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HELICOBACTER PYLORI INFECTIONS AND GASTRIC CANCER: THE WEST AFRICAN EXPERIENCE

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ABSTRACT

The prevalence of Helicobacter Pylori (Hp) in West Africa is high and infection occurs early in childhood but there are very few studies on association of Hp with GC. Despite the high prevalence of Hp, gastric cancer incidence is low and precancerous lesions are rare. Although most strains of Hp are positive for the virulent factor cagA gene as well as vacA s1, m1 or s1, m2; there is no consistent association with GC. Some studies have attributed the low incidence of GC to low prevalence of strains with multiple EPIYA-C segments of CagA gene and mixed infection by *cagA* positive and *cagA* negative strains which may be protective. Studies have also suggested that diets rich in anti-oxidants such as fresh fruits and vegetables decrease risk of GC while high salt diet increases the higher expression of CagA. More studies are therefore required to explain the dissociation between prevalence of Hp infection and gastric cancer in WA.

INTRODUCTION

Helicobacter pylori (Hp) infection is prevalent worldwide although its prevalence varies between countries. Although evidences have shown causal relationship between Hp and gastric cancer (GC), the incidence of GC in certain parts of the world such as Africa and some Asian countries is low, the so-called 'African' and 'Asian' enigmas[1,2]. The enigmas have been explained by several factors including host genetics and immune response, different oncogenic potential of the specific strains of Hp as well as environmental factors[1,3]. This communication reviews the available literature in West African subcontinent on *H pylori* infection vis-à-vis gastric cancer.

The Organism

Discovered in 1983, *H.pylori* infection is prevalent worldwide and the infection which is usually acquired in childhood tends to persist unless

treated. It is a spiral, microaerophilic, gram negative bacterium. Human beings are the only known reservoir and it spreads between persons by oral-oral and faeco-oral route. Nobel Prize for Medicine was awarded in 1985 to Robin Warren and Barry Marshall, who proved that most stomach ulcers are caused by *H pylori* not excess acid. The genome of this organism is one of the first bacterial genomes to be completely sequenced. About 30% of developed and 80% of developing countries is infected and the infection is acquired at an earlier age in the latter than developed countries. The infection has been associated with gastroduodenal diseases including gastritis, peptic ulcer disease, distal gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma

Diagnosis and Prevalence of *H pylori* infection in West Africa(WA)

Generally the prevalence of Hp infection is high in WA countries ranging between 70-90% depending on the method used[4-8]. In developing countries, infection occurs in childhood and increases with age while in developed countries, infection occurs in older age. Table 1 highlights several studies from parts of West Africa showing prevalence rates of Hp using various methods. Invasive and non-invasive methods are used in diagnosis of *H pylori* infection. Invasive most often requires endoscopy and include Campylobacter-like organism (CLO) tests, culture, CLO tests and histology; direct gram stain and PCR based tests. The non-invasive tests do not require endoscopy and include serology, Hp stool antigen test (HpSA) and Urea Breath Test (UBT). In WA sub-region, invasive methods are fraught with several problems such as unavailability or unaffordability. Also culture is often not done routinely due to erratic power supply[9]. In tissue biopsy, Hp can be demonstrated on the mucous coat of the mucosa as well as gastric pits using routine haematoxylin and eosin stain but usually better using modified Giemsa stain as depicted in Figure 1.

Prevalence of Gastric Cancer

Despite declining incidence in western countries, gastric cancer is currently the 4th most common malignancy in the world, accounting for 7.8% of the total with half the world total occurring in Eastern Asia mainly in China (Globocan 2008) [10]. Incidence varies between countries and regions.

