ORIGINAL CONTRIBUTION

A Case-Control Study on Familial Aggregation of Colorectal Cancer

Takashi Oishi^{1,2}, Yosikazu Nakamura³, Masaki Nagai⁴, Yoshiya Yamada¹, Terumi Kamisawa¹, Naoto Egawa¹, Kumiko Monma¹, Tomoaki Isawa¹, Nobuhiro Sakaki¹, Junichi Ishiwata¹, Tuyoshi Tajima⁵, and Hiroshi Yanagawa³

A Case-control study was conducted in 110 patients with colorectal cancer and, as control groups, 84 with gastric cancer, 50 with other cancer and 111 with benign gastroenterological disease. In this study we try to make it clear whether colorectal cancer has really familial aggregation and whether a positive family history can be used as one of screening procedures, by getting information more exactly about family history and by taking account of family size into analysis. 9.1% (OR 1.20) of colorectal cancer group and 11.3% (OR 1.70) of colon cancer group had positive family history of colorectal cancer, as compared with the benign disease group. 1.8% of their first-degree relatives were affected by colorectal cancer. No significant difference was seen, although these proportions were higher than those in 3 control groups. These results suggest familial aggregation of colorectal cancer is not so large as researchers have mentioned so far, although a tendency for familial aggregation was found in colon cancer. At the present stage in Japan, we should not perform screening for the first-degree relatives only by positive family history from the reason of efficiency, though those of patients with clinically diagnosed or suspected HNPCC should be screened. *J Epidemiol*, 1995; 5: 165-169.

colorectal cancer, familial aggregation, family history, family size, history taking

Most of epidemiologic studies in the Western countries have supported familial aggregation of colorectal cancer. Although the reports of similar argument have been published in Japan, most of them have some defects in history taking and analysis. It is not obvious whether colorectal cancer has familial aggregation in Japan.

In this study we try to make it clear whether colorectal cancer has really familial aggregation and whether a positive family history can be used as one of screening procedures, by getting information more exactly about family history and by taking account of family size into the analysis.

MATERIALS AND METHODS

651 patients were admitted at the Department of Gas-

troenterology in Tokyo Metropolitan Komagome Hospital from July 1990 to May 1991. Of those, study population was 327 patients taken family history exactly as mentioned below. These 327 patients included 24 with double cancers and 2 with tripple ones. This led the total study population to 355 patients. These 355 patients consisted of 110 with colorectal cancer (colorectal cancer group; colon cancer 80 cases, rectal cancer 35 cases, including overlapping) and, as control groups, 84 with gastric cancer (gastric cancer group), 50 with other cancers (other cancer group) and 111 with benign gastroenterological disease (benign disease group). The mean age was about 64 years old in the three malignancy groups, while 55 in benign disease group. The number of males was larger than that of females in all the groups (Table 1).

The first-degree relatives (parents and siblings, except

Received March 12, 1994; accepted September 14, 1995.

¹Department of Internal Medicine, Endoscopy, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan.

²Department of General Medicine, Omiya Medical Center, Jichi Medical School, Saitama, Japan.

³Department of Public Health, Jichi Medical School, Tochigi, Japan.

⁴Department of Public Health, Saitama Medical School, Saitama, Japan.

⁵Department of Internal Medicine, Tokyo Metropolitan Okubo Hospital, Tokyo, Japan.

Address for correspondence: Takashi Oishi, Department of General Medicine, Omiya Medical Center, Jichi Medical School, 1-847 Amanuma Omiya Saitama, 330 Japan.

Table 1. Age and sex distribution among 4 observed groups.

Type of Ca.	Male	Female	Total	Mean Age $\pm$ SD
Colorectal Ca.	71	39	110	64.3 $\pm$ 10.9
Gastric Ca.	51	33	84	65.4 $\pm$ 12.2
Other Ca.	31	19	50	63.7 $\pm$ 11.3
Benign Dis.	66	45	111	55.3 $\pm$ 16.2
Total	219	136	355	61.7 $\pm$ 13.7

Other ca : malignant neoplasms other than colorectal or gastric cancers

Benign dis : benign gastroenterological disease

Table 2. The numbers of first degree relatives observed.

