SURVEILLANCE

Positive family history promotes participation in colorectal cancer screening

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Abstract

Background: **Participation rates in colorectal cancer (CRC) screening are rather low. We evaluated the interest of first degree relatives (FDR) of CRC patients to participate in a colonoscopy screening and compared the findings to controls with a negative family history.**
Methodology: **There were 235 CRC patients diagnosed in our centre in 1984–2001. These were mailed an invitation letter for a preventive examination for their FDR older than 40 years and a questionnaire about occurrence of malignancies in their family. Colonoscopy was performed in 52 FDR and sex/age matched controls.**
RESULTS: The questionnaire was delivered to 196 patients. Thirty four (17.3 %) patients responded. Positive family history for CRC was reported in 12/34 (35.3 %) patients, compared to expected 3.4 patients (p=0.04; OR 4.2; 95 % CI=1.05–17.89). Fifty two of 94 (55.3 %) FDR participated in a screening and CRC was diagnosed in 2 and CRA in 18 patients compared to 1 CRC and 9 CRA in control group (p=0.04; Kaplan-Meier p=0.04).
Conclusions: **Positive family history seems to be a motivation factor for a participation in a CRC screening program. Consistent with previous studies the prevalence of CRA and CRC was significantly higher in the group of FDR compared to controls *(Tab. 3, Fig. 1, Ref. 20)*.**
Key words: colorectal carcinoma, screening, family history.

Abbreviations:
CRA – colorectal adenoma
CRC – colorectal carcinoma
FDR – first degree relative
HNPCC – hereditary nonpolyposis colorectal cancer
RR – relative risk
OR – odds ratio
CI – confidence interval

Colorectal carcinoma (CRC) represents one of the most difficult health problems in the majority of developed countries due to a rapidly increasing incidence and only a slowly improving prognosis. Therefore enormous efforts have been recently invested into the development of efficacious prevention strategies. Population based screening and colonoscopic polypectomy of adenomatous colorectal polyps are the mainstream of the colorectal cancer prevention and have been shown to be very successful in numerous clinical studies (1–4). However there are several difficulties with the population based programs. The most important one seems to be a low willingness to participate in the screening among the general population. Despite compelling rationale and evidence supporting screening most of eligible persons do not take advantage of it (5, 6).

Another important issue is the presence of high risk groups of population, where the screening recommendations significantly differ from those for the general population (1). The largest group of persons at risk for CRC is those with positive family history of colorectal cancer. Positive family history of one first-degree relative (FDR) is reported by about 10 % of population, of more than 1 FDRs by about 1 %. These persons are easily identified through a simple family history taking, which has been shown to

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This paper is considered for publication as a clinical study.

Tab. 1. Characteristics of colorectal carcinoma patients.

Characteristics	All cohort (n=235)
Demographic and clinical data	
Male/female	132/103 (56.2/43.8%)
University degree	26 (11.1%)
Mean age at diagnosis of CRC (years)	65.9+/-12.1
Time since the diagnosis of CRC	7.25+/-5.2
Indication for colonoscopy	
GIT symptoms*	86 (55.5%)
Anemia	28 (18.1%)
Positive FOBT	3 (1.9%)
Positive per rectum examination	5 (3.2%)
Finding on other examinations	7 (4.5%)
Other	26 (16.8%)
Data not available	80
Colonoscopic data	
Location of carcinoma	
Rectum	55 (24.2%)
Left colon	120 (52.9%)
Right colon	48 (21.1%)
Synchronous left and right	4 (1.8%)
Stenosing disease	44 (18.7%)
Synchronous CRA	40 (17.0%)
Distal to tumor	31 (75.6%)
Proximal to tumor	10 (24.4%)
Number of polyps in patient	
1	26 (65.0%)
2	8 (20.0%)
3	4 (10.0%)
>3	2 (5.0%)
Histological grading	
G1	73 (47.1%)
G2	71 (46.5%)
G3	10 (6.5%)
Not available	81

** GIT symptoms: change in bowel habits, enterorhagia, abdominal pain*

be moderately sensitive and very specific (7, 8). Recent large meta-analysis established the relative risk of CRC for a person with positive family history at RR=2.42 (95 % CI=2.0–2.53), being even higher in persons with ≥2 FDR with CRC or FDR diagnosed with CRC in a young age <60 years (9).

Turning the focus on the identification and subsequent special evaluation and surveillance of subjects at special risk for the development of CRC seems to be a promising and important approach to improve the success rates of prevention of CRC.

As the willingness of patients to participate in CRC screening programs is one of the major problems of screening programs and family history of CRC represents a specific situation due to a direct personal experience with the disease, the aim of this study was to evaluate the interest of FDRs of CRC patients to take part in a screening for CRC. Further we were interested in the incidence of CRC and colorectal adenomas (CRA) in a group of FDR and we aimed to compare it with the findings in a control group with a negative family history.

