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Helicobacter pylori infection and the risks of Barrett's oesophagus: a population-based case-control study

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Abstract

Infection with *Helicobacter pylori* is associated with significantly reduced risks of oesophageal adenocarcinoma, however few studies have examined the association between *H pylori* and Barrett's oesophagus (BO), the precursor lesion. We explored the relationship between *H pylori* infection and BO and sought to identify potential modifiers. We compared the prevalence of positive *H pylori* serology among 217 adults with simple BO (without dysplasia), 95 with dysplastic BO and 398 population controls sourced from the metropolitan Brisbane area. We determined *H pylori* serostatus using enzyme-linked immunosorbent assay. To estimate relative risks, we calculated odds ratios (OR) and 95% confidence intervals (CI) using multivariable logistic regression in the entire sample and stratified by factors known to cause BO. The prevalence of *H pylori* seropositivity was 12%, 3% and 18% respectively, among patients with simple BO, dysplastic BO and population controls. BO patients were significantly less likely to have antibodies for *H pylori* (Simple BO: OR=0.51, 95% CI: 0.30-0.86; Dysplastic BO: OR=0.10, 95% CI: 0.03-0.33) than population controls. For simple BO, the association was diminished after adjustment for frequency of gastro-oesophageal reflux (GOR) symptoms. Adjustment for frequency of GOR symptoms did not substantially alter the observed effect for dysplastic BO. While there was some variation in the magnitude of risk estimates across strata of age, sex, GOR symptoms, and use of PPIs or H2-receptor antagonists, the differences were uniformly nonsignificant. *H pylori* infection is inversely associated with BO, and our findings suggest that decreased acid load is not the only mechanism underlying the *H pylori* protective effect.

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Keywords

Barrett's oesophagus; environmental modifiers; epidemiology; *Helicobacter pylori*; gastro-oesophageal reflux

Introduction

Barrett's oesophagus (BO) is an acquired premalignant condition in which the oesophageal squamous epithelium is replaced by specialised intestinal metaplasia.[1] BO is a recognised precursor lesion of oesophageal adenocarcinoma (OAC), the incidence of which is rising more rapidly than that of any other malignancy in many Western populations.[2-6] People with BO have a 30- to 40-fold increased risk of OAC but there is currently no way of predicting which BO patients will progress to OAC.[7, 8] Evaluation of potential risk factors for BO may provide information on early events in oesophageal carcinogenesis that are amenable to intervention, with the long term aim of reducing the morbidity and mortality associated with OAC.

Helicobacter pylori is a bacterium that colonises the human stomach.[9] Epidemiological studies have shown that while infection with *H pylori* is causally associated with the development of gastric cancer,[10] infection with this organism is associated with reduced risks of OAC.[11-16] It is hypothesised that the reduction in risk is due to less frequent gastro-oesophageal reflux (GOR) resulting from diminished gastric acid secretion and the induction of atrophic gastritis in those infected with *H pylori*.[9, 17] However, there is some evidence that not all the protective effect may be explained by reduced gastric acid production. *H pylori* colonisation is found to increase gastric acid secretion in some subgroups of the population, thus *H pylori* may in fact contribute to GOR in certain patients.[18-21] It is postulated that the protective effect may act early in the oesophageal inflammation-metaplasia-dysplasia-adenocarcinoma sequence before BO. In comparison with OAC, few studies have examined the association between *H pylori* and BO, and the majority were conducted among referral populations of endoscopy patients and lacked a true population-based comparison group.[22, 23] These studies may be biased due to differences in health-care seeking behaviour of people who come to medical attention and those who do not. Only a small number of studies to date have compared patients with BO to population controls.[24, 25] Additionally, the magnitude of the association may differ across subgroups, however few studies have considered potential effect modifying by risk factors for BO.

Here, we report the findings of a population-based case-control study evaluating whether *H pylori* antibody status was associated with BO and, separately, BO with dysplasia. We also sought to identify potential modifiers of the associations.

Material and Methods

We compared the prevalence of circulating immunoglobulin G antibodies against *H pylori* using serum samples from participants in a population-based case-control study of BO conducted in Brisbane, Australia. Approval to undertake the study was obtained from the human research ethics committees of the Queensland Institute of Medical Research and from all participating hospitals. Case and control participants provided written informed consent to take part in the parent study and subsequent analyses. Patients who had died or who were mentally incompetent, too ill to participate, or unable to complete an English language questionnaire were excluded.

