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ORIGINAL ARTICLE

Meta-analysis of different test indicators: *Helicobacter pylori* infection and the risk of colorectal cancer

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Abstract
Background and aims Recent studies have demonstrated the relationship between *Helicobacter pylori* infection and the risk of colorectal carcinoma. However, the results of these studies remain controversial as the studies were relatively small in size and partially differed in designs, and so we reviewed the published studies and carried out a meta-analysis to further explore this relationship.
Materials and methods We performed an extensive systematic review to find all the published case–control studies up to Jan. 2007 using electronic searching, hand searching, and reference lists of retrieved articles. Odds ratio (OR) was employed to evaluate the relationship of *H. pylori* infection and risk of colorectal cancer. Summary estimates were obtained using random effect models according to the result of a statistical test for heterogeneity across the studies. The presence of possible publication bias was assessed using different statistical approaches.
Results Thirteen studies were included, and summary OR 1.49 (95% confidence interval [CI] 1.17–1.91) was estimated for the association between *H. pylori* infection and colorectal cancer. Summary OR 1.56 (95% CI 1.14–2.14) was estimated for the association between immunoglobulin G antibody and colorectal cancer risk. By trimming and filling, the number of inputted studies was zero, and summary OR was still 1.49 (95% CI 1.17–1.91). The graphical funnel plot appeared asymmetrical, but there was no statistical evidence of publication bias. The method of fail-safe suggested that the effect of publication bias was small.
Conclusion Current evidence, though limited, suggests that there is a possible increase in risk of colorectal cancer because of *H. pylori* infection.

Keywords Colorectal cancer · *Helicobacter pylori* · Meta-analysis

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths worldwide. The morbidity and mortality increased quickly in both developing and developed countries [1–4]. In America, it was estimated that 148,610 new cases of colorectal cancer would be diagnosed and 55,170 patients would die from colorectal cancer in 2006 [3]. In China, from 1992/1993 to 2000/2001, CRC incidence had increased from 13.06 to 19.37 per 100,000, and the morbidity and mortality in China will be 26.12 and 17.43 per 100,000 respectively in 2006 [4]. Given the substantial injury for human quality of life, cancer prevention in its forms emerges as a very attractive approach [5]. Study results supported the colorectal cancer etiological hypothesis of "deficiency of dietary fiber and vegetables", excessive intake of fatty food, cigarette smoking, alcohol consumption, and other environment factors [6–9]. The potent role of genetic instability in initiation and progression of colorectal cancers also has been well defined. Germline mutations of DNA mismatch repair genes are considered responsible for the development of colorectal cancer [10–12]. Recent publications reported higher levels of *Helicobacter pylori* antibodies in patients

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with colorectal cancer than that in control subjects. However, this is quite controversial for different studies hold various results [13–16].

H. pylori are Gram-negative bacterium. Its infection has been recognized as a major risk factor for gastric cancer by the International Agency for Research on Cancer in 1994 [17], and infected people are also at risk of developing a rare B cell tumor, so-called gastric mucosal-associated lymphoid tissue lymphoma [18–20]. Several studies suggested that *H. pylori* can increase plasma level of gastrin and stimulate mucosal cell proliferation. Persistent exposure to *H. pylori* for several years may result in gastric atrophy, cell mutation, and transformation of gastric mucosal cells into gastrin-producing cells, which also express gastrin receptors serving to stimulate cell proliferation and tumor growth. During this processes, the overexpression of cyclooxygenase-2 also stimulates the cells to release excessive amount of prostaglandin E_2, leading to further proliferation [21, 22]. Whereas, how *H. pylori* predisposes gastric epithelial cells to become cancerous is not fully understood [23], the role of *H. pylori* in the development of colorectal cancer is still uncertain.

Therefore, we carried out a systematic review and meta-analysis of published studies to confirm this association between *H. pylori* infection and the risk of colorectal cancer.

Materials and methods

Literature search and standard of selection

Literature search was conducted in PubMed, EBSCO, HighWire Press, and other databases for relevant articles published up to Jan. 2007 about the association of *H. pylori* infection and colorectal cancer and/or colorectal adenoma (known as the precancer). We used the following medical subject heading (Mesh) terms and/or text words: *Helicobacter pylori*, colorectal carcinoma, or colorectal cancer to look for case–control studies. Only original articles in English were used and the cited references in these published articles were also reviewed. Since the quality of studies is important for meta-analysis, they should provide the description of how patients and control subjects were selected, information on data collection, sample size, matching procedures, prevalence of each group, statistical methods, and how to control the potential confounding. All the studies in our review are full articles.