Methodology

Colorectal cancer patients

The population of CRC patients consisted of 235 cases (index patients) diagnosed at the endoscopy unit of the 1st Department of Internal Medicine, Faculty Hospital Bratislava in years 1984–2001. All colorectal carcinomas were confirmed by histology. Clinical, colonoscopic and histological characteristics of the index patients are summarized in Table 1.

Questionnaire and invitation for preventive examination

All index patients were mailed a letter with an invitation for their first degree relatives, who had not been examined before and were over 40 years or 10 younger than the youngest case of CRC in the family, to participate in a screening program. The letter was accompanied by a questionnaire about the family history of CRC (including questions about the age at diagnosis, the location of disease, therapy and therapy outcome) and other malignancies in the family.

Colonoscopy screening

Those FDR who were interested in a preventive examination were invited for a visit by telephone call. During the first visit the relative was given detailed information about the screening methods for colorectal cancer, their importance and effectiveness. In many instances family history provided in the questionnaire was reviewed and completed during this first visit. If the patient agreed the colonoscopy was performed on the second visit. Genetic testing for HNPCC was considered if a malignancy was found and Bethesda guidelines for genetic testing. Control patients were selected from patients referred to our centre for first colonoscopic examination for either screening colonoscopy or for other not acute symptoms. All control patients were matched by sex and age to the case patients. Exclusion criteria were positive family history for colorectal cancer, known ulcerative colitis, Crohn's disease or familial adenomatous polyposis, severe gastrointestinal or systemic symptoms and enterorhagia (except for known hemorrhoids).

Statistical analysis

All statistical analyses were performed using SPSS 12.0 statistical software package. Statistical analyses were considered significant at the p-value lower than 0.05.

Categorical variables were cross-tabulated and compared using $\chi 2$ tests with Yates correction or Fisher exact test as appropriate. For each statistically positive result odds ratio's (OR) with 95 % confidence intervals (CI) were calculated. Continuous variables were analyzed by student t-test or ANOVA analyses. A Kaplan-Meier survival curve S(t) was calculated for the time free of colorectal adenomatous polyps (t, years) based on age at diagnosis in relatives and evaluated by two-tailed Log-rank test.

Results

Response rates

The questionnaire was not delivered to 39 patients (16.6 %) mainly due to change of the address. Those with undeliverable

Tab. 2. Prevalence of malignancies in the first degree relatives of index patients with CRC.

Type of cancer	Father (n=30)	Mother (n=30)	Brother (n=97)	Sister	Daughter (n=80)	Son	Total (n=237)
Colorectal cancer	4	2	8	4	-	-	**18**
Stomach	1	2	1	-	-	-	**4**
Uterus	-	2	-	2	-	-	**4**
Lungs	1	1	1	-	-	-	**3**
Pancreas	-	1	-	1	-	-	**2**
Pharynx	1	-	-	-	-	-	**1**
Breast	-	1	-	-	-	-	**1**
Lymphoma	-	-	1	-	-	-	**1**
Hepatocelular	-	-	-	1	-	-	**1**
Prostate	1	-	1	-	-	-	**1**
Total	**8**	**9**	**12**	**8**	**0**	**0**	**36**

mail had, as expected, a significantly longer period since the diagnosis of colorectal carcinoma i.e. 9.4±5.9 years compared to those patients to whom the questionnaire was delivered 6.88±5.0 years (p=0.008). Thirty four of remaining 196 patients (17.3 %) responded to the questionnaire. Those who decided to participate in our research did not differ from those not responding in any characteristics listed in Table 1 or their combination.

Occurrence of malignancies in the families

Thirty four patients or their relatives completed in the questionnaire and provided us with the information about the occurrence of colorectal cancer and other malignancies in their families. We were able to collect information about 237 first degree relatives of these 34 patients. The data on the occurrence of CRC and other malignancies in these families are summarized in Table 2.

Fifty two out of 96 eligible FDRs meeting the indication criteria underwent a screening colonoscopy as discussed below. In this screening, we were able to diagnose another two asymptomatic colorectal cancers in two siblings of our index patients. These two CRC are included in the analysis of occurrence of CRC in families.

Presence of at least one first-degree relative with CRC in the family history was noted in 12 patients (35.3 %). The approximate expected number of patient with CRC with positive family history is 3.4 (upon an assumption that 10 % of the population has a positive family history). This percentage is significantly higher than would be expected (p=0.04; OR=4.2; 95 % CI 1.05–1.89).

Those CRC patients reporting a positive history of another family member were from larger families. The mean number of first degree relatives in the group of patients with positive family history was 6.3±3.4 as compared to 4.1±1.9 in the group of patients with negative family history; p=0.016.

