RESEARCH ARTICLE

Rare *Helicobacter pylori* Infection May Explain Low Stomach Cancer Incidence: Ecological Observations in Bali, Indonesia

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Abstract

The incidence rate of stomach cancer in Bali, Indonesia, is estimated to be strikingly lower than that in Japan. We conducted an on-site ecological study to investigate the association between the stomach cancer incidence and *Helicobacter pylori (H. pylori)* infection. Recruiting 291 healthy persons (136 men and 155 women) from the general population in Bali, Indonesia, we conducted a urea breath test (UBT) to examine *H. pylori* infection, along with a pepsinogen test to detect chronic atrophic gastritis and urine analysis to estimate sodium and potassium excretion. UBT positivities were 9% (2-15, 95% confidence interval) for men and 7% (1-12) for women, and positive cases for *H. pylori* IgG antibodies were 1% (0-3) for men and 3% (0-5) for women, significantly lower than the respective values in Japan. Positive pepsinogen tests in Bali were 0% (0-0) for men and 1% (0-4) for women, also significantly lower than the Japanese figures. Computed values for daily salt excretion were 13.3±4.1 g (mean ± SD) for men and 11.1±3.1 g for women, as high as corresponding Japanese consumption values. Moreover, the estimated potassium excretion was 3.2±0.7 g for men and 2.8±0.6 g for women in Bali, significantly higher than the figures in Japan. There were no associations across genetic polymorphisms of IL-beta, TNF-alpha, and PTPN11 with UBT positivity. The low incidence of stomach cancer in Bali may thus mainly be due to the rare *H. pylori* infection. Namely, the bacterium infection seems to be a critical factor for gastric cancer rather than host or other environmental factors.

Keywords: Bali - ecological study - incidence of stomach cancer - prevalence of *Helicobacter pylori* - urea breath test

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Introduction

Helicobacter pylori (H. pylori) is regarded as a carcinogen for stomach cancer along with other contributory factors, such as smoking and intake of salt and salty foods (IARC, 1994; 2003; Graham and Graham, 2002; WCRF/AICR, 2007). It destroys gastric mucous membranes and induces chronic atrophic gastritis which is the precursor lesion for stomach cancer (Parsonnet et al., 1991; Graham and Graham, 2002; Oishi et al., 2006).

Similar to Indonesian ethnic groups, Malay people are well-known to have a low stomach cancer incidence, compared with high-incidence populations like Japanese and Chinese (IARC, 2002; Ministry of Health, Malaysia, 2002; Soeripto et al., 2003; RGPCRJ, 2003). Since it has been suggested that the incidence of stomach cancer is low in Bali, Indonesia from a hospital-based cancer registry (Soeripto, 2003), we conducted an on-site ecological study of stomach cancer to elucidate the risk/preventive factors of stomach cancer by sampling breath, blood and urine, and by conducting a surveillance of smoking and alcohol drinking habits and consumption of vegetables and fruit, salt and salty foods.

Materials and Methods

Subjects

In February 2006, we (IKM, M, and TGO) recruited 291 healthy volunteers (136 men and 155 women) from the general population in Bali, Indonesia.

Questionnaire survey

At Sanglah Hospital in Bali, the subjects were requested to respond to an interview-based questionnaire on lifestyle

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factors, including smoking, alcohol consumption and dietary habits, recent use of antibiotics, and drinking well water along with ethnicity (Balinese or Javanese) and religion.

Breath sampling

Using UBiT-IR300 kits (Otsuka Pharmaceutical Co., Tokyo, Japan), breath was sampled at the hospital for 13C-UBT (Graham et al., 1987) with ≥2.5 ‰ denoting positive testing.

