Is Helicobacter pylori a Potential Risk Factor for Lung Cancer?

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Helicobacter pylori (H. pylori) is a Gram-negative bacterium known primarily for its role in gastric diseases, including gastric cancer. However, emerging evidence links H. pylori infection to extragastric malignancies, particularly lung cancer. This review examines H. pylori's biological characteristics, pathogenic mechanisms, and potential association with lung cancer development. It addresses H. pylori's direct infection pathways, such as aspiration and microbiome transfer, and explores its impact on the immune system via inflammatory responses and molecular mimicry. Epidemiological data demonstrate inconsistent associations between H. pylori infection and lung cancer risk, though some studies suggest H. pylori-derived proteins, like CagA and VacA, might enhance carcinogenicity in lung tissues. Mechanistically, H. pylori-induced upregulation of inflammatory cytokines and cyclooxygenase-2 (COX-2) may contribute to lung carcinogenesis. Understanding these links could inform future therapeutic and preventive strategies for lung cancer in H. pylori-infected individuals. Further research is essential to clarify these associations and underlying mechanisms.

1. Introduction

Helicobacter pylori (H.pylori) is a Gram-negative, spiral-shaped bacterium that infects the stomachs of up to half of the world's population. The prevalence varies by country, ranging from 20% to 80% [1]. H. pylori has been classified by the World Health Organization as the primary causative factor of gastric cancer [2]. However, as research into its pathogenic mechanisms has deepened, H. pylori has also been linked to extragastric diseases, such as lung cancer [3]. Lung cancer is one of the leading causes of cancer-related deaths worldwide, accounting for approximately one-fifth of all cancer-related mortality [4]. Smoking is the most significant risk factor for lung cancer [5]. In China, the smoking rate among women is significantly lower than among men, yet the annual incidence rate among women can still reach 270,000 cases [6]. In fact, about 15-20% of male lung cancer patients and 50% of female lung cancer patients are non- smokers [7]. Second-hand smoke and exposure to cooking oil fumes are the primary causes [8-9]. An interesting phenomenon is that, despite global anti-smoking policies reducing the overall lung cancer incidence as expected, the incidence rate among non-smokers has been increasing [10]. This suggests the presence of non-smoking factors in lung cancer development, such as air pollution, viruses, bacterial infections, and lung cancer allergens [11]. Among bacterial factors, H. pylori stands out as a significant bacterium, with some studies suggesting a causal relationship between H. pylori and lung cancer [12], while other studies have found no such association [13]. This paper aims to provide a systematic review of the relationship between H. pylori and lung cancer.

2. Biological Characteristics and Pathogenic Mechanisms of H. pylori

2.1 Basic Characteristics of H. pylori

H.pylori is a Gram-negative, spiral-shaped bacterium that survives in the acidic environment of the

stomach by breaking down urea through urease to neutralize gastric acid. The infection rate of H. pylori varies significantly worldwide, with the highest prevalence in Africa (70.1%) and the lowest in Oceania (24.4%) [14]. The pathogenicity of H. pylori depends on specific strains, genotypes, and the expression of virulence factors, which influence the interaction between the host environment and the bacterium [15].

2.2 Pathogenic Mechanisms

H.pylori affects the host through several virulence factors, including urease, cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), and lipopolysaccharide (LPS). Table 1 presents H.pylori-related Independent Factors and Their Pathogenic Mechanisms.

Virulence Factors	Mechanism	Effects
Urease	Production of HCO3- and H+	Neutralizing stomach acid and promoting bacterial colonization [16-17]Modulating host immune responses [18]Promoting cancer development [19]
Flagellum	Motility Flagellar protein activation	Enhancing bacterial motility [20-21]Facilitating colonization and protecting bacteria from escaping acidicenvironments [20, 22]
CagA	T4SSTyrosine phosphorylation	Facilitating the translocation of proteins and DNA into host cells [23] Enhancing cell vitality, reducing cell tight junctions, genomic instability, nucleotide damage [25-26]Promoting tumorigenesis [24]
VacA	Vacuolation of epithelial cellsEndoplasmic reticulum (ER) stress	Causes cell vacuolation [27] Leads to apoptosis [28] Autophagy activation [29] Promoting cell death [30]
LPS	Activation of cytokines Src pathwayAltered dendritic cell (DC) antigen- presenting capacity	Chronic systemic inflammation [34-36]Up-regulation of IL-1, IL-6, and TNF-α [35, 36]Inhibition of CD8 T cell antitumor response [39]

Table 1. H.pylori-related Independent Factors and Their Pathogenic Mechanisms.

