Risk Factors for Colorectal Cancer: an Epidemiologic Descriptive Study of a Series of 333 Patients

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Abstract

Aim. The purpose of the research was to evaluate several risk factors for colonic neoplasia and to institute a specialized colorectal cancer (CRC) registry in the 3rd Medical and Surgical Clinics Cluj-Napoca.

Material and methods. The study comprised 333 patients,155 women, mean age 61,32±12,42 years and 178 men, mean age 64,31±10,39 years, admitted to the 3rd Medical Clinic and 3rd Surgical Clinic Cluj-Napoca and diagnosed with CRC between January 2001 – September 2003. The diagnosis was made on the basis of clinical, endoscopical and histopathological findings. Age, geographical patterns, tumor location, family history, personal history and several lifestyle factors: dietary habits (intake of fat and red meat), long term smoking (more than 20 years), heavy alcohol consumption were analyzed. Evaluation was made using family history and epidemiologic lifestyle questionnaires.

Results. CRC occurred more frequently in the 7th decade. There was a strong correlation between age and CRC development. In the 5th decade, females developed CRC more frequently than males. The median age for developing right-sided tumors was significantly higher in males. Patients living in an urban area were dominant (69%). Family history was present in 1/3 of females and 1/4 of males. Personal history of colon polyps was more common in men, particularly among smokers for more than 20 years and among those with an excessive intake of fat. The cholecystectomized women had an increased frequency of sigmoidian tumors. All the patient's information was included in a specialized colon cancer registry.

Conclusion. High fat intake and cigarette smoking favour colon polyp development.CRC development and location of the tumor are associated with an older age (in men) and personal history of cholecystectomy (in women). Inheritance was significant in our study group.

Romanian Journal of Gastroenterology
September 2004 Vol.13 No.3, 187-193
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Key words

Colorectal cancer – risk factors - epidemiology

Rezumat

Scopul acestei lucrări este evaluarea prezenţei unor factori de risc mai frecvent incriminaţi în dezvoltarea cancerului colorectal (CRC) şi întocmirea unui registru de cancer colorectal al Clinicilor Medicală III şi Chirurgie III din Cluj-Napoca

Material şi metodă. Lotul studiat cuprinde 333 pacienţi, 155 femei cu vârsta medie de 61,32±12,42 ani şi 178 bărbaţi cu vârsta medie de 64,31±10,39 ani, internaţi şi diagnosticaţi cu CRC in Clinicile Medicală III şi Chirurgie III din Cluj-Napoca în perioada ianuarie 2001 - septembrie 2003. Diagnosticul s-a stabilit pe baza criteriilor clinice, endoscopice şi histologice. S-au analizat: vârsta, mediul de provenienţă, localizarea tumorilor, istoricul familial, istoricul personal şi anumiţi factori legaţi de stilul de viaţă: diferite obiceiuri alimentare (dieta bogată în grăsimi şi carne roşie), fumatul peste 20 de ani, consumul excesiv de alcool. Evaluarea s-a efectuat cu ajutorul unor chestionare de istoric familial şi al unor chestionare epidemiologice referitoare la stilul de viaţă.

Rezultate. CRC a fost mai frecvent întâlnit în decada a 7-a de vârstă. A existat o corelaţie puternic pozitivă a CRC cu vârsta. Vârsta medie de dezvoltare a tumorilor proximale a fost semnificativ mai crescută la bărbaţi. Au predominat net pacienţii provenind din mediul urban (69%). Agregarea familială a fost prezentă la 1/3 din femei si la 1/4 din bărbaţi. Istoricul personal de polipi colonici a fost mai frecvent întâlnit la bărbaţi, în particular la fumătorii peste 20 de ani şi la consumatorii de lipide in exces. Femeile colecistectomizate au dezvoltat mai frecvent tumori cu localizare sigmoidiană. Informaţiile cu privire la pacienţi au permis întocmirea unui registru de cancer colorectal.

Concluzii. Fumatul şi excesul de lipide favorizează dezvoltarea polipilor. Dezvoltarea CRC şi localizarea tumorilor este asociată cu vârsta înaintată (la bărbaţi) şi cu istoricul personal de colecistectomie (la femei). Ereditatea a fost semnificativă la lotul studiat.

