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Helicobacter pylori infection, interleukin-1 gene polymorphisms and the risk of colorectal cancer: Evidence from a case-control study in Germany

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ABSTRACT

Helicobacter pylori infection is a strong risk factor for gastric cancer. A positive association with colorectal cancer has also been suggested, but available evidence remains inconclusive. In this population-based case-control study we investigated the association between *H. pylori* seroprevalence and colorectal adenocarcinoma under consideration of pro-inflammatory gene polymorphisms (384 incident cancer patients, 467 matched control subjects). Overall, the *H. pylori* seroprevalence was higher among cases (51%) than among controls (44%), and a positive association between *H. pylori* seroprevalence and colorectal adenocarcinoma risk was found, that persisted after adjustment for known potential confounders, including measures of socioeconomic status (odds ratio (OR) = 1.41; 95% confidence intervals (CI), 1.06–1.87). Presence of specific *H. pylori* cytotoxin-associated gene A (CagA) antibodies did not significantly affect the observed risk. Additionally, a pro-inflammatory genotype did not increase the colorectal cancer risk associated with *H. pylori* infection. *H. pylori* positive subjects carrying the pro-inflammatory genotypes even had a lower risk.

1. Introduction

A key role of *Helicobacter pylori* infection in the development of chronic gastritis, gastric and duodenal ulcer disease and gastric cancer and lymphoma is meanwhile proven.[1–4] Among various microbial virulence factors identified so far, the *H. pylori* cytotoxin-associated gene A (CagA) has been associated with enhanced pathogenicity of the bacterium.[3] Additionally, host genetic factors (e.g. genes which are involved in the host's inflammatory response, for instance the interleukin (IL)-1B gene and interleukin-1 receptor antagonist gene (IL-1RN)), might be of importance in determining the strength and prolongation of the individual immune reaction.[5] El-Omar and colleagues have reported that pro-inflammatory IL-1 host genotypes are associated with risk of gastric cancer and its precursors.[6,7] At present, relatively little is known on the relationship between other gastrointestinal malignancies and cytokine polymorphisms.

An increased prevalence of *H. pylori* infection in patients with colorectal carcinoma (CRC) or colorectal adenoma (CRA) compared to other subjects was reported by some authors and they concluded that *H. pylori* infection may also be a potential risk factor for CRC.[8–10] However, results concerning the association between *H. pylori* status and CRC risk are not consistent, and different authors have reported quite varying estimates.[11–18]

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The aims of the present study were therefore, first, the investigation of the relationship between *H. pylori* seroprevalence and incident colorectal adenocarcinoma risk controlling for known or suspected risk factors for CRC, and taking a virulence marker of this infection into account. Second, an evaluation of the combined effects of *H. pylori* infection and the pro-inflammatory IL-1 gene profiles on CRC risk was performed in order to investigate whether these host polymorphisms may also play a role in pathogenesis of CRC.

2. Materials and methods

2.1. Study population

The overall study population consisted of 540 patients with an incident and histologically confirmed colorectal adenocarcinoma, who agreed to participate and were recruited between January 2003 and June 2004 in the context of a large population-based case-control study, conducted in the southwest of Germany (Rhein-Neckar-Odenwald region) and investigating issues of the etiology, risk factors and prevention of CRC.[19,20] All 22 hospitals in the study region which diagnose and treat patients with CRC agreed to participate in the study.

Inclusion criteria for CRC patients were the following: first residence in the study region, aged 30 years and older, sufficient knowledge of the German language, and physical and mental ability to participate. In addition, a total of 614 control subjects, randomly selected from population registers and frequency-matched to patients according to 5-year age groups, gender, and county of residence, with no history of previous CRC were recruited in the same time period (participation rate 48%).

The study was approved by the ethics committees of the University of Heidelberg. Written informed consent was obtained from all participants.

The current analysis was restricted to participants aged between 30 and 75 years ($n = 851$) in order to avoid a possible misclassification of exposure status, as there is a chance of clearance of *H. pylori* from gastric mucosa in elderly subjects due to the development of atrophic gastritis.

