Jpn. J. Cancer Res. 84, 844–851, August 1993

Does High Gastric Cancer Risk Associated with Low Serum Ferritin Level Reflect Achlorhydria? An Examination via Cross-sectional Study

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With respect to the inverse association of serum ferritin level (SFL) with the risk of gastric cancer (GC) observed in some recent epidemiologic studies, possible mediation by achlorhydria as well as atrophic gastritis (AG), both of which are strongly associated with GC risk at not only the individual but also the population level, was examined in a cross-sectional study of 634 men aged 40 to 49 years randomly selected from 5 populations in Okinawa, Iwate, Nagano, Akita and Tokyo. AG and achlorhydria were serologically diagnosed based on the criteria of pepsinogen (Pep) I level <70 ng/ml and Pep I/Pep II ratio <3.0, as described previously, and a serum gastrin level of over 140 pg/ml, respectively. In the results, while the mean SFL for all the subjects differed significantly by area, similar areal differences in SFL were also found even when only the non-AG cases were considered. However, both of the above differences were eliminated with the exception of those between Okinawa and each of the other 4 areas, when adjustments were made for medical histories of diabetes mellitus, ulcers and liver disease, body mass index and γ-glutamyltranspeptidase level. Therefore, no correlation among the 5 areas was observed between the adjusted areal mean SFLs and GC mortality in either case. However, in 17 (45%) achlorhydric cases identified among the 38 subjects with severe AG, which were further discriminated with stricter criteria (Pep I <30 ng/ml and Pep I/Pep II ratio <2.0), their averaged SFL was significantly lower than the values for the non-AG cases (3.78 vs. 4.64 ln(ng/ml), $P<0.001$) and mild/moderate AG cases (3.78 vs. 4.47 ln(ng/ml), $P<0.01$), while the differences were not significant with respect to the other 21 (55%) severe AG cases without achlorhydria. Thus, it is suggested that the negative association of SFL, for which no mechanism has been shown in cancer etiology, with GC risk is indirect, since both of them are associated primarily with achlorhydria found among the severe AG cases. Moreover, areal mean SFLs, which are not determined only on the basis of the prevalence of achlorhydric AG cases, could not be related to GC mortality rates, suggesting that no direct association exists at the population level either.

Key words: Ferritin — Achlorhydria — Atrophic gastritis — Gastric cancer risk — Cross-sectional study

Iron metabolism, especially iron stores in the body as indicated by serum ferritin level,[1] has been related to cancer risk in several recent studies. Positive correlations were found for all types of cancer,[2] and specifically for lung cancer[3] and liver cancer,[4] which have been linked with excess iron stores, but negative correlations were observed for gastric cancer in two recent studies.[5,6] However, it is likely that in the latter case, the correlation is secondary, possibly reflecting lowered ferritin levels due to achlorhydria, since the amount of absorbable dietary iron is reduced with pH increase in the stomach, as demonstrated in pernicious anemia.[7,8] Achlorhydria itself is strongly associated with the risk of gastric cancer.[7,9] Moreover, achlorhydria commonly develops from atrophic gastritis, another type of high-risk lesion, which category is characterized by atrophies spreading with a corresponding reduction in the area of acid-producing mucosa in the stomach.[10] It is possible that atrophic gastritis also contributes to the negative correlation. In fact, atrophic gastritis has been strongly associated with gastric cancer risk on an individual basis by clinical[11,12] and epidemiologic studies[13,14] as well as at the population level by our recent correlation study.[15] Thus, it was hypothesized that the risk correlated with ferritin level may be attributed to achlorhydria probably associated with atrophic gastritis.

On the other hand, serum ferritin level is known to vary largely according to such factors as age, hemochromatosis, hemosiderosis, bleeding, blood donation, ethanol-induced liver damage indicated by enhanced level of γ-GTP (γ-glutamyltranspeptidase), and exercise,[16] although serum ferritin level has not been examined precisely in relation to achlorhydria and/or atrophic gastritis as yet.

The present study is part of a cross-sectional study on randomly selected men aged 40 to 49 years in 5 areas.[17,18] Its primary purpose is to examine the suggested geographic correlation of areal mean ferritin level with gastric cancer mortality rates among the five areas at the population level, with consideration of possible

modifying effects by achlorhydria and atrophic gastritis, which were diagnosed serologically in terms of serum gastrin level and levels of pepsinogen (Pep) I and Pep II, respectively.

