RESEARCH ARTICLE

Physical Inactivity, Water Intake and Constipation as Risk Factors for Colorectal Cancer among Adults in Jordan

Reema Fayez Tayyem[1]*, Ihab Numan Shehadeh[2], Suhad Sameer AbuMweis[1], Hiba Ahmad Bawadi[3,4], Shatha Sabri Hammad[1], Kamal Eddin Bani-Hani[5], Tareq Mohammad Al-Jaberi[4], Majed Mohammed Alnusair[6]

Abstract

<u>Background</u>: Physical activity has been found to play a role in cancer prevention. The purpose of this matched case-control study was to investigate the association between physical activity levels, water intake, constipation and colorectal cancer (CRC). <u>Materials and Methods</u>: Two hundred and thirty-two patients diagnosed with CRC (125 male, 107 female) were enrolled in this case-control study. Cases were matched to 271 population controls (137 male, 134 female). <u>Results</u>: Drinking more than 4 cups of water daily decreased the risk of CRC by 33-42%; however, this effect was non-significant. Having constipation was found to be a significant risk factor for developing CRC with an OR=6.284 (95%CI=2.741-14.40). With reference to sedentary behavior, minimum activity (600-3000 Metabolic Equivalents Task (MET)) had 43% protection against CRC and the level of Health Enhancing Physical Activity OR was 0.58 (at 95%CI; 0.37-0.92). A significant negative association was found between CRC and physical activity levels expressed as both METs and MET-hours/week (p for trend=0.017 and 0.03, respectively). Among females, a significant trend of reduction in CRC by 62% was observed with increasing the level of physical activity expressed in MET (p for trend=0.04). <u>Conclusions</u>: The risk of CRC may be reduced by adopting a healthy lifestyle and practicing physically activity regularly, especially among females. Consuming adequate amounts of water and healthy bowel motility could also reduce the risk of CRC.

Keywords: Colorectal cancer - physical activity - water intake - constipation

Introduction

Globally, the most commonly diagnosed cancers are those of the lung, colorectal and breast. World health organization (WHO) estimates that there will be 20 million new cancer cases and 12 million cancer deaths by the year 2020 (WHO, 2003). In Jordan, cancer is a major cause of morbidity and mortality, and it is considered the second cause of death in Jordan. Cancer of colon and rectum ranked second for all new cancer cases among Jordanians; first among men and second among women according to the National Cancer Registry (2009).

Although about 5-10% of cancers result directly from inheriting genes associated with cancer, majority of cancers involves alterations or damages accumulated over time to the genetic material within cells. However, the causes of damage to the genetic material are both endogenous and exogenous. The exogenous factors include food and nutrition, tobacco smoking, and physical inactivity (World Cancer Research, 2007). Lifestyle characterized by low physical activity may result in a positive energy balance and weight gain (Marchand et

al., 1997). The role of physical inactivity and obesity in CRC prevention have been shown CRC in several studies (Whittemore et al., 1990; Marchand et al., 1997; Nilsen and Vatten, 2001).

Nowadays, interest in physical activity as a preventive factor of cancer is increasing. However, physical activity is one of environmental factors that can be modified through lifestyle/behavior change (Friedenreich and Orenstein, 2002). It is recommended to participate in moderate physical activity for at least 30 minutes every day and to limit sedentary habits (World Cancer Research, 2007).

Many studies divided the physical activity into occupational and recreational (Thune and Lund, 1996; Marchand et al., 1997; Simons et al., 2013). Thune and Lund (1996) and Marchand et al. (1997) documented that both occupational and recreational physical activities were inversely associated with colon cancer risk. Simons et al. (2013) found that the risk of distal colon and rectal cancer was decreased with higher occupational activity and lower occupational sitting hours, in men.