Type of Ca.	Father	Mother	Siblings	Total
Colorectal Ca.	110	110	459	679
Gastric Ca.	84	84	332	500
Other Ca.	50	50	204	304
Benign Dis.	111	111	393	615
Total	355	355	1388	2098

male : female : unknown = 1039 : 965 : 94

children) of those groups numbered 679 in the colorectal cancer group, 500 in the gastric cancer group, 304 in the other cancer group, and 615 in the benign disease group (Table 2). The age distribution of the first-degree relatives was shown in Table 3. Dead cases accounted for about a half in each group. This is because parents had already been dead in many cases.

In taking family history, we used an original questionnaire, defining objects as the first-degree relatives, and confirming the patient and/or his family whether or not to have past history of cancers one by one mainly in the gastroenterological system.

This study on familial aggregation was performed between the colorectal cancer group and the three control groups, according to the observation, first of family units and, secondly of individual family members. The former

was a case-control study and we observed adjusted Odds ratio by using Mantel-Haenszel method. Age was classified into three ; <50 years, 50~69 years, >70+. In addition, we divided colorectal cancer group into colon and rectal cancer group, and compared them with benign disease group.

Besides, we also examined the frequency of hereditary non-polypoid colorectal cancer (HNPCC). Criteria for HNPCC are defined as below : 1) a case with 3 or more colorectal cancer cases within the first-degree relatives, 2) a case with 2 or more colorectal cancer cases within the first-degree relatives and with any of the following ; a) age at onset of colorectal cancer is younger than 50 years old, b) the right colon involvement, c) multiple colorectal cancers, d) association with extracolorectal malignancies.

Table 3. Age Distribution of first degree relatives.

	Age of Living Subjects						Unkown	Dead	Mean Age at Death	Total
	-39	40-49	50-59	60-69	70-79	80-				
FDR of Colorectal Ca.	1 (0.1%)	49 (7%)	87 (13%)	92 (14%)	41 (6%)	29 (4%)	38 (6%)	342 (50%)	54.8 n = 131	679 (100%)
FDR of Gastric Ca.	3 (1%)	39 (8%)	67 (13%)	54 (11%)	34 (7%)	26 (5%)	47 (9%)	230 (46%)	54.7 n = 112	500 (100%)
FDR of Other Ca.	1 (0.3%)	23 (8%)	32 (11%)	23 (8%)	20 (7%)	14 (5%)	37 (12%)	156 (51%)	50.2 n = 60	304 (100%)
FDR of Benign Dis.	28 (5%)	53 (9%)	74 (12%)	76 (12%)	40 (7%)	14 (2%)	71 (12%)	259 (42%)	53.7 n = 119	615 (100%)
Total	33 (2%)	164 (8%)	260 (12%)	245 (12%)	135 (6%)	83 (4%)	193 (9%)	985 (47%)	53.8 n = 422	2098 (100%)

Table 4. Frequency of positive family history of colorectal cancer and risk of colorectal cancer among study population.

Type of Ca.	Subject	Frequency(%)	OR	95%CI
Colorectal Ca.	110	10 (9.1)	1.73	0.50-5.9
Gastric Ca.	84	5 (6.0)	1.0	
Colorectal Ca.	110	10 (9.1)	1.35	0.37-4.9
Other Ca.	50	4 (8.0)	1.0	
Colorectal Ca.	110	10 (9.1)	1.20	0.46-3.1
Colon Ca.	80	9 (11.3)	1.70	0.83-3.5
Rectal Ca.	35	2 (5.7)	0.81	0.26-2.5
Benign Dis.	111	7 (6.3)	1.0	

OR : Odds ratio, CI : Confidence interval

RESULTS

We first investigated a positive family history for cancers according to the observation of family units (Table 4). The highest proportion of a positive family history for colorectal cancer was 9.1% in the colorectal cancer group. No significant correlation was observed between the colorectal cancer group and the gastric cancer group (OR 1.73, 95% CI 0.5~5.9), the other cancer group (OR 1.35, 95% CI 0.37~4.9) or the benign disease group (OR 1.20, 95% CI 0.46~3.1). Analyzing colon and rectal cancer separately, the frequency of positive family history of colorectal cancer was 11.3% (OR 1.70, 95% CI 0.83~3.48) in the colon cancer group and 5.7% (OR 0.81, 95% CI 0.26~2.53) in the rectal cancer group (Table 4). On the other hand, the highest proportion of that for gastric cancer was 29.8% in the gastric cancer group.

