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EDITORIAL

Helicobacter pylori and gastric cancer in the Middle East: A new enigma?

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Abstract

The Middle East is the home of ethnic groups from three main backgrounds: Semitic (Arabs and Jews), Indo-European (Persians and Kurdish) and Turkic (Turkish and Turkmens). Its geographic location, which has been under continuous influences from Asia, Europe and Africa, has made it an ideal site for epidemiological studies on *Helicobacter pylori* (*H. pylori*) infection and genotyping. The gastric cancer rate differs in this region from very high in Iran ($26.1/10^5$) to low in Israel ($12.5/10^5$) and very low in Egypt ($3.4/10^5$). Epidemiological studies showed that the prevalence of *H. pylori* is almost similar in those countries with a high level of infection in childhood. Importantly, the frequency of *vacA* s1 and m1 regions and *cagA*+ genotypes were higher in non Semitic populations who inhabit the North than Semitic populations, the inhabitants of Southern parts of the Middle East. *H. pylori* infection prevalence, distribution pattern of virulence factors, diet and smoking could not have explained the difference in cancer rate. This reflects the multifactorial aetiology of gastric cancer and suggests that *H. pylori* infection does not always directly correlate with the risk for gastrointestinal disease, such as gastric cancer. Further detailed investigations and international comparative studies of each risk factor need to be performed to investigate whether this represents a true enigma.

Key words: *Helicobacter pylori*; Middle East; Gastric cancer; *dupA*; *cagA*; *vacA*; *iceA*

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INTRODUCTION

Helicobacter pylori (*H. pylori*) causes gastritis and peptic ulceration and it is an important risk factor for gastric adenocarcinoma, the second highest cause of cancer deaths worldwide. The disease process is thought to have a multifactorial aetiology, and bacterial strain type, pattern of gastritis, and environmental conditions, are all thought to contribute[1]. *H. pylori* strains differ, and possession of specific virulence factors greatly increases the risk of disease. The best recognised of these are the cag pathogenicity island and active forms of the vacuolating cytotoxin (VacA). Duodenal ulcer promoting gene A (*dupA*) is a recently described gene shown to be associated with duodenal ulceration and protective against gastric cancer[2]. It was observed that the early acquisition of *H. pylori* infection in childhood resulted in pangastritis in adulthood. This pattern of gastritis is usually associated with mucosal atrophy which is a precancerous condition[3]. Therefore, acquiring the infection at an early age is a recognised risk factor for the development of

gastric cancer[4]. Additionally, antral predominant gastritis is usually associated with duodenal ulcer. Furthermore, different environmental factors such as high salt intake and inadequate consumption of fruit and vegetables containing vitamin C has been regarded as risk a factor for development of gastric cancer[5].

The Middle East is home to ethnic groups from three main backgrounds: Semitic (Arabs and Jews), Indo-European (Persians and Kurdish) and Turkic (Turkish and Turkmens)[6-8]. Its geographic location, which has been under continuous influences from Asia, Europe and Africa, has made it an ideal site for epidemiological studies on *H. pylori* infection and genotyping. The prevalence of *H. pylori* infection has been reported from many Middle Eastern countries, including Iraq, Iran, Turkey, Libya, Egypt, Israel, Bahrain, Oman, Saudi Arabia, and the United Arab Emirates. It has been shown that the prevalence rates of infection in these countries are almost similar to each other and to the reported prevalence from Europe and United States. However, gastric cancer and other *H. pylori* related diseases rates vary from very high in Iran to rare in Iraq and Egypt (Table 1)[9]. It is not known whether the difference is due to host, environment, or bacterial factors or a combination of these factors. In this review I tried to find a reason for the difference in *H. pylori* related diseases amongst Middle Eastern countries by discussing the prevalence of *H. pylori* and its virulence determinants, the pattern of gastritis, and environmental factors that might influence the disease process in the Middle East.

