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Prevention and Early Diagnosis of Gastric Cancer

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Abstract: Gastric cancer is one of the most common malignant tumors, posing a serious threat to people's life and health. Therefore, prevention and early diagnosis are crucial for managing gastric cancer. This article provides an overview of the research progress in gastric cancer prevention, as well as related serological examinations, tumor markers, and endoscopic techniques.Serological tests and tumor markers are convenient, rapid, and easily accessible screening tools for gastric cancer. However, their sensitivity and specificity are not yet satisfactory and require further improvement. Endoscopic technology offers the advantage of directly observing lesion sites with a high detection rate. When combined with pathologic tissue biopsy, endoscopy serves as a means to confirm the diagnosis of gastric cancer. Nevertheless, it is important to note that endoscopy can be a cumbersome procedure with its detection rate depending on the level of experience of the examiner. Despite these advantages, due to its invasiveness to patients' digestive tracts and potential discomfort during examination procedures leading to patient intolerance towards pain; endoscopy has not been widely adopted as a screening tool for early gastric cancer.

Keywords: Gastric Cancer; Prevention; Early Diagnosis; Serological Examination; Tumor Markers; Endoscopy

Introduction

Gastric cancer is a significant malignant tumor that poses a threat to the health of Chinese people and the lives of cancer patients in China and worldwide. It ranks fifth in terms of incidence rate and fourth in terms of mortality rate among global cancers. According to data from the World Health Organization (WHO), there were over 1 million new cases of gastric cancer worldwide in 2020, with 479,000 cases occurring in China, accounting for 44% of global cases. The estimated global death cases from gastric cancer in 2020 are 769,000, with China accounting for 374,000 cases, or 48.6%[1].The early diagnosis and prevention of gastric cancer are crucial for both healthy individuals and patients due to its lack of obvious symptoms in the early stages leading to advanced stages upon diagnosis. Patients who undergo radical surgery combined with chemotherapy can achieve a 5-year survival rate as high as 90%[2]. This paper aims to review strategies for preventing and diagnosing gastric cancer at an early stage.

1 Gastric cancer prevention

1.1 Cigarette smoking

Smoking is a well-established risk factor for gastric cancer. In 2002, the International Agency for Research on Cancer (IARC) identified smoking as one of the causative factors for gastric cancer[3]. It has been observed that smoking increases the risk of developing gastric cancer, even in individuals who are negative for H. pylori infection. The risk is highest in smokers who are positive for H. pylori, as smoking can lead to more severe H. pylori infection[4]. A prospective study conducted in China, which involved 18,244 men, found that smokers had a significantly higher risk of developing gastric cancer[5].

1.2 Diet

The stomach is an essential organ within the digestive system. Maintaining a healthy diet can effectively reduce the risk of developing stomach cancer, whereas excessive consumption of high-salt and alcohol may significantly increase this risk[6]. Research studies have indicated that both high salt intake and frequent consumption of pickled foods are associated with an elevated risk of stomach cancer[7]. Furthermore, alcohol has been identified as a significant risk factor for gastric cancer. A cohort study conducted in Japan revealed that alcohol consumption was linked to an increased risk of gastric cancer among Japanese men[8].

1.3 Helicobacter pylori

Helicobacter pylori, the only bacterium capable of surviving in the stomach, is a gram-negative bacillus. In 1994, the World Health Organization classified Helicobacter pylori as a group I carcinogen. It has been demonstrated that Helicobacter pylori is associated with the development of various gastric diseases, including gastric cancer[9]. Studies have shown that eradicating H. pylori in mice can reduce gastric mucosal inflammation and prevent its progression to gastric cancer[10]. In human patients, the incidence of gastric cancer in those treated with H. pylori eradication is lower than in untreated patients, indicating that H. pylori eradication can reduce the occurrence of gastric cancer to some extent[11]. Convenient and rapid testing for H. pylori can help to some extent in preventing gastric cancer.

