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The association of *vacA* genotypes and *Helicobacter pylori*-related gastroduodenal diseases in the Middle East

M. Sugimoto,

Department of Medicine, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, 2002 Holcombe Blvd., (111D) Rm 3A-320, Houston, TX 77030, USA

M. R. Zali, and

Department of Internal Medicine and Gastroenterology, Research Center for Gastroenterology and Liver Disease, Shaheed Beheshti University, Tehran, Iran

Y. Yamaoka

Department of Medicine, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, 2002 Holcombe Blvd., (111D) Rm 3A-320, Houston, TX 77030, USA.
Department of Environmental and Preventive Medicine, Oita University Faculty of Medicine, Yufu, Japan

Y. Yamaoka: yyamaoka@bcm.tmc.edu

Abstract

The variations in the three regions of the *Helicobacter pylori vacA* gene, the signal (s1 and s2), intermediate (i1 and i2) and middle regions (m1 and m2), are known to cause the differences in vacuolating activities. However, it was unclear whether these *vacA* genotypes are associated with the development of gastric cancer and peptic ulcer in the Middle East. The aim was to identify the prevalence of *vacA* genotypes in the Middle East and the association with gastroduodenal diseases. We investigated the relationship of *vacA* genotypes to *H. pylori*-related disease development by meta-analysis using previous reports of 1,646 patients from the Middle East. The frequency of the *vacA* s1, m1 and i1 genotypes in the Middle Eastern strains was 71.5% (1,007/ 1,409), 32.8% (427/1,300) and 40.7% (59/145), respectively. Importantly, the frequency of *vacA* s- and m-region genotypes significantly differed between the north and south parts of the Middle East countries ($P<0.001$). The *vacA* genotypes significantly increased the risk of gastric cancer (odds ratio [OR]: 4.02, 95% confidence interval [CI]: 1.98–8.14 for the s1 genotype; 2.50, 1.62–3.85 for m1; 5.27, 1.97–14.1 for s1m1; 15.03, 4.69–48.17 for i1) and peptic ulcers (OR: 3.07, 95% CI: 2.08–4.52 for s1; 1.81, 1.36–2.42 for m1). The *cagA*-positive genotype frequently coincided with the s1, m1 and i1 genotypes. The *vacA* s- and m-region genotypes may be useful risk factors for gastrointestinal diseases in the Middle East, similar to European and American countries. Further studies will be required to evaluate the effects of the i-region genotype.

Introduction

Helicobacter pylori infect in the gastric mucosa of 50% of the world's population and infection levels exceed 70% of the population in developing areas, such as Latin America and Africa [1–3]. The Middle Eastern countries were also reported to have a high prevalence of *H. pylori* infection, such as 86% in Turkey [4] and more than 90% in the Iranian

population [5]. *H. pylori* infection is closely associated with the occurrence of peptic ulcers, gastric hyperplastic polyps, gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma [6–9]. Therefore, it is considered to have a higher incidence of *H. pylori*-related diseases in developing countries with higher infection rate. However, the incidence of gastric cancer in the Middle East (e.g. 8.28/100,000 in Turkey, 4.58/100,000 in Kuwait and 6.64/100,000 in Jordan) are relatively lower than that in East Asia (e.g. 124.63/100,000 in Japan and 48.25/100,000 in Korea) and South America (e.g. 33.22/100,000 in Colombia and 38.73/100,000 in Chile) (<http://www-dep.iarc.fr/>). The detailed reasons for this phenomenon are unknown, but they may be related to host immunological defences, host genetic factors, environmental factors, such as food and salt intake, and/or to the bacterial virulence factors.

Gastric epithelial cell injury is caused by a vacuolating cytotoxin, encoded by the *vacA* gene, which induces host cell vacuolation and, finally, cell death. The *vacA* signal (s) region encodes the signal peptide and the N-terminus of the processed *vacA* toxin: the *vacA* s1 genotype is fully active but the type 2 genotype has a short N-terminus extension that blocks vacuole formation [10]. On the other hand, the *vacA* middle (m) region encodes part of the 55-KDa subunit located in the C-terminal. The *vacA* m region also has two genotypes (m1 and m2), and the m1 genotype causes stronger vacuolating activities than the m2 genotype [10]. These variations in the s and m regions give rise to four possible *H. pylori* genotypes: s1m1, s1m2, s2m1 and s2m2, although the s2m1 genotype is reported to be rare [10, 11]. The *vacA* s1 and m1 genotypes can be further classified into s1a, s1b and s1c; and m1a, m1b and m1c, respectively. In general, *vacA* s1m1 strains produce a large amount of toxin and induce higher vacuolating activity in gastric epithelial cells, s1m2 strains produce moderate amounts and s2m2 strains produce very little or no toxin [10, 12].