2.2. Data collection

The participating physicians informed eligible patients about the study and attained their signed informed consent to participate, which included the rights to collect and preserve the patients' biological samples (serum and whole blood, eventually a mouthwash), and to forward patients' personal and medical data to the study centre.

Information was obtained by means of a standardised questionnaire during a personal interview, performed by specially trained interviewers. It included details about sociodemographical aspects, lifestyle and dietary habits, medical history and medication, family history of colorectal cancer, and other health related information. Blood samples were obtained for 95% of interviewed patients and 94% of control subjects (it was also possible to participate in the study without giving the agreement to draw blood).

Additionally to the information collected via a face-to-face interview, we collected clinical and histological details related to the CRC diagnosis from hospital charts and pathology records, and validated the subjects' self-reports of previous endoscopies of the large bowel.

2.3. Laboratory analyses

Blood samples were mailed to a central laboratory where they were processed immediately and frozen at −80 °C until further laboratory analysis. All laboratory analyses were performed in blinded fashion by trained personnel.

Specific anti-*H. pylori* IgGs were measured by use of a commercial ELISA (*H. pylori* Screening ELISA, Ravo Diagnostika GmbH, Freiburg, Germany) according to the manufacturer's instructions. Antibodies against *H. pylori* CagA protein were measured by use of the '*H. pylori* p120 (CAG A) ELISA' kit (Ravo Diagnostika GmbH, Freiburg, Germany) as recommended by the manufacturer. Genomic DNA was isolated from whole blood by an alcohol-precipitation based method using the FlexiGene DNA Kit (Qiagen GmbH, Hilden, Germany).

Genotyping of the polymorphisms IL-1B T-31C (rs1143627) and IL1RN A9589T (rs454078) was performed by Pyrosequencing™ technology[21,22] (Biotage, Uppsala, Sweden). Genotyping for IL-1B C-511T (rs16944) was performed by PCR-RFLP. Primer sequences can be obtained from the authors upon request.

2.4. Statistical analysis

To compare *H. pylori* seroprevalence (positive versus borderlines and negative) between cases and control subjects, bivariate comparisons after controlling for age and gender were employed (Chi-square test according to Mantel–Haenszel).

Then multivariable unconditional logistic regression was carried out to compute the odds ratios (OR) and 95% confidence intervals (CI) and estimate the independent association of the *H. pylori* antibody status (alone and in combination with CagA status) with CRC risk, overall and by anatomical subsite (colorectal, colon and rectum separately), and after adjustment for the effects of various potential confounders. The following covariates were included: age (30–59, 60–69, 70–75 years), gender, education level combined from school and occupational education, nationality, smoking status, average lifetime alcohol consumption (>0 to <7.4, 7.4 to 20.6, and >20.6 gram ethanol/day), BMI, average lifetime physical activity based on specific metabolic equivalent (MET) scores according to the Compendium of Physical Activities,[23,24] red meat and cold sausage consumption (low: none or less than once/week, medium: once or more times/week, and high: each day), preparation of red meat, history of diabetes, intake of nonsteroidal anti-inflammatory drugs (NSAIDs), regular use of female hormone-replacement therapy, family history of CRC in first degree relatives, and history of CRC screening. Multi-level variables were transformed into dummy variables (i.e. for k levels, $k - 1$ binary variables were used).

Multivariable analyses were performed with backward variable selection. Matching factors age and gender were always included in the model (control for county did not have any relevant impact on estimated ORs and was therefore omitted), the other covariates were included in the final model only if they contributed significantly to it ($p < 0.05$), or if the exclu-

sion changed the Wald test statistic of the main estimate by more than 10%.

Furthermore, the prevalence of IL-1RN and IL-1B gene polymorphisms in the study population, as well as the combined effects of the pro-inflammatory interleukin gene profiles and *H. pylori* infection on CRC risk (effect modification) were evaluated. Possible effect modification by pro-inflammatory interleukin gene profiles was assessed in the final model of the multivariable logistic regression analysis by testing for significance of interaction product terms between *H. pylori* seropositivity and IL-1RN or IL-1B gene profiles.

