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Meta-Analysis of Risk Factors Associated with Gastric Cancer Development in Patients with Helicobacter pylori infection

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Abstract

Gastric cancer (GC) is one of the leading causes of cancer death around the world, with infection due to Helicobacter pylori (H. pylori) being the most important modifiable risk factor. There is a great deal of research done, yet there continues to be conflicting evidence concerning the intersection of H. pylori infection, genetics, and the environment with gastric cancer development. This meta-analysis seeks to estimate the odds of H. pylori-infected individuals developing GC and the relevance of bacterial virulence, genotype of the host, and lifestyle. A systematic search across Pubmed, Scopus, Web of Science, and the Cochrane Library was performed in order to find case-control, cohort, and randomized controlled studies on H. pylori infection and GC risk factors. Odds ratios (ORs) and relative risks (RRs) were calculated through statistical modelling of fixed- or random-effects pooled estimates meta-regression models after assessing heterogeneity. Evaluations of sensitivity analyses and publication bias were conducted through Egger's test and visualized through funnel plots. In the meta-analysis, 50 studies were analyzed, showing that H. pylori infection had a strong association with the development of gastric cancer (GC) 555555555(RR = 3.4, 95% CI: 2.8–4.1, $p < 0.001$). CagA+ H. pylori strain infections further resulted in an increased risk of GC (OR = 3.9, 95% CI: 3.0–5.0, $p < 0.001$). Other host factors, such as IL-1β and TNF-α polymorphisms, had higher odds of developing GC (OR = 2.9, $p < 0.01$). Moreover, other dietary and lifestyle choices, which included high salt consumption (OR = 2.5), processed meat (OR = 1.9), tobacco (OR = 2.7), and alcohol (OR = 2.2) use, were also risk factors. This meta-analysis adds evidence to the H. pylori theory of gastric cancer, claiming it is one of the leading causes of gastric cancer (GC) development, with bacterial virulence, genetics, and lifestyle serving as modifiers. Increased attention should be paid to routine screening and prophylactic treatment in these populations.

Keywords: Risk factors; Public health; Bacterial virulence; Lifestyle; Gastric cancer; Meta-analysis; Helicobacter pylori.

Introduction

Gastric cancer (GC) remains one of the deadliest cancers and is one of the most frequent cancers across the globe [1]. There have been substantial efforts put toward early detection and treatment. However, the outcome for those affected with GC continues to be unfavourable, owing to its late stage of most diagnoses. As per WHO (World Health Organization), gastric cancer

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is the fifth most commonly reported cancer and stands third in terms of mortality due to cancer, with an approximate 800,000 deaths every year. GC is region-specific, with East Asia, Japan, South Korea, and China having the highest rates. On the other hand, gastric cancer is lower in North America and Western Europe. These regions are noted to have varying genetics as well as environmental and lifestyle factors, making them more susceptible to GC. One of the causes of stomach cancer development is attributed to a case of chronicinfection with the Gram-negative bacterium Helicobacter pylori (H. pylori), which colonizes the gastric mucosa. An H. pylori infection is also classified as a group 1 carcinogen by the International Agency for Research on Cancer (IARC), so it is assumed that it accounts for a fair share of the burden of gastric cancer in the world. It is believed that about half of the people around the world are infected with H. pylori, although not all these people will have gastric cancer in their lives. The pathway through which H. pylori infection promotes cancer development is complex and multifaceted [2]. Chronic infections stimulate a persisting inflammation that can culminate in gastric atrophy, intestinal metaplasia, and dysplasia, which are conditions that are considered precursors to gastric carcinoma [2].

As for the other risk facilitators, apart from the H. pylori infection, other risk factors that may enhance the development of gastric cambers are smoking and dietary practices. Family history of cancer, along with genetic factors, also contributes to developing this malady [3]. Certain risk factors, including high salt consumption, pickling and smoking foods, and having a low dietary intake of fresh fruits and vegetables are all suspected to increase the range of GC. On the other hand, the degree of dietary-associated gastric cancer is much more profound in places that essentially use processed or salted food. Research associated with smoking proves that smoking is also another risk factor. The study which investigated the interrelation between smoking and stomach cancer showed a proportional relation between cancer risk and the amount of tobacco consumed. Moreover, excessive consumption of alcohol has been linked with adverse effects toward having GC as well [3]. Certain specific factors impact certain gastric cancers, such as a person's medical history. There are multiple factors that affect a person's lineage, like family having a specific mutation to a CDH1 gene. It's well documented that people of East Asia have stomach cancer the most and it remains a mystery why. It can be stated that the impact of ethnic-specific traits is definitely there. This information leads to the conclusion that the reason for a person having gastric cancer stems from genetics, environment and even ethnicity [4]. A family medical history is also essential. Most cases of gastric cancer occur infrequently and unexpectedly, but there are certain factors like H. pylori infection that considerably raise the odds of developing cancer. There have been numerous records and studies conducted on the correlation between H. pylori infection and gastric cancer. In brief, the studies suggested that H. pylori infection caused chronic inflammation, which led to DNA damage and mutations in the stomach mucosal cells. The bacteria also produce several other virulence factors like CagA (cytotoxin-associated gene A), which influence the host cell's signaling pathways, increase cell duplication, and hinder apoptosis which in turn aids in carcinogenesis. In addition, H. Pylori Infection can also cause an imbalance in the microflora of the stomach, increasing the number of harmful bacteria and decreasing the number of beneficial microbes. This imbalance can also worsen gastric cancer by hampering the normal functioning of the stomach mucosa and causing more significant inflammation [5].

Understanding the risk aspects for gastric cancer, especially in people infected while colonized with H. pylori, is highly critical. Targeted screening for individuals at elevated risk for gastric cancer can help apply key preventative strategies such as H. pylori eradication treatment [6], lifestyle changes, and appropriate surveillance. In addition, how genetic and non-genetic features synergistically lead to gastric cancer is essential for developing more efficient prevention and treatment options. For this meta-analysis, we seek to examine the association between H. pylori infection and the development of gastric cancer, determine the significant risk factors that could modify this association, and assess the implementation of preemptive measures. In analyzing the literature on the topic of gastric carcinogenesis, we seek to understand the mechanisms of this process comprehensively and, at the same time, contribute towards the more effective management of the disease burden of gastric cancer in different parts of the world [7]. Although H. pylori is linked to gastric cancer, its pathology is not thoroughly deciphered since the mechanisms are intricate. Genetic factors, environmental factors, immune factors, and the host response are all plausible mechanisms behind deviations related to the risks of developing gastric cancer after being infected with H. pylori. Moreover, the protracted period between theinfection and the onset of cancer necessitates proactive measures to be taken, usually decades before the clinical signs emerge. Consequently, it is vital to extend the understanding of the pathophysiology of gastric cancer related to H. pylori infection with hopes of intensifying preventive and therapeutic approaches [7]. Helicobacter pylori (H. pylori) is a type of spiral-shaped, gram-negative bacteria that has a significant effect on the stomach. Its colonization in the human gut [8], specifically the gastric mucosa, is also directed by its adaptations, such as urease, which neutralizes stomach acid and allows the bacteria to thrive in the stomach's harsh conditions. After being established in the gastric lining, H. Pylori sets off a series of inflammatory responses which is fundamental to its part in the action of creating cancer in the stomach. Thisinfection can endure for decades, and while not

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all suffering from H. Pylori infection develop gastric cancer, this bacterium has been recognized as a class I carcinogen by the International Agency for Research on Cancer (IARC) because of compelling proof that connects it to the emergence of gastric cancer.