Blood sampling

Overnight-fasting venous blood was sampled by hospital technicians to detect serum IgG antibodies for *H. pylori* and HAV-Ab, and to assess serum concentrations of PG I and PG II. Serum *H. pylori* IgG antibodies were examined using enzyme immunoassay (EIA) kits (Eiken Chemicals, Tokyo, Japan), and EIA values of ≥ 10 U/ml were defined as positive. For the subjects showing positive UBT testing, serum CagA IgG antibodies were detected by enzyme-linked immunosorbent assay (ELISA) kits (Genesis Diagnostics Ltd., Cambridgeshire, United Kingdom) and ELISA values of ≥6.25 U/ml were defined as positive (Parsonnet et al., 1997; Ohata et al., 2004). Serum PG I and PG II were measured by chemical luminescence immunoassay (Abbott Japan Co. Ltd., Tokyo, Japan) with cut-off points at PG I <= 70 ng/ml and PG I/PG II <= 3.0 (Miki et al., 2003). HAV-Ab were analyzed by EIA (Abbott Japan Co. Ltd., Tokyo, Japan) (Fiore, 2004). Using white blood cells, we identified single-nucleotide polymorphisms (SNPs) of interleukin-1-beta C-31T (IL-1β C-31T), tumor necrosis factor-alpha T-1031C (TNF-α T-1031C), and PTPN11 G/A at intron 3 by two pairs of polymerase chain reaction (PCR-CTPP) (Ishida et al., 2006; Migita et al., 2007; Hamajima et al., 2008).

Urine sampling

In order to assess intakes of salt, fruit and vegetables, second morning voiding urine (SMVU) was sampled at the hospital. We estimated 24-hour urinary sodium and potassium excretions using SMVU according to Kawasaki's formula (Kawasaki et al., 1993).

Statistical analysis

Age-adjustment with the World Population (IARC, 2003) was made for values of stomach cancer incidence rates, *H. pylori*-related markers, smoking rates, and urinary excretions of salt and potassium. The relations between positive UBT and positive HAV-Ab were evaluated by Chi-square test. The associations across the SNPs (IL-1β C-31T, TNF-α T-1031C, and PTPN11 G/A at intron 3) and positive UBT were examined by Chi-square test after confirming that the frequencies of the control groups were within Hardy-Weinberg equilibrium. All data were analyzed by SAS software (ver. 8.0, SAS Institute) and Excel.

Approval from ethics committee

The protocol was approved by the Ethics Committee of the Nagoya City University Graduate School of Medical Sciences, and the Research and Development Unit/ Research Ethics Committee of the Medical Faculty of the University of Udayana/Sanglah Hospital, Denpasar, Bali in Indonesia.

Informed consent

All subjects voluntarily took part in this study. Written informed consent was obtained from all participants and from the parents of minors.

Results

Age-adjusted annual incidence rates of stomach cancer in Bali were estimated to be 0.6/105 for men and 0.5/105 for women, approximately 1/100th of those in Japan (RGPCRJ, 2003), and were also lower than those of Malay people in Malaysia (Ministry of Health, Malaysia, 2002) and Singapore (IARC, 2002) (Table 1).

As shown in Table 2, mean ages±SD were 37.7±15.4 years old for men and 38.4±15.4 for women. The major ethnic group was Balinese (92%) (data not shown), most of whom were Hindus (92%). Age-adjusted positive rates of UBT in Bali were 9% (95% confidence interval: 2-15) for men and 7% (1-12) for women. Positive rates of pepsinogen test were 0% (0-0) for men and 1% (0-4) for women in Bali, both of which were significantly lower than the Japanese values ($p<0.01$) (Watase et al., 2004).

In Bali, salt excretions were estimated to be 13.3±4.1 g/day for men and 11.1±3.1 g/day for women, and there was no significant difference between the excretions of the Balinese participants and the consumption in Japan (Ministry of Health, Labour and Welfare, Japan, 2008). In addition, we found no significant difference in the intake of salt and salty foods between *H. pylori*-positive and -negative Balinese subjects (data not shown). Potassium excretion figures were 3.2±0.7 g/day for men and 2.8±0.6 g/day for women in Bali, being significantly higher than those in Japan ($p<0.05$) (Ministry of Health, Labour and Welfare, Japan, 2008).

