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Helicobacter pylori infection increases the risk of colorectal adenoma and adenocarcinoma, especially in women

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Background. Recent reports suggest that *Helicobacter pylori* infection can potentially increase the risk of colorectal cancer. The purpose of this study was to assess the association between *H. pylori* infection and the risk of colorectal adenoma and adenocarcinoma, and to evaluate any differences on the basis of sex. ***Methods.*** The subjects were 669 (40- to 80-year-old) patients who underwent both barium enema examination and total colonoscopy, and who were evaluated for *H. pylori* infection by ^{13}C-urea breath test, urease test, or histological diagnosis of biopsied gastric specimens. There were 142 *H. pylori*-negative and 527-positive patients. The odds ratios (ORs) for *H. pylori*-positive patients with colorectal adenoma and adenocarcinoma, and for tumor patients with either adenoma or adenocarcinoma were calculated. ***Results.*** Among the *H. pylori*-negative patients, there were 52 patients without tumor, 63 with adenoma, 27 with adenocarcinoma, and 90 with tumor. Among the *H. pylori*-positive patients, there were 136, 264, 127, and 391 patients respectively. Pooling all subjects, those infected with *H. pylori* had a significantly increased OR for adenoma, adenocarcinoma, or tumor, compared to *H. pylori*-free patients (OR, 1.60, 1.80, and 1.66, respectively). For female *H. pylori*-positive subjects, the risk of having adenocarcinoma or tumor was significantly higher than that for their *H. pylori*-free counterparts, while for male *H. pylori*-positive and -negative subjects, there was no such significant difference. ***Conclusions.*** The results therefore suggest that, in patients aged 40–80 years, *H. pylori* infection increased the risk of colorectal adenoma and adenocarcinoma, with significantly higher risks for female patients.

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Introduction

There is a high possibility that *Helicobacter pylori* infection is associated with the development of gastric cancer.[1,2] It has been reported that *H. pylori* can be cultivated uniformly from cathartic stools [3–5] and vacuolating *H. pylori* toxin has been observed in human stool samples.[6] Many studies have shown that *H. pylori* infection is associated with rises in serum gastrin levels.[7–10] Furthermore, several endocrinological studies suggest that hypergastrinemia is associated with rectal cell proliferation[11] and that it stimulates the growth of colon cancer cell lines,[12] promotes the proliferation of colonic adenomas,[13] and promotes progression through the adenoma-carcinoma sequence.[14] These results suggest that *H. pylori* infection can potentially increase the risk of colorectal cancer.

A few studies have reported that colonic neoplastic lesions, especially adenomas, are associated with an increased prevalence of *H. pylori* infection.[15–19] A case-control study reported that *H. pylori* infection increased the risk of colonic adenoma.[20] On the other hand, recent studies have shown no relationship between *H. pylori* infection and the development of colorectal neoplasia.[21,22] Thus, results to date have been conflicting concerning the association of *H. pylori* infection with the development of colorectal neoplasia. However, there are no reports with a sufficient number of patients for satisfactory analysis, or studies investigating the relationship between sex and colorectal neoplasia in *H. pylori*-infected patients. The purpose of this study was therefore to assess the association between *H. pylori* infection and the risk of colorectal adenoma and adenocarcinoma, and to clarify any sex-based differences.

Table 1. *Helicobacter pylori* status in study subjects

Sex		*H. pylori*-positive (%)	*H. pylori*-negative (%)	Total
Male	No.	392 (83.4%)	78 (16.6%)	470
	Age (years)	61.4 ± 9.4	61.5 ± 10.1	61.4 ± 9.5
Female	No.	135 (67.8%)	64 (32.2%)	199
	Age (years)	60.0 ± 9.5	60.3 ± 10.2	60.1 ± 9.7
Total	No.	527 (78.8%)	142 (21.2%)	669

Eligible study patients were those 40–80 years old who had undergone both barium enema examination and total colonoscopy. Patients were evaluated for *H. pylori* infection using the ^{13}C-urea breath test, urease test, and histological diagnosis of biopsied gastric specimens

Patients and methods

Eligible patients

This study was performed at the Chiba Hokusou Hospital of Nippon Medical School from January 1996 through December 2003. At this hospital, a total of 6852 subjects were checked for *H. pylori* infection for the duration of this study. There were 3137/3840 (81.7%) male and 2205/3012 (73.2%) female *H. pylori*-positive subjects. The medical records of all subjects were analyzed for data regarding any colorectal lesions; 742 subjects were examined for colorectal lesions by barium enema examinations and colonoscopy within 3 years of checking for *H. pylori* infection. From this group were excluded: patients with inflammatory bowel disease, gastrointestinal polyposis, history of malignancies, history of *H. pylori* eradication therapy before colonoscopy, and those less than 40 or older than 80 years of age. Finally, 699 patients (male, 470; female, 199) were considered eligible for this study (Table 1). There were 392 (83.4%) male and 135 (67.8%) female *H. pylori*-positive patients. All subjects gave informed consent before participation. This study was approved by the Ethics Committee at Nippon Medical School.