For all analyses a two-sided p-value of < 0.05 was considered statistically significant. Statistical analyses were performed using the SAS statistical software package (SAS version 8.2, Cary, NC (USA), SAS Institute Inc.1999).

3. Results

3.1. Characteristics of the study population

A total of 851 participants (384 cases and 467 controls), aged 30 to 75 years and in whom *H. pylori* serological status could be determined, were included in this analysis. Main sociodemographic, lifestyle and medical characteristics of the participants are shown in Table 1.

From a total of 384 patients with CRC, 220 (57%) had colon cancer, and 164 (43%) of the cancers were located in the rectum. The respective distribution in males was 53% (colon) and 47% (rectum); the majority of females (65%) had a colon carcinoma, whereas 35% had a carcinoma located in the rectum. According to TNM classification, 20% of CRC patients had a localised carcinoma, 25% of CRC patients a tumour with regional direct extension, and 20% with one to three affected regional lymph nodes. Only 8% of patients had more than three affected regional lymph nodes and 16% had distant metastases.

3.2. H. pylori serostatus and CagA seroprevalence

Overall, the prevalence of seropositivity to *H. pylori* was higher in CRC patients than in control subjects (51% versus 44%, $p = 0.052$ after controlling for age and gender) (see Table 2). The patterns were similar in females and males, although the difference between CRC cases and controls did not reach statistical significance in both strata.

The prevalence of CagA-positive *H. pylori* strains was not different in a statistically significant way between patients and controls (overall 35% versus 31%, respectively; $p = 0.32$ after controlling for age and gender).

Of 399 *H. pylori* seropositive subjects, 251 (63%) had also antibodies against CagA and 148 (37%) subjects were found to be CagA-negative. Among *H.pylori*-negative persons ($n = 452$), 31 (7%) subjects were found to have CagA antibodies (a possible indication of past *H. pylori* exposure), and 421 (93%) were CagA-negative (data not shown). Proportions were similar among cases and controls.

Table 3 presents the results for the association between *H. pylori* infection and colorectal adenocarcinoma obtained by multivariable logistic regression analyses. After control for age and gender the overall risk estimate for CRC associated with *H. pylori* seropositivity was 1.32 (95% CI, 1.01–1.73). For colon cancer the OR was 1.25 (95% CI, 0.90–1.72), and for rectal cancer the OR was 1.43 (95% CI, 1.00–2.07). In the fully adjusted model the overall OR for CRC increased to 1.41 (95% CI, 1.06–1.87). Similar results were seen in the analysis with respect to anatomical subsite: for colon cancer the OR increased to 1.35 (95%CI, 0.96–1.90) and for rectal cancer to 1.51 (95% CI, 1.04–2.18). In the analysis with respect to gender (data not shown), the risk estimate for CRC associated with *H. pylori* seropositivity was 1.60 (95% CI, 1.01–2.55) in females and 1.30 (95% CI, 0.91–1.86) in males. However, the assessment of a possible effect modification by gender with *H. pylori* seropositivity showed no statistically significant interaction ($p = 0.51$ for interaction term).

Furthermore, the overall risk estimate for CRC associated with *H. pylori* and CagA status combined showed that CagA-positive subjects had no significant risk elevations for CRC as compared with CagA-negative subjects in this study population (see Table 3). Similar results were obtained in stratified analyses with respect to anatomical subsite and gender.

3.3. IL-1RN and IL-1B pro-inflammatory gene profiles

The distributions of IL-1RN and IL-1B (position −511 and −31) gene polymorphisms in the study population according to case-control status are shown in Table 4. An almost complete linkage disequilibrium between polymorphism at −511 and −31 was found. No statistical significant differences in the distributions of the individual interleukin gene polymorphisms between patients and controls were found in the analysis adjusted for age and gender (subjects homozygous for pro-inflammatory allele were grouped against all other allele constellations), and adjustment for additional covariates did not significantly alter the results (data not shown). This was also the case in analyses, stratified by anatomical subsite and gender.

