International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 4, Issue 2, pp: (1591-1596), Month: October 2016 - March 2017, Available at: www.researchpublish.com

Helicobacter Pylori and Its Related to Gastric Cancer; Review

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Abstract: **H. pylori infection installs a chronic inflammatory action resulting in an increased cell turnover that, over several years, might lead to an accumulation of mitotic errors, which may lead to gastric cancer by direct or indirect effect. This review aimed to discuss the role of H. pylori in the pathogenesis of gastric carcinoma, and how its most common risk factor on the risk of subsequent neoplastic transformation will also be discussed. We have conducted this review through searching the eligible articles in several databases; PubMed, and Embase, to have more evidence in the association of association between H. pylori and gastric cancer, our search was up to December 2016. and we included every study which discussed the relevant topic that our study aimed to overview. then we limited our search to English language and only to human trails. Evidence showed a significant association between infection with H. pylori and gastric cancer, as determined by the presence of raised concentrations of IgG antibodies to the organism, and the risk of gastric cancer. The small number of cases, nevertheless, indicates that the magnitude of the odds ratio doubts. However, the association we observed is not likely to be due to opportunity and supports other evidence suggesting a causal association based upon environmental research studies,' medical observations, and what is known about the function of H. Pylori in triggering chronic gastritis.**

Keywords: **Helicobacter pylori, chronic inflammatory action.**

1. INTRODUCTION

Gastric cancer (*GC*) is the fifth most common cancer on the planet and has the third highest mortality rates, for both sexes. In 2012, just fewer than 1,000,000 new cases of GC were diagnosed, and 723,000 deaths were attributable to it [(1,2)]. Helicobacter pylori (H. pylori) plays a predominant role in the etiology of GC and was characterized as a class I carcinogen by the World Health Organization in 1994 [(3)]. H. pylori is a microaerophilic gram-negative germ that colonizes the gastric mucosa of 50% of the human population [(4)]. Most of infections are asymptomatic, for that reason a screening and treatment program cannot be justified except for high-risk patients [(5)]. H. pylori infection rates vary throughout the world [(6)]. Nevertheless, there is little correlation in between locations of high H. pylori infection rates and those with high occurrence of GC [(6,7,8)]. African nations can view as high as 91% of their population contaminated with H. pylori, however have a very low frequency of GC [(8)]. A similar pattern has actually been reported in less industrialized nations in Asia such as India and Bangladesh. In more industrialized Asian countries such as Korea, Japan and China a positive connection was reported between H. pylori infection rates and GC occurrence [(9)].

H. pylori infection installs a chronic inflammatory action resulting in an increased cell turnover that, over several years, might lead to an accumulation of mitotic errors. The step-wise development of this inflammatory process was highlighted by Correa (**Figure 1**) [(10,11)].

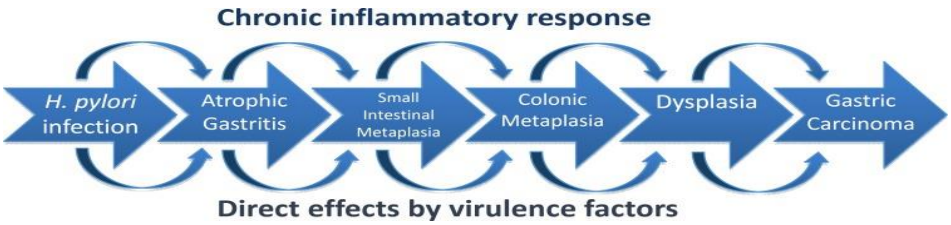

Figure 1: Correa's hypothesis – the histopathologic stages from normal gastric mucosa to gastric carcinoma [(10,11)]

This review aimed to discuss the role of *H. pylori* in the pathogenesis of gastric carcinoma, and how its most common risk factor on the risk of subsequent neoplastic transformation will also be discussed.

2. METHODS

We have conducted this review through searching the eligible articles in several databases; PubMed, and Embase, to have more evidence in the association of association between H. pylori and gastric cancer, our search was up to December 2016. and we included every study which discussed the relevant topic that our study aimed to overview. then we limited our search to English language and only to human trails.

3. RESULTS & DISCUSSION

Epidemiologic investigations on the favorable association between H. pylori and cancer date from 1991 when succeeding research studies conducted on large numbers of topics were released [12,13,14]. Since these were potential research studies, the findings were really convincing and had a strong influence on subsequent examinations. In 1993, a comparison of H. pylori antibody prevalence in between old and young patients in different countries, who were matched for the occurrence and mortality rate of gastric cancer, was reported. The nations in which asymptomatic patients revealed a high occurrence of H. pylori antibody likewise had high morbidity from gastric cancer [15]. On the other hand, Rudi et al. compared the frequency of H. pylori antibody in 111 patients with gastric cancer and 111 patients with large bowel cancer, matched with respect to age and sex [16].

