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Elnagar Aa, Mpho Kgomo, Mokoena T, S Mashoshoe, Nagel Gj. Helicobacter pylori Infection is Associated with an Increased Risk of Developing Squamous Cell Carcinoma of the Oesophagus. A Cross Sectional Case Control Prospective Study. *Journal of Bioanalysis & Biomedicine*, 2016, 8, <10.4172/1948-593x.1000154>. <hal-04026277>

HAL Id: hal-04026277

<https://hal.science/hal-04026277v1>

Submitted on 13 Mar 2023

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Helicobacter pylori Infection is Associated with an Increased Risk of Developing Squamous Cell Carcinoma of the Oesophagus. A Cross Sectional Case Control Prospective Study

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Abstract

Helicobacter pylori is an important causative factor in gastric carcinogenesis, its role in extra-gastric gastrointestinal malignancies such as oesophageal cancer, is controversial. *H. pylori* is thought to be associated with an increased risk of squamous cell carcinoma of the oesophagus. We conducted a case control study to determine the prevalence of *H. pylori* infection in patients with squamous cell carcinoma of the oesophagus and control group with no cancer.

Method: We collected biopsies from the antrum and corpus of 59 patients with confirmed squamous cell carcinoma of the oesophagus, two from each area and 215 control groups with no cancer. These were then examined by an experienced histo-pathologist using Giemsa staining for the presence of *H. pylori*. CLO was added to those with bleeding ulcers.

Results: *H. pylori* was found in 30 (51%) of the patients with squamous cell carcinoma of the oesophagus and 46 (21%) of the control group. The prevalence was found to be more than double of the control group in patients with squamous cell carcinoma of the oesophagus. A relative risk of 2.4 $p < 0.001$ CI OF 95%.

Conclusion: *H. pylori* infection is associated with an increased risk of developing squamous cell carcinoma of the oesophagus with a relative risk of 2.4. This is in keeping with several studies done previously.

Keywords: *Helicobacter pylori*; Squamous cell carcinoma; CagA; Antrum; Corpus; Oesophageal cancer; CLO test

Introduction

Helicobacter pylori is an important causative factor in gastric carcinogenesis. However, its role in extra-gastric gastrointestinal malignancies such as oesophageal cancer is controversial. David et al. [1] Conducted a case control study in 2010 and concluded that *H. pylori* infection was inversely associated with oesophageal adenocarcinoma and oesophageal gastric junction adenocarcinoma but not oesophageal squamous cell carcinoma (OSCC). Welmin et al. [2] Found in their study in 2003 that *H. pylori* infection increased the risk of squamous cell carcinoma of the oesophagus.

Nie et al. conducted a meta-analysis in 2014, to evaluate the relationship of *H. pylori* and cytotoxin-associated gene A (CagA) positive strains with esophageal neoplasm, including oesophageal adenocarcinoma and squamous cell carcinoma of the oesophagus (OSCC) and found no significant association between *H. pylori* infection/CagA positive strains and OSCC. They concluded that CagA-positive strains might have a positive association with OSCC in non-Asian population and an inverse association in Asian population [3,4].

Xie et al. [5] also conducted an updated meta-analysis looking at *H. pylori* infection and oesophageal cancer risk. They concluded that *H. pylori* infection is associated with increased risk of OSCC in Eastern populations and a decreased risk of oesophageal adenocarcinoma (OAC) in the overall population.

Islami and Ramanga [6], in their meta-analysis in Nov 2012, found no overall association between *H. pylori* and OSCC risk. They however found that when studies were classified by geographic region, there was a statistically significant association between *H. pylori* and OSCC in Western studies, with OR (95%CI) of 1.65(1.17-2.32). Khoshbaten et al. [7] Concluded in their study in Iran that *H. pylori* infection decreases the risk of OSCC and that this is not linked to a CagA positive status.

Studies of the relationship between *H. pylori* infection and OSCC in South Africa where the prevalence of this cancer is high are lacking. There is a need for such studies in this country as both OSCC and *H. pylori* infection are common. The literature both locally and internationally shows conflicting results.

