Clinical Features in Familial Polyposis Coli

Results of the Danish Polyposis Register

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Three hundred nineteen affected members of 94 Danish families with familial polyposis coli had been registered in the Danish Polyposis Register by the end of 1982. Of the 247 histologically verified cases, 168 were propositi and 79 were call-up patients. The frequency of colorectal cancer at the time of diagnosis of polyposis was 69 percent in propositi vs. 3 percent in call-up patients. The cumulative survival rate after ten years was 97 percent in call-up patients, as compared to 42 percent in propositi. The prognosis of polyposis patients has improved significantly since the establishment of the Danish Polyposis Register in 1971. [Key words: Familial polyposis coli; Hereditary adenomatosis coli; Polyposis register]

FAMILIAL POLYPOSIS COLI (FPC) is an autosomally dominant disease characterized by the development of from 100 to several thousand colorectal adenomas, of which one or more will degenerate into a carcinoma, unless colectomy is performed.[1]

The first register of polyposis patients was founded in 1925 at St. Mark's Hospital in London.[2] National polyposis registers have been established since then in the Nordic countries and regional registers in the U.S.A., Japan, Canada, and France.[3-11] The purpose of the registers is to improve the past poor prognosis by coordination of the discovery, prophylactic examination, and treatment of family members at risk.

The purpose of this paper is to present the clinical features of patients registered in the Danish Polyposis Register by the end of 1982.

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Patients and Methods

Propositi (probands) are patients with at least 100 colorectal adenomas and are ascertained irrespective of the presence of other cases in the family. Solitary propositi are propositi who do not have any relatives with FPC.

Call-up patients (secondary cases) are first-degree relatives of propositi with at least 100 colorectal adenomas diagnosed as the result of prophylactic examination.

Assumed cases are propositi with clinical and/or radiologic evidence of FPC, but without histologic verification.

The methods of establishing the Danish Polyposis Register, *i.e.*, discovery of propositi, registration of families, construction of pedigrees, and diagnosis of secondary call-up patients have been described in a previous paper.[6]

The chi-square test and the Mann-Whitney rank-sum test for unpaired data have been used in the statistical evaluation, and a significance level of 0.05 was chosen. The prognosis was evaluated by the life-table method using a computerized program[12] and the Mantel-Cox test was used in evaluation of the survival data.

Results

Total Material: Ninety-four families had been registered by the end of 1982. Fifty families included from two to 33 affected members, while 44 included only one, *i.e.*, a solitary propositus. A total of 319 patients were diagnosed: 168 propositi, 79 call-up patients, and 72 assumed cases. The year of the diagnosis in 247 propositi and call-up patients is illustrated in Fig. 1.

Propositi: The 168 propositi included 98 men and 70 women, all of whom had rectal adenomas at proctosig-

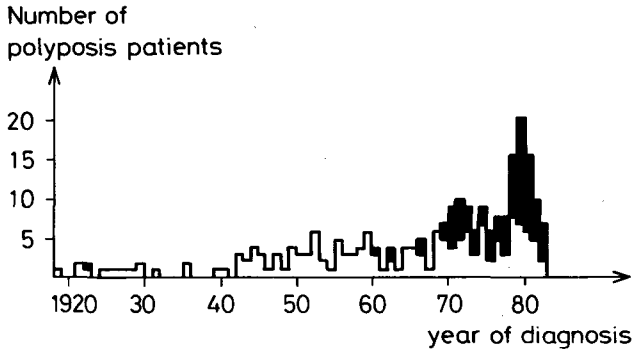

FIG. 1. The year of diagnosis of polyposis in 247 patients with histologically verified FPC. Dark areas represent call-up patients.

moidoscopy. At least one colorectal carcinoma was diagnosed in 115 patients (69 percent); the localization of the carcinomas is shown in Table 1. Of the 108 patients in whom information was available regarding the number of carcinomas, 88 (81 percent) had one tumor, 17 (16 percent) had two, and three (3 percent) had three synchronous carcinomas.