2 Serological examination

2.1 Serum pepsinogen test(PG)

Pepsinogen can be categorized into pepsinogen I and pepsinogen II. The former is secreted by the mucus neck cells and principal cells of the acid-secreting glands, while the latter can also be secreted by the cardia glands and the pyloric glands of the gastric sinus section. Therefore, the level of pepsinogen detection reflects the normal physiological function of the stomach. A study has indicated that in 116 patients suspected to have gastric cancer based on endoscopic examination, both PG I and PG I/II ratios were significantly decreased in gastric cancer patients[12]. This decrease may be attributed to atrophy of the gastric mucosa as the disease progresses in gastric cancer patients, leading to a reduction in pepsinogen levels. Due to its non-invasive nature, rapid results, and relatively low cost, serum pepsinogen testing can serve as a screening tool for gastric cancer to some extent.

2.2 Serum gastrin-17

Gastrin is a crucial hormone in the digestive system, primarily synthesized and secreted by gastric G cells in the gastric antrum, with 90% of it being gastrin-17. Gastrin-17 reflects the secretion function of the gastric mucosa and is closely associated with the physiological function of the stomach. A study conducted by some scholars compared 122 patients with gastric cancer (gastric cancer group) to 65 patients with benign gastric diseases (control group). The study observed differences in levels of gastrin-17, pepsinogen, and glycoconjugate antigen 72-4 (CA72-4) between the two groups. The findings revealed that levels of gastrin-17 and pepsinogen were significantly lower in patients with gastric cancer compared to those in the control group, while CA72-4 levels were notably higher. This suggests that serum gastrin-17 can be beneficial for detecting gastric cancer. Additionally, combining tests can enhance sensitivity and specificity for detecting this condition[13].

3 Tumour markers

Tumor markers are substances present in tumor cells or secreted by tumor cells, and they hold great significance for the diagnosis of tumors, making them a current focus of research. Some studies have observed that young patients with early gastric cancer show significantly higher positive rates of anti-Helicobacter pylori antibodies, CA72-4, CA199, and CEA compared to patients with gastritis and healthy individuals. This suggests that tumor markers have potential value as an auxiliary tool for the early diagnosis of gastric cancer[14]. Tumor markers related to gastric cancer include carcinoembryonic antigen (CEA), glycocalyx antigen 724 (CA-724), and glycocalyx antigen 199 (CA-199). However, these tumor markers lack specificity for gastric cancer, and their individual sensitivity is not satisfactory. Yu et al. developed a recommendation system for screening gastric cancer using serum CEA, CA72-4, and CA199. They improved the effectiveness of the tumor marker test by categorizing patients with suspected gastric cancer based on grading criteria. This approach was found to be significantly better than individual testing in case observation and detection, providing a new perspective for detecting early gastric cancer using tumor markers[15].

3.1 MicroRNA

MicroRNA (miRNA), a non-coding single-stranded RNA molecule, has been shown to be associated with dysregulated expression of

miRNAs in a variety of diseases, including cancer. Serum miRNAs have the potential to serve as biomarkers for the detection of various cancers and other diseases[16]. MiRNA exists in a stable state in human plasma and is not affected by endogenous RNA enzymes[17].Some scholars utilized real-time fluorescence quantitative PCR to detect differences in various miRNAs between gastric cancer patients and normal subjects. The results indicated that the expression of certain miRNAs in gastric cancer patients was significantly higher than that in normal subjects[18]. Additionally, Huang et al. conducted real-time fluorescence quantitative PCR on samples from 24 gastric cancer patients and 20 healthy individuals to detect the expression of miRNA-21-5p, miRNA-2-3p, and miRNA-29c-3p. They found that the level of miRNA-21 was significantly up-regulated in gastric cancer patients, while the levels of miRNA-22miRNA-29 were down-regulated[19].Furthermore, some scholars observed the expression of serum miRNAs in 578 cases of gastric cancers and healthy controls. They screened 68 miRNAs related to gastric cancer and subsequently established a 12-miRNA assay for gastric cancer. This assay was found to be sensitive and specific compared to pepsinogen, CEA, and CA199 in subsequent validation experiments, providing a new approach for detecting gastric cancer[20].In conclusion, it is anticipated that microRNA will become a novel tumor marker for diagnosing gastric cancer.

