Dietary Risk Factors and Odds of Colorectal Adenoma in Malaysia: A Case Control Study

Razinah Sharif a,b, Nur Mahirah Amani Mohammad a, Yau Jia Xin b, Nor Hidayah Abdul Hamid c, Suzana Shahar a and Raja Affendi Raja Ali d

aCentre for Healthy Ageing and Wellness, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; bNutrition Science Programme, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; cMinistry of Health, Putrajaya, Malaysia; dFaculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

ABSTRACT
Current evidence suggests that dietary and lifestyle factors may play an important role in colorectal cancer risk but there are only a few studies that investigated their relationship with colorectal adenomas (CRA), the precursors for colorectal cancer. A case-control study was conducted to determine the relationship between dietary and lifestyle factors associated with CRA risk among 125 subjects with CRA and 150 subjects without CRA at Hospital Canselor Tuanku Muhriz UKM (HCTM), Malaysia. We used dietary history questionnaire (DHQ) and International Physical Activity Questionnaire-Short Form (IPAQ) to estimate the diet and physical activity. The findings of this study showed that male gender (OR = 2.71 (95% CI= 1.01–7.27)), smoking (OR = 6.39 (95% CI= 1.04–39.30)), family history of cancer (OR = 6.39 (95% CI= 1.04–39.30)), high body fat percentage (OR = 1.25 (95% CI= 1.04–1.51)), high calorie and fat intake (OR = 1.03 (95% CI= 1.01–1.06)), and red meat intake more than 100 g per day (OR = 1.02 (95% CI= 1.01–1.04)) increased CRA risk. High fiber (OR = 0.78 (95% CI= 0.64–0.95)) and calcium intake (OR = 0.78 (95% CI= 0.98–1.00)) was found to decrease CRA risk. Some of these modifiable risk factors could be advocated as lifestyle interventions to reduce risk of CRA.

Introduction
Colorectal cancer is one of the most common forms of gastrointestinal cancer around the world and its incidence has been increasing in Asian countries over the past few years (1). In Malaysia, colorectal cancer is the second most diagnosed cancer in males and the third most diagnosed cancer in females (2). Most of the patients who are aged 50 years and above were diagnosed with colorectal cancer at a very late stage because it is asymptomatic during early stages (3, 4). Most colorectal cancer evolves from the progression of adenoma from small to large polyps and then to dysplasia and carcinoma. The duration for the progression of colorectal adenomas into carcinoma takes at least 10 years (5).

Colorectal adenoma can be categorized into two groups: conventional adenomas and sessile serrated polyps. In general, both are recognized as precursors of colorectal cancer (6). Ninety five percent of colorectal cancer arises from neoplastic adenomatous polyp. However, 40% of the cases are diagnosed in patients aged 60 and above (7, 8). Early detection and colonoscopic removal of these precancerous polyps remain as the most effective procedures in reducing incidence and mortality rate of colorectal cancer (1). However, it is estimated that the number of cancer cases and cancer-related mortality rate will increase in the following decades due to population growth and aging, as well as an increase in the prevalence of existing risk factors such as diet, smoking, obesity, physical inactivity, and changing reproductive trends associated with urbanization and economic development (9). Dietary pattern also has increasingly evident to be one of the important risk factor for early onset of colorectal cancer (10–13). Hence, it is important to take early preventive measures to reduce the number of colorectal cancer case.

Colorectal cancer is a multifactorial disease involving environmental and genetic factors. The
development of malignant cells from colorectal epithelium is caused by long-term exposure to the interactive effects of these factors causing oncogenic mutations and abnormal cellular proliferation which finally develops into adenoma and carcinoma (14). Unhealthy dietary pattern, physically inactivity, obesity, high intake of alcohol and smoking habit are, among all other environmental and life-style factors, the most dominant in the development of colorectal cancer (15–19). Most of these dominant factors are recognized to influence systemic inflammation. Immune-related cells may release pro-inflammatory cytokines which causes chronic systemic inflammation to occur and high level of cytokines is associated with incidence of CRC (20). Diet is also known to have a direct association with inflammation as suggested from previous research (21–23). Dietary Inflammatory Index (DII) was developed to measure the relation between the inflammatory potential of individual diet (24). According to Shivappa et al., the highest quartile score of DII is linked to increased CRC risk by 40% as compared to the group with the lowest or most anti-inflammatory DII scores (25).

Meanwhile, recent systematic reviews and meta-analyses paper by Godos et al. revealed that dietary pattern labeled as ‘unhealthy’ and characterized by a high consumption of red meat, processed meat, high sugar, salty food and refined carbohydrates were associated with increased risk of colorectal adenomas, whereas dietary patterns considered to be healthier are characterized by high intake fruits, vegetables, whole grains and fishes were associated with a decreased risk of colorectal cancer (26). Keum et al. reported that nutrient-based chemoprevention could also ameliorate CRC risk (27). Supplements also are related to chemoprevention by modulating inflammatory status or another related pathway as described previously (28–30).

Numerous studies have reported on the association between dietary factors and colorectal cancer risk (31–33), and evident is now increasing on how dietary factors can relate to risk of colorectal adenoma (CRA), which is considered as a precursor of colorectal cancer (34–39). Because colorectal cancer is now occurring in younger age groups and its prevention and treatment are much more efficacious when detected early, it is essential to know which risk factors affect CRA incidence (26). This study aimed to identify dietary and lifestyle factors associated with CRA risk in Malaysia using a case-control study method. Although no specific hypotheses were developed, it was expected that risk factors for CRAs seen in other populations such as dietary pattern and body composition would also be associated with CRAs in this Malaysian population.

Materials and Methods

Study Design and Setting

This case–control study was conducted at Colonoscopy Department, Hospital Canselor Tuanku Muhriz UKM (HCTM). Ethics approval was obtained from the Medical Research Ethics of the Universiti Kebangsaan Malaysia (UKM. PPI. 800-1/1/5/JEP-2019-243). Consent from subjects or their caregivers was obtained prior to data collection.

