Intake of Plant Based Foods and Colorectal Cancer. A Case-Control Study in Romania

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Abstract

Colorectal cancer (CRC) represents the third most common type of cancer worldwide with high incidence rates in our country as well. Both dietary habits and lifestyle factors have a strong contribution in preventing colorectal cancer. A healthy dietary pattern based on adequate intake of fruit, non-starchy vegetables, and whole grains is associated with positive outcomes regarding CRC development. The aim of the present study was to evaluate the dietary intake of plant-based food and food groups, along with lifestyle habits of CRC patients. A case-control study was conducted during April 2015 – October 2017. Patients (n=151) recently diagnosed with CRC and undergoing conventional treatment were recruited from Medisprof Oncology Hospital. Controls (n=151) were selected randomly from generally healthy adults. Dietary and lifestyle data were collected during a face to face interview and the applied lifestyle questionnaire included 74 items. The results showed that intake of specific food groups with high content of bioactive components was significantly higher in the control group compared to the CRC group ($p<0.05$), even though overall vegetable intake was similar between groups ($p=0.51$). Results also showed significant lower intakes of fiber-rich foods such as whole grains, nuts and legumes in the CRC group.

Keywords: colorectal cancer, bioactive dietary components, diet, lifestyle

Introduction

Colorectal neoplasia has become a global health problem being the third most common type of cancer in the world with high morbidity and mortality rates worldwide (American Cancer Society, 2015). Incidence of colorectal cancer (CRC) is higher in developed and industrialized countries and urban areas as well (Ferlay et al., 2014; Ferlay et al., 2013). Both dietary habits and lifestyle factors have a strong contribution in developing colorectal cancer. Also, environmental factors including sedentary lifestyle, smoking, and alcohol consumption are important determinants of CRC risk (Haggar and Boushey, 2009). A healthy dietary pattern based on adequate intake of fruit, non-starchy vegetables, and whole grains can protect from developing CRC (Terry et al., 2001). The proposed mechanism is mostly attributed to the bioactive food components such as resveratrol, curcumin, quercitin, Omega-3 fatty acids, etc.

known for their protective properties in CRC (Gavrilas et al., 2016). Even if there is extensive ongoing research on discovering new synthetic drugs with cytotoxic activity on cancer cells (Hangan et al., 2016), results from *in vitro* and *in vivo* studies support bioactive dietary components as important tools in chemoprevention and treatment. Moreover, caloric restriction and physical activity as part of a healthy diet have shown to reduce tumorigenesis (Olivo-Marston et al., 2014).

Although the relationship between diet and CRC has been extensively studied in most developed countries (Bingham et al., 2003; Gonzalez and Riboli 2010; Hansen et al.), there is lack of data in our country. Therefore, the aim of this study was to evaluate the pre-diagnosis lifestyle elements (physical activity, smoking, dietary habits) of CRC patients in Romania with focus on assessing intake of specific plant-based food groups and foods known to be rich in bioactive dietary components.

Materials and methods

Ethical consideration

According to Helsinki Declaration, the Amsterdam Protocol, and Directive 86/609/EEC, we obtained the approval of the Ethical Commission of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj- Napoca for this study.

Study population

Patients were recruited from Medisprof Oncology Hospital, Cluj-Napoca during April 2015 – October 2017. Patients recently diagnosed with CRC and undergoing conventional treatment were included in the present study. Controls were selected randomly from generally healthy adults. Inclusion criteria for people in the control group were: non-neoplastic conditions in the present and the past, without diagnosis of major chronic diseases and being on a regular diet (those on specific diet either by choice or by medical reasons were excluded from the study). Each patient with CRC was matched with one person in the control group by age (within a 5-year category). All participants provided written informed consent to participate in the present study. The final sample for statistical analysis was 151 cases and 151 controls.