Two reviewers independently applied eligibility criteria, assessed the studies for methodological quality, and finished data extraction simultaneously. The results were combined and cross-checked, and any differences were resolved by reviewing the original until conformity. Information abstracted included the author, year of publication, country of origin, type of design, number of patients and controls, matching condition, prevalence of *H. pylori* in each group, odds ratio (OR), adjustment of confounders, etc.

Assessment of homogeneity and treatment effect

OR with 95% confidence interval (CI) was computed for each study, and pooled estimates were generated by MIX (Meta-analysis with interactive explanations—version 1.51; http://www.mix-for-meta-analysis.info). Statistical homogeneity between studies was assessed using the Cochrane Q value. Since there was an obvious heterogeneity between studies (Q=31.11, P=0.0033, I^2=58.21%) [24], the random effect model was used, which has the effect of giving more weight to the smaller studies than the fixed effect model [25].

Graphical evaluation of publication bias and statistical analysis

One of the great problems in systematic review is that not all studies can be published. Those studies with statistically significant results are more likely to be submitted and published than studies without significant results. If smaller studies without significant results remain unpublished, publication bias may occur in meta-analysis [26]. The funnel plot is used as the main graphical method for identifying publication bias, which is a scatter plot of the effect estimates from individual studies (horizontal axis) against sample size or some other indicators of the estimates (vertical axis). The most precise estimates (those from larger studies) are at the top of the funnel and those from less precise or smaller studies are more likely spread at the base of the funnel because of their larger standard errors, but they should also be symmetrically around the average. In the absence of bias, the plot resembles a symmetrical inverted funnel plot. When the gap at the bottom of the graph and the asymmetry of funnel are detected, a causal relationship must be claimed with caution.

As the supplement of the funnel plot, another statistical approach "trim and fill" was used as a formal procedure [27] (first, the trimmed funnel plot is used to estimate the center of the funnel, and then the omitted studies and their missing counterparts around the center are replaced, and finally, received the true center and the adjusted effect, including the "filled" studies) to adjust the summary OR in our study. Furthermore, the possible presence of publication bias was assessed by rank correlation method, linear regression approach, and fail-safe method [28, 29].

Results

Study characteristics

From the primary electronic database (PubMed), a total of 68 studies have been identified. Fifty-nine of them were considered ineligible for our review. The reasons were as follows: 43 studies were irrelevant to association of *H. pylori* infection and colorectal cancer; there was one case study, one animal study, nine clinical case reports, four comments, and one meta-analysis. After excluding, nine case–control studies met the inclusion criteria. In addition, we conducted a manual search for the other four cited references in these articles in PubMed, EBSCO, HighWire Press and other databases, which met the inclusion criteria. Therefore, 13 studies published from Dec. 1991 to Jan. 2007 were included in the final analysis. Table 1 shows the main characteristics of these studies.

Of the 13 studies, two were nested case–control studies [30], and one only chose male smokers as subjects [16]. All the cases were matched by age, gender, or other factors (race, social class, education, etc.). But three studies did not offer any information for matching [14, 31, 32], and only convenience samples were chosen (convenience sample means the person that is easy to find). Since one study used two groups of control subjects [33] (both of the two groups of control subjects were enrolled in this paper), 14 groups of data from 13 studies were obtained.

Overall analysis

Data from 13 studies with a total of 1,709 patients were included in the first meta-analysis. Since heterogeneity was detected, the random effect model was used and summary OR for colorectal cancer related to *H. pylori* infection was 1.49 (95% CI 1.17–1.91). Figure 1 shows the ORs, 95% CIs of each study, and summary OR. The assessment result of heterogeneity was: Q=31.11, P=0.0033, I^2=58.21%.

There are serials of measures to detect the *H. pylori* infection status, such as the enzyme-linked immunosorbent assay (ELISA), C-urea breath test (UBT), rapid urease test, and histological diagnosis of biopsy specimens. One or more of them were used in the 13 studies. The detected results were indicated by different indicators, which represent different infection status of *H. pylori*. Therefore, carefully restricted analyses for certain determined assays of *H. pylori* status seem necessary.