To the best of our knowledge, the association between physical activity levels and CRC risk has not been

[1]Department of Clinical Nutrition and Dietetic, The Hashemite University, Zarqa, [2]Gastroenterology Division, KHCC, King Hussein, [3]Department of Nutrition and Food Technology, [4]Jordan University of Science and Technology, [5]Faculty of Medicine, Hashemite University, [6]Gastroenterology Division, Prince Hamza Hospital, Jordan *For correspondence: rtayyem@hu.edu.jo

evaluated in Jordan. Therefore, this case-control study was conducted to investigate the possible association between CRC and physical activity (total of occupational and recreational) expressed by Metabolic Equivalents Tasks (METs) among a sample of CRC patients in Jordan. In addition, the association between CRC risk and constipation frequency and amount of water consumed daily was investigated.

Materials and Methods

Participants and data collection

This case-control study was conducted in Jordan between January 2010 and December 2012. Two-hundred and fifty seven CRC patients were invited to participate in the study. However, two-hundred and thirty two Jordanian patients [125 male, 107 females; mean age 53.3 (±0.78) years] with a medical report confirming the diagnosis of CRC accepted to be included in the CRC group. The control group was made up of 271 individuals [137 male and 134 female with mean age 51.8 (±0.63) years] without CRC, who were randomly selected from the community For each case a control matched for age, gender, occupation and marital status (only for females) was randomly selected.

The inclusion criteria in this study were having Jordanian nationality, aged 18 years or more, able to communicate verbally, and free of diabetes mellitus, liver disease and/or rheumatoid arthritis. For the cases, patients who were diagnosed with CRC within the last year were recruited. The exclusion criteria were critically ill, hospitalized, unable to communicate verbally, and current smoker participants. An informed consent was obtained from all participants.

Cases were recruited from five hospitals that include an oncology center. These hospitals were King Hussein Cancer Center, King Abdullah University Hospital, Prince Hamzeh hospital, Jordan University Hospital, and Al-Basheer Hospital. Institute Review Board approval from each hospital was obtained for conducting the research. A private room with good physical conditions was specified to carry out the interviews to facilitate data and samples collection. The data of this study was obtained by completing two questionnaires; personal and physical activity questionnaires. The two questionnaires were completed during face-to-face interview by trained research assistants.

Personal questionnaire:

The personal questionnaire composed of questions related to age, gender, marital status, education, employment, family income/month, residency area and house condition, smoking status, medication and previous and current health problems including constipation. Constipation was defined as a bowel movement frequency of less than once daily. Amount of water the participants used to drink daily was also questioned.

Body weight and height were measured and BMI was calculated. Those measurements were taken by trained research assistants. Body weight was measured to the nearest 100 g, with minimal clothing and without shoes, using a calibrated portable scale. Height was measured to the nearest cm with the subject in the full standing position without shoes using calibrated portable measuring rod. Body mass index (BMI) was calculated as the ratio of weight (kilograms) to the square of height (meters) (Lee and Nieman, 2010).

Physical activity questionnaire:

The 7-day Physical Activity Recall (PAR), developed by Sallis et al. (1985) for the Stanford Five-City Project, has been used in the present study. 7-Day PAR is a structured interview that depends on participant's recall of time spent engaging in physical activity over a seven day period. It covers different levels of physical activity intensity such as aerobic exercise, work-related activities, gardening, walking, recreation, and leisure-time activities. When measuring physical activity, it is necessary to consider the frequency, intensity, time, and type of the physical activity. PAR interview focuses on collecting data on intensity, time or duration, and type of activity. Although the specific type of activity is not recorded, the PAR differentiates between occupational physical activities, such as stocking shelves, and construction work, and leisure activity (i.e., all other physical activities that are not done during paid work hours).

The number of hours spent in different activity levels were obtained and converted into MET. Average MET for walking=3.3METs, for moderate activity=4.0 METs, for vigorous activity=8.0. The score expressed as MET-min per week was calculated as shown in the following equation: (MET level×minutes of activity/day×days per week). Total Physical Activity MET-minutes/week is obtained by METs summation and transfer into categorical analysis; inactive, minimally active and Health Enhancing Physical Activity (HEPA) active. Scoring into categories was performed according to the standard scoring protocol of International Physical Activity Questionnaire (version 2, 2004). Where inactive category included subjects with activity level that is not enough to meet categories 2 or 3. Minimally active category included subjects who reported 3 or more days of vigorous activity of at least 20 minutes per day; or 5 or more days of moderate-intensity activity or walking of at least 30 minutes per day; or 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 MET-min/week. The category HEPA active included any subject who performed vigorous-intensity activity on at least 3 days a week and accumulated at least 1500 MET-min /week or who performed any combination of walking, moderate-intensity or vigorous intensity activities on 7 or more days achieving a minimum of at least 3000 MET-minutes/week. However, total physical activity expressed as MET in hours/week and hours/week, was calculated from moderate recreational activities and walking.

