

Dietary habits of colorectal neoplasia patients in comparison to their first-degree relatives

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Abstract

AIM: To compare the dietary habits between colorectal neoplasia patients, their first-degree relatives, and unrelated controls.

METHODS: From July 2008 to April 2011, we collected epidemiological data relevant to colorectal cancer from patients with colorectal neoplasias, their first-degree relatives, and also from a control group consisting of people referred for colonoscopy with a negative family history of colorectal cancer and without evidence of neoplasia after colonoscopic examination. The first-degree relatives were divided into two groups following the colonoscopic examination: (1) patients with neoplasia or (2) patients without neoplasia. Dietary habits of all groups were compared. A χ^2 test was used to assess the association between two dichotomous categorical variables.

RESULTS: The study groups consisted of 242 patients

with colorectal neoplasias (143 men, 99 women; mean age: 64 ± 12 years) and 160 first-degree relatives (66 men, 94 women; mean age: 48 ± 11 years). Fifty-five of the first-degree relatives were found to have a neoplastic lesion upon colonoscopy, while the remaining 105 were without neoplasia. The control group contained 123 individuals with a negative family history for neoplastic lesions (66 men, 57 women; mean age: 54 ± 12 years). Two hypotheses were tested. In the first, the dietary habits of first-degree relatives with neoplasia were more similar to those of patients with neoplasia, while the dietary habits of first-degree relatives without neoplasia were similar to those of the control group. In the second, no sex-related differences in dietary habits were expected between the particular groups. Indeed, no significant differences were observed in the dietary habits between the groups of patients, controls and first-degree relatives with/without neoplastic lesions. Nevertheless, statistically significant sex-related differences were observed in all groups, wherein women had healthier dietary habits than men.

CONCLUSION: In all groups examined, women had healthier dietary habits than men. Modification of screening guidelines according to sex may improve the efficiency of screening programs.

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Key words: Colorectal neoplasms; Family; Food habits; Risk factors; Mass screening

Core tip: We compared the dietary habits of patients with neoplasia (patients and their first-degree relatives with neoplasia) and without neoplasia (first-degree relatives without neoplasia and an unrelated control group). We did not identify significant differences in dietary habits between the groups; however, we did identify statistically significant differences between the

dietary habits of men and women in all groups. In all groups, women had healthier dietary habits. Modification of screening guidelines according to sex may improve the efficiency of screening programs, although further studies are needed to support this hypothesis.

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INTRODUCTION

Colorectal cancer is the second leading cause of cancer-related death in developed countries. The Czech Republic has the highest prevalence of colorectal cancer in the world. In 2008, the incidence of colorectal cancer in the Czech Republic was 94.2/100000 men and 61.8/100000 women^[1]. It is well established that colonoscopic screening reduces both the occurrence and mortality of colorectal cancer^[2]. In 2000, the Czech Republic introduced a nationwide cancer-screening program that included fecal occult blood testing of people over 50 years of age. The program was then updated in 2009 to include the possibility of a primary colonoscopy screening for those over 55 years of age^[3,4].

Colorectal neoplasias (CRN) are associated with non-hereditary as well as hereditary risks. Colorectal cancer is the most common familial form of cancer. More than 30% of cases can be attributed to hereditary causes, of which only 5% are due to hereditary cancer syndromes such as familial adenomatous polyposis syndrome and hereditary non-polyposis colorectal cancer^[5]. First-degree relatives (FDR) of patients with CRN (either colorectal cancer or advanced adenomas) show up to a 4-fold increased risk for CRN when compared with the general population and are at increased risk for advanced or multiple adenomas^[6-9].

Non-hereditary risk factors for colon cancer include advanced age, male sex, alcohol consumption and smoking^[10-12]. Dietary factors, such as elevated red meat consumption and low intake of fruit, vegetables, dairy products and dietary fiber, have been associated with an increased risk for CRN^[13]. Obesity, sedentary lifestyle, inflammatory bowel diseases and several other conditions such as acromegaly, diabetes mellitus and ischemic heart disease have also been shown to increase risk for colon cancer^[14-17].

