

# Family History of Cancer and Mortality among Patients Gastrectomized because of Benign Gastric Diseases

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A preliminary result from a cohort study on the association of a family history of cancer with mortality is discussed in this paper. Among 2200 patients (1912 males and 288 females) gastrectomized because of benign gastric diseases, 274 male patients, and 40 female patients had a family history of cancer. During 2750 person-years of observation, 22 patients with the family history of cancer were found to be dead and 111 patients without the family history died during 17,527 person-years, giving a relative risk of 1.26 (not significant). We focused on the male subjects that were followed up for more than 10 years; however, the observed/expected ratio of cancer deaths for subjects with a family history of cancer was about four times higher than that for those without family history. Since case-control studies on family history are vulnerable to biased recall and interchangeability of cases, more cohort studies like the present study should be conducted to assess the association of the family history of cancer.

## Introduction

Considering recent advances in carcinogenesis including oncogenes, epidemiological studies should be carried out regarding genetic traits and the environment.

Studying family history is one of the ways to determine the genetic factor on carcinogenesis, although family members have both the same genetic traits and similar environmental exposures during their lives.

There have been many reports showing familial aggregation of cancer, and the term "cancer family syndrome" for adenocarcinoma has been used (1). There are also many reports that showed a higher risk of cancer among those with a family history of cancer than among those without it (2,3). Most of the reports are based on case-control studies, and a few cohort studies were conducted on the relationship of cancer risk with the family history of cancer.

Although conducting case-control studies presents fewer difficulties in terms of time and cost, those that were focused on the family history tended to be very

vulnerable to biased recall (4), comparability including interchangeability of cases (5), and other problems.

This paper demonstrates a preliminary result from a cohort study on patients gastrectomized because of benign gastric diseases. The purposes of the original study (6) were first to measure the general prognosis, that is, the survival experience after gastrectomy; second, to examine how gastrectomy is associated with gastric stump cancer; and third, to determine which factors contributed to the mortality pattern among the gastrectomized patients.

The aim of the present study is to examine the roles of family history for cancer incidence. We also considered the advantages and disadvantages of cohort studies for evaluating the association of family history of cancer with cancer risk.

## Materials and Methods

Patients with benign gastric diseases who had received a gastrectomy during the period from August 1972 to December 1979 at one private gastrointestinal hospital in Nagoya, Aichi Prefecture, Japan, were listed as eligible subjects. Almost all surgical operations were performed by the three surgeons in the hospital, and one experienced pathologist histologically scrutinized all the resected specimens to confirm the diagnosis of benign diseases. All the patients were interviewed by the

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three surgeons, with particular attention to family history, previous illness, smoking and drinking habits, and other factors.

Among 2200 listed patients (1912 males and 288 females), 274 males and 40 females were found to have had first- and/or second-degree relatives with cancer (parents, children, grandparents, siblings, uncles, aunts, nephews, and nieces). They were followed up until May 1986 by periodical check-ups and a questionnaire that was mailed out. When the patients could not be followed up because they had moved out of the town, had died, or because of other reasons, the survival status was referred to the offices of population registry (Honseki). Finally, information was obtained on 98.8% of the male patients and 96.5% of the female patients. For the patients reported to be dead, the death certificates were referred to the registration offices in order to confirm the causes of death.

As a reference, expected mortality was calculated separately for the patients with and without a family history of cancer. Calculation of the expected numbers was based on the observed person-years of each patient group by age multiplied by sex-specific mortality rates of the 5-year age group in Aichi Prefecture, 1970, 1975, 1980, and 1983.

## Results

Age and sex distributions of the subjects are shown in Table 1; 14.3% of the male patients and 13.9% of the female patients had a family history of cancer. The percentage of the with-history patients among the male patients who were 30 to 69 years of age ranged from 13 to 17%, and there was little difference among age groups; 22 to 24% of the female subjects from 30 to 49 years of age had a family history of cancer, while about 15% of the female patients in their 20s and 50s had a family history of cancer. The mean age at the time of the surgical operation was 45.1 years old for with-history patients and 43.3 for without-history patients.

The frequency of the relatives' cancer by site is shown in Table 2; 64.2% of male probands and a 58.5% of female probands had a relative who had a history of stomach cancer. For the female probands, the proportion of colon cancer and liver cancer was relatively high while the proportion of uterine cancer was low (7.8%).

Table 3 shows the distribution of relatives who had a history of cancer. The proportion of fathers was highest (about 31%); the proportion of siblings was about two times higher among female probands than among male probands, though the proportion of uncles and aunts was higher among male probands.

Table 4 shows the smoking rate among the subjects by family history. Each subgroup showed a higher rate than the smoking rate among the general population in Japan. The smoking rate among the male with-history patients was slightly higher than that among without-history patients. The difference was statistically significant. There was no statistically significant difference between the female with-history patients and without-history patients.

The rates of alcohol drinking by family history is shown in Table 5. The rate for the male with-history subjects was not statistically different from that for without-history subjects. The female with-history patients showed a higher drinking rate than without-history patients.