Introduction

It is now clear that the development of colorectal cancer (CRC) represents an interaction between the genome of the colorectal epithelial cell and different environmental factors.The role of genetic factors and their interaction with the environment in the evolution of CRC are issues yet to be defined.

In Europe, an estimation of cancer incidence and mortality, using World Health Organization (WHO) and National Cancer Registries data, shows that CRC is the second most common neoplasia after lung cancer in males and breast cancer in females (1). Ethnic and racial studies completed in the last decades suggest that environmental factors play a major part in the etiology of the disease. An essential feature of CRC is the wide geographic variation in its incidence.These differences appear to be caused principally by life style and dietary habits.

We carried out an epidemiological descriptive study, in order to evaluate different variables.

Material and methods

The distribution of the variables and their general characteristics is based on existing data according to the relationship of people, place and time. People indices include demographic factors (age, sex), race, occupation, life style followed by variables like dietary habits, alcohol consumption etc. Familial factors are associated with inheritance, environment, customs and traditions. Place characteristics refer to the geographic distribution of the disease, including variations between zones or regions (urban, rural). The characteristics of time allow the comparison of the actual frequency of the disease with those in previous decades.

The study consisted of 333 patients with CRC, 155 females, mean age 61.3 ± 12.4 years and 178 males, mean age 64.3± 10.3 years. The patients were admitted to the 3rd Medical and Surgical Clinics and diagnosed with CRC between January 2001-September 2003, on clinical, endoscopical and histopathological criteria. The variables examined in our study included age, residence, tumor location, family history, personal history, lifestyle factors (dietary habits, smoking, heavy alcohol consumption). Information on the diagnosis, tumor location and histologic characteristics, were provided from the endoscopy files and department of pathology. Patients with family history were evaluated using questionnaires which request information on all first-degree relatives – parents, siblings or children, as well as details of second and third degree (see supplement). A control group of patients without CRC or other tumors (178 males and 155 females matched as sex and age) was also evaluated regarding the family history. The life style of study patients was evaluated using epidemiologic questionnaires structured on sections (dietary habits, medications, smoking, alcohol consumption, physical activity, antropometrics data –height,weight, body mass index-BMI) (see supplement).

Excessive consumption of foods was assessed (high fat and red meat consumption on one hand, and high fiber intake on the other). We could not perform a quantitative assessment,therefore, the comparison was made by estimating the number of meals containing fat or red meat / dayly and weekly. The patients were divided into three groups: 1.those with an excessive intake of animal fat and red meat at least once a day, 2. patients with a mixed diet (red/white meat, 2-4 times/week, milk, eggs, sweets, fruit, vegetables), 3. patients with an increased fiber intake and low consumption of fat and red meat.

Statistical analysis was performed using the Student"t" test, chi^2 test and correlation coefficient (r). A value of $p< 0.05$ was considered statistically significant.

Results

Age. In the study group we found a statistically significant difference for males developing CRC at an older age (p=0.0187). The age specific prevalence rates of CRC, globally and for both sexes are shown in Table I.

Table I Age specific prevalence rates of CRC

Decades (years)	Total %	Males %	Females %
21-30	4 (1.2)	1 (0.5)	3 (1.9)
31-40	13 (3.9)	6 (3.4)	7 (4.5)
41-50	20 (6)	6 (3.4)	14 (9)
51-60	78 (23.4)	42 (23.6)	36 (23.2)
61-70	129 (38.7)	71 (39.9)	58 (37.4)
71-80	81 (24.3)	46 (25.8)	35 (22.6)
81-90	8 (2.4)	6 (3.4)	2 (1.3)

An analysis of the association between the patient's age and CRC development indicated a good positive correlation for the 20-70 years interval (r=0.932). Separate analysis, for both age groups, showed the same positive correlation for the same interval, in women (r=0.952) and in men (r=0.914).

At the same time, we evaluated the CRC development in each decade, for both sexes. We found a significant difference in females,who developed CRC more frequently in the 5th decade compared to males (p=0.0297). No significant differences were found in the other decades.

Demographics. In the study group, a notable difference between rural (31%) and urban areas (69%) was seen. This was significantly higher comparatively with the distribution in the Romanian population (p=0.0227).