The goal of this study was to compare the dietary habits of patients with CRN and a control group with the dietary habits of FDR with regard to the findings obtained after a colonoscopy screening. The first tested hypothesis was that dietary habits of FDR with neoplasia are similar to those of patients with CRN and that the dietary habits of FDR without neoplasia are similar to

those of the control group. The second tested hypothesis was that there are no sex-related differences of dietary habits between the particular groups.

MATERIALS AND METHODS

Study subjects and clinical data

From July 2008 to April 2011, we collected epidemiological data relevant to colorectal cancer, both from patients with CRN and their FDR as well as from a control group. Epidemiological data, including smoking status (current/former *vs* never), fat intake (low *vs* high), body mass index (BMI; < 30 *vs* ≥ 30 kg/m²), beer consumption (daily/occasionally *vs* never), consumption of dairy products, fruits, vegetables and red meat (daily *vs* less frequent) and education attainment (primary *vs* secondary/tertiary), were collected from the patients with CRN, FDR and controls by a medical doctor. A single specialist in gastroenterology and nutrition performed the interview about the respondent's dietary habits (the amounts of red meat, fat, dairy products, *etc.*) and made a categorization according to the answers (high intake/low intake in each category). Collection of epidemiological data was part of The Family Project, a unique direct medical counseling project targeting FDR that took place at a single center (non-university), Hospital Frydek-Mistek. The goals of the project were to promote proper colonoscopic surveillance of FDR and to identify FDR at highest risk for CRN. The project was approved by the local ethics committee. All participants signed an informed consent. Simultaneously, an informative campaign was launched in the local media to promote and support public awareness of the project.

FDR were referred to colonoscopic examinations and, dependent on the findings, were divided into FDR with or FDR without neoplasia. The control group contained people with a negative family history that had been referred for colonoscopy and were confirmed to be without neoplasia according to the findings from the colonoscopic examination.

Statistical analysis

Ages are presented as mean \pm SD. The dietary habits of all groups (patients with CRN, FDR with neoplasia, FDR without neoplasia, and control group) were compared. A χ^2 or Fisher's exact test was used to assess the association between two dichotomous categorical variables. Because of a heterogeneous representation of men and women in the FDR without neoplasia group, the men and women in all groups were compared separately.

RESULTS

The study groups consisted of 242 patients with CRN (143 men, 99 women; 64 ± 12 years) and 160 FDR (66 men, 94 women; 48 ± 11 years). Fifty-five patients in the FDR group were found to have neoplastic lesions upon colonoscopy, while 105 patients had no evidence of neo-

Table 1 Characteristics of the study groups *n* (%)

Characteristics	Patients	FDR with neoplasia	FDR without neoplasia	Controls	<i>P</i> value (χ^2)
Male sex	143/242 (59)	30/55 (56)	36/105 (34)	66/123 (54)	0.001
Obesity	68/242 (28)	15/55 (27)	23/105 (22)	27/123 (22)	0.478
Smoking, current/former	123/242 (51)	28/55 (51)	32/105 (30)	48/123 (39)	0.006
High fat intake	102/242 (42)	28/55 (51)	35/105 (33)	52/123 (42)	0.175
High red meat consumption	171/242 (71)	37/55 (67)	65/105 (62)	62/123 (50)	0.002
Beer consumption	155/242 (64)	35/55 (64)	54/105 (51)	83/123 (67)	0.070
Low intake of dairy products	81/242 (33)	22/55 (40)	27/105 (26)	45/123 (37)	0.219
Low fruit and vegetable consumption	72/242 (30)	14/55 (25)	25/105 (24)	46/123 (37)	0.128
Primary education attainment	134/242 (55)	15/55 (27)	27/105 (26)	47/123 (38)	0.001

FDR: First-degree relatives.