Table 6 shows serum total cholesterol and total protein of the patients, which might be regarded as biological markers of nutrition and dietary habit that can be related to cancer. There was no difference between the with-history subjects and without-history subjects. However, the serum total protein was slightly higher among the without-history male patients than among the with-history patients.

The with-history patients were followed up for 9.0 years and the without-history patients, for 9.4 years on an average. The person-years of observation were 2,750 and 17,527, respectively. Twenty-two patients with family history and 111 patients without family history were found to be dead, giving a relative risk of 1.26 (not significant). Among those, 3 patients and 22 patients had died of cancer. The relative risk was 0.87 (not significant).

Table 7 shows the observed and expected numbers of deaths from all causes by sex. The ratio of the observed to the expected (O/E ratio) was less than unity except that for the male with-history patients. The statistically significant O/E ratio was not observed. The ratio of the O/E ratio of the with-history patients to the without-history patients was 1.22 in males and 0.53 in females.

Table 1. Age and sex distribution of subjects by a family history of cancer.

Age	Males			Females		
	(+) History	(-) History	Total	(+) History	(-) History	Total
0-19	3	27	30	0	3	3
20-29	30	252	282	3	17	20
30-39	62	416	478	10	36	46
40-49	84	484	568	9	59	68
50-59	55	276	331	12	69	81
60-69	36	172	208	6	59	65
70-79	3	12	15	0	5	5
Total	273	1639	1912	40	248	288
(%)	(14.3)	(85.7)	(100.0)	(13.9)	(86.1)	(100.0)

Table 2. Frequency of relatives' cancer by site.

Site of relatives' cancer	Proband	
	Male (%)	Female (%)
Stomach	194 (64.2)	30 (58.8)
Lung	5 ( 1.9)	1 ( 2.0)
Uterus	14 ( 4.6)	4 ( 7.8)
Colon	13 ( 4.3)	7 (13.7)
Breast	4 ( 1.3)	0 ( 0.0)
Liver	10 ( 3.3)	5 ( 9.8)
Esophagus	12 ( 4.0)	0 ( 0.0)
Other and unknown	50 (16.6)	4 ( 7.8)
Total	302 (100)	51 (100)

Table 3. Numbers of relatives with cancer.

Relative	Proband	
	Male (%)	Female (%)
Fathers	94 (31.1)	16 (31.4)
Mothers	50 (16.6)	9 (17.6)
Grandparents	32 (20.6)	5 ( 9.8)
Siblings	34 (11.3)	12 (23.5)
Uncles and aunts	54 (17.9)	6 (11.8)
Nephews and nieces	4 ( 1.3)	0 ( 0.0)
Children	6 ( 2.0)	0 ( 0.0)
Not specified	28 ( 9.3)	3 ( 5.9)
Total	302 (100)	51 (100)

Table 4. Percentage of smokers among the subjects by family history of cancer.

Cancer	Male, %	Female, %
(+) History	93.30	50.0
(-) History	88.20	35.0
	$p < 0.05$	Not significant

Table 5. Percentage of drinkers among the subjects by family history of cancer.

Cancer	Male, %	Female, %
(+) History	58.9	26.5
(-) History	56.9	13.4
	Not significant	$p < 0.05$

Table 6. Serum total cholesterol and total protein of the subjects by family history of cancer.

Cancer	Total cholesterol, mg/dL		Total protein, g/dL	
	Male	Female	Male	Female
(+) History	160.1	171.1	7.11	7.26
(-) History	159.5	172.3	7.24	7.31
	NS*	NS	$p < 0.01$	NS

\*NS, not significant.

Observed cancer deaths were fewer than the expected in any subgroup (Table 8). The O/E ratio of the with-history patients did not exceed that of the without-history patients, although the number of the observed was very small. But focusing on the male patients observed for more than 10 years, we recognized that the

Table 7. Observed (O) and expected (E) numbers of deaths from all causes by family history of cancer.

	Males		Females	
	(+) History	(-) History	(+) History	(-) History
O	21.00	95.00	1.00	16.00
E	20.00	109.90	2.30	17.50
O/E ratio	1.05	0.86	0.48	0.91

Table 8. Observed (O) and expected (E) numbers of deaths from cancer by family history of cancer.

	Males		Females	
	(+) History	(-) History	(+) History	(-) History
O	3.00	18.00	0.00	4.00
E	6.10	33.3	0.40	5.40
O/E ratio	0.49	0.54*	0.00	0.76

\* $p < 0.05$ .

Table 9. Observed (O) and expected (E) numbers of deaths from all causes and cancer by family history for over 10 years from gastrectomy in males.

Death	Cancer	O	E	O/E
All causes	(+) History	3	1.8	1.63
	(-) History	13	11.5	1.13
Cancer	(+) History	2	0.6	3.45
	(-) History	3	3.6	0.84

O/E ratio of cancer deaths for with-history subjects was about four times higher than that for without-history patients, as is shown in Table 9.