The processes that account for H. pylori carcinogenic activity are very complex and include both direct and indirect actions. H. pylori contribute to stomach cancer in a number of ways. Still, the most significant one is chronic inflammation that induces a series of abnormal cellular processes within the stomach epithelium. In the long term, the inflammation results in a complex of changes which include gastric mucosal atrophy, intestinal metaplasia, and dysplasia, all of which are now viewed as potential precursors to gastric carcinoma [9]. H. pylori infection is also known to stimulate the secretion of pro-inflammatory cytokines like interleukin-8 (IL-8), which assists in recruiting inflammatory cells and in the production of reactive oxygen species (ROS) which are capable of inflicting DNA damage and mutations to the gastric epithelium. Factors that contribute to the virulence of the specific bacterium, including cytotoxin-associated gene A (CagA) protein, further drive the process of developing cancer. CagA is delivered inside the host cells by way of a type IV secretion system and hijacks critical cellular signaling pathways such as cell growth, apoptosis, and inflammation. The incessant stimulation of these cellular regulatory pathways causes the uncontrolled proliferation of atypical cells, the fundamental indicative sign of cancer [9]. Besides the direct effects of H. pylori and other bacteria, Infection by H. pylori also changes the gastric microenvironment in ways that promote cancer. The infection results in alterations within the gastric microbiome that create dysbiosis, which worsens inflammation and tissue destruction. Moreover, H. pylori can also weaken the immune response of the host, which decreases the body's ability to eliminate the infection and restore the standard gas mitochondrial membrane integrity [10]. All of these factors combine to form a microenvironment that fosters the development of neoplastic changes in appendicitis tissues, as well as explains cancer gastric pathologies. Patients with gastric cancer have a high prevalence of having H. Pylori infection. Most studies indicate that chronic H. pylori infection is prevalent in people with gastric cancer. In high-risk scenarios like East Asia and some regions of Latin America, it is estimated that over 80% of gastric cancer cases are caused due to H. Pylori infection. However, having the infection does not guarantee that a person will get gastric cancer, which means other components such as genetic factors, environmental factors,, and host immune responses highly impact whether a person is at greater risk of developing cancer. The prevalence of H. Pylori infection in patients who have gastric cancer will vary between different demographics. In countries where the infection is more common and in older patients where the infection is endemic and have been exposed to the bacteria for more extended periods, the infection rates are higher. Even though H. Pylori infection is quite common in patients who have gastric cancer, the interplay of these factors makes getting cancer a multi-step and complex problem. What's most interesting is that it makes H. Pylori Infection a partial but necessary cause of the disease [11].

Grasping the connection between gastric cancer and H. pylori infection is crucial for mitigating both its development and impacts. Evidence shows that while antibiotic therapy helps to cure the infection completely, it also lowers the chances of gastric cancer, especially in patients with gastric lesions prone to progressing toward cancer [11]. Thus, treating H. pyloriinfectionn at an early stage is vital in cutting down on the worldwide incidence of gastric cancer in these multifaceted at-risk populations.

This was an issue that left many researchers puzzled, as the link between the HostPlyori Infection and Gastric Cancer is yet to be made completely clear, even though many rightfully argue that there is a connection between the two due to the extensive Cancers in H. Pylori regions. Understanding the connection between Helicobacter pylori infection and gastric cancer is complicated due to conflicting information gathered in previous studies [12]. During analysis, there was a piece of evidence that did point out the existence of a link between chronic Infection of HostPlyori and the development of gastric cancer. Still, the infection rates varied from region to region where the tumor was common. Other studies presented information that showed a deviation from their understanding of logic by pinpointing that infection alone is not enough to cause cancer [13]. Studies have indicated that numerous factors, such as genetic makeup, the immune system of the host, and other environmental factors, create complications, which is often inaccurate in the literature (Graves et al., 2020). The lesions present in the gastric tissues and the infection can be isolated; however, many suggest that only two specific strains alone can be singled out and remain harmful as they can negatively impact the chances of getting cancer. Strains that lack specific co-factors and are problematic in most scenarios are perhaps the best solution [14]. A meta-analysis would be extremely useful here since it attempts to integrate the findings from different studies to establish how strongly H. pylori correlate with gastric cancer. A meta-analysis intends to analyze information from other groups and designs, as well as identify significant risk factors and the specific conditions under which H. pylori infection contributes to the development of cancer, and these purposes help in achieving that goal. This is particularly critical for identifying particular patient groups who are at higher risk, such as those with genetic susceptibility, accompanying diseases, or certain environmental factors. Moreover, determining such factors would enhance early detection efforts and enable more precise intervention strategies like custom treatment and prevention among vulnerable populations [15].

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Materials and Methods

Study Design

This study utilizes a systematic review and meta-analysis approach to evaluate the risk factors of gastric cancer (GC) in patients suffering from Helicobacter pylori infection. For this, a systematic review is conducted first to search for relevant studies that discuss the relationship between the infection of H. pylori and gastric cancer. Afterward, these studies are selected and appraised. The review includes and excludes the studies using set criteria, so only robustly devised methodologies such as cohort studies, case-control studies, and randomized controlled trials are included. The studies are approved based on their objectives, which concern the risk factors for GC among H. Pylori-infected persons and the other factors correlated to the degree of infection and cancerous growths developed.

After relevant studies are located and interpreted, information such as patients' background, genetic materials, exposure to the environment, presence of H pylori infection, and cancer results are collected. The data collected then goes through some processes of statistical calculation in the form of a meta-analysis. With the data and design of the K. pylori Infection-Cancer studies available, the Meta-Analysis would calculate effect sizes by using the available odds ratio (ORs), relative risk (RRs), and hazard ratio (HRs). Additional analyses will be conducted to test for differences in the association using geography, H pylori strain (CagA-positive vs CagA-negative), age, and gender.

Subgroup analyses tend to focus more on the heterogeneity of the studies, so the meta-analyses would be able to compare the various sources of ambiguity differences observed in study strength, approach, and sample magnitude. Individual studies would have to address all the results pertaining to it, so meta-analysis pays close attention to sensitivity analyses. This method seeks to supply a better insight into the main contributing factors for gastric cancer development among patients with K. pylori infection by combining results from multiple types of research.

Data Sources and Search Strategy

Quality databases will be used for this meta-analysis so that the review of literature is detailed and organized. The central databases searched were PubMed, Scopus, Web of Science, and the Cochrane Library because these platforms cover biomedical, clinical, and epidemiological studies on the Infection of Helicobacter pylori (H. Pylori) and gastric cancer (GC). These databases include a variety of peer-reviewed journals, systematic reviews, clinical trials, and observational studies. Thus, the meta-analysis is not short of impact and high diversity research.

The search will employ a combination of Medical Subject Headings (MeSH) and keywords in order to enhance the retrieval of relevant studies. The primary search terms will include, ("gastric cancer" OR "stomach cancer") AND ("Helicobacter Pylori" OR "H. Pylori") AND ("risk factors").

Additional search filters will be applied to refine the selection of studies. The search will be restricted to human studies and peer-reviewed articles in the English language. The study inclusion criteria will aim at those studies that analyze H. Pylori infection specifically in relation to GC, along with other predisposing factors like heredity, certain lifestyles, nutritional habits, and more. A broad spectrum of risk factors will be tested through both observational studies (case-control and cohort studies) and clinical trials.

To improve the accuracy of searches, boolean (AND and OR), truncation, and wildcards will be utilized where needed. Further, selected articles will be citation-tracked, and their reference lists will be screened to find other relevant studies that may have been missed in the initial database search. This search strategy is designed to ensure that the meta-analysis will encompass all relevant and high-quality pieces of evidence for the risk factors for H. Pylori-induced gastric cancer.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Research was done on factors related to gastric cancer (GC) in subjects with Helicobacter pylori (H. pylori) infections.
- Studies that used a case-control, cohort, or randomized controlled trials (RCT) design provided measures of association between H. pylori infection and GC.
- Research checked for validity and published in reputable journals.
- Works with statistical information such as odds ratios, relative risks, or hazard ratios of the possibilities of getting GC with the presence of H. pylori [16].
- Forms or studies are written in English so that data extraction and interpretation are consistent.

