Life Style Factors Influencing Serum Pepsinogen Levels in Healthy Japanese: A Prospective Study

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ABSTRACTS

***Background**: Gastric cancer mass screening using serum pepsinogen has been recognized and several advantages of this methods over photofluorography have been shown by previous study.*

***Aims**: To determine the factors influence the serum pepsinogen levels in healthy subjects.*

***Subjects & Methods**: One thousand and one hundred fourteen subjects who were screened for gastric cancer as part of a periodic health check. Blood samples were taken after fasting and stored below –20 ° C, until pepsinogen levels were assayed.*

***Results**: The subjects consist of 338 males (mean age 52.6+14.0) and 776 females (mean age 49.0+11.9). Age ranges from 19 to 81 years. The overall prevalence of chronic atrophic gastritis using a criterion PG I £ 70 hg/ml and PG I/II ratio ≤ 3.0 was 21.99 % in 1996 and 23.97 % in 2000. Bivariate analysis revealed a significant association between age, more salt consumption, fish favorable over meat and less than three time meal intake covariates with the lowering of PG I/II ratio. Smoking, drinking, BMI, weight and gender did not affect the changes of PG I/II ratio.*

***Conclusion**: Age and more salt consumption covariates have a strongest association with the decreased of PG I/II by multivariate analysis.*

***Keywords**: pepsinogen - dietary - drinking - smoking - atrophic gastritis*

INTRODUCTION

The usefulness of gastric cancer screening using serum pepsinogen (PG) has been recognized and several advantages of this method over photofluorography have been shown by previous study.[1,2] It has been established that chronic atrophic gastritis is related to risk of gastric cancer.[3,4,5]

Many gastric cancer develop in stomach mucosa affected by severe and extensive atrophic gastritis.[6] As atrophic gastritis becomes more severe, normal gland function is lost and enzyme production is affected. This morphological and functional status could be reflected in the changes of serum pepsinogen concentration.[7] Indeed, the low PG I/II ratio has been claimed to be more sensitive than histology, which is based on a limited number of biopsies, in identifying this lesion.[1]

Whereas *Helicobacter pylori* infection is undoubtedly a cause of chronic atrophic gastritis,[8,9,10,11] information is sparse about other factors associated with chronic atrophic gastritis. Several study showed vegetables and fruits,[12] and increase level of carotenoids[13,14] to be associated with a lower prevalence of advanced chronic atrophic gastritis, intestinal metaplasia and dysplasia. High salt intake related positively to chronic atrophic gastritis or gastric dysplasia.[15] Current smoking elevates pepsinogen I and the I/II ratio, while drinking reduced pepsinogen I and II.[16] However case control study in Japan failed to find any significance association between gastric cancer related factors and endoscopically diagnosed chronic atrophic gastritis.[17]

Most of previous report regarding dietary habit has

been assessed by cross sectional study, however this association should be assessed prospectively. Furthermore this prospective study will determined the role of sex, age, BMI, smoking, drinking alcohol beverages, three time daily meal intake, vegetable, salt and fish consumption on the concentration of PG I and PG I/II ratio during four years span.

SUBJECTS AND METHODS

Assay of serum PG concentration was performed in 1114 subjects who were screened for gastric cancer as part of a periodic health check at The Health Care Center, Yamanashi Koseiren in 1996 and the next follow up in 2000. The subjects consist of 338 men and 776 women. Blood samples for routines laboratory test were taken after fasting, and aliquots of the separated sera were individually stored below –20 °C, until serum PG concentration were assayed using PG I and PG II Riabead Kits (Dinabot Co Ltd, Tokyo, Japan), a modified radio immune assay method which has been described previously.[18,19]

When PG I (unit: ηg/ml) value was compared, its crude values were used and also for PG I/II ratio as well. To observe the changes of serum PG values during the four years span, delta PG I and delta PG I/II ratio defined as PG I or PG I/II value in 2000 minus that in 1996 were used.

On further study we classified delta PG I and PG I/II ratio as increase and decrease according to mean and plus minus a half of standard deviation (SD). PG was defined as increased if the value of delta PG was more than mean plus a half SD and decreased if the value was less than mean minus a half of SD.

A self-administered questionnaire was used to ascertain smoking, alcohol use, dietary habits, and other life style characteristics. Subjects were classified as current smoker/non-smoker, current drinker/non-drinker, while history of smoking and drinking before year 1996 was classified as non-smoker/non-drinker. As to daily vegetable consumption, fish favorable over meat, three-time daily meal intake and salty food intake, subjects were classified as yes or no.

