An Indication for Correlation between the Serum ADA Level and Gastric Cancer Risk

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Abstract. *Background: Gastric atrophy caused by Helicobacter pylori (H. pylori) infection is a risk factor for gastric cancer. We aimed to evaluate the relationship between gastric cancer risk and tumor markers in the general population. Materials and Methods: A total of 688 volunteers were examined to test their serum pepsinogen (PG) levels and anti-H. pylori antibodies, in addition to a total of 22 serum tumor markers. The participants were classified into four groups according to their anti-H. pylori antibody and serum PG serological status. Accordingly, groups A and D were negative, whereas groups B and C were positive for anti-H. pylori antibodies; and groups A and B were normal, whereas groups C and D were abnormal for serum PG levels. All the blood examination results were statistically evaluated using Student's t-test among these groups. Results: There were 424, 202, 50, and 12 individuals in groups A, B, C, and D, respectively. Because of the small number of participants in groups C and D, we combined these two groups. Compared to the normal group (A), a statistically significant higher in adenosine deaminase level was found in group C+D (p=0.01). Conclusion: This result supports a previous study indicating that adenosine deaminase is involved in the regulatory system of chronic atrophic gastritis and gastric cancer risk.*

Recent studies have indicated that *Helicobacter pylori*c infection is a major risk factor for the development of gastric cancer. The *H. pylori* bacterium colonizes the stomach mucosa and triggers a series of inflammatory reactions, which are considered to cause chronic atrophic gastritis (CAG) as the first step in a sequence of mucosal changes in the stomach leading to cancer (1). The current model of stomach carcinogenesis begins with gastritis, proceeds to CAG, then to intestinal metaplasia and dysplasia, and finally to carcinoma. This hypothesis is supported by a considerable number of clinicopathological and epidemiological studies in countries with a high incidence of gastric cancer (2, 3).

The measurement of serum pepsinogens (PG) has gained attention as a new screening test for gastric cancer (4, 5). A newly evaluated gastric cancer predicting system, which uses a combination of anti-*H. pylori* antibody and serum PG tests, provides a good predictive marker for the development of gastric cancer and can be used to screen for early gastric cancer cost-effectively whilst avoiding the suffering of endoscopic examination (6, 7).

Since 2006, we have been investigating a newly designed heath check system using a computer interface (8). In this study, we aimed to evaluate the correlation between the results of this gastric cancer predicting system and the results of other blood examinations.

Materials and Methods

A total of 688 volunteers (male/female=336/352, mean±SD age 54±12 years) were subjected to this study. After obtaining informed consent, peripheral blood samples were obtained and their examination was carried out at Mitsubishi Chemical Medience (Tokyo, Japan) (8). The blood examinations included serum PG levels, anti-*H. pylori* antibodies, and 22 serum tumor markers levels (Table I) as reported elsewhere (8). Serum PG levels were examined by the Architect system provided by Abbott (Abbott Park, IL, USA), and the results of the serum PG tests were evaluated by taking the results for both PGI and PGII into account. Accordingly, when a patient had both PGI <50 ng/ml and a PGI/PGII ratio <3, the patient

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Table I. *The 22 examined tumor markers.*

Adenosine deaminase (ADA)
Basic fetoprotein serum (BFP)
β2-Microglobulin serum (BMG)
Breast cancer antigen 225 (BCA225)
Carbohydrate antigen 125 (CA125)
Carbohydrate antigen 15-3 (CA15-3)
Carbohydrate antigen 19-9 (CA19-9)
Carbohydrate antigen 72-4 (CA72-4)
Carcinoembryonic antigen (CEA)
Cross-linked carboxyterminal telopeptide of type I collagen (ICTP)
Cytokeratin 19 fragment (CYFRA)
γ-Seminoprotein (gamma-Sm)
Hyaluronic acid
KL-6 antigen (KL-6)
NCC-ST-439
Neuron-specific gamma-enolase (NSE)
Pro-gastrin-releasing peptide (Pro GRP)
Sialyl Lewis X-i antigen (SLX)
Sialyl Tn antigen (STN)
Squamous cell carcinoma antigen (SCC)
Thymidine kinase activity (TK)
Tissue polypeptide antigen (TPA)

