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Genotype and Phenotype Factors as Determinants for Rectal Stump Cancer in Patients With Familial Adenomatous Polyposis

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Objective

To identify factors influencing the occurrence of cancer in the rectal remnant in patients with familial adenomatous polyposis (FAP) after colectomy and ileorectal anastomosis (IRA).

Summary Background Data

The risk for rectal cancer in patients with FAP after colectomy and IRA remains a major concern.

Methods

Between 1955 and 1997, 371 patients (206 men, 165 women) from the Registry of Hereditary Colorectal Tumors underwent colectomy and IRA as a primary surgical procedure. Survival was estimated using the Kaplan-Meier method. Cox proportional hazard models were fitted to assess the relative excess risk of rectal cancer and to control for confounding factors. A multivariate analysis was performed to assess the relation between cancer risk in the rectum and sex, age, number of rectal polyps, colon cancer, and *APC* germline mutation.

Results

Median follow-up was 81 months. Eighty-nine patients (24%) had colon cancer at the time of surgery. The *APC* mutation was found in 200 patients. In 27 patients, cancer developed in the retained rectum 1 to 26 years after surgery. The incidence of rectal carcinoma appears to increase with time: at 10, 15, and 20 years after surgery, the cumulative risk was 7.7%, 13.1%, and 23.0%, respectively. Multivariate analysis identified as independent predictors the presence of colon cancer at IRA and a mutation occurring between codons 1250 and 1464; both factors increased the risk nine times.

Conclusions

The presence of cancer at IRA and *APC* mutation type are the most important risk factors for the future development of cancer in the rectal remnant in patients with FAP.

Familial adenomatous polyposis (FAP), an autosomal dominantly inherited disorder with a penetrance of nearly 100%, is characterized by the progressive development of hundreds of adenomatous colorectal polyps, some of which inevitably progress to cancer. The clinical features of this syndrome and its variants have been known for many years. Diagnosis still relies largely on the detection of numerous colorectal polyps during the second or third decade of life, as well as extracolonic lesions.

Mutations of the *APC* gene, identified in 1991, are responsible for the disease in most FAP families. Several reports have shown a correlation among mutations occurring within specific regions of *APC*, the severity of polyposis, and the presence of extracolonic manifestations.[1–6]

Treatment for FAP is the prophylactic surgical resection of affected colon to prevent malignant degeneration of adenomas. Colectomy with ileorectal anastomosis (IRA) is the most common surgical procedure in many institutions. This procedure carries low rates of complications and death

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and produces a good functional outcome. However, the rectal remnant should be carefully observed for the possible occurrence of cancer. Beginning in the 1980s, several reports have indicated that the risk of rectal cancer gradually increases with time, amounting to 10% to 55% after 20 years of follow-up.[5,7–15] However, some have reported spontaneous regression of the remaining polyps in the retained rectum,[16,17] for a reduced proliferation of the rectal mucosa.[18–20]

The aims of this study were to examine the risk of rectal cancer in patients with FAP after IRA and to identify clinical or genetic factors that can predict the development of cancer in the retained rectum.

METHODS

In 1980, the Hereditary Colorectal Tumor Registry of families with hereditary nonpolyposis colorectal cancer and FAP was founded at the National Cancer Institute in Milan. By the end of 1997, 569 FAP families were enrolled throughout the country. Data concerning patient demographics, patient features (sex, age at diagnosis of FAP, number of polyps at first examination, distribution of polyps, age at diagnosis of colorectal cancer, and cancer location), and surgical details were obtained at inclusion in the registry and from medical records.

Adenomas were classified according to their histopathologic characteristics, size, and location. The preoperative number of adenomas of the rectum was determined by reviewing endoscopic examinations and was divided into three groups (<10, 10–30, and >30 polyps). Histologic examination and polyp fulguration or removal were undertaken at every follow-up when appropriate.

The presence and type of *APC* mutations were assessed using different methods, including single-strand conformation polymorphism assay, blue/white assay, and protein truncation test, followed by sequence analysis, as described elsewhere.[21–23] When a mutation was identified in the family proband, its occurrence was verified in all affected relatives included in the analysis. Subjects were subdivided into three groups: mutation between codons 1250 and 1464 (correlated with a profuse phenotype)[1], mutation before codon 1250 and after codon 1464, or mutation not found.

The date of surgery was set at the index date for time calculation. "Last date" was defined as the date of diagnosis of rectal cancer or the date of last contact or death.

Survival was estimated using the Kaplan-Meier product limit method. Differences among groups were tested using the log-rank test. To assess the relative excess risk of rectal cancer and to control for confounding factors, proportional hazard models (including sex, age at IRA, and all available prognostic factors) were fitted, computing hazard ratios (HR) and the corresponding 95% confidence intervals (95% CI). The proportional assumption was examined with log-log survival plots or by adding time-dependent interaction terms to the model. Statistical analysis was performed using the Statistical Analysis System version 6.12 (SAS, Cary, NC).