SUBJECTS AND METHODS

This study is part of our cross-sectional study of possible factors based on geographic differences contributing to the incidence of cancer at various sites in Japan using multiple biologic markers, as described elsewhere.[17,18] Subjects were 634 men in their 40s who were randomly selected in each of the 5 public health center (PHC) districts as shown in Table I. Some basic characteristics of the subjects are also summarized in the table. The percentage of actual participants among the men randomly selected ranged from 61% in Tokyo, the lowest, to 78% in Akita, the highest. The percentages of participants whose birthplaces were in the same prefecture as their current residences were 75, 94, 84, 95 and 50% for Okinawa, Iwate, Nagano, Akita and Tokyo, respectively. The mean length of time that they had lived at their present residence was 24.8 years even in metropolitan Tokyo, with the highest population mobility rate.

The age-adjusted death rates (AADRs) for stomach cancer in males (adjusted with respect to the world population), which were obtained from each PHC district population for the 5-year period from 1985 to 1989 based on death certificates, showed marked differences (Table I). Health examinations, which consisted of interviews on health status and food intake, anthropometry, and some basic tests including blood pressure measurement and blood sampling were conducted during February and March in Okinawa and Iwate in 1989, in Akita and Nagano in 1990, and in Tokyo in 1991.

Serum samples obtained after about 60 min of clotting were kept at −70°C until the assays. Serum levels of ferritin and gastrin were measured radioimmunologically using kits purchased from Eiken Kagaku Co., Ltd. and Baxter Healthcare Co., respectively. Serum levels of Pep I and Pep II were determined by radioimmunometric assays using kits (PG I/PG II RIABEAD) from Dinabot Co., Ltd. Ferritin levels in the sera were within the range reported for Japanese males in the literature.[19] However, for 2 subjects in Akita and 5 subjects in Tokyo who showed ferritin levels below the detection limit of 5 ng/ml, half of the detection limit value (2.5 ng/ml) was utilized in the following calculations. Serum iron and transferrin levels, on the other hand, were determined using the guanidine/ferrozine method[20] and the immunoturbidimetric method, respectively, in the laboratory of Hoffman-La-Roche Co., Ltd. in Switzerland, where the samples were sent frozen in dry ice by air cargo immediately after blood collection. Serum γ-GTP activity was assayed using L-γ-glutamyl-3-carboxy-4-nitroanilide as a substrate. Hemoglobin (Hb) concentration in the whole blood was determined by the cyanmethemoglobin method.

Achlorhydria was discriminated based on serum gastrin level, since a gastrin level over 140 pg/ml is related mainly to a negative feedback increase in reduced gastric acid secretion in achlorhydria, and much less frequently in gastrinoma.[21]

As reported previously,[15] the criterion of a combination of Pep I level <70 ng/ml and Pep I/Pep II ratio <3.0, recommended by Miki *et al.*,[12,22] was used to diagnose atrophic gastritis, and stricter criteria of Pep I <30 ng/ml and Pep I/Pep II retio <2.0 were also employed to further discriminate severe atrophic gastritis. Atrophic gastritis cases other than the severe ones were regarded as mild/moderate atrophic gastritis cases.

Mean levels of measured items and distributions of medical histories of diabetes mellitus, gastric/duodenal ulcers and chronic liver disease are summarized in Table II.

Table I. Basic Profiles of the Subjects

Area (name of PHC[a])	No. of selected subjects	No. of participants (%)	Age in years (mean ± SD)	Years of residence[b] (mean ± SD)	AADR[c] of gastric cancer in males
Okinawa (Ishikawa)	170	129 (76)	44.3 (3.0)	30.0 (16.8)	17.27
Iwate (Ninohe)	175	134 (77)	43.9 (2.9)	37.4 (12.5)	29.34
Nagano (Saku)	170	120 (71)	44.5 (3.0)	30.1 (15.7)	38.33
Akita (Yokote)	170	133 (78)	43.8 (2.9)	36.1 (14.0)	49.08
Tokyo (Katsushika-kita)	195	118 (61)	45.3 (2.8)	24.8 (14.6)	49.11

a) Public health center.
b) Length of residence at the present address.
c) Mean age-adjusted death rate of gastric cancer calculated for each of the PHC populations for the period from 1985 to 1989.