PREVALENCE OF *H. PYLORI*

The prevalence of *H. pylori* infection varies between countries; generally, the prevalence is about 30% in developed and up to 80% in developing countries[5]. Diagnosis of *H. pylori* can be achieved by taking biopsies by endoscopy. However, this procedure is invasive and might not give accurate results if colonisation is patchy[10]. Furthermore, it does not suit population based studies. For population screening, serodiagnosis remains one of the methods of choice for detecting the prevalence of infection[11]. Systemic humoral immunoglobulin G (IgG) immune responses to the organism are developed by humans infected with *H. pylori*[12-14]. Serological tests are useful tools for the diagnosis of *H. pylon* infection because all *H. pylori*-infected patients produce an antibody response which can be detected in the serum[14]. The technique of choice is currently enzyme-linked immunosorbent assay because it is a simple, quick, and low-cost technique that permits immunoglobulin class-specific determinations[14].

In a study conducted in Iraq, the prevalence varied in various ages (age: percentage, 6 mo: 0%; 6-24 mo: 27%; 2-18 years: 58%). In the same study, it was shown that 78% of adults were infected with *H. pylori* which was significantly higher than children. The prevalence of *H. pylori* increased markedly with age with the maximum colonization (81.5%) occurring in adults (40-60 years)[15]. The same scenario was found in Saudi Arabia, Iran, Libya and Israel. In Saudi, the prevalence of *H. pylori* infection markedly increased with age. The prevalence of *H. pylori* infection rose from 32.4% in those aged 0-10 years to more than 66.4% in those aged 20-30 years and 75% in those over 50 years[16]. In Iran, the prevalence of *H. pylori* infection increased with age [age (years): percentage, 6-10: 46%; 10-20: 50%; 20-30: 67%; 30-40: 80%; 40-50: 85%; 50-60: 84%; 60-70: 81%; over 70: 83%][17]. In Libya, overall prevalence was 67% with a steady increase with age [age (years): percentage, 0-10: 50%; 10-20: 84%; 20-30: 66%; 30-40: 80%; 40-50: 88%; 50-60: 83%; 60-70: 83%; over 70: 94%][18]. In a study conducted in Israeli rural communal settlements with an age range from 6 to 90 years[19], the prevalence *H. pylori* infection was shown to be 72%. It was also found that the prevalence of *H. pylori* increased with age [age (years): percentage, 6-10: 10%; 10-20: 39%; 30-40: 60%; 40-60: 70%; over 60: 85%]. In the same study, a significant association was shown between *H. pylori* infection and the country of origin of Israeli migrants. The highest prevalence (85%) was found in migrants from the Mediterranean and Asia. While 80% of East European migrants were *H. pylori* positive, the prevalence in West Europeans was 57%. The prevalence in people born in Israel was 66%. The association between *H. pylori* infection and country of origin was not changed after age adjustment[19].

In Turkey[20], the overall prevalence of *H. pylori* infection was 81%. There is no marked difference in *H. pylori* prevalence in different ages [age (years): percentage, 0-10: 70%; 10-20: 83%; 20-30: 77%; 30-40: 87%; 40-50: 88%; 50-60: 90%].

In some countries in the Middle East, the prevalence of *H. pylori* infection has been studied using polymerase chain reaction and histopathology. The prevalence of *H. pylori* infection in Jordan and Bahrain was 77.5% and 79%, respectively[21,22]. In Kuwait and Egypt, *H. pylori*, as detected by H and E and *H. pylori* special stains, was present in 84% and 86% of the biopsy samples, respectively[23,24]. There was no significant difference in the prevalence of infection between male and female subjects in this region. In a study conducted in Western Saudi, the prevalence of VacA and CagA were significantly elevated in males *vs* females[25]. In another study in Jordan, there was a clear trend that females were infected with less virulent *H. pylori* strains, though the correlation was not significant[22].

