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Original Article

Statistical Analysis of Serum Pepsinogen I (PG I) and II (PG II) Levels, PG I/PG II Ratios and Serum Gastrin Levels in a General Population

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Abstract

To allow adoption of serum pepsinogen as a screening indicator of gastric cancer, serum pepsinogen I & II levels, the ratios of PG I/PG II and the serum gastrin levels in a general population were studied using 850 samples selected at random from a rural area in Japan. The collected data were analyzed statistically to determine the distribution characteristics by various categories of sex and age. The following results were obtained:

1. The distributions of PG I and PG II, the ratios of PG I/PG II and serum gastrin values largely deviated from the normal distribution. Therefore, the use of non-parametrical methods was recommended for analysis of these data.

2. Although no significant difference between all selected men and all selected women was observed in any of the three parameters of PG I and PG II levels and the ratios of PG I/PG II, a significant difference between men and women was observed for PG I levels in under-fifty age groups. On the other hand, the median serum gastrin value (92.0 pg/ml) in all selected men was significantly lower than that (101.0 pg/ml) in all selected women. A statistically significant difference between men and women was observed in serum gastrin levels both in the under-forty age group and in the sixty and over age group.

3. No significant difference was observed in the pattern of changes in PG I levels with increasing age in either men or women. While PG II levels in men varied irregularly with advancing age, PG II levels in women showed obvious increases with advancing age. The ratios of PG I/PG II showed a tendency to decrease with advancing age in both men and women. Conversely, serum gastrin levels increased with advancing age in both men and women.

Key words: Serum pepsinogen, Serum gastrin, General population, Gastric cancer screen-

Introduction

Recently, methods for determining serum pepsinogen levels have been used in screening for gastric cancer as part of adult medical checkups in several areas and by some companies in Japan[1-3]. Currently, an indirect X-ray method is most commonly used in screening for gastric cancer in the general population in Japan. This method is very useful and has played an important role in decreasing the death rate from gastric cancer[4-7]. However, it is difficult to increase the percentage of the general population undergoing such indirect X-ray screening for gastric cancer in Japan[8,9]. Furthermore, the traditional screening method using barium has many problems such as X-ray bombardment, pain as a result of taking barium, and low and/or variable degrees of accuracy and efficiency for gastric cancer screening etc.[10-13]. It has become possible to examine blood samples easily at the time when members of the general population receive basic health examinations at regular intervals because the Law of Health and Medical Services for the Elderly was revised in 1986 and the parts dealing with the content of medical checkups were changed. Consequently, it is possible that indirect X-ray screening will be replaced by determination of the serum pepsinogen levels to

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investigate for gastric cancer. This will be very useful and effective for most of the population who have no chance to undergo regular gastric cancer screening by the X-ray method.

Although the method using serum pepsinogen determination is considered to be useful and effective for gastric cancer screening as mentioned above, the cut-off value for gastric cancer screening has not been established and it is necessary to study how to combine data regarding PG I & PG II levels and the ratio of PG I/PG II. Serum gastrin levels were also studied in addition to those of the pepsinogens as these three may be useful for gastric cancer screening[14]. This investigation was, therefore, carried out to obtain basic data with which to solve the problems of the cut-off value and the combinations among indicators for gastric cancer detection. Epidemiological studies of sera obtained from a general population are very important, but no studies concerning PG I or PG II levels and the ratios of PG I/PG II including serum gastrin levels have been reported for a general population with a large number of samples.

Subjects and Methods

Subjects: Subjects were selected by random sampling, after obtaining informed consent, from 4,032 examinees, who remained after 41 examinees with a present history and/or past history of gastric resection or gastric cancer were excluded from the 4,073 examinees who had a regular health checkup in 1991. The residential area of these examinees was town S in Japan with a population of about 10,000, which had an average death rate due to gastric cancer[15]. Random sampling with a sampling rate of 0.2 was carried out using SPSS statistical analysis software. Eight hundred fifty samples with a sampling rate of 0.211 were selected because of the error in random sampling function. The standardized mortality ratio (SMR) of the sampling area in the study in Oita prefecture (SMR: 92.0) in the island of Kyushu was similar to that of Japan[15].

Methods: All blood samples were collected after a fasting period of about ten hours. After serum separation, all serum samples were kept frozen at -80 ℃ in our laboratory awaiting the following assays. Serum PG I, PG II and gastrin levels were measured by the BML Company, Ltd. (Tokyo, Japan). The measurements were taken by immunoradiometric assay with Pepsinogen I/II Riabead Kits (Dainabot Co. Ltd, Tokyo, Japan) and a Gastrin RIA kit II (Dainabot Co. Ltd, Tokyo, Japan).