Statistical analysis

Statistical analysis was performed with SPSS IBM-20 software. Chi-square test was used to evaluate the relationship between the personal characteristics and lifestyle variables and cancer. Moreover, odds ratio (OR)

test used to describe the strength of association between the occurrence of CRC and the tested variables. The significance level was set at p=0.05. Models for each measurement of physical activity were adjusted for BMI (Model 1) and for BMI, age, and gender (Model 2). A stratified analysis by gender was also performed for testing the association of BMI and different measures of physical activity and CRC risk.

Results

Demographic and lifestyle characteristics of the study participants are shown in Table 1. Since this study matched cases with controls for several parameters; including age, gender, education, marital status, and occupation, no significant differences were found between the two groups. Additionally, no significant difference was detected between case and control participants in smoking habit. However, both BMI and physical activity levels were found to be significantly different (p<0.022) as the cases compared to controls. A higher prevalence of overweight and obesity was detected in controls when compared to cases.

Table 2 shows that gender, age, education, and smoking did not significantly affect the risk of CRC. However, being male (OR=1.14, 95%CI: 0.80-1.62) or over 50 years old (OR=1.22, 95%CI: 0.86-1.74), increased the risk of CRC. In contrast, having high educational level (OR=0.37, 95%CI: 0.64-1.62) could reduce the risk for developing CRC for about 63%. Table 2 reveals that drinking more than 4 cups of water daily decreased the risk of CRC by 33-42%; although this effect was not statistically significant. In additions, the results show that having constipation was a significant risk factor for developing CRC with OR=6.284 (95%CI=2.741-14.403).

From the present study (not shown in Tables), average total MET per hours in females was 19.1 and 21.1 in cases and controls, respectively. While in males' average total MET was 8.0 hours in cases and 8.8 hours in controls. Multivariable-adjusted risk associated with total physical activity for HEPA versus inactivity was 0.58 (95%CI: 0.37, 0.92) (Table 3). The next analyses examined the effect of total physical activity expressed as hours/week and MET-hours/week. A statistical significant trend of risk reduction was found in both of physical activity levels expressed in METs and MET-hours/week. The results of the highest versus the lowest levels of both of them (p for trend=0.017 and 0.03, respectively) after adjustment for BMI were found to be protective against CRC significantly. However, further adjustment for age and gender in addition to BMI revealed a risk reduction of CRC by 42% with increasing hours/week spent in physical activity (p for trend=0.078) but not for physical activity expressed as MET-hours/week (p for trend=0.087).

The CRC risk associated with total physical activity was stratified by gender as shown in Table 4. Among females, a trend of reduction in CRC by 62% was observed with increasing the level of physical activity expressed in MET (p for trend=0.04).