RESULTS

Between 1988 and 1997, the registry collected 569 FAP pedigrees comprising 879 patients. Of these, 431 who underwent surgical procedures other than IRA and 77 with rectal cancer at surgery were excluded from the analysis. The study group consisted of 371 patients (206 men, 166 women) from 97 kindreds. None of the patients was participating in any chemoprevention trials.

Mean age at time of surgery was 32 years (33 for men, 31 for women). Median duration of follow-up after surgical treatment was 81 months (range 1–515).

Colon cancer was present in the colectomy specimen of 89 patients (24.0%); 50 were early stage (Dukes' A or B) and 39 were advanced stage. Thirty-one patients had multiple locations in the colon. The mean age of patients with colon cancer at initial surgery was significantly higher than in cancer-free patients (45.1 vs. 28.6, Wilcoxon rank-sum test, $P = .0001$).

Seventy-seven patients had more than 30 rectal polyps at the time of initial colectomy. The presence of synchronous cancer increased with the polyp count (chi-square for trend, 4.67; $P = .03$).

The *APC* mutation was sought in 297 patients and was found in 200 of them (67.3%). Thirty-six patients (12.1%) had a mutation between codons 1250 and 1464. The mean number of rectal polyps found was 42.5 for mutations detected between codons 1250 and 1464 and 22.0 for mutations before codon 1250 or after codon 1464 (Wilcoxon rank-sum test, $P = .001$). In contrast, the presence of mutations between codons 1250 and 1464 was not associated with colon cancer at surgery (Fisher exact test, $P = .6$).

Follow-up revealed development of cancer in the retained rectum in 27 patients (15 men, 12 women), with a median follow-up of 102 months (range 1–26 years). Of the patients

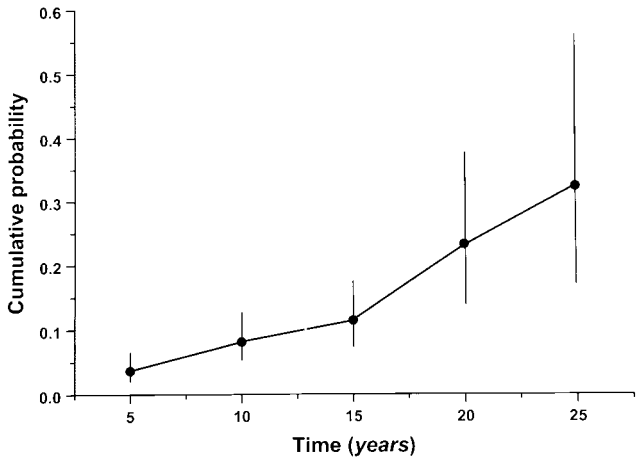

Figure 1. Cumulative probability of developing rectal cancer after colectomy and ileorectal anastomosis during 25 years of follow-up.

Table 1. RISK OF RECTAL CANCER AFTER COLECTOMY

Variable	Cumulative Probability				No. Censored at 20 Years	Log-Rank Test Chi-square (*P* value)
	5 years	10 years	15 years	20 years		
Sex						
Male	0.03 (0.01–0.07)	0.07 (0.03–0.12)	0.10 (0.05–0.19)	0.19 (0.09–0.37)	30	
Female	0.05 (0.02–0.10)	0.10 (0.05–0.19)	0.13 (0.07–0.24)	0.30 (0.14–0.57)	16	0.85 (.4)
Age at surgery (years)						
≤30	0.03 (0.01–0.07)	0.07 (0.04–0.13)	0.10 (0.06–0.20)	0.20 (0.10–0.39)	28	
>30	0.04 (0.02–0.09)	0.09 (0.05–0.17)	0.12 (0.06–0.22)	0.27 (0.13–0.54)	18	0.97 (.3)
Rectal polyps						
<10	0.03 (0.00–0.11)	0.03 (0.00–0.11)	0.03 (0.00–0.11)	0.23 (0.02–0.94)	4	
10–30	0.02 (0.01–0.08)	0.07 (0.03–0.16)	0.10 (0.04–0.22)	0.19 (0.07–0.48)	17	
>30	0.11 (0.05–0.22)	0.18 (0.10–0.31)	0.25 (0.14–0.41)	0.32 (0.18–0.55)	14	6.22 (.04)
Colon cancer						
No	0.01 (0.00–0.03)	0.06 (0.03–0.11)	0.10 (0.05–0.17)	0.20 (0.11–0.36)	40	
Yes	0.13 (0.07–0.24)	0.16 (0.09–0.29)	0.16 (0.09–0.29)	0.37 (0.12–0.80)	6	14.11 (.0002)
Mutation						
<1250, >1464	0.01 (0.00–0.05)	0.05 (0.02–0.12)	0.12 (0.05–0.24)	0.26 (0.12–0.53)	20	
1250–1464	0.10 (0.04–0.25)	0.21 (0.11–0.41)	0.21 (0.11–0.41)	0.46 (0.22–0.77)	10	
Not found	0.03 (0.01–0.10)	0.03 (0.01–0.10)	0.03 (0.01–0.10)	0.03 (0.01–0.10)	13	11.61 (.003)*
Overall	0.04 (0.02–0.07)	0.08 (0.05–0.13)	0.13 (0.07–0.18)	0.23 (0.14–0.37)	46	