Urease

H.pylori produces large amounts of urease, including intracellular urease and extracellular urease on the bacterial surface. Urease catalyzes the hydrolysis of urea to produce ammonia (NH3) and carbonic acid (H2CO3) [16], which further breaks down into bicarbonate (HCO3-) and H+, neutralizing gastric acid and creating a microenvironment conducive to H.pylori survival [17]. Additionally, urease modulates host immune responses through various mechanisms, such as altering opsonization, enhancing neutrophil and monocyte chemotaxis, promoting apoptosis via interaction with MHC class II receptors, or increasing pro-inflammatory cytokine release [18]. Urease also exhibits pro-angiogenic activity in gastric epithelial cells, activates platelets and neutrophils, and has pro-inflammatory properties independent of its enzymatic function, contributing to cancer development [19].

Flagella

Flagella are the locomotive organelles that allow bacteria to move within their environment. H.pylori has spiral-shaped flagella, typically 0.53 μm in diameter and approximately 3 μm long, with 2 to 6 sheathed flagella at one pole. Acid exposure activates flagellin proteins, which are recognized by TLR5 and drive NF-κB activation, enhancing motility [20-21]. The flagellar movement

is powered by a proton motive force, which is generated by urease-driven hydrolysis [22].

Virulence Factors Associated with Pathogenicity

CagA

CagA is a key virulence factor of H.pylori, crucial to its pathogenicity. It is the only known protein secreted by the type IV secretion system (T4SS), a large translocon complex expressed on the surface of Gram-negative bacteria and archaea, which facilitates protein and DNA transfer into host cells in a contact-dependent manner [23]. Once inside the host cell, CagA is phosphorylated at the EPIYA motif (tyrosine residues) by Src family kinases. Phosphorylated CagA causes cytoskeletal rearrangements, leading to the formation of the “hummingbird phenotype,” which interferes with cell proliferation and polarity. Phosphorylated CagA also enhances cell survival, disrupts tight junctions, causes genomic instability, DNA damage, and activates the Wnt signaling pathway, increasing the risk of carcinogenesis [24-26].

VacA

VacA weakens the host cell barrier by inducing vacuole formation, disrupting tight junctions, and promoting apoptosis in gastric epithelial cells. Different VacA genotypes (s1, s^2, m1, m^2) are closely associated with the severity of infection, and this diversity further influences its virulence [27]. Studies suggest that VacA induces apoptosis through the mitochondrial pathway by being internalized into gastric epithelial cells and targeting mitochondria via vacuole membrane ion channels or membrane disruption, leading to cell death [27-28]. Although the exact mechanism of VacA-induced mitochondrial apoptosis is unclear, some studies suggest that the VacA p33 subunit alone targets mitochondria to initiate apoptosis [29]. Other research indicates that VacA triggers endoplasmic reticulum stress, activating autophagy and increasing cell death in AGS cells [30].

Synergy Between CagA and VacA

CagA and VacA work synergistically to enhance pathogenicity. CagA induces DNA damage and genomic instability in host cells by activating inflammatory pathways, while VacA inhibits T cell proliferation, alters dendritic cell antigen presentation, and interferes with the immune system’s ability to recognize and eliminate infected cells. These mechanisms not only aggravate host cell damage but also facilitate persistent H. pylori infection, laying a potential foundation for carcinogenesis in distal organs, such as the lungs [31-33].

Lipopolysaccharide (LPS)

LPS is a major component of the H.pylori cell wall and triggers the upregulation of pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α, leading to chronic systemic inflammation and immune stimulation [34-36]. Other studies suggest that H. pylori infection promotes a chronic inflammatory environment by activating the Src kinase (Src) signaling pathway[37-38] and upregulating the expression of pro-inflammatory IL-1, IL-6, and TNF-α [35, 36]. Notably, H.pylori inhibits CD8 T cell antitumor responses by altering dendritic cell (DC) antigen presentation [39].

3. Epidemiological Evidence of H. pylori and Lung Cancer

Risk H.pylori infection has been shown to significantly increase the risk of lung cancer [40, 41]. Behroozian et al. [42] studied 66 patients with histologically confirmed primary lung cancer and 66 controls, finding that the H.pylori seropositivity rate was 73% in the lung cancer group compared to 51% in the control group (95% CI: 1.14-5.54, OR: 2.51, $P<0.01$), suggesting that the H.pylori antibody seropositivity rate was significantly higher in lung cancer patients than in non-cancer