Sampling and Subjects

We conducted a hospital-based case-control study in Hospital Canselor Tunku Mukhriz in Cheras, Malaysia. CRA cases were patients who had colorectal polyps as revealed in the colonoscopy and with histologically confirmed adenomatous polyp were assigned as they have been referred to the Endoscopy Center. Controls were selected randomly from patients admitted to the same hospitals as cases at the same time and same setting, with non-neoplastic conditions, not afflicted with diet-related chronic diseases assessed by doctors and aged 30–79. Both groups were matched in terms of age (±5 years).

Data Collection

Sociodemographic data, family history with cancer, smoking habit and alcohol consumption were some of the data obtained from interviews via questionnaires. For sociodemographic data we also included their monthly income, we classify them as B40, M40 and T20, respectively. According to the 2019 statistics in Malaysia, our government classified our population into three main groups based on their household income: Bottom (low income-less than RM 4850/USD1192), Medium (average income – RM 4850/USD1192-RM 10959/USD2695), and Top (high income-more than RM 10959/USD2695). These three groups had a percentage of 40%, 40% and 20%, respectively, thus creating the terms B40, M40, T20. Anthropometry measurements included body weight, height, body mass index (BMI), waist circumference, hip circumference, waist-hip ratio and fat percentage were performed. According to WHO (2006) guidelines, BMI was calculated using the formula [weight (kg)/height (m^2)] (40). Dietary intake was also being assessed based on a validated dietary history questionnaire (DHQ) (41).
**Dietary Data**

A validated version of DHQ by Shahar et al. (2000) was used in this study to determine dietary patterns. Detailed interviews to gather information about the food taken by subjects including the type, amount, method of cooking and frequency were conducted by the diettitian. This includes all foods and beverages taken from waking up in the morning until before going to bed. Subjects were asked in detail so that any snacks or beverages taken in between are also included. In addition, the subjects were also asked about the frequency of having each mealtime, ranging from every day, almost every day (five to six times per week), some time (three to four times per week), seldom (once to twice per week), very seldom (less than once a week) and never. The time, venue and with whom the meal were taken and recorded.

Information gathered from DHQ was analyzed by using Nutritionist Pro (Axxya Systems Stafford, USA) software. In addition, to detect under-reporting, energy intake was divided by the basal metabolic rate (energy intake/basal metabolic rate). Basal metabolic rate was calculated using the following formulas (42):

- **Basal metabolic rate for men (aged 30 to 60 years)**
  \[0.0432 \times \text{weight (kg)} + 3.112 \times \frac{1}{4.2 \times 1000} \]

- **Basal metabolic rate for women (aged 30 to 60 years)**
  \[0.0539 \times \text{weight (kg)} + 2.147 \times \frac{1}{4.2 \times 1000} \]

The classification of dietary intake based on the formula above was as shown in the below table. Please refer to the age group in the reference below to get the exact equation.

| Classification of dietary intake | Energy intake/basal metabolic rate |
|----------------------------------|-----------------------------------|
| Underreporting                   | <1.2                              |
| Normal reporting                 | 1.2–1.8                           |
| Overreporting                    | >1.8                              |

*Source: Bingham et al. (43).*

**Statistical Analysis**

Data analysis was performed by IBM Statistical Package Software for Social Science (SPSS), version 21 (SPSS Inc., Chicago, IL, USA). The normality of the data was checked using Kolmogorov–Smirnov’s test. Baseline characteristics of participants were expressed as mean (SD) for quantitative variables, and frequency and percentages for qualitative variables. Data were stratified using descriptive analyses by sex. Both parametric and non-parametric tests including Independent T-test, Mann–Whitney test, Pearson Chi-Square test as well as Binary Logistic Regression test were used to determine statistical significance. Binary logistic regression was used to determine the association between dietary factors and other related factors with colorectal adenoma risk. All models were adjusted for confounding variables. The odds ratio (OR) and 95% confidence interval (CI) for colorectal adenoma were adjusted for age, family history of cancer, smoking and alcohol intake.

**Results**

**Sociodemographic Profile**

Based on Table 1, a total of 275 subjects (125 cases and 150 controls) were included in the study. All the subjects were aged 60 years and above. The majority of the CRA cases were male (53.3%) whereas most of the controls were female (75.6%). Most of the subjects were Chinese and married. The majority of the male subjects had secondary education, 35.7% in case and 56.3% in control. Most of the females in the case group had secondary education (45.5%) but most of the control group had tertiary education (47.1%).

**Smoking History, Alcohol Intake and Family History of Cancer**

Table 2 shows the smoking history, alcohol intake and family history of cancer among subjects in case and control groups. There was a significant difference in smoking status among subjects in case and control groups \((p<0.05)\). The majority of the subjects in the case group consumed more than 20 cigarettes per day (57.1%). No significant difference was found in the history of alcohol intake. Data on smoking and alcohol intake are not reported in females as they did not report any intake of alcohol and cigarette smoking, respectively.

As shown in Table 2, the majority of subjects in the case group had a family history of cancer; 92.9% in males and 81.8% in females. Majority of the subjects in the control group had no family history of cancer, which were 56.3% in males and 61.8% in females. There was a significant difference in family history factor among those with and without colorectal adenoma \((p<0.05)\).

**Anthropometry Status**

Table 3 shows the anthropometry measurement status among subjects in case and control groups. The mean weight of the male category was significantly higher among subjects in control group \((78.4\pm9.8\text{kg})\) compared to subjects in the case group \((71.1\pm8.1\text{kg})\).
Mean height of the subjects showed a similar trend as it was significantly higher in control groups (173.2 ± 3.7 cm) as compared to case group (167.8 ± 6.3 cm) \( (p < 0.01) \). In contrast, subjects in the case group of male categories had a significantly higher mean of fat percentage (27.2 ± 2.2%) as compared to the control group (25.4 ± 2.0%) \( (p < 0.05) \).

### Dietary Factors

Table 4 shows the energy, macronutrients, micronutrients, red meat, vegetables and fruits intake of the subjects in case and control groups. The median of energy, carbohydrates, protein and fat intake among both genders in the case groups was significantly higher as compared to the control group.