INCIDENCE OF GASTRIC CANCER IN THE MIDDLE EAST

Despite declining incidence rates in Western countries, gastric cancer remains the second most common cancer type and second cause of cancer-related death worldwide. *H. pylori* infection is strongly associated with gastric cancer risk. Gastric cancer rate varies from country to country and from region to region. For example, it is very high in Japan ($62.7/10^5$) and estimated to be 12 times higher than India[9]. Gastric cancer occurs nearly 7 times more frequently in Iran than in Iraq (Table 1). These data might not be very accurate because of incompetent di-

Table 1 Prevalence of atrophy, gastric cancer and the distribution of *vacA* allelic types and *cagA* status among *H. pylori* strains isolated in the Middle East

Country	s1 (%)	s2 (%)	m1 (%)	m2 (%)	i1 (%)	i2 (%)	*cagA* (%)	Atrophy (%)	Male gastric cancer
Saudi Arabia	58.3[61]	41.7[61]	12.6[61]	87.4[61]	No data	No data	52.0[43]	3-19[77]	$5.7/10^5$
Kuwait	46.4[23]	53.6[23]	No data	No data	No data	No data	41.0[23]	28[75]	$4.8/10^5$
Jordan	45.3[22]	54.7[22]	48.9[22]	51.1[22]	No data	No data	26.4[22]	65[76]	$6.6/10^5$
Iran	69.2[39]	30.8[39]	30.8[39]	69.2[39]	36.5[39]	63.5[39]	76.0[39]	22-39[74]	$26.1/10^5$
Iraq	88.6[39]	11.4[39]	25.7[39]	74.3[39]	28.5[39]	71.5[39]	71.0[39]	3[69]	$4.5/10^5$
Turkey	94.8[40]	5.2[40]	22.2[40]	77.8[40]	No data	No data	78.0[40]	43-75[72,73]	$12.2/10^5$
Egypt	42.9[41]	57.1[41]	14.3[41]	85.7[41]	No data	No data	35.7[41]	54[24]	$3.4/10^5$

agnostic methods, limitation of medical services, and the lack of unique reporting systems. However, I searched through all published literature and could not find any major discordance. Despite the geographical proximity, the gastric cancer rate varies from very low in Iraq and Egypt to intermediate in Israel and Turkey to high in Iran (Table 1)[9,26-28]. Interestingly, *H. pylori* infection prevalence in these countries is relatively high and almost the same. This discordance between gastric cancer incidence and *H. pylori* seroprevalence might imply that *H. pylori* infection is not the only factor related to gastric cancer risk[29,30]. A 6-fold variation was found in the association between gastric cancer risk and *H. pylori* infection[31]. *H. pylori* virulence factors, immune response, diet, environment, and other factors should be considered.

BACTERIAL VIRULENCE FACTORS

Cytotoxin associated gene A

The cytotoxin associated gene A (CagA) protein, which is encoded by the *cagA* gene, is a highly immunogenic protein. *H. pylori* strains possessing *cagA* are associated with a significantly increased risk for the development of atrophic gastritis, peptic ulcer diseases and gastric cancer[32-36]. The *cagA* gene is situated at one end of a 40 kb DNA insertion called the *cag* PAI and may have been acquired from a non-*Helicobacter* origin[33,37]. The *cag* PAI contains approximately 30 genes which are multicistronic. The difference in the ability of *H. pylori* strains to trigger chemokines from gastric mucosa depends upon the expression of genes within the *cag* PAI[33,37,38].

Strains from Iraq, Turkey and Iran possessing *cagA* were found in 71%, 78% and 76% of the samples analysed, respectively. *cagA* presence was significantly associated with peptic ulcer disease incidence in Iraq and Turkey but not in Iran[39,40]. In Iraq, the majority of the population are Arabs. However in a study by Hussein *et al*[39], samples were collected from Kurdish majority (Kurdistan) region.

In Jordan, the *cagA* genotype was detected in 26.4%[22]. While Kuwaitis and other Arabian Gulf Arabs had essentially the same prevalence rate of about 41%, Egyptians had a modest positivity of 35.7%[23,41]. In a study conducted in Israel, *cagA* and *cagE* genes were present in only 25.5% and 24.5%, respectively[42]. The prevalence of *cagA* positivity in Saudi was 52%[43]. *cagA* was associated with gastric cancer and/or peptic ulceration in Iran, Iraq, Saudi, Turkey and Israel[39,42-45]. However, Hussein *et al*[39] could not find significant relationships between *cagA* status and disease risk in the Iranian population.

