Bouriat et al. | J Pure Appl Microbiol | 16(1):717-728 | March 2022
Article 7361 | https://doi.org/10.22207/JPAM.16.1.75
Published Online February 25, 2022
Print ISSN: 0973-7510; E-ISSN: 2581-690X

RESEARCH ARTICLE OPEN ACCESS

Are Inflammatory Bowel Disease and Colorectal Carcinoma Associated with *Helicobacter pylori* ? A Prospective Study and Meta-analysis

Kaoutar Bouriat[1,2], Soumia Cherif[1,3], Souad Sellami[2], Maria Dref[2], Khadija Krati[4], Meftah Elkhir Meriem[1], Said Elantri[1], Abdessamad Amine[1]* and Hanane Rais[2]

[1]Laboratory of Biochemistry, Environment, and Agrifood, Faculty of Sciences and Techniques-Mohammedia, University of Hassan II of Casablanca, Morocco.
[2]Department of Anatomy-pathology, The Arrazi Hospital CHU Mohammed VI of Marrakech, Morocco.
[3]Clinic of Gynecology, Charite -Universitatsmedizin, Berlin, Germany.
[4]Department of Gastroenterology, The Arrazi Hospital CHU Mohammed VI of Marrakech, Morocco.

Abstract

Observational studies regarding the correlation between colorectal carcinoma, inflammatory bowel disease and *Helicobacter pylori* infection are inconsistent. The present study aims to investigate the association between colorectal adenocarcinoma (CRA) and inflammatory bowel disease (IBD) with *H. pylori* status in 100 patients who have inflammatory bowel disease and colorectal carcinoma was confirmed disease by histological approach. Besides, a meta-analysis was performed of published studies, to evaluate the link between *H. pylori* infection and an increased risk of CRC and IBD. Among 67 cases with CRA and 33 cases with IBD, 59.7% and 51.5% were *H. pylori* positive; respectively. In the meta-analysis, thirty-nine articles were included, involving 13 231 cases with CRC and 2477 with IBD. The pooled odds ratio for CRC and IBD was 1.16 (95%CI = 0.73-1.82) and 0.42 (95%CI = 0.32-0.56); respectively. Our meta-analysis indicates that *H. pylori* is not associated with CRC.

Keywords: Colorectal adenocarcinoma, colorectal cancer, *Helicobacter pylori*, IBD, immunohistochemistry, meta-analysis

***Correspondence:** abdessamad.amine@fstm.ac.ma

(Received: October 6, 2021; accepted: January 26, 2022)

Citation: Bouriat K, Cherif S, Sellami S, et al. Are Inflammatory Bowel Disease and Colorectal Carcinoma Associated with *Helicobacter pylori*? A Prospective Study and Meta-analysis. *J Pure Appl Microbiol.* 2022;16(1):717-728. doi: 10.22207/JPAM.16.1.75

INTRODUCTION

Colorectal carcinoma (CRC) is the third most diagnosed cancer and the second most lethal cancer worldwide.[1,2] In Morocco, colorectal cancer is classified as the first digestive cancer and remains a burden in the country, as 2484 new cases are diagnosed and account for ~14.8% of deaths annually.[4,5] Additionally, it´s well known that colorectal cancer is sporadic. However, genetic and environmental risk factors are regarded as the most important.[6,7] Furthermore, inflammatory bowel disease (IBD) related to Crohn's disease (CD) and ulcerative colitis (UC); were associated positively with the occurrence of CRC.[8-10]

Despite the long-standing associations between bacterial infection and carcinogenesis, researchers have recently highlighted, the implication of *Helicobacter pylori* (*H. pylori*) in the initiation of colorectal carcinogenesis and the progression of CRC.[11] *H. pylori* is a well-known cause of gastroduodenal disease.[12] Beside gastric cancer, *H. pylori* infection has been correlated with other digestive tract cancers such as CRC.[13] However, the cause and effect relationship of *H. pylori* with colorectal carcinogenesis, is still under debate; several studies have detected Helicobacter spp. in IBD, colonic adenoma and colonic adenocarcinoma.[14-19] Nevertheless, the results were conflicting. In Morocco, there is no study linking *H. pylori* to colorectal adenocarcinoma and IBD.

To better evaluate the association of *H. pylori* infection with the risk of developing colorectal cancer, we aim to detect the presence of *H. pylori* in cases with IBD and colorectal adenocarcinomas (CRA).[20] We also aim to update and review systematically current information regarding *H. pylori* in CRC and IBD.

PATIENTS AND METHODS

Histological study

It is a prospective study, conducted at the department of pathological anatomy in Mohammed VI University Hospital Center in Marrakech. The biopsies were obtained by colonoscopy in the gastroenterology department in the University Hospital Center of Marrakech and examined histopathologically at the anatomy-pathology department in the Arrazi hospital CHU Mohammed VI in Marrakech. This study included 100 cases (67 colorectal adenocarcinoma, 23 ulcerative colitis and 10 Crohn's disease cases) over 2 years (May 2018-May 2020). Medical and pathology records of the included cases were retrieved. The histopathological aspect of the study was performed by pathologists in accordance with the World Health Organisation (WHO) pathology and genetics (2010). After formalin fixation and paraffin embedding, the samples were sectioned and stained with Hematoxylin and eosine (H&E), and then analyzed by optical microscopy. The study protocol was approved by the local ethics committee of the Marrakech University Hospital Center. Patient consent was signed before the colonoscopy. In the case of illiterate or semi-illiterate consenters the written consent was explained by the investigator.

Data such as: sex, age, macroscopic aspect, anatomical location, degree of infiltration, histological type and degree of tumor differentiation were collected prospectively from the medical records of the included cases.

The detection for *Helicobacter pylori* was performed by histological Stains: modified Giemsa, Warthin-Starry and immunohistochemical staining were used to detect *Helicobacter pylori*, as previously described.[13,21]

The statistical analysis was performed using the software SPSS v26. The χ^2 test was used to evaluate the association between the presence of *H. pylori* and the variable collected, $p < 0.05$ was considered statistically significant.

Meta-analysis

Literature search

We followed PRISMA guidelines to conduct the meta-analysis. A systematic search was conducted from 1998 to 2019 using EMBASE, Web of Science, PubMed, and Cochrane Database. Two researchers (S.C and K.E) conducted literature searches independently, using the following terms: "*H. pylori*" or "*Helicobacter pylori*" and "Inflammatory bowel disease" or" IBD" or "Colorectal cancer" or "CRC" or "Crohn disease" or "ulcerative colitis" or "colitis".

Inclusion criteria

The inclusion criteria were: i) observational studies including case-control studies, ii) detection of *H. pylori* by PCR, fast urease

test, immunohistochemistry, specific staining (Giemsa and Warthin Starry) and ELISA, and iii) studies limited to humans.