One or more extracolonic manifestations were recorded in 11 propositi (7 percent), including multiple epidermoid cysts (N = 3), clinically evident facial osteomas (N = 6), and desmoid tumors (N = 8).

The clinical course may be illustrated by the patient's age at various stages of the disease. The median age at the first bowel symptom was 29 years; at the diagnosis of FPC it was 33 years; and at diagnosis of colorectal cancer it was 36 years (Table 2). The time interval from the appearance of the first symptom to the diagnosis of colorectal cancer decreased with the age of the patient ($P < 0.001$).

The first bowel symptom in 44 solitary propositi developed at a median age of 27 years, as compared to 30 years in nonsolitary propositi. The median age at diagnosis of FPC was 28 years vs. 34 years in nonsolitary propositi, and 34.5 years at diagnosis of colorectal cancer in 27 solitary propositi with cancer (61 percent), as compared to 37 years in nonsolitary propositi. These differences are all statistically insignificant.

Surgical treatment was carried out on 152 propositi, and of these 81 (53 percent) were treated with colectomy

TABLE 1. *Localization of Colorectal Cancer in 109 Propositi**

	Number of Cancers	Percent
Right colon	8	6
Transverse colon	6	5
Descending colon	8	6
Sigmoid colon	31	24
Rectum	77	59
TOTAL	130	100

*Localization unknown in six patients.

(proctocolectomy N = 47, ileorectal anastomosis N = 25, ileoanal anastomosis N = 4, ileostomy and closed rectal stump N = 5). The postoperative mortality (*i.e.*, death within 30 days after the operation) was 4 percent.

Seen in retrospect, colectomy was, in all probability, possible and curative in 124 of 168 propositi. Table 3 illustrates the continuous increase in the proportion of correctly treated patients in this group during the period from 1920 to the end of the study in 1982. The cumulative incidence of metachronous carcinoma in the remaining part of the colon or rectum was evaluated according to the life-table method in the 39 of 124 propositi who were treated by segmental resection only (Fig. 2). The cumulative incidence was 65 percent after 20 years, and an attempt at extrapolation indicates that all FPC patients who are not treated with a colectomy will develop a second carcinoma within approximately 35 years of the first operation.

The cumulative survival rate in propositi after five and ten years was 56 and 42 percent, respectively (Fig. 3). The survival was lower in propositi with colorectal cancer, as compared to those without, $P < 0.001$ (Fig. 4), and lower in nonsolitary propositi, as compared with solitary propositi, $P = 0.024$ (Fig. 5). This difference was based on a lower survival in nonsolitary propositi with cancer, as compared to solitary propositi with cancer, $P = 0.022$ (Fig. 6), due to the fact that no statistically significant difference could be found when comparing survival in solitary propositi without cancer and nonsolitary propositi without cancer (Fig. 7).

Call-Up Patients: Seventy-nine call-up patients, 44 men and 35 women, were registered. Sixty-six of those

TABLE 2. *Age at Various Stages of Familial Polyposis Coli*

Stages of FPC	Subgroup of Patients	Number of Patients	Number of Patients with Information about Stage	Median Age at Stage (Years)	Range (Years)
Development of adenomas	Call-up patients	79	16	16	5-38
First bowel symptoms	Propositi	168	151	29	2-73
Diagnosis of FPC	Propositi	168	167	33	5-73
Diagnosis of colorectal cancer	Propositi with colorectal cancer	115	114	36	17-67
Death from colorectal cancer	Assumed nonoperated cases	72	48	40	26-68

TABLE 3. *Frequency of Colectomy among Polyposis Propositi, Who, in Retrospect, Might Have Been Treated with a Colectomy*

Period	Number of Patients	Number of Colectomies	Percent
1900-1949	16	2	13
1950-1959	27	13	48
1960-1969	23	15	65
1970-1979	44	41	93
1980-1982	14	14	100

were discovered after the establishment of the Danish Polyposis Register in 1971.