Argent *et al*[46], suggested that the presence or absence of *cagA* is not enough to understand the relationship between *cagA* and clinical outcomes. It was found that there was a size variation of the CagA protein and this variation was shown to be related to the presence of the repeat tyrosine phosphorylation motifs (TPM) sequences containing the EPIYA within the 3' variable ends[47]. It was found that *H. pylori* strains in Western and East Asian countries carry the EPIYA-A, EPIYA-B. While Western *H. pylori* strains carry Western *cagA*-specific EPIYA-C segments which vary in number ranging from 1-3[48], East Asian strains carry the CagA-specific EPIYA-D motif. We previously studied the TPM of the *cagA* in Iraq and Iran. The presence of *cagA* alleles with more than 3 phosphorylation motifs was significantly higher amongst Iranian strains than those from Iraq (there was no Iraqi *cagA*-positive strain with more than 3 TPM, 12% in Iran). We thought that the presence of *cagA* with more phosphorylation motifs in Iran may help explain the higher cancer incidence rate in Iran[39]. However, a recent study from Turkey, where the gastric cancer rate is much lower than Iran, found that 34% of *cagA*-positive Turkish strains carried more than three motifs. For the first time, in this study, they reported a *cagA* positive strain with 5 C motifs[49]. The absence of *cagA* with more than 3 motifs in Iraq can be due to a type 2 error.

There is clear discrimination in *cagA* distribution between Semitic (Arab and Jew) and non Semitic (Kurd, Turk and Persian) populations[39,40,50]. Semitic populations tend to carry less virulent *H. pylori*[22,23,41]. The *cagA* positivity in Saudi Arabia is higher than other Semitic countries. This might be due the fact that Saudi society has been influenced by Hajj.

VacA

The VacA is another *H. pylori* virulence factor[35]. Unlike *cagA*, almost all *H. pylori* strains posses the vacuolating cytotoxin gene (*vacA*). Vacuolating cytotoxin activity is related to the mosaic structure of *vacA*. In general, type s1/m1 and s1/m2 strains produce high and moderate levels of toxin activity, respectively, whereas s2/m2 strains produce no vacuolating activity[51]. A 12-amino-acid hydrophilic amino-terminal segment, present in type s2 but absent from type s1 *VacA* proteins, slows the capacity of *VacA* to form membrane channels and abolishes vacuolation.

Some type s1/m2 *VacA* toxins show cytotoxic activity toward selected cell types, including RK-13, but relatively little activity for HeLa or AGS cells[51-53]. Heterogeneity among *vacA* alleles may be an important factor in understanding variations in clinical manifestations among *H. pylori*-infected subjects. Several studies have demonstrated that gastric infection with *H. pylori* strains containing type s1 *vacA* alleles is associated with a higher risk for development of peptic ulcer disease than infection with strains containing type s2 *vacA* alleles[51]. This relation is not seen in East Asia as the vast majority of East Asian strains are *vacA* type s1[51,54-56]. Thus in these countries, s1 cannot be used as a marker for the presence of peptic ulcer disease because the prevalence of the s1 genotype is uniformly high.

Rhead *et al*[45] have described a novel determinant of VacA toxicity, called the intermediate or i-region. They showed that two allelic variants of this region existed, i1, and i2. Furthermore, only s1/m2 strains varied in i-type; s1/m1 and s2/m2 strains were exclusively i1 and i2, respectively. This novel region determines vacuolating activity among these s1/m2 strains. More importantly, a significant correlation has been established between the i1 region and gastric cancer[45]. In contrast to Rhead *et al*[45], no disease association between *vacA* i genotypes and outcome was found in East Asian and Southeast Asian countries. More studies, from other countries, are needed to determine whether this region is a true virulence determinant[57].

The studies from Turkey, Iran and Iraq (non-Semitic countries) had a high prevalence of *vacA* s1 genotype of more than 70%, whereas strains from Semitic countries such as Egypt, Jordan, Saudi Arabia, Kuwait and Israel, had a low prevalence of less than 60%. The prevalence of *vacA* s1 genotype in the non Semitic countries was significantly higher than that in the Semitic countries[41,58].