Moreover, the median intake of saturated fatty acids, monounsaturated fatty acids and polyunsaturated fatty acids among male subjects were significantly higher in the case group as compared to subjects in control group. On the other hand, subjects in the control group of both genders showed a significantly higher intake of dietary fiber and calcium as compared to the subjects in the case group. As shown in Table 4, the fruits intake of male subjects in the case group was significantly lower than the recommended servings from Malaysian Dietary Guideline (2010), in which 92.9% of case and 56.2% control group ate less than two servings per day \( (p < 0.05) \). However, the number of subjects who ate more than 100g red meat per day were significantly higher in case group; 64.3% in male and 72.7% in female as compared to those subjects in...
Table 3. Anthropometry measurement status among subjects in case and control group.

| Parameter                  | Male mean ± standard deviation | Female mean ± standard deviation | p value |
|----------------------------|--------------------------------|---------------------------------|---------|
| Weight (kg)                | 71.11 ± 8.07                   | 78.36 ± 9.79                   | 0.037*  |
| Height (cm)                | 167.82 ± 6.29                  | 173.16 ± 3.68                  | 0.008*  |
| BMI* (kg/m²)               | 25.25 ± 2.45                   | 26.08 ± 2.70                   | 0.388   |
| Waist circumference (cm)   | 98.18 ± 10.97                  | 90.25 ± 18.04                  | 0.164   |
| Hip circumference (cm)     | 100.32 ± 11.26                 | 106.70 ± 13.27                 | 0.934   |
| Waist-hip ratio            | 0.98 ± 0.08                    | 0.91 ± 0.22                    | 0.243   |
| Body fat percentage (%)    | 27.2 ± 2.2                     | 25.4 ± 2.0                     | 0.027*  |

Significant at * (p < 0.05), ** (p < 0.01) and *** (p < 0.001) by using Independent t-Test.
*BMI = Body Mass Index.

Table 4. Energy, macronutrients, micronutrients, red meat, vegetables and fruits intake among subjects in case and control group.

| Parameter                | Male Median (Q1,Q3) | Female Median (Q1,Q3) | p value |
|--------------------------|---------------------|-----------------------|---------|
| Energy (kcal)            | 2011 (1894, 2817)   | 1614 (1500, 1741)     | 0.001** |
| Carbohydrate (g)         | 267.2 (230.6, 312.5)| 203.3 (180.4, 205.5)  | 0.006** |
| Protein (g)              | 86.3 (76.7, 133.5)  | 71.8 (57.8, 72.4)     | 0.004** |
| Fat (g)                  | 73.8 (63.9, 112.3)  | 56.6 (52.3, 76.0)     | 0.009** |
| Sodium (mg)              | 2913.4 (1817.0, 3573.2)| 2540.0 (2670.0, 6743.8)| 0.317   |
| Potassium (mg)           | 1547.2 (1294.8, 1684.4)| 1232.5 (1190.0, 2674.8)| 0.279   |
| Vitamin A (RE)           | 1413.4 (564.4, 1564.1)| 964.2 (591.1, 1557.5)  | 0.802   |
| Vitamin C (mg)           | 78.9 (39.1, 111.7)  | 76.4 (45.7, 111.5)    | 0.739   |
| Vitamin E (mg)           | 2.7 (1.4, 5.5)      | 4.1 (2.6, 5.9)        | 0.229   |
| SFA (g)                  | 14.3 (11.7, 15.8)   | 4.8 (4.7, 11.3)       | <0.001***|
| MUFA (g)                 | 16.9 (8.5, 19.0)    | 6.0 (5.7, 8.3)        | 0.007** |
| PUFA (g)                 | 9.4 (4.4, 19.4)     | 3.8 (3.5, 4.6)        | 0.009** |
| fiber (g)                | 7.6 (5.3, 12.4)     | 13.1 (11.9, 13.5)     | 0.002** |
| Calcium (mg)             | 370.1 (293.3, 456.0)| 456.0 (329.0, 583.2)  | 0.256   |
| Sugar (g)                | 28.7 (8.7, 48.5)    | 33.1 (21.8, 48.6)     | 0.317   |
| Food groups (%)          |                      |                       |         |
| Fruits                   | 7.1                  | 43.8                  | 0.039** |
| Below requirementa       | 92.9                 | 56.2                  | 0.246   |
| Red Meat ≥ 100 g/d       | 64.3                 | 0                     | <0.001***|
| < 100 g/d                | 35.7                 | 100.0                 | 0.250   |

Significant at * (p < 0.05), ** (p < 0.01) and *** (p < 0.001) by using Mann-Whitney U Test.
Significant at * (p < 0.05), ** (p < 0.01) and *** (p < 0.001) by using Pearson Chi Square Test.
aTotal red meat intake reported to be associated with risk of colorectal cancer based on IARC (2015).
Recommended serving size based on Malaysian Dietary Guideline (2010).
the control group which is 0% for male and 11.8% for female \((p < 0.001)\).

**Association of Dietary and Other Life-Style Factors with Risk of Colorectal Adenoma**

The result of this study showed that smoking habits \([\text{Adjusted OR} = 6.39 \ (95\% \ CI= 1.04–39.30)]\), family history with cancer \([\text{Adjusted OR} = 6.39 \ (95\% \ CI= 1.04–39.30)]\), high body fat percentage \([\text{Adjusted OR} = 1.25 \ (95\% \ CI= 1.04–1.51)]\), high calorie \([\text{Adjusted OR} = 1.03 \ (95\% \ CI= 1.01–1.06)]\), and fat intake \([\text{Adjusted OR} = 1.01 \ (95\% \ CI= 0.95–1.09)]\), respectively, red meat intake more than 100 g per day \((\text{approximately half cup of chopped red meat}) \ [\text{Adjusted OR} = 1.02 \ (95\% \ CI= 1.01–1.04)]\) were significantly associated with risk of colorectal adenoma. On the other hand, high fiber and calcium intake were negatively associated with colorectal adenoma risk with \([\text{Adjusted OR} = 0.78 \ (95\% \ CI= 0.64–0.95)]\) and \([\text{Adjusted OR} = 0.78 \ (95\% \ CI= 0.98–1.00)]\), respectively (Table 5).