3.2 Long-stranded non-coding RNAs (lncRNAs)

Long-stranded non-coding RNAs (lncRNAs) are defined as RNAs with a nucleotide length greater than 200. Several studies have demonstrated that lncRNAs play a regulatory role in gene expression at various levels, including transcriptional, post-transcriptional, and epigenetic regulation. In the context of gastric cancer, certain long-stranded non-coding RNAs have been found to be associated with tumor size, macroscopic type, histological grading, tumor invasion, and metastasis[21]. For example, one study investigated the association between H19 (a specific lncRNA) levels and gastric cancer by detecting its presence in patients. The results showed that H19 levels were significantly higher in gastric cancer patients compared to healthy individuals[22]. Furthermore, other researchers found that circulating H19 levels were elevated in gastric cancer patients compared to normal individuals. Additionally, they observed that plasma H19 levels were higher in patients with smaller tumors than those with larger tumors and also higher in patients with T1-T2 staging compared to those with T3-T4 staging. Moreover, H19 levels were found to be greater in patients without lymph node metastasis compared to those with lymph node metastasis[23]. These findings suggest that high levels of long-stranded non-coding RNA may serve as potential biomarkers for early detection of gastric cancer.

3.3 Cell-free DNA cfDNA

Cell-free DNA (cfDNA) is a fragmented form of DNA that circulates freely in body fluids, such as blood. Studies have shown that the concentration of cfDNA in gastric cancer patients differs significantly from that in patients with benign gastric diseases and healthy adults. Furthermore, it has been found that the sensitivity of cfDNA for detecting gastric cancer is superior to that of traditional biomarkers such as CEA, CA199, and CA72-4. These findings suggest that cfDNA may hold potential for improved detection of gastric cancer[24]. Additionally, researchers have utilized Alu81-qPCR to measure plasma cfDNA levels in 54 gastric cancer patients and 59 healthy individuals. The results revealed significantly higher levels of cfDNA in the plasma of gastric cancer patients compared to those of healthy individuals[25]. The observed differences in cfDNA levels between gastric cancer patients and normal subjects indicate that cfDNA could serve as an adjunctive tool for detecting gastric cancer to a certain extent.

4 Endoscopy

4.1 White light endoscopy

Plain white light endoscopy combined with pathological tissue biopsy is a crucial method for diagnosing gastric cancer. This approach allows the examiner to directly observe abnormal areas of the gastric mucosa and obtain samples for pathological biopsy. While plain white light endoscopy is an important tool for diagnosing gastric cancer, its effectiveness depends on the experience and skill level of the examiner, which may result in missed diagnoses of early-stage gastric cancer. Nevertheless, this does not diminish the value of ordinary white light endoscopy as a screening tool for gastric cancer. In addition, more advanced endoscopic techniques such as magnifying endoscopy combined

with narrow-band imaging and pigmented endoscopy can be utilized to improve the detection rate of suspicious lesions that cannot be diagnosed using plain white light endoscopy[26].

4.2 Magnifying endoscope

Magnifying endoscopy has the capability to magnify the gastric mucosal tissue and microvessels by dozens or even hundreds of times. This feature makes it more conducive for observing gastric mucosal morphology and subtle changes compared to ordinary white light endoscopy. As a result, it improves the detection rate of early gastric cancer, particularly in cases where there are inconspicuous changes in the early stage of gastric mucosa. Additionally, magnifying endoscopy can be combined with endoscopic narrow-band imaging technology, which utilizes narrow-band filters instead of traditional broad-band filters. This technology takes advantage of the difference in penetration depth of different wavelengths of light to better observe the epithelium and blood vessels of digestive tract mucosa. This approach is also known as electron-stained endoscopy, making magnifying endoscopy an effective means for detecting early gastric cancer[27].

4.3 Pigmented endoscope

Chromoendoscopy involves staining the gastric mucosa with a staining agent and then observing it using endoscopy. Commonly used staining agents include indigo carmine, American blue, Congo red, acetic acid, and others. Gastrointestinal metaplasia is a pathological change that is associated with the development of gastric cancer. Some scholars have compared the detection rate of gastrointestinal metaplasia in patients with dyspepsia symptoms using ordinary white light endoscopy versus pigmented endoscopy combined with narrow-band imaging. They found that the detection rate of pigmented endoscopy combined with narrow-band imaging is significantly better than that of ordinary white light endoscopy alone. This method helps to detect cases that may be missed by ordinary white light endoscopy and is considered a more reliable means of examination[28,29].