Participation of relatives in the screening

Together there were 32 siblings and 64 children of 32 index CRC patients who fulfilled the indication criteria for screening i.e. were either older than 40 years or 10 years younger than the earliest diagnosis of CRC in the family. Eleven of 32 siblings (34.3 %) and 41 of 64 children (64.1 %) were interested to participate in the colonoscopy screening.

Colonoscopy screening among relatives and controls

Together 52 FDRs from 22 families underwent the screening procedure. From these there were 11 (26.2 %) siblings (5 brothers and 6 sisters) and 41 (73.8 %) children (21 sons and 20 daughters) of index CRC patients. The cohort of 52 control patients was examined in the same time period as the FDR screening cohort. Colonoscopic findings in these two groups are summarized in Table 3.

In the group of 52 FDR's the colonoscopy revealed a colorectal cancer in 2 asymptomatic patients (3.8 %) and one or more colorectal adenomatous polyps were diagnosed in 18 of 52 (34.6 %). As discussed below, both carcinomas occurred in families with multiple members affected with the colorectal cancer. In both families genetic testing for HNPCC was indicated (MSI testing followed by germline testing) and in one it turned out to be positive. In 18 patients a total of 53 polyps were diagnosed. Thirteen polyps (24.5 %) were located in the rectum 27 (50.9 %) in the left colon and 13 (24.5 %) in the right colon. In the control group there was only one colorectal cancer diagnosed (1.9 %) and a total of 10 polyps in 8 patients (15.4 %).

The difference in prevalence of colorectal adenomatous polyps in the study and control populations was statistically significant (p=0.04; OR 2.9; 95 % CI=1.04–8.40). Moreover there was a statistical difference (p=0.04) in the mean number of polyps per patients. In the study group the mean number of polyps was 2.9 per patient compared to 1.3 polyps in the control group. Although not statistically significant (p=0.07) there was also a tendency for more proximal location of polyps in the study group.

Finally we studied and compared the age dependent incidence of colorectal adenomatous polyp in the group of first degree relatives of CRC patients and control group. The results of Kaplan Meier analysis are shown in Figure 1. In the study group of FDRs we observed a significantly higher age-dependent incidence of adenomatous polyps compared to the control group (Log rank test p=0.036). In both groups the age-dependent incidence had a similar profile with a time shift of approximately 7 years as compared to the controls, i.e. the same incidence rate of CRA in the FDR was seen approximately 7 years earlier.

Tab. 3. Colonoscopic findings in family screening and control cohorts.

Colonoscopic findings	FDR of CRC patients (n=52)	Control group (n=52)	p value
Male/female	25/27 (48.1/51.9%)	25/27 (48.1/51.9%)	1.00
University degree	14 (26.9%)	8 (15.4%)	0.15
Mean age at diagnosis of CRC (years)	49.3+/-10.7	49.6+/-10.8	0.89
Normal findings	21 (40.4%)	24 (46.2%)	0.69
Adenomatous polyp diagnosed	18* (34.6%)	8** (15.4%)	**0.04**
Rectum	1	3	
Left sided	8	2	0.29
Right sided	3	1	
Left and right sided	6	2	
Mean number of polyps	2.9+/-1.3	1.3+/-0.5	**0.04**
Patients with 1 polyp	7 (38.9%)	6 (75.0%)	
Patients with 2 polyps	3 (16.7%)	2 (25.0%)	0.07
Patients with 3 or more polyps	8 (44.4%)	0 (0.0%)	
Colorectal cancer	2* (3.8%)	1** (1.9%)	1.0
Other findings			
Colitis	0 (0.0%)	6 (11.5%)	-
Diverticulosis	3 (5.8%)	5 (9.6%)	-
Haemorrhoids	10 (19.2%)	11 (21.2%)	-

**One of the patients from the screening group with CRC had also 7 CRA, the second one had also 1 small polyp*

***One of the patients from the control group with CRC had also 1 CRA*

Discussion

There has been a 17.3 % response rate to the questionnaires mailed to the patients with CRC. This number seems to be rather low compared to reported 40–60 % response rates to similar questionnaires published in other reports (10, 11). Probably the major difference between our method and those published in the literature is the time lag between the diagnosis of CRC and the delivery of questionnaires. In above mentioned studies the patient from a general population was addressed with a questionnaire inquiring about their willingness to participate in a screening program. In our study design it was not possible to use the advantage of a recent personal contact with the patient, because that would require a prospective study or a population based epidemiological study. The average time lag between the diagnosis of CRC and mailing the questionnaire in our study was 7.2 years. There are several possible reasons, why the patients did not respond. First, after such long time period the questionnaires did