Lifestyle assessment

The lifestyle questionnaire was designed by members of the research team using validated models from others European countries (Deschamps et al., 2009; Buscemi et al., 2015; de la Fuente-Arrillaga et al., 2010) and included 74 items in order to address specific elements associated with CRC. The questionnaire addressed: demographic data, anthropometric data, physical activities, long-term smoking, alcohol consumption and dietary habits. The dietary questions aimed to assess frequency of consumption using four possible response categories that ranged from "less than one time a week" to "more than 5 times a week". We favor designing our own questionnaire, in the absence of a national validated food frequency questionnaire, in order to emphasis on local foods and food aspects known to be important in colorectal cancer such as: culinary techniques, food containing bioactive dietary components and food items known to be risk/protective factors for CRC. Dietary and lifestyle data were assessed during an interview conducted by a trained dietitian, member of the research team. The interviewer clarified aspects regarding types of food within categories and food portions. Respondents were asked to report the frequency of consumption of a given serving of each food item. In the present paper, we report our findings regarding fruits, vegetables and other plant-based foods.

Statistical analysis

Statistical analyses were performed with SPSS software (Statistic Package for Social Sciences) version 20. The characteristics of the cases and controls were compared by the chi-squared (χ^2) test. A Mann-Whitney U test was used to determine intake differences between groups. A P-value less than 0.05 was considered statistically significant.

Results and Discussions

Comparison of general characteristics between cases and controls

Comparison of general characteristics between the CRC group and the control group is presented in Table 1. There was no significant difference in BMI (Body Mass Index) and living area distribution between the two groups, however, CRC patients were more likely to be less educated than participants in control group. Also, smoking history was not significantly different between groups.

Dietary intake

Fruits and vegetables. This study showed that consuming plant-based foods, rich in bioactive

dietary components, could be associated with CRC. Even if overall consumption of vegetables was similar between groups ($p>0.05$), when comparing intake of specific type of food or food groups, we found distinct frequency patterns (Table 2). In our study, participants in the control group were more likely to consume cruciferous vegetables ($p<0.001$), red fruits ($p<0.001$), nuts and seeds ($p<0.001$) and leafy vegetables ($p<0.001$). Likewise, as presented in Table 3, we found significant differences between groups regarding intakes of extra virgin oil, red wine or green tea ($p<0.001$).

These foods are rich sources of anti-tumorigenic agents such as folic acid, isothiocyanates, flavonoids, polyphenols, omega-3 fatty acids, etc, known to inhibit tumor growth by modulating molecular mechanisms that prevent cell proliferation and induce apoptosis (Nowak et al., 2013; Gavrilas et al., 2016). Even if the gene-regulator effect of diet and dietary components is yet an active research field, we already have some important insights from existing *in vitro* and *in vivo* studies that might explain in part findings from epidemiological and case-control studies.

Among the most studied bioactive compound is the active ingredient from turmeric. Curcumin can up-regulate pro-apoptotic proteins in colorectal cancer cells, such as p53, Bax, Bak, Bim, and Bid, while down-regulating anti-apoptotic ones (He et al., 2011; Han et al., 1999). Furthermore, EGCG (epigallocatechin-3-gallate) from green tea acts as an antioxidant agent and exerts CRC prevention effects alone or in combination with other compounds. At low and physiologically achievable concentrations, combination of EGCG and sodium butyrate is effective in promoting apoptosis by activating p53 protein and induces cell cycle arrest (Sabita Saldanha and Rishabh Kalaa; 2014). Likewise, curcumin together with resveratrol caused a greater inhibition of growth of CRC cells in vitro. In the same study, the combination treatment down-regulated EGFR (epidermal growth factor receptor) and IGF-1R (insulin-like growth factor 1 receptor) (Majumdar et al., 2009).

Extra virgin olive oil, the representative lipid source of the Mediterranean diet, has been previously associated with a low incidence of several chronic diseases including cancer. Epidemiological studies highlighted that the risk of CRC is lower in Mediterranean populations (Wang et al., 2014; Bamia et al., 2013) while mechanistic studies suggest that the polyphenolic fractions of extra virgin olive oil regulate pathways involved in proliferation and apoptosis (Grosso et al. 2013).