Table 2 Comparison of dietary habits between colorectal neoplasias patients and first-degree relatives with/without neoplasia (χ^2 /Fisher's exact test)

Comparison	Male patients <i>vs</i> FDR with neoplasia	Male patients <i>vs</i> FDR without neoplasia	Female patients <i>vs</i> FDR with neoplasia	Female patients <i>vs</i> FDR without neoplasia
Obesity	0.274	0.101	0.207	0.642
Smoking	0.975	0.001	0.727	0.645
High fat intake	0.247	0.912	0.451	0.460
High red meat consumption	0.621	0.738	0.956	0.474
Beer consumption	0.674	0.263	0.558	0.316
Low intake of dairy products	0.932	0.976	0.143	0.328
Low fruit and vegetable consumption	0.553	0.794	1.000	0.707
Education attainment	0.002 ¹	0.004 ¹	0.260	0.001 ¹

¹Higher education attainment in first-degree relatives (FDR).**Table 3** Comparison of dietary habits between controls and first-degree relatives with/without neoplasia (χ^2 /Fisher's exact test)

Comparison	Male controls <i>vs</i> FDR with neoplasia	Male controls <i>vs</i> FDR without neoplasia	Female controls <i>vs</i> FDR with neoplasia	Female controls <i>vs</i> FDR without neoplasia
Obesity	0.816	0.833	0.379	0.959
Smoking	0.281	0.078	0.289	0.578
High fat intake	0.281	0.090	0.375	0.685
High red meat consumption	0.284	0.187	0.052	0.041 ²
Beer consumption	0.045 ¹	0.749	0.456	0.535
Low intake of dairy products	0.618	0.522	0.215	0.315
Low fruit and vegetable consumption	0.049 ¹	0.780	1.000	0.794
Education attainment	0.095	0.188	0.444	0.199

¹Male controls have higher beer consumption and lower consumption of fruits and vegetables; ²Female controls have higher red meat consumption. FDR: First-degree relatives.

plasia. The control group consisted of 123 individuals with a negative family history of colon cancer and without neoplastic lesion following colonoscopic examination (66 men, 57 women; 54 ± 12 years). Characteristics of all groups are presented in Table 1.

We first tested the hypothesis that dietary habits of FDR with neoplasia are similar to those of patients with CRN and that dietary habits of FDR without neoplasia are similar to those of the control group. We next tested the hypothesis that there are no sex-related differences in the dietary habits between the particular groups. Comparisons of the groups are presented in Tables 2 and 3. The comparison between men and women in all groups is shown in Table 4.

In summary, both of our hypotheses were disproven. There were no significant differences in the dietary habits between the groups of patients, controls and FDR with/without neoplastic lesions. In all groups, however, there were statistically significant differences in the dietary habits between men and women, despite no differences in education attainment among them.

DISCUSSION

Our study was based on epidemiological data relevant to colorectal cancer that was obtained from patients with CRN, their FDR with neoplasia, FDR without neoplasia, and from a control group.

Table 4 Comparison of dietary habits in all groups: males *vs* females (χ^2 /Fisher's exact test)

Comparison	Males <i>vs</i> females			
	Patients	FDR with neoplasia	FDR without neoplasia	Controls
Obesity	0.023	0.472	0.659	0.831
Smoking	0.001	0.044	0.646	0.002
High fat intake	0.001	0.044	0.002	0.004
High red meat consumption	0.004	0.294	0.045	0.005
Beer consumption	0.001	0.102	0.001	0.001
Low intake of dairy products	0.024	1.000	0.026	0.028
Low fruit and vegetable consumption	0.016	0.537	0.098	0.001
Education attainment	0.756	0.104	0.727	0.508

FDR: First-degree relatives.

It is well established that risks for colorectal cancer can be either hereditary or non-hereditary. Non-hereditary risks are well described, as mentioned in the Introduction. There is also an association of colorectal cancer with the gut microbiome. Intestinal microbiota can transform food compounds into genotoxic agents, activate proto-oncogenes, or inactivate tumor suppressor genes^[18-20].