After measurement of serum pepsinogens and serum gastrin levels, collected data were analyzed statisically to determine the distributions by respective categories of sex and age (see Table 1 to Table 4 for numbers and classification of categories). To test the normality of the distributions in respective categories, Lilliefors' statistics based on the Kolmogorov-Smirnov test were used. Tests of normality were also carried out for the variables after the transformation of four parameters, which consisted of serum PG I and PG II values, PG I/PG II ratios and serum gastrin values. To transform the parameters, ten transformations, including the square root ($\sqrt{x}$), the square root of the cube ($\sqrt{x^3}$), the square (x^2), the cube (x^3), the logarithm (ln x), the reciprocal of the square root ($1/\sqrt{x}$), the reciprocal of the square root of the cube ($1/\sqrt{x^3}$), the reciprocal (1/x), the reciprocal of the square ($1/x^2$) and the reciprocal of the cube ($1/x^3$) were used. Statistical analysis of serum pepsinogens and gastrin levels according to sex and age groups was performed, and the box and whiskers plots were also displayed using SPSS/PC+ software (SPSS Inc.)[16]. Furthermore, to compare the statistical significance of differences between men and women or among age categories, the non-parametric one-way ANOVA of Kruskal-Wallis was used. All these statistical tests and analyses were carried out using SPSS/PC+ software (SPSS Inc.).

Results

1. Characteristics of the distribution of serum PG I and PG II values, PG I/PG II ratios and serum gastrin values.

Distributions of PG I and PG II values, and PG I/PG II ratios are shown in Tables 1, 2 and 3, respectively, and further in Figs. 1, 2 and 3, respectively. These distributions did not approximate the normal distributions in either men or women or in most of the age groups. In particular, the distributions of PG I/PG II ratios deviated from the normal distributions except in men in their forties, as indicated in Table 3 and Fig. 3.

Distributions of serum gastrin values are shown in Table 4. The distributions did not approximate the normal distributions in either men or women nor in most of the age groups, as with pepsinogens. In particular, the distributions of serum gastrin val-

Table 1 Basic results of statistical analysis of serum pepsinogen I values (μg/l) according to sex and age groups and results of tests between and among respective groups.

Sex	Men						Women						Total					
Age class (years)	-39	40-49	50-59	60-69	70+	Men	Women	-39	40-49	50-59	60-69	70+	-39	40-49	50-59	60-69	70+	Total
No.of subjects	43	39	57	103	81	323	527	74	74	128	147	104	117	113	185	250	185	850
Median PG I level (μg/l)	47.7	57.2	48.2	46.9	41.6	47.7	45.9	42.9	45.7	47.3	48.1	43.4	45.1	47.6	47.6	47.1	42.2	46.6
Quartile deviation of PG I (μg/l)	6.1	11.2	11.4	15.3	16.2	14.0	10.4	9.9	8.2	9.2	10.1	14.1	9.0	9.9	10.1	12.8	14.3	11.5
5th percentile of PG I (μg/l)	30.4	28.4	18.3	10.3	6.2	11.6	23.9	25.7	29.6	28.9	22.3	9.9	28.4	28.9	24.6	17.1	7.9	19.5
95th percentile of PG I (μg/l)	75.5	82.5	91.5	112.6	97.2	91.2	80.6	73.7	73.2	78.9	81.4	96.5	73.6	77.4	79.0	90.7	96.5	84.2
Minimum PG I level (μg/l)	28.3	6.3	3.7	1.9	2.7	1.9	2.0	20.6	23.3	19.9	2.0	2.5	20.6	6.3	3.7	1.9	2.5	1.9
Maximum PG I level (μg/l)	82.8	116.0	110.3	217.5	126.9	217.5	231.5	92.0	114.6	95.0	123.5	231.5	92.0	116.0	110.3	217.5	231.5	231.5
Mean PG I level (μg/l)	50.1	56.1	49.9	52.8	45.9	50.6	49.0	45.7	48.1	50.1	49.3	50.0	47.3	50.9	50.1	50.7	48.2	49.6
Standard error of PG I (μg/l)	2.03	3.04	2.72	3.36	2.98	1.47	0.86	1.72	1.85	1.33	1.49	2.94	1.33	1.63	1.24	1.64	2.11	0.77
Test by Lillifors statistics	*	N.S.	N.S.	***	N.S.	*	***	*	**	**	**	***	*	N.S.	***	***	**	***
Kurskal-Wallis test	N.S. (0.0582)					N.S.	N.S.						N.S.					

Note: N.S.; not significant, *; p<0.05, **; p<0.01, ***; p<0.001.

Table 2 Basic results of statistical analysis of serum pepsinogen II values (μg/l) according to sex and age groups and results of tests between and among respective groups.