It is for these reasons that we conducted a prospective case control study to evaluate the histological prevalence of *H. pylori* infection in 59 consecutive patients with OSCC and 215 control group seen in Gastroenterology Division of Steve Biko Academic hospital in Pretoria South Africa over a two year period, to determine the prevalence of this infection in patients with OSCC. The prevalence of *H. pylori* infection in Africa, ranges from 51% to 80% depending on tests used and age group, however, since the HIV epidemic that hit our country the use of anti-viral and antibiotics have increased and this is likely to have reduced the prevalence of *H. pylori* infection in this population. There has not been any new studies since the appearance of this epidemic. Histological prevalence being lower [8-10].

Methods

Consecutive patient with advanced non curable squamous cell carcinoma of the oesophagus and an age matched control group with

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Received July 31, 2016; Accepted August 12, 2016; Published August 19, 2016

Citation: Kgomo M, Elnagar AA, Mokoena T, Mashoshoe S, Nagel GJ (2016) *Helicobacter pylori* Infection is Associated with an Increased Risk of Developing Squamous Cell Carcinoma of the Oesophagus. A Cross Sectional Case Control Prospective Study. J Bioanal Biomed 8: 063-065. doi:10.4172/1948-593X.1000154

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gastroscopy indications other than cancer referred to Gastroenterology Division of Steve Biko Academic Hospital over a two year period were recruited. All patients with this cancer present late with no possibility of cure. All patients were questioned about the use of antibiotics and or proton pump inhibitors in the last 2 months.

Patients were referred to our hospital from four provinces of South Africa, Gauteng, Mpumalanga, North West and Limpopo. Patients were referred for diagnostic and/or therapeutic upper endoscopy. An informed consent was obtained from all patients for biopsies from their gastric mucosa for *H. pylori* testing. In patients with bleeding peptic ulcers or suspected of use of antibiotics/ proton pump inhibitors in the last 2 months, CLO test was added to histology testing to improve accuracy. In non-bleeding ulcers (control group) CLO test was used alone for *H. pylori* testing.

All cancers were tested by histology with Giemsa staining. At endoscopy, two additional biopsies were taken from the antrum and two from the corpus to improve accuracy of detecting *H. pylori*. These biopsies were then examined by an experienced histopathologist with Giemsa stains for *H. pylori*.

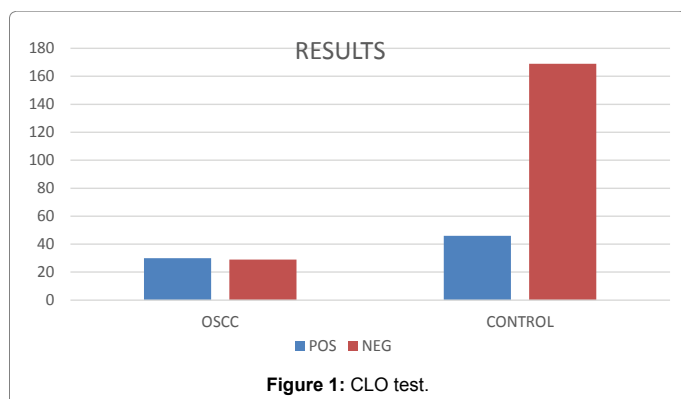
The organism burden was reported as mild, moderate or severe. Intestinal metaplasia, dysplasia and malignancy in the gastric mucosa were reported as present or absent. Inflammation was reported as chronic, acute or inactive.

Result

59 male and female patients with squamous cell carcinoma of the oesophagus and 215 control patients without cancer were recruited. The age range was 28–83 years. A reliable drug history could not be obtained from most of these patients because of low level of literacy, however, a combination of histology and CLO test was used in 42 (control group) bleeding ulcers (Tables 1-3). *H. pylori* was found in a total of 30 (51%) of the 59 patients with squamous cell carcinoma and 46 (21%) of the 215 control group giving us a prevalence of 51% and 21% respectively $p < 0.001$ χ^2 test. Relative risk 2.4 using csi command with chis square test in STATA. 95% CI (1.7-3.4). CLO test correlated (100%) well with histology (Table 4) (Figure 1).