As we have known, immunoglobulin G (IgG) demonstrates the previous infection of *H. pylori*; the results of other methods demonstrate the present infection status of *H. pylori*. Three studies with the determination of *H. pylori* status not measured with IgG antibody were excluded in the second meta-analysis. Summary OR of 11 data from ten studies was 1.56 in the random effect model (95% CI 1.14–2.14; the assessment result of heterogeneity: Q=28.54, P=0.0015, I^2=64.96%). Comparing with 1.49 (95% CI 1.17–1.91) in Fig. 1, summary OR 1.56 (95% CI 1.14–2.14) is a little higher. It seems that there is a strong relationship between *H. pylori* infection and colorectal cancer while using IgG as indicator of *H. pylori* infection (Fig. 2).

Figure 3 shows the funnel plot of publication bias with OR value as the horizontal axis and SE of OR as the vertical axis. Judged by means of eyeballing, the graphical funnel plot of the 13 case–control studies appears asymmetry. We can assume the possibility of publication bias. After adjustment by trimming and filling, summary OR was still 1.49 (95% CI 1.17–1.91). Therefore, *H. pylori* infection may increase the risk of colorectal cancer.

Additionally, in any case, eyeballing examination remains a qualitative and subjective matter and therefore prone to bias. We also used the rank correlation method proposed by Begg et al. and the linear regression approach proposed by Egger et al. to evaluate the publication bias. Both of the two approaches can be used to assess the relationship between treatment effects and SE, which are similar statistical methods with the funnel plot. The regression method is more sensitive than the rank correlation approach, but the sensitivity of both of the two methods is generally lower in meta-analysis based on less than 20 trials [29]. Neither the Begg's rank correlation (P=0.324, two-tailed) nor the Egger's regression tests (P=0.257, two-tailed) show any evidence of publication bias in our study. Based on the classical fail-safe method, there must be another 72 null studies in our analysis, which can make the summary OR nonsense.

In meta-analysis, any single study may influence the final result. We evaluated the stability of the result by calculating the summary OR and one-leave-out ORs. This method is used to exclude each study and see what happens to the combined value. In our analysis, ORs of 14 data ranged from 0.73 to 3.78. After excluding any one, ORs ranged from 1.36 (95% CI 1.10–1.68) to 1.58 (95% CI 1.23–2.02). No single study markedly influenced summary OR as shown in Fig. 4.

Discussion

It is estimated that about 50% of the world's population carry *H. pylori* in their stomach [34]. Hypergastrinemia is originating initially from G cells activated by *H. pylori* to release gastrin, leading to excessive production of ammonia and proinflammatory cytokines (IL-1, IL-8, TNF-α, etc.) and overexpression of growth factors such as TGF-α and EGF. During this process, cyclooxygenase-2 interacts with

