ORIGINAL CONTRIBUTION

Should Age, Sex, Subjective Symptoms in the Stomach and Past History of Peptic Ulcer be Regarded in the Evaluation of Efficacy of Serum Pepsinogen Values for Use in Gastric Cancer Mass-screening?

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The subjects were 13,500 employees. Sera and information on age, sex, subjective symptoms in the stomach and past histories of peptic ulcer were collected. Serum pepsinogen I and II values were measured and analyzed (LPI and LPII: natural logarithm of serum pepsinogen I and II (ng/ml) respectively).

Among those with stomach ache, heavy feeling of stomach or nausea, LPI and LPII levels were higher than among those without the symptoms, and it was suggested that those with subjective stomach symptoms should be dealt with separately in the evaluation of efficacy of gastric cancer mass-screening by serum pepsinogen values. Among those with a past history of duodenal ulcer, LPI and LPII levels were higher, and among those with a past history of gastric ulcer, LPI level was lower but LPII level was higher, and it was suggested that those with a past history of peptic ulcer should also be dealt with separately in the evaluation.

Because serum pepsinogen values changed depending on age and sex among those without any subjective stomach symptoms or past history of peptic ulcer, it was suggested that the evaluation of efficacy of these values for mass-screening should be done separately with respect to age and sex. J Epidemiol, 1993; 3: 71-76

Pepsinogen is an inactive precursor of pepsin, a well-known gastric acid protease. Pepsinogen is classified into two immunologically different subtypes: pepsinogen I (PGI) and pepsinogen II (PGII). The source of serum pepsinogens is gastric mucosa. PGI is mainly produced in the fundic area and PGII in the whole area of the stomach. Recently it has become easy to measure serum PGI and PGII, and the relationships between these values and the risk of gastric cancer has been shown.

These values have already been used in several mass-screening programs. The efficacy of these values for use in gastric cancer mass-screening should be evaluated by the analysis using receiver operator characteristics (ROC) curve before being put into the practical use. But such evaluation has not yet been done precisely and there seem to be some problems in the evaluation.

It is generally taken as a principle that those with some symptoms should not attend mass-screening but should take medical services clinically. However, in fact it is reported that in Japan a part of the screenees participating in mass-screening for gastric cancer have some symptoms in the stomach. So the first prob-
lem is whether those with some symptoms in the stomach should be removed from the evaluation or not. Since it has been proved that serum pepsinogen I is elevated among those with peptic ulcers, the second problem is whether those with a past history of peptic ulcer should be removed from the evaluation or not. The analyses by receiver operator characteristics (ROC) curve which have been done until now have not taken sex or age into account. The third problem is whether the evaluation should be done separately with respect to sex and age or not.

In this study, the data from 13,500 employees were analyzed to clarify these three problems.

**SUBJECTS AND METHODS**

Sera were collected from two groups of employees, one of which consisted of about 4,500 public service workers, the other of about 9,000 workers belonging to small or middle scale companies involved in textile products. The sera were the residues of serum examinations in the health-screening carried out from April 1989 to March 1990. The sera would have been going to be abandoned except for this study and they were used with the approval of the organization which administers the health-screening. In one group, PGI and PGII (mg/l) were measured by the BML Co. Ltd. after routine serum examination. In the other group, PGI and PGII were measured by the SMI BRISTOL Co. Ltd. after freezing preservation below -20°C for 3 to 15 months. The measurements were by immunoradiometric assay with Pepsinogen I/II RIABEAD KITS produced by DAINABOT Co. Ltd.

In addition to sex and age, information on subjective symptoms in the stomach and past history of peptic ulcer were collected by questionnaire. With respect to subjective symptoms in the stomach, the questions asked if he/she had stomach ache, heavy feeling of the stomach or nausea. With respect to past history of peptic ulcer, the questions asked if he/she had any past history of gastric ulcer or duodenal ulcer.

At first the relationships between serum pepsinogen values and five factors, — stomach ache, heavy feeling of stomach, nausea, past history of gastric ulcer and past history of duodenal ulcer — were analyzed by multiple regression analyses with LPI, LPII or LI/II (natural logarithm of serum PGI, PGII, PGI/PGII respectively) values as criterion variables and with age, sex and one of the five factors as explanatory variables. Relationships with p<0.10 were considered statistically significant.

Next the relationships between the values and sex and age were observed among the employees without any subjective stomach symptoms or past history of peptic ulcer. The employees were divided into several groups with respect to sex and age (20-29, 30-39, 40-49, 50-59, 60-69, 70-). LPI, LPII and LI/II values were compared mutually among the groups by Student's t-test when variances were not significantly different between two groups, and otherwise by Welch's t-test. Differences with p<0.05 were considered statistically significant.