Recently, a third polymorphic determinant of vacuolating activity has been described as located between the s region and the m region; an intermediate (i) region [13]. The *vacA* i region encodes part of the p33 *vacA* subunit and classifies into two types, i1 (vacuolating) and i2 (non-vacuolating) [13]. Recent studies showed that gastric mucosa infected with the *vacA* i1 strains significantly increased inflammation cell infiltration and inflammation activity compared with that of the *vacA* i2 strains [14].

The *vacA* s1 and m1 genotypes have been reported to associate with *H. pylori*-related diseases, especially in Western countries, and *vacA* s2 and m2 strains are rarely associated with peptic ulcer and gastric cancer because of the low or non-vacuolating activity [10, 11, 15–20].

Although 17 studies based in the Middle East were reported to perform the genotyping of *vacA* s, m or i regions (Table 1) [13, 21–36], it is still unclear whether the *vacA* genotypes are associated with an increased risk for gastrointestinal disease in the Middle East or not because of the small sample size in each report. Therefore, this study was designed to elucidate the relationship between the *vacA* genotype and gastric cancer and peptic ulcer susceptibility in *H. pylori*-infected patients living in the Middle East by using systematic analyses that avoids type 2 error.

Materials and methods

Study selection

Previous publications measuring the genotypes of the *vacA* s, m or i regions in *H. pylori* strains isolated in the Middle East were enrolled in this study. Some North-African countries such as Egypt are also included in the Middle East; however, since the relationship between the *vacA* genotypes and clinical outcomes in African countries had been meta-analysed previously [37], we excluded the countries in this study. All eligible studies were identified

by searching the PubMed database for manuscripts written in English and published before October 2008 using the following search criterion: “*vacA* or vacuolating cytotoxin” and “*Helicobacter* or *pylori*” and “genotypes”. The references cited in the enrolled manuscripts were also screened by the same criteria. Manuscripts that did not provide detailed genotype information were excluded. We conducted a meta-analysis to determine the association of the *vacA* s-, m- and i-region genotypes with the risk of developing gastrointestinal diseases.

Data analysis

In cases where patients were infected with multiple *H. pylori* strains, each strain was analysed separately [22, 27]. Since some studies did not measure all parameters simultaneously (*vacA* s-, m- and i-region genotypes, s- and m-region combined genotypes and *cagA* status), the patient number and strain number (*H. pylori* genotype number) did not match in the following analyses.

Statistical differences in the frequencies of *vacA* s-, m- and i-region genotypes among the individual countries were determined by one-way analysis of variance (ANOVA) or the Chi-square test. The effects of *vacA* s-, m- and i-region genotypes on the risk of gastric cancer and peptic ulcer development were expressed as odds ratios (ORs) with 95% confidence intervals (CIs) with reference to non-ulcer dyspepsia (NUD) subjects with *H. pylori* infection. NUD was defined as histological and/or endoscopic gastritis with no peptic ulcers or gastric cancer. Of those, six studies [22, 23, 25, 26, 31, 34] used control patients as ‘gastritis’, six studies [13, 21, 24, 29, 30, 32] used ‘NUD’ as controls and one study in Iraqi [33] used ‘non-ulcer disease’ as controls; therefore, we regarded the control group as ‘NUD’ in this study. All *P*-values were two-sided and *P*-values less than 0.05 were considered to be statistically significant.

Results

Included studies

Twenty studies investigating the Middle-Eastern population were found within our search criteria, and a report from Hussein et al. included two populations, Iranian and Iraqi [33]. Two studies from Farshad et al. [38] and Bulent et al. [39] did not provide detailed *vacA* genotype information and were excluded. Finally, a total of 17 studies with 1,646 patients were considered for the meta-analysis (Tables 1 and 2).

