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The relationship between H. pylori infection and lung cancer cross sectional study

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Abstract

Background: Helicobacter pylori infection is a common disease and leads to many gastrointestinal and respiratory diseases. It is suspected that one of these respiratory diseases is lung cancer.

Methods: sixty patients with lung cancer and one hundred twenty control subjects have been included to this study. All enrolled subjects (lung cancer patients and controls) underwent a15 minute, lateral flow immunoassay for the qualitative detection of IgG antibodies anti-H. Pylori in human serum (CTK Biotech, Inc USA) and a lateral immunochromatographic assay for the qualitative detection of H. Pylori antigen in human fecal specimen (CTK Biotech,Inc USA) , A p value of <0.05 was considered as significant. The statistical data analysis was performed with SPSS 22. .

Results: The H.pylori seropositivity was (41 /60) (68.3) %in patients with lung cancer but only (16/ 120) (13.3) %in controls and this difference in H.pylori seropositivity between cancers and controls was statistically significant P<0.016. The odds ratio for the association of H.pylori and lung cancer was 3.6 (95% CI =1.24 – 4.8), The H.pylori stool antigen was (22/60) (36.7) % in patients with lung cancer but only (14/120) (11.7) %there is statistically significant P<0.001.

Conclusion increase the prevalence of H.pylori seropositivity was (68.3) %in patients with lung cancer more than in normal controls (13.3) %.

Introduction

The lung cancer is a main health problem with a generally bad prognosis, It is one of the most common causes of mortality in the world [1,2], It is the commonest cause of cancer death for both male and female and accounts for 28% of the overall cancer death rate[3] The overall incidence of lung cancer has been strongly associated to cigarette smoking. It also occurs in association with occupational and environmental exposure to carcinogenic agents. There are another factors related to the development of lung cancer such as genetic alteration, familial predisposition, and Helicobacter pylori infection [4-6].

H. pylori (Hp) is Gram-negative , spiral, and has multiple flagella at one end, which make it motile, allowing it to burrow and live beneath the mucus layer adherent to the epithelial surface. H. pylori use an adhesin molecule (BabA) to bind to the Lewis b antigen on epithelial cells. Here the surface pH is close to neutral and any acidity is buffered by the organism's production of the enzyme urease. H. pylori synthesis ammonia from urea and elevate the pH around the bacterium and between its two cell membrane layers. H. pylori mainly colonises gastric-type epithelium and exclusively found in the duodenum in association with patches of gastric metaplasia. H. pylori cause chronic gastritis by producing a local inflammatory response in the underlying epithelium [7].

The pathogenesis of H. pylori majorly relay on the producing of several bacterial agents to the host, including cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), type IV secretion system (T4SS), outer inflammatory protein A and adherence factors [8].

Cytotoxins and carcinogenesis-associated proteins of Hp

The cytotoxin-associated protein (CagA) and the vacuolating cytotoxin(VacA), are important virulence determinants of Hp and may elaborate complex cellular responses of epithelial cells in Hp pathogenesis and carcinogenesis [9]. Based on the phenotypic analyses of clinical isolates of Hp, more of the strains can be classified into two broad groups—those expressing both VacA and CagA (type I) and those producing neither

(type II). The remaining Hp strains have an intermediate phenotype (type III), expressing CagA independently of VacA (CagA+VacA$^-$) or vice versa (CagA−VacA$^+$) [10]. The CagA gene is located within the Cag pathogenicity island region on the bacterial chromosome, which encodes proteins important for structure and function of T4SS [11]. Approximately, 60–70% of Western Hp strains and all of East Asian strains express CagA [12]. Many studies described that CagA+ strains are closely connected with the development of acute gastritis and pre-malignant and malignant lesions [13-15]. The relationship between CagA and malignancy were demonstrated in animal models [16],supporting strong evidence for the role of CagA as a bacterium-derived oncoprotein VacA, the second most extensively studied Hp factor, enhances Hp virulence though its pleiotropic functions in vivo. The gene encoding VacA is present in almost all Hp strains [17].There are relationship between VacA and gastroduodenal diseases (e.g. peptic ulcer, atrophic gastritis and gastric cancer) [18]. The differences in the VacA structure at the signal region (s1 and s2) and the middle region (m1 and m2) lead to variations in the vacuolating activity [19]. Many studies in Western countries showed that individuals infected with VacA s1 or m1 strains have an increased risk of peptic ulcer or gastric cancer compared with those with VacA s2 or m2 strains [20, 21].