Age-adjusted smoking rates of those 20 years of age or over were significantly lower for both men and women in Bali than those in Japan ($p<0.05$) (Ministry of Health,

Table 1. Age-adjusted Annual Incidence Rates of Stomach Cancer (per 100,000)

	Men	Women
Bali ¶	0.6	0.5
Japan ¶¶	67	27
Peninsular Malaysia ¶¶¶	7.6	5.1
Malay	3.4	2.1
Chinese	13.5	9.1
Indian	8.2	7.4
Singapore ¶¶¶¶		
Malay	6.6	4.0
Chinese	25.6	12.4
Indian	9.0	6.0

¶: Age-adjusted annual incidence rates during 2001-2005 calculated using the data from Bali Cancer Registration, ¶¶: Values were those of 1998 cited from the reference (RGPCRJ, 2003), ¶¶¶: Values were cited from the reference (Ministry of Health, Malaysia, 2002), ¶¶¶¶: Values were cited from the reference (IARC, 2002)

Table 2. Demographic Characteristics, *H. pylori*-related Markers, Urinary Excretion of Salt and Potassium, and Smoking and Alcohiol Consumption Rates in Bali vs. Japan

	Bali, Indonesia		Japan	
	Men n=136	Women n=155	Men	Women
Mean age ± SD	37.7±15.4	38.4±15.4		
BMI (95% confidence interval)	21.4 (20.6-22.2) n=129	21.7 (21.1-22.4) n=151		
Positive UBT (%)	9.0 (2.0-15.0) n=134	7.0 (1.0-12.0) n=153	NA	NA
Positive UBT => 30 yr (%)	7.3 (1.9-12.7) n=94	6.5 (2.0-11.1) n=112	NA	NA
Positive pepsinogen test (%)	0 (0.0-0.0)* n=133	1.0(0.0-4.0)* n=153	23.0 (22.0-25.0)#	22.0 (20.0-23.0)#
Estimated excretion of salt (mean±SD) (g/day)	13.3±4.1 n=136	11.1±3.1 n=155	11.8±5.1## n=4163	10.3±4.4## n=4732
Estimated excretion of potassium (mean±SD) (g/day)	3.2±0.7* n=136	2.8 ±0.6* n=155	2.5±1.0## n=4163	2.3±1.0## n=4732
Smoking rate => 20 yr (%)	18.8 (9.5-28.1)* n=105	1.1 (0.0-2.6)* n=127	45.3 (44.8-45.8) †	13.4 (13.1-13.7) †
Alcohol consumption => 20 yr (%)	15.2 (5.8-24.6)* n=104	1.1 (0.0-2.7)* n=124	36.7 (36.3-37.2)## n=3450	9.3 (9.0-9.5)## n=4047
Recent use of antibiotics (%)	17 (8-26) n=129	13 (5-22) n=151		
Drinking well water (%)	18 (9-26) n=129	21 (12-31) n=151		

*: Significantly different from Japan (p<0.01), †: Calculated using the 2006 data from the reference (Ministry of Health, Labor and Welfare, Japan, 2006) and age-adjusted by the World Population, NA: not available, #: Data from the reference (Watase et al., 2004), ##: 2005 data from the reference (Ministry of Health, Labor and Nutrition, Japan, 2008), All data in Bali were age-adjusted with the World Population

Table 3. *H. pylori* IgG Seroprevalence According to Survey Area¶

	Serum H. pylori IgG (+) (%)		
	Total	Men	Women
Bali, Indonesia	2.0 (0.0-4.0) n=286	1.0 (0.0-3.0) n=133	3.0 (0.0-5.0) n=153
>= 30 yr	3.6 (1.0-6.0) n=206	3.5 (0.0-8.0) n=94	3.7 (0.0-7.0) n=112
Yogyakarta, Indonesia*	4.6 (0.0-11.3) n=91	5.0 (0.0-13.0) n=52	4.0 (0.0-9.0) n=39
Japan**		62.0 (58.0-65.0)	57.0 (53.0-60.0)
Kuala Lumpur, Malaysia***	26.5	27.2	22.2
Malay	11.9		
Chinese	26.7		
Indian	49.4		
Kota Kinabalu, Malaysia***	55.0	56.6	43.5
Malay	29.2		
Chinese	49.3		
Indigenous native people	65.3		
Singapore****			
Malay		30.1	26.1
Chinese		46.8	45.8
Indian		51.1	45.1

*: Data from the reference (Tokudome et al., 2005a); **: Data from the reference (Kikuchi et al., 2000); ***: Data from the reference (Goh and Parasakthi, 2001); ****: Data from the reference (Ang et al., 2005); ¶All data in Indonesia were age-adjusted with the World Population

Labour and Welfare, Japan, 2006). Alcohol consumption rates of those 20 years of age or over in the Balinese were 15.2% (5.8-24.6) for men and 1.1% (0.0-2.7) for women, which were also significantly lower than those in Japan (Ministry of Health, Labour and Welfare, Japan, 2008). Percentages of recent use of antibiotics were 17% for men and 13% for women. Rates of using well water were 18% for men and 21% for women.