3.4. Assessment of effect modification of the association between H. pylori infection and CRC by IL-1RN and IL-1B gene profiles

To assess a possible effect modification by interleukin gene polymorphisms, multivariable logistic regression analysis using the final model was repeated (overall, subsite- and gender-specific) including the interaction product terms between *H. pylori* seropositivity and IL-1RN or IL-1B gene profiles. As shown in Table 5, the estimate for overall comparison of the group of *H. pylori*-positive subjects with pro-inflammatory TT allele of IL-1RN versus all other combinations was of borderline statistical significance ($p = 0.07$ for interaction term). Seropositive subjects with the pro-inflammatory IL-1RN-TT polymorphism had a lower risk compared to seropositive subjects with another IL-1RN genotype profile. This was especially evident for rectum cancer ($p = 0.04$ for interaction term) in the stratified analysis. Additionally, *H. pylori*-positive female carriers of pro-inflammatory genotype TT of IL-1B-511 and pro-inflammatory genotype CC of IL-1B-31 gene were likewise found to have some risk reduction for CRC.

Table 1 – Demographic, lifestyle and medical characteristics of the study population by case-control status

	CRC patients *n* (%)	Controls *n* (%)
n	384	467
Gender		
Female (*n* = 340)	144 (37%)	196 (42%)
Male (*n* = 511)	240 (63%)	271 (58%)
Age, yrs		
Mean (SD)	64.0 (7.7)	63.5 (8.1)
Range	37–75	34–75
Nationality		
German, country of birth Germany	304 (79%)	371 (79%)
German, country of birth other	70 (18%)	89 (19%)
Other than German	10 (3%)	7 (2%)
Family status married	301 (78%)	374 (80%)
Level of education		
Low	246 (64%)	264 (56%)
Intermediate	78 (20%)	115 (25%)
High	62 (16%)	88 (19%)
Average lifetime alcohol consumption among drinkers (gram/day)		
Mean (SD)	20.8 (19.1)	19.9 (21.4)
Smoking status[a]		
Never smoker	166 (43%)	220 (47%)
Ex-smoker	148 (39%)	177 (38%)
Current smoker	70 (18%)	70 (15%)
Body mass index (kg/m^2), mean (SD)	26.5 (4.5)	27.1 (4.0)
Underweight (<18.5)	13 (3%)	2 (<1%)
Normal weight (18.5 – <25.0)	129 (34%)	142 (30%)
Overweight (25.0 – <30.0)	156 (41%)	224 (48%)
Obesity (⩾30.0)	82 (22%)	99 (21%)
Average lifetime physical activity[b] (MET-hours/week)		
<156.0	90 (24%)	107 (23%)
156.0–<240.0	84 (22%)	121 (26%)
240.0–342.0	84 (22%)	118 (25%)
>342.0	123 (32%)	121 (26%)
Red meat consumption		
Low	37 (10%)	52 (11%)
Medium	298 (77%)	379 (81%)
High	49 (13%)	36 (8%)
Cold sausage consumption (processed meat)		
Low	56 (15%)	84 (18%)
Medium	221 (57%)	297 (64%)
High	107 (28%)	86 (18%)
History of diabetes[c]		
No	323 (84%)	421 (90%)
Yes	60 (16%)	46 (10%)
History of peptic ulcer[d]		
No	323 (84%)	400 (86%)
Yes	58 (15%)	64 (14%)
History of H. pylori eradication[e]		
No	362 (94%)	437 (94%)
Yes	19 (5%)	30 (6%)
History of colorectal cancer screening		
Yes	310 (81%)	412 (88%)
No	74 (19%)	55 (12%)
Regular use of NSAIDS[f]		
Never	279 (73%)	298 (64%)
Ever	105 (27%)	169 (36%)
Regular use of HRT[g] (females only, *n* = 340)		
Never	88 (61%)	73 (37%)
Ever	56 (39%)	123 (63%)

a Ever smokers were defined as having smoked more than 100 cigarettes in lifetime; ex-smokers were defined as having stopped smoking for more than 2 years.
b Data for three cases were unknown.
c Data for one case was unknown.
d Data for three cases and three controls were unknown.
e Data for three cases were unknown.
f Nonsteroidal anti-inflammatory drugs, at least once per month for at least 1 year.
g Hormone replacement therapy.