Extra gastric manifestations:

There are strong association between Hp and many abnormal conditions, e.g. cardiovascular [22–24], hematologic [25-27], eye and skin [28–30] and hepatobiliary diseases [31-33]; diabetes mellitus [34–36] and neurological disorders [37–39]. And also Hp infection has been associated to be involved in autoimmune pancreatitis and pancreatic cancer [40], and can increase the risk of transforming growth factor-β1-mediated tumorigenesis by disturbing the balance between apoptosis and proliferation of hepatocytes [31]. There is also relationship between Hp infection and colorectal, laryngeal–hypo pharyngeal malignancy [41, 42].

Diagnosis

Different methods of testing exist. One can test noninvasively for *H. pylori* infection with a blood antibody test, stool antigen test, or with the carbon urea breath test (in which the patient drinks ^{14}C— or ^{13}C-labelled urea, which the bacterium metabolizes, producing labelled carbon dioxide that can be detected in the breath)[43] Also, a urine ELISA test with 96% sensitivity and 79% specificity is available. None of the test methods is completely fail safe. Even biopsy is dependent on the location of the biopsy. Blood antibody tests, for example, range from 76% to 84% sensitivity. Some drugs can affect *H. pylori* urease activity and give false negatives with the urea-based tests. The most accurate method for detecting *H. pylori* infection is with a histological examination from two sites after endoscopic biopsy, combined with either a rapid urease test or microbial culture [44].

Material and Method

This study was conducted at the Department of Pulmonary Medicine, of the Baghdad teaching hospital Between February 2015 and October 2015, 60 consecutive patients with histologically verified primary lung cancer were enrolled in the study. Lung carcinoma diagnosis was confirmed by fiber optic bronchoscopy and/or transthoracic needle aspiration, tru cut biopsy.

Exclusion criteria were: prior Helicobacter eradication therapy, consumption of acid suppressive drugs, a history of operations on the upper gastrointestinal tract. The control population included patients hospitalized for any other disease other than lung cancer. We selected 120 controls and matched them with the patients for sex and age and smoking habit.

All enrolled subjects (lung cancer patients and controls) underwent a15- minute, lateral flow immunoassay for the qualitative detection of IgG antibodies anti-H. Pylori in human serum (CTK Biotech, Inc USA) and a lateral immunochromatographic assay for the qualitative detection of H. Pylori antigen in human fecal specimen (CTK Biotech,Inc USA) .

Statistical analysis

The relation between lung cancer and H. pylori infection was assessed by paired *t* test. All results were compared among two groups by percentage and frequency table sand charts. In addition odds ratio (OR) and 95% confidence interval were estimated for percentage of lung cancer and H. pylori infection relationship. A p value of <0.05 was considered as significant. The statistical data analysis was performed with SPSS 22.

Results

This cross sectional study was carried out in Baghdad teaching hospital a (60) histologically verified lung carcinoma patients (42) (70.0%) men and (18) (30.0%) women) with the median age of (57.8±11.4) years and (120) controls (44) (36.7%) men and (76) (63.3%) women) with the median age of (42.0±14.1) years .The demographic data of both patients and controls are shown in Table 1.

Table1 the demographic data of the age on both patients and controls

Statistics

Age		cancer	control
N	Valid	60	120
Mean		57.8000	42.0333
Std. Deviation		11.44597	14.13259

