

# Age at Establishment of *Helicobacter pylori* Infection and Gastric Carcinoma, Gastric Ulcer, and Duodenal Ulcer Risk<sup>1</sup>

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## ABSTRACT

*Helicobacter pylori* is an important risk factor for gastric cancer, gastric ulcer, and duodenal ulcer, yet most infected persons do not develop disease. We examined two correlates of acquisition age, sibship size and birth order, to evaluate the hypothesis that early life acquisition of *H. pylori* is a risk factor for the development of these illnesses. In earlier nested case-control studies of a cohort of Japanese American men in Hawaii, evidence of *H. pylori* infection was associated with the development of gastric cancer or gastric or duodenal ulceration during the subsequent period, 1968-1989. The present analysis included 102, 147, and 64 men who developed adenocarcinoma of the distal stomach, gastric ulcer, and duodenal ulcer, respectively, and a matched control for each. Sibship size and birth order data were analyzed as risk factors for development of these diseases. *H. pylori*-infected but not *H. pylori*-uninfected men from larger sibships (odds ratio, 2.06) and of higher birth order (odds ratio, 1.67) were at increased risk for developing gastric cancer. *H. pylori*-infected men but not uninfected men at higher birth order had increased risk of gastric (odds ratio, 1.64) but not duodenal ulcers. These data are consistent with the hypothesis that early life acquisition of *H. pylori* increases the risk of developing both gastric cancer and gastric ulcer but not duodenal ulcer.

## INTRODUCTION

A variety of studies now indicate that there is a strong association between chronic *Helicobacter pylori* infection and gastric adenocarcinoma (1-4), especially of the distal stomach (2-4). The central hypothesis raised by these observations is that *H. pylori* infection results in chronic gastric inflammation which may progress to atrophic gastritis and then to gastric cancer (5, 6). Similarly, *H. pylori* infection is strongly linked to both gastric and duodenal ulceration (7-10), and a wide body of evidence indicates an etiological role for this organism in "idiopathic" (*i.e.*, not associated with nonsteroidal anti-inflammatory agents or Zollinger-Ellison syndrome) peptic ulcer disease (7-10).

Nonetheless, most *H. pylori*-infected persons do not develop any of these disorders; the chronic superficial gastritis that the infection induces remains clinically silent (11, 12). Thus, it is important to identify other risk factors that might influence the risk associated with *H. pylori* infection. Several bacterial, host, and environmental cofactors (5, 13-15) have been considered to affect risk of these diseases.

Migrant studies indicate that the risk of gastric cancer is associated with early life exposures (reviewed in Ref. 16) but that on the average completion of the pathogenetic sequence requires several decades (6). Since *H. pylori*, a transmissible agent, has been associated with the risk of developing such cancers; the hypothesis we sought to test is that early life response to *H. pylori* is one of the relevant risk factors. Although this hypothesis is biologically plausible, and there is indirect

evidence that is consistent (17-19), it has not been evaluated by analytical methods because the postulated latency period is too extended to be subjected to traditional epidemiological analyses. However, investigations of the role of early exposure to hepatitis B virus in the development of hepatoma used alternative methodologies (20, 21). The approach of Hsieh *et al.* (20) utilized the principle that in the absence of vaccination, firstborn (and to a lesser extent, second-born) children are often exposed to common infections after enrollment in school, whereas later-born children are often exposed at a young age, via their older siblings.

We therefore used this approach to examine the effect of exposure age on the risk of developing gastric cancer among a cohort of Japanese American men in Hawaii (2). Because we also had been assessing the association of *H. pylori* infection with peptic ulceration in the same population (9) and because risk of disease also appears to involve factors acquired during childhood (22), we extended the analysis to include those with either gastric or duodenal ulceration.