Tumor location. We investigated the tumor distribution by anatomic sites (Table II). In 27% of patients, the tumors were located in the rectum, followed by location in the sigmoid. No significant differences between males and females were evidenced.

The tumor distribution by sex, mean age and the main segments of the colon is shown in Table III.

Table II Distribution of tumors by anatomic sites

Sex	Cecum	Ascend	Right flexure	Transv.	Left flexure	Descend.	Sigm	RS junction	Rectum
B	4	17	8	10	8	16	34	28	54
F	6	14	12	9	7	13	37	20	36
Total	10	31	20	19	15	29	71	48	90
Total%	3	9.3	6	5.7	4.5	8.7	21.3	14.4	27

Table III Distribution of tumors by sex, mean age and colon segments

Colon segment	Males N.	Mean age Males	Females N.	Mean age Females	Total N.	Mean age Total
RC	29	68.15	32	62.06	61	65.10
LC	58	64.10	57	62.14	115	63.12
RS+R	82	63.24	56	61.83	138	62.50

RC –right colon , LC- left colon , RS- rectosigmoidian junction, R - rectum

Similar values for the mean age in both sexes were found, with only one exception: the males with right-sided colon tumors had a significantly higher mean age (p=0.0407).

Family history. From the 333 patients included in the study, 92 (27.6%) had a family history of cancer in the first and second degree relatives, of whom 24 (7.2%) had a family history of CRC and 68 (20.4%) had a family history of other cancers – genital (endometrial, cervix, ovarian, breast, prostate), gastric,urinary tract, liver, bone, larynx, lung, leukemia. According to sex, one third of females (30.3%) and one fourth of males (25.3%) had a family history of cancers (CRC or others) in the first and second degree relatives. This was significantly higher than in the control group: only 22 (14.2%) females (p=0,0016) and 18 (10.1%) males (p=0,00017) had a family history of cancer.

No significant differences between the males and females from the study group regarding family history of CRC (p=0.518) or other cancers (p=0.530) were present.

Personal history. We evaluated the patients with one or more associated polyps at the time of CRC diagnosis, globally and by sex. In the study group, 70 (21%) patients had one or more polyps throughout the colon associated with CRC, of whom 49 were males (27.5%) and 21 were females (14.2%). Personal history of polyps was significantly more frequent in the male group (p=0.00176).

In the study group, 8 patients had synchronous tumors (2.4%), of whom 4 were females (2.6%) and 4 were males (2.2%) and 4 patients (1.2%) developed metachronous tumors in the period that the data were collected (Jan 2001- June 2003) – 1 man (0.6%) and 3 women (1.9%). No significant differences between males and females were present (p=0.829 for synchronous tumors and p=0.267 for metachronous tumors). Nine patients (2.7%), of whom 6 females (3.9%) and 3 males (1.7%) had a personal history of other cancers (p=0.222).

The presence of inflammatory bowel disease was very low; only two patients (0.6%) had a personal history of ulcerative colitis (a 30 year old female patient and a 62 year old male patient). None of the patients had a personal history of Crohn's disease.

Forty-four patients (13.2%), 27 females (17.4%) and 17 males (9.5%) had been cholecystectomized. The females with a personal history of cholecystectomy developed significantly more frequently sigmoidian tumors compared to the others (p=0.0054). We did not observe a significant association between cholecystectomy and tumor location in males.

Life style. We investigated the patient's distribution by body mass index (BMI>26 kg/m^2) and different dietary habits (Table IV).

Table IV Distribution of patients by BMI and dietary habits

Patients	BMI> 26 kg/m^2	High fat and red meat intake	Mixed diet	High fiber consumption
Males	52	70	82	26
%	29.4	39.3	46	14.6
Females	42	26	100	29
%	27.1	16.8	64.5	18.7
Total	94	96	182	55
%	28.2	28.8	54.4	16.5

According to BMI, no significant differences between males and females were found (p=0.660). The heavy intake of fat / red meat, was significantly increased in male patients (p<0.05). Intake of various food was more frequent in the female group (p=0.0184). There was no significant differences regarding the fiber intake (p=0.314). The males with an excessive consumption of fat / red meat, developed polyps associated with CRC more frequently compared to the others (p<0.05).