Reports from Turkey, Iraq and Iran showed that *vacA* m2 was found in around 70% of typed strains. In Egypt, Saudi and Israel, the percentage of *vacA* m2 was between 85% and 92%. 51.1% of Jordanian strains typed *vacA* m2. *vacA* i region was studied in Iran and Iraq only. *vacA* i1 was associated with gastric cancer and gastric ulcer in Iran and Iraq, respectively.

Studies from Iraq, Kuwait, Jordan, Israel and Iran did not show any association between *vacA* s and m genotypes and gastroduodenal diseases[22,23,39,42,59]. In Iraq, an association with gastroduodenal diseases and *vacA* i-region genotype was shown. Studies from Iran and Turkey[44,60] reported a significant relationship between *vacA* s1 genotype and peptic ulcers. The *vacA* m1 genotype was linked to an increased risk for peptic ulcers in Turkey and Saudi Arabia[61,62].

Studies from Iran, Iraq, Jordan, Turkey and Israel have shown a significant association between *cagA* status and *vacA* s1, m1 and/or i1 genotypes[22,39,42,44,45]. In *cagA*-negative strains, most of the *vacA* genotypes were i2 genotypes[58].

Other virulence factors

***dupA*:** Recently, a novel virulence factor *dupA* (duodenal ulcer promoting gene A) (jhp0917-jhp0918) was shown to be associated with duodenal ulceration and increased epithelial cell interleukin-8 secretion[2]. The *dupA* gene is located in the region of the bacterial genome that encodes surface proteins. A significant relationship between *dupA* and duodenal ulcer was found, and the presence of *dupA* was associated with neutrophil infiltration. These findings, however, were not confirmed in a study of Brazilian children and adults[63], thus indicating possible geographic differences. More recently, it has been found that *dupA* was not significantly associated with duodenal ulceration in populations from Belgium, South Africa, China, and the USA, but was significantly associated with gastric cancer development[64]. In the Middle East, *dupA* was studied in Iraq and Iran. *dupA* was found to be associated with duodenal ulcers in Iraq but not Iran[39]. In addition, *dupA*-negative *H. pylori* strains were found to associate with pre-malignant lesions in Iran[65]. No other studies have been conducted in the Middle East. More studies are needed to address the prevalence of *dupA*-negative strains and the association between this gene and clinical outcome.

***iceA*:** *iceA* (induced by contact with epithelium) exists in allelic variants including *iceA*1 and *iceA*2. *iceA*1 only can be induced in the gastric epithelium. The *iceA*1-positive *H. pylori* strains were shown to be associated with peptic ulceration and increased mucosal IL-8 secretion, while a higher prevalence of *iceA*2 strains was found among patients with non-ulcer dyspepsia[66,67]. In Turkey, *iceA*1 was found to be positive in 32.2% of the strains[68]. In Jordan, analyses of virulence genes revealed that *iceA*2 (73.6%) was the predominant genotype[22]. In a study conducted in Saudi, it was shown that all ulcer cases were infected with *iceA*1, while 94.6% of gastritis and 90.9% of normal subjects were infected with *iceA*2[43]. In Israel, *iceA1* was found in 37% and *iceA*2 in 52% of cases. Both *iceA* alleles were found in 11%[42]. More research is needed to study *iceA* and its association with diseases in this region.

HISTOPATHOLOGICAL CHANGES

All strains of *H. pylori* induce a marked inflammation in the gastric mucosa which is characterised by neutrophil, lymphocyte and other inflammatory cell infiltration. While antral-predominant gastritis leads to increased acid production from the uninflamed corpus and predisposes to duodenal ulceration, corpus-predominant gastritis leads to hypochlorhydria and predisposes to gastric ulceration and adenocarcinoma[3]. In studies conducted in Iraq, Turkey and UAE, it was found there is antral-predominant mononuclear cell infiltration[59,69,70]. In a study conducted in Iran, where the gastric cancer rate is very high, it was found that mononuclear cell infiltration was similar throughout the stomach; on average, patients had pangastritis[71].