Table 1. Demographic and Lifestyle Characteristics of the Study Participants

Characteristic		Control N (%)	Case N (%)	p value
Age	<50	132 (49.8)	103 (44.8)	NS
	>50	133 (50.2)	127(55.2)	
Gender	Male	137 (50.6)	125 (53.9)	NS
	Female	134 (49.4)	107 (46.1)	
Marital status	Married	242 (89.3)	210 (90.5)	NS
	Single	14 (5.2)	5 (2.2)	
	Divorced	2 (0.7)	3 (1.3)	
	Widowed	13 (4.8)	14 (6)	
Education	Illiterate	11 (4.1)	17 (7.4)	NS
	Primary and secondary	132 (49.1)	114 (49.4)	
	Diploma and BSc	107 (39.8)	89 (38.5)	
	MSc and PhD	19 (7.1)	11 (4.8)	
Smoking	Yes	47 (17.9)	40 (18.1)	NS
	No	216 (82.1)	181 (81.9)	
Health problems	Yes	121 (45)	91 (39.2)	NS
	No	148 (55)	140 (60.8)	
Occupation	Yes	95 (35.4)	66 (31.3)	NS
	No	173 (64.6)	145 (68.7)	
BMI	Normal	51 (19)	62 (28.6)	0.022
	Overweight	118 (44)	88 (40.6)	
	Obese	98 (36.6)	63 (29)	
Physical activity levels (MET)*				
	Inactive**	48 (17.7)	63 (27.2)	0.039
	Minimally Active†	90 (33.2)	67 (28.9)	
	HEPA active††	133 (49.1)	102 (44)	

*MET: Metabolic Equivalents; **Inactive: not fitting in "Minimally Active" or "HEPA active"; †Minimally Active: at least 600 MET per week; ††HEPA active: more than 3000 MET per week

Table 2. Associations Between Selected Risk Factors and CRC in Control and Patients in Jordan (n=503)

Factor		Control n	Case n	OR (95%CI)
Age	<50	132	103	1 (Referent)
	>50	133	127	1.22 (0.86-1.74)
Gender	Female	134	107	1 (Referent)
	Male	137	125	1.14 (0.80-1.62)
Education	Illiterate	11	17	1 (Referent)
	Primary and secondary	132	114	0.56 (0.25-1.24)
	Diploma and BSc	107	89	0.54 (0.24-1.21)
	MSc and PhD	19	11	0.37 (0.13-1.08)
Smoking	No	216	181	1 (Referent)
	Yes	47	40	1.02 (0.64-1.62)
Water intake per day (cups)	<2	15	1	(Referent)
	2	28	26	0.99 (0.41-2.40)
	2-4	54	52	1.03 (0.46-2.29)
	4-6	63	34	0.58 (0.25-1.31)
	>6	73	46	0.67 (0.30-1.49)
Constipation	No	82	45	1 (Referent)
	Yes	18	53	6.28 (2.74-14.40)

*OR: odd ratio, CI: confidence interval, BMI: body mass index

Discussion

The study aimed to investigate the association between the reported physical activity levels and the risk of CRC among Jordanians. This study found that being above 50 years old is a risk factor for developing CRC. Thune and Lund (1996) reported that the mean age at diagnosis of colon cancer was above 50 years old in both male and female. CRC was ranked the first for all new cancer cases among Jordanian men and the second among women according to the National Cancer Registry (2009). Our study supported that being male increased the risk for

Table 3. Associations Between Different Measurements of Physical Activity and CRC in Control and Patients in Jordan (n=503)

Factor	Control	Case	OR(95% CI) METs/Unadjusted		Model 1 Adjusted for BMI		Model 2 Adjusted for gender, age, BMI	
Physical activity levels (MET)*								
Inactive **	48	63	1	(Referent)	1	(Referent)	1	(Referent)
Minimally Active†	90	67	0.57 (0.35-0.93)		0.53 (0.33-0.86)		0.56 (0.34-0.94)	
HEPA active††	133	102	0.58 (0.37-0.92)		0.55 (0.33-0.91)		0.58 (0.36-0.96)	
p for trend			0.04		0.017		0.049	
Total physical activity (MET-hours per week)								
Zero physical activity	56	75	1	(Referent)	1	(Referent)	1	(Referent)
0.1-29.6	75	46	0.49 (0.28-0.76)		0.48 (0.29-0.81)		0.52 (0.31-0.87)	
29.7-72.6	72	55	0.57 (0.35-0.93)		0.57 (0.34-0.97)		0.50 (0.29-0.87)	
≥72.6	68	56	0.62 (0.38-1.00)		0.59 (0.34-1.03)		0.66 (0.39-1.13)	
p for trend			0.103		0.033		0.087	
Total physical activity (hours per week)								
Zero physical activity	56	75	1	(Referent)	1	(Referent)	1	(Referent)
0.1-9.0	75	46	0.46 (0.28-0.76)		0.48 (0.29-0.80)		0.48 (0.29-0.81)	
9.1-22.0	71	55	0.58 (0.35-0.95)		0.56 (0.34-0.93)		0.58 (0.34-0.99)	
≥22.0	69	56	0.61 (0.37-0.99)		0.53 (0.32-0.89)		0.58 (0.31-0.98)	
p for trend			0.096		0.03		0.078	