Study participants

The study population and methods have been described in detail previously.[26] Briefly, eligible case patients were residents of metropolitan Brisbane aged 18–79 years with a new (incident) histologically confirmed diagnosis of BO between 1 February 2003 and 30 June 2006. BO was defined as the presence of specialised intestinal metaplasia (i.e. columnar epithelium with goblet cells) in an oesophageal biopsy taken from the tubular oesophagus by upper gastrointestinal endoscopy, irrespective of the length of involvement. This analysis was restricted to patients with newly diagnosed BO (for simple cases), or newly diagnosed dysplasia (for dysplastic cases). A total of 1714 patients with presumptive BO were approached through pathology laboratories servicing metropolitan Brisbane (population 1.5 million), of whom 1096 gave permission (64% response rate) to the pathology laboratories to release their contact details to the study investigators. Of these, 487 patients were found to have a previous diagnosis of BO and a further 86 patients had only intestinal metaplasia of the gastro-oesophageal junction; both groups were deemed ineligible for this analysis. A further 130 potentially eligible patients were excluded for various reasons (too sick, unable to complete a questionnaire, etc). Thus, a total of 393 patients returned a completed questionnaire, with data available for 285 simple BO and 108 dysplastic BO patients.

Population control participants from the same geographic region were randomly selected from the Australian Electoral Roll (enrolment is compulsory by law in Australia), frequency matched to the case series of simple BO by sex and 5-year age group. Of 1554 potentially eligible controls that were contacted and invited to participate, 2 were ineligible due to a diagnosis of BO, 30 were excluded (2 deceased, 4 too ill, 17 were unable to read or write in English, 7 other exclusion) and 404 failed to respond to the invitation. Of 1118 remaining controls, 746 accepted the invitation, and 644 returned the completed questionnaires (the response rate among controls was 72% of those contacted). Population controls were not required to undergo endoscopy as part of their participation in the study.

Data collection

Data were collected through structured, self-completed health and lifestyle questionnaires, followed by standardised telephone interviews with trained research nurses. We elicited a history of GOR symptoms by asking about experience of heartburn (“a burning pain behind the breastbone after eating”) or acid reflux (“a sour taste from acid or bile rising up into the mouth or throat”). For analysis, we used the highest reported frequency for either symptom occurring during the 10 years before diagnosis or reference date. Height and weight one year ago were self-reported by participants, and body mass index (BMI) was calculated (kg/m^2). Participants were asked whether, over their whole life, they had ever smoked more than 100 cigarettes or cigars (or equivalent use of pipes). Positive responses led to further questions regarding levels and duration of smoking. We estimated each participant's lifetime cumulative quantity of tobacco smoked (dose) in pack-years, derived by dividing the number of cigarettes smoked on a typical day by 20 and multiplying by the total number of years smoked. Participants were asked to report the frequency with which they consumed six classes of alcohol (reduced-alcohol beer, regular beer, white wine, red wine, port/sherry, and spirits/liqueur) during the age intervals of 20–29 years, 30–49 years, and 50 years and older, as applicable. For these analyses, total alcohol consumption was summed across all age groups and we then calculated the average number of standard drinks (10 g ethanol) consumed per week between age 20 years and current age. Participants were also asked if they had ever used, separately, aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) during the past 5 years and, if so, the frequency of use on a seven-point scale. Finally, participants were asked whether they had ever used H2-receptor antagonists and proton pump inhibitors (PPIs).

Serum availability—Non-fasting samples of whole blood were collected in plain tubes from 91% and 90% of participating simple BO and dysplastic BO patients, respectively, and from 85% of participating population controls. We had useable serum available for *H pylori* assays for 398 (62%) population controls, 217 (76%) patients with simple BO and 95 (88%) patients with dysplastic BO. Controls for whom serological data were available were older, on average, and more likely to have experienced symptoms of heartburn or acid reflux than controls without serological data. Cases (i.e., simple BO and dysplastic BO) with serological data were similar to cases without serological data.

Serologic methods—Blood samples were collected, transported overnight to the processing centre and serum samples were then stored at -80°C according to a common protocol. Serum immunoglobulin G antibodies to *H pylori* were measured using a commercially available enzyme-linked immunosorbent assay kit (Genesis Diagnostics Ltd, Littleport, Cambridge, UK), used according to the manufacturer's instructions. Briefly, diluted serum samples were incubated with partially purified *H pylori* antigens immobilised on microtiter wells. After washing away unbound serum components, rabbit anti-human immunoglobulin G conjugated to horseradish peroxidise was added to the wells. Unbound conjugate was removed by washing, and a solution containing 3, 3′, 5, 5′-tetramethylbenzidine and enzyme substrate was added to trace specific antibody binding. The optical densities of the standards, controls, and samples were measured using a microplate reader at 450 nm. Each rack of assays contained a mixed batch of case and control samples and analysts were blinded to participant status. For each participant, duplicate samples were run. In addition, test samples known to be positive or negative for *H pylori* antibodies were run in the batch. For these analyses, an index of <0.9 was considered ‘negative’, an index of ≥1.1 was considered ‘positive’, and values between 0.9 and <1.1 were ‘equivocal’.

