

Effect of Smoking on Helicobacter Pylori Eradication in Gastric Cancer: A Review Article

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1. Abstract

1.1. Introduction: Gastric cancer is a global health problem that is the fifth most common cancer in the world and the fourth leading cause of cancer death. There was conflicting research results about that if eradication of Helicobacter pylori infection is a sound strategy for gastric cancer prevention or not.

1.2. Materials and Methods: This study is a review article that collected the results of 13 articles on the effect of smoking on the eradication of Helicobacter pylori in gastric cancer.

1.3. Results: Gastric cancer is a multifactorial disease, however, the most important causes of gastric cancer are Helicobacter pylori infection and smoking. The role of smoking in the incidence of gastric cancer is because of the components of cigarette smoke as direct effect and an indirect effect due to the increased risk of Helicobacter pylori persistence. The concentration of Helicobacter pylori in patients with gastric cancer and smokers was higher than those with non-smokers gastric cancers. However, some studies do not show any general association between smoking status, duration or severity of smoking, and Helicobacter pylori infection. Therefore, further studies on the effects of smoking on Helicobacter pylori eradication is needed.

1.4. Conclusion: Improvement in standard eradication protocols led to increasing the success of eradication beside the interaction of lifestyle-related factors, including smoking.

2. Introduction

Gastric cancer is a global health problem that is the fifth most common cancer in the world and the fourth leading cause of cancer death. About 5.6% of all cancers diagnosed in 2020 and 7.7% of all cancer deaths were related to gastric cancer [1]. The highest incidence of gastric cancer was reported from East Asia, Central and South America and Eastern Europe, and the lowest incidence was in Africa and North America, while 70% of gastric cancer deaths worldwide occur in low- and middle-income countries [2, 3]. The average incidence rate in countries with moderate to high Human Development Index (HDI) was 20 per 100,000 for men, while the average incidence of gastric cancer in countries with moderate to low HDI was 6.6 in 100,000 [4].

In 2020, over one million new cases of gastric cancer were diagnosed, of which about 769,000 deaths from gastric cancer were recorded. Incidence rates were 2-fold higher in males, and was the most common cancer in terms of incidence and mortality in men in several South Central Asian countries including Iran [1, 5]. However beside globally 25% increasing of incidence of stomach cancer between 2007 to 2017, by adjusting with population growth (13%) and population aging (19%), overall incidence was decreased by -6% worldwide [6].

Gastric cancer is a multifactorial disease in which many risk factors including bacterial, environmental factors and surgical injury

can be involved. However, the most important causes of gastric cancer are *Helicobacter pylori* infection and smoking [7, 8]. According to statistics extracted from Systematic Analysis for the Global Burden of Disease Study GBD, about 19% of the burden of gastric cancer is attributed to smoking, and smoking causes progressive lesions such as chronic atrophic gastritis, intestinal metaplasia and dysplasia. Meanwhile, smoking leads to a higher prevalence of *Helicobacter pylori* infection and can indirectly increase the risk of gastric cancer [6, 9]. Also eradication rate of *Helicobacter pylori* has been reported to be 11.19% in smokers compared with 57.7% among non-smokers. The overall eradication failure reported as 33.3%: 34.8% in current smokers and 32.8% in never smokers [10, 11].

Considering the incidence and mortality of gastric cancer, as well as the importance of *Helicobacter pylori* and smoking as the main risk factors for this disease and the possible role of smoking in preventing the successful eradication of *Helicobacter pylori*, the present study was performed as a review of most recent related studies. Evidences about the impact of smoking on the successful *H. Pylori* eradication are conflicting, even some sociodemographic factors may play as confounder to interaction of these two factors [11]. However, there was conflicting research results about that if eradication of *Helicobacter pylori* infection is a sound strategy for gastric cancer prevention or not.

3. Materials and Methods

To obtain studies related to the research topic, a complete search of electronic databases, Civilica, Pub Med, SID, SCOPUS, Web of Science ISI, google scholar was conducted from 2003 onwards, for a total of 43 articles. After reviewing the abstracts, studies that were not relevant to the study were excluded.

Finally, after reviewing the titles and abstracts of articles, 28 articles were selected as potential studies for inclusion in the present study. Finally, 13 articles were included in the study according to our search criteria.

4. Results

It has been well established that *Helicobacter pylori* infection is the most important risk factor for gastric cancer, but there were inconsistent results about the effect of *Helicobacter pylori* eradication on gastric cancer incidence. A meta-analysis of 32 studies showed that eradication of *Helicobacter pylori* had a significant effect on reducing the subsequent incidence of gastric cancer (OR: 0.46). In the subgroup analysis, the beneficial effect of *Helicobacter pylori* eradication was large in Japan (OR: 0.39) and this effect was much better among people with benign complications. (OR: 0.32) The duration of interventions was significantly associated with a reduction in gastric cancer (P: 0.01) [12]. However, to delay the onset of gastric cancer, eradication of *Helicobacter pylori* has been recommended as a primary prevention. However, the results of a meta-analysis study conducted on non-cardiac gastric

cancer showed that after the development of intervention activities and the passage of about 14 years, eradication of *Helicobacter pylori* significantly reduces the incidence of gastric cancer by about 39% [13].

