Noncardia GA ASIR was significantly higher than other histologies and demonstrated the greatest differences by race and ethnicity. APCs for GA and MALT lymphoma, both *H. pylori*-associated cancers, declined significantly over time, which was driven primarily by trends among individuals ≥50 years-old. NET and GIST APCs significantly increased irrespective of age group, with the highest APCs observed among non-Hispanic white individuals. Cardia GC was rarer than NCGC and comprised primarily by GA (87.9%). Cardia GC incidence fell during the study period, which was primarily driven by decline in cardia GA.

Takigawa et al[21] explored the predictive markers for eradication therapy efficacy in cases of MALT lymphoma patients that were negative for both API2-MALT1 and *H. pylori*. Although radiotherapy is the standard treatment for *H. pylori*-negative gastric MALT lymphoma, eradication therapy using antibiotics and an acid secretion suppressor can sometimes induce complete remission. Among 164 gastric MALT lymphoma patients who underwent eradication therapy as primary treatment, 36 were negative for both the API2-MALT1 fusion gene and *H. pylori* infection. Based on eradication therapy efficacy, two groups were established: complete response (CR) and no change (NC). The Kyoto Encyclopedia of Genes and Genomes pathway analysis showed that cancer-related genes and infection-related genes were highly expressed in the NC and CR groups, respectively. Based on this finding and transcription factor, gene oncology enrichment, and protein-protein interaction analyses, they selected 16 candidate genes for predicting eradication therapy efficacy.

Real-time PCR validation in 36 *H. pylori*-negative patients showed significantly higher expression of olfactomedin-4 (OLFM4) and the Nanog homeobox (NANOG) in the CR and NC groups, respectively. They concluded that OLFM4 and NANOG could be positive and negative predictive markers, respectively, for eradication therapy efficacy against gastric MALT lymphoma that is negative for both API2-MALT1 and *H. pylori* infection.

CONCLUSIONS

GC remains an important health issue especially in Asia, East and Central Europe and South America. *H. pylori* is type I carcinogen and is responsible for 89% of all GC outside of cardia. Studies in the field of primary prevention revealed an up to 63% reduction in GC rates after *H. pylori* eradication. Programs of secondary GC prevention are implemented in Asia and are also cost-effective. It is time that primary GC prevention programs are implemented not only in Asia but also in other parts of the world in those countries with medium to high GC incidence [22].

Conflict of Interest

The authors declare no conflict of interest.

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