Gradual loss of gastric glandular tissue as a consequence of long term mucosal destruction is called atrophic gastritis[3]. The tissue damage may involve progressive loss of all specific mucosal cells including the acid pro-

ducing parietal cells, pepsinogen producing chief cells and mucus producing gland cells. When these cell types have shrunk, the protective mucus layer will gradually disappear and acid secretion will cease[5]. Such pathological changes increase the risk of gastric ulceration and development of gastric adenocarcinoma[72]. However, this protects against duodenal ulcers because of low acid secretion[5]. In a study conducted in Turkey, histological evidence of mucosal atrophy was found in 43% of *H. pylori*-infected subjects[72] while in another study in Turkey atrophy was found in 75% of the subjects[73]. In UAE, gastric atrophy in *Helicobacter* associated gastritis was seen in 54% of cases[70]. In a study conducted in Iran, where the gastric cancer rate is much higher than Turkey, histological evidence of mucosal atrophy was found in 39% and 22% of antral and corpus biopsies, respectively[74]. In Iraq, glandular atrophy was found in only one (3%) specimen taken from the antrum. In Kuwait, *H. pylori* were found in 81.7% patients, of which 28.3% had atrophic gastritis and 15.1% intestinal metaplasia[75]. Atrophy was found in 65% and 54% of examined subjects in Jordan and Egypt, respectively[24,76] (Table 1).

In a study conducted in Saudi where a comparison of Sydney scores from younger and older patients was made, no significant differences were seen in the scores of *H. pylori* density, neutrophilic activity, or chronic inflammatory cell infiltration between the two groups. While intestinal metaplasia was not found in any young patient, 22% of older patients had focal metaplastic changes. The atrophic changes were seen in 19% of older patients and one (3%) younger patient[77].

In Turkey, while a significant relationship was found between *cagA* positivity and neutrophil activity and glandular atrophy in antral specimens, corpus neutrophil infiltration was found to be more severe in the *vacA* m1 group than in the v*acA* m2 group[59]. No association between virulence factors and histopathology was found in Iraq[69]. In Iran, *dupA*-negative strains were associated with premalignant histological changes[65].

In most of the studies conducted in the Middle East, histological changes seen in the antral sections (such as neutrophil infiltration of the lamina propria and the glands and the increase in the number of lymphocytes and plasma cells) were on average of mild scores.

DIET IN THE MIDDLE EAST

Diet pattern correlates with gastric diseases. Most populations in the Mediterranean region (including Middle Eastern populations) adhere to the Mediterranean dietary pattern. Mediterranean food has several common features including low consumption of meat and animal products, a high consumption of fish, vegetables, fruit, and cereal, and olive oil as the main source of fat. A Mediterranean diet, particularly olive oil, vegetable and fruit consumption, has been shown to be related to a low risk of cardiovascular disease and several cancers including upper gastrointestinal tract cancer[78,79]. Whole grain is also related to low risk of gastric cancer[78]. In contrast, intake of refined grains by some Mediterranean populations was associated with increased risk of stomach cancer[78]. Overall, the Mediterranean dietary pattern is associated with better health and protects against various chronic diseases. After revision of most recently published papers about diet and food in the Middle East, I did not find any significant differences in the diet pattern amongst the countries of this region[80,81].

Table 2 Smoking prevalence in different countries (%)

	Males	Females
Saudi: Male Adult (30-70 yr and older), 1996-2001	19.1	8.3
Kuwait: Adult, 1996	29.6	1.5
Italy: Adult (15 yr and older), 2002	31.1	22.3
Iraq: Adult (16 yr and older), 1990	40	5
Jordan: Adult, 1999	48	10
Japan: Adult (15 yr and older), 2002	51	10
Iran: Adult (15 yr and older), 1999-2000	22.2	2.1
Egypt: Adult (15 yr and older), 2000	40	18
Spain: Adult (16 yr and older), 2001	39.1	24.6
Turkey: Adult (20 yr and older), 1997-1998	50.9	10.9
Israel: Adult (25-64 yr and older), 1999-2001	38.6	22.1
Costa Rica: Adult (20-49 yr and older), 2001	29	9.7

SMOKING IN THE MIDDLE EAST

The association between smoking and increased risk of gastric cancer has been observed. In an epidemiological study conducted in Portugal it was shown that smoking is associated with gastric intestinal metaplasia[82]. In other studies, it was shown that tobacco can increase the risk of gastric cancer[83], and epidemiological evidence linking smoking and gastric cancer has been found[84]. The prevalence of smoking in Iraq where the gastric cancer rate is very low is twice as the prevalence in Iran where the gastric cancer is very high. On the other hand, the highest prevalence was found in Turkey[85]. The prevalence of smoking in other Middle Eastern countries can be seen in Table 2.