Sex	Men						Women						Total					
Age class (years)	-39	40-49	50-59	60-69	70+	Men	Women	-39	40-49	50-59	60-69	70+	-39	40-49	50-59	60-69	70+	Total
No.of subjects	43	39	57	103	81	323	527	74	74	128	147	104	117	113	185	250	185	850
Median PG II level(μg/l)	11.7	18.3	15.9	19.1	16.8	17.0	17.1	11.5	14.5	17.8	18.0	19.5	11.6	16.1	17.1	18.4	17.4	17.1
Quartile deviation of PG II (μg/l)	7.9	5.1	5.7	7.0	6.3	6.2	8.7	8.7	8.4	8.5	7.9	8.4	8.4	7.8	7.7	7.5	7.2	7.7
5th percentile of PG II (μg/l)	4.0	6.9	4.9	6.0	4.5	4.7	3.8	2.7	3.5	4.4	4.7	5.3	3.0	3.9	4.6	5.2	5.3	4.1
95th percentile of PG II (μg/l)	29.9	31.9	36.4	35.6	35.2	34.6	36.6	30.0	31.0	39.7	39.3	41.1	30.0	31.1	37.9	37.7	36.7	35.6
Minimum PG II level (μg/l)	3.4	6.7	4.1	2.5	2.4	2.4	2.4	2.6	2.4	2.7	2.6	3.4	2.6	2.4	2.7	2.5	2.4	2.4
Maximum PG II level (μg/l)	35.4	36.5	52.1	76.9	42.1	76.9	60.4	31.6	44.2	60.4	57.0	53.8	35.4	44.2	60.4	76.9	53.8	76.9
Mean PG II level (μg/l)	13.8	18.4	17.6	20.1	18.2	18.1	18.0	13.7	15.5	18.5	19.4	20.3	13.8	16.5	18.2	19.7	19.4	18.1
Standard error of PG II (μg/l)	1.37	1.13	1.29	1.05	1.00	0.54	0.48	1.09	1.16	1.00	0.91	1.09	0.85	0.86	0.79	0.69	0.76	0.36
Test by Lillifors statistics	*	N.S.	*	*	N.S.	N.S.	**	***	***	**	N.S.	*	***	**	*	*	**	***
Kurskal-Wallis test			**			N.S.			***						***			

Note: N.S.; not significant, *; p<0.05, **; p<0.01, ***; p<0.001.

Table 3 Basic results of statistical analysis of the ratios of PG I/PG II according to sex and age groups and results of tests between and among respective groups.

Sex	Men						Women						Total					
Age class (years)	-39	40-49	50-59	60-69	70+	Men	Women	-39	40-49	50-59	60-69	70+	-39	40-49	50-59	60-69	70+	Total
No. of subjects	43	39	57	103	81	323	527	74	74	128	147	104	117	113	185	250	185	850
Median PG I/PG II	4.4	3.2	2.8	2.4	2.4	2.8	2.8	3.9	3.6	2.9	2.6	2.4	4	3.3	2.8	2.4	2.4	2.8
Quartile deviation of PG I/PG II	2.3	0.7	1.0	0.9	1.0	1.1	1.6	2.5	1.9	1.6	1.4	1.1	2.8	1.4	1.4	1.2	1.1	1.3
5th percentile of PG I/PG II	1.8	1.3	1.1	0.8	0.6	0.9	1.3	1.9	1.7	1.5	1.2	1.0	1.9	1.6	1.5	1.1	0.7	1.2
95th percentile of PG I/PG II	9.9	6.2	8.3	6.0	5.6	8.0	8.6	10.8	8.8	8.2	8.5	6.5	10.3	8.5	8.2	7.4	5.9	8.3
Minimum PG I/PG II	1.5	0.4	0.6	0.4	0.3	0.3	0.3	1.6	1.4	0.9	0.4	0.3	1.5	0.4	0.6	0.4	0.3	0.3
Maximum PG I/PG II	11.2	8.5	10.0	23.0	9.9	23.0	14.4	12.7	14.4	8.8	10.7	9.1	12.7	14.4	10.0	23.0	9.9	23.0
Mean PG I/PG II	5.1	3.4	3.5	3.0	2.8	3.4	3.8	5.0	4.4	3.7	3.4	2.9	5.1	4.1	3.6	3.2	2.9	3.6
Standard error of PG I/PG II	0.41	0.24	0.28	0.25	0.18	0.13	0.10	0.35	0.30	0.19	0.18	0.17	0.27	0.22	0.15	0.14	0.13	0.08
Test by Lillifors statistics	*	N.S.	***	***	***	***	***	***	***	***	***	***	***	***	***	***	***	***
Kurskal-Wallis test			***			N.S.			***						***			

Note: N.S.; not significant, *; p<0.05, ***; p<0.001.

Table 4 Basic results of statistical analysis of serum gastrin values (pg/ml) according to sex and age groups and results of tests between and among respective groups.

Sex	Men						Women						Total					
Age class (years)	-39	40-49	50-59	60-69	70+	Men	Women	-39	40-49	50-59	60-69	70+	-39	40-49	50-59	60-69	70+	Total
No. of subjects	43	39	57	103	81	323	527	74	74	128	147	104	117	113	185	250	185	850
Median of serum gastrin values (pg/ml)	82.7	89.0	94.0	92.0	100.0	92.0	101.0	89.5	91.5	97.0	104.0	118.5	86.3	91.0	96.0	101.0	113.0	97.1
Quartile deviation of gastrin values (pg/ml)	18.6	18.4	27.4	33.0	36	28.5	36.0	22	24	28.9	47.0	63.1	18.8	22.3	27.8	36.4	49.8	32.1
5th percentile of gastrin values (pg/ml)	40.8	55.4	46.4	39.6	43.7	45.0	56.0	58.6	44.6	52.4	58.2	62.3	52.4	48.5	51.0	51.6	51.9	51.7
95th percentile of gastrin values (pg/ml)	140.3	194.3	260.1	344.8	380.5	250.2	380.2	282.2	233.0	244.3	481.6	512.5	237.1	212.9	254.5	383.9	486.7	324.0
Minimum gastrin level (pg/ml)	27	46.	24	24	11	11	32	32	35	39	40	54	27	35	24	24	11	11
Maximum gastrin level (pg/ml)	163	213	315	756	547	756	764	448	534	715	764	764	448	534	715	764	764	764
Mean gastrin level (pg/ml)	83.6	100.2	113.1	117.0	132.4	113.7	140.6	113.0	110.1	119.3	156.7	185.4	102.2	106.6	117.4	140.4	162.2	130.4
Standard error of gastrin values (pg/ml)	4.41	6.55	8.22	9.46	11.3	4.55	5.09	8.19	8.48	7.12	11.18	15.3	5.57	5.99	5.53	7.73	10.06	3.62
Test by Lillifors statistics	N.S.	**	***	***	***	***	***	***	***	***	***	***	***	***	***	***	***	***
Kurskal-Wallis test			*			***			***						***			