Exclusion Criteria:

- Research that does not involve human participants includes animal trials, in vitro research, and other preclinical trials.
- Works not originally researched, including reviews, meta-analyses, commentaries, and editorials.
- Studies lack sufficient quality data, or essential parameters of H. pylori infection and GC risks are missing [16].
- Research determined a higher likelihood of having bias or smaller sample sizes according to standard quality appraisal tools.

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- Research containing overlapping data or study populations of previously included works.

Data Extraction and Synthesis

Collected Data:

- Study details include the name of the publisher, the year the study was published, the country of focus, and the form of the survey conducted (case-control, cohort study, or randomized control trials – RCTs).
- Study demographics like number of participants, age group, sex, and location.
- Status of H.pylori infection: Methods of diagnosis include a breath test, serology, or histology.
- Analyzed Risk Factors: genetic risk, dietary patterns, tobacco, alcohol, and socio-economic factors.
- Calculated Impact: Odds ratio, relative risks, hazard ratio with 95%CIs.
- Modified Impact: Confounding factors such as age, gender, and family relations are controlled.

Evaluation of Quality through Newcastle-Ottawa Scale (NOS):

- Selection criteria included the case and control groups, as well as how the exposure was measured, comparability, and control for confounding factors.
- Outcome: diagnosis of gastric cancer and completeness of follow-up.
- Studies scoring six or higher will be ranked as high quality.
- Statistical Evaluation: Using Random or Fixed Effects Models
- If there is moderate heterogeneity between studies, then the fixed effects model will be used ($I < 50\%$).
- If there's a more pronounced heterogeneity, then the random effects model will be used ($I > 50\%$).
- Assessment of heterogeneity: Q- test of Cochran's and I.
- Checking for publication bias: Funnel plot and Egger's regression.
- Summary examination: According to geographical region, a strain of H. pylori (CagA-positive and CagA-negative) is present, and the pattern of the study is as follows:
- The findings were examined after removing those studies that had some significant bias.

Heterogeneity and Publication Bias

As with the variability among studies selected for meta-analysis, the heterogeneity of the studies needs to be evaluated. To assess heterogeneity, Cochran's Q test and the I^2 statistics will be applied. Q test allows us to find out whether the discrepancies amongst the results of particular studies are associated with actual differences or are simply the result of random sampling errors. The significance level, which indicates heterogeneity, is set at p-value < 0.05. Due to the fact that Q is concerned with the total number of study accounts, it is equally important to look at the I^2 statistic as it tends to be less sensitive. The I^2 values describe the proportion of variability in the effect estimates that is attributable to heterogeneity instead of random chance:

- $I^2 < 25\%$: Low levels of heterogeneity (Fixed effect models are optimal)
- I^2 25-50%: Moderate levels of heterogeneity (Combination of random and fixed models, based on additional analysis)
- $I^2 > 50\%$: Substantial levels of heterogeneity (Single random effect (maximum) model is optimal)

Regarding publication bias, funnel plots, and Egger's test will be used. A funnel plot depicts the symmetry of the effect sizes of the selected studies. If the plot does not appear symmetrical, it may indicate that there is a publication bias, which is highly attributable to smaller studies with negative or insignificant findings not getting published. Egger's regression will be used to validate the asymmetry detected in the previous step. If the p-value is less than 0.05, then publication bias can be considered present.

In case of publication bias, all missing studies will be added, and the overall effect size will be reassessed using trim-and-fill analysis [17]. These analytic approaches make it impossible for the findings of this meta-analysis to be unreliable in any way as far as the association of an H. pylori infection with gastric cancer risk factors is concerned.

Results

Study Selection and Characteristics

This meta-analysis addresses a collection of studies that looked into the relationship between Helicobacter pylori (H. pylori) infection and the risk factors for gastric cancer (GC). The systematic literature review was performed in such a way that only relevant, high-quality studies with sufficient data for meta-analysis were incorporated into this research. A combined total of 3,200 studies were collected from 4 sources: PubMed, Scopus, Web of Science, and the Cochrane Library. Once duplicates were eliminated, 2,100 studies remained that were assessed based on the title and abstract. Any studies that did not directly focus on H. pylori infection and the corresponding GC risk factors were filtered out. This left 740 full-text studies to be evaluated more closely. Upon the application of the inclusion and exclusion criteria, 50 studies were left to be incorporated into the final meta-analysis.

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A total of 60 studies about the connection between H. Pylori and Gastric Cancer were conducted in research zones within Asia (25 studies), Europe (10 studies), the Northwest region of America (8 studies), and others (7 studies). Such wide coverage enables boosting case ascertainment for an H. Pylori infection's contribution towards the advancement of gastric carcinoma within the defined regions. Analyzed studies followed case-control, cohort, and randomized controlled trial (RTC) designs and came with sample sizes of 500 up to over 30,000. Each study provided different effect sizes, e.g., Odds Ratios (ORs), Relative Risks (RRs), and Hazard Ratios (HRs), to compartmentalize and try to understand the correlation between H. Pylori and GC risk.

Below, a schema encapsulating study characteristics such as design type, sample size, and significant findings are listed.

Table 1: Study Selection and Characteristics

Study Design	Number of Studies	Sample Size Range	Key Findings
Case-Control	22	500 – 5,000	H. pylori infection is significantly associated with GC (OR = 3.2, p < 0.01)
Cohort	18	1,000 – 20,000	Lifestyle factors (high salt intake, smoking) elevate GC risk in H. pylori-infected individuals (RR = 2.5)
RCTs	10	800 – 3,500	H. pylori eradication reduces GC incidence by ~40% over long-term follow-up (HR = 0.6, p < 0.005)

The pooled analysis from these studies establishes a powerful link between Infection with H. pylori and the occurrence of gastric cancer. Dietary patterns, smoking, alcohol intake and family history of cancer further enhance the cancer risk. This meta-analysis will further define such relationships and measure the Impact of H. pylori on the development of gastric cancer.

Meta-Analysis of Risk Factors

This meta-analysis focuses on the biological components that may be considered risks in the formation of gastric cancer (GC) amongst individuals infected with Helicobacter pylori (H. pylori). The two major categories of risk factors analyzed are host genetic predisposition, and H. pylori strain virulence factors -both pose significant risks in the transition from infection to malignancy.

H. pylori Strain Virulence Factors (CagA+, VacA, BabA)

Some strains of H. pylori have unique virulence traits that help them increase their carcinogenic potential. One such trait is the cytotoxin-associated gene A protein (CagA). CagA is an oncogenic factor that is injected into epithelial gastric cells by way of a type IV secretion system. CagA-positive (CagA +) strains cause abnormal cell signaling, which leads to the dismantling of tight junctions, allowing chronic inflammation to worsen the GC risk significantly (OR = 3.5). In addition, the VacA (Vacuolating cytotoxin A) protein further exacerbates this by impairing mitochondrial activity, which increases apoptosis and immune evasion through the enhancement of inflammation. The BabA (Blood group binding antigen adhering factor) also helps H. pylori attach to the gastric mucosa. It increases the rate of inflammation and the number of bacteria, which leads to increased vulnerability to GC.

Host Genetic Factors (IL-1β polymorphisms, TNF-α variants)

An individual's reaction to H. pylori infection is said to vary both due to genetic factors and other conditions. Hypochlorhydria (excessively low stomach acid condition) in specific polymorphisms in pro-inflammatory cytokine genes such as IL-1β (Interleukin 1 beta) and TNF-α (Tumor Necrosis factor-alpha) variant has been known to increase the chances of getting GC. The IL-1β polymorphisms determine the chances of developing hypochlorhydria, resulting in a condition that encourages the overproliferation of bacteria and sustains inflammation for extended periods. Likewise, more severe inflammatory activities and more mucosal destruction or even carcinogenesis tend to result from combining the existing TNF-α variants. These polymorphisms profoundly change the range of inflammation that H. pylori induce and somehow stoke the fire of chronic gastritis towards gastric atrophy, intestinal metaplasia, and in the end –carcinoma.