Table II. Mean Values of Measured Items and Distribution of Medical Histories of Some Chronic Diseases

Measured item	Mean	SD	Range (min.-max.)
Ferritin (ng/ml)	134.0	100.4	(2.5–918.0)
Gastrin (pg/ml)	96.5	41.2	(39.3–352.7)
Transferrin (mg/dl)	339.4	54.6	(143.0–501.0)
Total iron (μg/ml)	0.97	0.38	(0.20–3.16)
BMI (kg/m^2)[a]	23.9	3.0	(17.1–36.4)
γ-GTP (mU/ml)[b]	45.6	56.2	(5.0–575.0)

Medical history of	Distribution (% (number of subjects)) by		
	no	yes	under medication
Diabetes Mellitus	94.6 (590)	3.9 (24)	1.6 (10)
Liver disease	94.5 (602)	3.0 (19)	0.5 (3)
Gastric/duodenal ulcers	83.5 (521)	14.7 (92)	1.8 (11)

a) Body mass index.
b) γ-Glutamyltranspeptidase.

Multiple regression analysis or covariate analysis was performed with the "general linear model" (GLM) procedure[23] using the "SAS" program on the mainframe computer at the University of Tokyo. Since the distribution of the serum ferritin level was skewed, its level was log-transformed for statistics unless otherwise stated.

RESULTS

Serum levels of ferritin and transferrin (Table II) were within the range reported for Japanese in the literature.[19] Serum ferritin levels were significantly but weakly correlated to those of hemoglobin (Hb, $r=0.261$, $P<0.001$), iron ($r=0.157$, $P<0.001$) and transferrin ($r=-0.161$, $P<0.001$), as reported to date.

In a stepwise regression analysis using the GLM procedures, serum ferritin level was significantly correlated not only with atrophic gastritis but also with medical histories of diabetes mellitus (DM), gastric/duodenal ulcers and chronic liver disease, Hb (g/dl), body mass index (BMI) (weight(kg)/height(m)^2) and γ-GTP level, but not with smoking (non-/current/ex-smoker) or alcohol intake (non-/current/ex-drinker), as shown in Table III. If examined further, however, γ-GTP levels were significantly higher in current drinkers (50.5 (60.8) mU/ml) on the average than those in nondrinkers (23.5 (12.9) mU/ml) and in ex-drinkers (28.8 (25.2) mU/ml), suggesting that γ-GTP is a sensitive indicator of ethanol intake or ethanol-induced liver damage, as previously indicated.[13] The transferrin levels did not show any significant correlation with the factors examined above.

Table III. A Multiple Regression Analysis[a] of Serum Ferritin Level

Independent variables	Regression coefficient	P[c]
Atrophic gastritis		
noncase	–	
mild/moderate case	22.8	
severe case[b]	−34.8	*
Medical history of		
Diabetes Mellitus		
no[b]	–	
yes	22.4	
currently medicated	72.9	*
gastric/duodenal ulcer		
no[b]	–	
yes	−8.6	
currently medicated	−50.3	*
liver diseases		
no[b]	–	
yes	38.1	**
currently medicated	−127.6	*
Smoking		
non-[b]	–	
current-	12.0	
ex-	7.9	
Drinking		
non-[b]	–	
current-	12.0	
ex-	1.9	
Hb (g/dl)	10.1	**
BMI	6.7	***
γ-GTP	0.3	***
r^2-value	0.167	
F-value	7.87	
P for significance	$P=0.0001$	

a) Analysis was done with the GLM procedure.
b) Reference category.
c) Significance is indicated by *, ** and *** for $P<0.05$, <0.01 and <0.001, respectively.

Mean serum levels of ferritin, but not of transferrin, differed significantly with the presence of atrophic gastritis when all subjects were considered (Table IV), but did not differ in Tokyo and Okinawa when each of the areas was examined separately (Table V). Results were the same even after the modifying factors identified above were taken into consideration.

Mean serum levels of ferritin, but not of transferrin, differed significantly by area (Table V) and only the former showed a good correlation with age-adjusted death rate (Table I) for gastric cancer $r=0.968$ $P<0.01$). However, the areal mean ferritin levels were significantly different even when only the nonatrophic gastritis cases (n=503) were taken into account, and also showd a good correlation with the mortality rates

Table IV. Mean Serum Ferritin, Transferrin and Hb Levels by Presence of Atrophic Gastritis

Item	Atrophic gastritis			$P^{a)}$
	noncases	mild/moderate cases	severe cases	
Ferritin level (ln(ng/ml))	4.64	4.47	4.03	***
Transferrin level (mU/ml)	337.9	337.3	353.3	n.s.
Hb conc. (g/dl)	16.0	15.7	15.4	**

a) Difference by atrophic gastritis categories was tested by one-way ANOVA and significance is indicated with ** for $P<0.01$. *** for $P<0.001$ and n.s. for not significant.

