A 15-year cohort study on the incidence of gastric cancer and the validity of testing based on serum pepsinogen screening test

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A 15-year cohort study on the incidence of gastric cancer and the validity of testing based on serum pepsinogen screening test

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Abstract

Objectives: The incidence of and mortality from gastric cancer in Japan have remained high and prophylaxis is important. However, the number of the individuals undergoing gastric mass radiography has decreased in recent years because the examination has a big burden at the time of the consultation. Many studies have reported the ease and effectiveness of the pepsinogen test and a higher incidence of gastric cancer in positive groups. However, the longest survey period was 10 years. Therefore, we conducted a 15-year cohort study to examine the validity of the testing period and the incidence of gastric cancer in serum pepsinogen positive and negative groups at a private company utilizing pepsinogen test. **Methods**: Subjects were 4383 employees who received a pepsinogen test. Subjects were followed for 15 years. For the purpose of examining the three periods over five-, 10-, and 15-year periods, we analyzed the validity of testing during each period, carried out a log-rank test, and analyzed hazard ratio in the Cox proportional hazard model. **Results**: The number of individuals who developed gastric cancer during the survey was nine in the five-year negative group, 18 in the five-year positive group, 16 in the 10-year negative group, 27 in the 10-year positive group, 31 in the 15-year negative group, and 29 in the 15-year positive group. The sensitivity of testing was 0.667 over the first five years, 0.628 over 10 years, and 0.483 over 15 years, and the specificity was 0.744 over the first five years, 0.745 over 10 years, and 0.745 over 15 years. The five-year incidence of gastric cancer was 57 per 100,000 person years in the negative group and 350 per 100,000 person years in the positive group. The ten-year incidences were 53 per 100,000 person years in the negative group and 279 per 100,000 person years in the positive group. The 15-year incidence was 75 per 100,000 person years in the negative group and 231 per 100,000 person years in the positive group. The hazard ratio of the positive group toward the negative group was 4.98 over the first five years, 4.71 over 10 years, and 2.76 over 15 years ($p<0.001$). **Conclusions**: This study clarified that the first five years after the testing showed the highest hazard ratio and validity, therefore, the validity of testing was approximately 10 years.

Key words

Cohort study, Gastric cancer incidence, Hazard ratio, Serum pepsinogen, Validity

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Introduction

Gastric cancer ranked second from the top for mortality in both males and females in Japan in 2010[1]. The incidence of gastric cancer in males in 2006 was top and third for females[2]. According to 2008 estimates by the International Agency for Research on Cancer (IARC), the mortality of gastric cancer in Japan was third following Korea and Russia[3], which highlights the importance of prophylaxis. While mass screening for gastric cancer is available through local governments, however, the number of individuals taking advantage of this service is low. According to statistics provided by the Ministry of Health, Labour and Welfare (MHLW), the percentage of individuals undergoing screening decreased from 13.8% in fiscal year 1995 to 10.1% in fiscal year 2009[4]. The Basic Plan to Promote Cancer Control Program approved in June 2007 by the MHLW set a target of 50%[5]; however, the rates for testing, including gastric radiography and pepsinogen (PG), remained at 32.5% for males and 25.3% for females in 2007[6].

In terms of the workforce, gastric cancer arises more often in middle-aged and older employees. Affecting the workforce's most experienced segment, gastric cancer exerts a significant impact on human resources and increases the cost of healthcare. In order to improve the quality of work life (QWL), find gastric cancer in asymptomatic periods, and prevent development and death, it is important to conduct mass screening. However, there are as yet no laws, the approaches companies have taken to gastric cancer screening are not standardized.

Although it was impossible to find nationwide data regarding the rate of gastric cancer screening by workplace, there were data revealing that in Ishikawa Prefecture, 60% of the workplaces with 300 or more employees mandate mass screening for gastric cancer, 73% of which is conducted in specially-equipped examination vehicles that visit the worksite[7]. In addition, according to a survey conducted in cooperation with workplaces in Namerikawa City, Toyama, volunteer screening conducted by companies in the city was 16.7% in 2007 and 21.6% in 2010, which is as low as the screening conducted by local governments[8]. According to a survey of individuals who elect not to undergo screening, the major reasons were "Because I don't have any symptoms," and "I don't like barium and bloating agent,"[9] followed by a dislike of the side effects caused by the examination such as "It makes me feel sick," "I become constipated or have diarrhea," and "The laxative gives me a stomachache."

