Gastric Cancer Screening by Combined Assay for Serum Anti-*Helicobacter pylori* IgG Antibody and Serum Pepsinogen Levels – The ABC Method

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Key Words

Gastric cancer · Cancer screening · ABC method ·
Helicobacter pylori · Pepsinogen

Abstract

Background: *Helicobacter pylori* (*Hp*) infection and gastric atrophy are both risk factors for gastric cancer. Recently it has been found that X-ray examination for gastric cancer screening does not have much effect on the detection rate for gastric cancer in Japan. A candidate for a new mass screening for gastric cancer, the ABC method, using the combination assay of *Hp* and serum pepsinogen, was useful for identifying the development of gastric cancer in high-risk and low-risk populations. People with higher cancer risk are recommended to receive endoscopy. The ABC method was carried out as a gastric cancer mass-screening on the initiative of Nishitokyo Medical Association in Nishitokyo city from 2011. This paper reviewed the present status of gastric cancer screening using the ABC method, including the latest results of our ongoing screening. **Summary:** We report results for 36,627 individuals from 2011 to 2013. Among them, 16,965 received blood examination for the ABC method. Of those, 8,083 planned to undergo endoscopic examination accord-

ing to stratification of the risk for the development of gastric cancer. In fact, a total of 2,911 individuals underwent endoscopic examination. Gastric cancer was detected in 65 patients, including 52 (80%) diagnosed with early gastric cancer. The ABC method was not organized screening but opportunistic screening. X-ray examination was the organized screening that was ongoing during the same period. Detection cost for 1 gastric cancer case using the ABC method was cheaper than the conventional X-ray screening method (¥1,267,452 vs. ¥2,807,763). **Key Messages:** Although further large epidemiological studies are required, the ABC method might be positioned as an effective mass screening for gastric cancer.

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Introduction

The discovery of *Helicobacter pylori* (*Hp*) in 1982 has not only changed the concept of upper gastrointestinal tract diseases, but also of clinical gastroenterological practice [1]. Results of clinical and basic research accumulated over the last decade clearly demonstrate the existence of a close relationship between *Hp* infection and

the risk of gastric cancer [2–8]. *Hp* infection is now recognized as the main acquired factor involved in the pathogenesis of peptic ulcer disease and chronic gastritis, and also gastric cancer [2].

Gastric cancer almost never occurs in the absence of *Hp* infection. Observation of 1,526 individuals over a period of 10 years revealed that gastric cancer was found in 5% of all individuals infected with *Hp* and in none of the uninfected individuals [5].

Serum pepsinogen (PG) was recently found to be a promising biomarker for predicting the status of the gastric mucosa [9–19]. Thus, the use of PG I concentration and PG I/II ratio for the detection of gastric atrophy was proposed. Consequently, PG may be useful in gastric cancer screening [12–19]. Recently, the combination of serum PG concentration and the presence of the *Hp* antibody has been recommended and used in some cases as a useful marker for gastric cancer screening [1, 6, 20, 21]. Miki and some researchers proposed a gastric cancer screening, the ABC method, by combined assay for serum anti-*Hp* IgG antibody and serum PG levels [15, 21]. The ABC method is classified based on serum anti-*Hp* IgG antibody and serum PG levels: group A (*Hp* (–) PG (–)), group B (*Hp* (+) PG (–)), group C (*Hp* (+) PG (+)), group D (*Hp* (–) PG (+)). The risk of gastric cancer is highest in group D, followed by that in groups C, B, and A, in descending order [8, 15]. If individuals are classified into a high-risk group or low-risk group through primary screening using the ABC method, it may be possible to recommend endoscopic examination for checking gastric cancer according to the risk level of the patients.