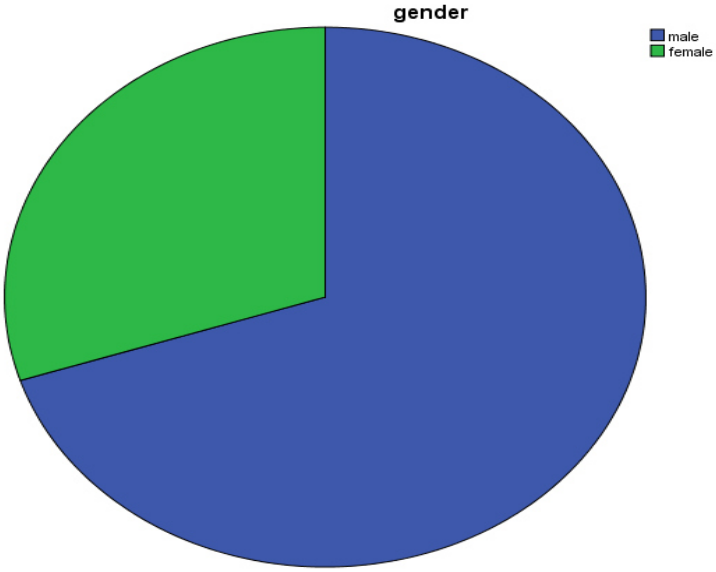

Figure 1: frequency of the gender on Cancer patients

Table2: the demographic data of gender on patients

cancer		Frequency	Valid Percent	Cumulative Percent
Valid	male	42	70.0	70.0
	female	18	30.0	100.0
	Total	60	100.0	

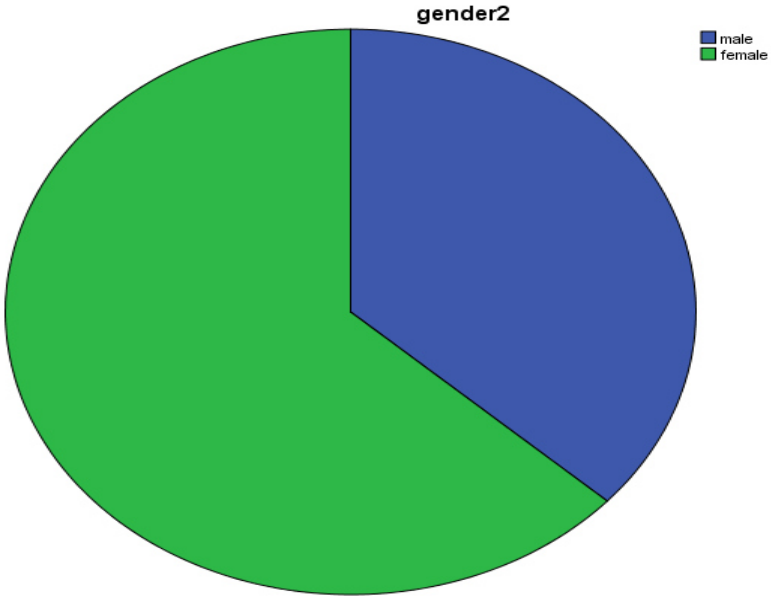

Figure 2-frquency of gender on control group

Table3: the demographic data of gender on control group

control		Frequency	Valid Percent	Cumulative Percent
Valid	male	44	36.7	36.7
	female	76	63.3	100.0
	Total	120	100.0	

Among the lung cancer patients, (34) (56.7 %) had adenocarcinoma, (26) (43.3 %) had squamous cell carcinoma, see table 4

Table 4: frequency of histological type cancer

Histological type		Frequency	Valid Percent	Cumulative Percent
Valid	squamous ca	26	43.3	43.3
	adenocarcinoma	34	56.7	100.0
	Total	60	100.0	

The prevalence of H.pylori seropositivity was (41 /60) (68.3) %in patients with lung cancer but only (16/ 120) (13.3) %in controls and this difference in H.pylori seropositivity between cancers and controls was statistically significant P<0.016. The odds ratio for the association of H.pylori and lung cancer was 3.6 (95% CI =1.24 – 4.8,) see table5 Characteristics of patient group and control group, and also the figure 3,4,5,6 revealed the differences in level of antigens and antibodies in control and lung cancer patients