Excessive alcohol consumption (more than 2 units / day in males and 1 unit / day in females) was recognized by 60 patients (18%), 55 males (30.9%) and 5 females (3.2%).

A statistically significant difference regarding male patients was found ($p<0.05$). There were no significant differences regarding polyp development in males with a regular alcohol consumption compared to the others ($p=0.13637$).

Long-term smoking, more than 20 years was present in 80 out of 178 males (44.3%) and 15 from 155 females (9.7%), significantly higher in males ($p<0.05$). Among smokers for more than 20 years, associated polyps development was more frequent compared to nonsmokers ($p=0.0429$).

Discussion

CRC can be defined as a disease of elderly people. Although several recent studies have suggested a decrease in the age of CRC development, the incidence remains relatively low under 40 years of age. (2,3). Some authors (4) show that the incidence and mortality of CRC rise exponentially by age, but incidence shows a slow increase over 70 years of age. A similar situation was found in our study too. Other studies (5) show a reduced number of cases in young patients (about 1% for the first two decades and 2-6% until 40 years of age); our observations were similar.

CRC is recognized as the "western countries" disease. Many studies have shown notable differences between urban and rural areas, with a predominance of the urban population. Our observations confirm this, 69% of our patients living in urban areas. This is significant for our study group, because in Romania, the urban population represents 53.3% and the rural one, 46.7% (6).

The tumor distribution throughout the large intestine depends on genetics and environmental factors involved in colorectal carcinogenesis, and on the sex, race and the patient's age (7-9). Several studies regarding colorectal carcinoma incidence have shown significant differences between colon and rectal cancers. Other reports have suggested that the frequency of right-sided colon cancers increases in elderly patients (over 65 years of age).Our observations have been similar, the age of male patients with right colon tumors being significantly higher in our study.

Inheritance plays a special role in CRC development, but most patients do not have any apparent evidence of genetic disorders. About 20% of all CRC are estimated to be hereditary. Familial CRC accounts for about 15% of all (10,11), HNPCC (Hereditary Non Polyposis Colorectal Cancer) for about 5%, and FAP (Familial Adenomatous Polyposis) for about 1%. The first step in a patient's evaluation and follow-up is a detailed review of the family history, to determine the number of relatives affected, their relationship to each other, the age at which the CRC was diagnosed, the presence of multiple primary colorectal cancers, and the presence of any other cancers (12,13). In our study, a positive family history for all cancers was present in 30.3% of females and 25.3% of males, and a positive family history for CRC in 7.2% of patients.

Epidemiologic studies have shown that a personal history of adenomatous polyps ensures an increased risk of developing colon cancer.The malignancy rate is higher for those with adenomas larger than 1 cm, villous architecture and severe dysplasia (14-16). It is difficult to estimate the real number of individuals with a personal history of adenomatous polyps in the general population. About 30% of people living in western countries are believed to have colorectal polyps. Many patients have adenomas discovered through screening examination, workups of colorectal symptoms, or other evaluations. In many cases, at the moment of diagnosis, the polyps became dysplastic or malignant. During the colonoscopy examination, it has been shown that adenomatous polyps can also accompany colorectal carcinoma, and this suggests their presence in the personal history of patients. A similar situation was found in our study group, but it is more likely that results may have been underestimated (we could not perform total colonoscopy in patients with stenosing tumors; data regarding the postoperative total colonoscopy in these patients are not complete, because a part of them were lost from follow-up).

Individuals with one colorectal carcinoma have an increased risk of developing a second carcinoma, either simultaneous-synchronous carcinomas, or subsequent-metachronous carcinomas.The frequency of more than one tumor in the same individual, ranges between 2 and 6 per cent (0.7 to 7.6 per cent for synchronous cancers and 1.1 to 4.7 per cent for metachronous cancers), (17-22), our results being similar (2.4% synchronous cancers and 1.2% metachronous cancers). It is more difficult to estimate the actual incidence of metachronous cancers; the risk is likely to be higher in patients who are younger at the time of the first tumor.