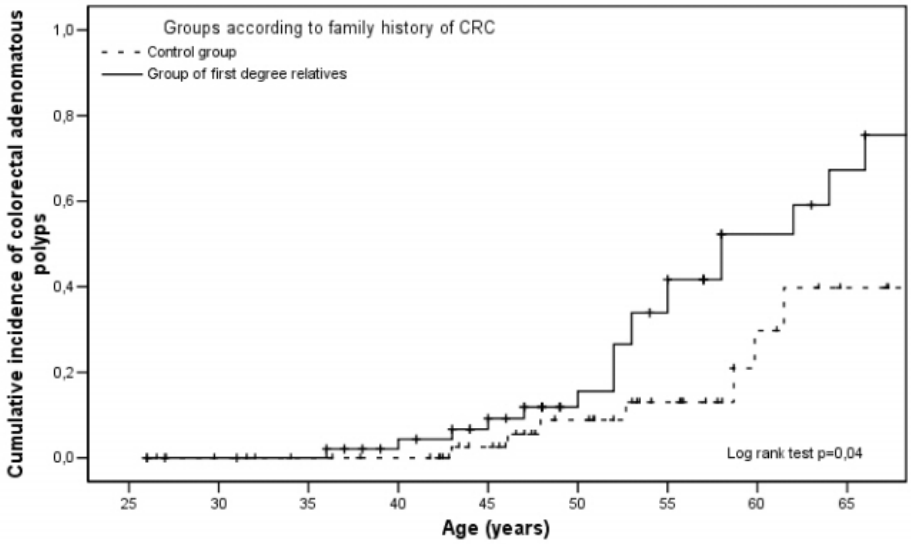

Fig. 1. Kaplan–Meier (1-survival) curve of age dependent incidence of colorectal adenomatous polyps in study and control groups.

not have to be delivered. Furthermore our study design allowed only addressing the patients diagnosed with CRC but not directly their relatives. Moreover most of the patients in the study population had a rather advanced age. Older individuals tend to have lower compliance for cooperation due to various factors (12). These might include health problems, social isolation and/or mental impairment. This rather low percentage of responders thus represents the major potential systematic bias for interpretation of analysis of familial history.

We found an interestingly high proportion of responding patients that had a positive family history of CRC in their first degree relatives (34.4 %). This number was significantly higher that would be expected. The possible and very suggestive interpretation of this finding is that patients with multiple experiences with CRC in their families were more interested to take part in screening that was offered to all family members. Compliance with CRC screening depends on several factors, including positive family history Individuals with first degree relatives diagnosed with CRC have been found to be twice as likely as others to be compliant with screening and especially more compliant with colonoscopic screening (13).

There are several factors that are discussed in this aspect. Relatives of patients with colorectal carcinoma might be motivated to participate in screening programs due to various reasons. First they might perceive a personal hazard as they recognise that shared genetic inheritance with affected family member might be involved. Second a personal experience with someone suffering from colorectal cancer imposes an emotional distress that can motivate to take part in a prevention screening. Although both factors and maybe even others might be involved, there is a lack of studies examining the issue of subjectively perceived risk in first degree relatives of CRC affected individuals. Especially the second component is not exclusive for relatives of CRC patients but concerns also their friends. Both factors however might be of importance in efforts to increase the effectiveness of prevention programs.

Our findings of an over-representation of patients with positive family history among those responding to our questionnaire are therefore consistent with previous similar reports. We have furthermore found out that once the patient or his relative responded to the questionnaire, most of his family members at risk were willing to take part in the offered screening program. Together there were 96 FDR older than 40 years (or 10 years younger than the youngest CRC case in the family) in these families and out of them 52 decided to participate (54.2 %). This finding further supports our conclusions that positive family history increases the motivation and interest for participation in prevention programs.

The question is how to utilise these findings in a screening program? This question has not yet been addressed thoroughly. However very recent report indicated that similar questionnaires using general practitioners records might be of high importance and many high-risk to moderate risk patients can be directly offered surveillance (14). Last but not least, the supposed higher motivation of relatives of CRC patients to participate in a screening program could be incorporated in awareness rising campaigns for colorectal cancer screening. Addressing specifically this subgroup of population with appropriate strategy could be very effective.

Although the control and study cohort undergoing colonoscopy did not differ in demographic and clinical characteristics, the colonoscopic findings differed significantly. Taken together first degree relatives who were interested to participate in the screening program had significantly higher incidence of adenomatous polyps with the odds ratio of 2.9 (95 % CI=1.04–8.40) These findings support the results from large population based studies showing a higher risk for development of CRA in first-degree relatives of CRC patients (15–19). As adenomas are established precursors of colorectal cancer, the higher predisposition for occurrence of CRA in first-degree relatives allows us to presume also higher predisposition to colorectal cancer in this group (20).

To conclude, we have observed a high interest for screening colonoscopy among the first degree relatives of CRC patients. Addressing this high-risk group might therefore mean a significant improvement of population-based CRC screening programs and lead to higher participation rates. Our observations should be confirmed in a prospective trial.

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