Impact of H. pylori on Gastric mucosa:

H. pylori is a gram-negative, spiral-shaped microaerophilic germ with 4-6 polar flagella that enable motility in the mucus layer of the gastric lumen. H. pylori infection is the main cause of gastritis, peptic ulcers, and gastric adenocarcinoma. Although H. pylori is found generally extracellular (**Figure 2**) [17], some studies show proof of intrusion to gastric mucosa and gastric lymph nodes [18,19]. It is believed that H. pylori contributes to gastric cancer advancement by direct action of its virulence factors and indirectly by initiation and upkeep of a persistent inflammation in the gastric mucosa [20].

H. pylori can have direct effects on the molecular make-up of the gastric epithelial cells through the poisonous action of virulence factors. Anomalies of cell-cycle regulating genes, shortages in DNA repair work systems, loss of a cell's epigenetic modifications and adhesive properties can change the behavior of the cell resulting in cellular autonomy and deadly change. Research studies in animals have actually shown an increased anomaly rate in gastric mucosa infected with H. pylori [21].

2 extensively looked into virulence factors are cytotoxin-associated gene A (CagA) contained with the Cag pathogenicity island (cagPAI) and vacuolating cytotoxin A (VacA). These virulent pressures have been shown to be connected with precancerous gastric sores and progression to a deadly phenotype [22,23]. CagA favorable strains have actually shown to produce a more powerful inflammatory reaction causing a development from gastritis to atrophy of the glandular mucosal cells and a higher risk of GC. CagA and peptidoglycan go into the epithelial cell through a bacterial type IV secretion system encoded by the cagPAI. CagA induces several cellular signalling pathways such as the mitogen-activated protein kinase (MAPK) cascade. Peptidoglycan causes NF-κB expression and phosphoinositide-3 kinase (PI3K-AKT) signalling paths [24].

In addition, cagPAI+ strains can straight induce gene anomalies by enhancing the expression of the enzyme Activation Induced Deaminase (AID) in gastric mucosal cells. AID is a master regulator of secondary antibody diversification. HELP causes anomalies in the DNA encoding immunoglobulins. AID is specifically revealed by B-lymphocytes, nevertheless H. pylori infection might lead to ectopic expression of AID and a high mutation rate of TP53 [25].

Gastric mucosal infection with H. pylori is accompanied by infiltration of neutrophils, and triggered inflammatory cells are known to produce oxygen radicals [26,27,28]. Davis et al. have reported a boost of oxygen radical production in both the duodenal and gastric pyloric mucosa after infection with H. pylori [29]. Oxygen radicals are called inducers and initiators due to the fact that they trigger direct DNA damage [30], but the relationship of these radicals with the onset of gastric cancer has actually not been sufficiently checked out. Ammonia/ammonium concentrations increase in the gastric mucosa due to infection with H. pylori, and Tsujii et al. have actually discovered that ammonia acts as a promoter in a rat design of gastric cancer caused by N-methyl-N-nitro-N-nitrosoguanidine (MNNG) [31]. Ascorbic acid is known to respond with nitroso substances derived from nitrous acid, which produces nitric oxide, thereby preventing the development of N-nitroso compounds [31].