* Comparison only for mutations <1250/>1464 vs. 1250–1464.

in whom rectal cancer developed, 50% had colon cancer and 58.3% had more than 30 polyps in the rectum at initial colectomy.

The rectal cancer was diagnosed at early stage (Dukes' A or B) in 22 patients (81.5%). Eighteen were still alive and disease-free at last follow-up, six died of metastatic diffusion, and three died of extracolonic malignancy.

Figure 1 shows the cumulative risk of developing rectal

Table 2. RISK OF RECTAL STUMP CANCER AFTER COLECTOMY

Variable	Censored	Events	Hazard Ratio*	95% Confidence Interval*
Sex				
Male	191 (55.5%)	15 (56.6%)	1†	—
Female	153 (44.5%)	12 (44.4%)	1.4	0.6–3.0
Age at surgery (years)				
≤19	57 (16.5%)	4 (14.8%)	1†	—
20–29	111 (32.3%)	9 (33.3%)	1.2	0.4–3.2
30–39	85 (24.7%)	6 (22.2%)	1.6	0.5–4.9
40–49	47 (13.7%)	4 (14.8%)	1.6	0.4–7.3
≥50	44 (12.7%)	4 (14.8%)	4.8	1.0–22.3
Rectal polyps				
<10	87 (32.3%)	3 (12.5%)	1†	—
10–30	120 (44.6%)	7 (29.2%)	1.8	0.4–7.1
>30	62 (23.1%)	14 (58.3%)	4.6	1.2–17.1
Histology of primary lesion				
Tubular adenoma	188 (59.9%)	8 (36.4%)	1†	—
Tubulovillous	24 (7.6%)	1 (4.6%)	1.1	0.1–8.3
Villous	24 (7.6%)	2 (9.1%)	1.9	0.4–8.8
Colon cancer	78 (22.7%)	11 (50.0%)	3.6	1.3–9.6
Mutation				
<1250 or >1464	156 (56.5%)	10 (47.6%)	1†	—
1250–1464	26 (9.4%)	8 (38.1%)	6.2	1.9–19.9
Not found	94 (34.1%)	3 (14.3%)	0.2	0.1–0.9

* Estimates from separate proportional hazard regression models including terms for sex and age as appropriate.
† Reference category.

Table 3. PRESENCE OF COLON CANCER AT SURGERY, NUMBER OF RECTAL POLYPS, AND RECTAL STUMP CANCER BASED ON MUTATION

Exon	Codon	*N*	Colon Cancer at Surgery	Rectal Polyps				Rectal Stump Cancer
				<10	10–30	>30	(mean)	
5	190	3	1		3		13.3	
	213	12	1	1	6	2	19.2	2
	216	2	1					1
8	302	1			1		20.0	
9	326	12	1	6	4	2	14.8	
	358	2		2			3.0	
	423	1	1			1	60.0	
11	470	4				1	60.0	
13	543	24	2	4	16	1	13.2	
	564	1			1		30.0	
14	629	3	1	1			1.0	
	640	4	1			4	90.0	1
15	654	1			1		10.0	
	658	1			1		20.0	
	677	1			1		26.0	
	713	2		1		1	23.0	
	835	2			2		30.0	
	843	3		1	1		18.0	1
	849	3	1		1	2	32.7	
	908	1			1		10.0	
	935	4		1	2	1	28.8	1
	964	4		1	2	1	18.3	
	965	2			1		20.0	
	975	2	2	1			3.0	
	1032	1				1	60.0	
	1061	27	4	2	11	3	22.7	1
	1062	2		1			3.0	
	1063	1			1		30.0	
	1068	1						
	1075	3			2	1	29.3	
	1110	9		1	4	1	24.2	1
	1123	2		1	1		7.0	
	1179	1						
	1180	2	1	1			3.0	
	1193	1				1	60.0	
	1194	1						
	1237	1	1			1	60.0	
	1266	3	1					
	1276	1			1		20.0	
	1294	2		1		1	40.0	1
	1301	2			1	1	50.0	
	1309	23	4	1	9	10	43.9	7
	1328	1		1			1.0	
	1377	1				1	45.0	
	1393	1				1	60.0	
	1451	2	1	1		1	45.5	
	1465	8	1	3	3	1	14.7	
	1539	2			1	1	37.5	1
	1540	1	1	1			3.0	
	1555	2	1		1		15.0	1
	1564	2			2		14.0	
	1579	1	1		1		20.0	
	2012	1			1		13.0	
Mutation not found		97	32	34	26	22	21.5	3
Mutation in progress		74	29	20	23	18	20.4	6