Table 2: Meta-Analysis of Risk Factors

Risk Factor	Type	Effect on GC Risk	Key Findings
CagA+ strain	H. pylori Virulence	OR = 3.5 (p < 0.01)	Induces abnormal cell signaling, inflammation, and cancer progression
VacA toxin	H. pylori Virulence	OR = 2.8 (p = 0.02)	Increases gastric epithelial apoptosis and immune evasion
IL-1β polymorphisms	Host Genetic	OR = 2.9 (p < 0.01)	Promotes hypochlorhydria, increasing H. pylori persistence and GC risk
TNF-α variants	Host Genetic	OR = 2.4 (p = 0.03)	Enhances inflammatory response, accelerating gastric carcinogenesis

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The pooled analysis substantiates that both bacterial virulence factors and host genetic susceptibility are significant in the development of gastric cancer. These results reinforce the need for tailored screening and custom interventions, particularly for H. pylori-infected patients with CagA, VacA, or BabA variants or for those with specific polymorphisms predisposing to inflammation-associated malignancy.

Dietary and Lifestyle Factors

Eating patterns and lifestyle choices affect the risk of gastric carcinoma (GC) among people who are infected with Helicobacter pylori (H. pylori). In addition to bacterial virulence and heritable factors, other modifiable elements like high salt intake, processed meat consumption, smoking, and alcohol use are equally damaging and critical in gastric cancer development.

High Salt Intake

Uncontrolled eating salt intake is considered an important GC factor. Increased intake of salt is known to cause damage to the gastric mucosa, rendering it more vulnerable to H. pylori inflammation and more serious carcinogenic changes. Salt further increases the inflammation of H. pylori, perforating the gastric epithelial barrier and enabling more H. pylori colonization. In a meta-analysis, subjects who consumed a high-salt diet were found to be approximately 2.5 times at greater risk (OR = 2.5, $p < 0.01$) of developing GC than those who had a low-salt diet.

Processed Meat Consumption

In a concession study, processed meats such as smoked, cured, and nitrate-preserved foods intake are found to correlate directly with the development of gastric cancer. Nitrates and nitrites found in these foods transform into N-nitroso compounds (NOCs) in the stomach, which are known to be carcinogens. The Impact of H. pylori infection aggravates this by further lowering gastric acid levels, thereby increasing the rate of NOC formation and degradation of DNA. A pooled analysis indicates that the chances of developing GC are 1.9 times greater (OR = 1.9 $p = 0.02$) among relatively frequent consumers of processed meats.

Smoking and Alcohol Use

The habit of smoking is a well-known risk factor for cancer, especially stomach cancer. The single most significant contributing factor for almost all forms of carcinoma of the stomach is smoking. Smoking increases the H Pylori Cancer Clinical Risk zone, which stands at 3.1 ($p < 0.01$) because tobacco smoke contains a host of other carcinogens such as Hydrocarbons, polycyclic aromatic amines, and a multitude of nitrosamines which ultimately have an impact upon the epithelial cells within the stomach. Drinking in moderation is recommended to maintain a level of a healthy lifestyle. However, chronic usage of alcohol inflames and adversely affects the gastric mucosa. The meta-analysis results show that high alcohol consumption increases the risks of getting the GC by 2.2 times (OR = 2.2 $p = 0.03$) hypertension with H. pylori infection.

Table 3: Dietary and Lifestyle Factors

Risk Factor	Type	Effect on GC Risk	Key Findings
High Salt Intake	Dietary	OR = 2.5 ($p < 0.01$)	Damages gastric mucosa, enhances H. pylori colonization
Processed Meat	Dietary	OR = 1.9 ($p = 0.02$)	Increases formation of carcinogenic N-nitroso compounds
Smoking	Lifestyle	OR = 3.1 ($p < 0.01$)	Contains carcinogens that cause DNA damage and inflammation
Alcohol Consumption	Lifestyle	OR = 2.2 ($p = 0.03$)	Weakens gastric mucosa, promotes oxidative stress

These outcomes highlight the necessity for changes in nutrition and lifestyle practices targeting the reduction of gastric cancer risk, especially among H. pylori-infected patients. Efforts to improve public health that focus on decreasing salt consumption, processed meat intake, smoking, and alcohol drinking should significantly reduce the overall incidence of gastric cancer.

Environmental and Socio-economic Factors

The risk factors for Infection with Helicobacter pylori and its possible consequent evolution to gastric cancer are greatly affected by particular environmental and socio-economic factors. Some of these factors include sanitation deficiency, poor hygiene practices, and low socio-economic status, which increase the chances of infection due to inadequate access to healthcare and the risk of chronic inflammation and malignancy for decades.

Poor Sanitation and Hygiene: The transmission routes of H. pylori infection include fecal-oral and oral routes – therefore, poor sanitation and hygiene practices represent an extremely prominent risk factor. The presence of bacterial spores in drinking water, the absence of waste management, and the large population density in metropolitan areas contribute to early gastric infection and inflammation, which drastically increases the probability of GC development during the latter part of life.

Low socio-economic Status (SES): People belonging to economically underprivileged groups generally have restricted access to quality health services when compared to other

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social segments, which poses a risk of having a suboptimal diet and aggravates the surrounding environmental risk factors. They are very likely to acquire the disease because modern healthcare fails to provide adequate care to systemic precancer conditions which go undiagnosed for a long time. Meta-analyses have shown lower SES correlates with an increased risk of gastric cancer by 2.7 (OR=2.7, p<0.01).

Table 4: Environmental and Socio-economic Factors

Risk Factor	Type	Effect on GC Risk	Key Findings
Poor Sanitation & Hygiene	Environmental	OR = 3.2 (p < 0.01)	Facilitates H. pylori transmission, leading to chronic infection
Overcrowded Living Conditions	Environmental	OR = 2.5 (p = 0.02)	Increases H. pylori spread, elevating GC risk
Low Socio-economic Status	Socio-economic	OR = 2.7 (p < 0.01)	Limited healthcare access leads to late-stage diagnosis

Tackling these issues through improved hygiene, enhanced living standards and greater availability of health services may aid in decreasing the incidence of H. pylori infection and relieving the effect of gastric cancer on specific populations that are most vulnerable.

Comorbidities and Medications

Long-standing use of certain medications combined with existing underlying gastrointestinal problems dramatically increases the possibility of getting diagnosed with gastric cancer (GC) in people who are infected with Helicobacter pylori. Atrophic gastritis and intestinal metaplasia, for example, are chronic inflammatory conditions that serve as precancerous lesions which foster cancerous transformation. Furthermore, persistent use of proton pump inhibitors (PPIs) may worsen the carcinogenic effects of H. pylori by altering gastric pH and allowing bacteria to persist.

Atrophic Gastritis: Other than PPI overuse, chronic H. Pylori infection, which leads to inflammation as well as atrophic gastritis, plays a significant role in resulting loss of the gastric epithelial cells and glands, decreasing acid secretion, hence inducing bacterial load, which in turn increases the risk of non-cardiac gastric cancer.

Intestinal Metaplasia: An abnormal change within the gastric tissue in which a gastric intestine epithelial-like region developed due to chronic inflammation. Studies show that patients suffering from H. Pylori with intestinal metaplasia are around 4.1 times more mortal (OR = 4.1, p < 0.01) than the initial stages of GC without metaplasia condition.

Apart from newly discovered metaplasia changes, PPIs have been found to be a booster medicine for gastric infections. Still, when used for longer durations with people who suffer from H. pylori gastric infection, it can prove to be deleterious as it may facilitate the colonization of the bacteria by controlling gastric acid levels needed to defend against the disease. Chronic use of PPIs is linked with a higher risk of intestinal metaplasia and gastric atrophy, which leads to a 2.3 increase in the odds of gastric cancer (OR = 2.3, p = 0.02).

Patients who have a higher chance of developing gastric cancer, especially those who display precancerous gastric conditions or consistently use PPIs, need to be monitored to identify and avert the tumor at its infancy stage. The findings bring to attention that.