**Discussion**

This study is one of the first few studies conducted in Malaysia to investigate dietary pattern and CRA. It is well established that almost all colorectal cancers arise from benign, neoplastic adenomatous polyps. The multivariable analysis performed demonstrated that gender, body fat percentage, smoking, red meat intake, high calories and high fat, low fiber and low calcium intake were significantly associated with risk of colorectal adenoma. This study showed that male subjects had a significantly higher risk of CRA compared to female subjects. Similar results had been reported by Jun, Tan and Jingyu (2019), where the detection rate of CRA cases was significantly higher in male population \((22.5\%)\) as compared to female \((17.1\%) \ (p < 0.05)\) (1). In Malaysia, colorectal cancer was the second most common cancer among male but the third most common cancer among female (2). Differences in the CRA incidence between males and females in our study may also reflect different effects of lifestyle and hormonal factors on anatomical location of CRAs given that colorectal cancer is generally more prevalent in the proximal colon for females, while for males it is more frequent in the distal colon (44). Furthermore, a recent meta-analysis found gender differences relating to the protective effect of fiber depending on the proximal or distal location of colorectal cancer (45).

Our study also showed that those who were working had a reduced risk of CRA relative to those who were retired or unemployed. Studies suggest that this is probably due to the increased physical activity level.

| Parameter | B     | Standard Error | Adjusted OR (95% CI) | p value |
|-----------|-------|----------------|----------------------|---------|
| Gender    | 0.995 | 0.50           | 2.71 (1.01–7.27)     | 0.048**|
| Male      |       |                |                      |         |
| Female (Reference) |       |                |                      |         |
| Smoking History | 2.056 | 0.57           | 7.82 (2.54–24.04)    | <0.001***|
| Smoker    |       |                |                      |         |
| Non-smoker (Reference) |       |                |                      |         |
| Family history with cancer | 1.854 | 0.93           | 6.39 (1.04–39.30)    | 0.046*  |
| Yes       |       |                |                      |         |
| No (Reference) |       |                |                      |         |
| Weight (kg) | 0.095 | 0.05           | 0.91 (0.82–1.00)     | 0.061   |
| Height (cm) | 0.028 | 0.09           | 1.03 (0.86–1.24)     | 0.764   |
| Body fat percentage (%) | 0.226 | 0.09           | 1.25 (1.04–1.51)     | 0.016*  |
| Energy (kcal) | 0.032 | 0.01           | 1.03 (1.01–1.06)     | 0.009** |
| Carbohydrate (g) | −0.062 | 0.04         | 0.94 (0.87–1.01)     | 0.094   |
| Protein (g)  | −0.092 | 0.06           | 0.91 (0.82–1.02)     | 0.108   |
| Fat (g)      | 0.083 | 0.06           | 1.01 (0.95–1.09)     | 0.006** |
| SFA (g)      | 0.011 | 0.08           | 1.01 (0.87–1.17)     | 0.886   |
| MUFA (g)     | 0.082 | 0.19           | 1.09 (0.76–1.56)     | 0.655   |
| PUFA (g)     | 0.111 | 0.16           | 1.12 (0.82–1.53)     | 0.485   |
| fiber (g)    | −0.247 | 0.10            | 0.78 (0.64–0.95)     | 0.015*  |
| Calcium (mg) | −0.008 | 0.01           | 0.99 (0.98–1.00)     | 0.015*  |
| Red Meat     | 0.023 | 0.01           | 1.02 (1.01–1.04)     | <0.001***|
| ≥ 100g/ day |       |                |                      |         |
| < 100g/ day (Reference) |       |                |                      |         |
| Fruits       | −0.239 | 1.05           | 0.22 (0.97–1.54)     | 0.023*  |
| ≥ 2 servings /d |       |                |                      |         |
| < 2 servings /d (Reference) |       |                |                      |         |
| Cooking method (Frying) | 1.781 | 1.06           | 5.93 (0.75–7.11)     | 0.092   |

Significant at *(p < 0.05), **(p < 0.01) and ***(p < 0.001) by using Binary Logistic Regression.
of the population during work. Individuals who are physically active were negatively associated with colorectal adenoma risk (26.0%). In contrast, those with sedentary working schedules were associated with higher risk of CRA (44.0%) (46).

Based on our findings, smoking is one of the modifiable risk factor of CRA and the result was consistent with the result from Bailie, Loughrey & Coleman (2017) which reported 2.5-fold increased risk of serrated polyps (SP) in smokers (47). The potential mechanisms for the increased risk can be explained through molecular level via specific mutations induced by carcinogens in cigarette smoke. It has been shown that BRAF gene mutations correlate with lung cancer risk and colorectal cancer in smokers (48, 49). SP is more likely to contain mutation in BRAF gene as compared to non-SP and raises the possibility that smoking status may be a contributing factor (47). In general, smoking may increase the risk of DNA mutations in colon cells which leads to malignant transformation via a serrated pathway. Based on this hypothesis we might expect that serrated polyps may be more prevalent in smokers relative to nonsmokers.

In addition, people who had a family history of cancer especially colorectal cancer or adenomatous polyps were considered more prominent to risk of colorectal cancer. Risk of developing colorectal cancer among those who had a family history of cancer were two folds higher than those who without (50). In a local case-control study, an association between variant allele and genotypes of IL-8-251 T > A and TNF-α-308 G > A polymorphisms and colorectal cancer susceptibility risk was observed suggesting that these two Single nucleotide polymorphisms in inflammatory response genes which undoubtedly contribute to individual risks to colorectal cancer susceptibility may be considered as potential genetic predisposition factors for colorectal cancer in Malaysian population (51). In addition, a previous study in 2012 reported that in colorectal cancer patients, frequency of KRAS mutation and PTEN loss, lower BRAF mutation rate, higher PI3KCA amplification frequency, and rare PTEN mutation were observed (52). Although both studies did not address gene polymorphism and mutation in colorectal adenoma, it had provided baseline data for gene mutation happened in colorectal cancer patients in Malaysia. We have limited studies addressing on gene mutations in Malaysia that may predispose to CRA, which hopefully will be addressed in future study design.