## Discussion

The relative risk of having a family history of cancer seems to be overestimated from case-control studies because of more serious recall in cases than in controls. There are no good methods to avoid the recall bias, especially when healthy controls are used. An adoption of controls with the other serious diseases (7) may be an alternative way to avoid the bias as long as the risk of the adopted controls is regarded as that in a general population.

Sometimes those patients whose relatives are selected as the case of the case-control study may be also included in the study. In that case, the independence of sampling of the subjects is not presumed, i.e., the problem of interchangeability; it also favors overestimation of the relative risk.

The comparison of the risk between those with and without a family history of cancer in a cohort study is free from the two previously mentioned influences.

In our study 14.3% of male patients and 13.9% of female patients had a family history of cancer. These percentages seem to be lower than the expected, considering familial tree studies (1). The percentage of family history for stomach cancer patients who were similarly examined in the same hospital, however, was 26.3% for males and 28.3% for females, which was quite

comparable with other studies, e.g., 24.4% in male cancer patients and 24.6% in female cancer patients listed in the Aichi Cancer Registry (7). Therefore, family history records on medical charts at this hospital seemed to be evaluative.

The low percentages of family history of cancer among the subjects may be due to the fact that the crude death rate of cancer in Japan was around 60% of that found in European countries (8). Judging from the occurrence of cancer in Japan between 1950 and 1970, the rate of the subjects with a family history of cancer and the proportion of stomach cancer found among the relatives' cancer did not seem to be deviated. On the other hand, the low proportion of liver cancer may have resulted from poor diagnostic techniques. The lower proportion of uterine cancer may be due either to recall bias, or to the different socioeconomic status among the subjects and the general population.

Misclassification between the with-history patients and without-history patients seem to be unavoidable because the information on family history were obtained only by interviewing subjects and/or their relatives without any medical confirmation. In this cohort study, however, the misclassification, if any, was thought to be nonselective. The misclassification may dilute difference in risk and reduce the statistical power. Even when the nonselective misclassification does not occur, a larger number of subjects are required in a cohort study, which seems to be a demerit in comparison with case-control studies. Provided that the relative risk is more than two, and mortality rate of the without-history exceeds 100 per 100,000 person-years, at least 23,500 person-years are necessary for each group with  $\alpha$  error of 0.05 and a power of 80%.

Concerning the association of a family history of cancer with the risk of cancer, we have to consider some other points.

**Mean Age of Subjects.** If the mean age of the patients at their surgical operation had been older, we could have observed larger number of deaths and the result would have been demonstrated more clearly.

**Number of Blood Relatives of Each Subject.** The more relatives a subject had, the more probability the subject had of having relatives with cancer. In this study, the data on the size of family were not available, but this problem has to be considered if we can obtain the information on family size.

**Cases That Have Two or More Relatives with Cancer.** In our study, 11.8% males with-history patients and 21.7% females with-history patients had two or more relatives with a family history of cancer. Because there were only a small number of subjects who had two relatives with cancer, we did not analyze them separately. The low percentages do not seem to be attributable to recall bias, considering the relatively young ages of the probands and the low rate of cancer mortality in the past.

The high smoking rate for both male and female subjects may be associated with the fact that the patients of benign gastroduodenal ulcer show a high smoking

rate; this may be because the socioeconomic status of the subjects was different from the general population. Although there were statistically significant differences in the smoking rate between the with-history patients and the without-history patients, the 5% difference does not seem to largely affect the occurrence of cancers except lung cancer.

The rate of alcohol drinking among female with-history subjects was significantly higher than that of without-history subjects, and this difference needs to be taken into account in the follow-up study in the future.

There was no difference in serum total cholesterol between the with-history patients and those without-history. The serum total protein was lower among the with-history patients than among those patients without-history.

So the two subgroups (with-history group and without-history group) seemed to be comparable from the viewpoint of several life-style factors that have relevance to the occurrence of cancer.

The follow-up for an average of 9 years did not lead to the significantly high relative risk for the with-history patients. This may be because the subjects at surgical operation were young on the average and the corresponding low mortality rate from cancer and other diseases. The insignificant relative risk may be also because of the small number of the with-history subjects.

The reason why the O/E ratios of cancer death were low both for the with-history patients and for without-history patients was not clarified. This may have been the result of the gastrectomy, because stomach cancer has the highest probability of developing among Japanese people. Another possible explanation is that the education by the surgeons on lifestyle after gastrectomy may have had the effect of reducing their mortality.

This preliminary result demonstrated that those with a family history of cancer had a slightly elevated, nevertheless not significant risk of mortality from all causes and cancer risk. The observed person-years were not enough to evaluate the relative risk of cancer death. Since the subjects were selected from patients gastrectomized because of benign upper gastrointestinal diseases, we have to be careful to extrapolate this result in the general population. In addition, the observed person-years were not enough to evaluate the relative risk of cancer death. However, the present study could suggest that cohort study is adequate for assessing the association of family history of cancer with risk of cancer when a large cohort can be followed up.

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