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The Role of Folic Acid in Gastric Precancerous Lesion: A Literature Review

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ABSTRACT

Folic acid appears to hold promise as a potential preventive and therapeutic agent in gastric precancerous lesions. Folic acid, as an essential cofactor in DNA synthesis and methylation, plays a crucial role in maintaining genomic stability and regulating gene expression. It promotes DNA repair processes and protects against DNA damage, thereby inhibiting the initiation and progression of precancerous lesions. Moreover, folic acid acts as an antioxidant, mitigating oxidative stress and reducing inflammation in the gastric mucosa, which are key factors in the development of these lesions. Preclinical studies consistently demonstrate its protective effects against lesion development and progression, while clinical studies provide preliminary evidence for its efficacy in lesion regression or risk reduction. However, further well-designed clinical trials are needed to establish a definitive causal relationship, optimize folic acid supplementation strategies, and determine the optimal dosage and duration for gastric precancerous lesion management.

Keyword: Folic Acid, Gastric Precancerous Lesion, DNA, Supplement

1 INTRODUCTION

Gastric cancer poses a significant global health challenge, with over 1 million individuals receiving a new diagnosis of gastric cancer annually worldwide. Although there has been a decline in its incidence and mortality rates globally in the past 50 years, gastric cancer still ranks as the third highest cause of cancer-related death.[1] Gastric precancerous lesions refer to morphological changes in the stomach lining that have an increased risk of progressing to gastric cancer. These lesions encompass various conditions, including gastric atrophy, intestinal metaplasia, and dysplasia, which are characterized by cellular and architectural abnormalities in the stomach mucosa.[2]

The prevalence of these lesions varies widely depending on geographic location, with higher rates reported in areas such as East Asia, Eastern Europe, and Latin America.[3] *Helicobacter pylori* (*H. pylori*) infection, a bacterial infection commonly associated with gastritis and peptic ulcers, is a major risk factor for the development of gastric precancerous lesions. Other factors influencing the epidemiology of these lesions include age, sex, dietary habits (e.g., high salt and low fruit/vegetable intake), tobacco smoking, alcohol consumption, and genetic predisposition.[4]

The identification and management of gastric precancerous lesions are crucial for early detection and prevention of gastric cancer. Gastric precancerous lesions often do not cause specific symptoms, resulting in late detection and diagnosis. These lesions are typically identified during endoscopic examinations or biopsies performed for

other reasons. The lack of early symptoms makes it challenging to identify and intervene at the precancerous stage, when the lesions are more treatable.[5] The optimal treatment approach for gastric precancerous lesions remains a subject of debate. Different options, including endoscopic resection, surveillance, and pharmacological interventions, are employed based on lesion characteristics and patient factors. Determining the most effective and least invasive treatment modality while ensuring long-term follow-up for surveillance and monitoring is a challenge in the management of these lesions.[6]

Folic acid, also known as vitamin B9, plays a crucial role in various cellular processes, including DNA synthesis, repair, and methylation. Given the importance of folic acid in these processes, extensive research has been conducted to elucidate its potential impact on gastric precancerous lesions. Clinical trials evaluating the efficacy of folic acid in preventing or reversing gastric precancerous lesions have yielded mixed results. Some studies have reported beneficial effects, such as regression or decreased progression of gastric lesions[7], while others have shown no significant impact. Variations in study design, dosage and duration of folic acid supplementation, patient populations, and assessment methods may contribute to the divergent findings.[8]

This review aims to synthesize the existing evidence and provide a comprehensive understanding of the role of folic acid in gastric precancerous lesions. The authors hope that this study can contribute to advancing our understanding of the potential benefits and mechanisms of action of folic acid in the prevention and management of gastric precancerous lesions, ultimately informing clinical practice and public health strategies.

2. METHODS

Information sources and search strategy

Literature search was performed in multiple databases including PubMed, Scopus, Cochrane, searching for studies about the epigenetic alterations involved in HCC from inception up to May 18th 2023 with the following keywords: “gastric precancerous conditions”, “Chronic atrophic gastritis”, “folic acid” or “folate”, and “randomized controlled trials”.

Inclusion and exclusion criteria

Along with study screening, the authors predetermined the following inclusion criteria: (1) patients with gastric precancerous cancer, age >18 years old; (2) randomized controlled trials;

(3) research reported cured rate, efficiency, invalid, and pathological changes with a clearly definitions; (4) intervention methods including folic acid supplementation (with or without vitamin B supplementation). Meanwhile, the exclusion criteria are set to: (1) unsuitable study design, including non-clinical trials; (2) studies with incomplete outcome data; (3) studies which are not completed yet at the time of retrieval; (4) studies with irretrievable full-text articles; and (5) studies in languages other than English.