In line with previous studies that reported positive association between intake of leafy green vegetables and decrease risk of CRC (Tantamango et al. 2011; Azzeh et al. 2017) , in our study patients in the CRC group had lower intakes compared with controls ($p<0.001$). One possible mechanism explaining the protective properties of leafy green vegetables might be associated with their chlorophyll content which can modify genotoxic effects of known toxins (Tantamango et al., 2011). Also, leafy green vegetables are a good source of folic acid which has been hypothesized to lower CRC risk (Terry et al., 2002). Furhermore, as important source of vitamin E and polyunsaturated fatty acids, food that belong to nuts and seeds group might exert beneficial properties. Along with the high content of bioactive phytochemicals, minerals, and vitamins which explain in part the positive effect of consuming a plant-based diet, fruits and vegetables are also a rich source of dietary fibers. Protective mechanisms of dietary fibers are described next.

Whole grains. Based on our findings, intake of other fiber-rich foods such as whole grains was also significantly higher in the control group compared to the CRC group ($p<0.001$). Several studies reviewing the evidence of the relationship between foods containing dietary fibers and CRC reported inverse association when comparing high vs. low intakes (Aune et al., 2011; Hansen et al., 2012), although The Pooling Project which included 13 studies, reported non-significant inverse association (Vogtmann et al., 2013). However, there is evidence for valid mechanisms operating in humans. Dietary fibers by fermentation in the colon increase the production of butyrate, a short-chain fatty acid which has been shown to have anti-proliferative effects *in vitro*. Mechanistic studies demonstrated that butyrate induces apoptosis and decreases cell proliferation in human colon cancer cells by down-regulation of c-myc and increased expression of p57 and p21 proteins (Hu et al., 2011; Hu et al., 2015). Other mechanisms by which high intake of dietary fiber may lower CRC risk include reduced transit time and increased faecal bulk which would, in turn,

Tab. 1. Comparison of general characteristics and lifestyle habits between participants in the study group

Parameter	Control	Case	*P* value
Sex			
Female	61 (40.4%)	59 (39%)	-
Male	90 (59.6%)	92 (60%)	
Age (years)	58.4 ± 11.4	57.1 ± 11.4	-
BMI (kg/m^2)			
<24.9	85 (56.3%)	81 (53.6%)	<0.001
25.0-29.9	62 (41%)	45 (29.8%)	
>30	4 (2.7%)	25 (16.6%)	
Education			
≤Secondary school	9 (6%)	19 (12.6%)	
Completed high school or equivalent	99 (65.6%)	118 (78.1%)	<0.001
Bachelor degree or higher	76 (50.4%)	14 (9.3%)	
Living area			
Urban	128 (84.8%)	121 (80.1%)	0.29
Rural	23 (15.2%)	30 (19.9%)	
Smoking			
YES	13 (8.6%)	14 (9.2%)	0.84
NO	138 (91.4%)	137 (90.8%)	
Regular physical activity			
YES	135 (89.4%)	54 (35.7%)	<0.001
NO	16 (10.6%)	97 (64.3%)	
Nr. of meals/day			
2	8 (5.3%)	31 (20.5%)	
3	12 (7.9%)	63 (41.7%)	<0.001
4	62 (41.1%)	29 (19.2%)	
>4	69 (45.7%)	20 (13.2%)	
Most consistent meal			
Breakfast	67 (44.4%)	1 (0.6%)	<0.001
Lunch	45 (29.8%)	136 (90%)	
Dinner	39 (25.8%)	14 (9.4%)	
Multivitamin use			
Never	52 (34.4%)	89 (58.9%)	<0.001
Occasionally	82 (54.3%)	50 (33.1%)	
Daily	17 (11.3%)	12 (8%)	

decrease the potential of carcinogens to interact with the colon mucosa (Aune et al., 2011).