Inflammatory bowel disease is well recognized as a risk factor for the development of CRC. In ulcerative colitis, the risk is higher in patients with a disease duration longer than 10-15 years and those with pancolitis (23,24). Reports showing a relationship between colorectal cancer and Crohn's disease are controversial. Several studies have been reported; some which showed patients who developed CRC (no different from that expected in the general population) (25,26); others suggested an increased risk for the patients.

It has been suggested that patients who have undergone cholecystectomy may be at a greater risk of developing colon cancer. However, this association is highly controversial. An increased proliferative activity has been demonstrated in the distal colonic mucosa of cholecystectomized patients (27), and an increased frequency of tubular adenomas has been found in patients with a postcholecystectomy interval greater than 10 years (28). Other studies have reported an increased risk of proximal colon tumors (29-30) or distal adenomas (31). Our observations show that cholecystectomized female patients had an increased frequency of sigmoidian tumors.

Life style and particularly dietary habits have been recognized as a strong factor in colon carcinogenesis, but the clinical evidence for such an association is contradictory (32-34). In Western countries with high incidence rates of colorectal cancer, on average, fat composes 40 to 45% of total caloric intake. Red meat consumption is also correlated with an increased risk of CRC. Prospective studies have suggested that a daily intake of 100 gr red meat is associated with an increased risk of 12-17%. Although we could not exactly calculate the amount of fat or meat consumed by each patient, we observed a significant association between excessive consumption and polyp development in males.

Many studies have demonstrated that heavy alcohol consumption is an independent risk factor in adenoma development (35,36). We did not find a statistically significant association between alcohol consumption and polyp development, as evaluated by questionnaires. But it is known that quantities of alcohol from the patient's history are mostly not very reliable.

On the other hand, it is well-known that long-term cigarette smoking over 20 years or more has been found to be a risk factor for many cancers, including colorectal neoplasia (37,38). Our observations were similar: in the study group, males who had smoked for more than 20 years, developed adenomatous polyps more frequently compared with nonsmokers.

The worldwide increase in incidence of CRC, according to WHO recommendations, supposes a number of measures and interventions that are applied for prevention, early diagnosis, treatment, posttherapeutical rehabilitation and patient care. Presently, because a large number of digestive neoplasms are diagnosed in Gastroenterology Departments, and a significant percentage is represented by CRC, we proposed the elaboration of a specialized Colon Cancer Registry in the 3rd Medical and Surgical Clinics which should include all patients admitted and diagnosed with colorectal cancer beginning with 1st of January 2001. The Registry included subsequent categories: patients with sporadic CRC, HNPCC, FAP and other rare hereditary syndromes (39).

Supporting the development of cancer registries is important, both for health care organisers and for medical assistance financiers. A proper functioning of the cancer registries is essential for monitoring the efficiency of any screening programme and for early cancer diagnosis.

Conclusions

Age represents a risk factor for CRC development and for the location of colon tumors. A positive family history was significantly present in both sexes. Polyp development was influenced by excessive fat consumption and long-term cigarette smoking in males. Personal history of cholecystectomy was associated with an increased frequency of sigmoid tumors in females.

Our epidemiological study has attempted to offer an overview regarding a major problem of public health. The descriptive data may be used for efficient education, screening and prevention programs, in particular, subgroups of the population.

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Supplement

Family History Questionnaire for HNPCC
(adapted from Cancer Center of Boston Facility)

First Degree Relatives	Colon Cancer		Endometrial Cancer		Other Cancers at any age (ovarian, gastric, kidney/tract, gallbladder, central nervous system, small bowel)
	Before age 50	After age 50	Before age 50	After age 50	
Yourself Mother Father Sister (s) Brother (s) Daughter (s) Son (s)					
Mother's side Grandmother Grandfather Aunt (s) Uncle (s) Cousin (s)					
Father's side Grandmother Grandfather Aunt (s) Uncle (s) Cousin (s)					