Two patients (3 percent) had colorectal carcinoma at the time of diagnosis of FPC. Eight had one or more extracolonic manifestations: multiple epidermoid cysts (N = 5), clinically evident facial osteomas (N = 3), and a desmoid tumor (N = 1).

The median age at development of rectal adenomas was 16 years in 16 patients, followed from normal proctosigmoidoscopic findings until the occurrence of rectal adenomas (Table 2). The median age at diagnosis of FPC was 19 years (range 5 to 51) and at diagnosis of colorectal cancer 45.5 years (range 44 to 47).

Fifty-seven patients (72 percent) have been subjected to colectomy (proctocolectomy, N = 19; ileorectal anastomosis, N = 32; ileoanal anastomosis, N = 6). One patient, diagnosed as the first Danish call-up patient in 1921, had an ileostomy only. The postoperative mortality was 0. Colectomy has been planned, but not performed, in 21 patients.

The cumulative survival rate of call-up patients was 97 percent after 10 years, and the prognosis thus far better than in propositi, $P < 0.001$ (Fig. 3). The survival rate of propositi and call-up patients steadily increased from the 1950s to the end of the study in 1982 (Fig. 8).

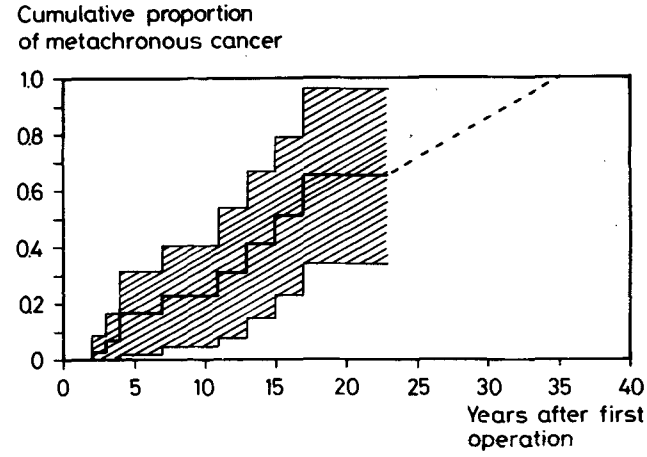

FIG. 2. The cumulative incidence of metachronous colorectal carcinoma in propositi, who might have been treated with colectomy, but in whom only a segmental resection was carried out. The shaded area represents 95 percent confidence limits.

Assumed Cases: Seventy-two assumed cases have been registered. The median age at death from colorectal cancer was 40 years; this has been calculated from 48 nonoperated assumed cases (Table 2).

Discussion

The first report of familial polyposis coli was published in 1881,[13] and the hereditary and premalignant nature of the disease came to be understood over the following decades. However, "the treatment was almost hopeless due to the nature and the extension of the disease."[14] This changed following reports on the use of colectomy and ileorectal anastomosis,[15] as well as proctocolectomy,[16] and following the establishment of the St. Mark's Hospital Polyposis Register.[17] The results of sur-

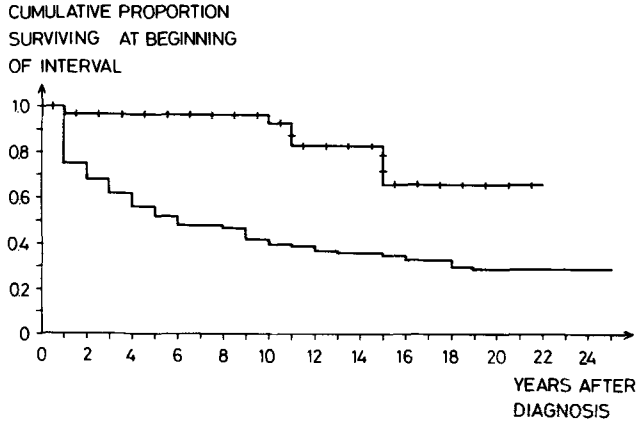

FIG. 3. Survival of 162 propositi (———) and 78 call-up patients (-+-+-+-), $P < 0.001$. Information was insufficient in six propositi and one call-up patients.