Data extraction

The following information was extracted: I) the first author's name, ii) the year of publication, iii) the study design, iv) the country where the study was conducted, v) the method used to detect *H. pylori*, vi) diagnosis; and vii) sample size.

Statistical analysis

Calculations were carried out by generating odds ratio "OR" with their 95% CIs using a random-effects model. Assessment of heterogeneity was performed using the Chi-square test and the I^2statistic. If I^2statistic value is >50%, then the level of heterogeneity is considered as high.

Publication bias detection was performed by using Begg's rank correlation test and Egger's test. A two-sided *P*-value of less than 0.05 was considered as statistically significant. All analyses were performed using the software Rstudio version 1.3.1093 (USA).

RESULTS

As shown in Table 1, the median age of patients with IBD is 29.99±8.77 years, and that of patients with adenocarcinomas is 64.5 ±15.933 years. The male to female ratios for IBD and CRA were 0.73:1 and 1.31:1, respectively. In the CRA group, the tumour is frequently located in the left colon and the rectum (40.3% each), while 19.4% of tumours are located in the right colon. Macroscopically, in the CRA group, ulcerative-burgeoning tumours were the most common type (86.5%). The Lieberkuhnian adenocarcinoma was the most common histologic type (98.5%), followed by Mucinous CRA (1.5%). And according to the degree of tumour differentiation, 74.6% of adenocarcinomas are moderately differentiated, 19.4% are poorly differentiated and 5.9% are well differentiated. Depending on the degree of locoregional invasion, 97% of adenocarcinomas are infiltrated into the sub-serosa followed by 1.5% that is infiltrated into the serosa.

Special stainings and the immunohistochemistry revealed that *H. pylori* was present in 59.7% of CRA and 51.5% of IBD (Fig. 1, Table 2). 41.3% of women with CRA were *H. pylori* positive vs 73.6% of men (p≤0.05). Also, a positive association was found between *H. pylori* presence and the anatomical location of the diseases and the macroscopic aspect of the tumour. No association was found between *H. pylori* positivity and age, histological type, degree of differentiation and infiltration of the tumour

Table 1. Clinical and histopathological characteristics of patients with CRA and IBD (N= 100)

Categories	Variables	CRA (N=67)	IBD (N=33)
Sex	Female (48/100)	29 (43%)	19 (57.57%)
	Male (52/100)	38 (57%)	14 (42.42%)
Age (median)		64,5 ±15.933	29,99±8.77
Anatomical localisation of the disease	Right colon	13 (19.4%)	10 (30.30%)
	Left colon	27 (40.3%)	15 (45.46%)
	Rectum	27 (40.3%)	8 (24.24%)
Macroscopic aspect of CRA	bourgeoning	9 (15.5%)	-
	ulcero-bourgeoning	58 (86.5%)	-
Histological types of CRA	Lieberkuhnien ACR	66 (98.5%)	-
	Mucinous ACR	1 (1.5%)	-
Degree of differentiation	Well-differentiated	4 (5.9%)	-
	Moderately differentiated	50 (74.6%)	-
	Poorly differentiated	13 (19.4%)	-
Infiltration of CRA	Infiltrating the muscularis	1 (1.5%)	-
	Infiltrating the serosal surface	1 (1.5%)	-
	Infiltrating the subserosal	65 (97%)	-

CRA: colorectal adenocarcinoma, IBD: Inflammatory bowel disease.

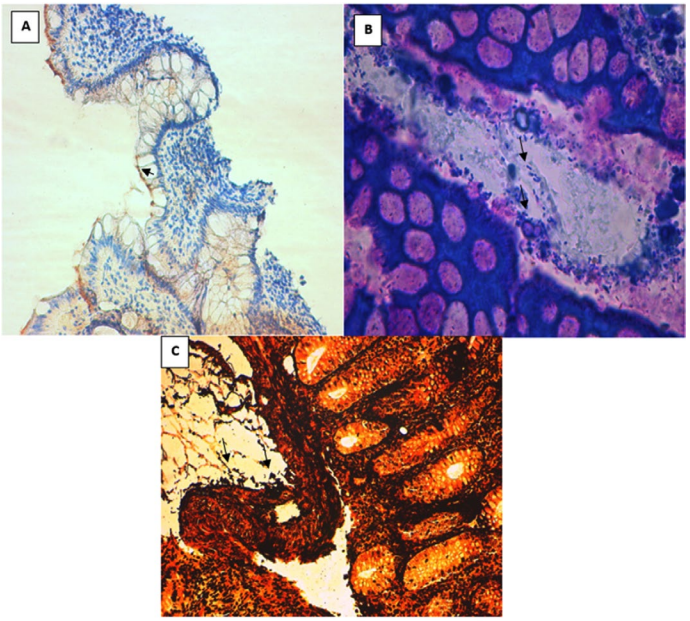

Fig. 1. Detection of *Helicobacter pylori* by histological staining techniques:
(A) by immunohistochemistry (× 100) B) Giemsa (× 1000) and (C) by Warthin starry (× 1000).

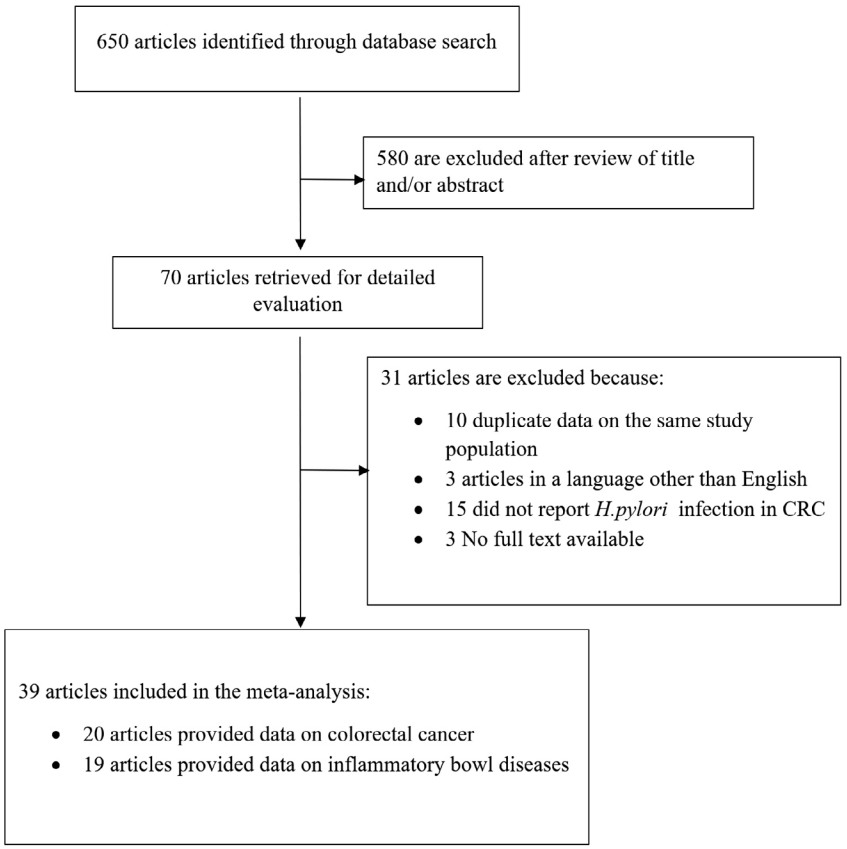

Fig. 2. Flow Diagram of the literature research.