The positive rates when criteria were defined by PGI, PGII and PI/II(PGI/PGII) were also observed with respect to each group. As to PGI and PI/II, the values that were less than some value (cut off value) were defined to be positive. As to PGII, the values that were more than some value (cut off value) were defined to be positive.

The calculations were done using the package program for personal computers "HALBAU".

**RESULTS**

The response rate to the questionnaire was 95.4%, and the subjects who did not respond to the questionnaire were excluded from the analysis. Age and sex distributions of total subjects which were used in the analysis is shown in Table 1. Positive rates of subjective symptoms and past history of peptic ulcer are shown in Table 2. The rates changed depending on sex and age. The relationships between serum pepsinogen values and the subjective symptoms or past history were analyzed by multiple regression analysis, and the results are shown in Table 3. LPI showed negative correlations with past history of gastric ulcer and positive ones with the other four factors, and they were statistically significant, though multiple correlation coefficients regarding subjective symptoms in the stomach were considerably small. LPII showed positive correlations with the five factors, and they were statistically significant except for that of heavy feeling of stomach. LI/II showed negative correlations with past history of gastric ulcer and positive ones with the other four factors, and ones with past history of gastric

| Age   | Men | Women | Total |
|-------|-----|-------|-------|
| 20-29 | 1,403 | 201 | 1,604 |
| 30-39 | 1,771 | 174 | 1,945 |
| 40-49 | 4,083 | 1,118 | 5,201 |
| 50-59 | 2,727 | 878 | 3,605 |
| 60-69 | 640 | 199 | 839 |
| 70-   | 158 | 30 | 188 |
| Total | 10,782 | 2,600 | 13,382 |
Table 2. Positive rates (%) of subjective symptoms in the stomach and past history of peptic ulcer.

| Age | Sex | Stomach ache | Heavy feeling of stomach | Nausea | Gastric ulcer | Duodenal ulcer |
|-----|-----|-------------|-------------------------|--------|--------------|---------------|
| 20-29 | M  | 8.5         | 4.6                     | 7.3    | 1.3          | 2.8           |
|     | W  | 6.4         | 1.5                     | 5.5    | 1.0          | 1.0           |
| 30-39 | M  | 8.4         | 6.5                     | 7.2    | 2.1          | 5.0           |
|     | W  | 9.2         | 8.6                     | 5.7    | 0.6          | 1.1           |
| 40-49 | M  | 9.8         | 8.0                     | 8.4    | 6.0          | 8.8           |
|     | W  | 11.3        | 10.1                    | 8.9    | 3.0          | 3.7           |
| 50-59 | M  | 6.6         | 7.2                     | 5.4    | 7.6          | 9.9           |
|     | W  | 7.4         | 9.0                     | 6.0    | 3.4          | 4.7           |
| 60-69 | M  | 3.4         | 6.9                     | 1.9    | 10.3         | 8.1           |
|     | W  | 5.5         | 6.0                     | 5.5    | 2.0          | 2.0           |
| 70-  | M  | 1.9         | 5.7                     | 1.9    | 10.8         | 5.1           |
|     | W  | 0.0         | 3.3                     | 0.0    | 6.7          | 3.3           |
| Total | M  | 8.1         | 7.0                     | 6.8    | 5.5          | 7.6           |
|     | W  | 8.9         | 8.6                     | 7.1    | 2.8          | 3.5           |

% for numbers of subjects in Table 1

Table 3. Fge and sex adjusted relationships between serum pepsinogens and subjective symptoms or past history of peptic ulcer.

| C.V.          | Factor            | P.R.C (p-value) | M.C.C |
|--------------|------------------|----------------|--------|
| LPI          | Stomach ache      | 9.68 × 10⁻²     | 0.076  |
| LPI          | Heavy stomach     | 7.13 × 10⁻²     | 0.068  |
| LPI          | Nausea            | 6.23 × 10⁻²     | 0.065  |
| LPI          | P.H. of U.G.      | -6.22 × 10⁻²    | 0.064  |
| LPI          | P.H. of U.D.      | 2.27 × 10⁻¹     | 0.119  |
| LPII         | Stomach ache      | 9.31 × 10⁻²     | 0.282  |
| LPII         | Heavy stomach     | 3.48 × 10⁻²     | 0.280  |
| LPII         | Nausea            | 5.62 × 10⁻²     | 0.280  |
| LPII         | P.H. of U.G.      | 9.89 × 10⁻²     | 0.281  |
| LPII         | P.H. of U.D.      | 1.75 × 10⁻¹     | 0.288  |
| LII/II       | Stomach ache      | 3.66 × 10⁻²     | 0.331  |
| LII/II       | Heavy stomach     | 3.64 × 10⁻²     | 0.332  |
| LII/II       | Nausea            | 6.09 × 10⁻³     | 0.331  |
| LII/II       | P.H. of U.G.      | -1.61 × 10⁻¹    | 0.336  |
| LII/II       | P.H. of U.D.      | 5.16 × 10⁻²     | 0.332  |

In addition to “factor”, age (years) and sex (men = 1, women = 2) were explanatory variables in each multiple regression analysis.

