RESEARCH COMMUNICATION

Natural History of Colorectal Adenoma and the Effect of Endoscopic Polypectomy on Occurrence of Subsequent Cancer

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Abstract

Colorectal cancer is thought to originate in colorectal adenoma and endoscopic polypectomy may prove prophylactic. To clarify the natural history of colorectal adenoma and the potential effects of endoscopic polypectomy, we retrospectively studied cohort patients undergoing full colonoscopies at 14 hospitals in Aomori Prefecture between January 1972 and December 1985. Subjects were divided into 3,574 non-adenoma controls and 1,020 adenoma patients, including 530 treated by polypectomy at initial examination. Subjects were followed up until the end of 1987 through record linkage with Aomori Colorectal Cancer Registry files to observe colorectal cancer occurrence. The ratio of observed number/expected number in the general population (O/E ratio) was 0.70 for the adenoma group and 0.36 for controls. The adenoma group was subdivided into polypectomy and non-polypectomy subgroups, with the O/E ratios of 0.39 for polypectomy patients and 0.75 for non-polypectomy patients. The O/E ratio in the adenoma group was about twice in controls, and this ratio in the nonpolypectomy subgroup was also about twice in thepolypectomy subgroup. Tha results suggest that colorectal adenoma provides a precancerous lesion that can be treated prophylactically by endoscopic polypectomy.

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Key words: colon polyp, polypectomy, adenoma-carcinoma sequence, de novo carcinogenesis

Introduction

In USA and European countries, colorectal benign polyps are believed to be precancerous lesions of colorectal cancers and most colorectal cancers are thought to arise from preexisting adenoma, i.e., the adenoma-carcinoma sequence (Gromme and Lane, 1958; Morson and Dawson, 1972; Morson, 1974; Lotfi et al., 1986; Stryker et al., 1987; Welin et al., 1987; Selby et al., 1992; Jorgensen et al., 1993, Bertario et al,. 1999). Therefore, endoscopic polypectomy is widely performed to treat colorectal polyps prophylactically (Atkin et al., 1992; Muller and Sonnenberg, 1995; Winawer et al., 1993) . In Japan, only Murakami et al. (1990) have described a relationship between colon polyps and colorectal cancer onset in a retrospective cohort study. This study is epidemiologically important because colorectal cancer has increased in Japan since World War II (Tamura et al., 1996), and because differences between Asian and non-Asian populations may exist in relations between colorectal polyps and cancers. However, their methodology was problematic in group selection, because they included subjects who had undergone barium enema examination instead of full colonofiberscopy (CF), and the accuracy of Osaka Cancer Registry which was used as a data base for detecting cancer case was not so high at that time.

The purpose of the present study was to clarify natural history of colorectal polyp and to evaluate the effect of endoscopic polypectomy among Japanese people using the accurate cancer registry, and to clarify whether there are any differences between Asian and non-Asian populations in these results.

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Materials and Methods

Subjects

The cohort consisted of patients who had undergone full CF of the large intestine due to digestive tract related disorder or symptom at Hirosaki University Hospital, and at 13 other hospitals in Aomori Prefecture, between January 1, 1972, and December 31, 1985. Patients assigned as controls had no abnormal endoscopic findings such as diverticular disease, nonspecific colitis, or nonadenomatous polyps. Patients diagnosed histologically with colorectal adenoma were assigned to the adenoma group. Adenomas were recognized macroscopically by CF as polyps. The adenoma group was subdivided into polypectomy-treated and untreated. Cases with polypectomy-untreated were due to small polyp or due to difficult location to perform polypectomy. If the cases with polypectomy-untreated at initial CF were performed polypectomy at next CF, these cases were classified into polypectomy group. When histological diagnosis of an excised polypectomy specimen differed from that at biopsy, the polypectomy specimen diagnosis was regarded as histological. Patients diagnosed with colorectal cancer, Crohn's disease, ulcerative colitis, or polyposis coli at initial CF and those with a history of colorectal cancer or large-intestine resection were excluded from our study.

Mean age and number in each group and subgroup are shown in Table 1. Distribution of adenoma sites is shown in Table 2. Number of subjects according to adenoma size is shown in Table 3 and those according to adenoma lesions in Table 4. The background of cancer cases is shown in Table 5.