(Table 2).

For the meta-analysis, a flow chart of study selection is reported in Fig. 2. The initial search identified 650 articles. Of these, 39 articles fulfilled the inclusion criteria and were retrieved for detailed evaluation. Twenty of these studies included 13231 patients with CRC, while nineteen articles were about 2477 patients with IBD.

In the included articles (Table 3), 22 were performed in Europe, 12 in Asia, 3 in America and two in Turkey. In terms of *H. pylori* detection methods, 24 studies used serological tests (ELISA), 8 used C-urea breath tests, 8 performed histological techniques (IHC, special staining), 3 used *H. pylori* culture used PCR. A combination of 2 to 3 detection techniques was used in 3 studies. The overall meta-analysis revealed no significant association between *H. pylori* and CRC (OR 1.16, 95%CI 0.73 to 1.82, *p*-value 0.74), and a negative association was found between *H. pylori* and IBD (OR 0.42, 95 % CI 0.32 to 0.56, *p*-value ≤0.0001) (Fig. 3, 4). However, heterogeneity was observed ($p < 0.0001$, $I2 = 95\%$) ($p < 0.0001$, $I2 = 69\%$) in CRC and IBD; respectively. As shown in Fig. 5, the funnel plots of publication bias appears asymmetric. Thus, we can assume the possibility of publication bias.

DISCUSSION

CRC accounts for 8% of cancer deaths worldwide.[4] This malignancy is asymptomatic until it reaches an advanced stage.[58] Nowadays, it is known that IBD has a high relationship with CRC.[59] The pathogenesis of CRC and IBD is still under debate. However, several pathways, have been proposed including TNF-α activation, which activates the transcription factor NF-κB. Besides, IL6 might also activate signal transducer and activator of transcription 3 (STAT), followed by the activation of JAKs (Janus kinase).[5,59-61]

Brackmann et al.,[18] mentioned that patients with CRC related to IBD are affected at a younger age. In our study, the median age of patients with IBD was 29 years old. Besides, the median age in patients with CRC was 64.5 years in the present study. A comparable result was reported in a retrospective study conducted in Rabat.[4]

CRC is influenced by sex and gender, with males having significantly higher mortality rates.[60,61] This might be due to several behavioural

Table 2. Characteristics of the patients linked with H. pylori infection (N=100) Chi square (χ2) test

Categories		Variables	*H. pylori* positive n (%)	*H. pylori* negative n (%)	P-value
Sex	IBD	Female	12 (36.36%)	5 (15.15%)	0.16
		Male	7 (21.21%)	9 (27.27%)	
	CRA	Female	12 (17.91%)	17 (25.37%)	0.01
		Male	28 (41.79%)	10 (14.92%)	
Age	IBD	A<50	15 (45.45%)	11 (33.33%)	0.67
		A≥51	5 (15.15%)	2 (6.06%)	
	CRA	A<50	7 (10.44%)	33 (49.25%)	0.001
		A≥51	15 (22.38%)	12 (17.91%)	
Anatomical location of IBD		Right colon	4 (12.12%)	6 (18.18%)	0.36
		Left colon	7 (21.21%)	8 (24.24%)	
		Rectum	6 (18.18%)	2 (6.06%)	
Anatomical location of CRA		Right colon	4 (5.97%)	9 (13.43%)	0.0007
		Left colon	23 (34.32%)	4 (5.97%)	
		Rectum	13 (19.4%)	14 (20.89%)	
Macroscopic aspect of CRA		Bourgeoning	3 (4.47%)	6 (8.95%)	0.015
		ulcero-bourgeoning	37 (55.22%)	11 (16.42%)	
Histological types of CRA		Lieberkuhnian	40 (59.7%)	26 (38.8%)	0.40
		Mucinos	0 (0%)	1 (1.49%)	
Differentiation		Well differentiated	2 (2.98%)	2 (2.98%)	
		Moderately differentiated	28 (41.79%)	22 (32.83%)	0.68
		Poorly differentiated	10 (14.92%)	13 (19.4%)	

Table 3. Characteristics of the studies included in the meta-analysis

Study	Country	Detection methods	Type of malignancy	Positivity in cases group(n/N)	Positivity in control group(n/N)
Wang et al[22]	China	histology	CRC	189/3044	890/2362
Butt et al[23]	USA	serology	CRC	1665/4063	1625/4063
Blase et al[24]	Gemany	serology	CRC	213/392	121/774
Zhang et al[25]	China	serology	CRC	265/569	205/569
Roka et al[26]	Greece	Histology+ culture+ UBT	IBD	2/34 UC 3/66 CD 1/ 59 unspecified	190/1443
Hansen et al[27]	Scotland	histology	IBD	0/29 CD 0/13 UC 0/2 unspecified	4/42
Jin et al[28]	China	UBT+culture	UC	46/153	69/121
Nam et al[29]	Korea	serology	CRC	6/9	248/470
Xiang et al[30]	China	UBT +culture	CD	62/229	119/248
Zhang et al[31]	Germany	serology	CRC	790/1712	669/1669
Strofilas et al[32]	Greece	serology	CRC	66/93	13/20
Engin et al[33]	Turkey	serology	CRC	77/110	71/116
Garza-Gonzalez et al.[34]	Mexico	serology	IBD	12/23 UC 12/21 CD	51/75
Hong et al[35]	Korea	histology	IBD	26/80	22/41
Lidar et al[36]	Italy	serology	IBD	11/80 CD 5/39 UC	27/98
Song et al[37]	Korea	UBT	IBD	54/169 UC 26/147 CD	165/316
Ando et al[38]	Japan	UBT	CD	3/38	5/12
Bulajic et al[39]	Serbia	PCR (ureA)	CRC	1/83	5/40
D'Onghia et al[40]	Italy	serology	CRC	13/29	19/50
Jones et al[41]	UK	histology	CRC	10/59	1/58
Montani et al[42]	Japan	serology	CRC	74/113	145/226
Zumkeller et al[43]	Germany	serology	CRC	195/384	204/467
Georgopoulos et al[44]	Greece	serology	CRC	62/78	53/78
Moriyama et al[45]	Japan	UBT	CD	3/29	5/7
Pronai et al[46]	Hungary	UBT	IBD	10/82 UC 7/51 CD	78/200
Piodi et al[47]	Italy	UBT	IBD	17/32 CD 17/40 UC	44/72
Limburg et al[48]	Finland	serology	CRC	89/118	184/236
Furusu et al[49]	Japan	Serology+ histology	IBD	0/25 UC 14/25 CD	0/25
Siddheshwar et al[50]	UK	serology	CRC	110/189	110/179
Matsumura et al[51]	Japan	serology	CD	15/90	211/525
Hartwick et al[17]	Poland	serology	CRC	34/40	96/160
Vare et al[52]	Finland	serology	IBD	55/185 UC 8/94 CD 3/17 Unspecified	26/70
Parlak et al[53]	Turkey	histology	IBD	46/66 UC 28/45 CD	48/77
Pearce et al[54]	England	Serology+UBT	IBD	11/51 UC 5/42 CD	10/40