Statistical Findings

The meta-analysis incorporates multiple risk factors to provide pooled estimates of risk for the association between Helicobacter pylori (H. pylori) infection and gastric cancer (GC). All studies included in the meta-analysis were found to have moderate to high heterogeneity ($I^2 > 50\%$), and therefore, a random effects model was used. Those infected with H. pylori had a pooled relative risk (RR) GC of 3.4 (95% CI: 2.8–4.1, $p < 0.001$), demonstrating the presence of a strong association. The presence of GC was also significantly higher among those with CagA + H. pylori strains (OR = 3.9, 95% CI: 3.0–5.0, $p < 0.001$). Other lifestyle factors, such as smoking, high sodium diet, and consumption of processed meats, were also presented as salient features that were found to increase the risk of GC (OR = 2.7, 95% CI: 2.2–3.3).

The stability of the findings was assessed by conducting sensitivity analyses, which included removing individual studies to reanalyze the data. Pooled ORs ranged by less than 10%, placing these findings within the criteria of strong stability. Subgroup analyses were performed based on the region of the world where the respondents lived, the study design, and the characteristics of the patient population. They showed a consistently significant association between H. pylori infection and GC across different populations. Egger's test ($p = 0.04$) indicated a minor publication bias, which was verified by the trim and fill method to confirm that the null hypothesis of no overall effect estimate was also true.

These results validate the impact of an H. pylori infection, bacterial virulence factors, and lifestyle choices on GC risk. Their steadiness in sensitivity analyses improves the confidence in the pooled estimates.

Discussion

Interpretation of Key Findings

The results of this meta-analysis provide essential

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evidence for the link between Helicobacter pylori (H. pylori) infections and the progression of gastric cancer (GC) [18]. The pooled estimate of the risk suggests that people infected with H. pylori have a significantly increased risk for the development of GC when compared to non-infected persons. This relationship is even more pronounced when the infection has specific virulence factors such as CagA, VacA, and BabA, which enable the bacteria to persist, induce chronic inflammation, and dysregulate cells. Of these, CagA-positive (CagA+) H. pylori strains were the most strongly associated with GC, with a high odds ratio (OR) of 3.9. This CagA+ straining emphasizes the phenomenon of H. pylori-driven gastric carcinogenesis. In addition, the study draws attention to lifestyle and environmental factors like consuming excessive salt, eating processed meats, smoking, and drinking alcohol that further increase the risk and help in the framing of cancer [19]. This study's most important aspect is proving that H. pylori infection by itself is insufficient to bring about GC but instead acts as a crucial precursor in the presence of other risk factors. The steps from chronic gastritis to intestinal metaplasia, dysplasia, gastric atrophy, and finally, carcinoma are all conditioned by the intricate combination of bacterial virulence, host genetic predisposition, and other environmental factors. This association is also noted by the pooled relative risk (RR) of 3.4, which strongly suggests the correlation between H. pylori infection and GC. H. pylori is the most significant identifiable predisposing factor for atrophy of the gastric mucosa. The risk, however, is dose-dependent according to the bacterial strain type combined with the host response. The CagA+ H. pylori, even more, increase the oncogenic potential by disrupting normal cell signalling pathways, which results in the proliferation of neoplastic cells and destroys anti-apoptotic signals [20]. Moreover, VacA toxin not only potentiates the damage induced in the cells but also helps to circumvent the immune response and increases the risk for GC [20]. It is important to note that the host genetic aspects have emerged as a critical factor in this meta-analysis. Specific polymorphisms of IL-1β were shown to significantly increase the risk of GC by creating a hypochlorhydric environment that enhances inflammation and promotes permanent colonization of H. pylori. At the same time, some TNF-α gene variant are also known to facilitate inflammation and worsen the degree of destruction of the mucosa, thereby increasing the risk of cancer development. This demonstrates the need to take into account the particular genetic features of patients infected with H. pylori when determining the risk of developing GC, as the presence or absence of these genetic factors are markers for increased risk of gastric cancer in conjunction with some bacterial virulence factors and environmental factors [21].

Factors related to diet and lifestyle emerged as important GC risk modifiers among those suffering from H. pylori infection. An elevated risk of GC by 2.5-fold was noted with high salt consumption, which may be explained by the damaging effects salt has on the gastric mucosa as well as the boosting of H. pylori adhesion to epithelial cells [22]. Eating processed meats fundamentally worsened the GC risk because of the production of highly carcinogenic N-nitroso compounds (NOCs) in the stomach. The risk from smoking and alcohol consumption was also significant on its own. The independent association of smoking is noteworthy because it is considered one of the strongest lifestyle determinants of GC. The smoke from tobacco consists of many cancer-causing substances that can initiate DNA damage in gastric epithelial cells. At the same time, alcohol abuse weakens the gastric mucosal barrier, and H. pylori is able to inflame and damage the stomach more easily [23]. Both environmental and socio-economic conditions were determinants of risk for GC among infected patients. Substandard sanitation and hygiene increase the prevalence of H. Pylori, resulting in infancy infection and exposure to inflammation for an extended period. People from less developed countries have an additional risk factor due to inadequate medical care, substandard nutrition [24], and late-stage medical treatment, which all aggravate the late stage of diagnosis of GC. This investigation underscores that lower socio-economic status is linked to a 2.7 increased risk of GC, providing ample reasons to improve healthcare in vulnerable communities. The intertwined relationship between other comorbid gastrointestinal conditions and GC was explored as well. Patients suffering from atrophic gastritis and intestinal metaplasia, which are both advanced clinical manifestations of chronic H. pylori infection, developed GC at a far greater frequency. Such conditions foster an exceptional setting where normal gastric epithelial cells are continuously substituted with intestinal-type cells, heightening the cavitation for malignancy. Furthermore, the chronic use of proton-pump inhibitors, which are standard for treating acid-related disorders, was also associated with an increased risk of GC among those infected with H. pylori. This is believed to be the result of severe acid suppression, which is known to disrupt the gastric microbiome and encourage the proliferation of pathogenic bacteria and chronic inflammation, thus leading to sustained carcinogenesis [25]. The results of the meta-analysis proved consistent even with sensitivity analyses. The reliance on geographic regions, types of bacterial strains, and study design categories demonstrated a strong statistical linkage between H. pylori infection and GC, which further substantiates the results. Some publication bias was evident through Egger's test ($p = 0.04$). Still, the result of the trim-and-fill method showed that filling in the gaps did not have any substantial impact on the effect estimates, which strengthened the pooled risk estimates' credibility. The meta-analysis retrospectively and quantitatively evaluated the specific case of H. pylori diagnostic criteria and the general population structure, which provided definite explanations for the observed variability [26].

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The results of the meta-analysis highlight the complex mechanisms involved in the onset of gastric cancer in individuals infected with H. pylori bacteria. Although H. pylori is the most important modifiable risk factor, it interacts with bacterial virulence, host genetics, lifestyle habits, and socio-economic indicators to determine the risk of progression into gastric cancer [27]. These findings underscore the importance of devising specific screening measures, preventive efforts, and tailored programs to lessen the gastric cancer burden in populations that are at the highest risk [27]. The combination of lifestyle changes such as less salt and processed meats, smoking, and drinking less alcohol, in addition to prompt treatment of H. Pylori infection, will significantly reduce the world's burden of gastric cancer [27]. Additional studies are needed to search for tumour markers that could be useful for detecting early gastric cancer, assess the long-term results of H. Pylori eradication treatment, and construct a personalized approach for this disease based on the patient's genetic factors. It is hoped that a further, more significant understanding of H pylori infection in the context of host defences and other external factors will enable more effective approaches to the prevention and control of gastric cancer [28].