3. RESULT AND DISCUSSION

Epidemiology of gastric precancerous lesion

Understanding the epidemiology of gastric precancerous lesions provides valuable insights into the burden, risk factors, and distribution of these lesions in different populations. This knowledge is essential for implementing effective prevention strategies, promoting early

detection, and optimizing the management of individuals at risk, ultimately reducing the incidence and mortality of gastric cancer.[9]

The prevalence of gastric precancerous lesions varies widely across different geographic regions. High prevalence rates are observed in areas with a high incidence of gastric cancer, such as Eastern Asia (e.g., China, Japan, and Korea), Eastern Europe, and parts of Latin America.[3] In these

regions, the prevalence of gastric precancerous lesions can be as high as 50% or more in the adult population. In contrast, lower prevalence rates are typically reported in North America, Western Europe, and many African countries.[9]

The distribution of gastric precancerous lesions exhibits substantial geographic variation. This variation is influenced by a combination of genetic, environmental, and lifestyle factors. The prevalence and risk of gastric precancerous lesions are strongly associated with the presence of *Helicobacter pylori* (*H. pylori*) infection, dietary habits (e.g., high salt intake, low fruit and vegetable consumption), tobacco smoking, alcohol consumption, socioeconomic factors, and regional variations in healthcare access.[4]

Gastric precancerous lesions can occur at any age but are more commonly diagnosed in older individuals. The risk of developing these lesions increases with age, with the highest incidence typically observed in individuals over 50 years old. Additionally, there are variations in the prevalence and risk of gastric precancerous lesions between males and females, with males often having a higher incidence.[9]

Chronic infection with *H. pylori* is the leading risk factor for the development of gastric precancerous lesions. It is estimated that more than half of the world's population is infected with *H. pylori*, and the prevalence of infection is generally higher in resource-limited settings. The presence of *H. pylori* significantly increases the risk of developing gastric atrophy, intestinal metaplasia, and dysplasia, which are key components of gastric precancerous lesions.[9-12]

Certain ethnic groups have a higher risk of developing gastric precancerous lesions. For example, individuals of East Asian descent, including Chinese, Japanese, and Korean populations, have a higher incidence of these lesions compared to other ethnic groups. Genetic factors also play a role in the susceptibility to gastric precancerous lesions, with certain genetic polymorphisms and variations influencing an individual's risk.[9]

Gastric precancerous lesions can progress to gastric cancer if left untreated. However, not all lesions progress, and the rate of progression varies depending on several factors, including the severity of the lesions, genetic factors, and environmental exposures. The natural history and progression of gastric precancerous lesions are areas of ongoing research to better understand the factors that contribute to lesion development and malignant transformation.[4]

Diagnosis of gastric precancerous lesion

The diagnosis of gastric precancerous lesions involves various methods and techniques that aim to identify and evaluate the presence, extent, and characteristics of these lesions. The diagnosis typically involves a combination of clinical evaluation, endoscopic examinations, and pathological assessments. [13]

1. **Clinical Evaluation:** The initial step in the diagnosis involves a thorough clinical evaluation, including a detailed medical history and physical examination. This helps to identify any risk factors or symptoms associated with gastric precancerous lesions and guide further diagnostic investigations.[13]
2. **Upper Endoscopy (Gastroscopy):** Upper endoscopy, also known as gastroscopy, is a standard procedure for visualizing the inner lining of the stomach. It involves inserting a flexible tube with a light and camera (endoscope) through the mouth and into the stomach. Gastroscopy allows direct visualization of the gastric mucosa, identification of suspicious lesions, and the collection of tissue samples for further examination.[10]
3. **Biopsy:** During gastroscopy, the endoscopist can take tissue samples or biopsies from suspicious areas in the stomach. These biopsy samples are sent to a pathology laboratory for microscopic examination. Pathologists

analyze the tissue samples to determine the presence of precancerous changes, such as gastric atrophy, intestinal metaplasia, or dysplasia.[13]

4. **Endoscopic Ultrasound (EUS):** Endoscopic ultrasound combines endoscopy with ultrasound technology to obtain detailed images of the layers of the stomach wall and nearby lymph nodes. EUS can help determine the depth of tumor invasion, assess lymph node involvement, and guide the selection of treatment options.[13]
5. **Molecular Testing**: Molecular testing techniques, such as polymerase chain reaction (PCR) or immunohistochemistry, may be used to detect specific molecular markers associated with gastric precancerous lesions. These markers can provide additional information on the presence, extent, or prognosis of the lesions.[13]
6. **Imaging Techniques:** In some cases, additional imaging techniques may be employed to evaluate the extent of the lesions or identify any metastatic spread. Computed tomography (CT) scans, magnetic resonance imaging (MRI), or positron emission tomography (PET) scans may be used for this purpose.[13]

Management of gastric precancerous lesion

The management of gastric precancerous lesions aims to prevent the progression to gastric cancer, reduce the risk of complications, and improve patient outcomes. The specific management strategies employed depend on the type and severity of the lesions.