Table V. Mean Serum Ferritin Level[a)] by Area and Presence of Atrophic Gastritis

Area	Total subjects	Atrophic gastritis			$P^{c)}$
		noncases	mild/moderate cases	severe cases	
Okinawa	5.19 (127)	4.98 (115)	4.97 (8)	4.72 (4)	n.s.
Iwate	4.91 (132)	4.74 (111)	4.45 (14)	3.88 (7)	***
Nagano	4.87 (119)	4.72 (96)	4.60 (13)	4.05 (10)	*
Akita	4.65 (117)	4.55 (87)	4.33 (19)	3.55 (11)	***
Tokyo	4.71 (106)	3.98 (78)	4.37 (22)	4.59 (6)	n.s.
$P^{b)}$	***	***	n.s.	n.s.	
Total	4.57 (601)[d)]	4.93 (487)	4.77 (76)	4.52 (38)	***

a) Values in ln(ng/ml) [mean (number of subjects)].
b) Difference by area was tested by one-way ANOVA. Significance is indicated with * for $P<0.05$, *** for $P<0.001$ and n.s. for not significant.
c) Difference by atrophic gastritis categories was tested by one-way ANOVA. Significance is indicated with *** for $P<0.001$ and n.s. for not significant.
d) Number of total subjects was 601, since serum ferritin could not be determined for 19 serum samples whose volume was too small for the assays.

Table VI. Mean Serum Gastrin Level by Area and Presence of Atrophic Gastritis

Area	Serum level of gastrin (pg/ml) [mean±SD (number of subjects)]			$P^{a)}$
	Atrophic gastritis			
	noncases	mild/moderate cases	severe cases	
Okinawa	91±22 (115)	89±18 (8)	143±64 (4)	***
Iwate	102±40 (112)	113±33 (14)	152±46 (7)	**
Nagano	71±29 (95)	78±28 (14)	153±97 (10)	***
Akita	102±31 (96)	112±42 (23)	140±87 (11)	*
Tokyo	88±29 (81)	99±42 (24)	147±77 (6)	**
Total	91±33 (499)	100±39 (83)	147±80 (38)	***

a) Difference by atrophic gastritis categories by one-way ANOVA. Significance is indicated with * for $P<0.05$, ** for $P<0.01$ and *** for $P<0.001$.

($r=0.979$, $P<0.01$). However, differences in the areal mean serum ferritin level disappeared (except for those between Okinawa and each of the other 4 areas), and the above correlation became insignificant, when adjustments were made for the above-identified modifying factors. This was also true for areal differences only found among the nonatrophic gastritis cases.

On the average, serum gastrin levels were markedly higher in severe atrophic gastritis cases than in the other cases, as shown in Table VI. Although achlor-

Table VII. Mean Serum Levels of Transferrin, Hb and Gastrin by Presence of Iron Deficiency Anemia and Atrophic Gastritis

	Atrophic gastritis		
	noncases	mild/moderate cases	severe cases
Iron deficiency anemia (ferritin level <20 ng/ml)			
(Number of subjects)	(30)	(3)	(8)
Transferrin level (mU/ml)	367.5**	360.2	412.2***
HB level (g/dl)	15.2***	15.7	14.2***
Gastrin level (pg/ml)	100.1	88.5	130.3
Non-iron deficiency anemia (20 ng/ml$\leq$ferritin level)			
(Number of subjects)	(457)	(73)	(30)
Transferrin level (mU/ml)	336.5	339.2	338.1
Hb level (g/dl)	16.1	15.7	15.8
Gastrin level (pg/ml)	90.7	101.4	151.6

The symbols ** and *** show that the mean level is significantly different from that of mild/moderate atrophic gastritis cases with $P<0.01$ and $P<0.001$, respectively.

hydria was basically defined as a gastrin level of more than 140 pg/ml, its levels in the severe cases were extremely high or exceeding 200 pg/ml. The numbers of severe cases with gastrin levels over 200 pg/ml and of 140–200 pg/ml were 9 and 8, or 24% and 21% of the 38 severe cases, respectively. Although the gastrin level of 140–200 pg/ml should be defined as hypochlorhydria rather than achlorhydria, all the cases with gastrin level over 140 pg/ml were called achlorhydria in the present study, since there was no difference in mean ferritin levels between the two groups, i.e., 3.88 and 3.66 ln(ng/ml) for gastrin levels over 200 and between 140 and 200 pg/ml, respectively.