Our study reported that high body fat percentage was positively associated with risk of CRA. This result was supported by a systematic review and meta-analysis on adult weight gain and CRA which revealed that the summary OR was 1.39 for CRA occurrence and with each 5 kg weight gain the odds increased by 7% (53). High body fat percentage may stimulate inflammatory response in the body, which can promote the development of colorectal cancer (54). Our study also reported that high energy and high fat intake were associated with higher risk of CRA. According to a case-control study by Sun et al. (2012), high-calorie intake associated with increased risk of colorectal cancer [Adjusted OR = 1.56 (95% CI= 1.21–2.01)] (p < 0.05) (55). This might be due to our westernized diet that has been reflected in nutrition transition in Malaysia. Additionally, excessive energy intake and low energy expenditure may lead to excess body weight.

In a review conducted recently, dietary patterns were suggested to have an association with the risk of colorectal adenomas (35, 36). In Ramadas and Kandiah (2009), a pre-tested quantitative food frequency questionnaire (FFQ) has been used to determine the dietary pattern of CRA subjects with good cognition and who were at least 30 years at the time of interview and have undergone colonoscopy in Hospital Kuala Lumpur (56). The results found that the protective factors against colorectal adenomas were soy, fruits and vegetables while on the other hand high intake of red meat and tubers increases the risk by two and a half fold. These findings is in agreement with our study which red meat intake more than 100 g per day (approximately half cup of chopped red meat) was significantly associated with increased risk of CRA. This was further supported by systematic and meta-analysis study by Zhao et al., (2018) which reported that there was positive association between red meat intake and incidence of CRA (RR = 1.23, 95% CI = 1.15–1.31) (57). Besides, a dose-response analysis had showed a consistent result with this study, whereby there was 14% increase in incidence of CRA with a daily intake of 100 g red meat, 1.14 (1.07–1.20) (p < 0.01).

In addition, Aune et al. (2013) concluded an increase in CRA risk with high consumption of red meat (58). In general, there were 19 case-control studies and seven prospective studies revealed that the overall relative risk, RR for each 100 g/d of red meat intake was 1.27 (95% CI = 1.16–1.40) followed by 1.20 (95% CI = 1.06–1.36) in prospective studies and 1.34 (95% CI = 1.12–1.59) in case-control studies (58). According to IARC (2015), a daily intake of 100 g red meat or more, enhances the risk of getting colorectal cancer by 17% (59). The possible mechanisms on the carcinogenic effects on red meat are the effects of heme iron. Red meat which is high in heme iron
induces cytotoxic damage on colonial epithelial cells that causes hyperplasia, promotion of oxidative stress and lipid peroxidation as well as formation of n-nitroso compounds (NOC), alteration of gut microbiota and leads to colorectal carcinogenesis (60). Besides that, red meat is pro-inflammatory which may lead to CRAs. There was a significant association between a high intake of red and processed meat with the increase in inflammation biomarkers that is C-reactive protein (CRP) (61, 62). Additionally, cooking meat under high temperature induce the production of carcinogenic compounds such as nitroso compounds (NOC), polycyclic aromatic hydrocarbons (PAH) and heterocyclic aromatic amines (HCA) which had been associated with colorectal carcinogenesis. Recent studies also showed the link between red meat intake with colorectal cancer adenoma (63–66). High intakes of red and processed meats are strongly and associated with sessile serrated lesion risk and part of the association may be due to heterocyclic amine intake (64).

Numerous studies reported on the protective effects of fruits and vegetables against colorectal adenoma and cancer which was consistent with the result of this study (27, 67, 68). According to a case-control study conducted by Bahrami et al. (2019) on dietary patterns and the risk of colorectal cancer and adenoma had reported that healthy dietary pattern was characterized by high consumption of anti-inflammatory foods such as vegetables, fruits, fish, legumes and poultry was associated with a decreased colorectal adenoma risk [Adjusted OR = 0.43 (95% CI= 0.27–0.69)] (69). Apart from containing high fiber which of high interest due to its anti-inflammatory effects, fruits are also rich in Vitamin C and E as well as a variety of bioactive compounds which may have anti-tumorigenic potential. These include folate, flavonoids, polyphenols and limonene which exert anti-oxidative properties and anti-inflammatory that can inhibit cellular damage and exposure to reactive oxygen species (70). However, WCRF/AICR (2018) report had revealed that the evidence suggesting that low consumption of fruit increase the risk of colorectal cancer is limited (54).

There was significantly lower risk of colorectal adenoma in those who had high dietary fiber intake (68). Based on WCRF/AICR (2018) report, consumption of food containing high dietary fiber probably protects against colorectal cancer (54). Several biologically plausible mechanisms had been proposed on the protective effect of dietary fiber against colorectal cancer. Dietary fiber which is fermented in the bowel will form short-chain fatty acids, such as butyrate which exert anti-proliferation effects. Besides, dietary fiber may exert anti-carcinogenic effects by reducing transit time and contact of carcinogens with the colonic mucosa, increase the binding of carcinogens and production of short-chain fatty acids as well as decrease the concentration of secondary bile acids (71). All these effects contribute to reduce the colorectal adenoma and cancer risk. Diet high in dietary fiber may also reduce insulin resistance, which is also a risk factor for colorectal cancer (72, 73).

Calcium also exerts protective effects against colorectal cancer. According to Ballie, Loughrey and Coleman (2017), individuals who had high intake of calcium, folate and fiber had lower risk of colorectal cancer (RR = 0.65, 95% CI = 0.49–0.85) (47). The protective effects of calcium may be explained by two mechanisms. Firstly, calcium will bind with secondary bile acids and fatty acids in the lumen and form insoluble calcium salts which will be then excreted from the body and thereby reduces the carcinogenic effects of all these bile acids on the colonial cells. Next, calcium can bind with calcium-sensing receptors of the apical membrane on the colorectal enterocytes and activates intracellular calcium signaling pathways which inhibits proliferations and enhance differentiation and apoptosis (74).