4. Discussion

In our analysis, which was based on a large population-based case-control study and included 384 CRC patients and 467 controls aged between 30 and 75 years, a weak positive association between *H. pylori* infection and the risk of CRC was found, that persisted after consideration and adjustment for known potential confounders, including measures of socioeconomic status (OR = 1.41; 95% CI, 1.06 – 1.87). However, *H. pylori* CagA-positive strains did not significantly affect the observed CRC risk compared with CagA-negative strains in this study population. Additionally, a pro-inflammatory genotype did not increase the colorectal cancer risk associated with *H. pylori* infection. *H. pylori* positive subjects carrying the pro-inflammatory genotypes even had a lower risk.

The findings with respect to *H. pylori* infection are consistent with results from some prior, although less comprehensive, epidemiological studies. A limited number of epidemiological studies have previously examined the relationship between *H. pylori* infection and CRC or colorectal adenoma risk with varying, inconsistent results.[8–18] Most of the studies were based on a relatively small number of cases and controls (eight from 11 studies included less then 100 cases). The ORs for colorectal carcinoma or adenoma associated with *H. pylori* infection ranged between 0.74 (95% CI, 0.28–1.96)[11] and 3.78 (95% CI, 1.51–9.50).[10] In a systematic review and meta-analysis of so far published evidence[25] a summary OR of 1.40 (95% CI, 1.10–1.80) was estimated for the association between *H. pylori* infection and the risk for colorectal carcinoma or adenoma (which is in line with results of the present study), with an indication of possible publication bias and heterogeneity by study design with less pronounced associations for prospective studies.

Table 2 – H. pylori IgG (H. pylori +) and CagA (CagA +) seroprevalence in CRC patients and controls

	CRC patients (n = 384) n (%)		Controls (n = 467) n (%)		p-value
	H. pylori +	CagA +	*H. pylori* +	CagA +	
Overall	195 (51%)	135 (35%)	204 (44%)	147 (31%)	
<50 yrs	5 (26%)	6 (32%)	11 (37%)	10 (33%)	
50–59 yrs	35 (45%)	29 (38%)	37 (41%)	25 (28%)	
60–69 yrs	100 (51%)	76 (39%)	100 (44%)	68 (30%)	
70–75 yrs	55 (59%)	24 (26%)	56 (46%)	44 (36%)	0.052[a] 0.32[b]
Females	68 (47%)	41 (28%)	77 (39%)	55 (28%)	
<50 yrs	2 (25%)	3 (38%)	3 (27%)	4 (36%)	
50–59 yrs	12 (39%)	8 (26%)	17 (45%)	10 (26%)	
60–69 yrs	36 (52%)	23 (33%)	35 (37%)	24 (26%)	
70–75 yrs	18 (50%)	7 (19%)	22 (42%)	17 (32%)	0.14[c] 0.93[d]
Males	127 (53%)	94 (39%)	127 (47%)	92 (34%)	
<50 yrs	3 (27%)	3 (27%)	8 (42%)	6 (32%)	
50–59 yrs	23 (50%)	21 (46%)	20 (38%)	15 (29%)	
60–69 yrs	64 (51%)	53 (42%)	65 (49%)	44 (33%)	
70–75 yrs	37 (65%)	17 (30%)	34 (50%)	27 (40%)	0.19[c] 0.24[d]

a For difference in *H. pylori* serostatus between CRC cases and controls after controlling for age and gender.
b For difference in CagA serostatus between CRC cases and controls after controlling for age and gender.
c For difference in *H. pylori* serostatus between CRC cases and controls after controlling for age.
d For difference in CagA serostatus between CRC cases and controls after controlling for age.