Studies showed that 11% of gastric cancer in the world and 17% of gastric cancer in Europe are related to smoking. The risk of gastric cancer in smokers is 1.53 times higher that of non-smokers [4]. In a study conducted in Japan, 28.4% of gastric cancers were significantly associated with smoking, and most people with gastric cancer smoked regularly and for a long time [14-17]. A study shows an increased risk of both types of gastric cancer (cardia and non-cardia) with smoking when compared to non-smokers [18]. A Cohort study conducted by Shin, A. et al., in Korea showed significant association between long-term smoking and the incidence of gastric cancer and mortality in men. The likelihood of gastric cancer in the age group of 20-39 years was 2.09 in smokers compared to non-smokers, this ratio increased by 3.3 times in the age group of 40 years [17]. The study of Itskovis et al. also revealed that the role of smoking in the incidence of gastric cancer was because of cigarette smoke ingredients as a direct effect and an indirect effect due to increased risk of *Helicobacter pylori* persistence [11].

There was a significant relationship between smoking and aging with increasing density of *Helicobacter pylori* [19]. However, the results of another study by Ferro, A. et al., showed that there is no general relationship between smoking status, duration or severity of smoking and being positive for *Helicobacter pylori* [10]. Moreover, *Helicobacter pylori* eradication failure among smokers with gastric cancer was 1.95 lower than non-smoker gastric cancers. In other words, smokers are almost twice as likely to fail to eradicate *Helicobacter pylori* as non-smokers [20]. The possible mechanisms of the negative effects of smoking on the eradication of *Helicobacter pylori* are as follows.

1. Smoking reduces the amount of blood secreted into the gastric mucosa. Therefore, the delivery of antibiotics to the gastric mucosa may be reduced.
2. Smoking stimulates gastric acid secretion, and because amoxicillin is an acid-sensitive antibiotic, success in treating and eradicating *Helicobacter pylori* may be reduced by smoking with amoxicillin [11, 20].

Camargo, M. et al. conducted a study in Colombia a high-risk area for gastric cancer. They revealed that although the eradication rate was 52.3% in overall, but this rate was 41.3% for smokers and 57.1% for non-smokers. Regression analysis showed that smokers had a 2-fold higher probability of *Helicobacter pylori* eradication failure than non-smokers. This ratio did not depend on age, gender and place of residence. They emphasized that smokers had a higher intestinal metaplasia, and lower scores of *H. pylori* density, total inflammation, neutrophil infiltration, and mucus depletion in the corpus mucosa, compared with non-smokers. However, there

was not any difference in the antrum changes between them [21]. The case-control study conducted by Wang, X.Q. et al., aimed to assess the interactions between CagA (cytotoxin-associated with gene) positive *Helicobacter pylori* infection and smoking in non-cardia gastric cancer. Their results revealed that although smoking and CagA positive *H. Pylori* infection are the most important risk factor in gastric cancer, however there was a multiplicative interaction between smoking and CagA positive *H. Pylori* infection. This means that smoking may increase the risk of gastric cancer by influencing the potential carcinogenesis of *H. Pylori* infection, and according to the results of this study in the presence of CagA, smoking is strongly associated with the risk of non-cardiac cancer [22].

Moreover, most recent clinical studies revealed that improvement in standard eradication protocols including adding Vonoprazan, Lansoprazole, Rabeprazole, and Esomeprazole led to increasing the success of eradication beside the interaction of lifestyle-related factors, including smoking [23].

5. Discussion

Helicobacter pylori infection and smoking are both well-known and important risk factors for gastric cancer. The role of smoking in the incidence of gastric cancer is because of the components of cigarette smoke as direct effect and an indirect effect due to the increased risk of *Helicobacter pylori* persistence. The concentration of *Helicobacter pylori* in patients with gastric cancer and smokers was higher than those with non-smokers gastric cancers. However, some studies do not show any general association between smoking status, duration or severity of smoking, and *Helicobacter pylori* infection. Therefore, further studies on the effects of smoking on *Helicobacter pylori* eradication is needed.

Smoking in people infected with *Helicobacter pylori* along with bacterial pathogens can exacerbate gastritis and gastric cancer as well [19]. However, lifestyle related factors, including smoking, drinking, and socioeconomic status have interaction with *H. Pylori* infection and eradication effect.

6. Declaration

Availability of data and material

Data are openly available in a public repository that issues datasets with the responsibility of the corresponding author.

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