patients. Ece et al. [43] conducted a study on 43 non-small cell lung cancer (NSCLC) patients and 28 controls, similarly demonstrating that the H.pylori seropositivity rate was significantly higher in lung cancer patients than in controls (93% vs. 42%, P<0.05). Additionally, they found that both VacA and CagA levels were higher in the lung cancer group, although only VacA reached statistical significance (81% vs. 42%, P<0.05). A prospective study by Yoon et al. [44] involving 295 newly diagnosed lung cancer patients and controls, examined 15 different H. pylori antibodies and found a positive association between H.pylori VacA (OR: 1.64; 95% CI: 1.02-2.62) and H.pylori Catalase (OR: 1.75; 95% CI: 1.11-2.77) with lung cancer risk. H.pylori-derived proteins have also been linked to smoking [45-46], and Yoon's study [44] showed that in smokers, H.pylori VacA (OR: 2.53; 95% CI: 1.25-5.13) and H. pylori CagA (OR: 2.77; 95% CI: 1.35-5.70) were similarly associated with an increased lung cancer risk. These findings suggest a potential association between H.pylori infection and lung cancer development.

Pulmonary nodules are considered a precursor to lung cancer, and the risk of malignancy increases as the size of the nodule grows, particularly when the diameter exceeds 1 cm [47]. Mahasish et al. [48] compared the lung microbiomes of lung cancer patients, those with lung nodules, and smokers as controls, finding the highest H. pylori positivity rate in lung cancer patients. They identified HP1341 antibody as the most reactive among 233 H.pylori antibodies. The study further used specific antibody combinations to distinguish between lung adenocarcinoma patients and those with benign lung nodules or smokers, utilizing ROC curves (Receiver Operating Characteristic) to evaluate the discriminatory power of these antibody combinations (0.88 vs. 0.8). Sven et al. [49] in a retrospective study, found that patients who underwent H.pylori eradication therapy were negatively correlated with bronchial and lung cancers during subsequent follow-up (HR: 0.60; 95% CI: 0.44-0.83), while those who did not receive eradication therapy had a strong association with subsequent bronchial and lung cancers (HR: 1.51; 95% CI: 1.03-2.20).

However, study have shown no association between H.pylori and lung cancer [13]. But Paul et al. [39], in a retrospective analysis of two independent cohort studies, found that in both the French Dijon research center (60 NSCLC patients) and the Canadian Montreal research center (29 NSCLC patients), H.pylori was associated with reduced efficacy of immunotherapy (HR: 3.35, 95% CI: 1.69-6.66, P=0.001; HR: 2.39, 95% CI: 1.01-5.65, P=0.048). A case-control study by Koshiol et al. [50] compared 700 lung cancer patients (350 with lung adenocarcinoma and 350 with squamous cell carcinoma) and 700 controls. The results showed no significant difference in H.pylori positivity rates between the adenocarcinoma or squamous carcinoma groups and the control group (OR: 1.1, 95% CI: 0.75-1.6; OR: 1.1, 95% CI: 0.77-1.7). Similarly, no significant associations were observed with H.pylori CagA (OR: 1.1, 95% CI: 0.73-1.7) or H. pylori VacA (OR: 1.0, 95% CI: 0.65-1.6).

These inconsistencies may be attributed to differences in study design, sample size, geographic variation, and inadequate control of confounding variables. Overall, the relationship between H.pylori and lung cancer remains under investigation, and further large-scale or prospective studies are needed to draw more definitive conclusions. Table 2 presents the basic information of articles on the epidemiological relationship between Helicobacter pylori and lung cancer.

Author	Sample	Male	Average age	H.pylori test	H.pylori rate(control, %l)	OR	CI	P
Najafizadeh K(2007) [13]	80	57	NA	H.pylori sero prevalence	52.5	1.35	0.56-3.25	0.65
Behroozian R(2010) [42]	132	103	NA	H.pylori sero prevalence	73	2.51	1.14-5.54	< 0.05
Ece F (2005)[43]	71	35	NA	H.pylori immunoblot	NA	NA	NA	< 0.01
Yoon HS(2022) [44]	590	306	57	H.pylori sero prevalence	56	1.29	0.85–1.95	> 0.05
Koshiol	1400	NA	58	H.pylori sero	78.8	1.1	0.75–1.6A0.7	> 0.05

J(2012) [50]				prevalence			7–1.7B	

Table 2. Basic Information of Articles on the Epidemiological Relationship between Helicobacter pylori and Lung Cancer.