Diagnosis of colorectal lesions

Patients with positive immunologic fecal occult blood tests, or suspected of having colorectal lesions at the time of screening, underwent barium enema examinations. All patients suspected of having colorectal lesions based on barium enema examinations underwent total colonoscopy. Colonoscopy was performed jointly by staff gastroenterologists. A colonoscope (Olympus, Tokyo, Japan) was inserted into the cecum, except in patients with advanced adenocarcinoma. All polypoid lesions found at colonoscopy, advanced lesions included, were biopsied, polypectomized, or removed by mucosal resection, and then immediately fixed in 10% formalin. After formalin treatment, specimens were stained with hematoxylin-eosin, and examined by light microscopy. Routine histological evaluation was performed by staff pathologists at our hospital. Adenocarcinoma in adenoma was defined as adenoma. Patients with hyperplastic polyps were defined as patients without tumor. Patients with adenoma and adenocarcinoma were defined as patients with adenocarcinoma. Patients with either adenoma or adenocarcinoma were defined as patients with tumor. Most of the patients with adenocarcinoma received a surgical operation and their diagnoses were confirmed.

Diagnosis of H. pylori infection

Patients were selected from a general pool of subjects who underwent routine upper gastrointestinal endoscopy for current or past abdominal complaints, and who were then also checked for *H. pylori* infection if diagnosed with gastritis (55%), gastric and duodenal ulcers (14%), or by patient request (20%). *H. pylori* infection was diagnosed by at least one method; the ^{13}C-Urea breath test, rapid urease test, or histological diagnosis of biopsied gastric specimens. UBIT (Otsuka Pharmaceutical, Tokyo, Japan) was used for ^{13}C-Urea breath tests. Samples of the ^{13}C-Urea breath test were analyzed by a single regional laboratory (Biomedical Laboratory [BML], Tokyo, Japan) and assayed by our staff medical technologists. The cutoff value of the ^{13}C-Urea breath test was 2.5‰. Helicocheck (Otsuka Pharmaceutical) was used for the rapid urease test of gastric mucosal specimens. The specimens were diagnosed for *H. pylori* infection by staff pathologists in our hospital. Gastric specimens not adequate for proper *H. pylori*-infection diagnosis were excluded from the study.

Data analysis

Data values are expressed as mean values ± SD. The proportion of *H. pylori*-infected and -uninfected patients with colorectal adenoma, adenocarcinoma, or tumor was compared by odds ratios (ORs) and 95% confidence intervals (CI), calculated by logistic regression analysis adjusting for age. *H. pylori* positivity in patients without tumor, with adenoma, with adenocarci-

Table 2. Odds ratios for adenoma, adenocarcinoma, and tumors for all patients

H. pylori		Without tumor	With tumor		
			Adenoma	Adenocarcinoma	Total
Negative	No.	52	63	27	90
	Age (years)	60.1 ± 10.3	60.3 ± 9.9	64.0 ± 10.1	61.4 ± 10.1
Positive	No.	136	264*	127*	391**
	Age (years)	59.5 ± 9.7	61.5 ± 9.2	61.6 ± 9.5	61.5 ± 9.3
Odds ratio		1.0	1.60	1.80	1.66
CI		Referent	1.18–2.02	1.28–2.32	1.27–2.05

Significant differences, $*P = 0.028$; $**P = 0.011$
Values are means ± SD
CI, 95% confidence interval
P value: versus patients without tumor, adjusted for age by means of logistic regression analysis

Table 3. Odds ratios for adenoma, adenocarcinoma, and tumors for male patients

H. pylori		Without tumor	With tumor		
			Adenoma	Adenocarcinoma	Total
Negative	No.	20	46	12	58
	Age (years)	60.0 ± 10.8	61.7 ± 10.0	63.4 ± 9.6	62.0 ± 9.9
Positive	No.	89	222	81	303
	Age (years)	60.0 ± 9.6	61.3 ± 9.3	63.1 ± 9.2	61.8 ± 9.3
Odds ratio		1.0	1.08	1.52	1.17
CI		Referent	0.50–1.66	0.74–2.30	0.61–1.73

Values are means ± SD
CI, 95% confidence interval
P value, versus patients without tumor, adjusted for age by means of logistic regression analysis. There were no significant differences

noma, or with tumor was compared by Fisher's exact test. The localizations of adenoma and adenocarcinoma in the large bowel were compared between *H. pylori*-positive and -negative patients by the χ^2 test. *P* values of less than 0.05 were considered significant.