Prevalence of *vacA* s-, m- and i-region genotypes

The prevalence of *vacA* s-, m- and i-region and *vacA* s/m combination genotypes differed significantly among the various countries within the Middle East ($P < 0.001$) (Table 2 and Fig. 1). The studies using strains isolated in the northern part of the Middle East, such as Turkey, Iran and Iraq, had a high prevalence of *vacA* s1 genotype of more than 70%, whereas strains from the southern part, such as Jordan, Saudi Arabia, Kuwait and Israel, had a low prevalence of less than 60% (Table 2). The prevalence of *vacA* s1 genotype in the northern part was 79.4%, which was significantly higher than that in the southern parts (44.5%, $P < 0.001$) (Table 2). Although there were only four studies investigating the subtyping of the *vacA* s1 genotypes, and all were from Turkey [21–24], 97.9% of the s1 genotypes was of the s1a subtype. There was no *vacA* s1c subtype in strains from the Middle East that were reported to be specific for East Asian strains [11]. Most of the Middle Eastern strains had frequencies of *vacA* m1 genotypes less than 50% and the prevalence of *vacA* m1 genotype in the northern part was 36.1%, which was significantly higher than that in the southern parts (18.1%, $P < 0.001$) (Table 2). Especially in Israel, the prevalence of *vacA* m1 genotype was only 8.0% [36]. In the combination of *vacA* s- and m-region genotypes, the predominant genotype was *vacA* s1m2 (42.1%), followed by s1m1 (30.5%) and s2m2

(26.1%). The frequency of the *vacA* s2m1 genotype was only 1.4% in our analyses, which was in agreement with most of the previous studies in other regions [10, 37]. No previous studies had examined the subtypes of m1 in the Middle East.

Although there were data of *vacA* i-region genotypes in only the Iranian and Iraqi populations [13, 33], the prevalence of the *vacA* i1 and i2 genotype had no significant difference between Iranian and Iraqi strains ($P=0.10$) (Tables 1 and 2).

The percentage of patients infected with more than two different *vacA* genotypes of *H. pylori* and non-genotypeable strains (including *vacA*-negative strains) by polymerase chain reaction (PCR) was 4.9% (80/1,646) and 13.1% (216/1,648), respectively. The rate of non-genotyped strains was relatively higher, especially in reports from Siavoshi et al. (51.8%, 71/137) [30] and Nimri et al. (57.3%, 63/110) [28], than previous reports [11, 37, 40].

Risk of gastric cancer and peptic ulcer development associated with the *vacA* s, m and i genotypes

Of 17 studies, five did not demonstrate the association with gastroduodenal diseases and *vacA* s and m genotypes [27, 28, 33, 35, 36]. Although two studies showed only an association with gastroduodenal diseases and *vacA* i-region genotype [13, 33], there was no detailed data of each patient in the Iranian study of Hussein et al. [33].

The *vacA* s1 genotype was linked to an increased risk in four of 11 (36.3%) studies for peptic ulcers [24, 26, 29, 31] and two of six (33.3%) studies for gastric cancer [13, 24], and especially Erzin et al. [24] reported its significance in the *vacA* s1a genotype. The *vacA* m1 genotype was linked to an increased risk in two of 11 (18.1%) studies for peptic ulcers [23, 34] and two of six (33.3%) studies for gastric cancer [13, 31]. One each (10%) of ten studies demonstrated significantly increased risk of peptic ulcers with the *vacA* s1m1 [31] and s1m2 [29] genotype, respectively (Tables 1 and 3).

Rhead et al. [13] reported that the *vacA* i1 genotype was significantly linked to gastric cancer in the Iranian population. Hussein et al. [33] reported that gastric ulcer development in the Iraqi population was associated with the *vacA* i1 genotype, but the same did not hold true for the Iranian population.

The frequency of *vacA* s1 (88.4%) and m1 (41.6%) in *H. pylori*-infected patients with peptic ulcers was significantly higher than that with gastritis alone (71.3% and 27.8%, respectively) (Table 3). There was a tendency of association with peptic ulcer and i1 genotypes (80.0% vs. 31.0% for NUD patients); this was not significant because of the low sample power. In the Middle East, the *vacA* s1, m1 and s1m1 genotypes significantly increased the risk of peptic ulcers (OR: 3.07, 95% CI: 2.08–4.52 for s1; 1.81, 1.36–2.42 for m1; 3.52, 2.24–5.54 for s1m1) (Table 4). The frequencies of *vacA* s1, m1 and i1 genotypes in patients with gastric cancer were 90.9%, 49.5% and 87.1%, respectively, which were significantly higher than the frequency of gastritis alone (71.3%, 27.8% and 31.0%, respectively) ($P<0.01$ for each). The risk of developing gastric cancer was significantly increased with the *vacA* s1 (OR: 4.02, 95% CI: 1.98–8.14), m1 (2.50, 1.62–3.85), s1m1 (5.27, 1.97–14.1) and i1 (15.03, 4.69–48.17) genotypes compared to patients with gastritis alone (Tables 3 and 4).