Note: N.S.; not significant, *; p<0.05, **; p<0.01, ***; p<0.001.

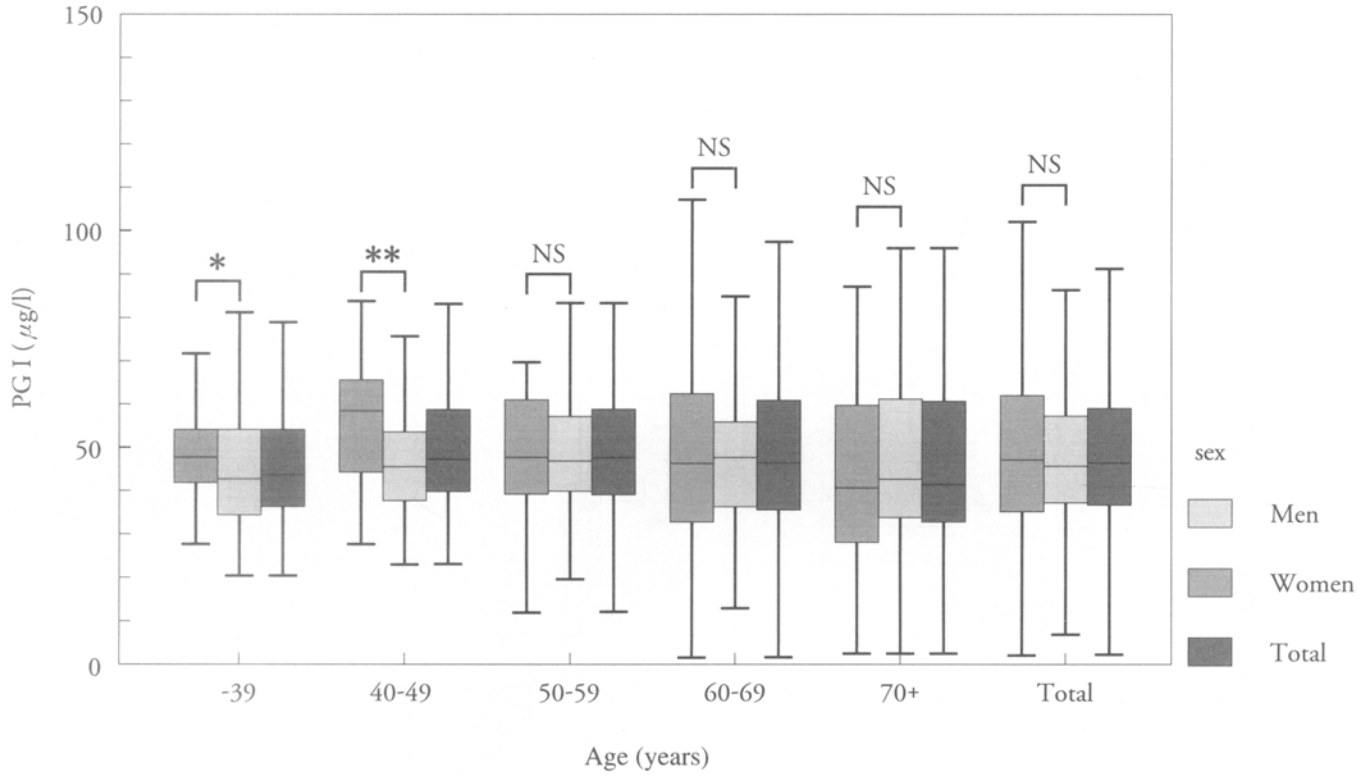

Fig 1. Box and whisker plots of serum pepsinogen I (μg/l) separated by sex.
**: p<0.01, *:p<0.05 and NS: not significant denote the results by Mann-Whitney U-Wilcoxon rank sum W test between men and women in each age-related category.