was evaluated as having an abnormal result (7). Anti-*H. pylori* antibodies were analyzed by immunoreactive kits (Eiken, Tochigi, Japan). The participants were classified into four groups according to their anti-*H. pylori* antibody and serum PG serological status, as described by Watabe *et al.* (6). Accordingly, groups A and D were negative, whereas groups B and C were positive for anti-*H. pylori* antibodies; and groups A and B were normal, whereas0 groups C and D were abnormal for serum PG levels. Gastric cancer risk therefore increases in the order A, B, C, and D (6). All the blood examination results were statistically evaluated using Student's *t*-test among the four groups. All statistical analyses were performed using the Microsoft Excel version 2004 for Macintosh.

Results

There were 424, 202, 50, and 12 individuals in groups A, B, C, and D, respectively (Table II). The mean levels of adenosine deaminase (ADA) were increased according to the serological classification from group A to group C. However, it was not highest in group D, despite group D having the highest risk. Furthermore, statistical analysis did not show a significant difference of ADA levels between group A and group C (p-value=0.08), and group A and group D (p-value=0.06). This finding may have been caused by the small number of participants in groups C and D, respectively. Accordingly, we combined these two groups as group C+D (Table II), which were indicated as the group with abnormal PG level. Group C+D combined had a significantly higher mean ADA level compared to group A (p=0.01). No other tumor marker showed any significant difference between the groups.

Discussion

Gastric cancer is the second (in males) and fourth (in females) lethal cause of malignancy in the world (9). *H. pylori* has been established as a carcinogen for gastric cancer, and is highly associated with CAG status (10). Since the 1990s, the serum PG test has been incorporated into gastric cancer screening programs as a marker of CAG, and was revealed to be useful for assessing gastric cancer risk (11). Watabe *et al.* first reported a large scale prospective follow-up study using a combination of anti-*H. pylori* antibody and serum PG test to estimate the incidence of gastric cancer in the general population (6).

In this study, we identified a significant increase in the serum ADA level in participant with an abnormal serum PG level. ADA is a crucial enzyme in adenosine inactivation and is expressed ubiquitously and rather predominantly in the lymphoid system (12). Lymphoid tissue hyperplasia is seen in most patients with *H. pylori* infection, and there have been several reports of ADA activity in human gastric mucosal specimens; however, the role of ADA in the stomach is still debated due to the existence of both positive and negative results (12-15). In our large cohort study, a positive relationship between the risk of gastric cancer and serum ADA level was newly identified. This evidence supports the hypothesis of Namiot *et al.* that ADA is involved in the regulatory system of gastric acid secretion (15-17). *H. pylori* produces ammonia to protect itself in the gastric mucosa, and the production of ammonia is catalyzed by adenosine synthesized by the gastric mucosa (18-19). This reaction modifies mucosal function and morphology. Consequently, PG synthesis gradually decreases, and the gastric mucosa becomes atrophic. Thus, abnormal PG levels are an important finding as a risk factor of early gastric cancer. Since the significant increase in serum ADA levels in the groups of participants at greater gastric cancer risk indicates the progression of gastric mucosal injury, there is a possibility for using serum ADA examinations to predict gastric cancer risk in combination with anti-*H. pylori* antibody and serum PG test.

As only volunteers were examined, and patients with gastric cancer were not included in this study, it is unclear whether ADA is really correlated with the mechanism of the progression of gastric cancer. This will be investigated in a future study.

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Table II. *Grouping of participants according to Watabe et al. (6).*

	Group A	Group B	Group C	Group D	Group C+D
Anti-*H. pylori* antibody	–	+	+	–	±
Serum PG test	Normal	Normal	Abnormal	Abnormal	Abnormal
Number of participants	424	202	50	12	62
Mean age (years)	51.4	56.8	61.8	67.0	63.0
Mean ADA level (IU/l)*	15.3	16.2	17.8	18.0	17.9
(SD)	4.9	4.8	4.9	3.7	4.6

*The normal value of ADA is below 18 IU/l.

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