Recently, Miki et al. suggested a method of identifying individuals at high risk for gastric cancer based on lowered PG I and PG I/II ratios[10-12]. This simple and low-cost method reduces the burden on the individual undergoing examination, and it provides accuracy and safety that equals or exceeds x-ray screening. Serum PG is an index for chronic atrophic gastritis (CAG). Samloff et al., reported that although PG I values decrease along with the expansion of atrophic changes from gastric pyloric glands to gastric fundal glands, PG II values either increase or remain unchanged[13]. In addition, Correa suggested that a part of the affected regions of CAG developed intestinal epithelium deformation, a part of which transdifferentiated into intestinal metaplasia that developed into differentiated gastric adenocarcinoma[14]. The creation of a CAG environment, which is the origin of gastric cancer, is strongly correlated with helicobactor pylori (H. pylori) infection[14]. In 1994, the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) recognized H. pylori infection and CAG as contributors, along with high sodium intake and smoking, to gastric cancer[15-19].

The majority of previous studies examined the incidence of gastric cancer in association with the efficacy of PG value criteria and classifications, and the correlation between H. pylori infection and gastric cancer. These studies support the PG value classification suggested by Miki et al. and show the high incidence of gastric cancer in a PG positive group and an H. pylori-infected group[20-24]. As noted above, serum PG is an excellent means of identifying patients at high risk for future gastric cancer; however, the longest period surveyed in previous studies was 10 years. There have been

no 15-year studies either in Japan or elsewhere, and there have been no five-year serial studies totaling 15 years focusing on a comparison of the incidence of gastric cancer and the validity of PG testing.

A metal product manufacturer (Company Y) in T Prefecture provided gastric cancer screening by x-ray and in 1990, shifted screening to a facility with a gastroenterologist on staff. An annual decrease of employees signing up for screening[25] prompted the company to opt for serum PG testing in a one-time trial in 1995. In the 15 years since then, approximately 80 individuals have been diagnosed with gastric cancer. Therefore, we conducted a five-year serial studies totaling 15 years on the individuals who underwent PG testing in 1995 for the purpose of examining the validity of testing in each period and the incidence of gastric cancer in PG positive and negative groups.

Subjects and Methods

1. Subjects

Subjects were 4531 full and part-time workers aged 35 years or older employed at Company Y in 1995. Among these, we analyzed 4383 subjects (96.7%), excluding 59 individuals who did not undergo PG testing (1.3%) and 51 individual who were 60 years of age or older, 35 individuals who developed gastric cancer before 1995, and three individuals who developed gastric cancer within six months after the measurement.

2. Data collection

Survey items were gender, age, PG value in 1995, the presence or absence of gastric cancer, and the date of gastric cancer diagnosis. We delivered printed explanations to employees about the periodic health examination and consent for PG testing. We considered participation in the health examination as consent. Nurses at Company Y obtained blood samples, and PG values were measured at a testing facility utilizing pepsinogen I RIA bead and pepsinogen II RIA bead manufactured by Dinabot Co., Ltd. with immunoradiometric assay (IRMA) or radioimmuno assay (RIA). Adopting the cut-off values suggested by Miki et al., PG I≦70ng/ml and PG I/II≦3.0 were classified into a positive group and others were classified into a negative group. The follow-up survey periods were the five-year period between 1995 and 2000, the 10-year period between 1995 and 2005, and the 15-year period between 1995 and 2010. We considered the date of gastric cancer diagnosis as the completion of follow-up survey for subjects who developed cancer. We considered the end of the final year of follow-up survey for employees who did not develop gastric cancer as the completion of the follow-up survey period. We considered the date of retirement from Company Y as the date of discontinuation of the follow-up survey, and considered the year in which retired employees whose date of retirement was unknown became 60 years of age as the date of discontinuation of the follow-up survey. Information on the diagnosis for gastric cancer, including the date of diagnosis, was obtained through physicians' reports and self-reports from the testing institutions, physicians, and subjects who had been advised to submit to a detailed examination based on the results of x-ray findings from the mass screening for gastric cancer and the subjects who had visited a physician because of symptoms. Finally, industrial physicians confirmed the date of diagnosis for gastric cancer from the primary physicians in writing. The numbers of Company Y employees who underwent x-ray testing for stomach and gastroscopy (rate) were 3842 and 197, respectively, (78.2%) in 1995, 3432 and 397, respectively, (70.9%) in 1999, 3167 and 723, respectively, (74.6%) in 2004, and 3068 and 1571, respectively, (82.4%) in 2009.

