

Association between Family History and Gastric Carcinoma among Young Adults

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The relationship between family history of gastric carcinoma and gastric carcinoma in Japanese under 40 years of age was analyzed. The subjects were 108 gastric carcinoma patients (86% were diffuse type) at 9 hospitals in the Kanto area of Japan. Firstly, incidence of gastric carcinoma among the parents of the subjects were compared with that in the general population. Observed/expected (O/E) ratios (*P*-value) were 1.8 (0.06) for all subjects, 1.3 (0.62) for male subjects, 2.1 (0.04) for female subjects, 0.5 (0.41) for early carcinoma, 2.6 (*P*<0.01) for advanced carcinoma, 2.3 (0.22) for intestinal-type carcinoma and 1.7 (0.13) for diffuse-type carcinoma. Association between gastric carcinoma and parents' history of gastric carcinoma was strong among women and regarding advanced carcinoma, and the difference in O/E ratios between early and advanced carcinoma was remarkable. Secondly, factors related to advanced-stage gastric carcinoma were analyzed. Histological type (diffuse and intestinal types) was not related, but family history of gastric carcinoma among parents and grandparents was related to advanced stage, and the relationship was independent of other factors. The odds ratio (95% confidence interval) was 3.3 (1.1-9.9). Family history may be related to stage of gastric carcinoma through its relationship to the manner or speed of the tumor's progression. We hypothesize that some genetic factor exists which is involved both in progression from early to advanced stage and in occurrence of gastric carcinoma.

Key words: Gastric carcinoma — Young adults — Family history — Advanced carcinoma — Stage

There have been many studies on the relationship between risk of gastric carcinoma and family history of gastric carcinoma, and it is accepted that family history is a risk factor for gastric carcinoma. This is suspected to be because of a strong relationship between family history and certain types of gastric carcinoma, and several studies have analyzed the relationship regarding intestinal and diffuse types of gastric carcinoma separately. Diffuse-type carcinoma has a stronger relationship to family history than intestinal type.^{1,2)} Among Finnish people under 40 years of age, a strong relationship has been reported between family history of gastric carcinoma and risk of gastric carcinoma.³⁾ However, so far

few studies have analyzed the relationship between stage of gastric carcinoma and family history.

In Japanese under 40, gastric carcinoma is relatively uncommon,^{4,5)} most of the tumors are of diffuse type⁶⁾ and the male/female ratio of gastric carcinoma death is less than 1.0.⁷⁾ The current study was performed to investigate what type of gastric carcinoma is strongly related to family history in Japanese under 40 years of age.

SUBJECTS AND METHODS

Data collection The subjects were 108 inpatients under 40 years of age with gastric carcinoma treated at 9 hospitals in the Kanto-Shin-Etsu area of Japan from August 1988 to November 1992. Any patients who had previously had an operation of the stomach or chemotherapy were excluded.

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Table I. Incidence of Gastric Carcinoma in Japan

Age	Incidence rate ^{a)}	
	Male	Female
10-14	0.0	0.0
15-19	0.5	0.3
20-24	0.6	1.8
25-29	4.4	5.5
30-34	11.2	13.6
35-39	23.7	24.3
40-44	45.9	36.2
45-49	78.8	47.9
50-54	139.0	61.6
55-59	224.1	82.2
60-64	329.4	124.1
65-69	450.9	172.9
70-74	588.0	242.3
75-79	708.0	281.7
80-84	736.1	341.3
85-	743.8	348.6

Per 100,000 person-years.

a) From Ref. 4.

Information on stage of gastric carcinoma (early or advanced) and histological type (intestinal or diffuse), was collected. Mixed diffuse and intestinal-type lesions were classified as intestinal type. The subjects were asked to answer a questionnaire, after informed consent had been obtained. They were asked to respond to the questionnaire between admission to the hospital and major therapy (surgical operation for 87 subjects and chemotherapy for 21 subjects). Information obtained included parents' date of birth and whether the parents and grandparents had any history of gastric carcinoma.

Comparison with the general population to investigate what type of gastric carcinoma was strongly related to family history In order to compare history of gastric carcinoma among the parents of the subjects with incidence in the general population, expected cumulative incidence of gastric carcinoma among the parents was calculated using the parents' birth year and cancer incidence rates in Japan in 1986 (Table I). Observed/expected (O/E) ratio, chi-square (one degree of freedom) and *P*-value were calculated comparing the observed history and the expected incidence among the parents. They were also calculated for both genders and for early, advanced, intestinal and diffuse types of carcinoma.