cancer per years of follow-up after surgery. At 10, 15, and 20 years after surgery, the cumulative risk was 7.7%, 13.1%, and 23.0%, respectively. Table 1 shows the cumulative risk of rectal cancer for several variables at 5, 10, 15, and 20 years after surgery.

Univariate analysis (Table 2) showed that the risk of developing rectal cancer was significantly higher in patients with colon cancer at the initial operation (HR = 3.6, 95% CI 1.3–9.6), in patients with more than 30 polyps in the rectum at the initial surgery (HR = 4.6, 95% CI 1.2–17.9), and with mutations between codons 1250 and 1464 (HR = 6.2, 95% CI 1.9–19.9).

Multivariate analysis identified as independent predictors of rectal cancer the presence of cancer in the resected colon (HR = 3.2, 95% CI 1.1–9.8) and mutations between codons 1250 and 1464 (HR = 4.4, 95% CI 1.3–15.0) (Table 3). The coexistence of cancer in the resected colon and a mutation between codons 1250 and 1464 increased ninefold the risk of rectal cancer (HR = 8.7, 95% CI 3.1–24.7).

DISCUSSION

The risk of rectal cancer in patients with FAP remains a major concern at the time of prophylactic surgery. The surgeon and patient often must choose between surgical procedures with distinctive issues: total colectomy with IRA is considered safer in terms of complications and quality of life, but restorative proctocolectomy eliminates the cancer risk.

Studies of patients with FAP after IRA have found an incidence of rectal cancer of 7.1% to 32.1%.[5,7–14] A large-scale study from the Scandinavian countries involving 297 patients found a rectal cancer risk of 9% after 20 years and 13% after 25 years of follow-up.[13] Feinberg et al[24] found a 15% risk of rectal cancer after 15 years. A Japanese study of 1,050 patients with FAP showed a much higher risk of developing rectal cancer in the retained rectum: 13% after 10 years and 37% after 20 years.[14] Several investigations conducted by the St. Mark's Polyposis Registry reported a high incidence of postoperative rectal cancer.[8,25] Nugent and Phillips[26] reviewed the risk of rectal cancer in 224 patients and found a 20% risk of developing cancer in the retained rectum after 10 years. Differences between studies may be due to different patient characteristics, different therapeutic strategies, the paucity of long-term results in large series of patients, variable follow-up policies, or the wide confidence intervals of estimates related to the few series with follow-up of more than 20 years.

Age at colectomy, sex, number of polyps, presence of cancer in the colectomy specimen, and length of the remnant rectum have been implicated as independent risk factors.[13,27] After the identification of *APC* mutations, genotype has been investigated as a risk factor. Several reports have found a correlation between specific mutations and the density of adenomas, the severity of the FAP phenotype, and the presence of extracolonic disease,[1–4,6] but one report has correlated the presence of specific mutations with the risk of subsequent rectal cancer, supporting a possible role of genotyping in the management of patients with FAP.[5] These authors found that patients with *APC* mutations beyond codon 1275 had a high risk of developing rectal cancer in the retained rectum. However, this result was obtained without taking into consideration the already confirmed clinical risk factors (e.g., number of rectal adenomas, presence of colon cancer at surgery), and therefore the real weight of the genotype could not be clearly evaluated. Wu et al[6] proposed that patients with a mutation at codon 1309 should undergo proctocolectomy because they have a more extended rectal disease.

Our findings suggest that the presence of a specific mutation associated with a severe phenotype, the presence of colon cancer at surgery, and a large number of rectal adenomas are strong predictors of cancer in the rectal stump after IRA. The estimated risk increased from 4 to 10 times for single or combined factors, and it was comparable to data published in the literature.

Our results confirm that important factors can be identified to predict the fate of the rectal stump in patients with FAP. The decision to undergo prophylactic surgery is a complex one, because many determinants must be considered to balance life expectancy and quality of life. Restorative proctocolectomy should be proposed to patients based on clinical features (presence of cancer, number of rectal adenomas) and also the genotype. In the future, when the functional aspects of each *APC* gene mutation are better understood, the controversy over rectum sparing will probably be settled.

APPENDIX

The Hereditary Colorectal Tumors Registry

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