3. Statistical methods

We used t-test to compare the mean values of age, age of onset, and follow-up period. The validity of testing during five-, 10- and 15-year periods was examined by calculating sensitivity and specificity utilizing a formula[26]. The incidence of gastric cancer for the 5-, 10-, and 15-year follow-up survey periods was examined by log-rank test utilizing PG classification, and the hazard ratio of gastric cancer incidence in the PG positive group was examined in relation to the PG negative group with Cox's Proportional Hazards Model identifying

proportional hazard after adjustment for gender and age. SPSS13.0 for Windows was used for statistical analyses and significance was set at 5%.

As an ethical consideration, the person in charge of mass screening for gastric cancer in the Occupational Safety and Health Management Section at Company Y linked the relevant anonymously processed files to us for analysis. We also obtained advance approval for the screening from the Medical Ethics Committee of Kanazawa University (No. 260).

Results

Subjects were 2847 males (65%) and 1536 females (35%). Of these a total of 1133 (25.8%) were classified as PG positive, including 754 males (17.2%) and 379 females (8.65%).

Table 1 provides a comparison of mean age by PG classification. The mean age in 1995 was 45.1±6.5 for male and 44.7±6.4 for female, revealing a significantly higher age in males than in females (p=0.032). According to PG classification, mean age of the negative group was 44.1±6.4 and that of the positive group was 47.3±6.0, revealing a significantly higher age in the positive than in the negative group (p<0.001). The mean age of the male negative group was 44.2±6.4 and that of the male positive group was 47.7±5.9; and the mean age of the female negative group was 44.1±6.3 and that of the female positive group was 46.5±6.2, revealing a significantly higher age in the positive group for both males and females (p<0.001).

Table 2 shows the validity of PG test including the number of individuals who developed gastric cancer, sensitivity and specificity in each period. The person-years and the follow-up year mean ± SD were 15,859.5 (confidence interval: 4.8± −0.5) in the five-year negative group, 5415.5 (4.8±0.7) in the five-year positive group, 29,909.5 (9.2±1.9) in the 10-year negative group, 9673.5 (8.5±2.4) in the 10-year positive group, 41,322.5 (12.7±3.7) in the 15-

Table1. Mean age by PG classification in 1995

Gender &PG classification	Subjects	Mean age ± SD	p value#
Male	2847	45.1 ± 6.5	0.032
Female	1536	44.7 ± 6.4	
PG (negative)	3250	44.1 ± 6.4	<0.001
PG (positive)	1133	47.3 ± 6.0	
Male PG (negative)	2107	44.2 ± 6.4	<0.001
Male PG (positive)	754	47.7 ± 5.9	
Female PG (negative)	1157	44.1 ± 6.3	<0.001
Female PG (positive)	379	46.5 ± 6.2	
Total	4383	45.0 ± 6.5	

#; t-test

Table2. The validity of Gastric cancer incidence by criteria of pepsinogen screeninng test at the point in time of the year.

	1995-2000			1995-2005			1995-2010			
	Nagative	Positive	p value#	Nagative	Positive	p value#	Nagative	Positive	p value#	Total
Subjects	3250	1133		3250	1133		3250	1133		4383
Mean age±SD (in 1995)	44.1±6.4	47.3±6.0	<0.001	44.1±6.4	47.3±6.0	<0.001	44.1±6.4	47.3±6.0	<0.001	45.0±6.5
Follow-up period [mean±SD]	15859.5 4.8±0.5	5415.5 4.8±0.7	<0.001	29909.5 9.2±1.9	9673.5 8.5±2.4	<0.001	41322.5 12.7±3.7	12562.5 11.1±4.3	<0.001	53885.0 12.3±3.9
Gastric cancer										
Mean age±SD	49.6±6.1	51.4±4.5	0.370	50.8±5.9	51.5±4.4	0.646	52.8±5.5	51.9±4.5	0.502	52.4±5.0
Follow-up period [mean±SD]	25.5 2.8±1.3	57.5 3.2±1.7	0.583	77.5 4.8±2.6	135.5 5.0±3.0	0.849	267.5 8.6±4.5	160.5 5.5±3.5	0.005	428.0 7.1±4.3
Caces	9	18		16	27		31	29		60
Evaluation										
Sensitivity (95%CI)	0.667 (0.479-0.813)			0.628 (0.480-0.756)			0.483 (0.363-0.606)			
Specificity (95%CI)	0.744 (0.743-0.745)			0.745 (0.743-0.746)			0.745 (0.743-0.746)			
Positive predictive value (95%CI)	0.016 (0.012-0.020)			0.024 (0.018-0.029)			0.026 (0.019-0.032)			
Negative predictive value (95%CI)	0.997 (0.996-0.998)			0.995 (0.993-0.997)			0.990 (0.988-0.993)			
Likelihood ratio of a positive test (95%CI)	2.604 (1.863-3.189)			2.464 (1.871-2.980)			1.893 (1.411-2.389)			
Likelihood ratio of a negative test (95%CI)	0.448 (0.251-0.701)			0.499 (0.327-0.700)			0.694 (0.528-0.858)			