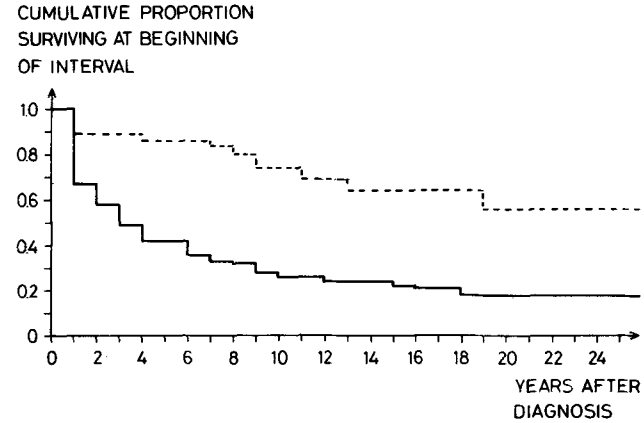

FIG. 4. Survival of 109 propositi with (———) and 53 without colorectal cancer (-----), $P < 0.001$.

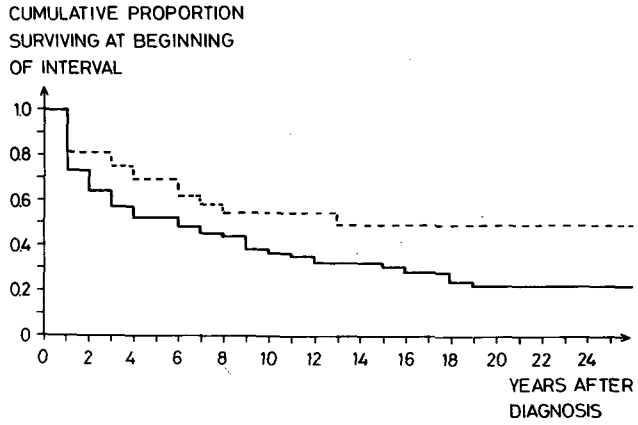

FIG. 5. Survival of 120 non solitary (———) and 42 solitary propositi (-----), $P = 0.024$.

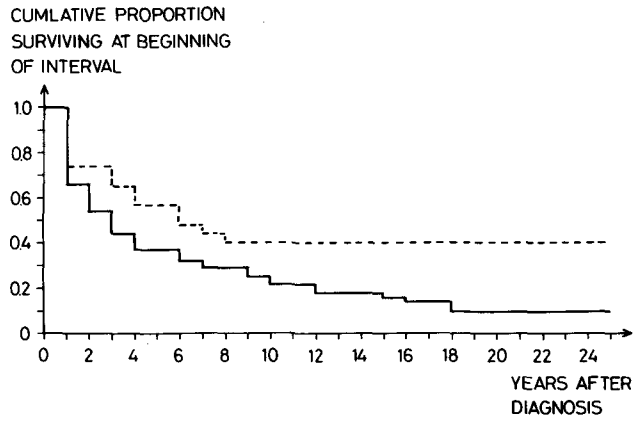

FIG. 6. Survival of 82 non solitary (———) and 27 solitary propositi with colorectal cancer (-----), $P = 0.022$.

gical treatment were discouraging, however, because of high postoperative mortality. Progress in surgery and anesthesiology during the late 1940s allowed a more active approach.[18]

Bussey published the excellent results of prophylactic surgery at St. Mark's Hospital in 1975, presenting convincing evidence of the value of a centralized polyposis register.[1] The Danish Polyposis Register was initiated in 1971.[19] The registration of propositi appears to have reached a constant level (Fig. 1). All newly diagnosed propositi have probably been registered during the last decade.[6] The registers in Denmark and Sweden are the only national registers with a nearly complete registration, and provide the most reliable figures from an epidemiologic point of view.