Ferritin levels were significantly lower in the 17 severe atrophic gastritis cases with achlorhydria on average than in the nonatrophic gastritis cases (3.78 vs. 4.64 ln(ng/ml), $P<0.001$) or the mild/moderate cases (3.78 vs. 4.47 ln(ng/ml), $P<0.01$), while no difference was found between the severe atrophic gastritis cases with and without achlorhydria (3.78 vs. 4.21 ln(ng/ml), respectively). Neither was there any difference observed between the severe atrophic gastritis cases without hypergastrinemia and the nonatrophic gastritis cases or the mild/moderate cases. Ferritin levels did not differ with gastrin level (<140 vs. 140–200 pg/ml) among the mild/moderate atrophic gastritis cases (4.46 vs. 4.57 ln(ng/ml)) or among the noncases (4.63 vs. 4.65 ln(ng/ml)), when the modifying factors were taken into consideration. Thus, it was concluded that reduction of ferritin levels in the severe atrophic gastritis cases is due to the presence of achlorhydria only in these cases, although this could not be demonstrated for the achlorhydric atrophic gastritis cases from Okinawa and Tokyo.

The distribution of subjects with iron deficiency anemia, which was tentatively defined as a serum ferritin level below 20 ng/ml according to Cook *et al.*,[6] and their serum transferrin levels as well as Hb levels were examined in relation to atrophic gastritis, as shown in Table VII. Iron deficiency anemia was more frequent in the severe cases, which were characterized by significantly enhanced transferrin levels and more markedly reduced Hb levels when compared to the other cases. However, no significant difference in serum gastrin level was observed between the severe atrophic gastritis cases with and without iron-deficiency anemia, whose numbers were 0 and 4, 3 and 4, 3 and 8, 1 and 9 and 1 and 5 in Okinawa, Iwate, Akita, Nagano and Tokyo, respectively.

DISCUSSION

Ferritin levels in sera were significantly lower in the cases of achlorhydria associated exclusively with severe atrophic gastritis but did not differ by area or population, with the exception of Okinawa, if the above-identified modifying factors were taken into consideration. Accordingly, the inverse association between serum ferritin and gastric cancer risk, suggested to exist on the individual level in recent epidemiologic studies,[4,5] was not apparent on the population level or in terms of geographical correlation, whereas the prevalence rates of atrophic gastritis were correlated almost perfectly to gastric cancer mortality rates in the same populations, as reported previously.[15] Here, gastric cancer risk associated with atrophic gastritis is expected to be enhanced further in subjects with concurrent achlorhydria, since it is known that achlorhydria may cause an increase in the

amount of nitrous compounds[6] and *Helicobacter pylori* infection,[24] by which the risk should be elevated. However, the numbers of those cases were too small, that is, 1, 4, 5, 4 and 3 in Okinawa, Iwate, Akita, Nagano and Tokyo, respectively, for geographical correlation study, although their prevalence rates by area were still roughly proportional to atrophic gastritis prevalence and gastric cancer mortality rate.

On the other hand, although it is generally accepted that serum ferritin level may reflect iron stores in the body,[9, 16, 19] it was shown that ferritin level varies to a large extent according to medical histories of DM, gastric/duodenal ulcers and chronic liver damage, Hb, BMI and γ-GTP level in addition to atrophic gastritis diagnosis. Most ferritin in sera is known to be apoferritin without iron, which possibly originates from damaged cells or cell secretion in various tissues including the liver and spleen. The ferritin level could be enhanced by chronic liver disease as well as by ethanol-induced liver damage, which is related to an enhanced γ-GTP level as shown in the present study. It is likely that a positive correlation of the ferritin level with BMI indicates increased iron storage due to increase of the amount of blood. The same explanation could be applied to subjects with a medical history of DM, which is frequently associated with obesity. A simple explanation was not obtained, however, for the significantly lowered ferritin levels in subjects currently on medication for ulcer or chronic liver disease, since the possibility that those diseases affect the dietary intake of iron cannot be ruled out.