Positive *H. pylori* IgG antibodies were only 1% (0-3) for men and 3% (0-5) for women in Bali, which were significantly lower than the 62% (58-65) and 57% (53-60) for men and women, respectively, in Japan (p<0.05) (Kikuchi et al., 2000) (Table 3). The values in Bali were lower than those of Malay people in Malaysia (Goh and

Table 4. CagA IgG Antibodies in *H. pylori* IgG-positive Subjects

	CagA(+)/HP(+)	CagA(-)/HP(+)	Total
Bali	5	2	7
(%)	71.4%	28.6%	100%
Japan*	281	102	383
(%)	73.4%	26.6%	100%

*: Measured in Japanese gastric cancer cases from the reference (Sasazuki et al., 2006); No significant difference according to Chi-square test

Table 5. Seroprevalence of Anti-HAV IgG According to Survey Area

	Serum HAV IgG (+) (%)		
	Total	Men	Women
Bali, Indonesia	76.3	78.9	74.2
	n=288	n=133	n=155
> 40 yr	96.0	98.6	93.4
	n=195	n=88	n=107
Japan*	12.2	12.7	11.7
Malaysia**	67.0	68.4	65.3
> 40 yr	96.0		
Malay	70.3		
Chinese	55.9		
Indian	80.6		

*: Data from the reference (Kiyohara et al., 2007); **: Data from the reference (Tan et al., 1986)

Table 6. Associations Across Genetic Polymorphisms and UBT Positivity

	UBT(+)	UBT(-)	Odds ratio (95% CI)
IL1-beta C-31T			
TT	5	37	
TC+CC	16	231	
			1.95(0.67-5.64)
TNF-A T-1031C			
TT	11	122	
TC+CC	10	146	
			1.32(0.54-3.20)
PTPN11 G/A at intron 3			
GG	13	163	
GA+AA	8	105	
			1.05(0.42-2.61)

The genetic polymorphisms in the control groups were within Hardy-Weinberg equilibrium

Parasakthi, 2001) and Singapore (Ang et al., 2005).

There was no significant difference between the percentages of positive CagA IgG among positive *H. pylori* IgG subjects of 71.4% (5/7) in Bali vs. 73.4% (281/383) in Japan (Sasazuki et al., 2006) (Table 4).

Positive rates of HAV-Ab were 78.9% in men and 74.2% in women in Bali, which were almost as high as those in Malaysia (Tan et al., 1986) (Table 5), but higher than the corresponding figures in Japan (Kiyohara et al., 2007). Positive rates of HAV-Ab of those over 40 years of age were 98.6% for men and 93.4% for women. There were no significant relations between positive UBT and positive HAV antibodies in the Balinese, being compatible with the observations in Japan (Furuta et al., 1997).

The genetic polymorphisms in the control groups were within Hardy-Weinberg Equilibrium. No significant associations were noted across IL-1β C-31T, TNF-α T-1031C, or PTPN11 G/A at intron 3 and UBT positivity (Table 6).

Discussion

We noted a very rare prevalence of *H. pylori* along with chronic atrophic gastritis and low incidence of stomach cancer in Bali, a result similar to those of our prior studies in other areas of Indonesia (Tokudome et al., 2005a; 2005b). However, there were low smoking rates together with high intakes of fruit and vegetables, and no difference in the consumption of salt and salty foods between Bali and Japan. Thus, the low incidence of stomach cancer in Bali appeared attributable to a rare *H. pylori* infection and chronic atrophic gastritis along with low smoking rates and high consumption of fruit and vegetables.

We used UBT to detect the current *H. pylori* infection. UBT is regarded as the gold standard, which may be more sensitive than serological examinations, including *H. pylori* IgG (Cohen et al., 1999). Actually, although all our subjects with positive *H. pylori* IgG showed positive UBT, those with positive UBT were not always positive for *H. pylori* IgG. In other words, the specificity of the UBT test was distorted by bacteria having a urease function other than *H. pylori*. Nevertheless, we confirmed the low prevalence of *H. pylori* in Bali not only by UBT but also by *H. pylori* IgG antibodies.