Helicobacter pylori* (*H. pylori*) Eradication:** ***H. pylori infection is a major risk factor for the development of gastric precancerous lesions. Eradication of *H. pylori* through antibiotic therapy is an essential component of management, particularly for individuals with confirmed infection. Eradication therapy helps to reduce inflammation, halt or reverse the progression of precancerous lesions, and decrease the risk of developing gastric cancer.[14]

Surveillance and Follow-up: Regular surveillance and follow-up are crucial in managing gastric precancerous lesions. Patients with confirmed lesions should undergo periodic endoscopic examinations to monitor the progression of the lesions and detect any changes. The frequency of surveillance depends on the severity of the lesions, the presence of risk factors, and individual patient factors. Surveillance allows for timely intervention if progression is observed.[15]

Endoscopic Resection: Endoscopic resection techniques, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), may be employed for selected cases of gastric precancerous lesions. These minimally invasive procedures involve the removal of abnormal tissue or early-stage cancers confined to the mucosal or superficial layers of the stomach. Endoscopic resection is suitable for lesions that are small, well-defined, and without evidence of deep invasion.[16]

Pharmacological Interventions: In some cases, pharmacological interventions may be considered to manage gastric precancerous lesions. For instance, studies have investigated the use of chemopreventive agents, including folic acid, vitamin C, and nonsteroidal anti-inflammatory drugs (NSAIDs), to reduce the risk of lesion progression or regression. However, the efficacy of pharmacological interventions requires further investigation, and their use should be guided by clinical evidence and individual patient factors.[13]

Lifestyle Modifications: Adopting a healthy lifestyle can contribute to the management of gastric precancerous lesions. Encouraging individuals to make dietary modifications, such as reducing salt intake, increasing fruit and vegetable consumption, and avoiding high-risk foods, may help reduce the risk of lesion progression. Smoking cessation, limiting alcohol consumption, and maintaining a healthy

weight are also beneficial.[13]

Patient Education and Counseling: Patient education and counseling play a crucial role in the management of gastric precancerous lesions. Informing patients about the nature of the lesions, their risk factors, and the importance of adherence to management strategies, including *H. pylori* eradication and surveillance, is essential. Providing support, addressing concerns, and ensuring regular follow-up appointments contribute to better patient engagement and compliance.[13]

Mechanism of action of folic acid

Folic acid plays a crucial role in DNA synthesis, repair, and methylation processes, which are essential for maintaining genomic stability and regulating gene expression. Its mechanism of action involves serving as a coenzyme in one-carbon transfer reactions and participating in DNA synthesis, and methylation reactions.

1. **One-Carbon Transfer Reactions:** Folic acid is converted into its active form, 5- methyltetrahydrofolate (5-MTHF), in the body. 5-MTHF acts as a coenzyme in one- carbon transfer reactions, where it accepts and donates one-carbon units required for the synthesis of nucleotides, amino acids, and other essential molecules. These reactions are vital for DNA synthesis, repair, and cell division.[17]
2. **DNA Synthesis and Repair:** Folic acid is essential for the synthesis and stability of DNA. It provides one-carbon units necessary for the production of purine and pyrimidine nucleotides, the building blocks of DNA. Adequate folic acid levels are crucial for normal DNA replication and repair processes, ensuring accurate genetic material transmission during cell division.[18]
3. **Methylation Reactions:** Folic acid is involved in methylation reactions, where it donates methyl groups to various molecules, including DNA, RNA, proteins, and lipids. Methylation is critical for regulating gene expression, controlling enzymatic activities, and maintaining cellular homeostasis. Folic acid contributes to the production of S-adenosylmethionine (SAM), the universal methyl donor in the body.[19]
4. **Homocysteine Metabolism:** Folic acid is involved in the metabolism of homocysteine, an amino acid derived from methionine. It facilitates the conversion of homocysteine to methionine in a reaction that requires vitamin B12 as a cofactor. By promoting the remethylation of homocysteine, folic acid helps regulate homocysteine levels, preventing its accumulation, which is associated with cardiovascular disease and other health problems.[20]

Deficiencies in folate metabolism have been associated with increased DNA damage and impaired DNA repair mechanisms, potentially contributing to the development and progression of gastric precancerous lesions. It's important to note that folic acid deficiency can be caused by inadequate dietary intake, malabsorption disorders, certain medications, alcoholism, and certain medical conditions.[18]