In the present series, all FPC patients had rectal adenomas, as did the FPC patients in other series,[1,3] and this justifies the use of proctosigmoidoscopy only in the regular prophylactic examination of first-degree relatives of FPC patients.[1] Colonoscopy is a more sensitive method than rigid proctosigmoidoscopy, but the possible superiority of the former procedure in screening first-degree relatives of FPC patients has not been proven. Furthermore, colonoscopy is only used routinely in a limited number of Danish hospitals. Radiologic examination of the colon[20] seems superfluous in this group, and complicates the organization of prophylactic examination without adding any relevant information.

Sixty-nine percent of the propositi had colorectal cancer at the time of diagnosis of FPC in the present series. This percentage is similar to others,[1,3] and reflects the natural history of the disease. The localization of the carcinomas also is similar to that given from England and Sweden, whereas the incidence of patients with more than one colorectal carcinoma in the present study (18 percent) is much lower than in the St. Mark's Hospital series (44 percent).[1,3] In all probability, this difference reflects a more careful examination for small carcinomas at St. Mark's Hospital than in a number of different Danish institutions. The frequency of colorectal cancer in call-up

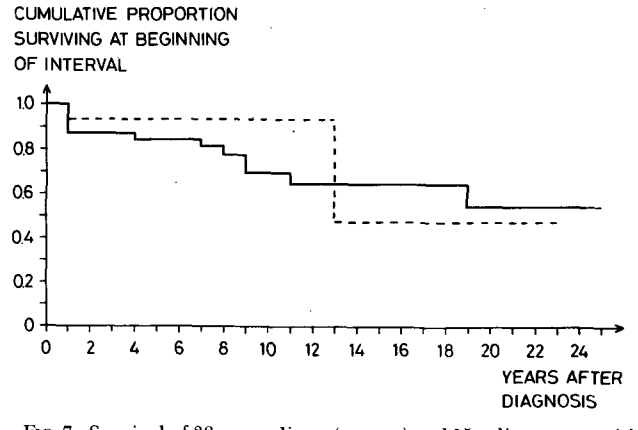

FIG. 7. Survival of 38 non solitary (———) and 15 solitary propositi without colorectal cancer (-----), $P = 0.5$.

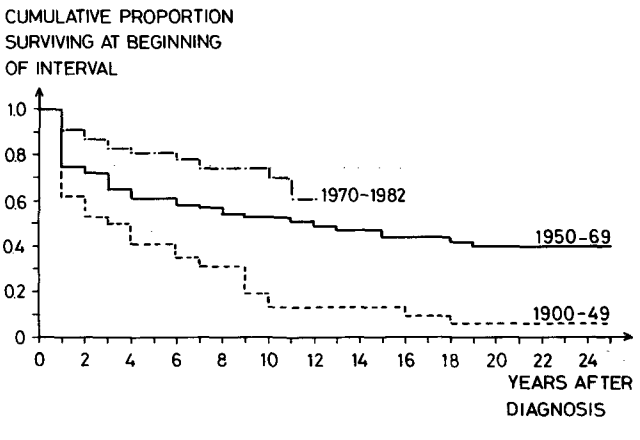

FIG. 8. Survival of polyposis patients according to time of diagnosis: 1900-1949 (N = 34), 1950-1969 (N = 134), 1970-1982 (N = 72), $P < 0.001$.

patients is of the same magnitude as in the English and Swedish series, and proves the value of prophylactic examination of family members at risk.

The frequency of extracolonic manifestations in the present series (19 of 247 = 8 percent) is probably an underestimate of the true occurrence.[21] A minority of the patients have undergone systemic examination for extracolonic manifestations; consequently, only conspicuous lesions have been recorded.