Results

The subjects were divided into eight groups, as follows: *H. pylori*-infected or -uninfected subjects without tumor, with adenoma, with adenocarcinoma, or with tumor, this last category including patients with either adenoma or adenocarcinoma. *H. pylori*-negative patients consisted of 52 without tumor, 63 with adenoma, 27 with adenocarcinoma, and 90 with tumor; compared to *H. pylori*-positive patients, in whom 136 were without tumor, 264 with adenoma, 127 with adenocarcinoma, and 391 with tumor. The rates of *H. pylori*-positivity in patients without tumor, with adenoma, with adenocarcinoma, and with tumor were 72.3%, 80.7% ($P = 0.037$), 82.5% ($P = 0.029$), and 81.3% ($P = 0.015$), respectively. ORs (*P* value adjusting for age; 95% CI) for all *H. pylori*-infected subjects with adenoma, adenocarcinoma, and tumor were 1.60 ($P = 0.028$; 1.18–2.02), 1.80 ($P = 0.028$; 1.28–2.32), and 1.66 ($P = 0.011$; 1.27–2.05), respectively, compared to *H. pylori*-free subjects (Table 2).

We next evaluated the effect of *H. pylori* infection on ORs for colorectal tumors in male subjects only (Table 3). There were 20 subjects without tumor, 46 with adenoma, 12 with adenocarcinoma, and 58 with tumor among the *H. pylori*-negative patients; and 89 subjects without tumor, 222 with adenoma, 81 with adenocarcinoma, and 303 with tumor among the *H. pylori*-positive patients. The rates of *H. pylori* positivity in male patients without tumor, with adenoma, with adenocarcinoma, and with tumor were 74.7%, 82.8% ($P = 0.77$), 87.0% ($P = 0.34$), and 83.9% ($P = 0.56$), respectively. Although ORs for adenoma, adenocarcinoma, and tumor were 1.08, 1.52, and 1.17 in male subjects infected with the *H. pylori*, these values did not vary significantly from *H. pylori*-free scores.

Female patients were similarly divided and their risk of having colorectal tumor development was calculated on the basis of *H. pylori* infection (Table 4). There were 32 female subjects without tumor, 17 with adenoma, 15 with adenocarcinoma, and 32 with tumor among the *H.*

Table 4. Odds ratios for adenoma, adenocarcinoma, and tumors for female patients

H. pylori		Without tumor	With tumor		
			Adenoma	Adenocarcinoma	Total
Negative	No.	32	17	15	32
	Age (years)	60.2 ± 10.1	56.7 ± 9.0	64.4 ± 10.8	60.3 ± 10.5
Positive	No.	47	42	46*	88**
	Age (years)	58.6 ± 9.8	62.7 ± 8.6	59.0 ± 9.6	60.8 ± 9.8
Odds ratio		1.0	1.68	2.09	1.87
CI		Referent	0.96–2.40	1.35–2.83	1.27–2.47

Significant differences: *$P = 0.048$; **$P = 0.040$
Values are means ± SD
CI, 95% confidence interval
P value: versus patients without tumor, adjusted for age by means of logistic regression analysis

Table 5. Location of adenomas

H. pylori	C	A	T	D	S	R	Total
Negative	4 (4/0)	21 (17/4)	31 (27/4)	21 (18/3)	32 (24/8)	20 (14/6)	129 (104/25)
Positive	16 (15/1)	69 (57/12)	130 (108/22)	70 (62/8)	182 (156/26)	82 (71/11)	549 (469/80)
Total	20 (19/1)	90 (74/16)	161 (135/26)	91 (80/11)	214 (180/34)	102 (85/17)	678 (573/105)

Total (male/female), C, cecum; A, ascending colon; T, transverse colon; D, descending colon; S, sigmoid colon; R, rectum
Many patients had a few colorectal polyps. There was no significant difference between the location of colorectal adenomas, according to the presence or absence of *H. pylori* infection

Table 6. Location of adenocarcinomas

H. pylori	C	A	T	D	S	R	Total
Negative	1 (1/0)	2 (1/1)	0 (0/0)	3 (1/2)	10 (3/7)	13 (7/6)	29 (13/16)
Positive	6 (3/3)	10 (4/6)	12 (8/4)	16 (11/5)	33 (18/15)	50 (37/13)	127 (81/46)
Total	7 (4/3)	12 (5/7)	12 (8/4)	19 (12/7)	43 (21/22)	63 (44/19)	156 (94/62)