## MATERIALS AND METHODS

**Patients.** The study subjects belong to a cohort of 8006 Japanese American men living on Oahu and identified from Selective Service records as described previously (2, 9). Serum and questionnaire data were obtained from 5924 study subjects in the late 1960s, and they were then followed until 1989 to determine whether they had developed gastric cancer, gastric ulceration, or duodenal ulceration; case ascertainment and other methods have been described in detail (2, 9). Because the risk of gastric cancer associated with *H. pylori* infection is with neoplasms of the distal stomach (2-4), the 5 persons who developed cancer of the cardia were excluded. In total, we studied 102, 147, and 64 cases of distal gastric cancer, gastric ulceration, and duodenal ulceration, respectively. Each case was matched to one control from the study cohort of the same age at examination and date of sera collection. Each control was alive at the time of hospitalization of the matched case so that death was not a competing factor.

**Ascertainment of *H. pylori* Status.** *H. pylori* status at the time of study entry in the late 1960s was ascertained on the basis of serum IgG antibodies to a purified *H. pylori* antigen, as described previously (2, 9). This method has been validated in relation to histological examination of gastric biopsy specimens and has sensitivity and specificity of 96.3 and 93.9%, respectively (23). Sera were coded, and the technical staff had been blinded to the characteristics and classification of the patients from whom they were derived. The age-adjusted mean time interval from phlebotomy to diagnosis, 9.7 years for the 18 *H. pylori*-negative and 10.8 years for the 295 *H. pylori*-positive cases, was not significantly different ( $P = 0.38$ ).

**Ascertainment of Demographic Data.** Demographic characteristics of the 626 cases and controls in this study have been described previously (2, 9). Sibship size and birth order were determined by taking into account the total number of liveborn children in the family, and twins were counted as independent births since the hypothesis to be tested focused on postnatal exposures as described (20). Birth order was divided into 3 strata to provide relatively equal study groups.

**Statistical Methods.** Two statistical analysis approaches were applied to the study data. First, a matched case-control study design was used to identify the subjects for birth order and sibship size. As a consequence, odds ratios, based on birth order and sibship size, were determined using conditional logistical regression methods (24). Tests for trend in the logit of risk were derived from conditional logistical regression models by using grouped birth order. All conditional logistical regression models were fitted by using iterative

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maximum likelihood methods and a special application of the proportional hazards regression models (25). Second, subjects were stratified into two groups without matching restriction, based on the results of the *H. pylori* IgG antibody test. Since this separated the subjects into two groups (based on *H. pylori* seropositivity), the matching between cases and controls was no longer preserved. Therefore, unconditional logistic regression methods (26) were used to obtain age-adjusted odds ratios by birth order, sibship size, and the status of serum tests. Tests for trend in risk with increasing birth order were determined by unconditional logistical regression models, with adjustment for age.

To properly conduct the above analyses, we first asked whether birth order and sibship size were correlated for the study subjects. Spearman's correlation coefficient between birth order and sibship size was 0.41 ( $P < 0.001$ ). Results for the 313 controls were identical. For the substrata of gastric cancer, gastric ulcer, and duodenal ulcer cases or their respective controls, Spearman's correlation coefficients ranged from 0.33 to 0.56 and all were highly significant ( $P < 0.001$  in each case). Because of these strong and expected correlations, we did not cross-adjust for sibship size in the birth order analyses, or *vice versa*.

**RESULTS**

**Gastric Cancer.** We first asked whether risk in our study population of developing gastric cancer during the observation period was associated with birth order. Although men of higher birth order had higher risks of developing gastric cancer in relation to firstborn men (the referent group), the trend did not reach statistical significance (Table 1A). Since not all persons in the study group were infected with *H. pylori*, we next stratified the sample into those with positive and negative *H. pylori* test results. For men who were *H. pylori* positive, development of gastric cancer during the observation period showed a slightly stronger trend toward being associated with higher birth order ( $P = 0.056$ ; Table 2A). For men who were *H. pylori* negative, there was no relationship between birth order and gastric cancer risk.

To examine the question of early life exposures in a different way, we next asked whether risk of developing gastric cancer was associated with sibship size (Table 3A). Men from larger families (sibship size,  $\geq 3$ ) were more likely to develop gastric cancer during the observation period, but results did not reach statistical significance. However, among the group of men who were *H. pylori* positive, being part of a larger subship was associated with more than twice the risk of developing gastric cancer ( $OR^3 = 2.06$ ) than being part of a smaller family (Table 4A), although there was no significant trend. In comparison, among men who were *H. pylori* negative, larger sibship size was not associated with an increased risk of developing gastric cancer (Table 4A).