#;t-test

Table3. Gastric cancer incidence and hazard ratio by pepsinogen classification by each period

	1995-2000			1995-2005			1995-2010			
	Negative	Positive	p value	Negative	Positive	p value	Negative	Positive	p value	Total
Subjects	3250	1133		3250	1133		3250	1133		4383
Mean age±SD (in 1995)	44.1±6.4	47.3±6.0	<0.001	44.1±6.4	47.3±6.0	<0.001	44.1±6.4	47.3±6.0	<0.001	45.0±6.5
Person-years	15859.5	5415.5	<0.001	29909.5	9673.5	<0.001	41322.5	12562.5	<0.001	53885.0
Follow-up period [mean±SD]	4.8±0.5	4.8±0.7	<0.001	9.2±1.9	8.5±2.4	<0.001	12.7±3.7	11.1±4.3	<0.001	12.3±3.9
Mean age±SD (at diagnosis)	49.6±6.1	51.4±4.5	0.370	50.8±5.9	51.5±4.4	0.646	52.8±5.5	51.9±4.5	0.502	52.4±5.0
Cases§	9	18	<0.001	16	27	<0.001	31	29	<0.001	60
Incidence rate (Per)#	57	350		53	279		75	231		111
HR (95%CI)‡	4.98(2.19-11.29)		<0.001	4.71(2.49-8.89)		<0.001	2.76(1.64-4.65)		<0.001	

#; Per 100,000 person-years

§; log-rank test

‡; The cox's proportional hazards model identified proportional hazard assumption after adjustment for gender and age.

year negative group, an 12,562.5 (11.1±4.3) in the 15-year positive group.

The number of individuals who developed gastric cancer during the survey was nine in the five-year negative group, 18 in the five-year positive group, 16 in the 10-year negative group, 27 in the 10-year positive group, 31 in the 15-year negative group, and 29 in the 15-year positive group, for a total of 60 individuals.

The average age of subjects who developed gastric cancer was 49.6±6.1 in the five-year negative group, 51.4±4.5 in the five-year positive group, 50.8±5.9 in the 10-year negative group, 51.5±4.4 in the 10-year positive group, 52.8±5.5 in the 15-year negative group, and 51.9±4.5 in the 15-year positive group. Throughout all 5-, 10-, and 15-year periods, there was no significant difference between negative and positive groups.

Examination of the validity of PG test showed that sensitivity was 0.667 (confidence interval: 0.479-0.813) in the five-year period, 0.628 (confidence interval: 0.480-0.756) in the 10-year period, and 0.483 (confidence interval: 0.363-0.606) in the 15-year period. The specificity was 0.744 (confidence interval: 0.743-0.745) in the five-year period, 0.745 (confidence interval: 0.743-0.746) over 15 years and the five-year period showed the highest validity.

Table 3 provides a comparison of the gastric cancer incidence, and hazard ratio by PG classification (person-year method). The five-year incidence of gastric cancer was 57 per 100,000 person years in the negative group and 350 per 100,000 person years in the positive group. Hazard ratio was 4.98 (confidence interval: 2.19-11.29). The ten-year incidence of gastric cancer was 53 per 100,000 person years in the negative group and 279 per 100,000 person years in the positive group, and the hazard ratio was 4.71 (confidence interval: 2.49-8.89). The 15-year incidence of gastric cancer was 75 per 100,000 person years in the negative group and 231 per 100,000 person years in the positive group, and the hazard ratio was 2.76 (confidence interval: 1.64-4.65). These findings revealed that the incidence and hazard ratio of gastric cancer were significantly higher in the positive group throughout the follow-up survey period ($p<0.001$). Cumulative survival rate by PG classification is shown in Figure 1.