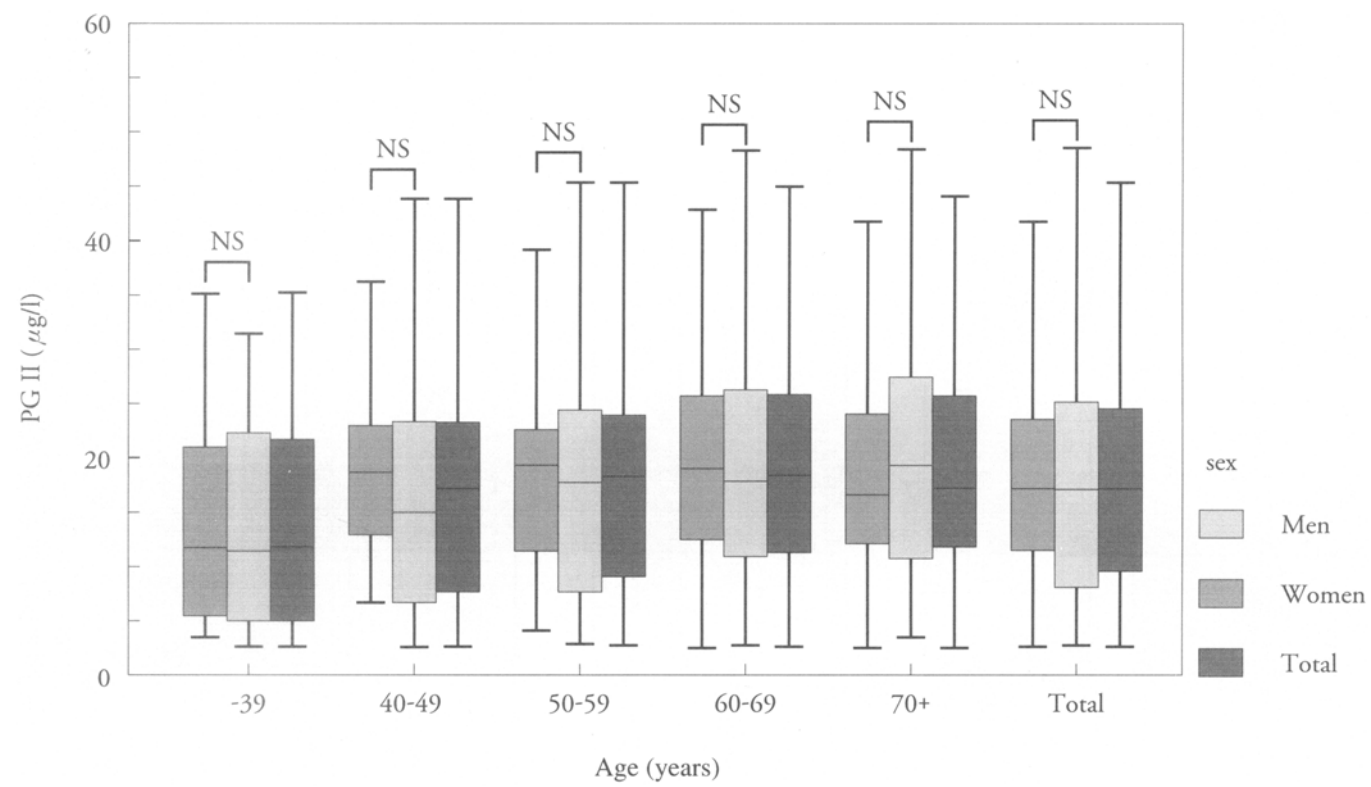

Fig 2. Box and whisker plots of serum pepsinogen II (μg/l) separated by sex.
No significant differences between men and women were observed for PG II levels in all age groups. NS denotes not significant by Mann-Whitney U-Wilcoxon rank sum W test.