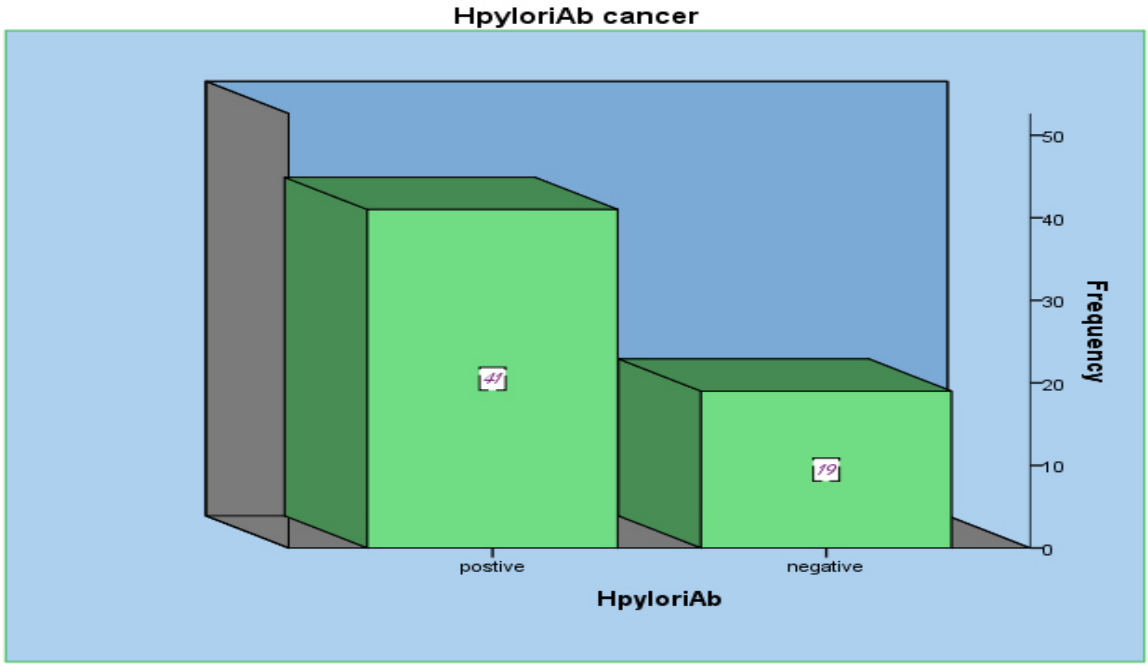

Figure 3: the level of antibodies in lung cancer pateints

Table5: Characteristics of patient group and control group

	Cancer	normal	P value
H. pylori Ab positive	41 (60) (68.3)%	16 (120) (13.3)%	0.016
H. pylori Ag positive	22(60) (36.7)%	14(120) (11.7)%	0.001
Age(year)	57.8± 11.4	42± 14.1	0.244