**Gastric Ulcer.** Higher birth order was associated with a progressively increased risk of developing gastric ulcer (Table 1B). This phenomenon was observed in both persons who were *H. pylori* positive or *H. pylori* negative (Table 2B), but the trend was statistically significant only in the former group. There was essentially no association between gastric ulcer risk and sibship size (Table 3B) even when data were stratified for *H. pylori* status (Table 4B).

**Duodenal Ulcer.** There were no significant associations of duodenal ulcer risk and birth order or sibship size even when data were stratified for *H. pylori* status (Tables 1C, 2C, 3C, and 4C).

**DISCUSSION**

The main purpose of this study was to determine whether early life acquisition of *H. pylori* infection might be a risk factor for the development of gastric cancer or peptic ulceration. The question of whether age at acquisition of *H. pylori* infection has a bearing on the

Table 1 Odds ratios for gastric cancer, gastric ulcer, and duodenal ulcer according to birth order in Japanese Americans residing in Hawaii

Birth order	No. of cases/controls	OR <sup>a</sup>	95% CI <sup>a</sup>
<b>A. Gastric cancer</b>			
1 <sup>b</sup>	27/37	1.00	
2-3	46/45	1.45	0.76-2.80
4+	29/20	2.17	0.96-4.93
P for trend <sup>c</sup>			
			0.062
<b>B. Gastric ulcer</b>			
1 <sup>b</sup>	33/47	1.00	
2-3	74/71	1.54	0.86-2.77
4+	40/29	2.09	1.04-4.18
P for trend <sup>c</sup>			
			0.037
<b>C. Duodenal ulcer</b>			
1 <sup>b</sup>	13/18	1.00	
2-3	32/26	2.00	0.71-5.68
4+	19/20	1.57	0.51-4.83
P for trend <sup>c</sup>			
			0.587

<sup>a</sup> OR, odds ratio; CI, confidence interval.

<sup>b</sup> Referent group.

<sup>c</sup> Determined by model  $\chi^2$  with 1 df from conditional logistic regression.

association with gastric cancer or ulcer disease is important in understanding the pathophysiology of the process, in ascertaining the prognosis of infection in individual persons, and in developing optimal vaccine strategies, as has been suggested for hepatitis B and hepatocellular carcinoma (20). A criticism of epidemiological analysis of childhood risk factors obtained during surveys of adults obtained 40-60 years after the event is recall bias (16). However, information on sibship size and birth order is less prone to recall bias (20).

Previous studies have suggested that most *H. pylori* infections are acquired during childhood (17, 18, 27), and factors such as family crowding and unavailability of hot water during childhood have been associated with increased risk of transmission (28). Finding an association of larger sibships and higher birth order with gastric cancer among *H. pylori*-infected persons suggests that the infection had been acquired at a younger age, although sibship size (but not birth order) may be a marker for socioeconomic status (29). These observations are consistent with the hypothesis that duration of *H. pylori* infection is a risk factor for development of gastric cancer. Such a result may be predicted from studies indicating that chronic superficial gastritis, which we now know to be largely due to *H. pylori* infection (11), progresses to chronic atrophic gastritis over several decades (30), and atrophic gastritis is an important risk factor for gastric cancer (6, 31). Alternatively, our findings could indicate that infection with *H. pylori* at a very young age may be a particularly vulnerable period and thus could lead to increased cancer risk. The maturity of the immune response to *H. pylori* at the time infection is acquired may affect both the acute pathology and the long-term outcome of infection. For example, acquisition age affects the severity of measles, varicella, and *Mycoplasma pneumoniae* infections, and the hepatitis B carrier state is significantly more common after neonatal infections (32, 33). The pioneering studies of Haenszel *et al.* (34) on early life exposure to an environmental agent as a risk factor for gastric cancer are entirely consistent with our findings with respect to *H. pylori* infection.