Statistical analysis

Our primary aim was to measure the relative risk of BO associated with *H pylori* antibody status, and then to assess the effect of potential modifiers if associations were observed. We fitted multivariate logistic regression models to calculate the odds ratios (OR) and the 95% confidence intervals (95% CI) for the association between *H pylori* seropositivity and the two BO outcomes. Our approach was, first, to fit simple age- and sex-adjusted models for each exposure. We then additionally adjusted for those variables that were significantly associated with BO in our data set, namely education, cumulative smoking history (‘never smoker’, ‘<30 pack-years’, ‘≥30 pack-years’), average lifetime alcohol consumption (Never drinkers, <1, 1–6, 7–20, ≥21 drinks/week), frequency of aspirin/NSAID use (‘never’, ‘ever’), and BMI (<25.0, 25.0–29.9, ≥30 kg/m^2). Fully adjusted models included the preceding variables as well as a term for frequency of GOR symptoms (‘never’, ‘less than weekly’, ‘at least weekly’). To explore whether any associations between *H pylori* antibody status and risk of BO were modified by exposure to known or suspected causal factors for BO, we repeated the above analyses within strata of sex, age (<60, ≥60 yrs), frequency of GOR symptoms, cumulative smoking history, BMI, use of H2-receptor antagonists and, separately, use of PPIs (‘never’, ‘ever’). To assess statistical significance of differences in associations across the strata of host characteristics, we assessed the *P* value for the type III analysis of effects for the interaction term.

We used imputation and sensitivity analysis to assess potential selection bias resulting from study participants (controls and cases) with missing serological data (termed ‘non-serology’ participants). For these analyses, we imputed the *H pylori* serostatus for ‘non-serology’ participants as per Pandeya et al.[27] Briefly, probabilities for *H pylori* serostatus (positive, negative and equivocal) were derived from the distributions among participants with

serological data for each stratum of age, sex and history of GOR symptoms. A random number from the uniform distribution U [0, 1] was then drawn for each 'non-serology' participant. 'Non-serology' participants with a random number less than or equal to the probability of *H pylori* seropositivity (π_1) were assigned a 'positive' status. Those 'non-serology' participants not assigned 'positive' were then assigned a 'negative' status if a second random number was less than or equal to the probability of being negative (π_2) excluding the positives (that is, $\pi_2/(1- \pi_1)$). Finally, 'non-serology' participants not assigned 'positive' or 'negative' were automatically assigned an 'equivocal' status. We then repeated our multivariate analyses by including all study participants (i.e., those who participated in the study for whom we had a measured serostatus and those for whom we had an 'imputed' serostatus).

Statistical significance was determined at $\alpha = 0.05$, and all tests for statistical significance were two-sided. All analyses were performed by using SAS version 9.1 (SAS Institute, Inc, Cary, NC).

Results

Study population

Characteristics of cases and controls with serological data are presented in Table 1. The distributions of age and sex were similar among simple BO cases and controls due to the frequency matching. Dysplastic BO cases were older and more likely to be male than controls. Compared with controls, cases were generally more likely to have a lower education status and a lower income (not shown). Cases were also more likely to have smoked or experienced symptoms of heartburn or acid reflux and the prevalence of overweight and obesity was higher among cases than controls.

The overall prevalence of *H pylori* seropositivity among controls was 18% (95% CI: 15-22%). Among controls, there was a significant trend towards increasing prevalence with increasing age and increasing number of pack-years smoked (*P* trend both = .01) and there was some evidence of an association between seropositivity and low levels of education (*P* = .05). We found similar prevalence of seropositivity among controls by sex and across categories of BMI, alcohol consumption, frequency of GOR symptoms, and frequency of aspirin or other NSAID use. There was no difference in the prevalence of seropositivity among controls who were never (18%) versus ever (21%) users of PPIs (*p*=0.59). Among patients with simple BO, the prevalence of *H pylori* was higher among never users (15%) than ever users of PPIs (8%), although again, this difference was not statistically significant (*p*=0.14).

Risk estimates associated with *Helicobacter pylori* infection

The risk of BO was inversely associated with *H pylori* seropositivity (Table 2). The prevalences of *H pylori* infection were 12% (95% CI: 8-15%) and 3% (95% CI: 0-6%) among patients with simple BO and dysplastic BO, respectively. Patients with simple BO (OR=0.51, 95% CI: 0.30-0.86) and dysplastic BO (OR=0.10, 95% CI: 0.03-0.33) were significantly less likely than controls to have antibodies to *H pylori*. Adjustment for frequency of GOR symptoms attenuated the association between a positive *H pylori* antibody test and simple BO to OR = 0.66 (95% CI: 0.37-1.17), but made little difference to the risk estimate for dysplastic BO (Table 2).