Follow-up

The Aomori Colorectal Cancer Registry had been conducted since 1974 (Tamura et al, 1996), and covers all of Aomori Prefecture (1985 population: 1.5 million). Subjects in this registry with colorectal cancer were determined by direct chart reading at hospitals. The mean Death Certificate Only (DCO) (International Agency for Research on Cancer, 1992] between 1982 and 1987 was 4.0%, indicating that the survey on incidence had the highest accuracy of all such reports in Japan.

To ascertain all incidents of colorectal cancer, groups were followed up by collation with Aomori Colorectal Cancer Registry files. Collation parameters were gender, date of birth, and address.

The follow-up start date was defined as the date of initial CF. In calculating person-years of observation, we assumed that all subjects but subsequent colorectal cancer patients were alive until the end of 1987. Thus, for all groups, the final date of follow-up was defined as the date of colorectal cancer diagnosis for cases who developed these cancers and 31 December 1987 for all other subjects.

About 29,000 inhabitants in Aomori Prefecture moved into other prefectures in this period, but this percentage is below 3% of total Aomori population.

Analysis

Observed numbers of colorectal cancers (O) for each group/subgroup were compared with expected numbers (E). E had been computed using a program developed by Monson (1974), applying the 5-year age, calendar period, and gender-specific incidence rate for colorectal cancer for the whole general population of Aomori Prefecture (Bureau of Statistics, Office of the Prime Minister, 1998) as prepared by the Aomori Colorectal Cancer Registry.

Differences between O and E that were statistically significant were determined using Bailar's table (Bailar and Ederer F, 1964), assuming a Poisson distribution in each group. $P<0.05$ was considered significant.

Results

Table 6 shows O, E, and the O/E ratio for colorectal cancer in the groups studied. The overall O/E ratio in controls was 0.36, meaning that O was significantly ($p<0.05$) lower than E. In the adenoma group, the O/E ratio was 0.70, and no significant difference was seen between O and E. The O/E ratio in the adenoma group was about twice that in controls, suggesting that colorectal cancer incidence was higher in the

Table 1. Number and Mean Age in Each Group

	Control group			Adenoma group		
	Males	Females	Total	Males	Females	Total
Number	1639	1935	3574	685	335	1020
Average age	49.1 ±15.8[a]	50.5 ±15.1	49.7 ±15.4	59.3 ±11.3	58.6 ±12.1	59.0 ±11.6
	Polypectomy subgroup			Non-polypectomy subgroup		
	Males	Females	Total	Males	Females	Total
Number	369	161	530	316	174	490
Average age	60.4 ±11.0	59.9 ±12.4	60.2 ±11.5	58.4 ±11.8	57.7 ±11.5	58.2 ±11.7

[a] Mean ±standard deviation

Table 2. Distribution of Adenoma Sites

Sites	R[a]	S	D	T	A	C	Total
Polypectomy subgroup							
Males	178 [b]	229	89	141	92	20	749
	(23.8 [c])	(30.6)	(11.8)	(18.8)	(12.3)	(2.7)	(100)
Females	68	80	23	47	38	6	262
	(26.0)	(30.5)	(8.8)	(17.9)	(14.5)	(2.3)	(100)
Total	246	309	112	188	130	26	1011
	(24.3)	(30.6)	(11.1)	(18.6)	(12.9)	(2.5)	(100)
Nonpolypectomy subgroup							
Males	70	137	70	98	65	21	461
	(15.1)	(29.7)	(15.1)	(21.3)	(14.1)	(4.7)	(100)
Females	34	60	15	55	28	11	203
	(16.7)	(29.6)	(7.4)	(27.1)	(13.8)	(5.4)	(100)
Total	104	197	85	153	93	32	664
	(15.7)	(29.7)	(12.8)	(23.1)	(14.0)	(4.7)	(100)

[a]R:Rectum, S:Sigmoid colon, D:Descending colon T:Transverse colon, A:Ascending colon, C:Cecum [b]Number of adenomas lesions, [c]Percentage