Table 1 Characteristics of 13 studies

Reference	First author	Country, year of publication	Type of design	Number of cases	Number and selection of control	Matching variables	Measures of *H. pylori* status	Age range (mean), year	
								Cases	Controls
[31]	Talley	USA, 1991	Case–control	80	76 healthy volunteers, 176 non-cancer patients	Convenience sample	IgG	NA (60.5)	NA (61.0)
[13]	Penman	UK, 1994	Case–control	42	34 hospital non-cancer patients waiting surgery	Age, gender	UBT	44–93 (68.3)	36–88 (67.7)
[52]	Moss	USA, 1995	Case–control	41	41 colonoscopy participants	Age, gender, race	IgG	30–90 (68.0)	31–85 (65.0)
[42]	Meucci	Italy, 1997	Case–control	38	100 hospital non-cancer patients attending a hematology clinic	Age, gender	IgG	35–81 (65.3)	37–81 (63.1)
[30]	Thorburn	USA, 1998	Nested case–control	233	233 participants of the health insurance program	Age, gender, education, region and date	IgG	NA (52.7)	NA (52.6)
[33]	Breuer-Katschinski	Germany, 1999	Case–control	98 population-based; 89 hospital-based	98 population-based: registered inhabitants in the same city; 89 hospital-based: colonoscopy non-adenoma patients	Age, gender	IgG	NA (61.9)[a] NA (62.2)[b]	NA (61.8)[a] NA (62.6)[b]
[14]	Fireman	Israel, 2000	Case–control	51	51 endoscopy patients with iron deficiency or abdominal pain	Convenience sample	IgG	36–87 (66.6)	20–93 (62.7)
[15]	Hartwich	Poland, 2001	Case–control	40	160 (not specified)	Age, gender	UBT, IgG	47–82 (64.0)	47–82 (63.0)
[51]	Siddheshwar	UK, 2001	Case–control	189	179 patients of gastrointestinal symptoms but with normal colonoscopy or barium enema results; patient of diverticular disease or angiodysplasia	Age, gender, social class	IgG	42–91 (72.0)	27–89 (61.0)
[32]	Shmuely	Israel, 2001	Case–control	67	47 other cancer patients and 45 TEE controls	Convenience sample	IgG, CagA	64–76 (69.0)	57–73 (63.0)
[16]	Limburg	Finland, 2002	Nested case–control	118	236 non-cancer (except non-melanoma skin cancer) male smoker	Age, gender[c], study center date of serum collection	CagA, whole cell assay	NA (59.1)	NA (58.8)
[53]	Mizuno	Japan, 2005	Case–control	142	119 identical study population	Age, gender	IgG	HP+ HP−	NA (58.5) NA (62.7)
[54]	Fujimori	Japan, 2005	Case–control	481	188 other patients in the same hospital	Age	UBT, urease test, histological diagnosis	HP+ (male 61.4 female 60.0) HP− (male 61.5 female 60.3)	

NA Not available, *TEE* transesophageal echocardiography
[a] Hospital controls
[b] Population controls
[c] Only male smokers were chosen for subjects in this study