Breuer-Katschinski et al[18]	Germany	serology	CRC	62/98	55/98
Thorburn et al[55]	USA	serology	CRC	159/233	158/233
D´inca et al[56]	Italy	histology	IBD	25/41 UC 33/67 CD	54/43
Duggan et al[57]	England	serology	IBD	59/213 UC 29/110 CD	63/223

CRC: colorectalcancer, IBD: Inflammatory bowl disease, CD: Crohn s disease, UC: ulcerative colitis, UBT: 13C urease breath test, PCR: Polymerase Chain Reaction.

and gender-related factors such as a diet with red meat, alcohol consumption, and smoking. In our study, 57% of the cases were male.

Depending on the CRC anatomical position, the disease progression and the overall survival of CRCs will differ. The difference between these tumours is due to different cancerogenic factors and to the developmental origin of the tumour.[62] Besides, a slight decrease in the incidence of the right-sided CRC was observed worldwide That can be explained by the progress of diagnostic, treatment and by the prevention of these cancers by ablation of the adenomatous polyps in the right part of the colon. An increase was reported in the left colon CRC.[9] In a study conducted in Morocco, 60.3% of tumours were located in the rectum, 23.2% were located in the left colon, and 16.5% of tumours were located in the right colon.[63] In our study, 19.4% of tumours are right-sided, 40.3% are left-sided and 40% are located in the rectum.

Regarding a probable correlation between colorectal carcinoma and *H. pylori* infection, several mechanisms have been proposed; such as the increasing release of gastrin that acts as a mitogen, the changing of gut microbiota and IBD induced during the migration of *H. pylori* from the mucosa to the light of the colon by faecal excretions.[11,64,65] Besides, *H. pylori* virulence factors, like Cag A and Vac A that are associated with gastric adenocarcinoma, might have the same effect on CRC.[66]

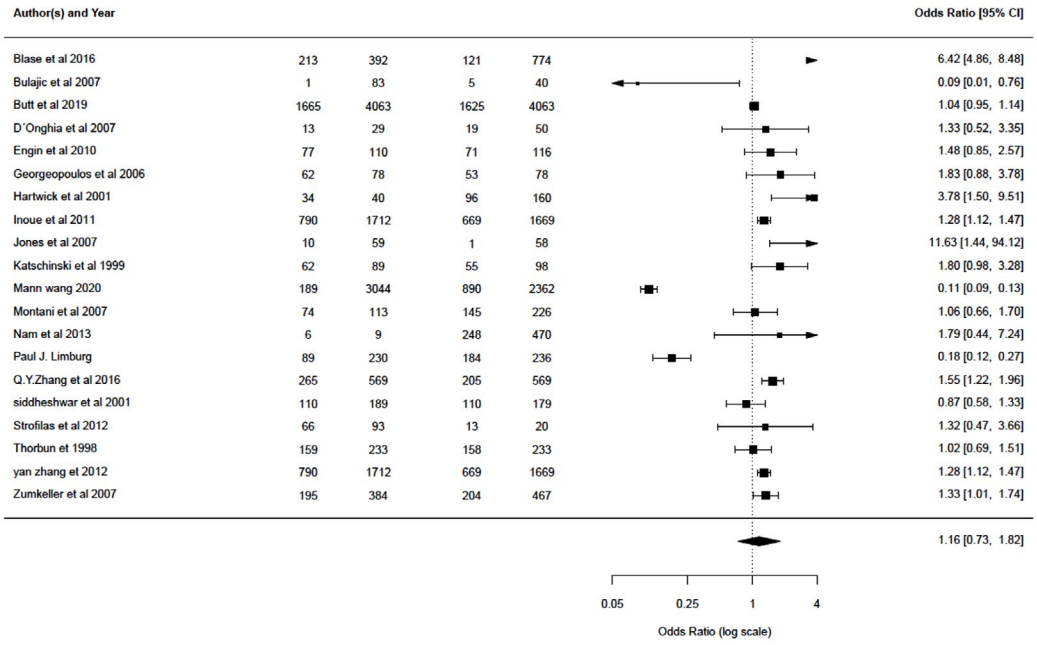

Fig. 3. Forest plot for the pooled OR of H.pylori infection and CRC.

In addition, an *in-vitro* study demonstrated that *H. pylori* lipopolysaccharides, can intervene with the DNA repair system of the colonic epithelial cells, promoting genotoxicity and then colon carcinogenesis.[67] Also, it was shown that *H. pylori* lipopolysaccharides induce the production of nitric oxide, by inhibition of DNA repair enzymes and pro-apoptotic effector proteins resulting from the nitrosylation of their tyrosine and cysteine residues, causing chronic inflammation and then cancer.[68,69]

Several epidemiological studies have associated *H. pylori* infection with CRC and precancerous lesions like IBD, while others failed to establish a statistical association.[11,70] Therefore, a quantitative evaluation of a possible association between CRC, IBD and *H. pylori* is required. In the current meta-analysis, 39 studies, with 13231 CRC cases and 2477 IBD cases, fit the selection criteria. The overall analyses showed no significant association between *H. pylori* and CRC (OR 1.16, 95%CI 0.73 to 1.82, p-value 0.74),