*MET: Metabolic Equivalents; **Inactive: not fitting in "Minimally Active" or "HEPA active"; †Minimally Active: at least 600 MET per week; ††HEPA active: more than 3000 MET per week; CI: confidence interval

Table 4. Associations of Physical Activity and BMI with CRC (Control and Case) according to Gender in Jordan (n=503)

Factor	Male			Female		
	Control	Case	OR (95% CI)	Control	Case	OR (95% CI)
Physical activity levels (MET)*						
Inactive**	37	43	1 (Referent)	11	20	1 (Referent)
Minimally Active†	52	39	0.64 (0.35-1.18)	38	28	0.40 (0.17-0.98)
HEPA active††	48	43	0.77 (0.42-1.41)	85	59	0.38 (0.17-0.86)
p for trend			0.423			0.04
Total physical activity (MET in hours per week)						
Zero physical activity	42	56	1 (Referent)	14	19	1 (Referent)
0.1-29.6	51	33	0.49 (0.27-0.89)	24	13	0.40 (0.15 -1.05)
29.7-72.6	27	23	0.64 (0.32-1.27)	44	32	0.52 (0.23-1.20)
≥72.6	17	13	0.57 (0.25-1.31)	52	43	0.62 (0.28-1.38)
p for trend			0.12			0.62
Total physical activity (hours per week)						
Zero physical activity	42	56	1 (Referent)	14	19	1 (Referent)
0.1-9.0	51	33	0.49 (0.27-0.88)	24	13	0.40 (0.15 -1.05)
9.1-22.0	27	23	0.64 (0.32-1.27)	45	32	0.54 (0.23-1.23)
≥22.0	17	13	0.57 (0.25-1.31)	51	43	0.61 (0.27-1.36)
p for trend			0.12			0.58

*MET: Metabolic Equivalents; **Inactive: not fitting in "Minimally Active" or "HEPA active"; †Minimally Active: at least 600 MET per week, ††HEPA active: more than 3000 MET per week; OR: odd ratio, CI: confidence interval, BMI: body mass index

developing CRC when compared to females.

In the present study, the highest educational level (MSc and PhD) was associated with 63% reduction in CRC risk. Even though this finding was not significant, the protective effect of education against being illiterate might indicate a possible protective pattern of education. However, Slattery et al. (2003) showed that controls had significantly higher educational level as compared to colon cancer cases. It could be suggested that education may increase the awareness toward healthful dietary and lifestyle choices and practicing cancer prevention behaviors (Breslow et al., 1997; Alharbi et al., 2012).

The results revealed that the risk for developing CRC had not been affected by smoking. This could be attributed to the lower number of smokers in our study (87 smokers: 397 non-smokers). Fu et al. (2012) detected

a positive relationship between smoking and CRC for both current and former smokers. Additionally, Wu et al. (1987) showed that smokers had higher risks of CRC than non-smokers but not as high as ex-smokers. On the other hand, Peppone et al. (2009) showed no association between long-term cigarette smoking and CRC risk.