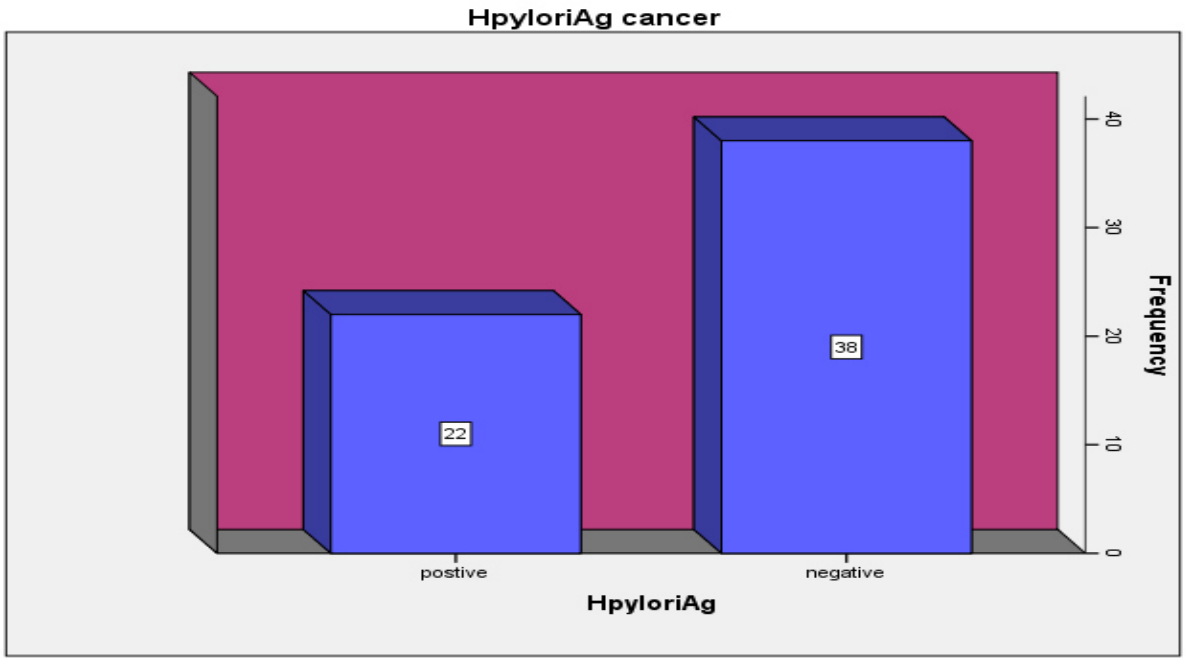

Figure 4: the level of antigen in lung cancer pateints

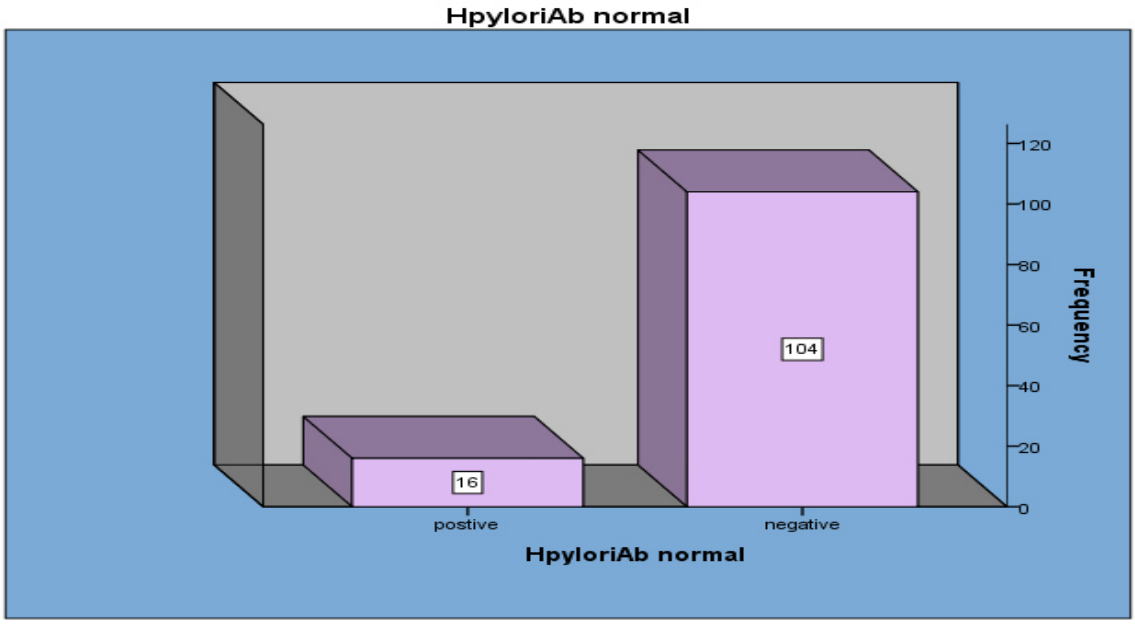

Figure 5: the level of antibodies in control group

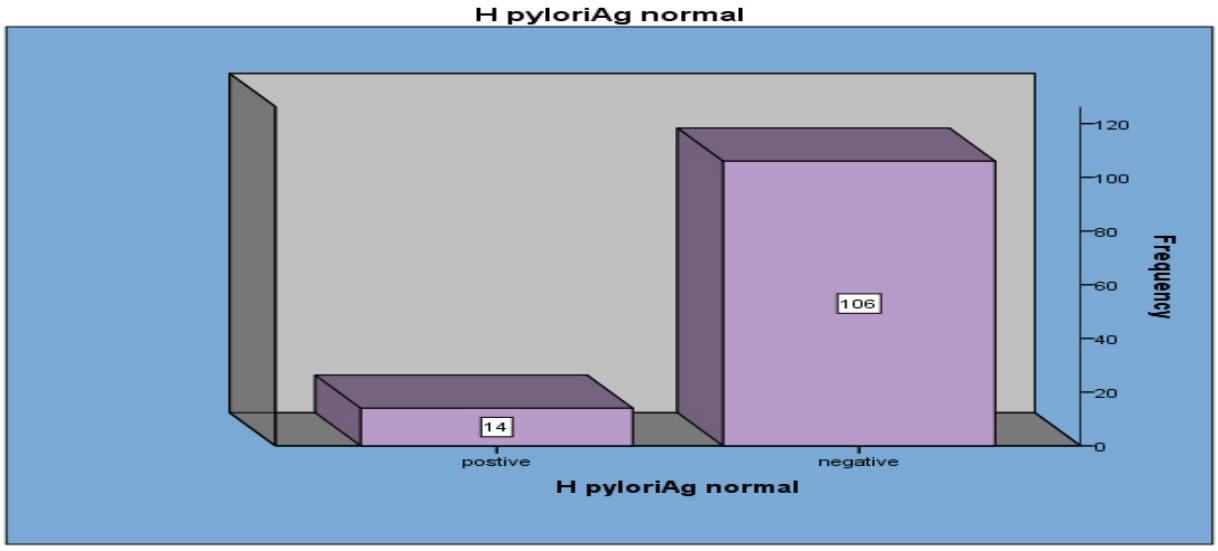

Figure 6: the level of antigen in control group

Discussion

H. pylori has become a world-wide infective agent ranging from 25% in developed countries to more than 80% in the developing world [45]. H. pylori infection has an important role in the development of chronic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue (MALTlymphoma), and gastric cancer [46-49].In our study; H. pylori seropositivity was significantly higher in cancer patients than in control subjects. Also more lung cancer cases were stool antigen positive patients than controls. Previous studies investigated the association between H. pyloriseropositivity and lung cancer. Ece et al, found a 93% seroprevalence of antibodies against H. pylori in 40 consecutive patients with lung cancer and a 42% seroprevalence in 12 control subjects[50]. Ferah Ece et al, study reported that CagA strain seropositivity inblung cancer patients was about thrice as high as in controls (63% vs. 21.5%, respectively, P≤0:05) [51]

Roussos et al, found a significant association between chronic bronchitis and H. pylori [52]

The results of previous study showed that the population of patients with lung cancer has a significantly higher rate of seropositivity for antibodies against H.pylori (48 of 66) than the population of subjects without lung cancer (34 of 66). (OR=2.51, 95%CI= 1.14 – 5.54 P<0.05). [53]

Gocyk et al [54] they demonstrated a significantly higher H pylori seroprevalence among patients with lung cancer in comparison with healthy subjects (89.5% vs64% respectively, P< 0.05).

Lungs arise embriologically from the same endodermal cells that form the lining of the gastrointestinal tract and possess similar cells releasing various hormonal peptides. [55]