Univariate and multivariate analyses for factors related to stage of gastric carcinoma Relationships between stage of gastric carcinoma and factors including family history of gastric carcinoma were analyzed, taking into consideration mutual interaction among the factors. Odds ratio (OR) and its 95% confidence interval (95% CI) for the relationships between stage of gastric carcinoma

Table II. Age and Sex Distribution of Early and Advanced Gastric Carcinoma

Age	Sex	Early (%)	Advanced (%)	Total
20-24	M	0 (0.0)	2 (100.0)	2
25-29	M	2 (50.0)	2 (50.0)	4
30-34	M	8 (57.1)	6 (42.9)	14
35-39	M	15 (51.7)	14 (48.3)	29
Total	M	25 (51.0)	24 (49.0)	49
20-24	F	1 (33.3)	2 (66.7)	3
25-29	F	1 (20.0)	4 (80.0)	5
30-34	F	2 (11.1)	16 (88.9)	18
35-39	F	11 (33.3)	22 (66.7)	33
Total	F	15 (25.4)	44 (74.6)	59
Total	M + F	40 (37.0)	68 (63.0)	108

Table III. Positive Percentages of Family History of Gastric Carcinoma

Family member	% (No. of subjects with positive family history)
Father	4.6 (5=0+5) ^{a)}
Mother	4.6 (5=1+4)
Paternal grandfather	7.4 (8=2+6)
Paternal grandmother	2.8 (3=0+3)
Maternal grandfather	7.4 (8=1+7)
Maternal grandmother	3.7 (4=1+3)
At least one of the parents and grandparents	25.9 (28=5+23)

Percentages in 108 gastric carcinoma (40 early and 68 advanced) patients.

a) Total number=in early + in advanced patients.

noma (early or advanced) and gender, family history (positive or negative) or histological type (intestinal or diffuse) were calculated with HALBAU.⁸⁾ As for family history, subjects were classified into the positive category if at least one of their parents and grandparents had a history of gastric carcinoma, and the remaining subjects into the negative category.

Logistic regression analysis was carried out with GLIM.⁹⁾ In the analysis, the criterion variable was stage, and the explanatory variables were sex, age (5-year classes, as shown in Table II), histological type and family history. Explanatory variables were selected by the backward elimination method so that the *P*-value of all remaining explanatory variables became less than 0.10. Since location of the carcinoma lesion may influence the stage, a model adjusted for location of tumors was also calculated. Adjustment was done by adding to the model two variables regarding the main location of the carcinoma lesion: upper, middle, lower third or whole of the stomach; and lesser, greater curvature, anterior, posterior wall or circle.

Table IV. Comparison of Observed History with Expected Incidence of Gastric Carcinoma among the Parents of the Patients

Patients	Number of parents	Observed	Expected	O/E	P-value
All	193	10	5.63	1.78	0.062
Men	81	3	2.27	1.32	0.624
Women	112	7	3.36	2.08	0.044
Early	70	1	2.19	0.46	0.413
Advanced	123	9	3.44	2.62	0.002
Intestinal	28	2	0.87	2.30	0.219
Diffuse	165	8	4.76	1.68	0.132

Expected incidence was calculated using cancer incidence rates in Japan in 1986, shown in Table I.

Table V. The Relationships between Progression Stage (Early and Advanced) of Gastric Carcinoma and Gender, Family History and Histological Types (Intestinal and Diffuse) of Gastric Carcinoma (Univariate Analysis)

Factor (High risk category for advanced stage)	Odds ratio (95% CI)
Gender (Female)	3.06 (1.26-7.48)
Family history (Positive) ^{a)}	3.58 (1.13-12.01)
Histological type (Diffuse) ^{b)}	1.21 (0.34-4.47)

a) Positive: at least one of the parents and grandparents had a history of gastric carcinoma. Negative: the remaining patients.
b) See text.

RESULTS

Table II shows the age and sex distribution of early and advanced gastric carcinoma. Advanced carcinoma was more frequent among women. No association was observed between age and stage of gastric carcinoma. Among the 108 patients, 93 (86%) had diffuse and 15 (14%) had intestinal-type gastric carcinoma. Table III gives the percentages of positive family history. Family history was more frequent among the subjects with advanced gastric carcinoma.

Table IV shows the results of comparison with the general population. For all subjects, the O/E ratio (P-value) was 1.8 (0.06). For male subjects, the O/E ratio was 1.3 (0.62) and for female subjects, it was 2.1 (0.04). For early carcinoma, it was 0.5 (0.41), while for advanced carcinoma, it was 2.6 (P<0.01). For intestinal type carcinoma, it was 2.3 (0.22) and for diffuse type, 1.7 (0.13).

Table V shows the results of univariate analysis. Female patients showed high risk for advanced stage, with an OR (95% CI) of 3.1 (1.3-7.5). Family history among parents and grandparents was related to risk for advanced stage, with an OR (95% CI) of 3.6 (1.1-12.0). Histological type of gastric carcinoma was not related to

Table VI. Final Model Using Multiple Logistic Regression with Backward Elimination to Assess Factors Associated with Risk for Advanced Stage of Gastric Carcinoma

Explanatory variables	Odds ratio (95% CI)
Sex	Male 1.0 Female 2.89 (1.26-6.62)
Family history of gastric carcinoma ^{a)}	(-) 1.0 (+) 3.33 (1.13-9.86)

n = 108.

a) (+) : at least one of the parents and grandparents had a history. (-) : the remaining patients.

risk for advanced stage; the OR (95% CI) was 1.2 (0.3-4.5). Table VI gives the results of logistic regression analysis. Female patients and patients with family history showed significantly high risk for advanced gastric carcinoma, with OR of 2.9 and 3.3, respectively. Adjustment for location of the carcinoma lesion had little influence on the results.