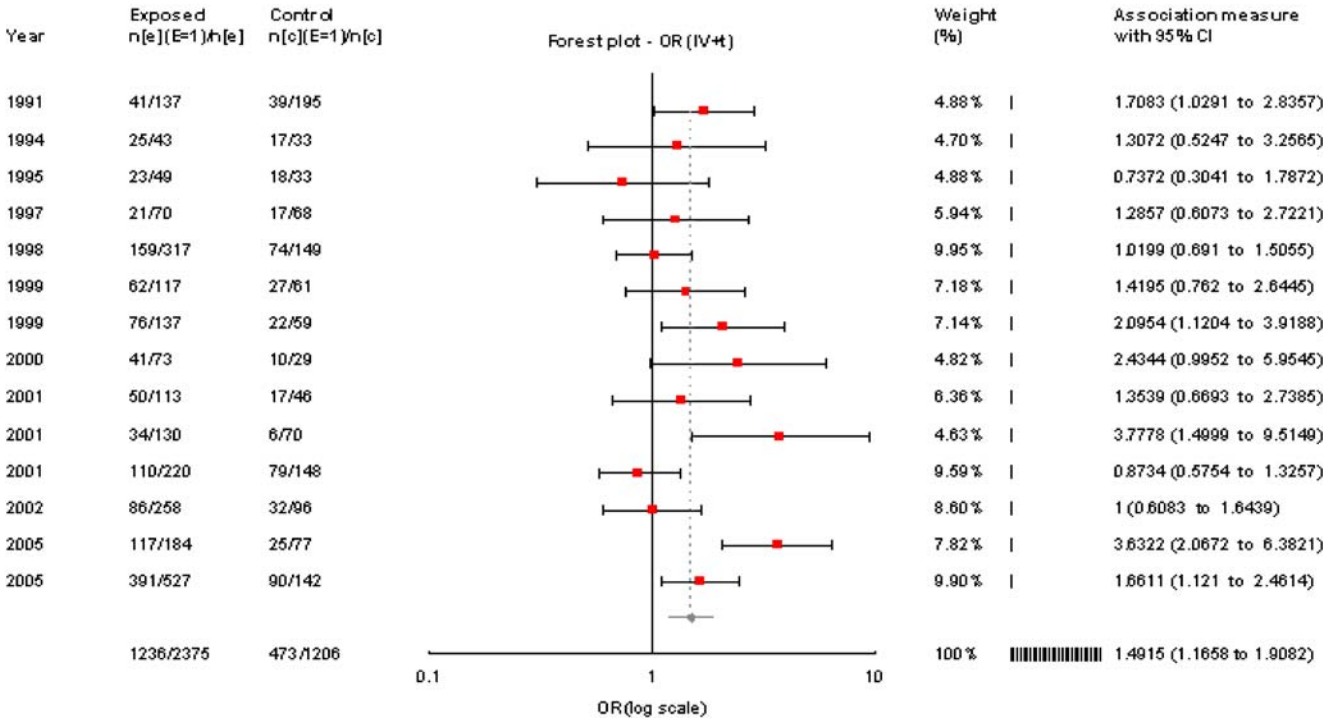

Fig. 1 Meta-analysis of 14 groups of data without discriminating the difference of *H. pylori* measures

cytokines and growth factors and stimulates inflamed tissue or cancer tissue to release excessive amount of prostaglandin E_2, which caused increased cell proliferation, angiogenesis, mutagenesis, and decreased apoptosis. Their joint action leads to the development of cancer [21].

It has been reported that *H. pylori*-infected people have a four- to sixfold increased risk of subsequently developing gastric adenocarcinoma [35, 36]. Several epidemiology studies have demonstrated the association between *H. pylori* seropositive and colorectal cancer risk. However,