C.V.: criterion variable (LPI, LPII and LII/II are natural logarithm of pepsinogen I (ng/ml), pepsinogen II (ng/ml) and LII/II)
Factor: explanatory variable except age and sex (yes = 1, no = 0)
P.R.C.: partial regression coefficient
M.C.C.: multiple correlation coefficient adjusted for the degree of freedom
Heavy stomach: heavy feeling of stomach
P.H. of U.G.: past history of gastric ulcer
P.H. of U.D.: past history of duodenal ulcer

ulcer and duodenal ulcer were statistically significant.

There were 9,983 employees without any of the five factors, and their age and sex distributions are shown in Table 4. The age and sex distributions of pepsinogens among these employees are shown in Table 5. Regarding both men and women, LPI increased slightly in proportion to age between 20 and 50, and decreased slightly over 50 years of age. LPI levels among men were higher than among women in the age groups of 20-29, 30-39 and 40-49, and the differences were statistically significant. Regarding both men and women, LPII increased slightly in proportion to age between 20 and 50, and reached a plateau over 50 years of age. LPII levels among men were also higher than among women for age groups of 20-29, 30-39 and 40-49, and the differences were statistically significant.

Over 70 years of age, both LPI level and LPII level among men were lower than those among women, but the differences were not statistically significant. Regarding both men and women, LII/II decreased while age increased and no statistically significant differences of LII/II level were observed between men and women for any age groups.

Positive rates when criteria were defined by PGI, PGII or PI/II are shown in Tables 6-1, 6-2, 6-3. As to both men and women, the cut off values of PGI and PI/II that showed positive rates of the same value decreased and those of PGII increased while age increased.
**Table 5.** Age and sex distributions of LPI, LPII, LI/II.

| Age  | Men                      | Women                   |
|------|--------------------------|-------------------------|
| 20-29| 3.743 (41.68) ± 0.346    | 3.579 (35.84) ± 0.363   |
| 30-39| 3.787 (40.12) ± 0.472    | 3.645 (38.28) ± 0.460   |
| 40-49| 3.815 (45.38) ± 0.493    | 3.730 (41.68) ± 0.432   |
| 50-59| 3.751 (42.56) ± 0.643    | 3.744 (42.27) ± 0.520   |
| 60-69| 3.637 (39.37) ± 0.778    | 3.637 (39.37) ± 0.591   |
| 70-   | 3.367 (29.99) ± 1.020    | 3.385 (29.52) ± 0.995   |

**Table 6-1.** Positive percent regarding age and sex when criteria are defined by PGI.

| Criteria | PGI | Men |
|----------|-----|-----|
| 20-29    |     |     |
| 30-39    |     |     |
| 40-49    |     |     |
| 50-59    |     |     |
| 60-69    |     |     |
| 70-      |     |     |

DISCUSSION

Because of the fact that regarding PGI, PGII and PI/II, natural logarithms (skewness: -1.265, 0.0703, -0.756 and kurtosis: 5.167, -0.533, 0.728 respectively) had smaller skewness and kurtosis than crude values (skewness: 6.059, 1.754, 1.029 and kurtosis: 140.8, 5.462, 6.271 respectively), multiple regression analyses, Student’s t-tests and Welch’s t-tests were done according to natural logarithms.

Among those with stomach ache, heavy feeling of stomach or nausea, LPI and LPII levels were higher than among those without the symptoms, but regarding LI/II no statistically significant differences were observed. Since the serum levels of pep-sinogens have been shown to be in proportion to excretion of pep-sinogen, the symptoms are thought to be associated with the high pep-sinogen excretion level. A part of the symptoms may be related to peptic ulcer but another part of them are probably related to inflammation of the stomach. Several studies have made it clear that superficial gastritis is associated with high PGI level. Though endoscopic confirmation may be necessary, it is suggested that high levels of LPI and LPII among those with stomach ache, heavy feeling of stomach or nausea are due to inflammation of the stomach.

Since there seem to be some differences of serum pep-sinogen values between those with some symptoms in the stomach and those without them, the two groups should not be dealt with in the same way in gastric cancer mass-screening programs by serum pep-sinogen values. It is suggested that those with symptoms should not attend gastric cancer screening programs but be treated clinically because the symptoms may be due to peptic ulcer or gastritis.

