ORIGINAL CONTRIBUTION

Correlation between Atrophic Gastritis Prevalence and Gastric Cancer Mortality among Middle-aged Men in 5 Areas in Japan

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The suggested association between atrophic gastritis as a precursor lesion and subsequent high risk of gastric cancer was examined at the population level in a cross-sectional study of men 40 to 49 years of age in 5 populations with different gastric cancer mortalities. Subjects totalled 634 men, randomly selected from each population of about 100,000, whose atrophic gastritis was diagnosed serologically based on a combination of the serum pepsinogen I (PG I) level <70 ng/ml and pepsinogen I/pepsinogen II (PG I/PG II) ratio <3.0. The number of atrophic gastritis cases discriminated was 121 among 624 evaluated men (19.4% overall) and its prevalence rates in 5 areas (range: 9.4-26.8%) correlated almost perfectly (r = 0.999, p < 0.0001) with age-adjusted mortality rates averaged for 1985-89 for gastric cancer (range: 17.3-49.1 per 100,000). Although some misclassifications could not be denied, especially in discriminating mild/moderate cases, which were separated from severe ones diagnosed more definitively under stricter criteria of PG I < 30 ng/ml and PG I/PG II ratio < 2.0, it was unlikely that they affected the above correlation significantly, since a similar good correlation was observed even when a criterion of PG I/PG II ratio < 2.5 alone, for which high specificity and sensitivity are known, was applied. Thus, the strong correlation found in the present study not only suggests that the number of middle-aged men with atrophic gastritis may be a basis on which gastric cancer mortality in an area can be determined almost exclusively but also that the serological diagnosis is useful in screening of a group of high risk for gastric cancer. Therefore, this diagnostic method provides a practical method of gastric cancer prevention, although a combination with other methods to diagnose particularly mild/moderate atrophic gastritis is recommended for following-up the high-risk group on an individual basis. J Epidemiol, 1993; 3: 35-39.

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Atrophic gastritis has been considered to be a precursor of gastric cancer, especially of intestinal type, based on pathological¹, clinical²,³ and epidemiological⁴,⁵ evidence. Since the suggested association between atrophic gastritis and gastric cancer is very strong, it is of particular interest to examine how strongly this precursor lesion is correlated with the incidence of or mortality from gastric cancer at the population level. There is a U.S.-Japan comparative study⁶, in which prevalence rates of atrophic gastritis by age group were 2-10-fold higher among Japanese than Americans and showed a good correlation with mortality rates of gastric cancer.

On the other hand, serum levels of pepsinogen I (PG I) and pepsinogen II (PG II) levels have been proposed as useful diagnostic methods of atrophic gastritis⁷-¹⁵ since secretion of PG I but not of PG II, is diminished with progression of extensive chronic gastritis from the antrum to the fundic region in the stomach. Thus, this study examined the correlation between prevalence rates of atrophic gastritis, as determined by the serum PG I level and PG I/PG II ratio, and mortalities from
Table 1. Basic profiles of the subjects by area.

| Area (name of PHC*) | No. of selected subjects | No. of participants (%)** | Mean age (±S.D.) in years | Mean length of residence (±S.D.) in years | AADR*** for of stomach cancer in males |
|---------------------|--------------------------|---------------------------|---------------------------|------------------------------------------|--------------------------------------|
| 1: Okinawa (Ishikawa) | 170                      | 129 (76)                  | 44.3 (3.0)                | 30.0 (16.8)                              | 17.27                                 |
| 2: Iwate (Ninohe)    | 175                      | 134 (77)                  | 43.9 (2.9)                | 37.4 (12.5)                              | 29.34                                 |
| 3: Nagano (Saku)     | 170                      | 120 (71)                  | 44.5 (3.0)                | 30.1 (15.7)                              | 38.33                                 |
| 4: Akita (Yokote)    | 170                      | 133 (78)                  | 43.8 (2.9)                | 36.1 (14.0)                              | 49.08                                 |
| 5: Tokyo (Katsushikakita) | 195                  | 118 (61)                  | 45.3 (2.8)                | 24.8 (14.6)                              | 49.11                                 |

*: PHC means Public Health Center. 
**: Number in parenthesis shows % participants of the selected subjects. 
***: AADR means age-adjusted death rate adjusted for age to world population (per 100,000 population).

Table 2. Mean serum PG I and PG II levels and PG I/PG II ratio by area. mean (±S.E.)

| Area     | No. of subjects | Serum levels of |          |          |          |
|----------|-----------------|-----------------|----------|----------|----------|
|          |                 | PG I ng/ml      | PG II ng/ml | PG I/PG II ratio |
| Okinawa  | 128             | 53.8 (2.4)      | 10.8 (0.7) | 5.32 (0.19) |
| Iwate    | 132             | 52.2 (2.4)      | 11.7 (0.7) | 4.87 (0.19) |
| Nagano   | 120             | 55.1 (2.5)      | 14.1 (0.7)** | 4.64 (0.21)** |
| Akita    | 131             | 56.1 (2.4)      | 15.5 (0.7)** | 4.01 (0.19)* |
| Tokyo    | 113             | 58.4 (2.5)      | 15.5 (0.7)** | 4.52 (0.20)** |

** and *** show the mean value is significantly different from that in Okinawa with p<0.01 and p<0.001, respectively, when significance of the differences were tested by t-test with one-way ANOVA.

gastric cancer in 5 areas with different mortality rates of gastric cancer.