DISCUSSION

“No answer responses” and possible bias “No answer responses” were frequent, especially regarding grandparents. The main reason for “no answer responses” was thought to be the subjects’ tendency to note only positive histories. In the univariate analysis, similar results were obtained when the subjects whose family history contained “no answer responses” were excluded from the analysis. In the logistic regression analysis, the result did not change and OR for the category of “no answer responses” was almost 1.0, when the subjects whose family history contained “no answer responses” were categorized separately. Hence, “no answer responses” were considered as negative history in the current study.

In studies which use only gastric carcinoma patients, collection of subjects might distort the results. In the current study, no selection regarding gender or stage of

gastric carcinoma was made when subjects were collected. We tried to recruit all suitable cases among the patients admitted to the 9 hospitals and only a few cases were missed. Essentially no bias was thought to exist in the collection of the subjects.

There might be recall bias among the subjects because of differences in the severity of abdominal symptoms. In the current study, the subjects were asked to respond to the questionnaire between admission to the hospital and major therapy. Their major concern at that time was considered to be not the symptoms, but the therapy they were about to undergo. Therefore little, if any, recall bias was considered to exist among the subjects.

Relationships between family history and gastric carcinoma with reference to gender, stage and histological type Parents' history of gastric carcinoma showed a weak association ($P < 0.10$) with risk for gastric carcinoma in Japanese under 40 years of age. For both genders, the O/E ratios were more than 1.0, but O/E for female subjects was larger and was significant. Advanced gastric carcinoma showed a significant association with parents' history, whereas the O/E ratio for early carcinoma was less than 1.0. For both intestinal and diffuse types of gastric carcinoma, O/E ratios were more than 1.0, but neither result was significant. There seemed to be no remarkable difference between the two types of carcinoma in association with family history, though the number of subjects with intestinal-type carcinoma was too small to allow a definitive conclusion.

In Japanese under 40 years of age, the association between gastric carcinoma and parents' history of gastric carcinoma was strong among women and regarding advanced carcinoma. The difference in O/E ratios between early and advanced carcinoma was remarkable.

Factors related to stage of gastric carcinoma In the univariate analysis, gender and family history of gastric carcinoma showed significant relationships to stage. In the logistic regression analysis, both gender and family history were also significantly associated with stage. The location of the main lesion sometimes influences the stage.¹⁰⁾ However, the association remained after adjustment for location of the main lesion. These results imply that both gender and family history of gastric carcinoma are related to advanced stage of gastric carcinoma in Japanese under 40 years of age, and the relationships are mutually independent.

Female patients had significant risk for advanced stage of gastric carcinoma. A Japanese study has shown that female patients have a bad prognosis among advanced gastric cancer patients under 50 years of age,¹¹⁾ which indicates a sex-related difference in growth of gastric carcinoma and is consistent with the difference in the current study. However, men under 40 undergo stomach examination more frequently than women of the same

age in mass-screening programs in Japan, because of the deleterious effect of roentgenography on the ovaries. The mass-screening programs may have something to do with the sex-related difference in stage of gastric carcinoma. We can not reach a clear conclusion on sex-related difference in growth of gastric carcinoma from the results of the current study.

Family history and stage of gastric carcinoma Some early gastric carcinomas grow to be advanced carcinomas and some remain at an early stage.¹²⁾ Two factors are thought to determine the stage of gastric carcinoma at the time of diagnosis. One factor is when examination for gastric carcinoma is carried out. The other factor is the manner or speed of the tumor's progression from early to advanced stage.¹³⁾ Family history should not influence the former factor, because it can not be true that those without family history undergo stomach examination more frequently than those with family history. Curable duration, that is the duration between the time when gastric carcinoma becomes detectable and the time when it becomes advanced carcinoma, is variable.¹⁴⁾ Thus, family history might be related to stage of gastric carcinoma through an influence on the manner or speed of the tumor's progression, and the curable duration of gastric carcinoma in patients with family history may be relatively short.

Some genetic factor should be responsible for the relationship between stage of gastric carcinoma and family history. The relationship implies that the factor is involved in both progression and occurrence of gastric carcinoma. In other words, the genetic factor which promotes the growth of gastric carcinoma from early to advanced stage must also influence the carcinoma at some point between its initiation and the time when it becomes clinically detectable. Otherwise, the incidence in the families of patients with advanced gastric carcinoma would be the same as that in the general population and no relationship between stage and family history would be observed.

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