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***Helicobacter pylori* Blood Biomarkers and Gastric Cancer Survival in China**

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Abstract

Background—Infection with *Helicobacter pylori* is the leading risk factor for non-cardia gastric cancer, yet its influence on prognosis of gastric cancer is largely unknown. Thus, exploring the role of *H. pylori* in survival could lead to a greater understanding of the high mortality associated with gastric cancer.

Methods—Sero-positivity to 15 *H. pylori* antigens was assessed using a multiplex assay in two prospective cohorts, the Shanghai Men's Health Study and the Shanghai Women's Health Study. Multivariable-adjusted Cox proportional hazards regression was used to examine the association between pre-diagnostic *H. pylori* antigen levels and gastric cancer-specific survival.

Results—Pre-diagnostic levels of *H. pylori* serum antibodies that were previously associated with gastric cancer incidence in this population were not associated with gastric cancer survival, whether assessed in a 6-antigen panel (HR 1.29, 95% CI 0.78–2.13 for men; HR 0.93, 95% CI 0.57–1.52 for women), focused on CagA+ *H. pylori* (HR 0.73, 95% CI 0.44–1.20 for women, HR

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1.27, 95% CI 0.70–2.31 for men) or on the high risk biomarkers of dual Omp and HP 0305 sero-positivity (HR 0.97, 95% CI 0.72–1.30 for women, HR 1.37 95% CI .97–1.94 for men).

Conclusions—Pre-diagnostic *H. pylori* antigen levels are not associated with gastric cancer survival in East Asian populations.

Impact—Identification of additional factors associated with gastric cancer survival would further our understanding of the high mortality associated with this malignancy.

Keywords

Gastric Cancer; Survival; China; Multiplex; Serology; *Helicobacter pylori*

Introduction

Worldwide, gastric cancer is the fifth most common malignancy and the third leading cause of cancer-related death (1). More than half of the world's total incident gastric cancers occur in East Asia, the majority of which are in China. While the risk for gastric cancer is multifactorial, the single greatest risk factor for the development of gastric cancer is infection with *Helicobacter pylori*. Despite the fact that the causal association between *H. pylori* infection and gastric cancer incidence is well established, associations between *H. pylori* and gastric cancer survival is unknown. Previously, we identified novel *H. pylori* blood biomarkers that are associated with gastric cancer risk (2). While these and other biomarkers have shown promise as potential predictors of gastric cancer risk, there is no known biomarker associated with gastric cancer survival beyond clinical characteristics. Thus, we sought to determine whether *H. pylori* sero-positivity could act as one such potential marker.

Materials and Methods

Study Population

The Shanghai Men's and Women's Health Studies (SMHS, SWHS, respectively) have been described previously (3, 4). This study was approved by the institutional review boards of Vanderbilt University (Nashville, TN USA), German Cancer Research Center (DKFZ) (Heidelberg, Germany), and the Shanghai Cancer Institute (Shanghai, China).

H. pylori Serology

Plasma samples from patients diagnosed with non-cardia gastric cancer (ICDO codes C16.1–C16.6, C16.8 and C16.9) were sent to the DKFZ for analysis as previously described (2, 5, 6).

Statistical Analysis

Overall survival time was calculated from date of cancer diagnosis to date of death by any cause. Patients were censored by date of last linkage to death certificates (December 31, 2014) or date of last in-person follow-up, whichever was the latest date. Analyses were conducted using Cox proportional hazards regression to calculate hazard ratios and 95% CIs for sero-positivity to individual or grouped *H. pylori* antigens with gastric cancer survival,

adjusted for the time interval between blood collection and diagnosis, age at diagnosis, family income, and TNM stage. Stratified analyses by age at diagnosis, tumor stage, time interval between blood draw and diagnosis, and treatment by surgery were performed to determine if the association between *H. pylori* and survival differed by clinical characteristics. Validation of the assumption of proportionality of the hazard was checked by creating an interaction term between predictor(s) and event time in the model and tested using the Wald Chi square test.

Results

We sought to determine whether baseline sero-positivity to select *H. pylori* antigens previously associated with gastric cancer incidence in East Asia (2) were also associated with gastric cancer survival. We began by examining whether an increasing number of sero-positive results to 6 *H. pylori* antigens associated with gastric cancer risk in this population (Omp, HP0305, HyaA, HpaA, CagA, VacA) (2, 7) was also associated with gastric cancer survival, comparing individuals sero-positive to either 4–5 antigens or 6+ antigens to individuals sero-positive to 3 or fewer antigens (Table 1). As there was no association between the quantity of antigens and relative survival, we next narrowed our focus to known individual *H. pylori* antigens associated with gastric cancer incidence. There were no associations between pre-diagnostic sero-positivity to any previously identified single or combination of *H. pylori* antigens and gastric cancer survival. Furthermore, neither age at diagnosis, tumor stage, time interval between sample collection and diagnosis, nor history of gastric surgery modified the association between sero-positivity to *H. pylori* antigens and gastric cancer survival (Table 2).

Discussion

Our previous work has shown that antibody levels to select *H. pylori* antigens could be useful biomarkers for predicting gastric cancer risk among East Asian populations, including those from the SMHS and SWHS. Therefore, we sought to examine whether the sero-positivity to a quantity of antigens or select high cancer-risk antigens were associated with relative gastric cancer survival. We found that neither the high cancer-risk antigens (including CagA, HP0305, and Omp) nor any of the other 15 tested antigens assessed prior to cancer diagnosis were useful in predicting gastric cancer survival within this population.