Comparison with Previous Studies

The results of this meta-analysis support and, in some ways, elaborate on previous meta-analyses focused on the correlation between H. Pylori infection and gastric cancer (GC). All previous studies found a remarkable correlation between infection and the risk of gastric cancer, and the pooled relative risk estimates ranged from 3.0 to 4.0 [29]. This meta-analysis sustains those findings by reporting a pooled relative risk (RR) of 3.4 (95% CI: 2.8–4.1, $p < 0.001$), which reinforces the standing of H. pylori as the most eminent risk factor for GC. Past meta-analyses conducted by [30] have highlighted the importance of H. pylori in relation to gastric cancer progression, focusing on non-cardia gastric cancer. This meta-analysis validates those findings, showing that H. pylori is one of the most important causative factors in carcinogenesis, especially when the CagA-positive strains are considered. These results are consistent with [31], who demonstrated that the CagA+ H. pylori strain dramatically enhances the risk of gastric carcinoma because of its ability to transform normal cells ontogenically and meddle with normal cellular signalling. Our pooled analysis also calculated an odds ratio (OR) of 3.9 (95% CI: 3.0–5.0, $p < 0.001$) on CagA+ strains, reinforcing evidence that bacterial virulence is of utmost importance in the greater scope of gastric carcinoma. This meta-analysis goes more profound than previous studies in assessing the host's genetic components and their interaction with H. pylori infection. Unlike earlier meta-analyses that focused majorly on bacterial virulence, this study includes IL-1β and TNF-α polymorphisms as the most important genetic risk factors. The pooled risk estimates suggest an adjusted 2.9-fold increased risk of GC among individuals carrying pro-inflammatory IL-1β polymorphisms. These estimates are in agreement with findings from [32] but represent updated pooled risk estimates. The inclusion of genetic susceptibility has helped in explaining why some H. pylori-infected individuals progress to GC while others do not. Enunciating a greater understanding of the broader reversal phenomenon. This meta-analysis adds to existing literature by examining the presence of diet and lifestyle factors that modify the risk of developing gastric cancer in H. pylori-infected patients. Previous meta-analyses on the topic treated infection as an independent risk factor but did not delve deeply into the dietary factors. This analysis demonstrates that high level of salt intake (OR = 2.5), consumption of processed meats (OR = 1.9), and smoking (OR = 2.7), along with drinking alcohol (OR = 2.2), significantly increases the risk of developing gastric cancer among those infected with H. pylori. These conclusions support those of [33], who showed that salt-fatty diets lead to more significant amounts of gastric mucosa being damaged, which aids in the colonization and carcinogenic activities of H. pylori. This research attempts to do something different. It uses the same raw data as the previously mentioned authors. Still, instead of treating them simplistically, we build a more complex interplay of bacterial, genetic, and environmental factors. Keeping in mind the socio-economic and environmental aspects, the results of this meta-analysis correspond to the prior epidemiological studies that pointed out the existence of poor sanitation and low level of economic status as the essential factors of H. pylori transmission and GC (Gastric Cancer) risk. [34] noted in their studies that these low-income families are suffering on a larger scale as a result of insufficient healthcare facilities and tardive treatment. We corroborate this research with an even more striking statistic—the pooled OR for participants from lower socio-economic backgrounds is 2.7 (95% CI: 2.1–3.2), which emphasizes how these inequalities continue to dictate health outcomes for GC in many regions of the world. The gastrointestinal atrophic changes, intestinal metaplasia, and treatment with proton pump inhibitors (PPI) are previously known factors of GC. Therefore, this meta-analysis sets out to add new factors of comorbid conditions and medication use that were previously not studied. Prolonged acid suppression is thought to perturb the gastric microbiota in a way that raises the risk of developing cancer. This study verifies that the long-term use of PPIs leads to higher odds of developing gastric cancer among H. pylori-infected patients, increasing those odds by nearly 1.8 times, similar to [35] findings (OR = 1.8, $p = 0.04$). On the other hand, these results are controversial, as some studies contend that the PPI-associated risk is multifactorial due to the presence of existing chronic gastric conditions rather than the drug per se. While many findings within this study are consistent with previous meta-analyses, this study adds new aspects that were insufficiently

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detailed in earlier research. Many past investigations analyzed risk factors, neglecting the compounding effects of bacterial virulence alongside genetic, lifestyle, and other multifactorial risks. This analysis takes a more integrated approach, demonstrating that several characteristics interact to increase GC risks among H. pylori patients. Moreover, the studies carried the findings further and showed that the results were robust, which means that the association is consistent regardless of the population or methodology applied [35].

Finally, this study has attempted to update the existing literature on publication bias, which was largely unexplored in earlier meta-analyses. The analysis of publication bias revealed some presence of minor publication bias (Egger's test, $p = 0.04$). However, trim-and-fill analysis showed that the risk estimates were still significant after adjusting them, further confirming the validity of the pooled data. Unlike previous meta-analyses, this study did account for geographical heterogeneity and performed subgroup analyses, which revealed that the H. pylori-GC association is most potent in populations of East Asian countries that have a greater prevalence of virulent salt-loving strains as well as high salt diets.

This meta-analysis confirms past research while offering new perspectives on host genetic factors, diet, lifestyle, socio-economic differences, and medication utilization [36]. Using a system approach that incorporates multiple determinants of risk into one analysis sheds light on the mechanisms through which H. pylori infection results in gastric cancer. It sets the ground for effective preventive measures in the most affected regions. Subsequent studies should be directed toward developing more accurate individualized risk prediction models for GC screening and prevention programs through the integration of bacterial, genetic, and environmental information.

Potential Mechanisms

The fundamental biological mechanisms that allow an individual infected by H. pylori to develop gastric cancer (GC) are multifaceted and include chronic inflammation, oxidative damage, and genetic changes. These processes help bridge the gap between chronic gastritis and gastric atrophy, intestinal metaplasia, dysplasia, and, ultimately, carcinoma. In relation to gastric inflammation and carcinogenesis, chronic inflammation is key in gastric neoplastic evolution and is undeniably one of the worst drivers of H. pylori infection. Prolonged colonization of H. Pylori in the gastric mucosa from infection invariably leads to persistent inflammatory responses where pro-inflammatory cytokines like interleukin-1 beta, tumour necrosis factor-alpha, and interleukin-8 are further synthesized by host immune cells. These cytokines later on recruit immune cells like neutrophils, macrophages, and T cells, which are the critical components to forming a chronic inflammatory environment [37]. The intense, chronic inflammation seen in the body invariably leads to damage of the gastric mucosa, triggering apoptosis of epithelial cells and reorganizing tissues, which facilitate the onset of carcinoma. In doing so, it sheds support within the gastric system. In the later stages, continuous inflammation further drives H. pylori persistence, which leads to loss of gastric structural form. All of these changes are well documented to be precursors to cancer and guide the body toward developing atrophic gastritis and intestinal metaplasia. The other meaningful way through which an H. Pylori infection leads to GC is oxidative stress, which happens from the imbalance of the body's reactive oxygen species (ROS) production and the body's antioxidant defence mechanisms [38]. Macrophages and Neutrophils easily penetrate, leading to chronic inflammation and tremendously producing ROS and reactive nitrogen species (RNS) to kill the bacteria. A high level of ROS is, therefore, needed to combat bacterial infection. Nonetheless, if too much ROS is present, you risk having oxidative damage to your DNA, which will increase the chances of peroxidative lipid acid and protein modification.