The HNPCC patients were 4 (3.6%) out of 110 with colorectal cancer.

Secondly we investigated the frequency of colorectal cancer among the first-degree relatives (Table 5). The cases noted to suffer from colorectal cancer were 12 out of 679 (1.8%) first-degree relatives in the colorectal cancer group, 6 out of 500 (1.2%) in the gastric cancer group, 4 out of 304 (1.3%) in the other cancer group and 7 out of 615 (1.1%) in the benign disease group. No significant difference was seen among them, although the highest propor-

tion of colorectal cancer was found in the first-degree relatives of the colorectal cancer group. The highest proportion of gastric cancer was 5.6% in the first-degree relatives of the gastric cancer group. Similarly the highest proportion of other cancer was 10.2% in those of other cancer group.

DISCUSSION

This case-control study suggests familial aggregation of colorectal cancer is not so evident as researchers have shown so far.

Studies on familial aggregation of colorectal cancer were advanced mainly by researchers in the Western countries. In 1958, Woolf¹⁾ reported that colorectal cancer had hereditary background. In 1960, Macklin²⁾ reported that gastric cancer had familial aggregation of gastric cancer and colorectal cancer had that of colorectal cancer. The frequency of positive family history of colorectal cancer has been reported as follows: 11.3% (2.36-fold as high as that in the control group) by Bonelli et al.³⁾, 7.8% (2.5-fold) by Fisher et al.⁴⁾, 17% (2.13-fold; colon cancer 2.49-fold, rectal cancer 1.76-fold) by Kune et al.⁵⁾ 7.3% (colon cancer 2.3-fold, rectal cancer 1.7-fold) by Vecchia et al.⁶⁾, and 16% (2.1-fold) by John et al.⁷⁾. Leon et al.⁸⁾ showed that 3.1% (OR 7.5) of the first-degree relatives of patients with colorectal cancer were affected by colorectal cancer according to the observation of individual family members. Each

Table 5. Frequency of cancers in first degree relatives of subjects.

	Total No.	Colorectal Ca. No.	%	Gastric Ca. No.	%	Other Ca. No.	%	Total No.	%
FDR of Colorectal Ca.	679	12	1.8	29	4.3	41	6.0	82	12.1
FDR of Gastric Ca.	500	6	1.2	28	5.6	28	5.6	62	12.4
FDR of Other Ca.	304	4	1.3	12	3.9	31	10.2	47	15.5
FDR of Benign Dis.	615	7	1.1	19	3.1	34	5.5	60	9.8
Total	2098	29	1.4	88	4.2	134	6.4	251	12.0

FDR : First degree relatives

report has suggested that the frequency of positive family history was more than 2-fold of that in the control group.

We could not find many reports about familial aggregation of colorectal cancer in Japan. According to the report of the Japanese Research Society for Cancer of the Colon and Rectum⁹⁾, the frequency of positive family history (including the second-degree relatives) was 6.5% in 15369 cases of colorectal cancer. Yoshida et al.¹⁰⁾ reported that the proportion was 8.2% (OR : male 2.18, female 2.15), being significantly higher than that in the control group. It was 5.9% by Murata et al.¹¹⁾. Kato et al.¹²⁾ also reported that the relative risk was 2.8-fold in the colon cancer group and 1.8-fold in the rectal cancer group compared with the other cancer group, though their data included the second-degree relatives. Most of the reports in Japan have also suggested that positive family history is one of the risk factors for colorectal cancer. The only exceptional report is the one by Watanabe et al.¹³⁾. They showed it was not evident whether positive family history might be a risk factor of colorectal cancer.