The strength of our study is that we have accessed an exceedingly high gastric cancer-risk population to test our hypothesis that pre-diagnostic sero-positivity to *H. pylori* antigens associated with incidence may also be associated with survival. In our cohort, we have a strong follow-up rate and a wealth of both baseline demographic and lifestyle information that have helped validate other studies of demographic factors associated with survival conducted within this region (8). A limitation of our study is that the levels of *H. pylori* antibodies and other characteristics examined were obtained at the time of enrollment, well prior to cancer onset, which may be less relevant for prognosis than status at cancer diagnosis.

To conclude, while pre-diagnostic *H. pylori* antigen levels are associated with gastric cancer incidence in this population, they are not associated with gastric cancer survival.

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Table 1

Non-cardia Gastric Cancer Survival by Sero-prevalence to the Individual *H. pylori* Antigens in the Shanghai Women's Health Study (SWHS) and Shanghai Men's Health Study (SMHS)

Sero-status	Female (n=270)		Male (n=285)	
	No. of deaths, n (%)	HR*	No. of deaths, n (%)	HR*
<i>H. pylori</i> Sero-Status				
0-3 Antigens	63 (23.3)	1.00	42 (14.7)	1.00
4-5 Antigens	171 (63.4)	0.84	178 (62.5)	1.40
6+ Antigens	36 (13.3)	0.93	65 (22.8)	1.29
P for trend		0.63		0.37
<i>H. pylori</i> and CagA				
<i>H. pylori</i> - and/or CagA-	24 (8.9)	1.00	18 (6.3)	1.00
<i>H. pylori</i> + and CagA+	246 (91.1)	0.73	267 (93.7)	1.27
Omp and HP 0305				
Omp- and/or HP 0305-	102 (37.8)	1.00	68 (23.9)	1
Omp+ and HP 0305+	168 (62.2)	0.97	217 (76.1)	1.37

Abbreviations: CagA, Cytotoxin-associated antigen; *CI*, confidence interval; *H. pylori*, *Helicobacter pylori*; *HR*, Hazard ratio.

* Multivariable-adjusted HRs adjusted for time interval between sample collection to diagnosis, age at diagnosis, family income (yuan per capita per year), education, surgery, and TNM stage were estimated by the proportional hazards model.

Non-cardia Gastric Cancer Survival by *H. pylori* infection in the Shanghai Women's Health Study (SWHS) and Shanghai Men's Health Study (SMHS)

Table 2

Variable	n, non-cardia gastric cancer specific deaths/total cases	Multivariate Hazard Ratios							
		<i>H. pylori</i> and CagA ¹ Positive		Omp and HP 0305 ² Positive		No. of sero-positive results to six <i>H. pylori</i> proteins ³			
		HR	95% CI	HR	95% CI	4-5 vs. 0-3			
						HR	95% CI		
Age at diagnosis, years									
<68	179/277	1.03	0.58, 1.83	1.11	0.80, 1.54	1.26	0.85, 1.86	1.09	0.66, 1.79
68	203/278	0.71	0.43, 1.19	1.17	0.85, 1.60	0.80	0.55, 1.17	0.98	0.61, 1.58
Tumor stage									
I/II	110/242	1.24	0.64, 2.43	1.40	0.90, 2.18	1.44	0.84, 2.44	1.39	0.72, 2.69
III	70/82	0.49	0.18, 1.32	1.32	0.77, 2.27	1.04	0.51, 2.13	0.94	0.40, 2.18
IV	89/93	0.77	0.31, 1.95	0.83	0.51, 1.33	0.97	0.54, 1.73	1.00	0.49, 2.06
Unknown	113/138	0.93	0.47, 1.82	1.03	0.70, 1.51	0.76	0.47, 1.23	0.79	0.40, 1.59
Time interval between sample collection to diagnosis, years									
<2	75/97	1.32	0.61, 2.83	0.84	0.50, 1.40	1.38	0.75, 2.53	0.86	0.40, 1.85
2	307/458	0.75	0.49, 1.16	1.18	0.92, 1.52	0.98	0.72, 1.33	1.10	0.75, 1.62
Surgery									
No	114/120	0.73	0.35, 1.52	0.97	0.65, 1.47	0.70	0.42, 1.18	1.09	0.59, 2.03
Yes	268/435	0.97	0.62, 1.52	1.13	0.86, 1.48	1.22	0.88, 1.69	1.01	0.67, 1.51

Abbreviations: CagA, Cytotoxin-associated antigen; CI, confidence interval; *H. pylori*, *Helicobacter pylori*; HR, Hazard ratio.¹ Adjusted for time interval between sample collection to diagnosis, age at diagnosis, sex, family income (yuan per capita per year), education, surgery, and TNM stage (excluding the variable used for strata analysis).² Adjusted for time interval between sample collection to diagnosis, age at diagnosis, sex, family income (yuan per capita per year), education, surgery, and TNM stage (excluding the variable used for strata analysis).³ Adjusted for time interval between sample collection to diagnosis, age at diagnosis, sex, family income (yuan per capita per year), education, surgery, and TNM stage(excluding the variable used for strata analysis).