Paper IX

Scandinavian Journal of Gastroenterology
2007, 1–7, PrEview article

informa
healthcare

ORIGINAL ARTICLE

Prevention of colorectal cancer by colonoscopic surveillance in families with hereditary colorectal cancer

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Abstract

Objective. In recent years persons at risk for colorectal cancers (CRC) have been subjected to follow-up with colonoscopy in many centres. There is, however, limited knowledge about the effect of such interventions. The objective of this study was to report the results of our observations during the past 15 years. ***Material and methods.*** Healthy persons were included in the study according to their family history of CRCs, and prospectively followed with colonoscopies. ***Results.*** Altogether, 1133 individuals were included and observed for a total of 3474 follow-up years from the first to the last colonoscopy initiated by our activity. Mismatch repair (MMR) mutations were detected in 6.5% of cases. A total of 1383 polyps were removed, 72% were less than 5 mm in diameter. Findings were scored as hyperplastic polyps ($n=887$), adenomas with mild to moderate dysplasia ($n=460$), adenomas with high-grade dysplasia ($n=30$) and cancers ($n=6$). Two cancers were observed after the first colonoscopy, compared with 2.6 expected by chance and more than 20 expected under the hypothesis of predominant inherited diseases in the families. Observed annual incidence rates for adenomas were similar in all groups, while in the mutation carriers there was a higher frequency of progression to severe dysplasia or infiltrating cancer. ***Conclusions.*** A simple explanation for the combined findings may be that all selected families had a similar tendency to produce adenomas, while mutation carriers more frequently demonstrated dysplasia/cancer in the adenomas. The low annual incidence rates for CRC indicated that the removal of adenomas may have prevented cancers.

Key Words: *Adenomas, colonoscopy, colorectal cancer, HNPCC, incidence, MMR mutations, polyps, prevention, prospective, surveillance*

Introduction

Colorectal cancer (CRC) is the most common cancer among men and women in Norway [1]. About 10% of colorectal cancers may be inherited [2]. Individuals belonging to families where cancers previously have occurred have an increased risk of developing cancer; they may develop cancer at a young age (30–40 years) and have an increased risk of having multiple primaries [3–5].

Colorectal adenomas are known to be the precursors of sporadic and hereditary CRC [6,7]. Several studies have shown that removal of adenomas may reduce the incidence of CRC [8–10]. Because CRC can be cured by early diagnosis and treatment [8], it has become a challenge to identify those at risk, and to subject them to early diagnosis and treatment. An accurate history of cancer in the family is the initial tool in identifying persons at risk. A family history of cancer may, *per se*, provide the rationale for follow-up, and it is the starting-point for mutation testing.

If no cellular dysplasia is visible in the microscope, a polyp is scored as hyperplastic [11]. Rijcken et al. [12] have shown that it seems unlikely that hyperplastic polyps are precursors for cancers in patients with hereditary non-polyposis cancer coli (HNPCC).

Two to six percent of CRCs are caused by germline mutations in the mismatch repair (MMR) genes MLH1, MSH2, MSH6, PMS1 and PMS2 [13–16]. The genes encode protein products that recognize

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(Received 8 May 2006; accepted 12 September 2006)

ISSN 0036-5521 print/ISSN 1502-7708 online
DOI: 10.1080/00365520601010230

and correct errors that arise when DNA is replicated [13,17]. Mutation carriers develop intestinal polyps at about the same frequency as the general population, but at a younger age [18]. The adenomas are more likely to undergo malignant transformation and to display an accelerated adenoma to carcinoma transition as compared to the adenomas seen in the general population [19,20]. In HNPCC, the progression from adenoma to carcinoma may take <3 years [18,20]. In sporadic cancer this progression takes approximately 10–15 years [21]. Distal cancers are suggested to be related more to environmental factors and proximal cancers, usually genetically caused [22]. In general, there seems to be an increasing prevalence of proximal cancers with increasing age [23–25].

We have been inviting cancer kindred to our outpatient cancer genetic clinic since 1989, and have offered follow-up by colonoscopy to members of CRC families. The aim of this prospective study was to evaluate the results of screening with respect to tumours demonstrated and annual incidence of adenomas and cancers, stratified on clinical classification of the families and on results of mutation testing.