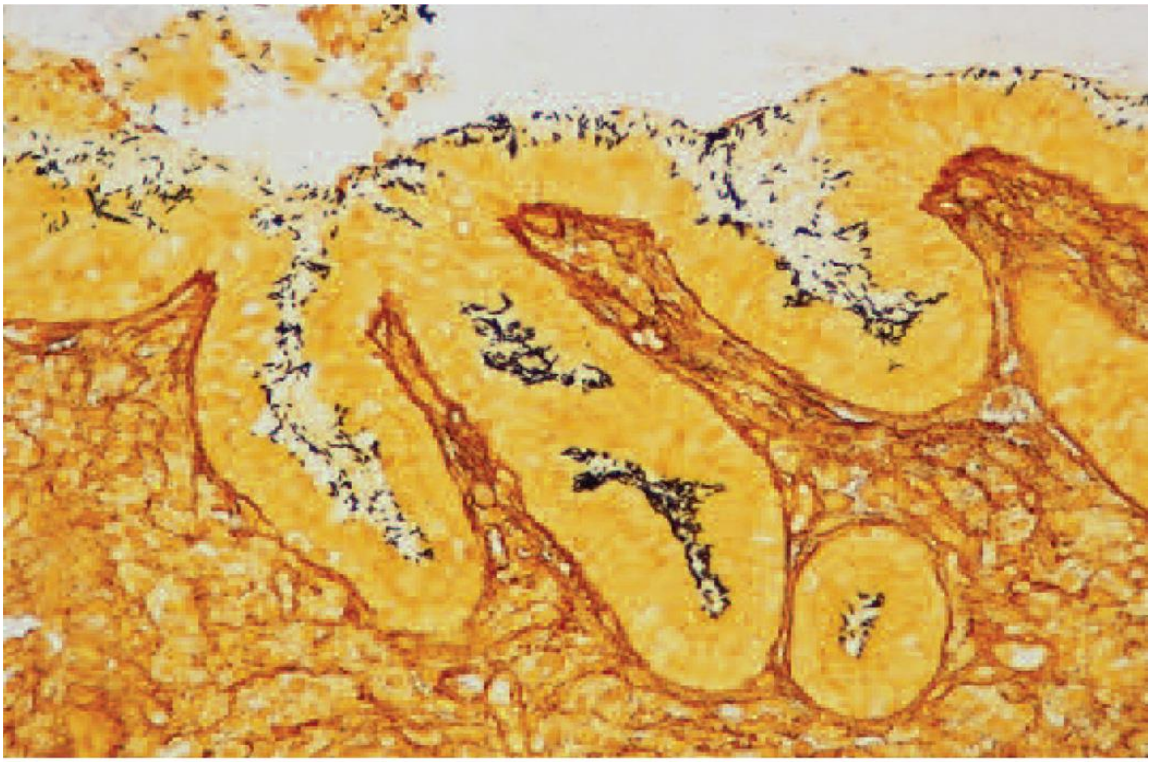

Figure2: Histologic Section of Human Gastric Mucosa Colonized by *Helicobacter pylori*. Abundant microorganisms (black staining) are seen attached to the epithelial cells and surrounding mucus layer (modified Steiner silver stain, ×400). [17]

A recent meta-analysis of six randomized controlled trials has revealed obliteration of H. pylori to reduce the GC incidence by 44%. This relates to 124 H. pylori infections have to be dealt with to prevent one case of GC [32]. In a 15-year follow up of a placebo-controlled trial, Ma et al. observed a 39% reduction in incidence of precancerous lesions after eradication [33]. In addition, Vannella et al. found that, 8 years after obliteration, 50% of patients treated for H. pylori had a reversal of atrophic body gastritis [34].

However, Fuccio et al. examined the available proof and concluded that no study showed a considerable decrease in the incidence of GC with removal treatment if the damage had exceeded atrophic gastritis. On the other hand, Fuccio et al. concluded that obliteration might prevent the progression of preneoplastic lesions [35]. This might suggest that infection eradication during the earlier stages of H. pylori infection elimination might be among scientific benefits, however later there may be a 'point-of-no-return' where cancer risk is only minimized instead of completely eliminated. Li et al. challenged the principle of the 'point-of-no-return'. Li et al. recommends that any age, with any histopathological stage as late on as dysplasia might benefit from obliteration treatment [36]. Elimination treatment does not constantly avoid GC or allow for regression of preneoplastic sores [37,38]. Even after eradication of H. pylori infection, extensive atrophic gastritis might stay, which is a substantial risk factor for metachronous GC. Predictive markers such as pepsinogen I can be utilized to evaluate the future risk of cancer and security endoscopy has a crucial function in keeping track of those at high risk [39].

Roles of H. pylori on programmed cell death (apoptosis) and cell proliferation:

The maintenance of gastric mucosal integrity depends on the balance in between cell loss due to configured cell death (apoptosis) and cell expansion [40,41]. In the uninfected stomach, apoptotic cells are shallow and uncommon, but during H. pylori infection, apoptotic cells are more various and situated throughout the depth of gastric glands [42]. The apoptotic index is higher in specimens from patients with H. pylori gastritis than in noninflamed controls, and apoptosis reduces following H. pylori elimination and resolution of gastritis [43]. H. pylori stress bring the cag pathogenicity island in general reveal CagA. Infection with CagA-positive strains led to increased gastric cell expansion as compared to CagA-negative strains, since CagA-positive pressures induced a lesser degree of apoptosis. This finding may explain the increased risk for gastric carcinoma that has been reported in some research studies to be related to infection by CagA-positive H. pylori pressures [44,45].

4. CONCLUSION

Evidence showed a significant association between infection with H. pylori and gastric cancer, as determined by the presence of raised concentrations of IgG antibodies to the organism, and the risk of gastric cancer. The small number of cases, nevertheless, indicates that the magnitude of the odds ratio doubts. However, the association we observed is not likely to be due to opportunity and supports other evidence suggesting a causal association based upon environmental research studies,' medical observations, and what is known about the function of H. Pylori in triggering chronic gastritis. Other proof showed that there are distinctions in the incidence of gastric cancer in populations with a comparable high occurrence of H. pylori infection can be related to the differences in the age of acquisition of persistent atrophic gastritis, which, in turn, relates to an interaction in between environmental factors, particularly diet, and H. pylori infection. The incidence of gastric cancer differs in different areas and can fall quickly, even in the very same population in relation to levels of sanitation, standards of living.

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