Epidemiologic Questionnaire

SECTION A. Personal medical history, medication, screening
A1. Have you ever had a test for blood in your stool called a smear test or a Hemocult ? When did you have this test and what were the reasons ?
A2. Have you ever had a sigmoidoscopy ? When did you have this test and what were the reasons ?
A3. Have you ever had a colonoscopy ? When did you have this test and what were the reasons ?
A4. Have you been diagnosed with polyps in your colon or rectum?
A4a. When did your doctor first tell you that you had a polyp ?
A4b. Do you know if your polyps were benign, adenomatous or malignant ?
A4c(1). When did you first have the polyp(s) removed ?
A4c(2). Have you had a polyp removed more than once ?
A4c(3). When did you last have the polyp(s) removed ?
A5. Has a doctor ever told you that you had familial adenomatous polyposis (FAP) ?
A6. Has a doctor ever told you that you had inflammatory bowel disease (Crohn's disease or ulcerative colitis) ?
A7. Has a doctor ever told you that you had irritable bowel syndrome (IBS) ?
A8. Has a doctor ever told you that you had diverticular disease ?
A9. Have you ever had any of your large bowell or colon removed (total or subtotal colectomy) ?
A10. Did you have your gallbladder removed ?
A11. Has a doctor ever told you that you had diabet or high cholesterol/ triglycerides in your blood ?
A12. Has a doctor ever told you that you had any type of cancer?
A13. Have you ever taken the following medication at least twice a week for more than a month ?
A13a. Aspirin, Acetaminophen, Ibuprophen-based medication ?
A13b. Bulk forming laxatives or other laxatives ?
A13c. Multivitamin pills or folate pills ?
A13d. Separate calcium pills or tablets, not including antacids ?
A13e. Calcium-based antacids ?
A13e(1). When you were taking regularly, how often did you take it?
A13e(2). How long, in total, have you taken (medication) ?

SECTION B. Menstruation, reproductive history, menopause
B1. How old were you when you had your first menstrual period?
B2. Have you ever been pregnant ? (including miscarriages, stillbirths, tubal pregnancies and abortions)
B3. Have you ever used birth control pills or other hormonal contraceptives for at least a year ?
B4. In total, how long did you take these hormonal contraceptives?
B5. Have you had a menstrual period in the last 12 months ? That is a natural menstrual period, or one that occurred when you were taking hormonal contraceptives or hormone replacement therapy?
B6. Have you had any gynecologic surgery ? (hysterectomy, one or both ovary removed)
B7. Have you ever used a pill or patch form of hormone replacement therapy?

SECTION C. Alcohol consumption
C1. Did you ever consume any alcoholic beverages at least once a week for 6 monhs or longer ?
C1a. In your 20s, did you ever consume beer or hard cider at least once a week for 6 months or longer?
C1b. In your 20s, did you ever consume spirits, mixed drinks or cocktails at least once a week for 6 months or longer ?
C1c. In total, how long did you consume alcoholic beverages ?

SECTION D. Smoking
D1. Have you ever smoked at least one cigarette a day for 3 months or longer ?
D1a. When did you first start smoking at least one cigarette / cigar / pipe for three months or longer ?
D1b. During periods when you smoked regularly**,** how many cigarettes did you typically smoke in a day ?
D1c. Do you currently smoke at least one cigarette a day ?
D1d. Did you ever stop and restart smoking during periods when you smoked regularly ?
D1e. How many years, in total, did you smoke ?

SECTION E. Diet
E1. On average, how often did you eat a serving of fruit ?
E2. On average, how often did you eat a serving of vegetables ?
E3. On average, how often did you eat a serving of red meat ?
E4. How often did you eat a serving of chicken / fish ?

SECTION F. Height and weight
F1. About how tall are you, without your shoes on ?
F2. How much did you weigh about two years ago ?
F3. How much did you weigh when you were about 20 years old ?
F4. Presently, how much do you weigh ?

SECTION G. Physical activity
G1. Did you walk for at least 30 minutes a week for 3 months or longer ?
G1a. For how many months of the year did you do this ?
G2. Did you practice different sports (jogging, cycling, running, swimming, football, rugby) for at least 30 minutes a week for 3 months or longer ?
G2a. For how many months of the year did you do this ?
G3. Did you do any strenuous tasks in or around the house for at least 30 minutes a week for 3 months or longer ?
G3a. For how many months of the year did you do this ?
G4. What was your usual occupation ?

SECTION H. Demographics
H1. What is the highest level of education that you completed ?
H2. In which country were you born ?
H3. Where do you live (urban / rural area) ?
H4. What is your race or ethnicity ?
H5. Have you or your family participated in other research studies of familial cancer ?