GENERAL CONSIDERATIONS

H. pylori is a causative agent of peptic ulcer disease and an important risk factor of gastric cancer. Despite the high *H. pylori* infection rate in Middle Eastern countries, gastric cancer incidence is low in all countries but Iran. Previous reports have shown that the age of patients at the onset of infection may help predict the disease development process as the early acquisition of infection carries more risk of disease development. As shown above, *H. pylori* infection is acquired early in life in this region. In spite of this, the cancer rate is low.

In the Middle East, the populations can ethnically be divided into two main groups: Semitic populations (Arab and Jew who are southern region inhabitants) and non Semitic populations (Kurd, Turk, and Persian who are northern region inhabitants).

The prevalence of virulence factors in countries inhabited by non Semitic populations (Turkey, Iran and Iraq) is similar to what was found in South Asian and

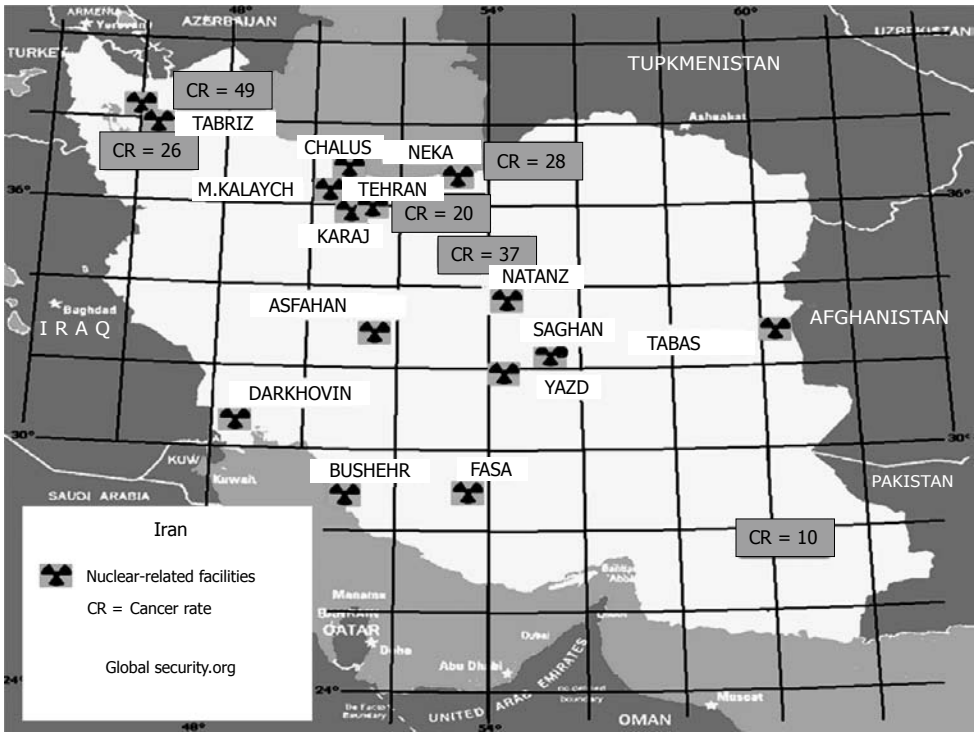

Figure 1 Map showing Iran's nuclear sites and annual incidence of gastric cancer in Iran reported from different cancer registries presented as male age standardized rate per 100 000.

Europe[41] and significantly more than what was found in countries with a Semitic background. This might be because populations which lived in the northern part of the Middle East near Europe and south Asia might correlate with European and south Asian populations. Additionally, this provides more evidence of the ethnical tropism of *H. pylori* infection. It is noticed that virulence factor rates in Saudi *H. pylori* are higher than other Arabic countries. This might be due the fact that Saudi society has been an open society due to continued population movement into this region to perform pilgrimage (Hajj).