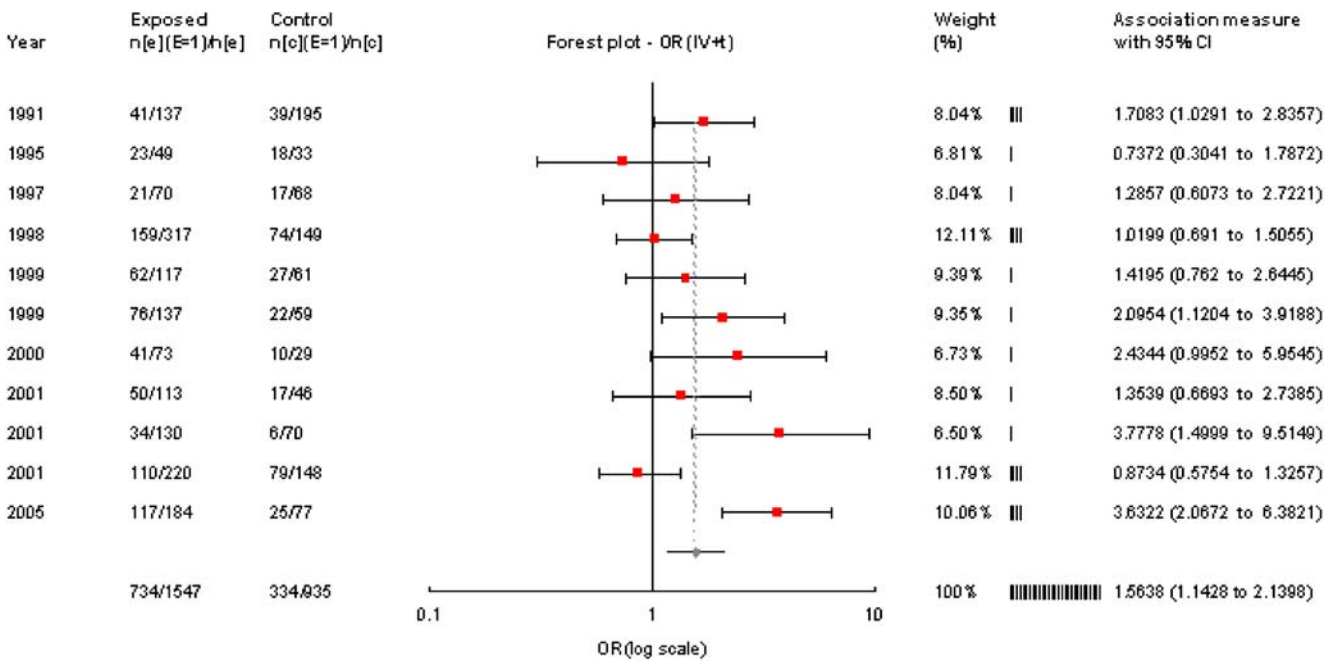

Fig. 2 Meta-analysis of 11 groups of data for using the IgG antibody

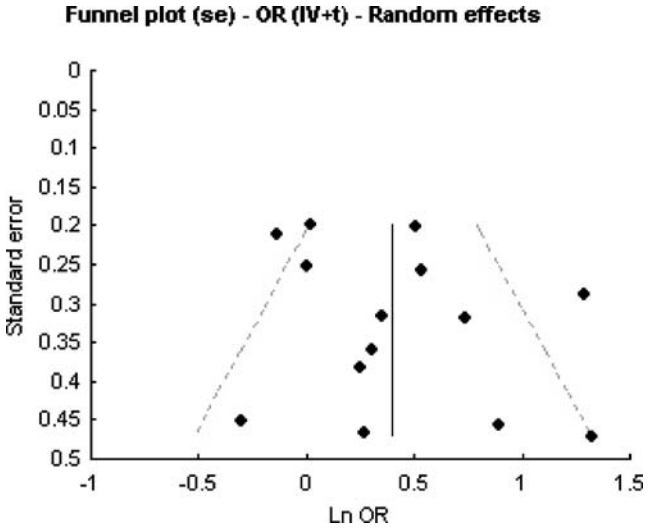

Fig. 3 Funnel plot for 13 case–control studies. The *solid line* represents the estimate of summary OR and the *dashed lines* show the confine of 95% CIs

the results from these studies remain inconclusive [16, 30, 33]. Until now, there was no systematical review on the relationship between *H. pylori* infection and colorectal neoplasia concerning the difference of methods for testing *H. pylori* infection with satisfactory analysis. The purposes of this study were therefore to assess the association between *H. pylori* infection and the risk of colorectal carcinoma and to clarify any test-based differences.

A total of 13 studies with 14 data have been cited in this paper (due to one study used two groups of control subjects). In total, 72.3% (1,236/1,709) of patients and 60.8% (1,139/1,872) of control subjects were infected with *H. pylori*. As can be seen in Fig. 1, ORs of these 14 data ranged from 0.73 (95% CI 0.30–1.79) to 3.78 (95% CI 1.50–9.51) and summary OR was 1.49 (95% CI 1.17–1.91). It indicated that *H. pylori* infection may increase the risk of colorectal cancer. Although the graphical funnel plot appeared asymmetrical, neither rank correlation method nor linear regression approach supported statistical evidence of publication bias, and the result of fail-safe also suggested that the effect of publication bias was small.

Current diagnostic tests for *H. pylori* involve histological diagnosis of biopsy specimens, UBT, rapid urease test, serological tests, etc. The test for *H. pylor*i serum IgG is a rapid, accurate, and reliable method. Moreover, the IgG antibody presents the previous infection of *H. pylori* to some extent, and other indicators illustrate that *H. pylori* exists while colorectal carcinoma was detected. If a person is infected with *H. pylori* ahead of neoplasia, it will be more reasonable to presume that *H. pylori* may be a risk factor of carcinoma. If we could not ensure the temporal relationship between *H. pylori* infection and neoplasia, the causal relationship cannot be assessed. In the meta-analysis of Zumkeller et al., different testing methods (ELISA assay, UBT, urease test, histological diagnosis of biopsied gastric specimens) were combined to determine the *H. pylori* infection status, which raised doubts about their conclusions [37]. In our meta-analysis, the IgG antibody was detected in ten of the 13 cited studies. Studies of detecting IgG antibody were further analyzed, the results of which showed a little more strength of the association between *H. pylori* infection and colorectal cancer (OR increased from 1.49 to 1.56).

Some case reports suggested the regression of colorectal cancer after eradication of *H. pylori* [38–40] and disappearance of rectal mucosa-associated lymphoid tissue lymphoma following antibiotic therapy [41]. van de Wouw et al. reported that after antibiotic therapy the number of *H. pylori* decreased and consequently led to a negative result of UBT and some other tests [42, 43]. Kosunen et al. pointed out that after 6 weeks of eradication therapy, the IgG titers had fallen by 20–30%, and 6 to 12 months after treatment the titer was 50% or less [44]. Little information is mentioned about whether the patients included in this meta-analysis used antibiotic therapy or not. Compared with control subjects, colorectal cancer patients were more possible to use antibiotic therapy. If the colorectal cancer