Genetic factors associated with an increased risk for CRN include low-penetrant susceptibility loci and specific polymorphisms. Certain genetic variants and polymorphisms in a number of genes have been associated with increased colon cancer risk; APC-I1307K, HRAS1-VNTR and MTHFR variants represent the strongest candidates for low penetrance susceptibility alleles^[21,22]. In genome-wide association studies, as many as 170 common but separate genetic variations have been implicated in CRN susceptibility^[23]. Based on current data, there are three main pathways of colorectal carcinogenesis: chromosomal instability, microsatellite instability, and hypermethylation^[24,25]. One important question, however, is how hereditary risks may be confounded by familial similarities in diet, physical activity level, or other environmental exposures.

Our first tested hypothesis was that the dietary habits of FDR with neoplasia are similar to those of CRN patients, while the dietary habits of FDR without neoplasia are different and more similar to those of the control group. We hypothesized that both the controls and FDR without neoplasia have a healthier lifestyle, while patients with CRN and FDR with neoplasia have worse, shared dietary habits. Because of the heterogeneous representation of men and women FDR without neoplasia, men and women in all groups were compared separately.

To our surprise, all groups had very similar dietary habits. We only observed a difference in the male CRN patients, where there were significantly more smokers than in the group of FDR males without neoplasia. It has been shown that smoking can increase risk of colorectal cancer by up to 18%^[12]. Paradoxically, male controls consumed more beer and lower amounts of fruits and vegetables than FDR males with neoplasia. Female controls consumed more red meat than FDR females without neoplasia. It is surprising that we did not observe any as-

sociation between poor dietary habits and occurrence of neoplasia in patients with CRN and their FDR with neoplasia, despite all the proven non-hereditary risk factors.

The second tested hypothesis was that there would be no sex-related differences between the particular groups. Regardless of the colonoscopic findings in all groups, however, males had worse dietary habits than females, despite no difference in education attainment between the men and women. It is well known that women gain more health resources in their screening programs. This fact, together with a known higher incidence of CRN in men, places men at a disadvantage. Thus, we can assume that the one-third higher incidence of colorectal cancer in men could be, in part, attributed to their less healthy lifestyle. Media campaigns should, therefore, be targeted to the male population, since there is a great need for improvement of their lifestyle and dietary habits.

This study has several limitations. The sample size of each group was relatively small and made up of individuals stemming from a population with the highest prevalence of colorectal cancer in the world. The results, therefore, are specific and may only apply to the Czech population surveyed. Diabetes mellitus was not observed throughout all groups (only in the CRN group of patients), so we cannot evaluate obesity and dietary habits with respect to diabetes mellitus. The mean ages across the groups examined were different and represent another weakness of the study.

In conclusion, we did not find significant differences between patients and their FDR with/without neoplastic lesions, although we did identify statistically significant differences between the habits of men and women in all groups. Women in all groups had healthier dietary habits. We propose that media campaigns should be targeted to the male population, due to a need to improve their lifestyle. Modification of screening guidelines according to sex may improve the efficiency of screening programs but further studies are needed to support this hypothesis.

COMMENTS

Background

Colorectal neoplasias are associated with hereditary and non-hereditary risks. Colorectal cancer is the most common familial form of cancer. First-degree relatives of patients with colorectal neoplasia, both colorectal cancer and advanced

adenomas, show up to a 4-fold increased risk for colorectal neoplasias when compared to the general population.

Research frontiers

It is important to understand how hereditary risks may be confounded by familial similarities in diet, physical activity level or other environmental exposures and whether it is possible to modify screening programs according to different risk groups to achieve higher efficiency in reduction of colorectal neoplasia.

Innovations and breakthroughs

The authors did not find significant differences between healthy controls, patients and their first-degree relatives with/without neoplastic lesions. The authors identified statistically significant differences between the dietary habits of men and women in all groups. In all groups examined, women had healthier dietary habits.

Applications

The authors propose a media campaign to target the male population and promote ways to improve the health-related aspects of their lifestyle. Modification of screening guidelines according to sex may improve the efficiency of screening programs, but further studies are needed to support this hypothesis.