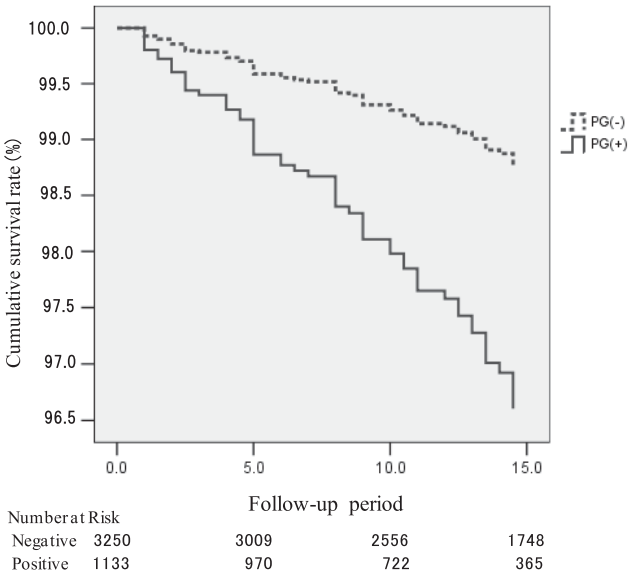

Fig. 1. Cumulative suvival rate of gastric cancer in PG positive group and PG negative group by cox's proportional hazards model

Discussion

This study was a 15-year follow-up survey on the incidence of gastric cancer with 4383 individuals who underwent serum PG testing and were classified into negative and positive groups based on PG value criteria for the purpose of examining the validity of testing and gastric cancer incidence over five-, 10-, and 15-year periods.

The mean age of male and both male/ female PG positive groups in this study was high; however, there were no significant differences in age. Samloff reported no gender differences in PG I/II ratio, and a higher number of CAG subjects in older age groups; however, he reported that subjects in younger age groups with CAG revealed lower PG I and PG I/II ratios[13]. The mean age of the PG positive group in previous studies[22-24] was also high; therefore, the subjects of this study were similar.

The sensitivity indicating the validity of testing in this study was lower than the 77% reported by Dinis-Riberiro et al.[12] and the 77.8% reported by Samloff[13]. These studies targeted subjects 40 years of age or older; however, this study targeted subjects 35 years of age or older and stopped survey when they became 60 years of age. Gastric cancer patients increase along with aging[27], which is why previous studies that followed subjects 40 years of age or older within a 10-year period showed higher incidence and sensitivity.

Company Y used PG test only in 1995. Detailed examination was noted in writing and attached to the screening report; however, testing was not specially recommended to those who were in the positive group. Because the validity of PG test was not clarified[28], the company has carried out gastric cancer screening employing the existing method. Recently, subjects of the screening have been allowed to choose either x-ray photography or gastroscopy, which increased the number of individuals who undergo gastroscopy. However, gastrofiberscopy was used for a limited number of people and the annual rate of gastrofiberscopy screening was only 70 to 80%, which limited the follow-up survey of subjects. The same method was used for both negative and positive groups, and previous studies showed that gastric cancer incidence was higher in positive group[20-24]. Therefore, this study revealed lower sensitivity compared with the previous studies that carried out gastrofiberscopy[12·13] on all subjects, resulting in the underestimation.

In this study, subjects were examined for 15 years, divided into three periods, from 1995 and 2010, Subjects in the positive group in this study revealed the highest incidence in the positive group and hazard ratio of onset during each three periods after the adjustment of age and gender. The higher incidence of gastric cancer revealed in the positive group is the same as in previous studies[20~24].

This study revealed that number of individuals who developed gastric cancer after 2005 was greater in the negative group. Many previous studies indicate the efficacy of the cutoff values suggested by Miki et al. Although the incidence was low, gastric cancer was observed. In this study, too, 0.96% subjects in the negative group developed gastric cancer during the 15 years. According to Ohata et al. and Uemura et al., there was no gastric cancer in H. pylori-negative subjects during the 10-year follow-up survey period; therefore, the gastric cancer may have developed from H. pylori infection[21·29]. This study suggested that those who were in the PG negative group in 1995 either changed to the PG positive group, or have been infected by H. pylori during these 15 years.

Additionally, Ohta et al. and Watabe et al. reported that the progression of gastric atrophy causes H. pylori to die off naturally and decrease, and PG positive and H. pylori-negative subjects have the highest risk of gastric cancer[21·30].