H. pylori was also identified as a causative factor for chronic atrophic gastritis, a precursor lesion of stomach cancer, as was diagnosed using a PG test in a non-invasive examination (Oishi et al., 2006). The low positive rate of PG tests conducted in Bali was consistent with the fact that a history of gastric lesions rarely encountered by local clinicians (Moestikanigsih, personal communication), which may be due to the low positive rate of *H. pylori*. These results also appeared to be compatible with the low incidence of stomach cancer in Bali.

The cagA gene of *H. pylori* has been suspected of being a virulent factor for atrophic gastritis and stomach cancer (Parsonnet et al., 1997). We found that positive rates of CagA IgG detected in those with positive *H. pylori* IgG in Bali were as frequent as those in Japan. However, since the numbers of positive CagA IgG subjects in Bali appeared insufficient to establish the virulence of the cagA gene, we were unable to detect any statistically significant associations between that gene and stomach cancer.

The intake of salt and salty foods has been regarded as one of the risk factors for stomach cancer (WCRF/AICR, 2007; Tsugane et al., 2004). It is conceivable that high intakes of salt and salty foods along with *H. pylori* infection synergistically affect the development of stomach cancer. However, the high consumption of salt and salty foods observed in both Bali and Japan does not in itself seem sufficiently responsible to explain the difference in the stomach cancer incidence between both areas.

We observed that the estimated excretion of potassium in Bali as a marker of the consumption of fruit and vegetables was significantly higher than the intake in Japan (Ministry of Health, Labour and Welfare, Japan,

2008). Case-control studies have suggested that such consumption reduces gastric carcinogenesis (Kato et al., 1990; Inoue et al., 1994; Nishimoto et al., 2002; Goh et al., 2007). On the other hand, smoking has been well-known as a risk factor for stomach cancer (IARC, 2003). From our results, the low incidence of stomach cancer may be in part attributable to the higher consumption of fruit and vegetables and lower smoking rates in the Balinese.

It is suggested that *H. pylori* infection spreads via a fecal-oral, gastro-oral or oral-oral route (Graham and Graham, 2002), in contrast with HAV infection which is used as a marker of fecal-oral infection (Furuta et al., 1997). HAV may be transmitted by HAV contaminated foods and water (Serres et al., 1999). In agreement with a previous study (Furuta et al., 1997), the seropositivity of HAV did not synchronize with the seroprevalence of *H. pylori* in Bali. These results were compatible with the observations in Malay people in Malaysia (Goh and Parasakthi, 2001; Tan et al., 1986) (Table 5). One reason we were unable to verify the difference in infection routes/modes between the two microorganisms may be that HAV is contracted directly by a single infection, whereas *H. pylori* infections appear to be established by multiple transmissions.

The inflammatory cytokine genes including IL-1β C-31T, TNF-α T-1031C, and PTPN11 G/A at intron 3 have been suggested to be associated with developing atrophic gastritis and gastric cancer (El-Omar et al., 2000; Goto et al., 2006; Sugimoto et al., 2007; Santos et al., 2012; Tahara et al., 2012; Zhao et al., 2013). However, the present study could not detect the association across these genetic polymorphisms and UBT positivity partly due to the small number of study subjects. Further investigation is warranted to identify an individual having a high risk of gastric cancer.

In terms of study limitations, an ecological study is admittedly generally recognized to be a rather unreliable method of generating evidence because it is not completely possible to eliminate ecological fallacies. The cancer incidence data were derived from a hospital-based cancer registry, not a population-based registration. Moreover, subjects were not all randomly recruited from the people of Bali, and the sample size in this study may be rather small to be representative with respect to the risk factors being studied. However, the very low prevalence of *H. pylori* observed in this study did not seem to be due to ecological errors or the small sample size.

In conclusion, we have confirmed that the exceptionally low prevalence of *H. pylori* infections may bring about not only a rare prevalence of chronic atrophic gastritis but also a low incidence of stomach cancer. Thus, *H. pylori* infection appeared to be a critical factor that determines gastric carcinogenesis, indicating that the prevention and control of stomach cancer may be successfully achieved by infection control and the eradication of *H. pylori*.

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