The association between *cagA* status and *vacA* genotypes in the Middle Eastern population

There were seven studies that reported an association between *cagA* status and *vacA* genotypes [13, 24, 26, 30, 32, 33, 36]. The *cagA* status of *H. pylori* strains was strongly associated with the *vacA* s1, m1 and i1 genotypes ($P<0.01$), and the prevalence of *vacA* s1, m1, and s1m1 genotypes significantly differed among patients with/without *cagA*-positive

strains ($P<0.01$) (Table 5). The prevalence of *vacA* s1 and *cagA*-negative strains was 47.1%, which was relatively higher than previous reports of other areas. In *cagA*-negative strains, most of the *vacA* genotypes were i2 genotypes (90%) (Table 5).

In seven studies which reported the association of *cagA* status and *vacA* genotypes [13, 24, 26, 30, 32, 33, 36], the *cagA* status was associated with increased risk of gastric cancer and peptic ulcer development (Tables 6 and 7). In the Middle East, the *cagA* status significantly increased the risk of peptic ulcers (OR: 1.82, 95% CI: 1.26–7.04) and gastric cancer (3.51, 1.75–7.04) (Table 7). However, in the Iranian population, there were no significant relationships between *cagA* status and diseases risks.

Discussion

Most gastric cancer patients were at stages III and IV of the OLGA system with severe mucosal atrophy in the whole stomach [41, 42]. More virulent genotypes were connected to gastric epithelial damage, including gastric mucosal atrophy, in *H. pylori*-infected patients [18]. In fact, *H. pylori* strains with the *vacA* s1, m1 and i1 genotypes and *cagA*-positive strains have been linked to higher degrees of inflammation cell infiltration compared to that with *vacA* s2, m2 and i2 genotypes and *cagA*-negative strains [43, 44]. However, two-thirds of previous reports carried out in the Middle East had shown no significant relationship between *vacA* genotypes and gastrointestinal diseases because of the low sample power (only one study with more than 100 NUD patients and more than 50 disease patients [31]); it was unclear whether the connection between virulence factors and disease development has an association (Table 1) [13, 21–36]. As summarized in Table 1, the sample number of each study was small and insufficient to clarify the significance of the relationship between virulence factors of *H. pylori* and gastroduodenal diseases. Therefore, by meta-analysis using many patients, the association between *vacA* genotypes and diseases risk in the Middle East needs to be clarified. We found that the *vacA* s1 and m1 genotypes increased the risk of gastric cancer and peptic ulcer by 2–5 times in these countries, as well as in developed Western countries and Latin America [11, 37, 40, 45, 46]. Therefore, we concluded that the *H. pylori* virulence factor, *vacA*, causes enhanced gastric mucosal inflammation and damage, leading to gastric cancer and peptic ulcer development in the Middle East.

In the Middle East, the frequencies of the *vacA* s genotype significantly differed between the northern part (Turkey, Iran and Iraq) and the southern part (Kuwait, Jordan, Saudi Arabia and Israel). The higher detection rate of the *vacA* s1 genotype was revealed from South Asian countries, such as India and Bangladesh, to East Europe throughout the northern part of the Middle East, as observed in this study [47]. Moreover, 97.9% of the *vacA* s1 genotype was of s1a sub-type in four Turkey studies which performed the sub-typing of *vacA* s1 [21–24]. This pattern of which *vacA* s1a sub-type was the dominant allele in Turkey was the same as the European type, and the population that lived in a part of the Middle East, including Turkey, might correlate with the European population. On the other hand, Saudi Arabia in middle part of the Middle East was liable to be equally infected with the *vacA* s1 and s2 alleles, whereas most of the Israeli population near African Arabs had the *vacA* s2 genotype. Van Doorn et al. [20] reported that the prevalence of the *vacA* s1 and m1 genotypes in strains from Egypt was 42.9% and 14.3%, respectively. This finding suggested that the population which lived in the southern part of the Middle Eastern population near African Arabs might correlate culturally with African countries and not the north side of the Middle Eastern population.

Gastric cancer is uncommon in the Middle East, despite high levels of *H. pylori* infection [4, 5], as observed in so-called ‘African enigma’ [48]. This phenomenon might explain that the widespread prevalence of weakly cytotoxic strains may be the reason for the low frequency

of *H. pylori*-associated diseases in African populations [37]. In this study, the prevalence of the *vacA* m1 region in the Middle Eastern population and the s1 region in its southern part was lower than in the East Asian and Latin American populations with a higher risk of gastric carcinogenesis [11, 37]. Therefore, it might be explained that the lower prevalence of higher virulent strains may be the reason for the low frequency of gastric cancer, especially in the southern part of the Middle East. However, the *vacA* s1 and m1 genotypes significantly increased the risk of gastric cancer and peptic ulcer development. Therefore, the bacterial factors are important in determining gastric cancer risk.