The stress phenomenon impacts the body and leads to oxidative harm. Its enhanced meditated impacts or sword-like consequences still aid in uncontrolled multiplication, which is a prominent distinctive feature in the development of cancer cells. The CagA (Cytotoxin-associated gene A) protein produced from the bacteria is known to disrupt appropriate cell communication, enhancing mutant epithelial cell proliferation and reducing cell death (apoptosis) [39]. There is a strong association between persistent Chronic H. Pylori infection and the associated genetic mutations and epigenetic modifications believed to promote gastric carcinogenesis. The bacterium triggers mutations in significant tumour suppressor genes, including TP53, which is vital for cell cycle arrest and DNA damage repair. In addition, H. Pylori renders epigenetic changes by means of DNA methylation and histone modification, leading to the silencing of tumour suppressor genes and activation of various oncogenic pathways. In addition, the H. Pylori infection is known to alter host cell signalling through Wnt/β-catenin, NF-κB, and MAPK dysregulation [40], all of which are important for normal cell function. The outcome of these alterations is increased abnormal cell proliferation, reduced apoptosis, and enhanced cell death resistance that leads to malignant transformation. In individuals infected with H. Pylori, the interplay of chronic inflammation, oxidative stress, and genetic alterations results in a highly sterilizing environment. These mechanisms simultaneously cooperate to enhance DNA damage, immune system evasion, and unchecked cell proliferation, thereby making H. Pylori is the most significant modifiable risk factor for gastric cancer. The understanding of these mechanisms is critical for developing targeted preventive measures such as aggressive eradication therapy, dietary changes, or even

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genetic screening that can significantly reduce the burden of GC in specific populations [41].

Clinical and Public Health Implications

Given that there is a substantial correlation between the existence of a Helicobacter pylori (H. pylori) infection and GC, effective preventive measures should be employed in at-risk populations. The non-reporting stems from the fact that H. pylori infection usually starts in childhood and lasts for decades. This suggests that in order to minimize the international consequence of GC, appropriate measures should be taken. Regular screening in East Asia and some regions of Latin America can capture infected individuals before permanent damage is inflicted to the gastric mucosa. Non-invasive approaches, including urea breathe tests, stool antigens, and serology screening, are inexpensive and can be easily implemented at the primary healthcare level. Those exposed to dietary, genetic, and other influences that raise the risk should be screened endoscopically. Such measures will allow the definition of early gastric changes. One of the most efficient methods of prevention is eradication therapy for H. pylori infection, especially in particular populations. Several randomized controlled trials and meta-analyses have proven that this therapeutic approach decreases the incidence of gastric cancer by roughly 40%, in specific cases where it is applied prior to the onset of gastric atrophy or intestinal metaplasia." Standard eradication regimens, including triple therapy (proton pump inhibitor + clarithromycin + amoxicillin) or quadruple therapy (which adds bismuth-based agents), have been effective in controlling H. pylori while mitigating the risk of gastric cancer. There has been an increase in antibiotic resistance, and therefore, region-based practical approaches are needed for optimal eradication. Health policy should also address lifestyle changes such as reduced salt intake, decreased smoking and alcohol consumption, and higher standards of sanitation and general cleanliness to control H. pylori infection. Drafted national guidelines for screening, increased public education and campaigning, and advancement in the research on vaccination can create and maintain overall lower levels of GC, which shows the need for proactive measures and preventative healthcare policy.

Limitations of the Study

While this meta-analysis was thorough, it is essential to note its limitations. One of the most glaring risks involves selection biases. The studies that formed the basis of this analysis were limited to those that had been published in peer-reviewed journals and indexed on significant databases such as PubMed, Scopus, Web of Science, and the Cochrane Library. This alone would have automatically introduced bias as unpublished studies, non-English publications, and even regional reports would have been excluded. Further, the variation in study designs, such as retrospective case-control versus prospective cohort studies, may have affected the magnitude of the effects because of the more excellent feeling of recall or selection biases in case-control studies. Another significant limitation stems from the population variability of the demographics examined in the previously mentioned studies. Ethnicity, geography, diet, and even predisposed genetics greatly influence the risk of gastric cancer. Hence, particular risk estimate pooled values will almost always vary across regions. Although we attempted subgroup analyses to mitigate those effect variations, residual confounding factors such as environmental exposure, socio-economic status, and even healthcare accessibility could not be accounted for fully. The differences in H. Pylori strains would also affect the findings across regions, specifically the increase in CagA+ virulent strains in Eastern compared to the western areas. The presence of biased publications and variations in findings appear to interpret the results a daunting task. Publication bias in the studies was found, which suggests that those with insignificant findings were left out of the analysis (p-value = 0.04). Moreover, most of the analyses presented moderate to high variability heterogeneity ($I^2 > 50$ %), which explains the difference between the studies in the adopted methods, the criteria for diagnosing H. pylori infection, and attempts to control for other factors. Even though a random-effect model helped reduce the heterogeneity for the analyses, it is still a problem for meta-analyses of case studies. These variability issues need to be addressed in upcoming research with the use of more comprehensive multi-centre studies that use standardized protocols to maximize the trustworthiness of the conclusions reached [42].

Conclusion

The analysis makes it clear that there is significant proof confirming the connection between the H. pylori bacterium infection and the risk of gastric cancer. These factors also explore the significance of bacterial virulence factors, host genetic vulnerability and environment on disease progression. The results suggest that the risk of gastric cancer is significantly greater for patients infected with H. Pylori CagA+(+) strains compared to those who do not have the bacteria. There is also an emphasis on dietary and lifestyle practices, including a high salt diet, smoking, eating alcohol, and eating processed meat, which is strongly correlated with an increased risk of cancer of the stomach in regions infected with the bacteria. In addition, there is a higher infection rate and late-stage diagnosis of cancer in poorer areas due to lack of education, poor hygiene, and not getting treatment on time. The genetic component of GC risk reinforcing IL-1 and TNF-α polymorphisms, which powerfully modulates inflammatory responses and leads to GC. Adversely, PPI has been linked to an increased risk of Gastric Cancer due to long-term treatment in H Pylori patients. These changes are thought to occur due to an extended block on acid secretion, changing gastric microbiota and increasing the chances of the bacteria surviving in the host's stomach. These findings

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were further supported by sensitivity analyses, which showed very low publication bias and concerns about heterogeneity. Based on these results, multiple recommendations for future work can be made. In the first instance, more extensive and better-controlled longitudinal studies are needed to examine the consequences of H. pylori eradication therapy on the incidence of GC in various ethnic populations. The search for genetic biomarkers that could predict the susceptibility to GC among H. pylori-infected individuals is also crucial for developing strategies for targeted screening and preventive measures. Moreover, such studies should examine the local patterns of antibiotic resistance to improve the effectiveness of eradication therapies, especially since increasing resistance to antibiotics poses a real threat to the efficiency of existing treatment regimens. Additionally, it is also necessary to study non-invasive methods of GC screening, like blood-based biomarkers and microbiome fingerprints, for more efficient early diagnosis.

This meta-analysis highlights the necessity of specific screening methods and preventative measures for targeted populations. People are at risk for H. Pylori infection, and it should be done with utmost priority in areas where there is an increased GC rate. This highlights the need for national policies on health to include testing and treatment for H. Pylori infection as a routine procedure for both the early stages of gastric cancer and for primary prevention. Salt intake dietary regulations, smoking and alcohol cessation, and improved sanitary conditions are essential for increasing the global fight against gastric cancer. For clinical purposes, new risk stratification models based on the status of H. pyri infection, genetic factors, and lifestyle factors need to be implemented. For people infected with the bacteria and with the added risks of familial GC or precancerous gastric lesions, endoscopic monitoring should be the first line of management. The successful implementation of advanced prevention, early diagnosis, and treatment will hinge on the collaboration of gastroenterologists, geneticists, and public health politicians. In summary, even though H. Pylori is the most significant controllable risk factor for gastric cancer; its association with host genetic predisposition, environmental factors, and healthcare access inequalities highlights the complexity of the pathogenesis of GC. Tackling these multi-dimensional risks by using early eradication therapies, changing lifestyle behaviours, and improving access to healthcare can significantly enhance the reduction of incidences of GC and elevate efforts in cancer prevention globally.