It is useful to have a group of men who developed gastric cancer but who had been *H. pylori* negative as a comparison group in this study, but in this population the proportion of *H. pylori*-negative men who had distal gastric cancer was small. Since atrophic gastritis is an apparent step in the pathogenetic pathway toward gastric cancer (6), and *H. pylori* infection may be lost as a result of atrophic gastritis (31), it is possible that some of the *H. pylori*-negative men had previously been infected. Nevertheless, the trends observed were not consistently in the same direction as those observed for the *H. pylori*-infected persons. Previous analyses (1-3) suggest that approximately 60% of gastric cancer may be attributable to *H. pylori* infection; thus,

<sup>3</sup> The abbreviation used is: OR, odds ratio.

Table 2 Odds ratio for gastric cancer, gastric ulcer, and duodenal ulcer by birth order and the status of H. pylori test results

Birth order	H. pylori positive		H. pylori negative	
	No. of cases/controls	OR (95% CI) <sup>a</sup>	No. of cases/controls	OR (95% CI) <sup>a</sup>
<b>A. Gastric cancer</b>				
1 <sup>b</sup>	26/32	1.00	1/5	1.00
2-3	45/33	1.33 (0.85-2.24)	1/12	1.77 (0.05-57.5)
4+	28/14	1.67 (0.98-2.86)	1/6	3.23 (0.08-130.5)
P for trend		0.056		0.52
<b>B. Gastric ulcer</b>				
1 <sup>b</sup>	31/36	1.00	2/11	1.00
2-3	69/56	1.31 (0.86-2.01)	5/15	2.28 (0.36-14.5)
4+	37/23	1.64 (1.01-2.66)	3/6	3.11 (0.40-24.2)
P for trend		0.043		0.29
<b>C. Duodenal ulcer</b>				
1 <sup>b</sup>	12/14	1.00	1/4	1.00
2-3	30/21	1.46 (0.75-2.86)	2/5	1.05 (0.09-12.2)
4+	17/16	0.99 (0.47-2.09)	2/4	1.29 (0.10-16.2)
P for trend		0.88		0.83

<sup>a</sup> OR, odds ratio; CI, confidence interval.

<sup>b</sup> Referent group.

<sup>c</sup> Determined by model  $\chi^2$  with 1 df from unconditional logistic regression, with adjustment for date of phlebotomy and age at phlebotomy.

Table 3 Odds ratio for gastric cancer, gastric ulcer, and duodenal ulcer according to sibship size in Japanese Americans residing in Hawaii

Sibship size	No. of cases/controls	OR <sup>a</sup>	95% CI <sup>a</sup>
<b>A. Gastric cancer</b>			
1-2 <sup>b</sup>	10/20	1.00	
3-6	54/42	2.48	1.04-5.90
7 <sup>b</sup>	38/40	1.89	0.75-4.75
P for trend <sup>c</sup>			0.40
<b>B. Gastric ulcer</b>			
1-2 <sup>b</sup>	12/12	1.00	
3-6	78/79	0.99	0.38-2.54
7 <sup>b</sup>	57/56	1.02	0.39-2.70
P for trend <sup>c</sup>			0.92
<b>C. Duodenal ulcer</b>			
1-2 <sup>b</sup>	4/7	1.00	
3-6	34/24	2.72	0.70-10.51
7 <sup>b</sup>	26/33	1.26	0.35-4.60
P for trend <sup>c</sup>			0.57

<sup>a</sup> OR, odds ratio; CI, confidence interval.

<sup>b</sup> Referent group.

<sup>c</sup> Determined by model  $\chi^2$  with 1 df from conditional logistic regression.

different factors must be involved in the other cases. The results of the present study suggest that a transmissible agent may not be significant in those cases.

The association of higher birth order with gastric ulcer risk also is consistent with earlier observations. Gastric inflammation and injury

in persons with gastric ulceration is on the average more severe than in persons with duodenal ulceration (35, 36). Increased inflammation may reflect either longer duration of infection or less down-regulation of inflammation by the host (5); either of these possibilities is consistent with earlier acquisition of infection. Later birth order also appeared to be associated with risk in men not infected with *H. pylori*, although numbers were low; such an association could be due to another transmissible agent. Since later birth order was associated with gastric ulcer risk, an association with larger sibships would have been expected as well. Lack of such an association indicates that despite their interdependence, birth order is more important than sibship size in gastric ulcer risk.