Recently, a third polymorphic determinant of vacuolating activity was identified as the *vacA* i region [13]. Although in East and Southeast Asia the *vacA* s, m and i combined genotypes did not add any advantage as disease-determinant markers to s- and m-region genotyping [49], *vacA* i1 genotypes were associated with gastric cancer in the Iranian and Italian populations and gastric ulcer in the Iraqi and Italian populations [13, 14, 33]. Hussein et al. [33] reported that 80% (4/5) of *H. pylori* strains isolated from gastric ulcer Iraqi patients were *vacA* i1 genotype, which was significantly higher than 13% (4/29) from non-ulcer patients, but not in the Iranian population. Despite the geographical proximity of Iraq and Iran, the incidence of gastric cancer differs hugely between these countries; in Iran, it ranges from 38–69/100,000 population [50, 51], whereas in Iraq, the incidence is 5/100,000 population (<http://www-dep.iarc.fr/>). This difference in the *vacA* i region of the *H. pylori* strains between two countries may partially explain the difference between gastric cancer incidence, because the *vacA* s and m genotypes were almost equal between countries. Therefore, the *vacA* i genotyping might be a better predictor of *H. pylori* carcinogenic potential than previous s- and m-region genotyping in the Middle East and South Europe. However, because the data of the *vacA* i-region genotype in gastroduodenal disease patients was insufficient for analysing the risk of gastric cancer and peptic ulcer developments with sufficient sample power, further reports would be required.

Two reports from Siavoshi et al. (51.8%) [30], using DNA extracted from multiple colonies of *H. pylori*, and Nimri et al. (57.3%) [28], using DNA extracted directly from gastric biopsy samples, had higher rates of non-genotyped strains than previous reports, whereas the PCR condition is acceptable [11, 37, 40]. Nimri et al. [28] used primer pairs of VA1-F and VA1-R for the *vacA* s region and VAG-F and VAG-R for the m-region, as previously reported [10, 19], and Siavoshi et al. [30] used primer pairs of VA1-F and VA1-R for the *vacA* s region [10, 19] and VA3-F/VA3-R for the m1 region and VA4-F/VA4-R for the m2 region as originally. Most of the studies using the VA1-F/VA1-R pairs for the *vacA* s region and VAG-F/ VAG-R for the m region were reported to be able to detect more than 95% of samples in the Western and Asian populations [10, 19]. Although detailed reasoning was unclear, it might have been caused by technical problems, including failure of the primer setting. There was also the possibility that half of the *H. pylori* strains had specific sequences in parts of primers previously reported and that *H. pylori* with a third genotype, such as s2 or m3, consisted in the Middle East, especially in the limited area of Iran and Jordan. Further studies will be necessary to clarify this by sequence analysis.

In conclusion, we demonstrated that the *vacA* s1 and m1 genotypes increase the risks of gastric cancer and peptic ulcer in the Middle East, and that the prevalence of specific *vacA* s and m genotypes varies significantly among the individual countries. Genotype testing of *vacA* will be useful in screening individuals for risk factors associated with gastric cancer and peptic ulcer development not only in Western countries, but also in the Middle East as well. Although it is still possible that the *vacA* i1 genotypes are risk factors for diseases development, the present data is insufficient to evaluate the effect of the *vacA* virulence factor in *H. pylori*-related diseases. Therefore, the clinical usefulness of this genotyping test must be evaluated in future studies under the appropriate study design using many

individuals with several *vacA* genotypes. However, it might be difficult to explain the 'Middle Eastern enigma' by only the genotyping of *vacA* genotypes, and, therefore, we had to evaluate the pathogenesis of gastric cancer and peptic ulcer by combination analysis of bacterial factors, the host's genetic factors and environmental factors.

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Fig. 1.
The proportions of *vacA* s, m and i genotypes in different Middle Eastern populations; the frequencies of *vacA* s, m and i genotypes significantly differed among the individual countries of the Middle East