Terminology

First-degree relatives: a family member who shares approximately 50% of their genes with a particular individual in a family; first-degree relatives include parents, offspring and siblings.

Peer review

This is an important epidemiological study comparing the dietary habits of persons with and without colorectal neoplasia. This is a well-designed study and has clinical applications for understanding the risks of colorectal cancer.

REFERENCES

- 1 **UZIS - Czech National Cancer Registry.** Cancer Incidence 2008 in the Czech Republic, 2008. Available from: URL: <http://www.uzis.cz/en/publications/cancer-incidence-2008>
- 2 **Manser CN, Bachmann LM, Brunner J, Hunold F, Bauerfeind P, Marbet UA.** Colonoscopy screening markedly reduces the occurrence of colon carcinomas and carcinoma-related death: a closed cohort study. *Gastrointest Endosc* 2012; **76**: 110-117 [PMID: 22498179 DOI: 10.1016/j.gie.2012.02.040]
- 3 **Zavoral M, Suchanek S, Zavada F, Dusek L, Muzik J, Seifert B, Fric P.** Colorectal cancer screening in Europe. *World J Gastroenterol* 2009; **15**: 5907-5915 [PMID: 20014454]
- 4 **Zavoral M, Suchanek S, Majek O, Seifert B, Dusek L.** National colorectal cancer screening programme – past, present and future. *Gastroent Hepatol* 2012; **66**: 345-349
- 5 **Winawer SJ, Schottenfeld D, Flehinger BJ.** Colorectal cancer screening. *J Natl Cancer Inst* 1991; **83**: 243-253 [PMID: 1994053]
- 6 **Johns LE, Houlston RS.** A systematic review and meta-analysis of familial colorectal cancer risk. *Am J Gastroenterol* 2001; **96**: 2992-3003 [PMID: 11693338]
- 7 **Neklason DW, Thorpe BL, Ferrandez A, Tumbapura A, Boucher K, Garibotti G, Kerber RA, Solomon CH, Samowitz WS, Fang JC, Mineau GP, Leppert MF, Burt RW, Kuwada SK.** Colonic adenoma risk in familial colorectal cancer—a study of six extended kindreds. *Am J Gastroenterol* 2008; **103**: 2577-2584 [PMID: 18671820 DOI: 10.1111/j.1572-0241.2008.02019.x]
- 8 **Wark PA, Wu K, van 't Veer P, Fuchs CF, Giovannucci EL.** Family history of colorectal cancer: a determinant of advanced adenoma stage or adenoma multiplicity? *Int J Cancer* 2009; **125**: 413-420 [PMID: 19358277 DOI: 10.1002/ijc.24288]
- 9 **Cottet V, Pariente A, Nalet B, Lafon J, Milan C, Olschwang S, Bonaiti-Pellié C, Faivre J, Bonithon-Kopp C.** Colonoscopic screening of first-degree relatives of patients with large adenomas: increased risk of colorectal tumors. *Gastroenterology* 2007; **133**: 1086-1092 [PMID: 17919484]
- 10 **Brenner H, Altenhofen L, Hoffmeister M.** Sex, age, and birth cohort effects in colorectal neoplasms: a cohort analysis. *Ann Intern Med* 2010; **152**: 697-703 [PMID: 20513827 DOI: 10.7326/0003-4819-152-11-201006010-00002]
- 11 **Cho E, Smith-Warner SA, Ritz J, van den Brandt PA, Colditz GA, Folsom AR, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Holmberg L, Kim DH, Malila N, Miller AB, Pietinen P, Rohan TE, Sellers TA, Speizer FE, Willett WC, Wolk A, Hunter DJ.** Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. *Ann Intern Med* 2004; **140**: 603-613 [PMID: 15096331]
- 12 **Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P.** Smoking and colorectal cancer: a meta-analysis. *JAMA* 2008; **300**: 2765-2778 [PMID: 19088354 DOI: 10.1001/jama.2008.839]