Gastric cancer screening using X-ray examination is widespread in Japan, a nation with high rate of stomach cancer mortality [22]. However, the present X-ray screening system leaves much to be desired; the number of subjects screened has recently been decreasing, and the screening program itself covers less than 10% of the at-risk population. At Nishitokyo city in the northwestern Tokyo area, only 4% of residents participated in X-ray examination for gastric-cancer screenings that were organized by the local governments from 2007 to 2009 [23]. Thus, the detection rate of gastric cancer was low, from 0.14 to 0.2%.

The ABC method allows stratification of the risk for the development of gastric cancer into 4 (A, B, C, and D) groups. The advantages of this examination are as follows: (1) serum PG levels do not vary greatly within 10 years or so in more than 90% of adults, (2) *Hp* infection is originally acquired in childhood in most cases, (3) the antibody titer is relatively stable in people aged 40 years

or older, and (4) this examination can be performed simultaneously with a regular health checkup.

Therefore, the ABC method has been carried out as a gastric cancer mass screening on the initiative of the Nishitokyo Medical Association in Nishitokyo city since 2011.

Here, the authors review the present status of gastric cancer screening using the ABC method, including the latest results of our ongoing screening.

Materials and Methods

Materials

The blood examination for the ABC method is performed simultaneously with the organized regular health checkups.

Since 2011, the ABC method has been provided for Nishitokyo national health insurance system subscribers who are between the ages of 40 and 74 of even-numbered years, for example, 42, 44, and so on. Information about the ABC method was mailed to eligible individuals by the Nishitokyo city office.

X-ray examination as the organized screening was ongoing during the same period.

The ABC Method

Serum samples collected at the time of the organized general health checkup were used to measure the serum PG I and II levels (PG I and II kit: latex agglutination method) and serum anti-*Hp* antibody (E-plate 'Eiken' *Hp* antibody: enzyme immunoassay method). Individuals with PG I levels of ≤ 70 $\mu\text{g/l}$ and PG I/II ratio of < 3 were classified as PG-positive, and those with a serum *Hp* antibody titer of > 10 U/ml were classified as *Hp*-positive.

According to the ABC method [21], it is recommended that the risk for gastric cancer be stratified into 4 groups according to the anti-*Hp* IgG antibody titer before the eradication of *Hp* and the serum PG levels, as follows: group A (*Hp* (–) PG (–)), group B (*Hp* (+) PG (–)), group C (*Hp* (+) PG (+)), and group D (*Hp* (–) PG (+)).

To ensure correct stratification, people with a history of *Hp* eradication, treatment of proton pump inhibitors (PPIs), previous gastric resection and impairment of renal function were excluded. The subjects who had special symptoms were also excluded.

The eligible individuals in Nishitokyo city were permitted the ABC method only one time. Because *Hp* infection is chronic until eradication and because PG levels do not vary greatly within 10 years or so in more than 90% of adults, the ABC method generally would only be necessary once in a lifetime.

Endoscopic Examination

People in groups B, C and D are recommended to have endoscopic examination.

In Nishitokyo city, 4 hospitals and 83 clinics can perform health checkups. Of those institutions, 4 hospitals and 20 clinics can perform endoscopic examinations. Diagnosis is made solely by the performing expert endoscopist in each institution, each of whom has over 10 years of endoscopic experience. Gastric cancer is diagnosed on the basis of histological examination of forceps biopsy specimens.

In the original ABC method [21], people in group A were advised to have endoscopic examinations every 5 years, those in group B every 3 years, those in group C every 2 years, and those in group D annually. However, in our screening, each endoscopist decides the time for the follow-up endoscopic examination based on the finding of the first endoscopic examination.

Endoscopic examinations following the ABC method are covered by the Japanese health insurance system.

Comparison of Detection Costs for 1 Gastric Cancer Case

We compared the cost benefit between the ABC method and the conventional X-ray examination for detection costs for 1 gastric cancer case.

Ethics

The ABC method was not organized screening but opportunistic screening. Therefore, the gastric cancer screening program, the ABC method, had to obtain approval from the ethics committee of Nishitokyo Medical Association. Participants were defined as those who provided written informed consent.