The current evidence is consistently proving that westernized diet affects risk for CRA as reflected by meat intake, high energy and high fat diet. This study is not without limitations. The study population was relatively small, partly due to COVID-19 pandemic that have impacted the whole study including data collection, and it is possible that some associations were not detected due to insufficient power. The fact that it focused on subjects in one location may limit the extrapolation of these findings to the entire Malaysian population hence warranted future studies for analyzing dietary pattern covering all geographical locations in Malaysia. Further subgroup analysis or expanding the data collection could not be possible due to COVID-19 pandemic that starts in December 2019 until now. The characteristics of the CRA were also not reported as access to the hospital are very limited. This could provide a clearer view on the risk factors associated with CRA. The possibility that the associations may be confounded or modified by other genetic or dietary factors could not be excluded. Also, this study had not explored dietary risk factors with colorectal subsites which could be worth exploring.

Despite these few limitations, the results of our study may be crucial for Malaysian CRA and CRC as guidance in dietary intake aiming to prevent or delay the occurrence of CRA and CRC. The comprehensive collection on individual dietary history and exclusion of subjects who reported a changed in their
dietary lifestyle after diagnosis contributes to the strength for this study.

**Conclusion**

Risk factors which include gender, body fat percentage, smoking, family history of cancer, red meat intake, high fat, high energy, low fiber and inadequate calcium have a significant association with risk of colorectal adenoma in the Malaysian population. The results of this study will help to inform the design of healthy lifestyle promotions which are necessary to reduce the risk of colorectal adenoma.

**Acknowledgments**

The authors acknowledge all staff at Endoscopy Centre, Pusat Hospital Canselor Tuanku Muhriz Universiti Kebangsaan Malaysia for the help in data collection. They also thank all participants who have contributed to the development of this important body of knowledge.

**Authors’ contributions**

Razinah Sharif led conception and initial design of the study, conducted the analysis and interpretation of data, drafted the manuscript, and revised content based on feedback. Yau Jia Xin, Nor Hidayah Abdul Hamid and Nur Mahirah Amani Mohammad assisted with data collection and data analysis. Raja Affendi Raja Ali assisted with the design of the study and data collection. Suzana Shahar contributed to the study design, data analysis and critical input for the manuscript.

**Disclosure statement**

The authors report no conflict of interest.

**Funding**

We acknowledge internal grant from Universiti Kebangsaan Malaysia (GUP 2018-065) and FRGS grant from Ministry of Higher Education (FRGS/1/2020/STG02/UKM/02/5) for the financial assistance.

**ORCID**

Razinah Sharif  http://orcid.org/0000-0001-7174-7353
Suzana Shahar  http://orcid.org/0000-0002-7191-9212