Since adenocarcinoma of the stomach, gastric ulcer, and duodenal ulcer disease are each associated with *H. pylori* infection, an association of each to the other is expected and has been described (37). The incidence of gastric ulceration relative to duodenal ulceration in specific populations varies significantly; in general, populations with high ratios of idiopathic gastric to duodenal ulcer (38) also have high gastric cancer rates (16). Similarly, the pathological lesions (*e.g.*, multifocal atrophic gastritis) associated with gastric cancer and gastric ulcer show common features (39), and risk of stomach cancer years after surgery for benign ulcer disease is higher in those with gastric ulcer (40). Our data suggest that an early *H. pylori* acquisition age

Table 4 Odds ratios for gastric cancer, gastric ulcer, and duodenal ulcer by sibship size and the status of H. pylori test results

Sibship size	H. pylori positive		H. pylori negative	
	No. of cases/controls	OR (95% CI) <sup>a</sup>	No. of cases/controls	OR (95% CI) <sup>a</sup>
<b>A. Gastric cancer</b>				
1-2 <sup>b</sup>	9/17	1.00	1/3	1.00
3-6	54/36	2.07 (1.02-4.20)	0/6	0.00
7+	36/26	2.05 (0.98-4.28)	2/14	0.58 (0.04-7.90)
P value for trend <sup>c</sup>		0.11		0.96
<b>B. Gastric ulcer</b>				
1-2 <sup>b</sup>	12/8	1.00	0/4	1.00
3-6	73/60	1.08 (0.58-2.00)	5/19	- <sup>d</sup>
7 <sup>b</sup>	52/47	1.00 (0.53-1.91)	5/9	- <sup>d</sup>
P value for trend <sup>c</sup>		0.84		
<b>C. Duodenal ulcer</b>				
1-2 <sup>b</sup>	4/6	1.00	0/1	1.00
3-6	31/21	1.63 (0.57-4.67)	3/3	- <sup>d</sup>
7 <sup>b</sup>	24/24	1.10 (0.38-3.23)	5/9	- <sup>d</sup>
P value for trend <sup>c</sup>		0.50		

<sup>a</sup> OR, odds ratio; CI, confidence interval.

<sup>b</sup> Referent group.

<sup>c</sup> Determined by model  $\chi^2$  with 1 df from unconditional logistic regression, with adjustment for date of phlebotomy, and age at phlebotomy.

<sup>d</sup> Indeterminate.

may be one factor in which gastric ulcer and gastric cancer pathogenesis are linked. *H. pylori*-induced gastric antral and duodenal inflammation may also be intense in patients with duodenal ulcers (41), yet the differences in the epidemiology of gastric and duodenal ulcers suggest that the specific pathogenesis of the inflammatory processes must be substantially different.

A general hypothesis may be that early acquisition of infection results in more intense inflammation and the early development of atrophic gastritis with higher risk of both gastric cancer and gastric ulcer. Such individuals are protected from duodenal ulceration since by the age at which the stimulus for the physiological increase in gastric acidity is encountered, they have insufficient parietal cell mass to permit duodenal ulcer development. This hypothesis is consistent with the known stronger relationship between gastric hyperacidity and duodenal ulceration than gastric ulceration (42), and with epidemiological data indicating a cohort effect for duodenal ulceration (43). Duodenal ulcer incidence rose in the United States and Great Britain at the time when sanitation improved and household crowding lessened, all of which are consistent with an increasingly older acquisition age of *H. pylori* infection. Gastric ulcer rates rose and fell earlier (43) and parallel gastric cancer rates more closely than duodenal ulcer rates (37, 43). Thus, early life infection with *H. pylori* may protect against duodenal ulceration at the cost of causing gastric ulcer and cancer. Changes in *H. pylori* acquisition age over the course of industrialization and subsequently may help explain the changing epidemiology of these diseases. Further validation of these hypotheses will be needed.

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