In our study those who have a positive family history in the colorectal cancer group was 10 out of 110 cases (9.1%) according to the observation of family units. This proportion was higher than that of the previous Japanese reports^{9-11,14)}, but odds ratio was only 1.2 compared with the benign control group. If HNPCC might be excluded from colorectal cancer group, the proportion would be 5.7% and lower than that of control group. According to the observation of individual family members, 1.8% of their first-degree relatives of the colorectal cancer group were affected by colorectal cancer. Although these proportions were also higher than those in 3 control groups, there was no significant difference. This study suggests that familial aggregation of colorectal cancer may not be, even if any, so large as researchers in the Western countries have mentioned so far.

On the other hand, analyzing colon and rectal cancer groups separately, Odds ratio of the former increased to 1.70, and that of the latter decreased to 0.82. Although colon cancer may have a tendency for familial aggregation, it was not so large as researcher have mentioned so far. Rectal cancer may not have a tendency for familial aggregation.

We can not deny a tendency toward familial aggregation of colorectal cancer, because it is now evident that colorectal cancer is derived from accumulation of gene disorders. Since common colorectal cancers may be derived from gene disorders in the somatic cell line except special cases such as familial adenomatous polyposis, HNPCC and so on, such disorders would not necessarily be transmitted to the next generation. Recently, Fuchs et al.¹⁵⁾ reported by a prospective study that the relative risk of the colorectal cancer for persons with affected first-degree relatives was 1.72 (colon cancer : 1.99, rectal cancer : 0.86)

as compared with those without a family history of the disease. They also said the relative risk increased to 5.37 especially for persons under the age of 45 years with affected first-degree relatives. This suggests the age is one of the significant factors. In addition John et al.⁷⁾ reported, by a case-control study, that odds ratio was 1.8 in those who have one affected first-degree relative and that it increased to 5.7 in those who have two. It suggests a patient should be regarded as a high risk group based on not only a positive family history but also on his age and on the age at diagnosis and number of affected first-degree relatives.

HNPCC should be obviously regarded as a high risk factor. It is evident HNPCC has hereditary susceptibility, and its gene disorder is now revealed^{16,17)}. Although genetic diagnosis may be possible in future, at present we should perform screening examinations positively for the first-degree relatives of the patients clinically diagnosed HNPCC.

We must recognize to have some problems in this study. One is that sample size was not so large. Secondly sex and age in some of family members were unknown. The last is that we chose benign gastroenterological disease, of which familial aggregation might be a little higher than that of general population, as a control group.

Two things are pointed out on analysis of family history. One is the way of getting information and another is the way to analyze it. In taking family history, one of the biggest problems is uncertainty that it may be influenced by personal memory. As the means of settling it, three conditions as below are thought to be needed. They are 1) to restrict the objects only to the closest possible relatives, 2) to interview patients and their family directly, instead of self-recording, 3) to confirm the name of the disease by death certificates or medical records as far as possible. The only report which met all of these three conditions was presented by Leon et al.⁸⁾ among all reports in Japan and the Western countries within the limits of our investigation. We could find nothing satisfying the conditions of only 1) and 2) among the Japanese reports.

In our study we restricted the objects of the questionnaire to the first-degree relatives and interviewed the patient and/or his family directly presenting them the concrete name of disease and confirming them about its existence one by one. In this way, we could obtain much more exact and detailed family history.

Another problem is the way to analyze family history. Family size has not generally been considered, when thinking about the frequency of positive family history of cancers. In studying family history, it is pointed out we should take family size into consideration¹⁸⁾. We could find such a consideration in a few reports by Macklin²⁾, John et al.⁷⁾, Leon et al.⁸⁾, and Watanabe et al.¹⁹⁾ within the limits of our investigation.

As a matter of course, it depends on the family size how often colorectal cancer occurs in the family of patients with colorectal cancer. When the number of the first-degree relatives may be decreased by a decline of birth rate, the prevalence of colorectal cancer with positive family history would reduce. However, according to the observation of individual family members, an error of the prevalence might be fewer because a base population could also reduce at the same time. In addition, when more than 2 first-degree relatives had colorectal cancer in the same family, more correct prevalence could be presented by treating the first-degree relatives as a denominator. Consequently, it is necessary to use frequency of cancers among the first-degree relatives in analyzing family history.