**References**

1. Tan YJ, Wendy T, Chieng JY. Detection rate of colonic polyp among patients who had undergone colonoscopy at gastroenterology unit of Serdang Hospital, Malaysia. Med J Malaysia. 2019;74:20–4.
2. Veetil SK, Lim KG, Chaiyakanaprak N, Ching SM, Abu Hassan MR. Colorectal cancer in Malaysia: its burden and implications for a multiethnic country. Asian J Surg. 2017;40(6):481–9. doi:10.1016/j.ajjsur.2016.07.005
3. Wolf AMD, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, Etzioni R, McKenna MT, Oeffinger KC, Shih Y-CT, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68(4):250–81. doi:10.3332/caac.21457
4. Kim J, Lee JY, Ham NS, Oh EH, Chang H-S, Park H, Do YS, Hwang SW, Yang D-H, Choe JW, et al. Association between carotid ultrasonography findings and colorectal adenoma in asymptomatic adults. Dig Dis Sci. 2020;65(6):1816–28. doi:10.1007/s10620-019-05899-7
5. Nguyen LH, Goel A, Chung DC. Pathways of colorectal carcinogenesis. Gastroenterology. 2020;158(2):291–302. doi:10.1053/j.gastro.2019.08.059
6. Winawer SJ, Fletcher RH, Miller L, Godlee F, Stolar MH, Mulrow CD, Woolf SH, Glick SN, Ganiats TG, Bond JH, et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology. 1997;112(2):594–642. doi:10.1053/gast.1997.v112.agast970594
7. Martinez Góngora V, Matthes KL, Castaño PR, Linseisen J, Rohrmann S. Dietary heterocyclic amine intake and colorectal adenoma risk: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2019;28(1):99–109. doi:10.1158/1055-9965.EPI-17-1017
8. Levine JS, Ahnen DJ. Clinical practice. Adenomatous polyps of the colon. N Engl J Med. 2006;355(24):2551–7. doi:10.1056/NEJMcp063038
9. Torre LA, Bray F, Siegel RL, Frolay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108. doi:10.3332/caac.21262
10. Zheng X, Hur J, Nguyen LH, Liu J, Song M, Wu K, Smith-Warner SA, Ogino S, Willett WC, Chan AT, et al. Comprehensive assessment of diet quality and risk of precursors of early-onset colorectal cancer. J Natl Cancer Inst. 2021;113(5):543–52. doi:10.1093/jnci/dja164
11. Yuan F, Deng L, Sun X, Chen Z, Shivappa N, Sheth AK, Cooper GS, Hebert JR, Li L. Dietary inflammatory index and risk of colorectal adenoma: effect measure modification by race, nonsteroidal anti-inflammatory drugs, cigarette smoking and body mass index? Cancer Causes Control. 2021;32(8):837–47. doi:10.1007/s10552-021-01436-y
12. Joh HK, Lee DH, Hur J, Nimptsch K, Chang Y, Joung H, Zhang X, Rezende LFM, Lee JE, Ng K, et al. Simple sugar and sugar-sweetened beverage intake during adolescence and risk of colorectal cancer precursors. Gastroenterology. 2021;161(1):128–42.e20. doi:10.1053/j.gastro.2021.03.028
13. Sharif R, Shahar S, Rajab NF, Fenech M. Dietary pattern, genomic stability and relative cancer risk in Asian food landscape. Nutr Cancer. 2021;20:1–17. doi:10.1007/s01635581.2021.1952627
14. Smith RA, Andrews K, Brooks D, DeSantis CE, Fedewa SA, et al. Cancer screening in the United States, 2016:
16. Mehta M, Shike M. Diet and physical activity in the prevention of colorectal cancer. J Natl Compr Canc Netw. 2014;12(12):1721–6. doi:10.6004/jnccn.2014.0174
17. Ortega LS, Bradbury KE, Cross AJ, Morris JS, Gunter MJ, Murphy N. A prospective investigation of body size, body fat composition and colorectal cancer risk in the UK Biobank. Sci Rep. 2017;7(1):17807. doi:10.1038/s41598-017-17997-5
18. Suzana S, Jr., Azhar Y, Fatimah A. Association between dietary fibre and cancer: a case-control study in Malaysia. Malays J Nutr. 2004;10:173–82.
19. Shahar S, Shafurah S, Hasan Shaari NS, Rajikan R, Rajab NE, et al. Roles of diet, lifetime physical activity and oxidative DNA damage in the occurrence of prostate cancer among men in Klang Valley. Malays Asian Pac J Cancer Prev. 2011;12:605–11.
20. Tuomisto AE, Mäkinen MJ, Väyrynen JP. Systemic inflammation in colorectal cancer: underlying factors, effects, and prognostic significance. World J Gastroenterol. 2019;25(31):4383–404. doi:10.3748/wjg.v25.i31.4383
21. Tabung FK, Liu L, Wang W, Fung TT, Wu K, Smith-Warner SA, Cao Y, Hu FB, Ogino S, Fuchs CS, et al. Association of dietary inflammatory potential with colorectal cancer risk in men and women. JAMA Oncol. 2018;4(3):366–73. doi:10.1001/jamaoncol.2017.4844
22. Kökten T, Hansmannel F, Ndiaye NC, Heba A-C, Quilliot D, Dreumont N, Arnone D, Peyrin-Biroulet L. Calorie restriction as a new treatment of inflammatory diseases. Adv Nutr. 2021;12(4):1558–70. doi:10.1093/advances/nmaa179
23. Del Cornò M,vari R, Sczaznocchio B, Varano B, Masella R, Conti L. Dietary fatty acids at the crossroad between obesity and colorectal cancer: fine regulators of adipose tissue homeostasis and immune response. Cells. 2021;10(7):1738. doi:10.3390/cells10071738
24. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 2014;17(8):1689–96. doi:10.1017/S1368946213002115
25. Shivappa N, Godos J, Hébert J, Wirth M, Piuri G, Speciani A, Grosso G. Dietary inflammatory index and colorectal cancer risk – a meta-analysis. Nutrients. 2017;9(9):1043. doi:10.3390/nu9091043
26. Godos J, Bella F, Torsiti A, Sciacca S, Galvano F, Grosso G. Dietary patterns and risk of colorectal adenoma: a systematic review and meta-analysis of observational studies. J Hum Nutr Diet. 2016;29(6):757–67. doi:10.1111/jhn.12395
27. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019;16(12):713–32. doi:10.1038/s41575-019-0189-8
28. Ooi TC, Chan KM, Sharif R. Antioxidant, anti-inflammatory, and genomic stability enhancement effects of zinc l-carnosine: a potential cancer chemopreventive agent? Nutr Cancer. 2017;69(2):201–10. doi:10.1080/01635581.2017.1265132
29. Ooi TC, Chan KM, Sharif R. Zinc L-carnosine protects CCD-18co cells from L-buthionine sulfoximine-induced oxidative stress via the induction of metallothionein and superoxide dismutase 1 expression. Biol Trace Elem Res. 2020;198(2):464–71. doi:10.1007/s12011-020-02108-9
30. Ooi TC, Chan KM, Sharif R. Protective effects of zinc L-carnosine against hydrogen peroxide-induced DNA damage and micronucleus formation in CCD-18co human colon fibroblast cells. Free Radic Res. 2020;54(5):330–40. doi:10.1080/10715762.2020.1763333
31. Azizi H, Asadollahi K, Davtalab E, Mirzapoosh M. Iranian dietary patterns and risk of colorectal cancer. Health Promot Perspect. 2015;5(1):72–80. doi:10.15171/hpp.2015.009
32. Bravi F, Edefonti V, Bosetti C, Talamini R, Montella M, Giacosa A, Franceschi S, Negri E, Ferraroni M, La Vecchia C, et al. Nutrient dietary patterns and the risk of colorectal cancer: a case-control study from Italy. Cancer Causes Control. 2010;21(11):1911–8. doi:10.1007/s10552-010-9619-1
33. Chen Z, Wang PP, Woodrow J, Zhu Y, Roebothan B, McLaughlin JR, Farrey PS. Dietary patterns and colorectal cancer: results from a Canadian population-based study. Nutr J. 2015;14:8. doi:10.1186/1475-2891-14-8
34. Nguyen LH, Cao Y, Hur J, Mehta RS, Sikavi DR, Wang Y, Ma W, Wu K, Song M, Giovannucci EL, et al. The sulfur microbial diet is associated with increased risk of early-onset colorectal cancer precursors. Gastroenterology. 2021;161(5):1423–X. doi:10.1053/j.gastro.2021.07.008
35.ucci N, Fatigoni C, Salvatori T, Nardi M, Realdon S, Gianfredi V. Association between dietary fibre intake and colorectal adenoma: a systematic review and meta-analysis. IJERPH. 2021;18(8):4168. doi:10.3390/ijerph18084168
36. Fliss-Isakov N, Zelber-Sagi S, Ivanovskiy-Wajcman D, Shiboleo O, Kariv R. Ultra-processed food intake and smoking interact in relation with colorectal adenomas. Nutrients. 2020;12(11):3507. doi:10.3390/nu12113507
37. Safari A, Shariff ZM, Kandiah M, Rashidkhani B, Fereidooni F. Dietary patterns and risk of colorectal cancer in Tehran Province: a case-control study. BMC Public Health. 2013;13:222. doi:10.1186/1471-2458-13-222
38. Botma A, Vasen HFA, van Duijnhoven FJB, Kleibeuker JH, Nagengast FM, Kampman E. Dietary patterns and colorectal adenomas in Lynch syndrome: the GEO Lynch cohort study. Cancer. 2013;119(3):512–21. doi:10.1002/cncr.27726
39. Makambi KH, Agurs-Collins T, Bright-Gbehry M, Rosenberg L, Palmer JR, Adams-Campbell LL. Dietary patterns and the risk of colorectal adenomas: the Black Women's Health Study. Cancer Epidemiol Biomarkers Prev. 2011;20(5):818–25. doi:10.1158/1055-9965.EPI-10-1213
40. World Health Organisation: Body mass index classification. [accessed 2020 April 16]. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi.