4.4 Blue laser imaging technology

Blue laser imaging is an image-enhanced endoscopic technique that utilizes a laser light source to observe microvessels and microstructures in the superficial layer of the gastric mucosa. Its observation effect on the microvessels and microstructures of the gastric mucosa is comparable to that of magnified endoscopy combined with narrow-band imaging[30]. A study conducted by Japanese scholars, involving 530 patients, found that the sensitivity of blue laser imaging technology increased by 46.9%, specificity by 11.6%, and accuracy by 20.4% compared with ordinary white light endoscopy. This indicates that blue laser imaging technology can enhance the diagnostic effectiveness for early gastric cancer[31].

4.5 Confocal laser microendoscopy

Confocal laser microendoscopy is a combination of endoscopy and laboratory confocal microscopy, which can magnify the image of the gastric mucosa up to a thousand times, allowing direct observation of the cellular level of the gastric mucosa. Gong et al.[32] conducted plain white light endoscopy, magnifying endoscopy combined with narrow band imaging, and confocal laser microscopy for 82 patients. The sensitivity, specificity, and accuracy of confocal laser microscopy were found to be 90%, 93.48%, and 91.86% respectively, comparable to magnifying endoscopy combined with narrow band imaging. Confocal laser microendoscopy was observed to provide real-time assessment of the gastric mucosa, facilitating the identification of tumor and non-tumor tissues[33].

4.6 Capsule endoscopy

Capsule endoscopy is an emerging technology for visualizing lesions in the gastrointestinal tract. It involves orally ingesting a miniature camera shaped like a capsule[34].Through continuous research and development, magnetically controlled capsule gastroscopy has been introduced. In comparison to traditional capsule endoscopy, the examiner is able to manipulate the movement and direction of the magnetically controlled capsule gastroscope within the body in order to purposefully observe local lesions. Several studies have demonstrated that

magnetically controlled capsule gastroscopy is more effective in examining gastric lesions[35]. It is less invasive than traditional endoscopy, causes less discomfort for patients, and has become a crucial examination modality for gastrointestinal diseases.

5 Conclusion

Primary prevention of cancer involves the intervention and control of causative factors and risk factors before the occurrence of cancer[36]. For the general population, it is crucial to focus on preventing gastric cancer by addressing risk factors such as smoking, high salt diet, alcohol consumption, and Helicobacter pylori infection. Helicobacter pylori is a type of G-bacillus that can survive in the gastric mucosa and has a close association with the development of gastric diseases including gastritis, gastric ulcers, and gastric cancer. Detecting and eradicating Helicobacter pylori can help to some extent in preventing gastric cancer[37]. In patients with gastric cancer, the timing of treatment significantly impacts their survival and prognosis. Therefore, early diagnosis of gastric cancer is particularly important[38]. This paper provides a review of serological examination, tumor markers, and endoscopic techniques for early diagnosis of gastric cancer. Among them, pepsinogen and serum gastrin-17 are secreted by the digestive tract and are closely related to the physiological function of the stomach. They play a certain auxiliary role in the early diagnosis of gastric cancer[39,40]. Tumor markers are currently a research hotspot and have good prospects for the early diagnosis of gastric cancer[41]. The advantages of these methods, including convenience, speed, affordability, and patient acceptance, make them potential screening tools. However, they can only assist in the early diagnosis of gastric cancer and their sensitivity and specificity are not ideal. Therefore, they cannot be used as a means to confirm the diagnosis of early gastric cancer. Although combined testing can partially address issues with sensitivity and specificity, it is still necessary to find tumor markers with better sensitivity and specificity. Endoscopy has always been an important diagnostic tool for gastric cancer. Endoscopy combined with pathologic tissue biopsy forms an important basis for diagnosing gastric cancer[42]. With continuous advancements in science and technology, new endoscopic techniques such as magnifying endoscopy combined with narrowband imaging technology, pigment endoscopy, and confocal laser microendoscopy have significantly improved the detection rate of early gastric cancer[43]. However, due to its invasiveness and patient tolerance issues, endoscopy cannot be used as a screening tool for early gastric cancer. While magnetic capsule endoscopy reduces patient discomfort during examination significantly compared to traditional techniques; its detection rate is not as high as that of traditional endoscopic techniques; furthermore it lacks capability for pathological sampling which remains unresolved.

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