Table 3. Number of Subjects According to Lesion Size

Size(mm)	-4	5-9	10-14	15-19	20-	Total	Unknown
Polypectomy Subgroup							
Males	100	145	61	18	12	336	33
	(29.8[a])	(43.3)	(18.3)	(5.4)	(3.6)	(100)	
Females	57	60	17	8	3	145	16
	(39.3)	(41.4)	(11.7)	(5.5)	(2.1)	(100)	
Total	157	205	78*	26*	15*	481	49
	(32.6)	(42.6)	(16.2)	(5.4)	(3.2)	(100)	
Non-polypectomy subgroup							
Male	106	95	15	3	4	223	93
	(47.5)	(42.6)	(6.7)	(1.3)	(1.9)	(100)	
Female	57	52	10	0	1	120	54
	(47.5)	(43.3)	(8.3)	(0.0)	(0.9)	(100)	
Total	163	147	25*	3*	5*	343	147
	(47.5)	(42.9)	(7.3)	(0.9)	(1.4)	(100)	

a Percentage, * $p<0.01$

Table 4. Number of Subjects According to Adenoma Lesions

	1	2	3	4	5	6-	Total
Polypectomy subgroup							
Male	138	99	71	31	13	17	369
	(37.4[a])	(26.8)	(19.2)	(8.4)	(3.5)	(4.6)	(100)
Female	94	34	21	6	4	2	161
	(58.4)	(21.1)	(13.0)	(3.7)	(2.5)	(1.2)	(100)
Total	232	133	92	37	17	19	530
	(43.8)	(25.1)	(17.4)	(7.1)	(3.2)	(3.5)	(100)
Non-polypectomy subgroup							
Male	152	85	32	25	9	13	316
	(48.1)	(26.9)	(10.1)	(7.9)	(2.8)	(4.2)	(100)
Female	116	32	15	8	3	0	174
	(66.7)	(18.4)	(8.6)	(4.6)	(1.7)	(0.0)	(100)
Total	268	117	47	33	12	13	490
	(54.7)	(23.9)	(9.6)	(6.7)	(2.4)	(2.7)	(100)

[a] Percentage, The subject who has 2 adenomas or more was counted as 2 subjects or more.

Table 5. Background of Cancer Cases

Subject no.	Sex	Age	Site	Dukes	Histology	Interval[a]
Non-polypectomy subgroup						
1.	Female	39	Rectum	B	well[b]	75
2.	Female	77	Sigmoid	B	well	76
3.	Male	62	Rectum	A	well	10
4.	Female	70	Rectum	A	well	23
Polypectomy subgroup						
5.	Male	75	Ascending	B	moderate[c]	14
6.	Female	73	Ascending	A	well	23
7.	Male	61	Cecum	C	well	105
Control group						
8.	Male	72	Ascending	C	well	145
9.	Female	58	Ascending	B	well	55
10.	Female	77	Cecum	A	well	112
11.	Female	52	Descending	C	moderate	42
12.	Male	54	Ascending	C	moderate	32
13.	Female	57	Rectum	C	moderate	25
14.	Female	74	Ascending	A	well	8
15.	Male	81	Rectum	A	well	65
16.	Male	74	Rectum	A	well	11

a: interval between initial colonoscopic examination and diagnosis of cancer
b: well differentiated adenocarcinoma
c: moderately differentiated adenocarcinoma

Table 6. The Observed Value(O), Expected Value(E) and O/E Ratio of the Development of Colorectal Cancer

	Control			Adenoma			Polypectomy			Non-polypectomy		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
0	4**	5*	9*	3*	4	7	2	1	3*	1	3	4
E	14.2	11.0	25.2	7.7	2.3	10.0	3.7	4	7.7	4	1.3	5.3
O/E	0.28	0.45	0.36	0.39	1.74	0.70	0.57	0.25	0.39	0.25	2.31	0.75
95%CI	0.07	0.15	0.16	0.08	0.47	0.28	0.06	0.00	0.08	0.00	0.46	0.20
	-0.72	-1.06	-0.68	-1.14	-4.55	-1.44	-1.95	-1.39	-1.14	-1.39	-6.74	-1.93

*:p<0.05, **:p<0.01, compared to E value, 95%CI: 95% confidence interval

adenoma group. The O/E ratio in male controls was 0.28 and 0.39 in adenoma group males, both O significantly lower than E (p<0.01, p<0.05, respectively). The O/E ratio in female controls was 0.45, with O significantly, lower than E (p<0.05). The O/E ratio in adenoma group females was 1.74, with no significant difference between O and E. The overall O/E ratio was 0.39 in the polypectomy subgroup, with O significantly (p<0.05) lower than E, but no significant differences were seen between O and E in the nonpolypectomy subgroup. The O/E ratio in the polypectomy subgroup was about half that in the nonpolypectomy subgroup, suggesting that the incidence of colorectal cancer was lower in the polypectomy subgroup. No significant difference was seen between males and females in any group for any values.