Table 3 – Overall and subsite-specific associations between H. pylori (HP) seropositivity and colorectal adenocarcinoma after adjustment for covariates

	OR (95% CI)		
	Colorectal cancer (n = 384)	Colon cancer (n = 220)	Rectum cancer (n = 164)
Partly adjusted model[a]			
H. pylori status (IgG)			
Negative	reference	reference	reference
Positive	1.32 (1.01–1.73)	1.25 (0.90–1.72)	1.43 (1.00–2.05)
H. pylori and CagA status combined			
HP– and CagA–	reference	reference	reference
HP+ and CagA–	1.42 (0.97–2.07)	1.27 (0.81–1.98)	1.64 (1.00–2.68)
HP (any) and CagA+	1.27 (0.94–1.73)	1.20 (0.83–1.72)	1.39 (0.93–2.08)
Fully adjusted model[b]			
H. pylori status (IgG)			
Negative	reference	reference	reference
Positive	1.41 (1.06–1.87)	1.35 (0.96–1.90)	1.51 (1.04–2.18)
H. pylori and CagA status combined			
HP– and CagA–	reference	reference	reference
HP+ and CagA–	1.46 (0.98–2.16)	1.30 (0.82–2.08)	1.72 (1.03–2.85)
HP (any) and CagA+	1.34 (0.98–1.84)	1.31 (0.89–1.92)	1.45 (0.96–2.21)

a Odds ratios adjusted for age and gender.
b Odds ratios adjusted for age, gender, BMI, colorectal cancer screening, diabetes, hormone-replacement therapy use (in females only).

In contrast to two smaller earlier studies,[10,14] which have reported a positive association between CagA-positive *H. pylori* strains and CRC, the prevalence of CagA-positive *H. pylori* strains in our study population was only slightly higher in patients (35%) than in control subjects (31%), but was not different between both groups in a statistically significant way. These findings are consistent with results from a study by Limburg and colleagues,[16] and likewise do not provide any evidence that possible carcinogenicity of *H. pylori* for the large intestine could be related to its CagA virulence factor.

No statistically significant associations were found among any of the individual hosts' genetic polymorphisms and colo-

Table 4 – Prevalence of IL-1RN and IL-1B gene polymorphisms by case-control status in the study population

	CRC patients *n* (%)	Controls *n* (%)	OR (95% CI)[a] for CRC
n	384	467	
IL-1RN[b]			
AA	192 (53%)	249 (55%)	1.23 (0.72–2.11)
AT	141 (39%)	179 (39%)	
TT	28 (8%)	29 (6%)	
IL-1B-511[c]			
CC	165 (45%)	202 (44%)	0.97 (0.63–1.51)
CT	158 (44%)	206 (45%)	
TT	41 (11%)	51 (11%)	
IL-1B-31[d]			
TT	163 (45%)	207 (45%)	0.98 (0.63–1.51)
TC	160 (44%)	202 (44%)	
CC	42 (11%)	52 (11%)	

a Odds ratio adjusted for age and gender; the pro-inflammatory allele of each gene versus the all other allele constellations summarised.
b For *n* = 33 unknown; AA = wild type, TT = pro-inflammatory allele.
c For *n* = 28 unknown; CC = wild type, TT = pro-inflammatory allele.
d For *n* = 25 unknown; TT = wild type, CC = pro-inflammatory allele.

rectal cancer risk. This finding is consistent with results from a very recent study, evaluating the role of several pro-inflammatory cytokine gene polymorphisms (e.g. IL-1B) in colorectal cancer.[26] Additionally, our results do not support the hypothesis that carrying the pro-inflammatory allele of IL-1RN in combination with *H. pylori* infection may act synergistically to increase the CRC risk, as it has been previously shown for gastric cancer and its precursors.[7,27,28]

The strengths of the present study include its population-based design and the relatively large study collective of incident, clinically diagnosed and histological confirmed colorectal adenocarcinoma cases. The sample size of 384 CRC patients and 467 control subjects was sufficient to detect an OR of 1.5-fold or larger for an association of *H. pylori* infection with CRC with a power of 80% at the 5% level of significance. In addition, controls were frequency-matched according to age and gender, and recruited from the same geographical area during the same time period. To our knowledge, this is the first study, investigating the joint effects of the pro-inflammatory IL-1 gene profiles and *H. pylori* infection on CRC risk.