Table 1

The genotypes of *vacA* s, m and i regions in studies used in the meta-analysis

Area/ country	Authors	Year	Disease	Patients (n)	Mix (n)	No detected strain	Strain					
							s1 (n/%)	s2 (n/%)	m1 (n/%)	m2 (n/%)	i1 (n/%)	i2 (n/%)
Turkey	Aydin et al. [21]	2004	NUD, DU	98 ^s	0	0	87 (88.8)	11 (11.2)	50 (51.0)	48 (49.0)	NA	NA
Turkey	Saribasak et al. [22]	2004	NUD, PU, GC	65	29 ^m	1	55 (94.8)	3 (5.2%)	8 (22.2)	28 (77.8)	NA	NA
Turkey	Salih et al. [23]	2005	NUD, DU	21	0	3 ND	20 (100)	0 (0)	12 (66.7)	6 (33.3)	NA	NA
Turkey	Erzin et al. [24]	2006	NUD, PU, GC	91	0	0	81 ^a (89.0)	10 (11.0)	38 (41.8)	53 (58.2)	NA	NA
Turkey	Caner et al. [25]	2007	NUD, DU	46	0	0	41 (89.1)	5 (10.9)	11 (23.9)	35 (76.1)	NA	NA
Turkey	Bolek et al. [26]	2007	NUD, PU	44	0	0	41 (93.2)	3 (6.8)	24 (54.5)	20 (45.5)	NA	NA
Turkey	Umit et al. [27]	2008	NA	57	7 ^m	2	32 (64.0)	18 (36.0)	23 (43.4)	30 (56.4)	NA	NA
Jordan	Nimri et al. [28]	2006	NA	110	0	63 ND	34 (45.3)	41 (54.7)	23 (48.9)	24 (51.1)	NA	NA
Iran	Mohammadi et al. [29]	2003	NUD, DU	132	0	19	78 ^b (69.0)	35 (31.0)	39 (34.5)	74 (65.5)	NA	NA
Iran	Siavoshi et al. [30]	2005	NUD, PU, GC	137	13	71	48 (90.6)	5 (9.4)	12 (22.6)	41 (77.4)	NA	NA
Iran	Kamali-Sarvestani et al. [31]	2006	NUD, PU, GC	298	0	34	191 ^c (72.3)	73 (27.7)	81 (30.7)	183 (69.3)	NA	NA
Iran	Rhead et al. [13]	2007	NUD, GC	75	2	2	57 (80.3)	14 (19.7)	31 (43.7)	40 (56.3)	30 ^d (51.7)	28 (48.3)
Iran	Jafari et al. [32]	2008	NUD, PU, GC	96	0	7	62 (69.7)	27 (30.3)	30 (33.7)	59 (66.3)	NA	NA
Iran	Hussein et al. [33]	2008	NA	59	7	0	36 (69.2)	16 (30.8)	16 (30.8)	36 (69.2)	19 (36.5)	33 (63.5)
Iran	Hussein et al. [33]	2008	NUD, PU	49	14	19	31 (88.6)	4 (11.4)	9 (25.7)	26 (74.3)	10d (28.5)	25 (71.5)
Saudi Arabia	Momenah et al. [34]	2006	NUD, PU	103	0	0	60 (58.3)	43 (41.7)	13 (12.6)	90 (87.4)	NA	NA
Kuwait	Al Qabandi et al. [35]	2005	NA	67	8	3	26 (46.4)	30 (53.6)	NA	NA	NA	NA
Israel	Benenson et al. [36]	2002	NA	98	0	11	23 (26.4)	64 (73.6)	7 (8.0)	80 (92.0)	NA	NA

NA = no data associating *H. pylori* disease development and *vacA* polymorphism; s = the use of single colonies [21] and the remaining studies refer to the use of gastric biopsy sample, paraffin-embedded biopsy sample and pool of cultured colonies

When patients were determined to be infected with multiple different *H. pylori* strains, each *H. pylori* strain was analysed as a different *H. pylori* genotype (m = mixed strains) [22, 27]. ND means no detailed information of *H. pylori* strain, whereas only *vacA* s or m region was detected [23, 28]. The study of Rhead et al. [13] had 15 i1 and i2 mixed strains. Therefore, these reports do not match with the patient number and strain number (*H. pylori* genotype number)

GC = gastric cancer; NA = not available; NUD = non-ulcer dyspepsia (gastritis alone without peptic ulcer and gastric cancer); PU = peptic ulcer (gastric ulcer and/or duodenal ulcer)

^a $P < 0.05$ (significantly increased risk of gastric cancer and duodenal ulcer developments when it was the *vacA* s1a genotype);

^b $P < 0.05$ (significantly increased risk of peptic ulcer when it was the *vacA* s1m2 genotype);

$P_c < 0.05$ (significantly increased risk of peptic ulcer when it was the *vacA* s1m1 genotype);

$P_d < 0.05$ (significantly increased risk of peptic ulcer or gastric cancer when it was the *vacA* i1 genotype)