Material and methods

The patients included in the study had been referred to the Section of Genetic counselling, Rikshospitalet-Radiumhospitalet, from 1989 to spring 2005. They were included according to their family history of colorectal- and other cancers applying wide clinical criteria [26]. The family history was expanded and information on the site and classification of cancers and polyps and age at diagnosis were obtained and verified in the medical files and/or in The National Cancer Registry, whenever possible. Patients with familial adenomatous polyposis and other well-defined cancer syndromes were excluded. The remaining CRC families were classified according to the following criteria:

I. Mutation positive: Any family with a detected mutation in one of the MMR genes MLH1, MSH2 or MSH6. (PMS1 and PMS2 were not tested).

II. HNPCC: At least three relatives in two successive generations with histologically verified adenocarcinoma in the colon, rectum, endometrium, duodenum, ureter or pelvis, and at least one being diagnosed at <50 years of age (Amsterdam criteria II) [27], but without any mutation being demonstrated.

III. HNPCC-like: Families not meeting the above criteria, but meeting the Amsterdam criteria if other HNPCC-related cancers such as cancer of the stomach, hepatobiliary tract, pancreas or ovarium are scored as affected in addition to CRC, or families meeting the Amsterdam criteria but with one skipped generation.

IV. Late-onset hereditary gastrointestinal cancer (LOCRC): Families not meeting the above criteria, but with four or more gastric- or colorectal cancers in one lineage, all diagnosed at over 50 years of age [28], and skipped generations allowed for. One of the four may be other HNPCC-related cancers.

Mutation testing

When mutation testing became available, those affected were examined as previously reported [29,30]. When a mutation was found, the healthy family members were offered predictive testing and those not carrying the family mutation were excluded from further follow-up. Owing to lack of resources, mutation analyses have not been performed in all families.

Colonoscopy

In the selected families, all patients considered to be cured of CRC and/or other HNPCC-related cancers and all 1st degree relatives of the cancer patients were offered surveillance by colonoscopy from age 35 years on. From 1989 to 1996 colonoscopy every third year was recommended. From 1997 onwards we followed the ICG-HNPCC guidelines [31] and offered colonoscopy every two years from 25 to 30 years of age in HNPCC and HNPCC-like kindred, and every fifth year from age 40 years on in LOCRC [28]. Whenever a tubular adenoma was demonstrated, the next colonoscopy was recommended within one year. If the finding was a CRC, a villous adenoma, a tubulovillous adenoma or an adenoma with grave dysplasia, the gastroenterologist could schedule additional intervention. The screening was nation-wide as the colonoscopies were performed at the patients' local hospitals.

Number of cancers expected to occur by chance

The number of infiltrating CRCs expected to occur by chance was estimated based on population annual incidence rates [1] with respect to age, gender and follow-up time for each person controlled. The calculations were done twice; once when considering age for the whole observation period to be the age at the first control, the other using age at the last control, and the result was estimated as the mean of the two.

Database and statistics

All data were kept in our computerized medical file using an Oracle© database and a dBase Plus© application. The database was analysed using TOAD© and statistical tests performed by Systat10© and StatXact5©.

Ethics

Permission to access the medical files for information was obtained in writing from all living persons, and from the relatives of the deceased. Written informed consent underlay all requests for tumour specimens and genetic testing. All activities reported were approved by the government, under health care. All information was kept in our medical files. No results identifying any individual patient were exported from the medical files. No research registry was set up. All activities complied with national legislation and included genetic counselling of every person participating in the study.

Findings

Polyps were removed and classified by a pathologist. The histopathological scores were copied from the medical files for the present study. Results were scored as normal, hyperplastic polyp, adenoma with low-grade dysplasia (=adenoma I) or moderate-grade dysplasia (=adenoma II) or high-grade dysplasia with the pathologist's discussion excluding invasive cancer (=adenoma III) or adenocarcinoma in the colon/rectum (=cancer). Information was noted when obtainable on size and various histopathological subtypes. Location of a finding was scored as proximal (including the caecum, ascending and transverse colon), the distal (including the descending and sigmoid colon) and rectum.

Results

In all, 1133 individuals from 398 families were included in the study. The total number of years of follow-up was 3474 and a total of 2748 colonoscopies were performed; 715 persons had been examined twice or more times. For details, see Table I.