A liner protective pattern was found between BMI and the risk of CRC, especially in females. However, obesity has been linked to insulin resistance and hyperinsulinemia. Several possibly causative mechanisms have been suggested; diabetes may slow down bowel transit (Iber et al., 1993); production of bile acids that promote colon carcinogenesis may increase (Narisawa et al., 1974; Nakamura et al., 1993); and high insulin levels may promote colon tumor growth (McKeown-Eyssen, 1994; Giovannucci, 1995). The results from studies

about the association between CRC and BMI are matter of controversy. Thune and Lund (1996) found that higher BMI may consider as a risk factor for developing colon cancer, in men only. Campbell et al. (2007) concluded that obesity is associated with colon and rectal cancer only in women but not men. Nilsen and Vatten (2001) study revealed that no association was found between BMI and CRC neither in males nor females of the study. However, the lower BMI among cases which has been detected in this study may reflect the effect of chemotherapy and other therpies that were used to treat cancer patients (Dobrila-Dintinjana et al., 2012). Sánchez-Lara et al. (2013) showed that gastrointestinal symptoms can lead to weight loss in cancer patients in the presence of persistent nausea, vomiting and anorexia and therefore an early nutritional intervention should be considered (Sánchez-Lara et al., 2013).

Increased water intake has been reported to be an important factor in reducing CRC risk (Shannon et al., 1996). In this study, even though the association between CRC and water intake was not significant, consuming more than 4 cups of water daily could affect the risk of CRC negatively. This finding supported by the results of Tang et al. (1999); who found protective but insignificant effect of water consumption on CRC risk.

Regarding suffering from constipation and its association with developing CRC, our study shows the risk for developing CRC increases about 600%, OR 6.284 (2.741-14.403). Those results are in agreement with many studies which found an increased risk of CRC in association with a history of constipation (Roberts et al., 1995; Marchand et al., 1997; Kotake et al., 2003). Kotake et al. (2003) illustrated that constipation was associated with a greater than two-fold risk of colon cancer (OR 2.36; 95%CI=1.41-3.93) adjusted for age, race, sex, and relevant confounders. The association was greater for women (OR 2.69; 95%CI=1.46-4.94) than for men (OR 1.73; 95%CI=0.61-4.88).

Several proposed mechanisms explained the association between CRC and constipation. One of them is that fermented bile acids (Reddy et al., 1997), ammonium acetate (Zarkovic et al., 1993) as well as fecapentaene-12 (Clinton et al., 1988), which are present in stools, are considered to be carcinogenic particularly the longer contact time they have with the colonic mucosa. The other one stated that constipation may increase the exposure for colon epithelial cells to stools for a longer time, and the significance of developing colon cancer from this exposure has been demonstrated in several animal studies (Ugajin, 1989).

The findings of our study showed that minimum physical activity (600-3000 METs/week) and HEPA (>3000 METs/week) reduced the risk of CRC significantly by about 43% and 42%, respectively. The protective effect of physical activity on the risk of CRC has been explained by two proposed mechanisms. The first one stated that physical activity stimulates colon peristalsis, and this may reduce exposure to carcinogens (McTiernan, 2008; Simons et al., 2013). Secondly, physical activity may increase insulin sensitivity and reduce plasma insulin, which therefore may inhibit the growth of cancer cells

(Nilsen and Vatten, 2001; McTiernan, 2008; Simons et al., 2013). Physical activity has been shown consistently to reduce CRC incidence (Peters et al., 1989; Kune et al., 1990; Lee et al., 1991). Many studies demonstrated very obvious protective effect of physical activity on the risk of CRC, the risk reduction in such studies were found to be 40-70% (Marchand et al., 1997; Steindorf et al., 2000; Boutron-Ruault et al., 2001). Friedenreich and Orenstein (2002) reviewed the results of more than 50 studies that conducted to assess the association between CRC and physical activity and they demonstrated that physical activity was capable of reducing the risk of colon and CRC up to 70% (averaged 40-50%). Slattery et al. (2003) found that the greatest protection for both men and women resulted from participation in vigorous activity over the past 20 years. The odd ratio showed a significant dose-response protective relationship between physical activity and CRC risk in females; the OR (CI) was 0.40 (0.17-0.98) for minimum physical activity and 0.38 (0.17-0.86) for HEPA. This could be due to the higher average activity that was detected in females compared to males. In the study of Thune and Lund (1996), physical activity showed a negative dose-response relationship with colon cancer risk among females, but not in males. Simons et al. (2013) concluded that regular long-term physical activity and fewer sedentary hours may protect against CRC. The benefit of physical activity on CRC exceeds the protective effect to improving the survival of patients; Meyerhardt et al. (2006) suggested that physical activity after a CRC diagnosis might lower the risk of death from the disease.