Summary of *vacA* s- and m-region genotypes in different countries

Table 2

Paper (n)		Patient (n)	Strain														
			s1 (n/%)	s1a (n/%)	s1b (n/%)	s1c (n/%)	s2 (n/%)	m1 (n/%)	m2 (n/%)	s1m1 (n/%)	s1m2 (n/%)	s2m1 (n/%)	s2m2 (n/%)	i1 (n/%)	i2 (n/%)		
North Middle East																	
Turkey	7	422	357 (87.7)	237 (97.9)	5 (2.1)	0 (0)	50 (12.3)	166 (43.0)	220 (57.0)	122 (43.7)	128 (45.9)	1 (0.4)	28 (10.0)	NA	NA		
Iran	6	797	476 (73.7)	NA	NA	NA	170 (26.3)	209 (32.6)	433 (67.4)	194 (30.2)	278 (43.3)	15 (2.3)	155 (24.1)	49 (44.5)	61 (55.5)		
Iraq	1	49	31 (88.6)	NA	NA	NA	4 (11.4)	9 (25.7)	26 (74.3)	9 (25.7)	22 (62.9)	0 (0)	4 (11.4)	10 (28.6)	25 (71.4)		
Sub-total	14	1,268	864 (79.4)	237 (97.9)	5 (2.1)	0 (0)	224 (20.6)	384 (36.1)	679 (63.9)	325 (34.0)	428 (44.8)	16 (1.7)	187 (19.5)	59 (40.7)	86 (59.3)		
South Middle East																	
Jordan	1	110	34 (45.3)	NA	NA	NA	41 (54.7)	23 (48.9)	24 (51.1)	12 (46.2)	2 (7.7)	0 (0)	12 (46.2)	NA	NA		
Saudi Arabia	1	103	60 (58.3)	NA	NA	NA	43 (41.7)	13 (12.6)	90 (87.4)	13 (12.6)	47 (45.6)	0 (0)	43 (41.7)	NA	NA		
Kuwait	1	67	26 (46.4)	NA	NA	NA	30 (53.6)	NA	NA	NA	NA	NA	NA	NA	NA		
Israel	1	98	23 (26.4)	NA	NA	NA	64 (73.6)	7 (8.0)	80 (92.0)	7 (8.0)	16 (18.4)	0 (0)	64 (73.6)	NA	NA		
Sub-total	4	378	143 (44.5)	NA	NA	NA	178 (55.5)	43 (18.1)	194 (81.9)	32 (14.8)	65 (30.1)	0 (0)	119 (55.1)	NA	NA		
Total	17	1,646	1,007* (71.5)	237 (97.9)	5 (2.1)	0 (0)	402 (28.5)	427a (32.8)	873 (67.2)	357a (30.5)	493 (42.1)	16 (1.4)	306 (26.1)	59 (40.7)	86 (59.3)		

Hussein et al. [33] reported two populations, Iranian and Iraqi, and, therefore, a number of entries had one study taken off. When patients were determined to be infected with multiple different *H. pylori* strains, each *H. pylori* strain was analysed as a different *H. pylori* genotype. Therefore, the reports do not match with the patient number and strain number (*H. pylori* genotype number)

* *P* < 0.05 (significant differences among different countries in the same area)

NA = not available

Table 3

Summary of *vacA* s, m and i genotypes in relation to peptic ulcer and gastric cancer risk