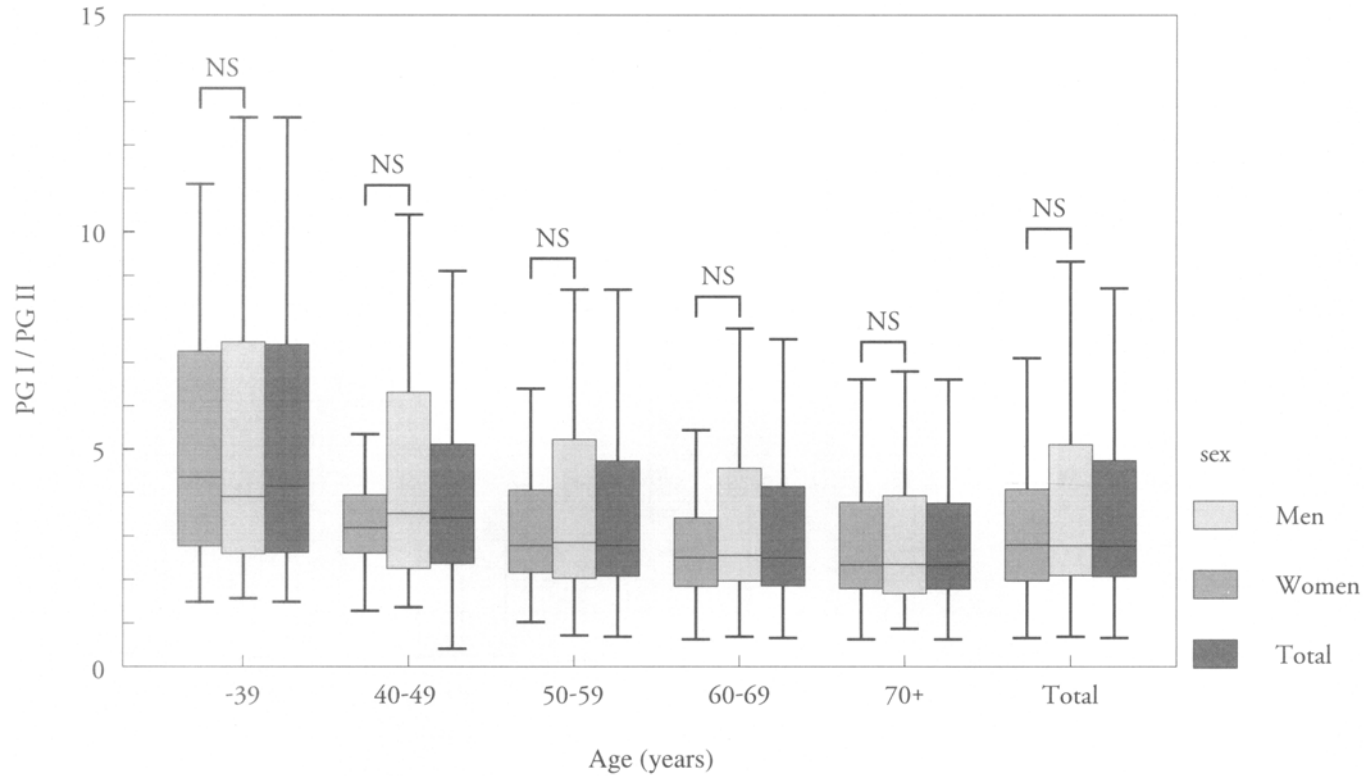

Fig 3. Box and whisker plots of the ratios of PG I/PG II separated by sex.
No significant differences between men and women were observed for the ratio of PG I /PG II in all age groups. NS denotes not significant by Mann-Whitney U-Wilcoxon rank sum W test.

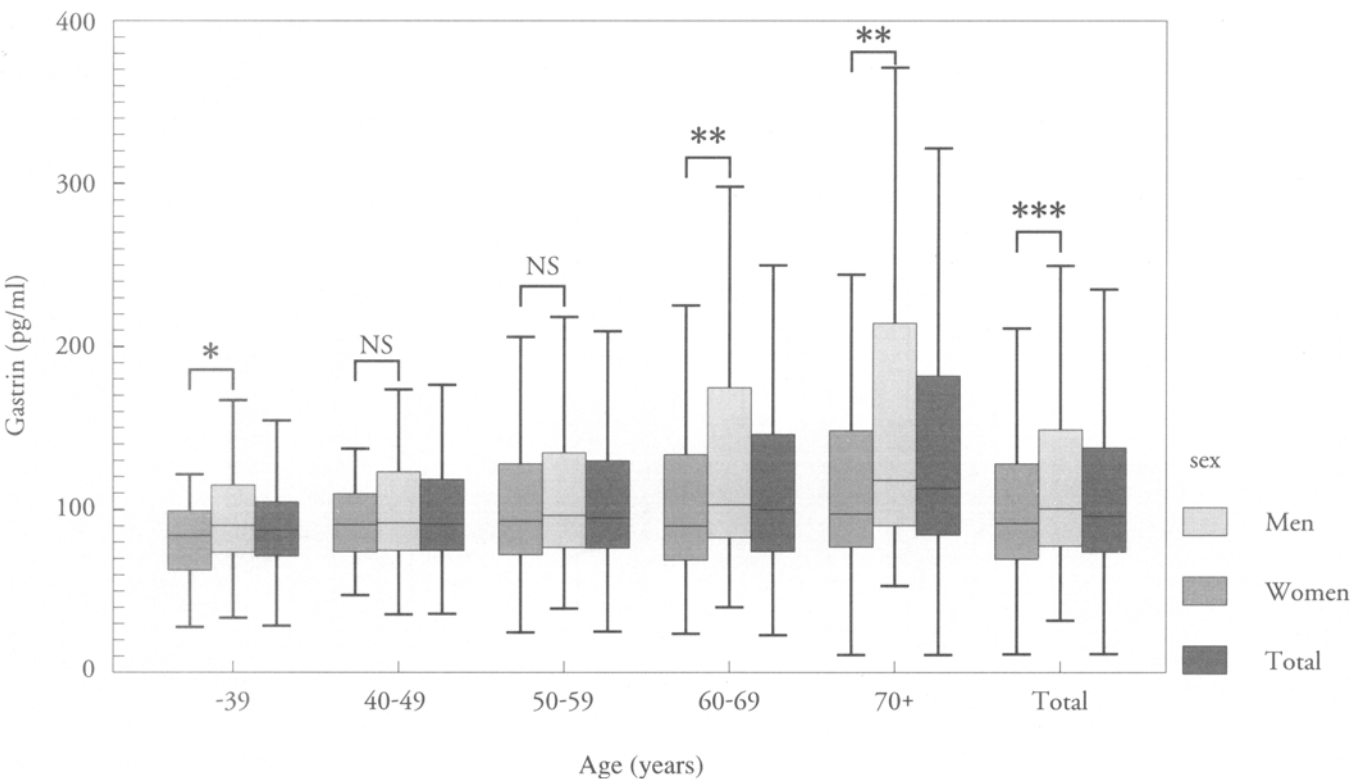

Fig 4. Box and whisker plots of serum gastrin levels (pg/ml) separated by sex.
***: p<0.001, **: p<0.01, *: p<0.05 and NS: not significant denote the results by Mann-Whitney U-Wilcoxon rank sum W test between men and women in each age-related category.