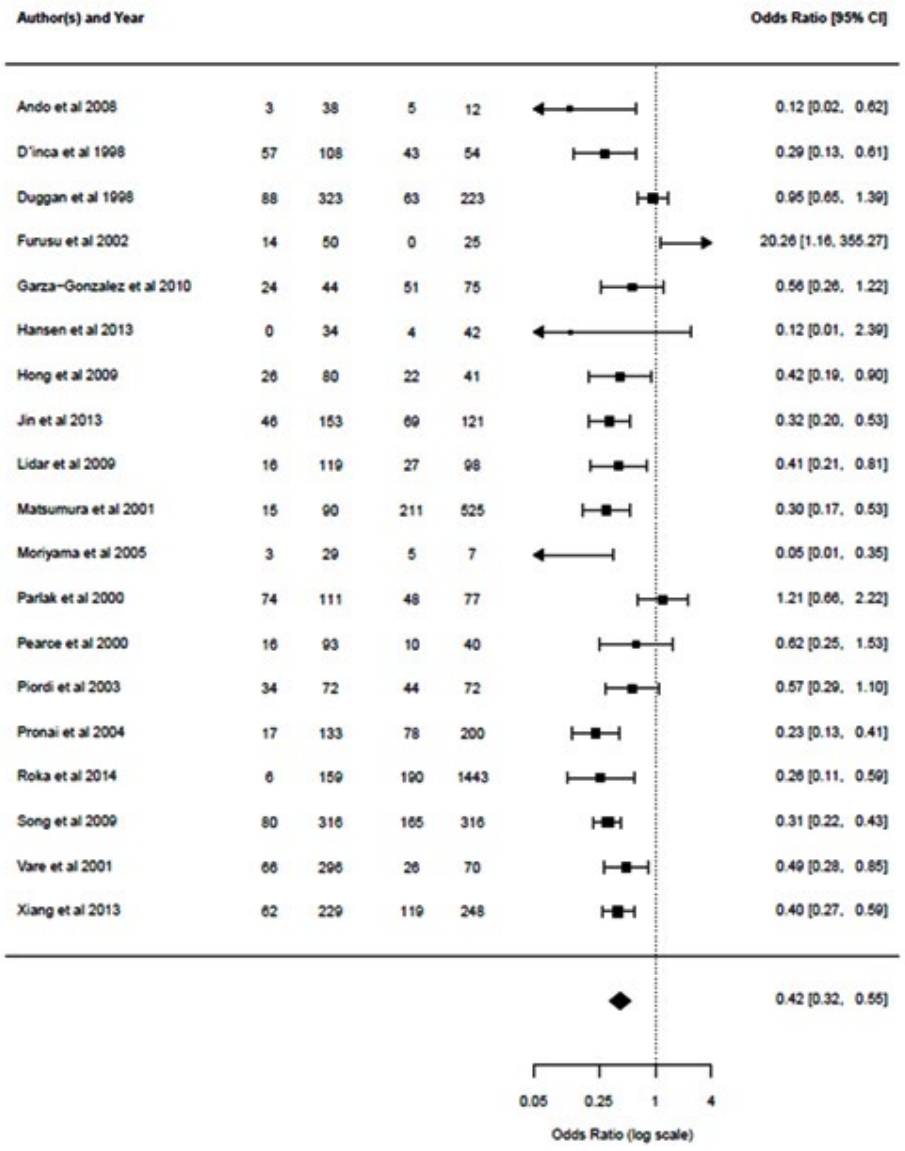

Fig. 4. Forest plot for the pooled OR of H.pylori infection and IBD.

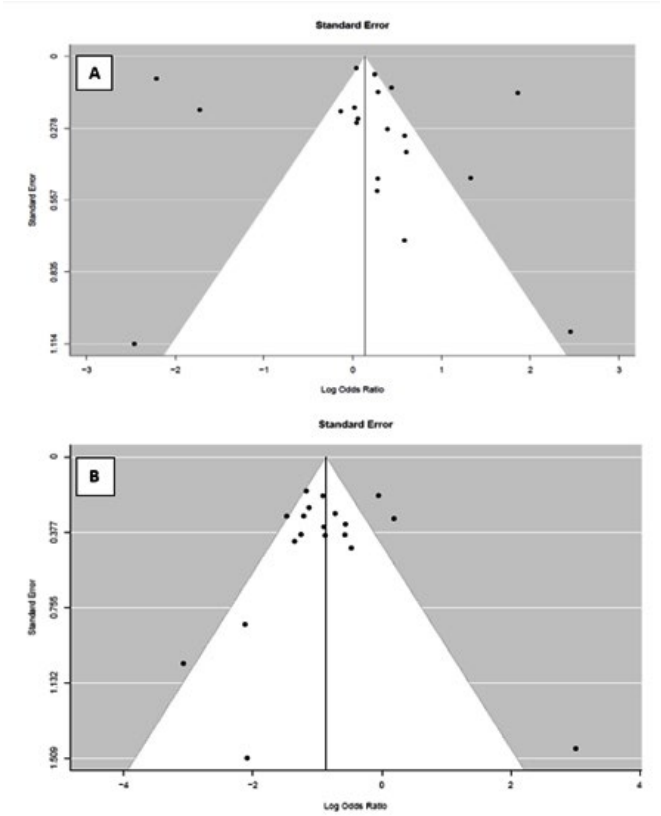

Fig. 5. Funnel plots of the published studies evaluating the association between H.pylori infection and the risk of CRC (A) and IBD (B).

and a negative association between *H. pylori* and IBD (OR 0.42, 95% CI 0.32 to 0.56, p-value ≤0.0001). Moreover, in the present prospective study, no correlation between *H. pylori* and IBD was addressed. Consistently, this study has shown a negative association between *H. pylori* and IBD The mechanism of the protective effect is the production of IL-18 by the suppressive T cells.[71] Another immunoregulatory mechanism has been proposed involving the production of *H. pylori* neutrophil-activating protein, that decreases inflammation by agonist ligation of toll-like receptor 2, and *H. pylori* DNA, that averts sodium dextran sulfate-included colitis in mice.[72]

However, an association was found between sex, age, anatomical location, macroscopic aspect of the tumour in CRA patients and *H. pylori* (P≤0.05). These findings, plus the fact that very few studies have used PCR and histology to identify *H. pylori* in colorectal tissues, lead to the necessity to use more sensitive techniques to detect *H. pylori* in CRC subjects.

Our study presented had several limitations. First, several studies included in our meta-analysis used serological tests that can't distinguish the exact location of *H. pylori*. Second, few have reported the exclusion of patients who have been administrated an *H. pylori* eradication treatment. Third, significant heterogeneity was found across studies, which might be explained by the geographic distribution and detection methods used.[73,74]

CONCLUSION

To the best of our knowledge, this is the first study that assesses the association between IBD and CRC with *H. pylori* infection in Morocco. Our results assert a possible association between *H. pylori* and sex, age, anatomical location and macroscopic aspect of the tumour in CRA patients. In the present meta-analysis, no association between *H. pylori* and CRC was established. Moreover, a negative association between *H. pylori* and IBD was addressed. However, more studies are

needed to investigate the association of *H. pylori* with CRC risk using molecular techniques.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

SC and KB conceptualize and designed the study. KB, SC, SS, MD, KK, MEM, SE, AA and HR collected, generated, assembled, analyzed and interpreted the data and drafted the manuscript. All authors read and approved the final manuscript for publication.