Miki et al. recommended ABC (D) mass screening method using concomitant measurement of PG and H. pylori antibodies as an accurate and cost-effective means of detecting cancer in negative groups[29-32]. Due to the high risk of gastric cancer in the PG positive group in spite of being H. pylori-negative[30], it is desirable to perform PG testing on all subjects initially, recommend that those with positive results undergo gastrofiberscopy, and

recommend that those with negative results be tested for H. pylori, and then recommend that H. pylori-positive subjects undergo eradication therapy or gastrofiberscopy, rather than testing all subjects for PG and H. pylori. In addition, PG testing can find gastric cancer in an earlier stage than x-ray photography[33], endoscopic mucosal resection (EMRC)[34] is also possible. Therefore, it is important for companies to provide screening to employees, including those 35 years of age or older and reluctant to undergo x-ray screening. In addition, it is important for companies to understand high and low risk groups, and to take continual preventive measures according to subject type.

Hamashima in Miki's study group reported that subjects with negative PG testing results and H. pylori require PG testing once every five years[32]. This study conducted over three periods revealed that the positive group showed the highest incidence, hazard ratio, and validity of testing for five years between 1995 and 2000, which supports the recommendation of PG testing every five years that was advocated by Miki et al.

This study was carried out for 15 years divided into three periods of five, 10, and 15 years. This is the first such study in Japan or elsewhere. The results revealed a high incidence of gastric cancer in the PG positive group and showed the validity of PG testing in five-year and 10-year periods over the 15 years. The findings that validity was highest in the first five years, and that the validity of PG testing was approximately 10 years were important. PG testing is used to identify individuals at high risk for gastric cancer[29-32], and this study revealed that such high risk individuals have high potential of developing gastric cancer within five years.

It is suggested that onset of gastric cancer is lowered through H. pylori eradication[35,36]. Because H. pylori measurement was unavailable in 1995, we were unable to identify and evaluate H. pylori-positive subjects who underwent treatment for the eradication of the virus. Although we were unable to identify the subjects with renal failure or those who were taking a proton pump inhibitor (gastric secretion inhibitor) at the basic survey, they were only a few subjects according to the health examination data reviewed afterwards.

It is necessary to conduct further surveys through multiple PG measurement considering the limitation of this study, state of H. pylori infection and changes in values.

Conclusions

This study was carried out for 15 years, divided into three periods of five, 10, and 15 years, targeting subjects who underwent PG testing in 1995. Results revealed that the validity of PG testing was approximately 10 years, the incidence and hazard ratio of gastric cancer in PG positive groups in the five years between 1995 and 2000 were high, and that the validity of PG testing was high.

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血清ペプシノゲン検査に基づく胃がん発生率と有効性に関する15年間のコホート研究

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要　　旨

【目的】我が国の胃がんの死亡率及び罹患率は現在も上位であり、その予防対策は重要である。けれども、近年X線の胃集団検診の受診者は、受診時の負担が大きいことから減少している。一方職域の胃がん予防対策は、法的義務が無いため、企業により様々であるが地域同様減少している。多くの先行研究では、血清ペプシノゲン検査法が簡便で有益としており、陽性群に発症率が高いとしているが、調査期間は最長10年であり、15年間の調査はなかった。そこで、一企業において15年間の“陽性群”と“陰性群”での発症率の違いと検査の有効性の期間を検討することを目的にコホート調査を行った。
【方法】ペプシノゲン検査を受診した4,383名を15年間追跡した。5年間、10年間、15年間の3期間に区切って各期間の検査の有効性を算出し、発症率をLog-rankで検定し、発症危険度をCox比例ハザードで分析した。
【結果】追跡期間中に陰性群と陽性群のそれぞれの胃がん発症数は、5年間で9人と18人、10年間で16人と27人、15年間で31人と29人であった。検査の感度は5年間で0.667、10年間で0.628、15年間で0.483であり、特異度は、5年間で0.744、10年間で0.745，15年間で0.745であった。発症率では、5年間の陰性群と陽性群で57、350per 100,000 person yearsであり、10年では53、279 per 100,000 person yearsであり、15年では75、231 per 100,000 person yearsであった。陰性群に対する陽性群の発生危険度は、5年間4.98、10年間4.71、15年間2.76であった（$p<0.001$）。
【結論】胃がんの発症率及び発症危険度や検査の有効性が最も高かったのは、2000年までの5年間であり、検査の有効性は、約10年であることが明らかになった。