Among those with past history of duodenal ulcer, LPI and LPII levels were higher, and among those with past history of gastric ulcer, LPI level was lower but LPII level was higher. These facts are compatible with the fact that duodenal ulcer mostly occurs under hyperacidity but gastric ulcer occurs under both hyperacidity and hypoacidity, and with the hypothesis that...
Table 6-2. Positive percent regarding age and sex when criteria are defined by PGII.

| Criteria | PGII | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70 |
|----------|------|-------|-------|-------|-------|-------|----|
| >90.0    | 0.0  | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0|
| >54.6    | 0.1  | 0.4   | 0.8   | 0.8   | 0.8   | 0.8   | 0.8|
| >33.1    | 2.4  | 4.3   | 6.6   | 6.2   | 6.5   | 6.5   | 6.5|
| >20.0    | 6.9  | 16.4  | 21.5  | 27.2  | 27.7  | 26.8  | 26.8|
| >12.1    | 20.7 | 38.9  | 49.1  | 61.0  | 62.5  | 62.6  | 62.6|
| >7.3     | 39.7 | 63.4  | 74.5  | 85.5  | 85.5  | 86.2  | 86.2|
| >4.4     | 71.0 | 92.5  | 94.8  | 98.0  | 97.7  | 95.9  | 95.9|
| >2.7     | 98.6 | 99.7  | 99.5  | 99.8  | 99.4  | 95.9  | 95.9|
| >1.6     | 99.9 | 100.0 | 99.9  | 99.9  | 99.6  | 99.2  | 99.2|

PGII : serum pepsinogen II (ng/ml)

Table 6-3. Positive percent regarding age and sex when criteria are defined by PI/II.

| Criteria | PI/II | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70 |
|----------|-------|-------|-------|-------|-------|-------|----|
| <0.4     | 0.0   | 0.0   | 0.0   | 0.2   | 0.2   | 1.6   | 1.6|
| <0.7     | 0.1   | 0.4   | 0.8   | 1.4   | 2.3   | 6.5   | 6.5|
| <1.0     | 0.1   | 1.5   | 2.6   | 5.5   | 8.9   | 17.1  | 17.1|
| <1.7     | 1.0   | 4.3   | 8.2   | 15.4  | 21.5  | 39.0  | 39.0|
| <2.8     | 7.6   | 17.9  | 25.2  | 39.7  | 47.6  | 57.7  | 57.7|
| <4.5     | 29.5  | 46.1  | 54.6  | 71.2  | 75.4  | 84.6  | 84.6|
| <7.4     | 79.3  | 85.1  | 87.4  | 94.4  | 96.1  | 98.4  | 98.4|
| <12.2    | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0|
| <2.0     | 2.7   | 7.9   | 13.0  | 21.9  | 29.8  | 41.5  | 41.5|
| <3.0     | 10.4  | 22.6  | 31.2  | 45.6  | 44.3  | 63.4  | 63.4|

PI/II : serum pepsinogen I/serum pepsinogen II

duodenal ulcer tends to occur under excess of peptic factors and gastric ulcer tends to occur under weakness of defending factor\(^{15}\). It is widely believed that past history of peptic ulcer has no relationship with risk of gastric cancer\(^{16}\). But it is unknown if the relationships between serum pepsinogen levels and risk of gastric cancer among those with past history of peptic ulcer are similar to the relationships among those without it. As to this problem, a well-designed cohort study is thought to be necessary. At least it may be concluded that those with past history of peptic ulcer should be dealt with separately in the evaluation of efficacy of gastric cancer mass-screening by receiver operator characteristics (ROC) curve, because the influence of past history of peptic ulcer on serum pepsinogen values is considerably large.

Among those without subjective symptoms or past history of peptic ulcer, LPI increased slightly in proportion to age between 20 and 50, and decreased slightly over 50 of age, while level of LPII increased gradually in proportion to age. This is thought to be related to the oral-ward migration of the border between the fundic gland area and the pyloric gland area\(^{12}\). In the 20-49 age group, both LPI and LPII levels among men were higher than those among women, and the differences were statistically significant. But over 50 years of age no sexual differences were observed regarding either LPI or LPII. The reason why the sexual differences exist in younger age is unknown, but it may have something to do with the serum total protein level, which is higher among men. These results were almost similar with other studies\(^{17,18}\), though the subjects of the studies contain those with subjective stomach symptoms or past history of peptic ulcer.

Since the probability that healthy employees have gastric cancer is very small, positive rates when criteria are defined by PGI, PGII or PI/II correspond to false-positive rates when screening for gastric cancer is done by the above criteria. The false-positive rates changed depending on age and sex. In another study, when criterion is that PI/II is less than 3.0 and PGI is less than 70.0, positive rates also change depending on age and sex\(^{19}\). Though several analyses by receiver operator characteristics (ROC) curve that have been done till now to evaluate the efficacy of serum pepsinogen values in gastric cancer mass-screening\(^{8,17}\) have not
taken age or sex into account, it is suggested on the basis of the present study that the evaluation of efficacy of these values for mass-screening should be done separately with respect to age and sex.

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