The proportion of solitary propositi (44 percent) is similar to the figures from St. Mark's Hospital and the Finnish register, whereas the Swedish Register has only 30 percent.[1,5,20] There are three possible explanations of the nature of solitary propositi. They may be fresh mutations, nonfamilial phenocopies, or normally inherited cases, in which there is insufficient knowledge of the family history. It has been suggested that nonfamilial phenocopies do not exist.[22] Incorrect information about the family may be responsible for a few solitary cases, due to either insufficient information in the public registers or to purposeful suppression of correct information about illegitimacy in some cases. Descendants of solitary propositi carry the same risk of developing the disease as do the descendants of FPC patients in families with more than one affected member. Consequently, the number of solitary cases may change over the course of time, as the development of FPC in a child of a solitary propositus transfers this family to the group of families with more than one member with FPC.[1] The development of colorectal cancer in 61 percent of solitary propositi is not statistically different from the occurrence in nonsolitary propositi (71 percent), neither do the median ages at different stages of the disease differ from those of nonsolitary propositi.

The natural history of FPC can be illustrated by different stages of the disease in relation to age. The ages found in the present series do not differ from the figures found by others.[1,20,23] The interval from onset of symptoms to the diagnosis of cancer decreases significantly as the age of the patient increases, suggesting a shorter premalignant phase with increasing age. It is unlikely that the value of this observation will be tested, as this would require follow-up from the development of adenomas to the development of cancer in a series of call-up patients who had not undergone surgery. Follow-up of this type would be necessary to estimate the length of the true premalignant phase; obviously this would be unethical.

Knowledge regarding the correct treatment of FPC patients has increased during the last decades, and today all patients are subjected to primary colectomy. The Danish attitude is to treat call-up patients with colectomy and ileorectal anastomosis if no rectal cancer has developed and on the condition that the patients accept lifelong postoperative control. This policy has resulted in a cumulative risk of developing rectal cancer of 13 percent at ten years after the operation.[24]

The assumed 100 percent cumulative occurrence of a metachronous colorectal cancer 35 years after a segmental colorectal resection supports the theory that all FPC patients, if untreated, will develop colorectal cancer; as they almost all did a few generations ago.

Bussey reported a five-year survival rate of 58 percent among FPC patients with colorectal carcinoma,[1] apart from this, however, no estimation of the survival of FPC patients has been published. The present calculations demonstrate the expected unfavorable prognosis of propositi as compared to call-up patients; the higher survival in solitary propositi as compared to nonsolitary propositi is surprising. That this difference is found in the cancer group may suggest a basic difference between solitary and nonsolitary propositi. However, because no differences between the two groups of patients can be pointed out with regard to pathologic findings, frequency of colorectal cancer or age at various stages of the disease, a hypothesis of solitary propositi representing a separate type of FPC does not seem likely at the present time.

The prognosis of FPC patients diagnosed during the 1950s and 1960s was considerably better than that of those diagnosed during the first half of the century (Fig. 8), which probably reflected improved surgical techniques and increased knowledge of the disease. The significant improvement in the survival rate since 1970 proves the effectiveness of prophylactic examination and treatment of family members at risk, and thereby of the value of the Danish Polyposis Register.

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Announcement

ONE-DAY COURSE IN COLORECTAL SURGERY

A one-day course in colorectal surgery will be held on March 19, 1986, from 8:00 A.M. to 4:00 P.M. at the Teaching Center Auditorium, Long Island Jewish Medical Center, New Hyde Park, New York. The course is open to surgeons, oncologists, proctologists, gastroenterologists, nurses, and radiation therapists. It will be sponsored by the Department of Surgery. Dr. Eric Munoz is the Program Chairman. Topics will include: Treatment of Anal Diseases in the Homosexual and Patients with Crohn's Disease; Anal Vaginal Fistula and Anal Incontinence; Adjuvant Radiation Therapy in Colo-Rectal Cancer; Chemotherapy in Large Bowel Cancer; Follow-up of Patient with Colo-Rectal Cancer; Update in Inflammatory Bowel Diseases; and Stoma: Construction, Functions, Problems and Correction. Tuition is $125.00. This course meets the criteria for 7 credit hours in Category 1 from the Accreditation Council for Continuing Medical Education (ACCME). Contact: Ann J. Boehme, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, New York 11042. Telephone: (718) 470-8650.