We additionally performed analysis combining the participants with simple and dysplastic BO in a single case group and there was a significant inverse association with *H pylori* status for the fully adjusted model (OR=0.47, 95% CI: 0.27-0.81).

Effect modification

The association between *H pylori* antibody status and BO was assessed within strata of known risk factors for BO (Table 3). We found consistently that the greatest risk reductions associated with *H pylori* seropositivity were observed among those who ever used PPIs (versus never used), and also among those who ever used H2-receptor antagonists (versus never used), although the interaction terms were uniformly nonsignificant. There was some evidence that the inverse association between *H pylori* seropositivity and BO was stronger among men than women, participants aged ≥ 60 years than those < 60 years, and participants with a history of GOR symptoms than those without. We observed strong inverse associations between *H pylori* seropositivity and BO among participants in the lowest and highest categories of cumulative smoking history and BMI, but not among those in the middle categories. These apparent differences in the magnitude of risks across strata of known causal factors were uniformly nonsignificant, and thus within the bounds of random variation. Stratified analyses could not be performed for dysplastic BO due to the small number of *H pylori* seropositive cases (n = 3).

Sensitivity analysis

We used sensitivity analysis to assess the robustness of our results to possible misclassification of measured *H pylori* serostatus, and also to examine the effects of missing serology information among study participants. Thus, we first considered the impact of reclassifying all participants with a measured 'equivocal' reading as either 'negative' or 'positive'. We observed essentially the same patterns for the risk estimates of simple BO and dysplastic BO as above (data not shown). Secondly, we used an imputation technique to assess sensitivity to missing serostatus information among case and control participants.[27] Given the relationship between reduced acid secretion and *H pylori* infection, exclusion of 'non-serology' control participants may bias any inverse associations towards the null (i.e., given the characteristics of the 'non-serology' control participants, we would expect them to have a higher prevalence of *H pylori* seropositivity than that observed for controls with a measured serostatus). All sensitivity analyses were adjusted for potential confounders, including frequency of GOR symptoms. Under the first imputation model, *H pylori* serostatus among 'non-serology' participants was imputed assuming the same distribution as that for participants with a measured serostatus. Compared with the original analysis, the risks of simple BO (OR=0.66, 95% CI: 0.39-1.12) and dysplastic BO (OR=0.11, 95% CI: 0.03-0.40) were essentially the same under this model. The next model assumed that the prevalence of *H pylori* seropositivity among 'non-serology' participants was two-fold higher than we observed among participants with a measured serostatus. Relative risk estimates were strengthened for both simple BO (OR=0.52, 95% CI: 0.30-0.90) and dysplastic BO (OR=0.08, 95% CI: 0.02-0.30). Finally, we assumed that the prevalence of *H pylori* seropositivity among 'non-serology' participants was half that observed among participants with a measured serostatus. Under this extreme scenario, the risk estimates for both simple BO (OR=0.68, 95% CI: 0.38-1.21) and dysplastic BO (OR=0.14, 95% CI: 0.04-0.52) were again similar to our original analyses.

Discussion

In this case-control study, we found a strong inverse association between serological evidence of a past infection with *H pylori* and the risk of BO. The magnitude of the risk reduction was larger for BO with dysplasia than for BO without dysplasia. Notably, the association between *H pylori* and BO without dysplasia was attenuated after adjustment for the frequency of GOR symptoms. These findings suggest that *H pylori* infection is inversely associated with the risk for BO and this association may be at least partly mediated through the suppression of GOR by *H pylori* infection.

Of note in our study was the very low prevalence of *H pylori* seropositivity. At 18% among controls, the prevalence was considerably less than that observed in a comparable population-based study of BO in Ireland,[25] and moderately less than the prevalence observed in a population-based study of BO conducted in northern California.[24] Prevalence estimates for *H pylori* seropositivity in Australia vary with the sampling frame, but are typically lower than in the United States and other developed countries.[28]

The magnitude of the inverse association we observed between *H pylori* seropositivity and simple BO was similar to that reported in the recent Californian study,[24] but weaker than that reported in the Irish study.[25] In keeping with the findings of both of those prior studies, we observed that the association between *H pylori* and BO was attenuated after adjusting for GOR symptoms. Our results are also in keeping with a meta-analysis of 9 studies, that showed *H pylori* infection was significantly associated with reduced risks of BO in those studies that compared BO cases to endoscopically normal controls.[23]