Results

Results of the ABC method in Nishitokyo city are shown in table 1. During the 3 years from 2011 to 2013, the number of individuals who received the ABC method was 16,965 after excluding those who met the exclusion criteria based on the information obtained from them by interview. There are no repeat individuals among the 16,965. There were 9,843 individuals in group A (58%), 3,186 individuals in group B (19%), 3,288 individuals in group C (19%), and 648 individuals in group D (4%). In group A, 961 individuals (10%) were identified as having previous *Hp* eradication and/or taking PPI and/or having epigastric abdominal symptoms, as it turned out after the ABC method. All 961 in group A were advised to get the secondary endoscopic examination. Thus, 8,083 of 16,965 individuals were advised to undergo endoscopic examination, and 2,911 actually underwent endoscopy. Of the 2,911 individuals, 65 were found to have gastric cancer (detection rate of gastric cancer: 0.34%). Of those, 13 (20%) of them were found to have advanced cancer. The remaining 52 (80%) had early gastric cancer. Endoscopic resection was performed in 26 of the patients (40%), radical surgical resection was possible in 29 (45%), and the results of remaining 10 were not received from therapeutic institutions.

Other neoplasms were detected as follows: 4 esophageal cancers, 4 MALT lymphomas, 1 duodenal cancer and 14 gastric adenomas.

Table 2 showed the comparison of detection costs for 1 gastric cancer case between X-ray screening and the ABC method. Total costs of gastric X-ray screening in

Table 1. Results of the ABC method in Nishitokyo city for 3-year periods (2011–2013)

	Number of 3 years
Screened case	16,965 (100)
Group A*	9,843 (58)
Group B*	3,186 (19)
Group C*	3,288 (19)
Group D*	648 (4)
Requiring endoscopy	8,083 (48)
Underwent endoscopy	2,911 (36**)
Detection of gastric cancer	
Early gastric cancer	52
Advanced gastric cancer	13
Total	65
Detection of other neoplasms	
Esophageal cancer	4
MALT lymphoma	4
Duodenal cancer	1
Gastric adenoma	14
Total	23

* group A *Hp* (–) PG (–), group B *Hp* (+) PG (–), group C *Hp* (+) PG (+), group D *Hp* (–) PG (+).

** Percentage of underwent endoscopy in requiring endoscopy.

Table 2. Comparison of detection costs for 1 gastric cancer case in Nishitokyo city

	X-ray from 2011 to 2013	ABC method from 2011 to 2013
Number of subject screened, n	10,259	16,965
Total cost of each screening	¥46,165,500	¥49,199,000
Total cost of secondary endoscopy	¥7,182,000	¥33,185,400
Number of gastric cancer, n	19	65
Cost detect one case of gastric cancer	¥2,807,763	¥1,267,452

Nishitokyo city from 2011 to 2013 were ¥46,165,500. In this period, 630 individuals underwent endoscopy followed by X-ray screening. Of those 630, gastric cancer was detected in 19. Endoscopic examination costs ¥11,400 per person. Detection costs for 1 gastric cancer case through X-ray screening was ¥2,807,763 (¥46,165,500 + ¥11,400 × 630/19). On the other hand, total costs of the ABC method from 2011 to 2013 were ¥49,199,000. Endoscopy following the ABC method was used for 2,911 individuals. Of those

Table 3. Comparison between X-ray screening in Japan and the ABC method

	X-ray screening in Japan 2006	The ABC method			
		Takasaki 2007	Fushimi 2012	Meguro 2008–2011	Nishitokyo city 2011–2013
Number of subjects screened, n	4,262,048	16,955	4,981	23,952	16,965
Number of subjects required endoscopy, n	4,27,949	8,357	3,192	9,356	8,083
Rate of subjects required endoscopy, %	10	50.7	64.1	39	48
Number of subjects underwent endoscopy, n	3,21,855	4,491	1,013	5,955	2,911
Detection of gastric cancer, n	6,551	44	21	54	65
Detection rate of gastric cancer, %	0.15	0.25	0.42	0.22	0.38

2,911, gastric cancer was detected in 65. Detection costs for 1 gastric cancer case using the ABC method was ¥1,267,452 (¥49,199,000 + ¥11,400 × 2,911/65). The ABC method was cheaper than X-ray screening.