Three cancer cases (No. 1, No. 2 and No. 7) were coincide with polypectomy-untreated adenoma at initial CF. The size of these adenomas were 4 mm (No. 1), 6 mm (No. 2) and 3 mm (No. 7), respectively (Table 5).

Discussion

Murakami et al. (1990) have studied on malignant change of adenoma of the large intestine and on prophylactic effect of endoscopic polypectomy. This is the first epidemiological study in Japan. They concluded that adenoma is a risk factor in colorectal cancer and that polypectomy provides effective prophylaxis. Their methodology was problematic in group selection, because they included subjects who had undergone barium enema examination instead of full CF. Barium enema examination could have caused small polyps to overlooked (Kihara et al., 1989), underestimating the number in the polyp group. In addition, 28.9% polyp group subjects had not been evaluated histologically as having adenoma. To ensure result reliability, we made certain that all subjects underwent full CF and that all with adenoma were diagnosed histopathologically.

In our controls, O was significantly lower than E, but the adenoma group showed no significant difference between O and E. The O/E ratio in the adenoma group was twice that in controls, and the cancer incidence in the adenoma group was higher than that in controls. These results would thus appear to support the adenoma-carcinoma sequence theory.

Since like other studies, ours was not a randomized study, results must be interpreted with great care. One possible bias

in our study includes overestimated E, in which could be inflated due to person-year calculation assuming that all subjects survived until the end of the observation period while, in fact, some deaths may have occurred. However, it seems unlikely that the degree would differ among groups and subgroups even if the O/E ratio were underestimated. A second possible bias is that patients with colorectal cancer may have been overlooked. As described previously, however, statistics colorectal cancer incidence are extremely precise, so overlooked patients would be highly unlikely.

Routine CF and polypectomy generally used in colorectal adenoma patient follow-up could also contribute bias, since cancer incidence in the adenoma group could increase due to earlier cancer (including cancer being existent in mucosa) detection from CF and polypectomy in this group compared to controls. In our study, the proportion of Dukes A (Dukes, 1932] was relatively high: 3 of 9 subjects among controls and 3 of 7 subjects in the adenoma group. No significant difference in incidence between the two groups was seen, however.

Another question is whether endoscopic polypectomy, currently widely employed, is actually prophylactic in colorectal cancer. In the present study, the O/E ratio in the adenoma group was 0.39 for the polypectomy subgroup and 0.75 for the nonpolypectomy subgroup. O was significantly lower than E value in the polypectomy subgroup, and no difference was seen in the nonpolypectomy subgroup. The O/E ratio in the polypectomy subgroup was about half that in the nonpolypectomy subgroup, indicating that the colorectal cancer incidence was somewhat lower in the polypectomy group. These results strongly support the results of European and American reports that polypectomy is prophylactic in colorectal cancer. However, we should take account of the following bias. The size and number of adenoma in the polypectomy subgroup significantly ($p<0.01$) greater than those in the nonpolypectomy subgroup (Tables 3 and 4). This difference of backgroung shows that the polypectomy subgroup was changeable to cancer, resulting to underestimate the efficacy of polypectomy. Thus, in the present study, the usefulness of polypectomy may have been underestimated.

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Personal Profile: **Yuyang Tu**

Yuyang Tu was born in Shanghai, China, in 1960. After graduating from Hirosaki University School of Medicine, he trained in internal medicine for 5 years (1985-1989), specializing in digestive diseases, in the First Department of Internal Medicine. Following this training, in 1990 he transferred to the Department of Digestive Diseases of the Tokyo Metropolitan Komagome Hospital.

He is now a clinical epidemiologist in Hirosaki, specializing in digestive diseases. He is bilingual in Japanese and Chinese and we have great expectation that he will be able to create a solid bridge linking our two countries in his chosen field.