- 13 **Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, Overvad K, Olsen A, Tjønneland A, Clavel F, Boutron-Ruault MC, Kesse E, Boeing H, Bergmann MM, Nieters A, Linseisen J, Trichopoulou A, Trichopoulos D, Tountas Y, Berrino F, Palli D, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita HB, Peeters PH, Engeset D, Lund E, Skeie G, Ardanaz E, González C, Navarro C, Quirós JR, Sanchez MJ, Berglund G, Mattisson I, Hallmans G, Palmqvist R, Day NE, Khaw KT, Key TJ, San Joaquin M, Hémon B, Saracci R, Kaaks R, Riboli E.** Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst* 2005; **97**: 906-916 [PMID: 15956652]
- 14 **Renahan AG, Tyson M, Egger M, Heller RF, Zwahlen M.** Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008; **371**: 569-578 [PMID: 18280327 DOI: 10.1016/S0140-6736(08)60269-X]
- 15 **Chan AO, Jim MH, Lam KF, Morris JS, Siu DC, Tong T, Ng FH, Wong SY, Hui WM, Chan CK, Lai KC, Cheung TK, Chan P, Wong G, Yuen MF, Lau YK, Lee S, Szeto ML, Wong BC, Lam SK.** Prevalence of colorectal neoplasm among patients with newly diagnosed coronary artery disease. *JAMA* 2007; **298**: 1412-1419 [PMID: 17895457]
- 16 **Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, Stampfer MJ.** Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst* 1999; **91**: 620-625 [PMID: 10203281]
- 17 **Delhougne B, Deneux C, Abs R, Chanson P, Fierens H, Laurent-Puig P, Duysburgh I, Stevenaert A, Tabarin A, Delwaide J, Schaison G, Belaïche J, Beckers A.** The prevalence of colonic polyps in acromegaly: a colonoscopic and pathological study in 103 patients. *J Clin Endocrinol Metab* 1995; **80**: 3223-3226 [PMID: 7593429]
- 18 **Rowland IR.** The role of the gastrointestinal microbiota in colorectal cancer. *Curr Pharm Des* 2009; **15**: 1524-1527 [PMID: 19442169]
- 19 **Bures J, Horák V, Fixa B, Komárková O, Zaydlar K, Lonský V, Masurka V.** Colicinogeny in colorectal cancer. *Neoplasma* 1986; **33**: 233-237 [PMID: 3520352]
- 20 **Davis CD, Milner JA.** Gastrointestinal microflora, food components and colon cancer prevention. *J Nutr Biochem* 2009; **20**: 743-752 [PMID: 19716282 DOI: 10.1016/j.jnutbio.2009.06.001]
- 21 **Jaspersion KW, Tuohy TM, Neklason DW, Burt RW.** Hereditary and familial colon cancer. *Gastroenterology* 2010; **138**: 2044-2058 [PMID: 20420945 DOI: 10.1053/j.gastro.2010.01.054]
- 22 **Houlston RS, Tomlinson IP.** Polymorphisms and colorectal tumor risk. *Gastroenterology* 2001; **121**: 282-301 [PMID: 11487538]
- 23 **Tenesa A, Dunlop MG.** New insights into the aetiology of colorectal cancer from genome-wide association studies. *Nat Rev Genet* 2009; **10**: 353-358 [PMID: 19434079 DOI: 10.1038/nrg2574]
- 24 **Grady WM.** Genomic instability and colon cancer. *Cancer Metastasis Rev* 2004; **23**: 11-27 [PMID: 15000146 DOI: 10.1023/A:1025861527711]

- 25 **Weisenberger DJ**, Siegmund KD, Campan M, Young J, Long TI, Faasse MA, Kang GH, Widschwendter M, Weener D, Buchanan D, Koh H, Simms L, Barker M, Leggett B, Levine J, Kim M, French AJ, Thibodeau SN, Jass J, Haile R, Laird PW.

CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer. *Nat Genet* 2006; **38**: 787-793 [PMID: 16804544 DOI: 10.1038/ng1834]

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