NOTE:A represents adenocarcinoma, B represents squamous cell carcinoma

4. Possible Mechanisms of H. pylori-Induced Lung Cancer

4.1 Direct or Indirect Infection Mechanisms

It is currently theorized that H.pylori infection spreads directly through oral-oral or fecal-oral transmission within families [53]. The oral cavity, shared by both the respiratory and digestive systems, has been shown to harbor H.pylori [52]. Studies have detected H. pylori in the saliva of patients with laryngopharyngeal reflux [53] and in tracheal secretions [54]. Nur et al. [55] found H.pylori in lung cancer tissues using Giemsa staining, as well as in lung cancer specimens and bronchoalveolar lavage fluid, identifying H.pylori-derived proteins such as VacA. These proteins were shown to induce the production of IL-6 and IL-8 in human lung cells [3, 56]. This suggests that H.pylori may colonize lung tissue directly or cause disease indirectly through virulence factors like VacA. We hypothesize that H.pylori may colonize the lungs through the following pathways:

Aspiration

H.pylori can cause acid reflux, leading to reflux esophagitis [57]. H.pylori may enter the lower respiratory tract through vomiting, reflux, or aspiration, providing a physical pathway for colonization in the lungs.

Microbiome Transfer

The early colonization of gut and lung microbiota shows homology, as the microbiota enters the gut or lower respiratory tract via the oropharynx. The gut and lung engage in bidirectional regulation through microbial and immune interactions, amplifying immune signals in what is known as the gut-lung axis [58]. Dysbiosis in the gut microbiome could hypothetically enable the transfer of pathogens like H.pylori via this axis, affecting the lung microbiome and promoting H. pylori colonization.

4.2 Inflammatory and Immune Responses

Arismendi et al. [59] discovered that H.pylori induces lung damage by recruiting inflammatory cells and promoting the secretion of inflammatory cytokines. Lipopolysaccharide (LPS), a major component of H.pylori’s cell wall, can trigger the upregulation of pro- inflammatory cytokines such as IL-1, IL-6, and TNF-α, leading to chronic systemic inflammation and immune stimulation [34-36]. These cytokines may induce DNA double-strand breaks and genetic damage, leading to mutations that promote carcinogenesis [60]. H.pylori promotes the secretion of inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-8) and induces lung damage through its VacA exotoxin, thereby activating NF-κB signaling pathways [61].

4.3 Molecular Mimicry

Some studies suggest that the host immune response to bacteria can induce damage to both gastric and extra-gastric tissues through molecular mimicry [62]. This cross-reactivity may lead to the activation of self-reactive T or B cells, or direct damage from bacterial inhalation, which may contribute to chronic airway inflammation. Over time, this inflammation could lead to the malignant transformation of lung epithelial cells. Shan Xu et al. [63] reported six cases of drug-induced interstitial pneumonia following H.pylori eradication therapy, presenting with cough, shortness of

breath, and fever. It is hypothesized that H. pylori may express antigens that mimic lung epithelial cell antigens, thereby activating antigen-specific immune responses through molecular mimicry, leading to chronic inflammation and eventual malignancy in the lung epithelium.

4.4 Host Response

Deng et al. [64] suggest that the interaction between H.pylori and the host primarily occurs at local adhesion points. H.pylori adhesin CagL, located at the tip of the Type IV secretion system (T4SS), can bind to β1 integrin receptors on epithelial cells, potentially activating focal adhesion kinase (FAK) and Src kinases. Activation (phosphorylation) of FAK and Src leads to the injection of CagA. Initially, CagA is phosphorylated by Src and subsequently interacts with tyrosine phosphatase (Shp-2) and C-terminal Src kinase (Csk), eventually deactivating FAK and Src. p130cas, a substrate of Src kinase, can be activated and recruited by Src, playing an oncogenic role in lung cancer cell invasion and migration.

4.5 Upregulation of Gastrin and Cyclooxygenase-2 (COX-2)

H. pylori infection induces the upregulation of COX-1, COX-2, and gastrin expression, which may further promote lung cancer by inducing bronchial epithelial cell proliferation [65]. There are also embryological explanations [66-68], suggesting that the lungs and digestive tract share the same origin from endodermal cells. When H.pylori infects the stomach, it can lead to an increased and prolonged release of gastrin into the circulation, which may stimulate the proliferation of lung cells.

5. Conclusion and Future Directions

Although increasing studies are exploring the relationship between H.pylori and lung cancer, current results are inconsistent. The main limitations are insufficient sample sizes, differences in study designs, and inadequate consideration of confounding factors. Future large-scale, multi-center prospective studies are needed to confirm this association. Future research should further investigate the molecular mechanisms linking H.pylori infection to lung cancer, as well as the specific impact of different H. pylori virulence factors on lung cancer development. If H.pylori infection is indeed associated with lung cancer, screening and eradication of H.pylori may become part of lung cancer prevention. Additionally, assessing H.pylori infection status may help inform personalized treatment strategies in lung cancer immunotherapy.

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Statement of Transparency and Principals

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute.

• Study’s data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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