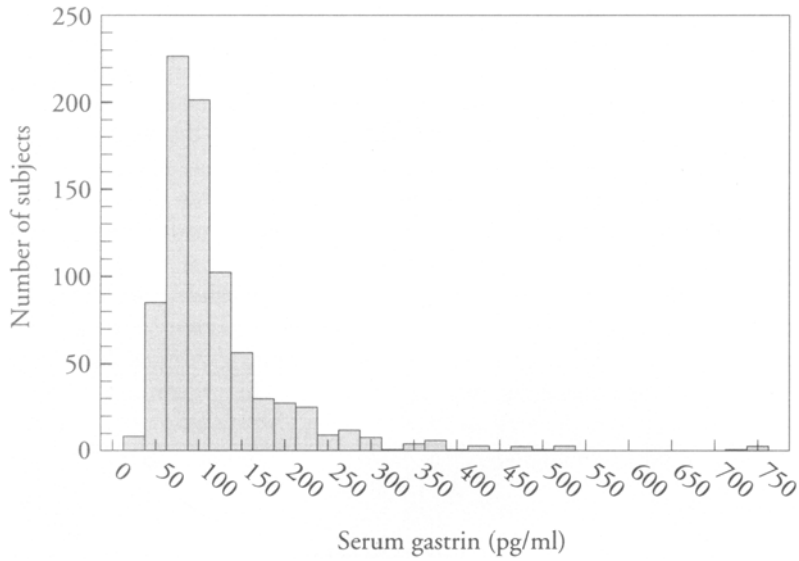

Fig 5. Distribution of serum gastrin (pg/ml) in the total study population (crude data).

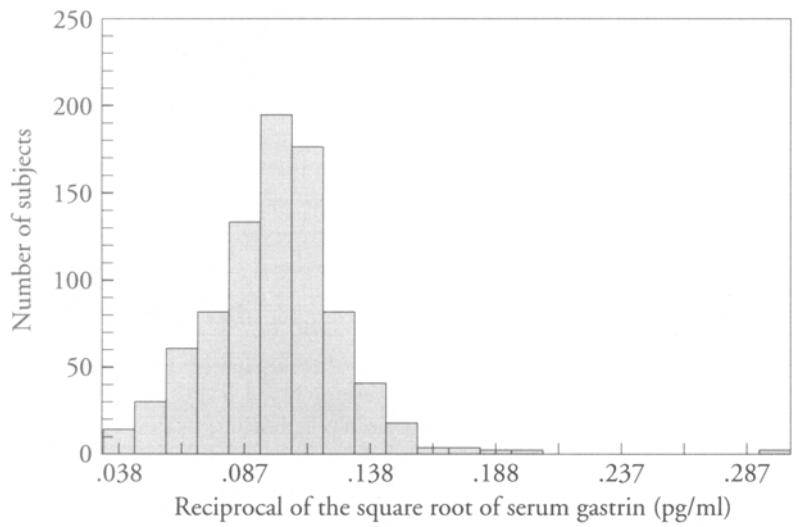

Fig 6. Distribution after the transformation by the reciprocal of the square root of serum gastrin (pg/ml) in the total study population.

ues deviated from the normal distributions except in men below the age of 40, as indicated in Table 4 and Fig. 4.

Fifth percentile and ninety-fifth percentile values of serum PG I and PG II, PG I/PG II ratios and serum gastrin are also shown in Tables 1-4. The ninety-fifth percentile values of serum gastrin were 324 pg/ml in total, 250 pg/ml in men, and 380 pg/ml in women.

2. Sex differences in PG I and PG II levels, PG I/PG II ratios and serum gastrin levels.

As shown in Tables 1-3, the medians of PG I and PG II values, and PG I/PG II ratios were 47.7 μg/l & 45.9 μg/l, 17.0 μg /l & 17.1 μg/l and 2.8 & 2.8 in men and women, respectively. Although no significant difference between all selected men and all selected women was observed for any of the three parameters, a significant difference between men and women was observed in PG I levels in under-50 age groups as shown in Fig. 1.

On the other hand, as shown in Table 4, the medians of serum gastrin values were 92.0 pg/ml & 101.0 pg/ml in men and women, respectively. The serum gastrin level in women was significantly higher than that in men. As shown in Fig. 4, a significant difference between men and women was observed in serum gastrin levels both in the under-40 age group and in the 60-and-over age groups.

3. Changes in serum PG I and PG II levels, PG I/PG II ratios and serum gastrin levels with advancing age.

As shown Tables 1-3, PG I and PG II levels, and PG I/PG II ratios changed with increasing age. Although the changes in PG I levels were not statistically significant with increasing age in either men or women, the statistical probability value determined by the Kruskal-Wallis test was at the margin of significance (p=0.0582) for men. PG II levels increased significantly with advancing age in women. Conversely, PG I/PG II ratios decreased significantly with advancing age in both men and women.

Furthermore, as shown in Table 4, serum gastrin levels increased significantly with advancing age in both men and women except for men in their 60s.