Total (male/female), C, cecum; A, ascending colon; T, transverse colon; D, descending colon; S, sigmoid colon; R, rectum
One patient had two colonic adenocarcinomas. There was no significant difference between the location of colorectal adenocarcinomas according to presence or absence of *H. pylori* infection

pylori-negative patients; and 47 without tumor, 42 with adenoma, 46 with adenocarcinoma, and 88 with tumor among the *H. pylori*-positive patients. The rates of *H. pylori* positivity in female patients without tumor, with adenoma, with adenocarcinoma, and with tumor was 59.5%, 71.2% ($P = 0.21$), 75.4% ($P = 0.072$), and 73.3% ($P = 0.045$), respectively. The ORs for adenoma, adenocarcinoma, and tumor were 1.68, 2.09, and 1.87, respectively, in those infected with *H. pylori,* as compared to those without *H. pylori* infection; with the latter two values having statistical significance when adjusted for age ($P = 0.048$; 1.35–2.83 and $P = 0.040$; 1.27–2.47).

There was no significant difference between patients positive or negative for *H. pylori* infection and location of colorectal adenomas (Table 5) or adenocarcinomas (Table 6) in the large bowel.

Discussion

We report here, for the first time, an increased risk of colorectal neoplasia in *H. pylori*-infected female patients. Previous studies have shown that colonic neoplastic lesions such as adenomas[15–18] and colorectal cancer[19] are associated with increased seroprevalence of *H. pylori* infection. One case-control study has shown that *H. pylori* seropositivity was more common in 182 patients with colorectal polyps than in hospital and population control groups: multivariate analysis showed that the relative risk of colorectal adenoma in *H. pylori*-positive subjects was 2.6, as compared to population controls.[20] On the other hand, a similar case-control study showed no differences in *H. pylori* seroprevalence between 57 patients with colorectal polyps and 179 controls.[22] Thus, to date, there has been no consensus on the relationship between *H. pylori* seropositivity and the development of colorectal tumor. However, our study

clearly supports a significant association between *H. pylori* infection and the risk of colorectal neoplasia; although we cannot exactly account for other studies showing no such association, there are a few possibilities that may explain this difference. One possibility is that previous studies did not enroll a sufficient number of subjects with colorectal neoplasia, as compared with our study. We checked over 6800 medical records on *H. pylori* status and analyzed 481 patients with colorectal neoplasia with or without *H. pylori* infection. Another possibility is that only *H. pylori* seropositivity was examined in previous studies. In the present study, we diagnosed *H. pylori* status by the ^{13}C-urea breath test, rapid urease test, or histological examination, because even subjects infected with *H. pylori* occasionally test seronegative, especially among the elderly. It has been suggested that when *H. pylori* status is evaluated only by *H. pylori* IgG seropositivity, the risk of *H. pylori*-associated gastric cancer would appear to be lower than the de-facto risk. Thus, such bias might have affected previous studies. Take together, our results suggest that *H. pylori* infection may increase the risk of colorectal adenoma and adenocarcinoma development in subjects aged 40–80 years.

In this study, there was no difference in age between *H. pylori*-positive and -negative patients. The prevalence of *H. pylori* infection in Japan has been reported to be 73% for those aged 40–59 years[23] and 74% for those aged 35–64 years.[24] Because many patients were infected with *H. pylori* before age 40 years, patients aged more than 40 years were chosen in this study. We found a lower rate of *H. pylori* infection for female than for male patients, corresponding to recent reports.[25] The association between gastric lesion type and colorectal tumor was not examined in our study, due to lack of standardized data for atrophic gastritis. We saw no significant difference between subjects with the presence and absence of *H. pylori* infection in the location of colorectal adenoma or adenocarcinoma, although a recent report suggests a proximal shift in the distribution of colorectal cancer with aging in Japan.[26]

The mechanism through which *H. pylori* infection is involved in an increased risk of colorectal tumor has yet to be elucidated. However, it is reasonable to speculate that gastrin might be a key factor triggering colorectal tumor development. There are a number of reports showing that gastrin is a growth factor for colonic epithelial cells and colon cancer.[11–14] In addition, a few studies have shown that plasma gastrin levels are elevated in patients with colorectal adenoma or adenocarcimona.[11,27] All these studies therefore suggest that hypergastrinemia may be associated with colorectal tumor development. Although data regarding serum gastrin levels were not available in the present study, a number of studies have shown that *H. pylori* infection may induce hypergastrinemia in patients with duodenal ulcers.[7–9] In addition, hypergastrinemia has been commonly seen in patients with advanced corpus atrophy,[10] the main feature of gastritis observed in elderly subjects in Japan.[23,24] Therefore, we should consider the possibility that hypergastrinemia may be involved in the increased risk of colorectal tumor development in *H. pylori*-infected subjects.