No case of incidental disease or endoscopy-related infection discovered by endoscopic examination and requiring medical intervention has yet been discovered.

Discussion

Gastric cancer screening by combined assay for serum anti-*Hp* IgG antibody and serum PG levels, the ABC method, has been proposed by some researchers since the early 1990s [15, 21]. The ABC method has already been carried out at some work places and by some local governments [21]. Our study shows results similar to those of previous reports (table 3) [24]. From 2011 to 2013, the number of patients who were detected as having gastric cancer through the ABC method was more than 3 times that detected through X-ray screening in Nishitokyo city (table 2). Moreover, the ABC method for detection cost of 1 gastric cancer case was cheaper than X-ray screening. Thus, our data provide supporting evidence of the efficacy of the ABC method. At the turning point of gastric cancer screening in Japan, mass screening using endoscopy following the ABC method for stratifying gastric cancer risk may open a new era for gastric cancer screening.

However, there are some problems with the ABC method, which are shown in this report. One of the problems is that group A, the low risk group, included subjects who had received *Hp* eradication, as was also the case in previous reports [25]. Those subjects still have risk of gastric cancer. In our study, 10% in group A included subjects with the exclusion criteria such as previous *Hp* erad-

ication. It is not efficient to attempt to eliminate subjects with *Hp* eradication and/or *Hp* natural disappearance and/or taking PPI only by including a careful interview before examination. Because of time constraints and because of subjects who were unclear about their own medical history, the elimination of subjects with a history of *Hp* eradication was not completely successful, and some subjects who had received *Hp* eradication were included in group A.

The low rate of secondary endoscopic examination following the ABC method is also a negative factor for successful gastric cancer screening. The mean rate of secondary endoscopy in this report was only 36%. It is clear that an increase in the secondary endoscopic examination rate is important for determining the effectiveness of gastric cancer screening. Efforts to increase screening rates require the creation of an organized system for screening. Moreover, it is recommended that endoscopic examination be performed for subjects with cancer risk into the future. We, especially the attending doctor for each participant, have the responsibility for advising endoscopy to the subjects in groups B–D repeatedly. Therefore, partnership with local governments is crucial for development of the ABC method.

In the original practice of the ABC method [21], people in group A were advised to have endoscopic examinations every 5 years, those in group B every 3 years, those in group C every 2 years, and those in group D annually. However, there were not a few patients with advanced atrophic gastric mucosa in groups B and C. Thus, it was difficult to decide the time for the follow-up endoscopic examination based on stratification according to the original ABC method.

The ABC method in Nishitokyo city was performed as opportunistic screening. The ABC method for organized screening is still in question because satisfactory evidence

showing decreased mortality rates from gastric cancer has not yet been demonstrated. Organized screening requires more responsibility for the eligibility requirement, more quality assurance, and better specificity of follow-up and evaluation. It cannot be completely denied that the participants in the ABC method received harmful effects associated with low quality. To make the ABC method more practical for communities, a large epidemiological study is desirable [26].

In conclusion, the ABC method might be premature for organized screening for gastric cancer. However, previous papers and this paper have been reporting a

cancer detection rate and cost benefit better than that found using conventional X-ray mass screening. Also, subjects diagnosed as *Hp* positive may be receiving eradication through the use of the ABC method. Thus, we can expect greater ability to reduce gastric cancer incidence and mortality through the ABC method in future.

Disclosure Statement

The authors report no conflicts of interest.

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