Graham *et al*[86] suggested a better strategy for the explanation of the relationship between *H. pylori* and diseases by focusing on underlying patterns of gastritis. This, to a certain extent, is true in this region because all histopathology reports have shown that antral predominant gastritis is the main pattern of gastritis in this region apart from Iran where corpus or pan gastritis is the main pattern. However, if atrophic gastritis, which is precancerous and shown to be associated with cancer, is considered, the high cancer rate in Iran cannot be explained because atrophic gastritis is very high in Turkey, Jordan, UAE, and Egypt with much lower cancer rates. Yet another question to be answered: why this difference in gastritis pattern? Previous reports have blamed environmental factors and diet. For the sake of argument, one would accept the blame but which environmental factor can play such a role in a region which has almost the same environment and traditions. Moreover, as seen above, most Mediterranean countries (including Middle Eastern and South European countries) adhere to a Mediterranean diet pattern and neither diet pattern nor smoking rates seem to explain the difference in cancer rate. The only difference, however, that can be found between Iran and other countries (apart from Israel) is the presence of nuclear facilities in Iran. Examining the map of Iran's nuclear sites, Iranian uranium mines, nuclear reactors, and uranium processing facilities that include three known uranium enrichment plants can be found in Iran's most populous urban areas especially in the northwest and central region where there is a very high gastric cancer rate (Figure 1)[87]. On the other hand, there is no nuclear facility in the southeast where the gastric cancer rate is similar to that found in neighboring countries[87]. In Israel, these facilities are in the desert and relatively isolated areas. But if the theory of the relationship between those facilities and cancer is true, one would expect high rates of other cancers in Iran and this is not true[28].

Host genetics play an essential role in the inflammatory process and in the interactions between the host and *H. pylori* (see review by Kusters *et al*[88]). It has been shown that proinflammatory genetic polymorphisms tend to increase the risk of development of gastric cancer. Hence, would the genetic make-up explain the dilemma of cancer rate in this region? Proinflammatory host genetic facilitates gastric cancer through the development of hypochlorhydric and atrophic gastritis which has been studied and could not have explained the difference in cancer rate. Graham *et al*[86], suggested that host genetics affect individuals and generally cannot explain widespread changes. In addition, the genetic markers we have at present are not sensitive or specific enough to form the basis of a screening strategy[89]. According to Canedo *et al*[89], any genetic association studies should fulfil specific criteria among which there should be no evidence of population admixture. This criterion is almost impossible to fulfil in this region. When looking back through history, you will find that Indo-European races (Kurd and Iranian) are not indigenous. In addition, after the rise of Islam and the Arab conquest of the surrounding countries, there was much

intermixture between Indo-European and Semitic populations. Further evidence for this intermixture is that in a study of human genetics, a close relatedness of Semitic and Indo-Europeans with each other and with neighbouring geographic groups was shown. In the same study it was shown that Semitic North African groups are more distant genetically from Semitic-speaking groups from the Near East and Iran[90]. Hence, avoiding a mixed population is insuperable in this region. However, this does not negate the importance of the host genetic analyses of cytokine polymorphisms affecting mucosal inflammation and gastric acid secretion. Carefully planned projects would provide additional information to identify predictive markers for an individual's risk for gastric atrophy and malignancy.

CONCLUSION

To conclude, there is unexplained variation in the distribution of virulence factors and gastritis patterns in the Middle East. These variations fail to explain the discordance between *H. pylori* infection rates and the variations in gastric cancer prevalence. Although detailed studies are needed to investigate dietary pattern, generally diet is unlikely to contribute because all the countries are following the same Mediterranean pattern. Smoking rates could not explain the variation in cancer rates as we have seen countries with a very high smoking rate but low cancer rate. This might indicate the presence of an enigma similar to or part of that reported (controversially) in Africa and Asia[91,92]. Further detailed investigations and international comparative studies of each risk factor need to be performed to investigate whether this phenomenon represents a true enigma.

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