Statistical Analysis

Correlation between delta PG I, delta PG I/II and several numerical variable were analyzed. Differences in mean of delta PG I and delta PG I/II ratio to several categorical variable were analyzed by Mann-Whitney U-test. Another bivariate analysis has been done using Chi-square test and Kruskal-Walis test, lastly multivariate analysis was conducted based on logistic regression models. A probability (p) level less than 0.05 was considered statistically significant.

RESULTS

The study subjects included in this analysis were 1114 participants, male 338 (mean age 52.6+14.0) and female 776 (mean age 49.0+11.9). Age range from 19 to 81 years old, which were enrolled in 1996 and underwent a follow up evaluation in 2000.

The overall prevalence of chronic atrophic gastritis using a criterion PG I ≤ 70 ηg/ml and PG I/II ratio ≤ 3.0 [20] was 21.99 % (245 of 1114) in 1996 and 23.97 % (267 of 1114) in 2000.

Changes in Pepsinogen

Pepsinogen I increased by 4.33 hg/ml on average (SD=26.64), while PG I/II ratio decreased by 0.75 (SD=1.09). When pepsinogen were divided; according to the criterion for increase, decrease and no-change, the PG I and PG I/II ratio increase in 161 and 237 subjects, decrease in 113 and 235 subjects, no-change in 840 and 624 subjects, respectively.

The changes of PG I and PG I/II ratio have a good correlation with age. On the other hand, body weight, height and BMI failed to show such a correlation. Body weight and BMI tended to increase during the four years span, however these changes were not significant, statistically.

Mean of delta PG I was significantly higher in women and also in less than three-time meal intake covariate (Table I). Mean of delta PG I/II ratio was significantly lower in less than three time daily meal intakes, fish favorable over meat and more salt intake covariate.

Using the criterion of PG I and PG I/II ratio changes during the four year span and the above analysis were repeat, a significant association were found between more salt consumption, fish favorable over meat and less than three time meal intake covariates with the lowering of PG I/II ratio (Table II). Smoking, drinking and gender did not affect the changes of PG I/II ratio.

Multivariate logistic regression analysis was conducted to evaluate the strongest effect of these covariates to the changes of PG I/II ratio (in term of decrease and increase of PG I/II ratio). Age and more salt intake revealed the strongest effect on the lowering of PG I/II ratio during four years span.

Table 1. Mean Delta PG I and Delta PG I/II Ratio by Sex, Dietary and Personal Habit

Variable	N	Delta PG I		Delta PG I/II ratio	
		Mean (SD)	p	Mean(SD)	P
Sex					
• Male	338	3.07(34.46)	0.031	-0.68(0.90)	0.416
• Female	776	4.87(22.41)		-0.78(1.17)	
Smoking					
• Smoker	242	6.50(22.47)	0.084	-0.71(0.94)	0.495
• Non-smoker	872	3.73(27.67)		-0.76(1.14)	
Drinking					
• Drinker	441	3.49(32.97)	0.329	-0.75(0.89)	0.143
• Non-drinker	673	4.88(21.52)		-0.75(1.21)	
Meal three times					
• Yes	973	3.85(28.05)	0.28	-0.74(1.13)	0.019
• No	141	7.61(12.90)		-0.85(0.80)	
Fish favorable					
• Yes	511	5.01(20.70)	0.262	-0.78(0.98)	0.012
• No	603	3.76(30.80)		-0.72(1.18)	
Salt					
• More	169	6.09(12.19)	0.985	-0.60(0.89)	0.047
• Less	945	4.02(28.46)		-0.75(1.13)	
Vegetable					
• Daily	962	4.15(27.49)	0.385	-0.73(1.10)	0.104
• Non-daily	152	5.45(20.51)		-0.90(1.05)	
Total	1114				

Test : Mann-Whitney U Test

Table 2. The Changes of PG I and PG I/II Ratio During 4 Years Span According to Sex, Dietary and Personal Habit