This study aimed to examine the possibility that exposure to other risk factors known to be strongly associated with risk of BO may confound or modify the association between *H pylori* and BO. We found consistently greater risk reductions among those who had used PPIs. As PPIs are used in combination with antibiotics to eradicate *H pylori* infection, the observed associations may be due to confounding by indication since BO patients are more likely to have used PPIs than controls, and use of PPIs is associated with treatment for infection. While not conclusive, our study found that BO patients were less likely than population controls to have positive *H pylori* serology, regardless of PPI use. We did not collect detailed information regarding duration and dose of PPIs, and thus we cannot definitely exclude PPI use as a possible explanation of the inverse associations. However, these results combined with the previously reported inverse association between *H pylori* and risks of OAC,[12, 13] suggests that confounding by PPI use is unlikely to fully explain the inverse association between *H pylori* and BO. Although not statistically significant, the strength of association between *H pylori* seropositivity and BO also varied by sex, age and GOR symptoms. Additionally, there was variation in the risk estimates across strata of BMI and cumulative smoking history. Pooled analyses of published data are needed to establish definitively whether any of these factors modified the associations.

There are several potential mechanisms through which *H pylori* infection could be associated with reduced BO risk. Firstly, it is generally recognised that the presence of *H pylori* decreases gastric acid secretion and increases the risk of gastric atrophy.[17, 29-32] Therefore, *H pylori* colonisation reduces the risk of GOR and this, in turn, directly reduces the risk of BO. In our study, adjustment for the frequency of GOR symptoms did not entirely eliminate the associations between *H pylori* and BO and thus our results suggest that decreased acid load is not the only mechanism underlying the *H pylori* protective effect. Secondly, *H pylori* also appears to suppress levels of ghrelin,[33-35] a hormone known to increase gastric emptying and potentially decrease GOR. Thus, if *H pylori* infection suppresses ghrelin, it might impair emptying and enhance GOR. However, there is no evidence that *H pylori* infection affects gastric emptying.[36, 37] Ghrelin is also a potent appetite stimulant and potential contributor to obesity.[38] As obesity is consistently observed to increase the risk of GOR, BO and OAC,[39-42] it is therefore feasible that *H pylori* colonisation may decrease the risks of these diseases. However, the findings from a recently published prospective study do not provide support for this hypothesis,[43] reporting that, independent of *H pylori* infection, high ghrelin levels (rather than low) were associated with reduced risks of OAC. Our study also found no statistical evidence to support this hypothesis, as adjustment for BMI made little difference to the effect estimates.

Strengths of the present study include the prospective, population-based recruitment of patients with newly diagnosed BO and the use of population controls. The relatively large sample size and the collection of information on a wide range of potential confounders enhanced the accuracy of risk estimates. We adopted strict and consistent criteria throughout the study ascertainment period, using standardised histologic and endoscopic definitions to make the formal diagnosis of BO and dysplasia.[44] The possibility of recall bias, associated with long-standing awareness of a BO diagnosis and reflecting on possible causes, was minimised by recruiting incident cases soon after diagnosis. Also, if present at all, recall bias would be limited to self-reported exposures (i.e., confounders) and would not apply to the main exposure (*H pylori* antibody status). Assays were performed blinded to participant status, and there is no reason to suspect that our findings were the result of systematic differences in laboratory analysis.

A limitation of these analyses was the relatively low rate of participation, raising concerns about possible biased selection of cases and controls. The distribution of BMI and the prevalence of GOR symptoms among our controls were similar to population data from the Australian National Health Survey 2007,[45] and to another Australian survey,[46] respectively. In contrast, the prevalence of current smokers in our controls was lower than the population average, which suggests our estimates might be under-estimates of the true effect as *H pylori* infection is positively associated with smoking. The most notable limitation was the absence of serological data for a proportion of study participants. This may have introduced bias as controls with serological data were older but also more likely to have experienced symptoms of heartburn or acid reflux than those controls missing serostatus information. As *H pylori* infection is more common among older than younger people, but less common among those with frequent symptoms of GOR, the likely direction of any bias due to missing serostatus is difficult to predict. We took account of these possible contrasting influences in our sensitivity analyses and found that when the *H pylori* antibody status among ‘non-serology’ participants was imputed assuming the same distribution as that among participants with a measured serostatus, the magnitude of the inverse association was unchanged. When we modelled higher prevalences of *H pylori* seropositivity among ‘non-serology’ participants, the inverse associations were strengthened. We can therefore conclude that missing serology status is unlikely to account for our findings; indeed the observed effect may actually underestimate the true effect.