FUNDING

None.

DATA AVAILABILITY

Not applicable.

ETHICS STATEMENT

This study was apporved by the Ethics Committees of the Arrazi Hospital CHU Mohammed VI of Marrakech, Morocco.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer J Clin.* 2018;68(6):394-424. doi: 10.3322/caac.21492.
2. Prashanth R, Tagore S, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factor*. Prz Gastroenterol.* 2019;14(2):89-103.doi: 10.5114/pg.2018.81072
3. Chbani L, Hafid I, Berraho M, Nejjari C, Amarti A. Digestive cancers in Morocco: Fez-Boulemane region. *Pan Afr Med J.* 2012;13:46.
4. Haimer A, Belamalem S, Habib F, Soulaymani A, Abdelrhani M, Hami H. Colorectal Cancer in Morocco: Results of a Retrospec-tive Study. *Biosciences, Biotechnology Research Asia*. 2019;16:79-83. doi:10.13005/bbra/2723
5. Haggar FA, Boushey RP. Colorectal Cancer Epidemiology: Incidence, Mortality, Survival, and Risk Factors. *Clin Colon Rectal Surg.* 2009;22(4):191-197. doi: 10.1055/s-0029-1242458
6. Drewes JL, Housseau F, Sears CL. Sporadic colorectal cancer: microbial contributors to disease prevention, development and therapy. *Br J Cancer.* 2016;115(3):273-280. doi: 10.1038/bjc.2016.189
7. Hope ME, Hold GL, Kain R, El-Omar EM. Sporadic colorectal cancer-role of the commensal microbiota. *FEMS Microbiol Lett.* 2005;244(1):1-7. doi: 10.1016/j.femsle.2005.01.029
8. Wang ZH, Fang JY. Colorectal Cancer in Inflammatory Bowel Disease: Epidemiology, Pathogenesis and Surveillance. *Gastrointest Tumors.* 2014;1(3):146-154. doi: 10.1159/000365309
9. Kim ER, Chang DK. Colorectal cancer in inflammatory bowel disease: the risk, pathogenesis, prevention and diagnosis. *World J Gastroenterol.* 2014;20(29):9872-9881. doi: 10.3748/wjg.v20.i29.9872
10. Brand MI, Church JM. High Risk Premalignant Colorectal Conditions*. Surgical Oncology.* 2003;346-363. doi: 10.1007/0-387-21701-0_38
11. Butt J, Epplein M. *Helicobacter pylori* and colorectal cancer-A bacterium going abroad? *PLOS Pathogens.* 2019;15(8):e1007861. doi: 10.1371/journal.ppat.1007861
12. Cherif S, Bouriat K, Rais H, Elantri S, Amine A. *Helicobacter pylori* and Biliary Tract Cancers: A Meta-Analysis. *Can J Infect Dis Med Microbiol*. 2020;2020:9287157. doi: 10.1155/2020/9287157
13. Cherif S, Rais H, Hakmaoui A, Sellami S, Elantri S, Amine A. Linking *Helicobacter pylori* with gallbladder and biliary tract cancer in Moroccan population using clinical and pathological profiles. *Bioinformation.* 2019;15(10):735-743. doi: 10.6026/97320630015735
14. Tatishchev SF, Vanbeek C, Wang HL. *Helicobacter pylori* infection and colorectal carcinoma: is there a causal association? *J Gastrointest Oncol.* 2012;3(4):380-385. doi: 10.3978/j.issn.2078-6891.2012.058
15. Zumkeller N, Brenner H, Zwahlen M, Rothenbacher D. *Helicobacter pylori* Infection and Colorectal Cancer Risk: A Meta-Analysis. *Helicobacter.* 2006;11(2):75-80. doi: 10.1111/j.1523-5378.2006.00381.x
16. Meucci G, Tatarella M, Vecchi M, et al. High prevalence of *Helicobacter pylori* infection in pa-tients with colonic adenomas and carcinomas. *J Clin Gastroenterol.* 1997;25(4):605-607. doi: 10.1097/00004836-199712000-00011
17. Hartwich J, Konturek SJ, Pierzchalski P, et al. Molecular basis of colorectal cancer - role of gastrin and cyclooxygenase-2. *Med Sci Monit.* 2001;7(6):1171-1181.
18. Breuer-Katschinski B, Nemes K, Marr A, et al. *Helicobacter pylori* and the risk of colonic adenomas. Colorectal Adenoma Study Group. *Digestion*. 1999;60(3):210-215. doi: 10.1159/000007661
19. Butt J, Jenab M, Pawlita M, et al. Antibody responses to *Helicobacter Pylor*i and risk developping colorectal cancer in a European cohort. *Cancer Epidemiol Biomarkers Preven.* 2020;29(7):1475-1481. doi: 10.1158/1055-9965.EPI-19-1545
20. Pronai L, Schandl L, Orosz Z, Magyar P, Tulassay Z. Lower Prevalence of *Helicobacter Pylori* Infection in Patients With Chronic Obstructive Pulmonary

Disease- Antibiotic Use in The History Does Not Play a Significant Role. *Helicobacter*. 2004;9(3):278-283. doi: 10.1111/j.1083-4389.2004.00223.x