In conclusion, we have shown that familial aggregation of colorectal cancer is not so large as researchers especially in the Western countries have mentioned so far, although a tendency for familial aggregation was found in colon cancer. At the present stage in Japan, we should not perform screening examinations for the first-degree relatives only by positive family history from the reason of efficiency, though those of patients with clinically diagnosed or suspected HNPCC should be screened.

REFERENCES

1. Woolf C. A genetic study of carcinoma of the large intestine. *Am J Human Genet*, 1958; 10: 42-47.
2. Macklin M. Inheritance of cancer of the stomach and large intestine in man. *J Nat Cancer Inst*, 1960; 24: 551-571.
3. Bonelli L, Martines H, Conio M, Bruzzi P, Aste H. Family history of colorectal cancer as a risk factor for benign and malignant tumors of the large bowel. A case control study. *Int J Cancer*, 1988; 41: 513-517.
4. Fisher G, Armstrong B. Familial colonic cancer and the screening of family members. *The Medical Journal of Australia*, 1989; 150: 22-25.
5. Kune G, Kune S, Watson L. The role of heredity in the etiology of large bowel cancer-data from the Melbourne Colorectal Cancer Study. *World J Surg*, 1989; 13: 124-131.
6. Vecchia CL, Negri E, Franceschi S, Gentile A. Family history and the risk of stomach and colorectal cancer. *Cancer*, 1992; 70: 50-55.
7. St John DJ, McDermott FT, Hughes ES, et al. Cancer risk in relatives of patients with common colorectal cancer. *Ann Intern Med*, 1993; 118: 785-790.
8. Leon MP, Sassatelli R, Sacchetti C, et al. Familial aggregation of tumors in the three-year experience of a population-based colorectal cancer registry. *Cancer Research*, 1989; 49: 4344-4348.
9. Registry Committee, Japanese Research Society for Cancer of the Colon and Rectum. Clinical and Pathological Analyses of Patients with a Family History of Colorectal Cancer. *Jpn J Clin Oncol Clinic*, 1993; 23: 342-349.
10. Yoshida K, Oku T, Ohba S, et al. A case-control study of colorectal cancer.—Association between smoking, drinking, family history of cancer and colorectal cancer—. *Jpn J Cancer Clin*, 1992; 38: 371-378 (in Japanese with English abstract).
11. Murata M, Takahashi T. A geneto-epidemiological study of colorectal cancer. *Jpn J Cancer Clin*, 1984; 30: 243-250 (in Japanese).
12. Kato I, Tominaga S, Ikari A. A case-control study of male colorectal cancer in Aichi Prefecture, Japan: with special reference to occupational activity level, drinking habits and family history. *Jpn J Cancer Res*, 1990; 81: 115-121.
13. Watanabe Y, Tada M, Kawamoto K, et al. A case-control study of cancer of the rectum and the colon. *Jpn J Gastroenterol*, 1984; 81: 185-193 (in Japanese with English abstract).
14. Tomoda H, Inoue T, Furusawa M. Familial occurrence of a non-polypoid colorectal cancer. *Jpn J Cancer Clin*, 1991; 37: 949-952 (in Japanese with English abstract).
15. Fuchs CS, Giovannucci EL, Willett WC, et al. A prospective study of family history and the risk of colorectal cancer. *N Eng J Med*, 1994; 331: 1669-1674.
16. Fishel R, Lescoe MK, Rao MRS et al. The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. *Cell*, 1993; 75: 1027-1038.
17. Bronner CE, Baker SM, Morrison PT, et al. Mutation in the DNA mismatch repair gene homologue hMLH1 is associated with hereditary non-polypoid colon cancer. *Nature*, 1994; 368: 258-261.
18. Morio S, Nakayama H, Okamoto N, Fukutomi K. Problem point of studying familial aggregation in chronic diseases. *Jpn J Pub Health*, 1989; 36: 686-691 (in Japanese).
19. Watanabe Y, Saito M, Morita M, Tada K, Kawai K, et al. A case-control study of family history in colorectal adenoma. *Jpn J Cancer Clin*, 1992; 38: 280-283 (in Japanese with English abstract).