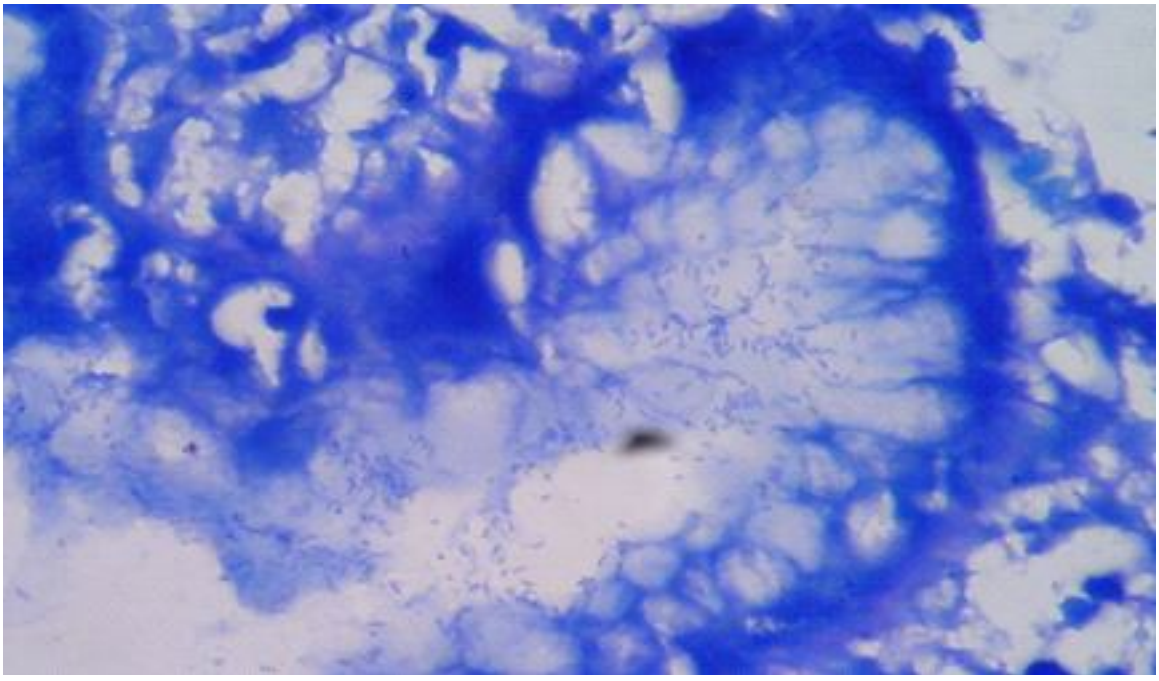

Fig. 1: Showing numerous *H.Pylori* organisms within gastric pit (Modified Giemsa stain x40)

Table 1: Prevalence of Hp from various studies and method used

Study	Hp prevalence	Method used
Lawal, *et al* (Ife), SW, Nigeria	77.50%	Histology & Culture
Jemilohun, *et al* (Ibadan), SW, Nigeria (2011)	64%	Histology & UBT
Hameed, *et al* (Lagos), SW, Nigeria (2012)	41%	Histology
Tanko, *et al* (Jos), North Central, Nigeria (2008)	79%	Histology
Fowora, *et al* SW, Lagos (2012)	91.20%	UBT
Secka, *et al* Gambia (2012)	71.6%	PCR
Baako, *et al* Ghana 1996	75.40%	UBT

In WA, the incidence is low with estimated age standardized rate of 11.4/100,000 for both sexes compared to >63/100,000 in East Asia[10]. It is reported to be the fifth most common cancer in males. In Nigeria, relative frequency ratio ranges between 1.3 and 3.6%[11-13] of all cancers and it accounts for 14% to 48.4% of all malignant gastrointestinal tumours[14-16]. Table 2 shows prevalence of gastric cancer recorded in various studies from Nigeria while Table 3 compares the clinicopathological parameters recorded in three separate studies from different parts of Nigeria.

Table 2: Prevalence of gastric cancer in various studies from Nigeria

Gastric Cancer	Frequency
Ogunbiyi, Ibadan (2000)	4.45%
Pindiga, Maiduguri (2004)	3.40%
Okobia, *et al,* Benin (2005)	2.70%
Muhammad, *et al,* Kano (2008)	1.30%
Mandong, *et al,* Jos (2010)	3.59%
Abdulkareem, *et al,* Lagos (2010)	1.60%

The peak age is in the 6th decade and male to female ratio of 2:1. Majority is adenocarcinoma, accounting for over 90% of cases and the intestinal type is the predominant histologic type. Majority of tumours are located in the antrum and patients present at advanced stage with attendant poor prognosis.

Pathogenesis of Hp

Pathogenesis of Hp is an interplay of the:

(a) bacterial factors

(b) host genetics and immune responses and

(c) modulating co-factors such as diet and cigarette smoking.

The response of the host cell depends on production of the virulent factors produced by Hp such as CagA (cytotoxic associated gene A), VacA(vaculating cytotoxin A) and others OipA(outer membrane inflammatory protein), babA(blood group antigen binding adhesin), alpAB(adherence-associated lipoprotein).

Cag A is a highly immunogenic and variable protein. The size of Cag A varies due to the presence of a variable number of repeat sequences in the 3' region of the gene; thus the structure of East Asian strain differs from the western type. The number of

Table 3: Compares the clinicopathological parameters of gastric cancer recorded in three separate studies from different parts of Nigeria

	Abdulkareem, *et al* 2010	Oluwasola and Ogunbiyi 2003	Mandong, *et al* 2011
Intestinal type	60%	56%	51.20%
Diffuse	40%	22%	34.10%
Mean age	55yrs		51yrs
M:F ratio	2:01	2:01	2.4:1
Hp in adjacent mucosa	15.50%	17.80%	-

second repeat motifs is related to gastric cancer in both East Asian and Western strains. Strains with multiple repeats are significantly associated with higher incidence of gastric cancer compared with those infected with a single repeat.