As the majority of BO cases remain undiagnosed in the general population,[47-49] our study may be subject to selection bias if, for example, patients diagnosed differ from those who remain undiagnosed. However, this is the same for all studies of BO. Moreover, if the prevalence of undiagnosed BO in the general population is high, this would attenuate the observed inverse associations since our control group would very likely include some people with undiagnosed BO. Misclassification of *H pylori* exposure cannot be ruled out, especially false negative tests, since the patients with dysplasia were older than population controls. It is possible that some such cases may have been infected at young ages but then seroreverted over time. While our study collected self-reported data on prior *H pylori* diagnosis and treatment, it was not of sufficiently high quality to merit further analysis. This would be unlikely to account for the overall strength of the inverse association however. The inverse association between *H pylori* and BO may be partly mediated by CagA (cytotoxin-associated gene product A) status.[24] Although we did not test for antibodies to the CagA protein, had we measured CagA status, it is likely that the inverse association with BO would have been strengthened. Finally, we attempted to control for known confounders, however it is possible that unknown or unmeasured variables related to *H pylori* infection and BO might have influenced our results.

In summary, we found a reduced risk of BO associated with serological evidence of infection with *H pylori*. Understanding the mechanisms through which *H pylori* mediates its effect on oesophageal epithelium remains the focus of ongoing research.

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Abbreviations used

BMI	body mass index
BO	Barrett's oesophagus
CI	confidence interval

GOR	gastro-oesophageal reflux
OAC	oesophageal adenocarcinoma
OR	odds ratio
PPI	proton pump inhibitors

Background

- Barrett's oesophagus, a metaplastic change of the oesophageal lining, is the only known precursor to oesophageal adenocarcinoma.
- While Helicobacter pylori infection is causally associated with gastric cancers, infection with this organism is associated with reduced risks of oesophageal adenocarcinoma.
- It is not known when the apparent protective effect of *H pylori* occurs in the metaplasia-dysplasia-carcinoma sequence.

Novelty of the paper

- In a population with low prevalence of H pylori infection, serological evidence of a past infection with H pylori still had a strong protective effect on Barrett's oesophagus.
- The inverse association between H pylori infection and Barrett's oesophagus was greater among users of PPIs or H2-receptor antagonists than among never users of these medications.
- The inverse association remained following adjustment for reflux symptoms, suggesting that acid load is not the only mechanism underlying the *H pylori* protective effect.

Impact of the paper

- Systematic eradication of H pylori infection may, in the future, contribute to even higher rates of Barrett's oesophagus and oesophageal adenocarcinoma.