Supplementation with folic acid and consuming foods rich in folate, the natural form of the vitamin, are key strategies for preventing and treating folic acid deficiency and mitigating associated health problems. Folic acid supplementation may enhance DNA repair capacity, promote normal cell differentiation, and inhibit cell proliferation, potentially exerting protective effects against gastric precancerous lesions.[21]

Role of folic acid in gastric precancerous lesion

Folic acid has been studied for its potential role in gastric precancerous lesions. In a 7-year prospective clinical cohort study conducted in China [22], it was observed that daily supplementation of 5-10 mg of folic acid improved histopathological abnormalities in the gastric mucosa of patients with gastric precancerous lesions (GPC). Additional research by You et al [23] has indicated that folic acid deficiency

may contribute to the development of gastric malignancy, while folic acid supplementation may prevent the progression of gastric cancer.

In a meta-analysis by Lei et al [7], although the results did not show significant effectiveness of folic acid in relieving symptoms of gastric precancerous lesions (GPC), the analysis of folic acid's effectiveness in treating GPC symptoms indicated a relatively high success rate of 68%. This suggests that folate has a positive impact on GPC treatment. Furthermore, a meta-analysis of pathological changes following treatment in two comparison groups revealed that folic acid supplementation can promote the recovery of gastric mucosal atrophic lesions. Additionally, in this meta-analysis, it also demonstrated a 77% effectiveness of folic acid treatment in reversing intestinal metaplasia in GPC patients. Moreover, administering a daily dose of 30 mg of folic acid for one month resulted in better and more effective treatment of pathological changes in GPC. These findings provide evidence supporting the feasibility of folic acid treatment for GPC.[7]

Furthermore, through the comparison of serum levels of PG I, PG II, and G17 before and after treatment in two different groups, we also confirmed that folic acid can impede the progression of gastric mucosal carcinogenesis by modulating the levels of gastrin and pepsinogen.[7] While the exact mechanisms are not fully understood, here are some ways in which folic acid may play a role:

1. **DNA Synthesis and Methylation:** Folic acid is essential for DNA synthesis and methylation processes. Adequate levels of folic acid are needed to maintain proper DNA integrity and regulate gene expression. In gastric precancerous lesions, disturbances in DNA synthesis and methylation patterns can contribute to the development and progression of these lesions. Folic acid supplementation may help support normal DNA synthesis and methylation, potentially reducing the risk or slowing the progression of gastric precancerous lesions.
2. **Antioxidant Activity:** Folic acid exhibits antioxidant properties and helps protect cells from oxidative stress. Oxidative stress, characterized by an imbalance between the production of reactive oxygen species (ROS) and antioxidant defense mechanisms, is believed to play a role in the development of gastric precancerous lesions. Folic acid's antioxidant activity may help mitigate oxidative damage and inflammation in the gastric mucosa, potentially reducing the risk or severity of precancerous lesions.
3. **Homocysteine Metabolism:** Folic acid is involved in the metabolism of homocysteine, an amino acid that, when elevated, is associated with an increased risk of various health conditions, including gastric cancer. Folic acid helps convert homocysteine into methionine, an essential amino acid. By regulating homocysteine levels, folic acid may indirectly influence the development of gastric precancerous lesions.
4. **Immune Function:** Folic acid plays a role in maintaining a healthy immune system. It supports the production and maturation of immune cells and promotes the proper functioning of the immune system. A well-functioning immune system is essential for recognizing and eliminating abnormal cells, including those involved in gastric precancerous lesions. Folic acid's role in immune function may contribute to its potential preventive effects on gastric precancerous lesions.

Future recommendations

In order to further explore the role of folic acid in gastric precancerous lesions, future research should consider to conduct well-designed RCTs to assess the efficacy of folic acid supplementation in preventing and treating gastric precancerous lesions. These studies should include larger sample sizes,

appropriate control groups, and longer follow-up periods to establish a definitive causal relationship and determine the optimal dosage and duration of folic acid supplementation. Moreover, future studies should also perform subgroup analysis to assess the differential effects of folic acid supplementation in various populations, considering factors such as age, sex, genetic variations, dietary habits, and lifestyle factors. This will help identify specific subgroups that may benefit the most from folic acid interventions and tailor treatment strategies accordingly. Finally, future research should also consider to evaluate the long-term outcomes of folic acid supplementation in individuals with gastric precancerous lesions. Assess not only the regression or prevention of lesions but also the impact on the development of gastric cancer, overall survival rates, and quality of life measures. Long-term follow-up studies are necessary to determine the sustained effects of folic acid supplementation on gastric precancerous lesions. By addressing these research recommendations, we can gain a deeper understanding of the role of folic acid in gastric precancerous lesions and optimize its potential as a preventive and therapeutic agent.

Declaration by Authors

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