Number of findings/annual incidences

Including the first control, the total number of findings amounted to 1383; hyperplastic polyps = 887, adenomas I/II = 460, adenomas III = 30 and cancers = 6. Forty-six percent of the adenomas I/II, 80% of the adenomas III and 67% of the cancers were found during the first control. Findings at follow-up and calculated annual incidence rates are summarized in Table II.

The number of cancers expected to occur by chance was 2.6 compared with 2 cancers found at follow-up examinations. Assuming a 2% annual incidence rate of cancer in MMR mutation carriers, an annual incidence rate of about 1% in 1st degree relatives of those affected could be expected in HNPCC kindred. This being the case, we observed 1 cancer and expected 16 in the HNPCC group ($\chi^2 = 14.4$, $p < 0.05$), and we observed 1 cancer and expected 6 in the mutation carriers ($\chi = 4.2$, $p < 0.5$), and the one cancer was cured.

Taking the life-time risk for cancer to be the observed annual incidence rates × the 40 years at risk, we arrived at an estimated life-time risk for CRC inside our health-care programme to be 0% in LOCRC, $0.0006 \times 40 = 2.4\%$ in HNPCC and $0.003 \times 40 = 12\%$ in mutation carriers – all of which are considerably below the expected rates.

Grouping the findings at follow-up as cancer or severely dysplastic adenomas, compared to total number of adenomas and cancers, the findings were 1/60 = 1.7% for LOCRC, 3/118 = 2.5% for HNPCC and 4/23 = 17.4% for mutation carriers (Table II), resulting in a two-sided Fisher exact p-value of 0.014 for mutation-positive compared to HNPCC, 0.02 for mutation-positive compared to LOCRC and 1.00 for HNPCC compared to LOCRC.

The total findings according to family history are listed in Tables III and IV. The total number of findings per person is not included, but the

Table I. Number of colonoscopies and follow-up years.

Ascertainment	Mut. carriers	HNPCC	HNPCC-like	LO CRC	Total
Families included in the study and follow-up					
Number of persons	73	528	186	346	1133
Number of families	24	158	75	165	398
Number of colonoscopies	220	1342	559	627	2748
Total years of follow-up	302	1630	798	744	3474
Median follow-up time (range)	4.3 (1–15.2)	4.1 (0.2–15.2)	4.9 (0.3–14.2)	4.9 (0–12.6)	
Median age 1.control (range)	48.8 (22.4–75.9)	45.2 (19.8–80.2)	40.3 (20.4–68.9)	47.9 (27.5–82.6)	

Abbreviations: HNPCC = hereditary non-polyposis cancer coli; LOCRC = late-onset gastrointestinal cancer.

Table II. Annual incidence rates of findings according to family history (number of findings in follow-up controls).

Family class	Hyperplastic polyps	Adenomas I/II	Adenomas III	Cancers
Mut. carriers	0.109 (33)	0.063 (19)	0.01 (3)	0.003 (1)
HNPCC	0.169 (275)	0.071 (115)	0.0012 (2)	0.0006 (1)
HNPCC-like	0.123 (98)	0.069 (55)	0	0
LOCRC	0.195 (145)	0.079 (59)	0.001 (1)	0
Total	0.159 (551)	0.071 (248)	0.0017 (6)	0.0066 (2)

Abbreviations: HNPCC = hereditary non-polyposis cancer coli; LOCRC = late-onset gastrointestinal cancer.

distributions fit the expectations if the polyps were randomly or multifactorially caused, but with two exceptions: 1) A limited number ($n = 6$) demonstrated ≥ 20 hyperplastic polyps. Three of them belonged to LOCRC families, and three were in HNPCC kindred, among whom none were verified as mutation carriers. 2) One patient harboured 14 adenomas III and 15–19 TAI/II. This patient had been investigated for mutations in the APC and MYH genes, but the findings were normal. The family was classified as HNPCC-like, because of other HNPCC-related cancers in the family.

Description of polyps

Details are shown in Tables III and IV.

Size was measured in 79% (1089/1377) of all polyps. Seventy-two percent (71.6) (780/1089) were <5 mm. Among the six cancers, size was unknown in three, and 6 mm, 15 mm and 30 mm, respectively, in the remaining three.

Of the adenomas that were graded, 195 of the tubular adenomas, 28 of the tubulovillous adenomas, 1 villous and 1 flat adenoma all showed moderate dysplasia, while the remainder (including 4 adenomas of unknown pattern) showed mild dysplasia. Six and a half (6.4) percent (73/1133) of the participants were mutation carriers. Almost 6% (5.7) (24/419) of the tubular adenomas and 18% (8/44) of the tubulovillous adenomas belonged to mutation carriers.