SUBJECTS AND METHODS

Subjects were middle-aged male residents in 5 Public Health Center (PHC) districts, who were randomly selected in a cross-sectional study\textsuperscript{16-18}. The 5 PHC districts are located in Okinawa, Iwate, Nagano, Akita prefecture and the Tokyo metropolitan area (this order is preserved throughout the following sentences) and the basic profiles of the subjects are summarized in Table 1, which shows that gastric cancer mortality rates were very different in those areas. Male age-adjusted mortality rates (adjusted to the world population) for gastric cancer were obtained for each district for a five-year period from 1985 to 1989 based on information on death certificates.

Surveys including blood sampling were conducted during the same periods of February to March in Okinawa and Iwate in 1989, in Akita and Nagano in 1990 and in Tokyo in 1991. The sera obtained after clotting for 60 min or less at room temperature were kept frozen at $-80^\circ$C until the following assays. Serum PG I and PG II levels were determined simultaneously by means of radioimmunometric assays using kits (PG I/PG II RIA BEAD, Dinabot Co., Ltd.)\textsuperscript{8,9,13} for all the samples. The subjects numbered 634 in all (Table 1) but serum samples were obtained from only 624.

Atrophic gastritis was diagnosed basically on a criteria of PG I < 70 ng/ml and PG I/PG II ratio < 3.0 as recommended for diagnosis of atrophic gastritis and for the gastric cancer screening test\textsuperscript{8,9,13}. A stricter criterion of only PG I/PG II ratio < 2.5, for which high specificity (84.1%) and sensitivity (87.1%) were demonstrated pathologically by Miki et al\textsuperscript{12}, was also used for examining the feasibility of the above criterion. Moreover, severe cases of atrophic gastritis were discriminated further from other cases, on stricter criteria of PG I < 30 ng/ml and PG I/PG II ratio < 2.0, which were adopted according to the values reported by Samloff et al\textsuperscript{14}. 


The mean (±S.D.) levels of PG I and PG II determined were 54.6 (±27.2) ng/ml and 13.5 (±7.9) ng/ml, respectively, for all subjects. The mean PG II level was lower and mean PG I/PG II ratio was higher in Okinawa when compared to those in Nagano, Akita and Tokyo, while mean PG I levels did not differ significantly among the 5 areas, as shown in Table 2.

The prevalence rates of atrophic gastritis discriminated on criteria of PG I <70 ng/ml and PG I/PG II ratio <3.0 (Table 3) were almost perfectly cor-

**RESULTS**

The mean (±S.D.) levels of PG I and PG II determined were 54.6 (±27.2) ng/ml and 13.5 (±7.9) ng/ml, respectively, for all subjects. The mean PG II level was lower and mean PG I/PG II ratio was higher in Okinawa when compared to those in Nagano, Akita and Tokyo, while mean PG I levels did not differ significantly among the 5 areas, as shown in Table 2.

The prevalence rates of atrophic gastritis discriminated on criteria of PG I <70 ng/ml and PG I/PG II ratio <3.0 (Table 3) were almost perfectly cor-
related with the age-adjusted death rates of gastric cancer \((r=0.999\), \(p<0.0001)\), as illustrated in Figure 1. When this criterion of the ratio \(<2.5\) alone was used, prevalence rates (numbers) of atrophic gastritis became 7.1\% \((9)\), 11.3\% \((15)\), 16.0\% \((19)\), 19.2\% \((25)\) and 23.4\% \((28)\) in Okinawa, Iwate, Nagano, Akita and Tokyo, respectively, which were also correlated well with the death rates \((r=0.970\), \(p<0.01)\). Moreover, although the numbers of severe atrophic gastritis discriminated with the stricter criterion mentioned above were too small \((38\) cases) \((Table 3)\) and their prevalence rates by area did not have statistical significance, there was a tendency for them to be proportional to those of atrophic gastritis diagnosed with each of the above two criteria.

On the other hand, when distributions of the subjects based on the cut-off levels of PG I and the PG I/PG II ratio in each of the criteria were examined \(\text{(Table 4 a and 4 b)}\), it was indicated that the PG I/PG II ratio was more critical in diagnosing mild/moderate cases of atrophic gastritis rather than the PG I level. Since PG II levels in the subjects classified as mild/moderate cases of atrophic gastritis were generally higher than those in other subjects, as shown by their mean values, it was clear that the adopted criterion emphasizes the importance of the enhancement of PG II among them. The mean PG I and PG II levels and PG I/PG II ratio, however, were 60.0 ng/ml, 12.7 ng/ml and 5.3 in nonatrophic gastritis cases, respectively. Those values were 15.9 ng/ml, 12.5 ng/ml and 1.2 in severe cases and were 43.0 ng/ml, 19.0 ng/ml and 2.3 in mild/moderate cases \((\text{atrophic gastritis excluding the severe cases})\), respectively.