4. Transformation of parameters.

Tests of normality were carried out on original data and variables after the transformation of parameters using ten transformations. No deviations from the normal distribution were observed in the variables after transformation of the following parameters: the square root of PG I, the square root or the logarithm of PG II, the logarithm of the ratio of PG I/PG II and the logarithm or the reciprocal of the square root of the serum gastrin level. As an example of the distribution after the transformation approximating the normal distribution, histograms of serum gastrin concentrations before and after the transformation are shown in Fig.5 and Fig.6, respectively.

Discussion

Sampling method : Although the sampling in this study was different from that of our previous study [17], it was thought that the subjects selected by this method were more representative than those chosen by our previous method [17]. A constant sampling rate was maintained for each sex-and age-related category because random sampling with a sampling rate of 0.2 was carried out for all examinees. Therefore, it seemed that the distributions of respective parameters in all examinees were better characterized by the subjects selected in this random sampling than by the sampling method employed in our previous study [17].

Demographic characteristics of town S where blood samples were collected : This sampling area was not special concerning the gastric cancer death in 1991 and was considered to be an area having an average incidence of gastric cancer death [15]. Subjects in the present study were examinees who had received health checkups at regular intervals in this area. Most of those examinees (87%) were aged 40 years and over and recommended to receive a health checkup by the town office. Some examinees were aged less than 40 years old, including the public personnel and their families in town S who voluntarily received the health checkups to helping with this study.

Characteristics of the distributions of PG I and PG II values, PG I/PG II ratios, serum gastrin values and statistical analysis of these parameters : In the present study, the distributions of PG I and PG II levels, PG I/PG II ratios and serum gastrin levels deviated greatly from normal distributions. Stemmermann et al. reported that due to the heavy skew in serum pepsinogen distributions, non-parametric methods of statistical analysis should be employed [18]. Westerveld et al. used square root transformation to remove the skewness of the distributions of PG I & PG II values and serum gastrin values, and used the ratio of PG I/PG II in statistical analyses without transformation [19]. Furthermore, Kikuchi et al. reported the use of natural logarithms of PG I and PG II values or PG I/PG II ratios as criterion variables for multiple regression analyses [20, 21]. Carmel performed statistical analysis of pepsinogens and gastrin levels in 147 patients with pernicious anemia after logarithmic transformations because their values displayed a skewed distribution [22]. However, several studies of the serum pepsinogens and gastrin levels have been reported with no reference to their distributions [23-29]. If it is necessary to use parametric methods in statistical analyses, it is recommended that transformation of these parameters be used to analyze the data. Statistical analyses after some transformations of these parameters might provide better results than those using non-transformed data. The present study suggested that it was possible to use statistical methods in studies of serum pepsinogens and gastrin levels if transformations were made as follows: square root of PG I, square root or logarithm of PG II, logarithm of the ratio of PG I/PG II and the logarithm or reciprocal of the square root of serum gastrin.

Sex-related differences in PG I and PG II levels, PG I/PG II ratios and serum gastrin levels: Conflicting results have been reported regarding sex-related differences of PG I levels in general populations in the present and in previous studies. The PG I level in men was reported to be significantly higher than that in women [17, 24, 30-32], while in other studies no significant difference was observed in PG I levels between men and women [26, 33-35]. In this study, although no significant difference was observed in PG I levels between all selected men and all selected women, a significant difference between men and women was observed for PG I levels in under-50 age groups. These discrepancies may be related to racial and/or geographic factors and the age constitution of the selected groups. No significant differences were observed here for PG II levels or the ratios of PG I/PG II between men and women in accordance with the results of previous studies [33, 36]. Although few investigations of sex-related differences in serum gastrin levels in a general population have been reported, in the present study the serum gastrin level in women was significantly higher than that in men and a significant difference between men and women was observed in serum gastrin levels in both the under-40 group and in the 60-and-over group. Since the origin of the sex-related difference of serum gastrin levels in unclear at present, further studies are necessary to clarify its significance.

Changes in PG I and PG II levels, PG I/PG II ratios and serum gastrin levels with increasing age: Changes with increasing age were observed in PG II levels, PG I/PG II ratios and serum gastrin levels, but not in PG I levels. These findings were somewhat different from the results in previous investigations in which PG I levels were almost constant in subjects younger than 70 but showed a marked decrease in men aged 70 and over [17, 37]. This discrepancy was considered to be due to differences in sample size in respective categories. It has been reported in previous studies that PG II levels increased until the fifties or sixties, and that they then decreased after the sixties or seventies [37, 38]. In this study, increases in PG II levels with advancing age were observed in woman but not in men. This discrepancy may be related to the sample size in respective categories and/or differences in lifestyles. The ratios of PG I/PG II decreased with increasing age in both men and women in agreement with the results of previous reports [17, 36]. In this study, serum gastrin levels increased in men and more obviously in women with advancing age. This was in agreement with the results reported by McGuigan et al. who found that fasting serum gastrin levels rose with increasing age [29]. On the other hand, Strickland reported that the positive age-gastrin correlation was confined to Type A atrophic gastritis [39]. Thus, as aging and changes due to atrophic gastric mucosa are confounders, it is necessary to remove the confounders and to investigate serum gastrin levels by using a larger population size to clarify the changes in serum gastrin levels with advancing age.

Further fundamental studies on serum pepsinogens and serum gastrin levels should contribute to the improvement of sys-

tematic gastric cancer screening.

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