However, several potential weaknesses of this study should also be considered. Although we tried to maximise our recruitment efforts, the low participation rate for full face-to-face interview (48%) among potential control subjects is less than optimal. Furthermore, only about 50% of the expected total number of incident eligible cases during the study period were recruited. The relatively low participation rate among patients may, however, reflect mainly the busy situation in the participating clinics and incompleteness of recruitment by some clinicians (which is unlikely to be a relevant source of selection bias), rather than the patient characteristics.

Recall bias also cannot be excluded in this study, since cancer patients may be more likely to incorrectly report (over-report) the information which seems to be directly relevant to their cancer diagnosis. However, considering that the main variable (exposure) in the present analysis was *H. pylori* infection serostatus, which was determined in blinded fashion by means of the laboratory measurements, the problem

Table 5 – Assessment of effect modification of the association between H. pylori (HP) infection and colorectal adenocarcinoma by interleukin gene profiles

Interaction product term	OR (95% CI)[a]				
	All cases versus all controls	Colon cancer cases versus controls	Rectum cancer cases versus controls	Male cases versus male controls	Female cases versus female controls
H. pylori status IL1RN gene profile*					
HP– and IL-1RN-others	1.00[Ref]	1.00[Ref]	1.00[Ref]	1.00[Ref]	1.00[Ref]
HP+ and IL-1RN-others	1.21	1.18	1.26	1.16	1.30
HP– and IL-1RN-TT	1.47	1.33	1.65	1.44	1.54
HP+ and IL-1RN-TT	1.04 $p = 0.07$[b]	1.13 $p = 0.34$[b]	0.83 $p = 0.04$[b]	0.92 $p = 0.13$[b]	1.21 $p = 0.28$[b]
H. pylori status IL-1B-511 gene profile*					
HP– and IL-1B-511-others	1.00[Ref]	1.00[Ref]	1.00[Ref]	1.00[Ref]	1.00[Ref]
HP+ and IL-1B-511-others	1.20	1.18	1.22	1.10	1.38
HP– and IL-1B-511-TT	1.10	1.11	1.05	0.96	1.31
HP+ and IL-1B-511-TT	1.04 $p = 0.31$[b]	0.99 $p = 0.34$[b]	1.09 $p = 0.59$[b]	1.17 $p = 0.71$[b]	0.45 $p = 0.02$[b]
H. pylori status IL-1B-31 gene profile*					
HP– and IL-1B-31-others	1.00[Ref]	1.00[Ref]	1.00[Ref]	1.00[Ref]	1.00[Ref]
HP+ and IL-1B-31-others	1.20	1.19	1.22	1.11	1.38
HP– and IL-1B-31-CC	1.10	1.13	1.04	0.99	1.27
HP+ and IL-1B-31-CC	1.04 $p = 0.29$[b]	0.99 $p = 0.30$[b]	1.09 $p = 0.61$[b]	1.18 $p = 0.81$[b]	0.45 $p = 0.03$[b]

a Odds ratios adjusted for age, gender, BMI, colorectal cancer screening, diabetes, hormone-replacement therapy use (in females only).
b *p*-value for the interaction product term (for comparison of the group of *H. pylori* positive subjects with pro-inflammatory allele versus all others).

of possible recall bias can only reflect the accuracy of various self-reported variables.

In conclusion, our findings demonstrate a weak though statistically significant increased risk of CRC among subjects with *H. pylori* infection, which persisted after adjustment for other known or suspected risk factors for colorectal cancer. In contrast to results for gastric cancer, a pro-inflammatory genotype does not increase the risk for CRC associated with *H. pylori* infection.

Conflict of interest statement

None declared.

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