Legumes. In our study, intake of legumes between groups differ significantly, with participants in the control group having more frequent intakes ($p<0.001$). This food group includes mostly peas, lentils, beans, chickpeas and soybeans, all of which being powerful sources of nutrients and bioactive components that may be protective against cancer. Previous studies suggested that soybeans, due to their isoflavone content, are associated with a reduced risk of CRC (Shin et al., 2015). Besides that, legumes are a good source of bioactive constituents such as saponins, protease inhibitors, γ-tocopherol, vitamin E and selenium, which may also account for their beneficial effect (Lanza et al., 2006; Zhu et al., 2015). Furthermore, legumes due to their fiber-rich content may reduce postprandial glycemic response and prevent insulin resistance, which is a known risk factor for CRC (Haggar and Boushey 2009). Also, higher intakes of plant-based sources of protein may replace other sources rich in heme iron. Despite such beneficial properties of legumes, epidemiological studies generated

Tab. 2. Dietary intake of selected plant-based foods and food groups

Parameter	Control (n=151)	Case (n=151)	*P* value
Vegetables (servings/week)			
<1	14 (9.2%)	8 (5.3%)	
1 2	12 (7.9%)	16 (10.6%)	0.51
3 5	58 (38.4%)	55 (36.4%)	
>5	67 (44.5%)	72 (47.6 %)	
Leafy Green Vegetables (servings/ week)			
<1	16 (10.6%)	56 (37%)	<0.001
1 2	51 (33.7%)	75 (49.6%)	
3 5	82 (54.3%)	18 (11.9%)	
>5	2 (1.3%)	2 (1.5%)	
Cruciferous vegetables (servings/ week)			
<1	35 (23.1%)	77 (51%)	<0.001
1 2	95 (62.9%)	65 (43%)	
3 5	15 (10%)	4 (2.6%)	
>5	6 (4%)	5 (3.3%)	
Legumes (servings/week)			
<1	15 (9.9%)	54 (35.8%)	
1 2	45 (29.8%)	94 (62.2%)	<0.001
3 5	87 (57.6%)	1 (0.7%)	
>5	4 (2.7%)	2 (1.3%)	
Fruits (servings/week)			
<1	1 (0.6%)	3 (2%)	
1 2	10 (6.6%)	5 (3.3%)	0.019
3 5	51 (33.8%)	33 (21.8%)	
>5	90 (60%)	110 (72.9%)	
Red fruits (servings/week)			
<1	55 (36.4%)	98 (64.9%)	
1 2	35 (23.1%)	43 (28.5%)	<0.001
3 5	39 (25.8%)	9 (5.9%)	
>5	22 (14.5%)	1 (0.7%)	
Nuts and seeds (servings/week)			
<1	21 (13.9%)	78 (51.6%)	
1 2	46 (30.4%)	37 (24.5%)	<0.001
3 5	73 (48.4%)	26 (17.2%)	
>5	11 (7.3%)	10 (6.7%)	
Whole grains (servings/week)			
<1	31 (20.5%)	97 (64.3%)	
1 2	25 (16.5%)	44 (29.1%)	<0.001
3 5	74 (49%)	8 (5.3%)	
>5	21 (14%)	2 (1.3%)	

conflicting results on the association between intake of legumes and risk of CRC (Lanza et al., 2006; Millen et al., 2007).