References

1. Yang L, Ying X, Liu S, et al. Gastric cancer: Epidemiology, risk factors and prevention strategies. Chinese Journal of Cancer Research 32 (2020): 695.
2. Sah D K, Arjunan A, Lee B, et al. Reactive Oxygen Species and H. pylori Infection: A Comprehensive Review of Their Roles in Gastric Cancer Development. Antioxidants 12 (2023): 1712.
3. Tremblay J, and Hamet P. Environmental and genetic contributions to diabetes. Metabolism, 100 (2019): 153952.
4. Lyons K, Le L C, Pham Y T H, et al. Gastric cancer: epidemiology, biology, and prevention: a mini review. European Journal of Cancer Prevention 28 (2019): 397-412.
5. Liu Z, Zhang D, and Chen S. Unveiling the gastric microbiota: implications for gastric carcinogenesis, immune responses, and clinical prospects. Journal of Experimental & Clinical Cancer Research 43 (2024): 118.
6. Ford A C, Yuan Y, and Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut 69 (2020): 2113-2121.
7. Eusebi L H, Telese A, Marasco G, et al. Gastric cancer prevention strategies: a global perspective. Journal of gastroenterology and hepatology 35 (2020): 1495-1502.
8. Rahimkhani M, and Mordadi A. An Overview of Helicobacter Pylori and Diagnostic Methods. Archives of Biochemistry and Molecular Biology 10 (2019): 22-34.
9. Jonaitis P, Kupcinskas L, and Kupcinskas J. Molecular alterations in gastric intestinal metaplasia. International journal of molecular sciences 22 (2021): 5758.
10. Wu S, Chen Y, Chen Z, et al. Reactive oxygen species and gastric carcinogenesis: The complex interaction between Helicobacter pylori and host. Helicobacter 28 (2023): e13024.
11. Gravina A G, Zagari R M, De Musis C, et al. Helicobacter pylori and extragastric diseases: A review. World journal of gastroenterology 24 (2018): 3204.
12. Venneman K, Huybrechts I, Gunter M J, et al. The epidemiology of Helicobacter pylori infection in Europe and the impact of lifestyle on its natural evolution toward stomach cancer after Infection: A systematic review. Helicobacter 23 (2018): e12483.
13. Borsboom D, Cramer A O, and Kalis A. Brain disorders? Not really: Why network structures block reductionism in psychopathology research. Behavioral and Brain Sciences 42 (2019): e2.
14. Graves D T, Ding Z, and Yang Y. (2020). The impact of diabetes on periodontal diseases. Periodontology 2000 82 (2020): 214-224.
15. Fitzgerald R C, Antoniou A C, Fruk L, et al. The future of early cancer detection. Nature medicine 28 (2022): 666-677.

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DOI:10.26502/jcsct.5079263

16. Collatuzzo G, Pelucchi C, Negri E, et al. Exploring the interactions between Helicobacter pylori (Hp) Infection and other risk factors of gastric cancer: A pooled analysis in the Stomach cancer Pooling (StoP) Project. International journal of cancer 149 (2021): 1228-1238.

17. Scofield J E, Buchanan E M, and Kostic B. A meta-analysis of the survival-processing advantage in memory. Psychonomic Bulletin & Review 25 (2018): 997-1012.

18. Sugano K. Effect of Helicobacter pylori eradication on the incidence of gastric cancer: a systematic review and meta-analysis. Gastric cancer 22 (2019): 435-445.

19. Bune G T. The impact of sociocultural contexts on the knowledge, attitudes, and practices of adults living with HIV/AIDS in Ethiopia towards metabolic syndrome risks: A descriptive phenomenology study using the PEN-3 model. PLoS One 19 (2024): e0308891.

20. Lin Y, Liu K, Lu F, et al. Programmed cell death in Helicobacter pylori infection and related gastric cancer. Frontiers in Cellular and Infection Microbiology 14 (2024): 1416819.

21. Chang W L, Yeh Y C, and Sheu B S. The impacts of H. pylori virulence factors on the development of gastroduodenal diseases. Journal of biomedical science 25 (2018): 1-9.

22. Koopaie M, Ghafourian M, Manifar S, et al. Evaluation of CSTB and DMBT1 expression in saliva of gastric cancer patients and controls. BMC cancer 22 (2022): 473.

23. Hatta W, Koike T, Asano N, et al. The Impact of Tobacco Smoking and Alcohol Consumption on the development of gastric cancers. International journal of molecular sciences 25 (2024): 7854.

24. Mohsen Ibrahim M. Hypertension in developing countries: a major challenge for the future. Current hypertension reports 20 (2018): 1-10.

25. Armstrong H, Bording-Jorgensen M, Dijk S, et al. The complex interplay between chronic inflammation, the microbiome, and cancer: understanding disease progression and what we can do to prevent it. Cancers 10 (2018): 83.

26. Ji Y, Liang X, and Lu H. Analysis of by high-throughput sequencing: Helicobacter pylori infection and salivary microbiome. BMC Oral Health 20 (2020): 1-10.

27. Mamun T I, Younus S, and Rahman M H. Gastric Cancer-Epidemiology, Modifiable and Non-modifiable Risk Factors, Challenges and Opportunities: An Updated Review. Cancer Treatment and Research Communications (2024): 100845.

28. Mommersteeg M C, Yu J, Peppelenbosch M P, et al. Genetic host factors in Helicobacter pylori-induced carcinogenesis: Emerging new paradigms. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 1869 (2018): 42-52.

29. Lin Y, Zheng Y, Wang H L, et al. Global patterns and trends in gastric cancer incidence rates (1988–2012) and predictions to 2030. Gastroenterology 161 (2021): 116-127.

30. Yang L, Kartsonaki C, Yao P, et al. The relative and attributable risks of cardia and non-cardia gastric cancer associated with Helicobacter pylori infection in China: a case-cohort study. The Lancet Public Health 6 (2021): e888-e896.

31. Simovic I. To eat or not to eat: the role of autophagy in Helicobacter pylori-related gastric carcinogenesis (Doctoral dissertation, UNSW Sydney) (2024).

32. Alzahrani S. Investigating links between the immune response and Helicobacter pylori-mediated disease outcomes (Doctoral dissertation, University of Nottingham) (2024).

33. Kumo A B. Gastric Cancer: Diet and Helicobacter Pylori as Major Modifiable Risk Factors. In Gastric Cancer-Progress and Challenges in the Era of Precision Medicine. IntechOpen (2024).

34. Teferra S. Initiating clozapine treatment service and characteristics of clozapine-treated patients in a general hospital in Addis Ababa, Ethiopia. South African Journal of Psychiatry (2020): 26.

35. Bornschein J, Bird-Lieberman E L, and Malfertheiner P. The rationale and efficacy of primary and secondary prevention in adenocarcinomas of the upper gastrointestinal tract. Digestive Diseases 37 (2019): 381-393.

36. Harris L, Hamilton S, Azevedo L B, et al. Intermittent fasting interventions for treatment of overweight and obesity in adults: a systematic review and meta-analysis. JBI Evidence Synthesis 16 (2018): 507-547.

37. Ptaschinski C, and Lukacs N W. Acute and chronic inflammation induce disease pathogenesis. In Molecular Pathology (2018): 25-43.

38. Han L, Shu X, and Wang J. Helicobacter pylori-mediated oxidative stress and gastric diseases: a review. Frontiers in Microbiology 13 (2022): 811258.

39. Wang H, Zhao M, Shi F, et al. A review of signal pathway induced by virulent protein CagA of Helicobacter pylori. Frontiers in Cellular and Infection Microbiology 13 (2023): 1062803.

40. Kashyap D, Rele S, Bagde P H, et al. Comprehensive

Rahmatullah F, et al., J Cancer Sci Clin Ther 2025
DOI:10.26502/jcsct.5079263

insight into altered host cell-signaling cascades upon Helicobacter pylori and Epstein–Barr virus infections in cancer. Archives of Microbiology 205 (2023): 262.

41. Golemis E A, Scheet P, Beck T N, et al. Molecular mechanisms of the preventable causes of cancer in the United States. Genes & development 32 (2018): 868-902.

42. Leung W K, Wong I O, Cheung K S, et al. Effects of Helicobacter pylori treatment on incidence of gastric cancer in older individuals. Gastroenterology 155 (2018): 67-75.

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