VacA inserts into the host cell membrane and induces cytoplasmic vacuolation. There is variation in vacuolating activities due to differences in vacA gene structure at the signal region (s1, s2) and mid-region(m1, m2). VacA s1/m1 strains are associated with gastric carcinoma while s2/m2 are non-toxic and rarely associated with disease.

Hp Genotypes and Association with GC

The African and Asian enigmas have been explained in part by the different genotypes of Hp Cag A and Vac A circulating in different geographic areas. CagA is highly immunogenic and varies widely. Populations with high rates of GC correspond almost exactly with regions where east Asian type Cag A predominates while those with low incidence of GC are those with western type Cag A(Africa, Europe South Asia). It has been shown that strains with multiple EPIYA-C segments of CagA gene is an important risk factor for GC in Western Hp strain[18, 19]. There is also polymorphism in VacA genes and although patients with VacA s1m1 and s1m2 strains are disease associated, patients with GC usually have s1m1[19].

There is a dearth of studies on genotyping of Hp in WA. A few of such from Nigeria, Senegal and The Gambia show that majority of Hp strains have virulent factors but there is no significant association with gastro duodenal diseases (GDD). In Nigeria, Smith, *et al* studied 41 isolates from 19 patients with duodenal disease and 22 patients with dyspeptic symptoms by PCR. They found that vacA s1/m2, iceA1 and cagA+ are common genotypes in Nigeria and CagA gene was present in over 90% of cases irrespective of clinical diagnosis and there was no association between these genotypes and duodenal ulcer disease[20]. A recent multicenter report also from Nigeria by Fowora et al (2012) studied a total of 40 biopsies obtained from 20 patients who were positive for UBT. The virulence potential of the isolates were assessed using PCR for the vacA s1, s2, m1 and m2 regions. Cag A was positive in 97.1% and vacA s1/m1was present in 100%. All isolates carry virulence genes irrespective of their clinical diagnosis.

In The Gambia, the CagA gene and more toxigenic VacA s1 and m1 gene were found in 61.2%, 76.9% and 45.5% respectively[21]. CagA gene was also present in 73.3% of Senegalese isolates and was significantly associated with GC; present in 14 of 15 cases of GC [22]. In addition, they reported that only 2.4% of the strains harbour at least two EPIYA-C segments compared to 11.5 -30% reported from other continents. Thus, they concluded that low prevalence of strains with multiple EPIYA-C segments of CagA gene might contribute to the low incidence of GC in Senegal[22].

Table 4: Showing low prevalence of pre-cancerous lesions such as glandular atrophy, intestinal metaplasia and dysplasia

	Ife (Badmus, *et al* 2012)	Jos (Tanko, *et al* 2008)	Ibadan (Oluwasola, *et al* 2003)	Lagos (Abdulkareem, *et al* 2011)
Number of Cases studied	1036	100	84	454
Atrophic gastritis	4.3	38%	16.70%	18.30%
Intestinal metaplasia	9.2	28%	9.40%	9.60%
Dysplasia	0.7	-	-	4.30%
Hp detection	80%	79%	22.40%	15.20%

Prevalence of Precancerous Gastric Lesions and Association with Hp

Generally, precancerous lesions are low in patients with GDD in WA. The few studies reviewed as detailed in Table 4 show low prevalence of glandular atrophy, intestinal metaplasia and dysplasia which are known to precede gastric cancer. The

prevalence of glandular atrophy, intestinal metaplasia and dysplasia range from 4.3%-38%, 9.2-28% and 0.7-4.3% respectively in patients with chronic gastritis[4, 12, 16, 23]. In Senegal, precancerous lesions were present in 22.7% of 220 cases of gastric cancer studied[15].

CONCLUSION

The prevalence of Hp in West Africa is high and infection occurs early in childhood but there are very few studies on association of Hp with GC. Despite the high prevalence of Hp, gastric cancer incidence is low with ASR of less than 11.4 compared to 63 per 100,000 in South East Asia. Prevalence of precancerous lesions such as glandular atrophy, intestinal metaplasia and dysplasia are also low. Although most strains of Hp are positive for the virulent factor cagA gene as well as vacA s1, m1 or s1,m2; there is no consistent association with GC. Only one study (from Senegal) shows strong association between these factors and GC. Low prevalence of strains with multiple EPIYA-C segments of CagA gene which has been associated with GC risk, higher incidence of mixed infection by CagA positive and CagA negative strains which is thought to be protective. Yet to be investigated in WA is the role of immune response and diet. The study of Fox, *et al* has suggested that the presence of concurrent enteric helminthes may modulate the immune response to Hp in Africans to favour a Th-2 type and this may protect against gastric cancer. Studies have also suggested that diets rich in anti-oxidants such as fresh fruits and vegetables decrease risk of GC while high salt diet increases the higher expression of CagA. More studies are therefore required to explain low gastric cancer incidence in West Africa despite high prevalence of *H.pylori* infection.

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