Lung cancer patients were characterized by a significant increase of gastrin concentration in both serum and Broncho alveolar lavage (BAL). They also demonstrated that m-RNA expression for gastrin and its receptor, as well as for cyclooxygenase (COX)-2, is enhanced in the tumor tissue. Increased plasma level of gastrin which is accompanied by H. pylori infection may contribute to the lung cancerogenesis by inducing mucosal cell proliferation of bronchial epithelium. [56, 57]

Zhou et al. [58] it has been shown that serum from patients with lung cancer contained a high concentration of gastrin, and serum gastrin was found to decrease gradually after the removal of the tumor and to return to normal on the 14th postoperative day.

H. pylori infection is accompanied by an increased plasma level of gastrin, suggesting that this hormone could contribute to the lung carcinogenesis by inducing higher mucosal cell proliferation of bronchial epithelium leading to atrophy and induction of COX-2[59,60] . This finding that lung cancers exhibit higher

expression and content of gastrin and its receptors is akin to up regulation of gastrin biosynthesis already described for gastric cancers and colorectal cancers[61] .

Reason for the increased risk of lung cancer in H. pylori infected patients can be explained in several ways. (i) H. pylori is Gram-negative bacteria with lipopolysaccharideas the major component of the cell wall. Lipopolysaccharide stimulates the production of proinflammatory cytokinesIncluding interleukins and tumor necrosis factor-alpha [62]. This leads to chronic inflammation and immune stimulation, which may contribute to carcinogenesis [63, 64, and 65]. (ii) The lungs arise embryological from the same endoderm cells that form the lining of the gastrointestinal tract and possess, similar neuroendocrine and paracrine cells releasing various hormonal peptides and their receptors including gastrin releasing peptide and gastrin [66, 67].

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