Authors	Country	Non-ulcer dyspepsia			Peptic ulcer			Gastric cancer		
		s1	m1	i1	s1	m1	i1	s1	m1	i1
Aydin et al. [21]	Turkey	46/51 (90.2)	28/51 (54.9)		41/47 (87.2)	22/47 (46.8)				
Saribasak et al. [22]	Turkey	19/20 (95.0)	2/14 (14.3)		28/29 (96.6)	3/15 (20.0)		8/9 (88.9)	3/7 (42.9)	
Salih et al. [23]	Turkey	7/7 (100)	1/6 (16.7)		13/13 (100)	11/12 ^b (91.7)				
Erzin et al. [24]	Turkey	23/30 (76.7)	10/30 (33.3)		28/28 ^a (100)	15/28 (53.6)		30/33 ^a (90.9)	13/33 (39.4)	
Caner et al. [25]	Turkey	15/16 (93.8)	4/16 (25.0)		26/30 (86.7)	7/30 (23.3)				
Bolek et al. [26]	Turkey	5/7 (71.4)	0/7 (0)		36/37 ^b (97.3)	24/37 (64.9)				
Mohammadi et al. [29]	Iran	58/90 (64.4)	33/90 (36.7)		20/23 ^b (87.0)	6/23 (26.1)		5/5 (100)	1/5 (20.0)	
Siavoshi et al. [30]	Iran	30/33 (90.9%)	6/33 (18.2)		13/15 (86.7)	5/15 (33.3)		15/18 (83.3)	12/18 ^b (66.7)	
Kamali-Sarvestani et al. [31]	Iran	122/181 (67.4)	48/181 (26.5)		54/65 ^b (83.1)	21/65 (32.3)		29/31 ^a (93.5)	19/31 ^a (61.3)	27/31 ^a (87.1)
Rhead et al. [13]	Iran	30/42 (71.4)	13/42 (31.0)	18/42 (42.9)				3/3 (100)	0/3 (0)	
Jafari et al. [32]	Iran	50/69 (72.5)	26/69 (37.8)		9/17 (52.9)	4/17 (23.5)				
Hussein et al. [33]	Iraq			4/29 (13.8)			4/5 ^a (80.0)			
Momenah et al. [34]	Saudi	53/96 (55.2.5)	8/96 (8.3)		7/7 (100)	5/7 ^b (71.4)		90/99 ^a (90.9)	48/97 ^a (49.5)	27/31 ^a (87.1)
Total		458/642 (71.3)	179/645 (27.8)	22/71 (31.0)	275/311 ^a (88.4)	123/296 ^a (41.6)	4/5 (80.0)			

^a $P < 0.05$ (vs. significant prevalence rate of gastritis patients by study);

^b $P < 0.05$ (vs. significant prevalence rate of gastritis patients by our analysis)

Table 4The risk of gastrointestinal disease development in relation to *H. pylori* virulence factors

Diseases	Factor	n	OR	95% CI	P-value
Peptic ulcer, N=311	s1	275	3.07	2.08–4.52	< 0.01
	m1	123	1.81	1.36–2.42	0.01
	slm1	98	3.52	2.24–5.54	< 0.01
	slm2	125	2.51	1.63–3.89	< 0.01
	tl	4	8.91	0.94–84.4	0.06
Gastric cancer, N=99	s1	90	4.02	1.98–8.14	< 0.01
	m1	48	2.50	1.62–3.85	< 0.01
	slm1	25	5.27	1.97–14.11	< 0.01
	slm2	36	3.55	1.34–9.38	0.01
	tl	27	15.03	4.69–48.17	< 0.01

Table 5The association of *cagA* status and *vacA* genotypes

<i>cagA</i> status	s1 (n/%)	s2 (n/%)	m1 (n/%)	m2 (n/%)	slm1 (n/%)	slm2 (n/%)	s2m1 (n/%)	s2m2 (n/%)	i1 (n/%)	i2 (n/%)
Positive	255 (86.4)	40 (13.6)	62 (46.3)	72 (53.7)	60 (48.0)	57 (45.6)	2 (1.6)	6 (4.8)	29 (60.4)	19 (39.6)
Negative	89 (47.1)	100 (52.9)	12 (16.7)	60 (83.3)	10 (15.8)	43 (68.3)	2 (3.2)	8 (12.7)	1 (10.0)	9 (90.0)

Table 6The association between gastroduodenal diseases and *cagA* status

Authors	Year	Country	Total	NUD	PU	GC
Erzin et al. [24]	2006	Turkey	67/91 (74%)	15/30 (50%)	24/28 (86%)	28/33 (85%)
Bolek et al. [26]	2007	Turkey	43/52 (83%)	7/10 (70%)	36/42 (86%)	
Benenson et al. [36]	2002	Israel	24/97 (25%)	22/86 (26%)	2/11 (18%)	
Siavoshi et al. [30]	2005	Iran	61/136 (45%)	28/61 (46%)	21/57 (37%)	12/18 (67%)
Jafari et al. [32]	2008	Iran	73/96 (76%)	55/74 (74%)	15/19 (79%)	3/3 (100%)
Rhead et al. [13]	2007	Iran	63/73 (86%)			
Hussein et al. [33]	2008	Iran	45/59 (76%)	32/42 (76%)	13/17 (76%)	
		Iraq	35/49 (71%)	16/29 (55%)	19/20 (95%)	
Total			411/653 (63%)	175/332 (53%)	130/194 (67%)	43/54 (80%)

NUD = non-ulcer dyspepsia; PU = peptic ulcer; GC = gastric cancer

Table 7

The risk of gastric cancer and peptic ulcer development in relation to *cagA* status

Diseases	N	n	OR	95% CI	P-value
Peptic ulcer	194	130	1.82	1.26–2.64	0.01
Gastric cancer	54	43	3.51	1.75–7.04	<0.01