21. Farouk WI, Hassan NH, Ismail TR, Daud IS, Mohammed F. Warthin-Starry Staining for the Detection of *Helicobacter pylori* in Gastric Biopsies. *Malays J Med Sci.* 2018;25(4):92-99. doi: 10.21315/mjms2018.25.4.9
22. Wang M, Kong W-J, Zhang J-Z, et al. Association of *Helicobacter pylori* infection with colorectal polyps and malignancy in China. *World J Gastrointest Oncol.* 2020;12(5):582-591. doi: 10.4251/wjgo.v12.i5.582
23. Butt J, Varga MG, Blot WJ, et al. Serologic Response to *Helicobacter pylori* Proteins Associated With Risk of Colorectal Cancer Among Diverse Populations in the United States. *Gastroenterology.* 2019;156(1):175-186. e2. doi: 10.1053/j.gastro.2018.09.054
24. Blase JL, Campbell PT, Gapstur SM, et al. Prediagnostic *Helicobacter pylori* Antibodies and Colorectal Cancer Risk in an Elderly, Caucasian Population. *Helicobacter.* 2016;21(6):488-492. doi: 10.1111/hel.12305
25. Zhang Q-Y, Lv Z, Sun L-P, Dong N-N, Xing C-Z, Yuan Y. Clinical significance of serum markers reflecting gastric func-tion and *H. pylori* infection in colorectal cancer. *J Cancer.* 2019;10(10):2229-2236. doi: 10.7150/jca.27134
26. Roka K, Roubani A, Stefanaki K, Panayotou I, Roma E, Chouliaras G. The Prevalence of *Helicobacter pylori* Gastritis in Newly Diagnosed Children with Inflammatory Bowel Disease. *Helicobacter.* 2014;19(5):400-405. doi: 10.1111/hel.12141
27. Hansen R, Berry SH, Mukhopadhya I, et al. The Microaerophilic Microbiota of De-Novo Paediatric Inflammatory Bowel Disease: The BISCUIT Study. *PLOS ONE.* 2013;8(3):e58825. doi: 10.1371/journal.pone.0058825
28. Jin X, Chen Y-P, Chen S-H, Xiang Z. Association between *Helicobacter Pylori* infection and ulcerative colitis--a case control study from China. *Int J Med Sci.* 2013;10(11):1479-1484. doi: 10.7150/ijms.6934
29. Nam KW, Baeg MK, Kwon JH, et al. *Helicobacter pylori* seropositivity is positively associated with colorectal neoplasms. *Korean J Gastroenterol.* 2013;61(5):259-264. doi: 10.4166/kjg.2013.61.5.259
30. Xiang Z, Chen Y-P, Ye Y-F, et al. *Helicobacter pylori* and Crohn's disease: a retrospective single-center study from China. *World J Gastroenterol.* 2013;19(28):4576-4581. doi: 10.3748/wjg.v19.i28.4576
31. Zhang Y, Hoffmeister M, Weck MN, Chang-Claude J, Brenner H. *Helicobacter pylori* Infection and Colorectal Cancer Risk: Evidence From a Large Population-based Case-Control Study in Germany. *American Journal of Epidemiology.* 2012;175(5):441-450. doi: 10.1093/aje/kwr331
32. Strofilas A, Lagoudianakis EE, Seretis C, et al. Association of *helicobacter pylori* infection and colon cancer. *J Clin Med Res.* 2012;4(3):172-176. doi: 10.4021/jocmr880w
33. Engin AB, Karahalil B, Engin A, Karakaya AE. Oxidative Stress, *Helicobacter pylori*, and OGG1 Ser326Cys, XPC Lys939Gln, and XPD Lys751Gln Polymorphisms in a Turkish Population with Colorectal Carcinoma. *Genetic Testing and Molecular Biomarkers.* 2010;14(4):559-564. doi: 10.1089/gtmb.2009.0195
34. Garza-Gonzalez E, Perez-Perez GI, Mendoza-Ibarra SI, Flores JP-Gutierrez, Bosques-Padilla FJ. Genetic risk factors for inflammatory bowel disease in a North-eastern Mexican population. *Int J Immunogenet*. 2010;37(5):355-359. doi: 10.1111/j.1744-313X.2010.00932.x
35. Hong CH, Park DI, Choi WH, et al. The clinical usefulness of focally enhanced gastritis in Korean patients with Crohn's disease. *Korean J Gastroenterol.* 2009;53(1):23-28.
36. Lidar M, Langevitz P, Barzilai O, et al. Infectious Serologies and Autoantibodies in Inflammatory Bowel Disease. *Ann N Y Acad Sci.* 2009;1173(1):640-348. doi: 10.1111/j.1749-6632.2009.04673.x
37. Song MJ, Park DI, Hwang SJ, et al. The Prevalence of *Helicobacter pylori* Infection in Korean Patients with Inflammatory Bowel Disease, a Multicenter Study. *Korean J Gastroenterol.* 2009;53(6):341-347. doi: 10.4166/kjg.2009.53.6.341
38. Ando T, Watanabe O, Ishiguro K, et al. Relationships between *Helicobacter pylori* infection status, endoscopic, histopathological findings, and cytokine production in the duodenum of Crohn's disease patients. *J Gastroenterol Hepatol.* 2008;23(s2):S193-S197. doi: 10.1111/j.1440-1746.2008.05438.x
39. Bulajic M, Stimec B, Ille T, et al. PCR detection of *helicobacter pylori* genome in colonic mucosa: normal and malignant. *Prilozi.* 2007;28(2):25-38.
40. D'Onghia V, Leoncini R, Carli R, et al. Circulating gastrin and ghrelin levels in patients with colorectal cancer: Correlation with tumour stage, *Helicobacter pylori* infection and BMI. *Biomed Pharmacother.* 2007;61(2):137-141. doi: 10.1016/j.biopha.2006.08.007
41. Jones M, Helliwell P, Pritchard C, Tharakan J, Mathew J. *Helicobacter pylori* in colorectal neoplasms: is there an aetiological relationship? 2007;5:51-. doi: 10.1186/1477-7819-5-51
42. Machida-Montani A, Sasazuki S, Inoue M, et al. Atrophic gastritis, *Helicobacter pylori*, and colorectal cancer risk: a case-control study. *Helicobacter.* 2007;12(4):328-332 doi: 10.1111/j.1523-5378.2007.00513.x
43. Zumkeller N, Brenner H, Chang-Claude J, Hoffmeister M, Nieters A, Rothenbacher D. *Helicobacter pylori* infection, interleukin-1 gene polymorphisms and the risk of colorectal cancer: Evidence from a case-control study in Germany. *Eur J Cancer.* 2007;43(8):1283-1289. doi: 10.1016/j.ejca.2007.03.005
44. Georgopoulos SD, Polymeros D, Triantafyllou K, et al. Hypergastrinemia is associated with increased risk of distal colon adenomas. *Digestion.* 2006;74(1):42-46. doi: 10.1159/000096593
45. Moriyama T, Matsumoto T, Jo Y, et al. Mucosal proinflammatory cytokine and chemokine expression of gastroduodenal lesions in Crohn's disease. *Aliment Pharmacol Ther.* 2005;21(s2):85-91. doi: 10.1111/j.1365-2036.2005.02480.x
46. Pronai L, Schandl L, Orosz Z, Magyar P, Tulassay Z. Lower Prevalence of *Helicobacter pylori* Infection in Patients With Inflammatory Bowel Disease But Not With Chronic Obstructive Pulmonary Disease - Antibiotic

Use in the History Does Not Play a Significant Role. *Helicobacter.* 2004;9(3):278-283. doi: 10.1111/j.1083-4389.2004.00223.x