HNPCC-, HNPCC-like- and LOCRC families all showed the same distribution of hyperplastic polyps and adenomas I/II throughout the colon, while half of the adenomas III and 2/3 of the cancers were located in the proximal colon. Mutation carriers were different. Fifty-three percent of the hyperplastic polyps and 35% of the adenomas I/II were located in the rectum, while four of the proximal adenomas I/II and both of the proximal adenomas III were located in the caecum.

Characteristics of the cancers

Of the six cancers detected, four were located in the proximal colon, one in the distal colon and one in the rectum (Table IV). Median age at cancer diagnosis was 57.5 years (43–71 years).

Two cancers were detected at follow-up. One patient had previously had a colon cancer at the age of 44 years and a second colon cancer at 46 years of age. The patient still had part of the colon left, and at follow-up, at 53 years of age, two years after a normal colonoscopy, a third colon cancer was

Table III. Number of hyperplastic polyps according to family history, location and size.

Hyperplastic polyps	Mut. carriers	HNPCC	HNPCC-like	LOCRC	Total
Findings at 1st control	14	151	60	111	336
Findings at follow-up	33	275	98	145	551
Location					
Proximal colon	8 (17%)	137 (32.2%)	59 (37.3%)	81 (31.6%)	285 (32.1%)
Distal colon	11 (23.4%)	140 (32.9%)	52 (32.9%)	102 (39.8%)	305 (34.4%)
Rectal colon	25 (53.2%)	131 (30.8%)	40 (25.3%)	62 (24.2%)	258 (29.1%)
Unknown	3 (6.4%)	18 (4.2%)	7 (4.4%)	11 (4.3%)	39 (4.4%)
Total	47 (100%)	426 (100%)	158 (100%)	256 (100%)	887 (100%)
Size					
01–04 mm	28	276	91	156	551
05–09 mm	3	51	21	46	121
10–19 mm	1	5	5	5	16
20 ++ mm	0	10	2	0	12
Unknown	15	84	39	49	187

Abbreviations: HNPCC = hereditary non-polyposis cancer coli; LOCRC = late-onset gastrointestinal cancer.

Table IV. Numbers of adenomas I/II/III and cancers according to family history, location, size, form and histology.

	Mut. carriers	HNPCC	HNPCC-like	LOCRC	Total
Tubular adenomas I/II					
Findings at 1st control	10	95	51	56	212
Findings at follow-up	19	115	55	59	248
Location					
Proximal colon	10 (34.5%)[1]	82 (39.1%)	42 (39.6%)	47 (40.9%)	181 (39.3%)
Distal colon	6 (20.7%)	90 (42.3%)	41 (38.7%)	39 (33.9%)	176 (38.3%)
Rectal colon	10 (34.5%)	30 (14.3%)	16 (15.1%)	19 (16.5%)	75 (16.3%)
Unknown	3 (10.3%)	8 (3.8%)	7 (6.6%)	10 (8.7%)	28 (6.1%)
Total	29 (100%)	210 (100%)	106 (100%)	115 (100%)	460 (100%)
Size					
01–04 mm	15	118	46	48	227
05–09 mm	4	46	31	29	110
10–19 mm	4	8	3	7	22
20++ mm	0	3	0	2	5
Unknown	6	35	26	29	96
Form					
Tubular	22	168	101	104	395
Tubulovillous	5	21	2	11	39
Villous	0	1	0	0	1
Serrated	1	1	0	0	2
Flat	0	1	0	0	1
Unknown	1	18	3	0	22
Histology					
Low grade	11	93	35	53	192
Moderate grade	15	87	64	59	225
Unknown	3	30	7	3	43
Tubular adenomas III					
Findings at 1st control	2	3	14	5	24
Findings at follow-up	3	2	0	1	6
Location					
Proximal colon	2[2]	1	9[3]	3	15
Distal colon	3	3	3[3]	3	12
Rectal colon	0	1	2[3]	0	3
Total	5	5	14	6	30
Size					
01–04 mm	0	2	0	0	2
05–09 mm	3	0	14	2	19
10–19 m	1	1	0	2	4
20++ mm	0	0	0	0	0
Unknown	1	2	0	2	5
Form					
Tubular	2	3	13	6	24
Tubulovillous	3	1	1	0	5
Unknown	0	1	0	0	1
Histology					
High grade	5	5	14	6	30
Cancers					
Findings at 1st control	0	2	0	2	4
Findings at follow-up	1	1	0	0	2
Location					
Proximal colon	1	2[4]	0	1	4
Distal colon	0	1	0	0	1
Rectal colon	0	0	0	1	1