**DISCUSSION**

An almost perfect correlation between atrophic gastritis prevalence rates and gastric cancer mortalities, both of which showed marked differences in the 5 areas, was demonstrated. The regression line obtained was characterized not only by an excellent correlation coefficient but also by the small value of the intercept, suggesting a possibility that deaths from, and therefore incidence of, gastric cancer can be related exclusively to the prevalence of atrophic gastritis. This is likely if a recent epidemiologic finding by Kato et al.\(^{15}\) suggesting that atrophic gastritis can be associated not only with the risk of intestinal but also, although weaker, with that of diffuse type, another major type, of gastric cancer is taken into consideration. The observed correlation was also supported by the findings that geographic difference \((\text{not magnitude})\) of gastric cancer mortality has been stable for the last 20 years in Japan\(^{16}\) and that the subjects examined had lived at the same address for more than 24.8 years on average even in metropolitan Tokyo which has the highest population mobility. The randomness of the subjects in addition to their long residence at the same address are expected to have a favorable effect on the correlation.

However, the reliability of the serological diagnostic methods adopted in the present study should be discussed here, since a possibility of the methods affecting the correlation cannot be denied. The criteria based not only on the PG I/PG II ratio but also on the PG I level were adopted for discriminating atrophic gastritis according to the data recently shown by Samloff et al.\(^{14}\) as well as by Miki et al.\(^{3,11,12}\). Namely, Miki and co-workers showed that a PG I/PG II ratio of less than 2.5 alone can give the most reliable indication, with a sensitivity of 87.2\% and specificity of 84.1\% for the diagnosis of histologic atrophic gastritis \((\text{open type})\), whereas specificity was very high \((96.3\%)\) but sensitivity was low \((59.0\%)\) when PG I level \(<30\) ng/ml alone was applied. Thus, it was expected that their combination improves the diagnoses of atrophic gastritis, at least as far as severe cases are concerned.

The mean PG II level in the mild/moderate cases was significantly higher when compared to that of the other two groups. This was consistent with the result on histologic atrophic gastritis by Samloff et al.\(^{14}\), suggesting that the present mild/moderate cases correspond to their histologic mild/moderate type. However, since in their study\(^{14}\), histologically defined superficial gastritis showed enhanced levels of PG I and PG II instead of PG II alone, it was expected that the superficial type was eliminated from the mild/moderate cases based on the criteria including PG I/PG II ratio \(<3.0\) in addition to PG I \(<70\) ng/ml. Such a superficial type may correspond to about 10\% \((14\) out of \(135)\) of atrophic gastritis cases which were diagnosed based on the PG I/PG II ratio \(<3.0\) alone, not with a combination of PG I \(<70\) ng/ml and PG I/PG II ratio \(<3.0\), as shown in Table 4a.

As for diagnosing mild/moderate atrophic gastritis, especially borderline cases, however, some misclassifications in terms of false-negative and -positive results of tests cannot be denied, as commonly observed for endoscopic and histologic, as well as biopsy, methods. However, as was shown in the Results, a similarly perfect correlation was observed even when PG I/PG II ratio \(<2.5\), which gives high specificity and sensitivity as mentioned above, was applied. This was also the case for PG I/PG II ratio \(<3.0\) alone \(\text{(data not shown)}\). Thus, it was unlikely, in spite of the possibility of misclassifications, that those misclassifications affected the above correlation among the 5 areas significantly, although a combination with other
methods to diagnose particularly mild/moderate atrophic gastritis is recommended for examinations on the individual basis.

A possibility that the length of serum storage might have affected the levels of PG I and PG II determined, especially for the sera from Okinawa and Iwate which were obtained two years before those from Tokyo cannot be denied, either, since PG II levels were significantly lower in Okinawa and Iwate than in the other areas (Table 2). However, this seemed unlikely, since the data on serum ferritin, which were determined for the same serum specimens and measured simultaneously with PG I and PG II, showed consistently higher levels in Okinawa and Iwate when compared to those in the other areas, as reported separately^{20}, suggesting that proteins in sera kept under -80°C were not affected substantially by storage.

In conclusion, the strong correlation found in the present study not only suggests that the number of middle-aged men with atrophic gastritis may be a basis on which gastric cancer mortality of a population can be determined but also that the serological diagnosis is useful in screening of a group of high risk for gastric cancer and provides a more practical method of gastric cancer prevention. Here, if we suppose that gastric cancer develops solely among the atrophic gastritis cases diagnosed, approximately 40% of atrophic gastritis cases and all severe cases are expected to die from gastric cancer when estimated based on the mortality rates in 1985-89. However, a follow-up study is essential, since possible increase of atrophic gastritis with age^{20} and additional factors such as incidence rate instead of mortality and gradually decreasing secular trend of gastric cancer incidence/mortality should be considered in the probability of future occurrence of gastric cancer among these groups. Moreover, diagnosis, particularly of borderline cases, should be improved to follow-up the highrisk group on the individual basis.

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