47. Piodi LP, Bardella M, Rocchia C, Cesana BM, Baldassarri A, Quatrini M. Possible Protective Effect of 5-Aminosalicylic Acid on *Helicobacter pylori* Infection in Patients With Inflammatory Bowel Disease. *J Clin Gastroenterol.* 2003;36(1):22-25. doi: 10.1097/00004836-200301000-00008
48. Limburg PJ, Stolzenberg-Solomon RZ, Colbert LH, et al. Helicobacter Pylori Seropositivity and Colorectal Cancer Risk. A Prospective Study of Male Smokers. 2002;11(10):1095-1099.
49. Furusu H, Murase K, Nishida Y, et al. Accumulation of mast cells and macrophages in focal active gastritis of patients with Crohn's disease. *Hepatogastroenterology.* 2002;49(45):639-643.
50. Siddheshwar RK, Muhammad KB, Gray JC, Kelly SB. Seroprevalence of *Helicobacter Pylori* in Patients With Colorectal Polyps and Colorectal Carcinoma. *Am J Gastroenterol.* 2001;96(1):84-88. doi: 10.1111/j.1572-0241.2001.03355.x
51. Matsumura M, Matsui T, Hatakeyama S, et al. Prevalence of *Helicobacter pylori* infection and correlation between severity of upper gastrointestinal lesions and *H. pylori* infection in Japanese patients with Crohn's disease. *J Gastroenterol.* 2001;36(11):740-747. doi: 10.1007/s005350170015
52. Vare PO, Heikius B, Silvennoinen JA, et al. Seroprevalence of *Helicobacter pylori* Infection in Inflammatory Bowel Disease: Is *Helicobacter pylori* Infection a Protective Factor? *Scand J Gastroenterol.* 2001;36(12):1295-1300. doi: 10.1080/003655201317097155
53. Parlak E, Ulker A, Disibeyaz S, Alkim C, Dagli U. There Is No Significant Increase in the Incidence of *Helicobacter pylori* Infection in Patients With Inflammatory Bowel Disease in Turkey. *J Clin Gastroenterol.* 2001;33(1):87-88. doi: 10.1097/00004836-200107000-00025
54. Pearce CB, Duncan HD, Timmis L, Green JR. Assessment of the prevalence of infection with *Helicobacter pylori* in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2000;12(4):439-443. doi: 10.1097/00042737-200012040-00012
55. Thorburn CM, Friedman GD, Dickinson CJ, Vogelman JH, Orentreich N, Parsonnet J. Gastrin and colorectal cancer: A prospective study. *Gastroenterology.* 1998;115(2):275-280. doi: 10.1016/s0016-5085(98)70193-3
56. D'Inca R, Sturniolo G, Cassaro M, et al. Prevalence of Upper Gastrointestinal Lesions and *Helicobacter pylori* Infection in Crohn's Disease. *Dig Dis Sci.* 1998;43(5):988-992. doi: 10.1023/a:1018870415898
57. Duggan AE, Usmani I, Neal KR, Logan RFA. Appendicectomy, childhood hygiene, *Helicobacter pylori* status, and risk of inflammatory bowel disease: a case control study. *Gut.* 1998;43(4):494-498. doi: 10.1136/gut.43.4.494
58. Kuipers EJ, Grady WM, Lieberman D, et al. Colorectal cancer. *Nat Rev Dis Primers.* 2015;1(1):15065. doi: 10.1038/nrdp.2015.65
59. Hnatyszyn A, Hryhorowicz S, Kaczmarek-Rys M, et al. Colorectal carcinoma in the course of inflammatory bowel diseases. *Hered Cancer Clin Pract.* 2019;17:18. doi: 10.1186/s13053-019-0118-4
60. Stidham RW, Higgins PDR. Colorectal Cancer in Inflammatory Bowel Disease. *Clin Colon Rectal Surg.* 2018;31(3):168-178. doi: 10.1055/s-0037-1602237
61. Dyson JK, Rutter MD. Colorectal cancer in inflammatory bowel disease: what is the real magnitude of the risk? *World J Gastroenterol.* 2012;18(29):3839-3848. doi: 10.3748/wjg.v18.i29.3839
62. Baran B, Ozupek NM, Tetik NY, Acar E, Bekcioglu O, Baskin Y. Difference Between Left-Sided and Right-Sided Colorectal Cancer: A Focused Review of Literature. *Gastroenterology Res.* 2018;11(4):264-273. doi: 10.14740/gr1062w
63. Allali I, Chaqsare S, Boukhatem N et al. A Moroccan Colorectal Cancer Database. 2017;5(3):10-14. http://www.warse.org/IJBMIeH/static/pdf/file/ijbmieh01532017.pdf
64. Raskov H, Burcharth J, Pommergaard HC. Linking Gut Microbiota to Colorectal Cancer. *J Cancer.* 2017;8(17):3378-3395. doi: 10.7150/jca.20497
65. Cavallo P, Cianciulli A, Mitolo V, Panaro MA. Lipopolysaccharide (LPS) of *Helicobacter* modu-lates cellular DNA repair systems in intestinal cells. *Clin Exp Med.* 2011;11(3):171-179. doi: 10.1007/s10238-010-0118-1
66. Ohshima H, Bartsch H. Chronic infections and inflammatory processes as cancer risk factors: possible role of nitric oxide in carcinogenesis. *Mutat Res*. 1994;305(2):253-264. doi: 10.1016/0027-5107(94)90245-3
67. Campbell DI, Thomas JE. *Helicobacter pylori* infection in paeddiatric practice. *Arch Dis Child Educ Pract Ed.* 2005;90(2):25-30. doi: 10.1136/adc.2004.065698
68. Diaz P, Valderrama MV, Bravo J, Quest AFG. *Helicobacter pylori* and Gastric Cancer: Adaptive Cellular Mechanisms Involved in Disease Progression. *Front Microbiol.* 2018;9:5. doi: 10.3389/fmicb.2018.00005
69. Papastergiou V, Karatapanis S, Georgopoulos SD. *Helicobacter pylori* and colorectal neoplasia: Is there a causal link? *World J Gastroenterol.* 2016;22(2):649-658. doi: 10.3748/wjg.v22.i2.649
70. Arnold IC, Hitzler I, Muller A. The Immunomodulatory Properties of *Helicobacter pylori* Confer Protection Against Allergic and Chronic Inflammatory Disorders. *Front Cell Infect Microbiol.* 2012;2:10. doi: 10.3389/fcimb.2012.00010
71. Luther J, Owyang S, Takeuchi T, et al. *Helicobacter pylori* DNA de-creases pro-inflammatory cytokine production by dendritic cells and attenuates dextran sodium sulphate-induced colitis. *Gut.* 2011;60(11):1479-1486. doi: 10.1136/gut.2010.220087
72. Michetti P. Gutjnl. Experimental *Helicobacter pylori* infection in humans: a multitaced challenge. *Gut.* 2004;53(9):1220-1221. doi: 10.1136/gut.2004.042135
73. Choi DS, Seo SI, Shin WG, Park CH. Risk for Colorectal Neoplasia in Patients With *Helicobacter pylori* Infection: Asystematic Review and Meta-analysis. *Clinical and Translational Gastroenterology.* 2020;11(2):E00127. doi: 10.14309/ctg.0000000000000127