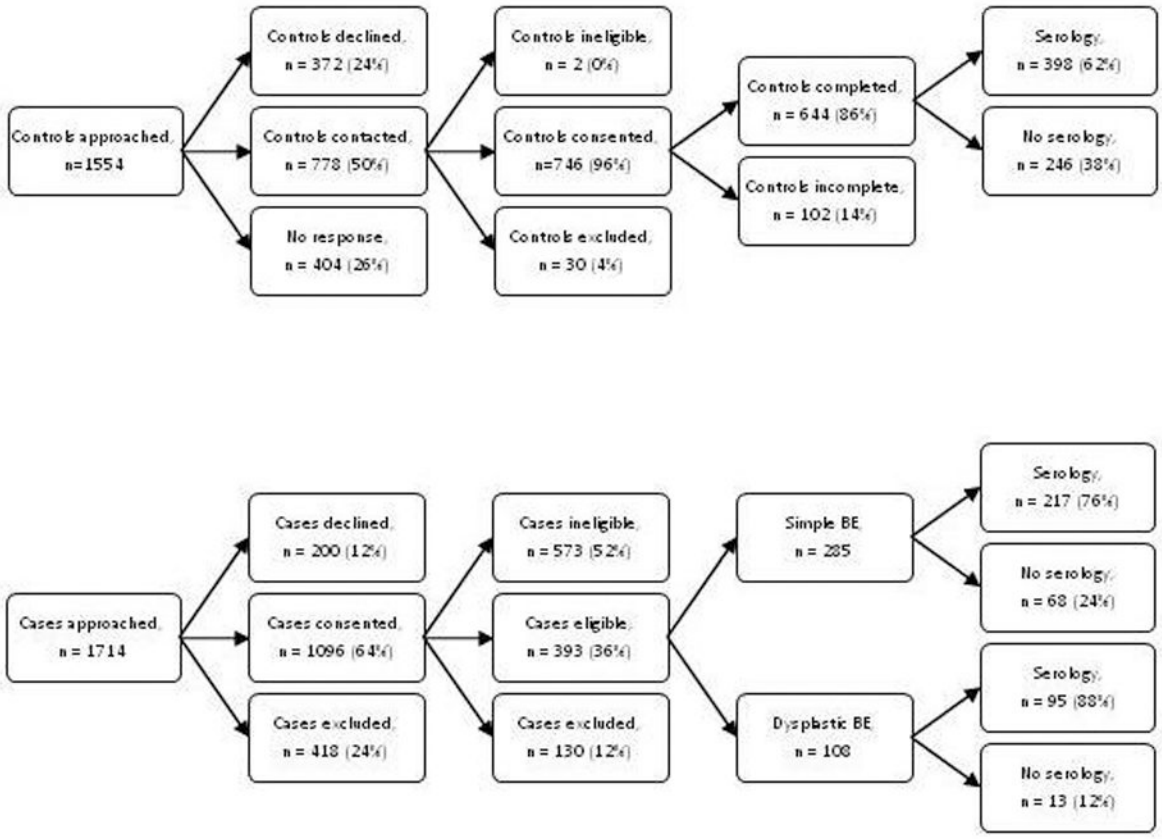

Figure 1.
Flow chart of recruitment and serum availability.

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Table 1

Characteristics of controls and Barrett's oesophagus patients (with and without dysplasia)

Variables	Categories	Controls (n = 398) n (%)	Simple BO (n = 217) n (%)	Dysplastic BO (n = 95) n (%)
Age, y				
	≤ 49	64 (16.1)	41 (18.9)	12 (12.7)
	50 – 59	137 (34.4)	71 (32.7)	22 (23.2)
	60 – 69	126 (31.7)	68 (31.3)	36 (37.9)
	70 – 79	71 (17.8)	37 (17.1)	25 (26.3)
Sex				
	Female	138 (34.7)	74 (34.1)	20 (21.1)
	Male	260 (65.3)	143 (65.9)	75 (78.9)
Highest level of education				
	School only	149 (37.4)	103 (47.5)	31 (32.6)
	Technical college/diploma	162 (40.7)	84 (38.7)	52 (54.7)
	University	87 (21.9)	30 (13.8)	12 (12.6)
	P value[1]		.02	.03
BMI last year (kg/m^2)				
	< 25.0	142 (35.9)	62 (29.1)	27 (29.0)
	25.0 – 29.9	171 (43.3)	84 (39.4)	44 (47.3)
	≥ 30.0	82 (20.8)	67 (31.5)	22 (23.7)
	P value		.01	.45
Smoking history				
	Never smoker	212 (53.3)	72 (33.2)	23 (24.2)
	< 30 pack-years	118 (29.6)	92 (42.4)	46 (48.4)
	≥ 30 pack-years	68 (17.1)	53 (24.4)	26 (27.4)
	P value		<.001	<.001
Mean alcohol consumption[2] (standard drinks/week)				
	Never drinkers	47 (11.9)	29 (13.6)	3 (3.2)
	< 1	29 (7.4)	16 (7.5)	11 (11.8)
	1 – 6.9	123 (31.2)	63 (29.4)	26 (28.0)
	7 – 20.9	115 (29.2)	58 (27.1)	32 (34.4)

Variables	Categories	Controls (n = 398) n (%)	Simple BO (n = 217) n (%)	Dysplastic BO (n = 95) n (%)
	≥ 21	80 (20.3)	48 (22.4)	21 (22.6)
	P value		.91	.07
Frequency of symptoms of heartburn or reflux[3]				
	Never	192 (48.9)	31 (14.6)	9 (9.7)
	Less than weekly	168 (42.7)	86 (40.4)	41 (44.1)
	At least weekly	33 (8.4)	96 (45.1)	43 (46.2)
	P value		<.001	<.001
Frequency of use of aspirin/NSAIDs past 5 years				
	Never	92 (23.1)	56 (25.8)	22 (23.2)
	Less than weekly	219 (55.0)	102 (47.0)	43 (45.3)
	At least weekly	87 (21.9)	59 (27.2)	30 (31.6)
	P value		.15	.11

BMI, body mass index; Dysplastic BO, Barrett's oesophagus with dysplasia; NSAIDs, non-steroidal anti-inflammatory drugs; Simple BO, Barrett's oesophagus without dysplasia.

[1] *P* value for χ^2 test for heterogeneity for comparing group of cases to the controls for the distribution of each categorical variable.

[2] One standard drink is equivalent to 10 g of ethanol.

[3] Symptoms reported in the age interval 10 years prior to the reference age.