Red wine. Moderate intake of red wine was significantly higher in control group when compared with CRC group (p<0.001). Red wine is a good source of resveratrol, a polyphenol known for its beneficial health-related properties. However previous investigations generated conflicting results on the association between red wine consumption and colorectal cancer. In the California Men's Health Study, moderate red wine intake was not associated with reduced risk (Chao et al., 2010), whereas a Danish cohort study

Tab. 3. Frequency of consumption of foods with high content of bioactive dietary components

Parameter	Control (n=151)	Case (n=151)	*P* value
Green tea (servings/week)			
<1	53 (35.1%)	123 (81.4%)	
1 2	20 (13.2%)	16 (10.6%)	<0.001
3 5	53 (35.1%)	4 (2.6%)	
>5	25 (16.5%)	8 (5.3%)	
Turmeric (servings/week)			
<1	43 (28.5%)	140 (92.7%)	<0.001
1 2	89 (58.9%)	3 (2%)	
3 5	14 (9.2%)	4 (2.7%)	
>5	5 (3.4%)	4 (2.6%)	
Red wine (servings/week)			
<1	28 (18.6%)	134 (88.7%)	
1 2	22 (14.6%)	17 (11.3%)	<0.001
3 5	86 (56.9%)	0 (0%)	
>5	15 (9.9%)	0 (0%)	
Extra virgin olive oil (servings/week)			
<1	15 (9.9%)	45 (29.8%)	<0.001
1 2	30 (19.9%)	61 (40.4%)	
3 5	79 (52.3%)	41 (27.2%)	
>5	27 (17.9%)	4 (2.6%)	

reported an anticarcinogenic effect of red wine reflected by the lower relative risk of CRC between participants which include wine in their alcohol intake compared with alcohol drinkers which consume only beer and sprits (Pedersen et al., 2003). Moreover, there is a strong evidence that a Mediterranean dietary pattern which includes moderate red wine consumption, has beneficial effects on certain cancers including CRC (Wang et al., 2014; Bamia et al., 2013; Grosso et al., 2013). In addition, experimental studies showed that resveratrol promotes apoptosis in CRC cells by activating p53 protein, caspase-3 and -8 while suppressing oncogenic pathways including IGFR1/PI3K/Akt and Wnt/β-catenin (Vanamala et al., 2010; Chen et al., 2012). Also, it has been suggested that the cytotoxic activity of resveratrol might be enhanced by caloric restriction (Fouad et al., 2013).

Lifestyle factors

Besides dietary intake, we observed that overall healthy lifestyle habits were more common in the control group compared to CRC group (Table 1). Regarding physical activity, there was significant difference between groups ($p<0.001$). Having an active lifestyle is known as one of the most important protective factors for CRC (Vrieling and Kampman; 2010). Regular exercise reduces body fatness and therefore has a positive effect on CRC since abdominal adiposity is strongly associated with CRC risk (Moon et al., 2008). Furthermore, participants in the control group reported more frequent meals and tend to consider more often breakfast as the most important meal of the day (Table 1). Having longer intervals between meals might relate with overeating and slow digestion. Even if this is not especially related to colorectal cancer, these observations may suggest the overall attention that people show to dietary and lifestyle habits. There are studies suggesting that people eating smaller portions and frequent meals tend to have lower BMI and an improved diet quality (Aljuraiban et al., 2015)which can be important drivers of the obesity epidemic.

This study is limited by the relatively small sample size which is not representative for the entire population group. Also, participants in the control group were more educated and may have misestimated some of their food consumption due to information available in the media of the

potentially beneficial or harmful effects of specific foods or food groups. Finally, there are inherent limitations due to the instrument used to collect the information. However, the fact that a member of the research team conducted face-to-face interviews for data collection might offset the outcome. Eventually, there is a pressing need for a national validated food frequency questionnaire to better evaluate the relationship of individual food intake and disease.

Conclusions

This study highlights that consuming foods and drinks that are high sources of bioactive dietary components such as cruciferous and green leafy vegetables, red fruits, extra virgin olive oil and green tea may prevent colorectal cancer development mostly because these food groups contain powerful antioxidant, anticancer, anti-inflammatory and antiproliferative properties. Also, we confirmed that fiber-rich foods such as whole grains, nuts and legumes are important constituents of a protective diet against colorectal cancer. Since colorectal cancer is one of the most diet-related and preventable type of cancer, our findings may be of use for those shaping dietetic recommendations for patients and people at risk.

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