Abbreviations: HNPCC = hereditary non-polyposis cancer coli; LOCRC = late-onset gastrointestinal cancer.
Adenomas I = low-grade dysplasia; II = moderate-grade dysplasia; III = high-grade dysplasia; cancers = adenocarcinomas.
[1]Four located in the caecum; [2]both located in the caecum; [3]all the adenomas were found at first control in one patient; [4]one located in the caecum.

detected. At this point he underwent a total colectomy. He belonged to a HNPCC family, and later we demonstrated an MSH2 mutation. Thirteen years have now passed and the patient is healthy. The other patient had a tubular adenoma in the sigmoideum and a histologically normal biopsy taken from a thickening of the caecal mucosa at her first colonoscopy at 58 years of age. Two months later the patient underwent surgery to remove her uterus and ovaries because of descensus of the uterus. Metastases were found in one of her ovaries. The primary focus of the cancer was a low differentiated adenocarcinoma from the location where the normal biopsy had been taken two months earlier. After three years, the patient died of her cancer. Her family met the Amsterdam II criteria because one young family member had an endometrial tumour. One affected obligate carrier has been sequenced for MLH1, MSH2 and MSH6 without detection of mutation.

Discussion

We observed no more cancers than was expected by chance alone, 2 compared with 2.6. The low annual incidence rate for cancer in HNPCC kindred and in MMR mutation carriers conflicts with the reported penetrance for the mutations in question [32,33]. Obviously, the number of events was limited for these forms of calculations, but in all the ways we analysed the figures, we arrived at the conclusion that our intervention may have prevented CRC by removing adenomas. The estimated life-time risks in the subgroups were planned and carried out despite the low numbers of cancers found. The finding was the low numbers of cancers, which in turn invalidated the calculations because of the low numbers.

We demonstrated an annual incidence rate of $256/3474 = 7.4\%$ of adenomas (including cancers), and there was no difference between HNPCC and LOCRC kindred. In the mutation carriers, however, the adenomas more frequently had progressed to severe dysplasia or cancer. The adenomas appeared to be randomly distributed between the persons examined. The hyperplastic polyps had a similar distribution, but with an excess of persons with more than 20 polyps. The observation was that the demonstrated MMR mutation carriers did not have increased annual incidence rates of adenomas compared with all the members of HNPCC and/or LOCRC kindred.

Our findings are in keeping with the notion that all kindred were demonstrated to have a similar annual incidence rate of polyps, and in the mutation carriers/HNPCC kindred the adenomas progressed more rapidly to carcinomas. This has also been suggested by Vasen et al. [18], and we found the material insufficient to allow further speculatation. Findings in all groups were distributed throughout the colon, making it appropriate to continue recommending full colonoscopic surveillance. In mutation carriers/HNPCC, colonoscopic surveillance every two years if the colon is clear, as recommended [31], seems reasonable. The genetic basis of LOCRC is unknown. In our study no cancers were detected at follow-up, and the adenoma-carcinoma sequence is not thought to be accelerated. Five-year intervals of colonoscopy if the colon is clear, as suggested by others, should be appropriate [34,35].

One of the strengths of our study was the nationwide selection of CRC families, and the large number of persons at risk included. A limitation was the low prevalence of mutation carriers demonstrated, but this probably reflected a low prevalence in our population. The low number of cancers demonstrated, and the low power of demonstrating a protective effect of an intervention, is a general problem in studies of this kind and not a limitation specific to our study. This problem calls for broad collaborative studies in order to arrive at more definite conclusions.

In conclusion, we observed that the families selected by family history of CRC prospectively produced adenomas. Our findings support the notion that the adenoma formation has a separate mechanism, while MMR mutation carriers have a rapid progression from adenoma to carcinoma once an adenoma is established. Our intervention may have prevented cancers, as demonstrated by the low annual incidence rate observed compared with expectations based on retrospective reports in similar kindred, and the one cancer found at follow-up in a mutation carrier was cured.

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