Table 2

Relative risks of Barrett's oesophagus (with and without dysplasia) associated with *H pylori* seropositivity

		Controls		Cases		Model 1[1]		Model 2[2]		Model 3[3]	
***H pylori* serostatus**		**n**	**(%)**	**n**	**(%)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Simple BO	Negative	317	(80)	183	(84)	1.00	(Referent)	1.00	(Referent)	1.00	(Referent)
	Positive	73	(18)	25	(12)	0.60	(0.37–0.98)	0.51	(0.30–0.86)	0.66	(0.37–1.17)
Dysplastic BO	Negative	317	(80)	85	(90)	1.00	(Referent)	1.00	(Referent)	1.00	(Referent)
	Positive	73	(18)	3	(3)	0.13	(0.04–0.41)	0.10	(0.03–0.33)	0.13	(0.04–0.45)
All cases[4]	Negative	317	(80)	268	(86)	1.00	(Referent)	1.00	(Referent)	1.00	(Referent)
	Positive	73	(18)	28	(9)	0.44	(0.27–0.70)	0.37	(0.22–0.61)	0.47	(0.27–0.81)

BMI, body mass index; CI, confidence interval; Dysplastic BO, Barrett's oesophagus with dysplasia; OR, odds ratio; Simple BO, Barrett's oesophagus without dysplasia.

NOTE: There were 8 (2%) controls, 9 (4%) simple BO and 7 (7%) dysplastic BO cases with equivocal index readings.

[1] Adjusted for sex and age.

[2] Adjusted for sex, age, education level, cumulative smoking history, BMI category, average lifetime alcohol consumption, and frequency of aspirin/NSAID use in past 5 years.

[3] Additionally adjusted for frequency of reflux or heartburn symptoms in 10 years before study.

[4] A single case group combining Simple BO + Dysplastic BO.

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Table 3

Relative risks of Barrett's oesophagus associated with *H pylori* seropositivity, stratified by other risk factors for Barrett's oesophagus

	Controls		Simple BO				All cases[1]			
	No. Pos	No. Neg	No. Pos	No. Neg	OR[2]	(95% CI)	No. Pos	No. Neg	OR[2]	(95% CI)
Female	18	115	8	59	1.21	(0.43–3.41)	8	76	0.93	(0.34–2.58)
Male	51	195	16	117	0.51	(0.25–1.03)	19	182	0.36	(0.19–0.69)
					P^3 = .15				P = .12	
< 60 years of age	25	164	11	93	1.06	(0.43–2.58)	11	122	0.83	(0.34–2.02)
≥ 60 years of age	44	146	13	83	0.49	(0.22–1.06)	16	136	0.34	(0.16–0.68)
					P = .33				P = .15	
GOR never	29	154	5	25	1.14	(0.36–3.57)	5	34	0.68	(0.23–2.04)
GOR less than weekly[4]	37	128	14	68	0.53	(0.25–1.13)	16	104	0.39	(0.19–0.78)
GOR at least weekly[4]	3	28	5	83	0.49	(0.08–3.03)	6	120	0.37	(0.07–1.91)
					P = .65				P = .75	
Never smoker	30	175	5	63	0.67	(0.22–2.06)	6	83	0.53	(0.19–1.51)
< 30 pack-years	22	91	13	72	1.09	(0.46–2.60)	14	113	0.71	(0.31–1.63)
≥ 30 pack-years	17	44	6	41	0.28	(0.08–0.96)	7	62	0.24	(0.08–0.72)
					P = .28				P = .40	
BMI < 25 kg/m^2	26	110	7	48	0.52	(0.18–1.49)	8	72	0.42	(0.15–1.14)
BMI 25 – 29.9 kg/m^2	24	141	11	70	1.33	(0.52–3.44)	13	112	0.77	(0.32–1.83)
BMI ≥ 30 kg/m^2	19	59	6	58	0.28	(0.08–0.94)	6	74	0.20	(0.06–0.67)
					P = .28				P = .40	
Never used H2-receptor antagonists	56	265	16	110	0.73	(0.37–1.43)	18	152	0.56	(0.29–1.07)
Ever used H2-receptor antagonists	13	43	8	65	0.47	(0.13–1.66)	9	104	0.24	(0.07–0.77)
					P = .55				P = .29	
Never used PPI	59	267	18	106	0.79	(0.41–1.54)	18	125	0.66	(0.35–1.28)
Ever used PPI	10	41	6	69	0.33	(0.08–1.32)	9	131	0.22	(0.06–0.73)
					P = .41				P = .19	

BMI, body mass index; CI, confidence interval; Dysplastic BO, Barrett's oesophagus with dysplasia; GOR, gastro-oesophageal reflux; OR, odds ratio; PPI, proton pump inhibitors; Simple BO, Barrett's oesophagus with no dysplasia.

[1] A single case group combining Simple BO + Dysplastic BO.

[2] Adjusted for sex, age, education level, cumulative smoking history, BMI category, average lifetime alcohol consumption, frequency of aspirin/NSAID use in past 5 years, and frequency of reflux or heartburn symptoms in 10 years before study.

[3] *P* value for the type III analysis of effects for the addition of the interaction term to the saturated model.

[4] Symptoms reported in the age interval 10 years prior to the reference age.