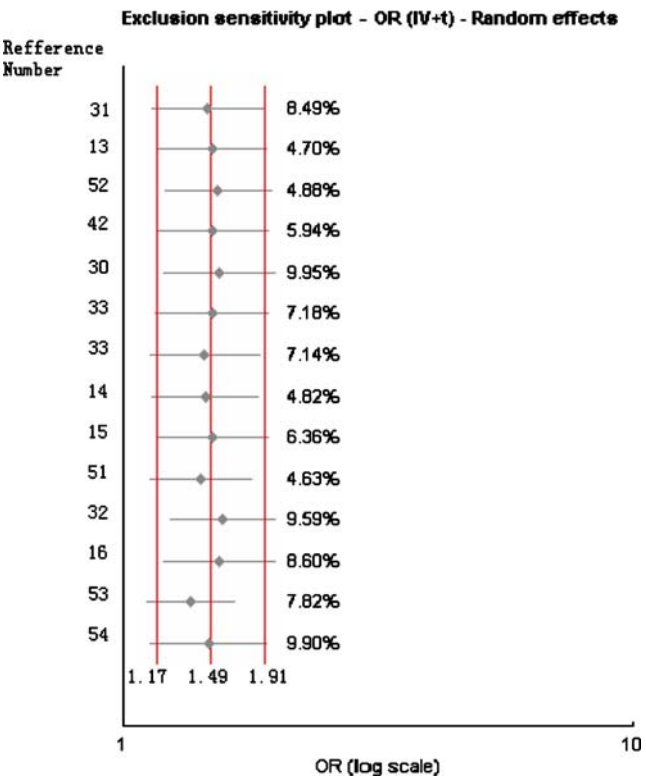

Fig. 4 The *vertical solid line* represents the original combined value when all studies are included, and the *interrupted vertical line* represents its confidence interval limitation. The *solid plots* represent combined values of one-leave-out ORs, not values of individual studies (inverse variance graph of ORs and confidence interval limitations for combined studies). Numbers and weights of the leave-out studies are indicated on the figure

patients who have been treated with *H. pylori* eradication therapy were also recruited in these case–control studies, and at the same time *H. pylori* infection status was detected without using IgG antibody, a false negative result of the relationship would be concluded.

Heterogeneity of these studies may be partially explained by one or more of the following design features of most reviewed studies: clinic- or hospital-based (rather than community-based) subject populations, small sample sizes, and inadequate consideration of potential confounding variables in the data analyses. Meta-analysis is a statistical procedure which is susceptible to various biases. First, the studies reviewed in this paper were carried out in different countries (three in America, two in Israel, two in Japan, two in western Europe, and one in eastern Europe). The race, environment, geography, or other conditions may influence the prevalence of *H. pylori*. Second, the selection of control subjects in some case–control studies may distort the results because hospital-based controls may not be as representative as population-based controls. Third, development of colorectal carcinoma is a long lasting process and is effected by multiple factors, such as body mass index, dairy foods, nutrients intake, and physical exercise [45–48]. It has been found that men were more susceptible to *H. pylori* infection compared to women, which may be caused by the propensity of smoking and drinking [49, 50], heavy physical labor in men, and different work environment between men and women. The estimate ORs were adjusted for age and gender only in the studies of Talley et al. [31] and Siddheshwar et al. [51]. The estimate ORs were adjusted for body mass index, nutritional level, etc. only in the studies of Breuer-Katschinski et al. [33] and Limburg et al. [16].

We excluded the studies published in non-English language and letters and clinical reports about the association of *H. pylori* infection and colorectal cancer. Since the data provided usually were not sufficient for assessing the quality of their studies, bias may result and influence the analysis result.

With these limitations in mind, all analyses in this paper supported the hypothesis of the relationship between *H. pylori* and colorectal cancer. Moreover, both of the two meta-analyses before and after concerning the difference of testing methods for *H. pylori* infection revealed that there are small risk increases of *H. pylori* infection in colorectal cancer (OR increased from 1.49 to 1.56). With the possible presence of publication bias, this result should be interpreted cautiously. We recommended that the important role of *H. pylori* in the development of colorectal cancer should not be disregarded. Larger and methodologically rigorous analytical studies with confounders being controlled using reliable outcomes and exposure measures are needed to further confirm this association.

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