There are, of course, additional factors that, through their interaction with *H. pylori* infection, could also lead to increased risk of colorectal cancer, including the types and composition of the intestinal flora, ammonia levels, and the activation of intracellular tumorigenic mechanisms. The diversity in virulence between *H. pylori* strains must also be kept in mind. However, little is known regarding the interaction between *H. pylori* infection and bacterial flora. Human fecal water analysis has shown the presence of mutagenic and genotoxic substances of unknown bacterial origin.[28] Also, human gut microflora can interact with dietary components to produce substances with genotoxic, carcinogenic or tumor-promoting activity.[29] Studies have also correlated high concentrations of luminal ammonia with colon carcinogenesis[30] and *H. pylori* urease can also turn gastric juice urea into ammonia and carbon dioxide.[31] On the other hand, it has also been reported that ammonia acts as an antimitotic agent against HT-29 colonic cells.[32] Finally, studies have shown that the lineage of *H. pylori* isolates infecting Asian subjects may differ from that of isolates in other parts of the world.[33] In fact, the predominant *H. pylori* strain in Japanese has been shown to be a genotype expressing the *cag* PAI antigen, which has been associated with an increased risk for gastric cancer.[34]

We further analyzed the effect of *H. pylori* infection on the risk of colorectal tumor development on the basis of sex. Interestingly, female subjects infected with *H. pylori* were found to have a stronger association with a risk of colorectal tumor development. The OR for colorectal adenocarcinoma in *H. pylori*-infected female subjects was 2.09, while male subjects infected with *H. pylori* showed an OR value of only 1.52, which was not statistically significant. Thus, our data suggest that the apparent increase in OR for all subjects infected with *H. pylori* may be primarily due to the increased risk for female subjects (Fig. 1). The higher risk of colorectal neoplasia in female subjects infected with *H. pylori* suggests that variation in genetic factors or difference in lifestyles, might be contributing to the difference in risk of colorectal neoplasia seen between the sexes. Especially where females are concerned, the percentage of patients with colorectal carcinoma over the age of 70 has increased in Japan.[26] Generally, estrogen is a factor that reduces the risk of colorectal adenoma and cancer development.[35] Estrogen plus progestin is associated

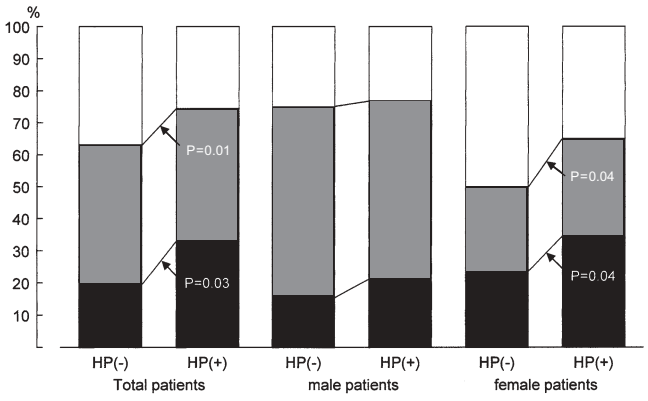

Fig. 1. The proportion of tumors for all patients with or without *Helicobacter pylori* (*HP*) infection, with male patients and female patients represented. *White bars*, patients without tumor; *gray bars*, patients with adenoma; *black bars*, patients with adenocarcinoma

with a decreased risk of colorectal cancer.[36] Studies suggest that the estrogen receptor gene may be involved in the prevention of colon tumor development.[37] Estrogen has also been suggested to decrease serum levels of insulin-like growth factor-1, which may play a role in colon cancer development.[38] However, the interaction between *H. pylori* infection and the female-hormone environment, and its effects on colorectal tumor development, have yet to be elucidated.

This case-control study is the first to examine the relationship between *H. pylori* infection and the risk of colorectal adenoma and adenocarcinoma in an Asian population. We showed that *H. pylori* infection increased the OR for the risk of colorectal adenoma and adenocarcinoma, with significant impact on female patients. Paradoxically, while *H. pylori* infection has been steadily decreasing in Japan, colorectal carcinoma has been on the rise. Thus, it appears that factors other than *H. pylori* infection may account for the increased risk of colorectal carcinoma. Further study of the interaction between *H. pylori* infection and the various factors linked to colorectal carcinoma is clearly warranted.

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