As a conclusion from the present study, being physically active and consuming adequate amount of water (not less than 4 cups daily) could reduce the risk of developing CRC, especially in women. Prevention of constipation and having healthy bowel movement may significantly reduce the risk of CRC significantly.

Study limitation

Body weight of cases was measured during the first year after diagnosis, which might be affected by cancer treatment and its side effects. PAR questionnaire depends on participants' recall which may not give the precise physical activity level.

Acknowledgements

References

Alharbi N, Alshammari M, Almutairi B, Makboul G, El-Shazly M (2012). Knowledge, awareness, and practices concerning breast cancer among Kuwaiti female school teachers. *Alexandria J Med*, **48**, 75-82.

Boutron-Ruault MC, Senesse P, Meance S, Belghiti C, Faivre J (2001). Energy intake, body mass index, physical activity, and the colorectal adenoma-carcinoma sequence. *Nutr. Cancer*, **39**, 50-7.

Breslow R, Sorkin J, Frey C, Kessler L (1997). Americans' knowledge of cancer risk and survival. *Prev Med*, **26**, 170-7.

Campbell P, Cotterchio M, Dicks E, et al (2007). Excess body weight and CRC risk in Canada: associations in subgroups of clinically defined familial risk of cancer. *Cancer Epidemiol Biomarkers Prev*, **16**, 1735-44.

Clinton SK, Bostwick DG, Olson LM, Mangian HJ, Visek WJ (1988). Effects of ammonium acetate arid sodium cholate on N-methyl-N0-nitro-N-nitrosocolon colon carcinogenesis of rats. *Cancer Res*, **48**, 3035-9.

Dobrila-Dintinjana R, Trivanovic D, Zelic M, et al (2012). Nutritional support in patients with CRC during chemotherapy: does it work? *Hepatogastroenterology*, **60**, 475-80.

Friedenreich C, Orenstein M (2002). Physical activity and cancer prevention: etiologic evidence and biological mechanisms. *J Nutr*, **132**, 3456-64.

Fu Z, Shrubsole M, Smalley W, et al (2012). Lifestyle factors and their combined impact on the risk of colorectal polyps. *Am J Epidemiol*, **176**, 766-76.

Giovannucci E (1995). Insulin and colon cancer. *Cancer Causes Control*, **6**, 164-79.

Iber FL, Parveen S, Vandrunen M, et al (1993). Relation of symptoms to impaired stomach, small bowel, and colon motility in long-standing diabetes. *Dig Dis Sci*, **38**, 45-50.

Kotake K, Koyama Y, Nasu J, Fukutomi T, Yamaguchi N (1995). Relation of family history of cancer and environmental factors to the risk of CRC: a case-control study. *Jpn J Clin Oncol*, **25**, 195-202.

Kune GA, Kune S, Watson LF (1990). Body weight and physical activity as predictors of CRC risk. *Nutr Cancer*, **13**, 9-17.

Lee IM, Paffenbarger RS Jr, Hsieh C (1991). Physical activity and risk of developing CRC among college alumni. *J Natl Cancer Inst*, **83**, 1324-9.

Lee RD, Nieman DC (2010). Nutritional Assessment. 5th ed. New York: McGraw Hill.

Marchand L, Wilkens L, Kolonel L, Hankin J, Lyu LC (1997). Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of CRC. *Cancer Research*, **57**, 4787-94.

McKeown-Eyssen G (1994). Epidemiology of CRC revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiol Biomarkers Prev*, **3**, 687-95.

McTiernan A (2008). Mechanisms linking physical activity with cancer. *Nat Rev Cancer*, **8**, 205-11.

Meyerhardt J, Giovannucci E, Holmes M, et al (2006). Physical activity and survival after CRC diagnosis. *J Clin Oncol*, **24**, 3527-34.

Nakamura T, Imamura K, Kasai F, et al (1993). Fecal excretions of hydroxy fatty acid and bile acid in diabetic diarrheal patients. *J Diabetes Complications*, **7**, 8-11.