Variable	N	PG I in 1996 to 2000				PG I/II 1996 to 2000			
		Increase	Decrease	Unchange	P	Increase	Decrease	Unchange	p
Age									
• <40	195	12	13	170	0.011	34	57	104	0.0001
• 40-49	234	40	16	178		41	70	123	
• 50-59	329	49	38	242		57	66	206	
• 60-69	226	42	25	159		60	26	140	
• >70	130	18	21	91		45	18	60	
Sex									
• Male	338	49	41	248	0.361	82	68	188	0 200
• Female	776	112	72	592		155	167	454	
Smoking									
• Smoker	242	38	20	184	0.283	54	57	131	0 745
• Non-smoker	872	123	93	656		183	178	511	
Drinking									
• Drinker	441	60	45	336	0.706	89	105	247	0.134
• Non-drinker	673	101	68	504		148	130	395	
Meal 3 times									
• Yes	973	137	103	733	0.142	214	195	564	0.021
• No	141	24	10	107		23	40	78	
Fish favorable									
• Yes	511	64	44	403	0.901	101	125	285	0 027
• No	603	97	69	437		136	110	357	
Salt Intake									
• More	169	25	12	132	0.284	28	46	95	0 023
• Less	945	136	101	708		209	189	547	
Vegetable									
• Yes	962	142	98	722	0 714	208	190	564	0 043
• No	152	19	15	118		29	45	78	
Total	**1114**	**161**	**113**	**840**		**237**	**235**	**642**	

Test: Chi-square, and Kruskal-Wallis

PG, pepsinogen; PG I, pepsinogen I, PG II: pepsinogen II,
PG I/II ratio: the ratio between the levels of pepsinogen I and pepsinogen II.
SD. Standard deviation

DISCUSSION

The present study had several advantages in terms of prospective design, number of subjects and multivariate analysis. However, methodological weaknesses also need to be clarified when interpreting the results.

This study used the criterion of PG I ≤ 70 ηg/ml and PG I/II ratio ≤ 3.0 to determined the presence of chronic atrophic gastritis. The change of PG I/II ratio has a correlation with age. The prevalence rate of chronic atrophic gastritis observed in this study did not differ much from the reported rates in other studies in Japan using the same methods and the same criterion. The rates were 20-70% in male blood donors, varying with survey area in one study[21], and 13.3 - 28.8 % in male residents aged 40-49 years in another study.[6]

A study in United States showed a positive association between smoking and atrophic gastritis[12]. However, a study in Venezuela found that there was a clear inverse association between severe decrease in the PG I/II ratio and tobacco use.[22] Another study in Japan showed that cigarette smoking was associated with a decrease risk of chronic atrophic gastritis as determined by serum PG I level and the PG I/II ratio in Japanese men.[23] In the present study, the changes of PG I and PG I/II ratio tend to be lower in non-smoker and non-drinker group, but not significant statistically. The mean delta PG I and delta PG I/II ratio in smoker/ non-smoker groups were 6.5/3.7 and -0.7/-0.8, respectively.

Vegetables and fruits are generally considered to be protective against gastric cancer. The inverse associations between fresh fruits and plantain consumption and the risk of atrophic gastritis were showed by a study in Venezuela, although the results of plasma levels in this analysis were only suggestive.[22]

Histology-based study and pepsinogen-based study also suggested that high consumption of vegetables or fruits have a protective effect in the development of advanced precancerous lesion in gastric mucosa.[12,13,14] The present study showed that the decrease of PG I/II ratio was greater in non-daily vegetable consumption group than in daily consumption group and statistically significant in bivariate analysis. However this association was reduced in multivariate analysis.

There was very little study if any exist, regarding the meat or fish consumption and pepsinogen levels. This study revealed fish favorable over meat has an association with the decreased of PG I/II ratio (p=0.012). Again, this association was reduced in multivariate analysis.

Another important dietary factor associated with increase risk gastric cancer is high intake of salt or salty foods. More salt intake was positively related serologically determined severe chronic atrophic gastritis in Italy, [24] but not in Japan[25] or Venezuela.[22] High salt intake was found to be positively associated with gastric dysplasia in Colombia.[26] The present study revealed that more salt consumption to be positively associated with the reduced of PG I/II ratio in healthy Japanese subjects. Interestingly, this association still exists in multivariate analysis. This result supported by previous study in Japanese men[27] that high noodle consumption which is salt-rich was associated with nearly twofold increased risk of chronic gastritis, but our study is based on a larger number, wider range of subjects and was designed prospectively.

In conclusion, our findings revealed that age and more salt consumption are factors that have a strongest association with the decreased of PG I/II ratio among healthy Japanese subjects. Our speculation is that less salt intake will reduce the risk of atrophic gastritis and lastly will reduce the risk of gastric cancer.

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