Possible variation of ferritin level due to iron intake[25] could not be examined directly in the present study, although iron intake may be one of the major factors affecting the ferritin level as suggested by the consistently higher ferritin levels in Okinawa compared to those in the other 4 areas. In fact, as described separately,[17, 18] meat consumption, which is much greater in Okinawa than in the other areas, could be related to the finding that the ferritin levels in Japanese Americans in Hawaii are markedly higher (mean: 5.49 ln(ng/ml) or 291.3 ng/ml in their controls, as reported by Nomura *et al.*[5]) than those of the nonatrophic gastritis cases in Okinawa (mean: 4.29 ln(ng/ml) or 139 ng/ml) in the present study. It should be noted that ferritin levels were significantly lower in subjects with atrophic gastritis even among Japanese Americans with such high ferritin levels, as was the case for Japanese in Japan. Thus, it is unlikely that an elevation of ferritin to the level found in Okinawa might have caused the not-lowered ferritin level in the severe atrophic gastritis observed in Okinawa. Instead, this should be attributed to the small number of subjects with achlorhydria associated with severe atrophic gastritis, which was only one in Okinawa, although no good explanation was obtained for the results from Tokyo.

The serological methods for diagnosing atrophic gastritis in the present study are thought to be qualitative as long as the severe cases are included as described previously.[12] Although some misclassification cannot be denied, as commonly pointed out for other currently used methods (especially for subjects on the borderline between nonatrophic gastritis cases and mild/moderate cases), it was unlikely that this affected the present results at the population level.[12] Moreover, with the present criteria of a combination of the cut-off level of Pep I/Pep II ratio <3.0 and that of Pep I level <70 ng/ml, it is expected that superficial gastritis cases (in which Pep II level does not increase, unlike mild/moderate atrophic gastritis[6] and, therefore, the ratio is not lowered), as well as atrophic gastritis of Type B (in which the pyloric gland area is preferentially lesioned and Pep I level is not lowered[6]), were eliminated from among the present atrophic gastritis cases. Thus, the present results coucern only atrophic gastritis of Type A, in which mainly the fundic gland area is affected.

On the other hand, achlorhydria was related rather definitively to a gastrin level over 200 pg/ml for the severe atrophic gastritis cases, since such a high level was not observed in the nonatrophic gastritis cases or mild/moderate cases. Although the level of 140–200 pg/ml, mostly observed among the noncases and mild/moderate cases, should be categorized as hypochlorhydria rather than achlorhydria, the ferritin level was shown not to vary significantly with the presence or absence of hypochlorhydria in either category. It is suggested, therefore, that the ferritin level is affected only when gastric acid secretion is suppressed in advanced atrophic gastritis. However, it should be noted that, since the gastrin level may reach, for example, 300 pg/ml 40 min after a meal,[26] the gastrin levels between 140 and 200 pg/ml found especially among the nonatrophic gastritis cases and mild/moderate cases, whose ferritin level was not lowered, may be due to food, although blood samplings were performed at least 3 h after the last meal (whether breakfast or lunch). Possible effects of diurnal rhythm[26] of gastrin secretion on the results were ruled out by the results of multiple regression analyses with adjustment for time of blood sampling (data not shown). Anyway serum levels of gastrin and ferritin should be studied further in relation to achlorhydria with more direct diagnostic methods to get more definite conclusions.

Serum transferrin is another protein that reflects iron stores in the body, and its levels are usually inversely correlated to those of serum ferritin. The correlation coefficient of -0.161 ($P<0.001$) observed in the present study agreed well with that obtained by Nomura *et al.*[5] On the other hand, the cases of iron-deficiency anemia, which was defined as serum ferritin levels below 20 ng/ml, showed significantly enhanced transferrin levels,

and were distributed more frequently among the severe atrophic gastritis cases (8/38 or 21%) than among the other cases (30/487 or 6.2% in the nonatrophic gastritis cases and 3/76 or 3.9% in the mild/moderate cases). However, since serum gastrin level did not differ with the presence of iron-deficiency anemia, achlorhydria, whether associated with severe atrophic gastritis or not, could not be regarded as a predominant determinant of iron-deficiency anemia.

In conclusion, the present results suggest that the reported negative association of ferritin level with gastric cancer risk on an individual basis is indirect, in that ferritin level is lowered by achlorhydria accompanying severe atrophic gastritis. It was also evident that the areal mean ferritin levels, which are not significantly affected by prevalence of those cases with lowered ferritin levels, could not be associated with the risk at the population level either.

ACKNOWLEDGMENTS

This study was supported by a Grant-in-Aid for the Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health and Welfare. The authors are grateful to the participants in this study and the supervisors and staff in the Public Health Centers and hospitals concerned for their kind cooperation and assistance.

(Received February 18, 1993/Accepted May 26, 1993)

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