Narisawa T, Magadia NE, Weisburger JH, Wynder EL (1974). Promoting effect of bile acids on colon carcinogenesis after intrarectal instillation of N-methyl-N´-nitro-N-nitrosoguanidine in rats. *J Natl Cancer Inst*, **53**, 1093-7.

Nilsen T, Vatten L (2001). Prospective study of CRC risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. *Bri J Cancer*, **84**, 417-22.

Peppone L, Hyland A, Moysich K, et al (2009). Examining the association between cigarette smoking and CRC using historical case-control data. *Cancer Epidemiol*, **33**, 182-8.

Peters RK, Garabrant DH, Yu MC, Mack T (1989). A case-control study of occupational and dietary factors in CRC in young men by subsite. *Cancer Res*, **49**, 5459-68.

Reddy BS, Watanabe K, Weisburger JH, Wynder EL (1977). Promoting effect of bile acids in colon carcinogenesis in germ-free and conventional F344 rats. *Cancer Res*, **37**, 3238-42.

Roberts M, Millikan R, Galanko J, Martin C, Sandler R (2003).

Constipation, laxative use, and colon cancer in a North carolina population. *Am J Gastroenterol*, **98**, 857-64.

Sallis JF, Haskell WL, Wood PD (1985). Physical activity assessment methodology in the five-city project. *Am J Epidemiol*. **121**, 91-106.

Sánchez-Lara K, Ugalde-Morales E, Motola-Kuba D, Green D (2013). Gastrointestinal symptoms and weight loss in cancer patients receiving chemotherapy. *Br J Nutr*, **109**, 894-7.

Shannon J, White E, Shattuck A L, Potter JD (1996). Relationship of food groups and water intake to colon cancer risk. *Cancer Epidemiol Biomarkers Prev*, **5**, 495-502.

Simons C, Hughes L, Engeland M, et al (2013). Physical activity, occupational sitting time, and CRC risk in the Netherlands cohort study. *Am J Epidemiol*, **177**, 514-30.

Slattery ML, Ballard-Barbash R, Edwards S, Caan BJ, Potter JD (2003). Body mass index and colon cancer: an evaluation of the modifying effects of estrogen (United States). *Cancer Causes Control*, **14**, 75-84.

Slattery M L, Edwards S, Curtin K, et al (2003). Physical activity and CRC. *Am J Epidemiol*, **158**, 214-24.

Steindorf K, Tobiasz-Adamczyk B, Popiela T, et al (2000). Combined risk assessment of physical activity and dietary habits on the development of CRC. A hospital-based case-control study in Poland. *Eur J Cancer Prev*, **9**, 309-16.

Stewart BW, Kleihues P (2003). World cancer report. Geneva, World Health Organization/Lyon, International Agency for Research on Cancer.

Tang R, Wang J, LO S, Hsieh L (1999). Physical activity, water intake and risk of CRC in Taiwan: a hospital-based case-control study. *Int J Cancer*, **82**, 484-9.

Thune I, Lund E (1996). Physical activity and risk of CRC in men and women. *Bri J Cancer*, **73**, 1134-40.

Ugajin H (1989). The role of bile acids with physiological concentration in colon carcinogenesis. *Nippon Shoukakibyo Gakkai Zasshi*, **86**, 1627-37.

Whittemore A, Wu-Williams A, Lee M, et al (1990). Diet, physical activity, and CRC among Chinese in North America and China. *J Natl Cancer Inst*, **82**, 915-26.

Wolin K, Tuchman H (2011). Physical activity and gastrointestinal cancer prevention. *Recent Results Cancer Res*, **186**, 73-100.

Wu AH, Paganini-Hill A, Ross RK, Henderson BE (1987). Alcohol, physical activity and other risk factors for CRC: a prospective study. *Bri J Cancer*, **55**, 687-94.

Zarkovic M, Qin X, Nakatsuru Y, et al (1993). Tumor promotion by fecapentaene-12 in a rat colon carcinogenesis model. *Carcinogenesis*, **14**, 1261-4.