Discussion

This study suggests that *H. pylori* infection may increase the risk of developing squamous cell carcinoma of the oesophagus by a factor of 2.4. The study, however, has a limitation in that most of the control group patients were tested with CLO test only because of resource limitation. The prevalence of *H. pylori* infection in South Africa is estimated to be between 50% and 80%, it would



	ALL	NO	YES	P overall	N
	N=173	N=131	N=42		
Age	56.8 (15.3)	55.8 (15.5)	59.9 (14.3)	0.117	173
GENDER					1
F	92 (53.2%)	70 (53.4%)	22 (52.4%)		
M	81 (46.8%)	61 (46.6%)	20 (47.6%)		
RACE					0.023
B	82 (47.4%)	69 (52.7%)	13 (31.0%)		
W	91 (52.6%)	62 (47.3%)	29 (69.0%)		
PPI				0.044	173
NO	111 (64.2%)	90 (68.7%)	21 (50.0%)		
YES	62 (35.8%)	41 (31.3%)	21 (50.0%)		
ANTIBIO					0.076
NO	143 (82.7%)	104 (79.4%)	39 (92.9%)		
YES	30 (17.3%)	27 (20.6%)	3 (7.1%)		
CLO TEST					0.404
NEG	134 (77.5%)	99 (75.6%)	35 (83.3%)		
POS	39 (22.5%)	32 (24.4%)	7 (16.7%)		
-----Summary descriptives table by 'PPI'-----					
Bleeders and Non Bleeders					
	ALL	NO	YES	P overall	N
	N=173	N=111	N=62		
CLO TEST					0.347
NEG	134 (77.5%)	83 (74.8%)	51 (82.3%)		
POS	39 (22.5%)	28 (25.2%)	11 (17.7%)		
PPI in Bleeders					
	ALL	NO	YES	P overall	N
	N=42	N=21	N=21		
HISTOLOGY TEST					1
NEG	35 (83.3%)	18 (85.7%)	17 (81.0%)		42
POS	7 (16.7%)	3 (14.3%)	4 (19.0%)		

Table 1: Results control group.

Gender		Race	
Male	Female	Black	Caucasian
45	14	54	5
76%	23%	91%	9%

Table 2: Race and gender distribution of OSCC patients.

Gastro Finding in OSCC			
n		results	
59		Stage IV OSCC	
SQUAMOUS CELL CARCINOMA 59 BLACK PATIENTS		CONTROL GROUP 215	
H/P POS	H/P NEG	H/P POS	H/P NEG
30 (51%)	29 (49%)	46 (21%)	169 (79%)
TOTAL CLO/HIST		42	

INDEX: H/P=*Helicobacter pylori*.
 POS=Positive
 NEG=Negative
 CLO/HIST=CLO test plus histology.

Table 3: Gastro finding in OSCC patients.

therefore be expected to be at least this high in control group. Multiple studies have suggested that *H. pylori* infection is protective against adenocarcinoma of the oesophagus, but increased the risk of developing squamous cell carcinoma of the oesophagus. There are no local studies in South Africa looking at this relationship but this study is in keeping with similar studies done elsewhere. Larger

Gastro Finding in control	
n	results
215	Gastric ulcers 173 bleeding gastric ulcer 42

Table 4: Gastro finding in control group.

and longer studies are needed to further clarify this association. The prevalence is highest in developing countries like South Africa and increases with age as shown in this study. The role of this infection in OSCC remains controversial; however, there is a suggestion that it may play a role in Europe and Japan. In South Africa both *H. pylori* infection and squamous cell carcinoma of the oesophagus are common and this difference in prevalence in these two groups is important. We did not look at Cag A status of *H. pylori* as studies have previously shown that the Cag A status doesn't matter in these patients.

Conclusion

The prevalence of *H. pylori* infection in patients with oesophageal squamous cell carcinoma in this study was found to be 51%, more than double that found in control group of 21%. The lower prevalence of *H. pylori* in the control group could be due to the HIV epidemic in our country. This result suggest that patients with squamous cell carcinoma of the oesophagus are 2.4 times more likely to be *H. pylori* positive than the control group. The relative risk ratio is 2:4. CLO test was found to be as sensitive and as specific as histology in those with bleeding ulcers.

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