41. Shahar S, Earland J, Abdulrahman S. Validation of a dietary history questionnaire. Malays J Nutr. 2000;6(4):33–44.

42. Ismail M, Chee S, Roslee R, Zawiah H. Predictive equations for the estimation of basal metabolic rate in Malaysian adults. Malays J Nutr. 1998;4(1):73–80.

43. Bingham SA, Gill C, Welch A, Day K, Cassidy A, Khaw KT, Sneyd MJ, Key TJ, Roe L, Day NE. Comparison of dietary assessment methods in nutritional epidemiology: weighed records v. 24 h recalls, food-frequency questionnaires and estimated-diet records. Br J Nutr. 1994;72(4):619–43. doi:10.1079/BJN19940064

44. Kim S-E, Paik HY, Yoon H, Lee JE, Kim N, Sung M-K. Sex- and gender-specific disparities in colorectal cancer risk. World J Gastroenterol. 2015;21(17):5167–75. doi:10.3748/wjg.v21.i17.5167

45. Ma Y, Hu M, Zhou L, Ling S, Li Y, Kong B, Huang P. Dietary fibre intake and risks of proximal and distal colon cancers: a meta-analysis. Medicine (Baltimore). 2018;97(36):e11678. doi:10.1097/MD.0000000000011678

46. Mahmood S, MacInnis RJ, English DR, Karahalios A, Ma Y, Hu M, Zhou L, Ling S, Li Y, Kong B, Huang P. Predictive equations for the estimation of basal metabolic rate in Malaysian adults. Malays J Nutr. 1998;4(1):73–80.

47. Bailie L, Loughrey MB, Coleman HG. Lifestyle risk factors for serrated colorectal polyps: a systematic review and meta-analysis. Gastroenterology. 2017;152(1):92–104. doi:10.1053/j.gastro.2016.09.003

48. Sasaki H, Shitara M, Yokota K, Okuda K, Hikosaka Y, Moriyma S, Yano M, Fujii Y. Braf and erbB2 mutations correlate with smoking status in lung cancer patients. Exp Ther Med. 2012;3(5):771–5. doi:10.3892/etm.2012.500

49. Samowitz WS, Albertsen H, Sweeney C, Harrick J, Caan BJ, Anderson KE, Wolff RK, Slattery ML. Association of smoking, CpG island methylator phenotype, and V600E BRAF mutations in colon cancer. J Natl Cancer Inst. 2006;98(23):1731–8. doi:10.1093/jnci/dji468

50. Henrikson NB, Webber EM, Goddard KA, Scrol A, Piper M, Williams MS, Zallen DT, Calonge N, Ganiats TG, Janssens AC, et al. Family history and the natural history of colorectal cancer: systematic review. Genet Med: Off J Am Coll Med Genet. 2015;17(9):702–12. doi:10.1038/gim.2014.188

51. Ramzi N, Latella G. Role of heme iron in the association between red meat consumption and colorectal cancer. Nutr Cancer. 2018;70(8):1173–83. doi:10.1080/01635588.2018.1521441

52. Johnson IT. The cancer risk related to meat and meat products. Br Med Bull. 2017;121(1):73–81. doi:10.1093/bmb/lwdw051

53. Choi W, Morimoto Y, Cooney RV, Franke AA, Shvetsov YB, Le Marchand L, Haiman CA, Kolonel LN, Goodman MT, Maskarinec G. Dietary red and processed meat intake and markers of adiposity and inflammation: the multi-ethnic cohort study. J Am Coll Nutr. 2017;36(5):378–85. doi:10.1080/07315724.2017.1318317

54. Budhathoki S, Iwasaki M, Yamaji T, Hamada GS, Miyajima NT, Zampieri JC, Sharma S, Pakseerseth M, Kolahdooz F, Ishihara J, et al. Doneness preferences, meat and meat-derived heterocyclic amines intake, and N-acetyltransferase 2 polymorphisms: association with colorectal adenoma in Japanese Brazilians. Eur J Cancer Prev. 2020;29(1):7–14. doi:10.1097/CEJ.0000000000000506

55. Mosley D, Su T, Murff HJ, Smallie WE, Ness RM, Zheng W, Shrubsole MJ. Meat intake, meat cooking methods, and meat-derived mutagen exposure and risk of sessile serrated lesions. Am J Clin Nutr. 2020;111(6):1244–51. doi:10.1093/ajcn/nqaa030

56. Carr PR, Holleczek B, Stegmaier C, Brenner H, Hoffmeister M. Meat intake and risk of colorectal polyps: results from a large population-based screening study in Germany. Am J Clin Nutr. 2017;105(6):ajcn.148304–1461. doi:10.3945/ajcn.116.148304

57. Chiavarini M, Bertarelli G, Minelli L, Fabiani R. Dietary intake of meat cooking-related mutagens (HCAs) and
risk of colorectal adenoma and cancer: a systematic review and meta-analysis. Nutrients. 2017;9(5):514. doi:10.3390/nu9050514

67. Hidaka A, Harrison TA, Cao Y, Sakoda LC, Barfield R, Giannakis M, Song M, Phipps AI, Figueiredo JC, Zaidi SH, et al. Intake of dietary fruit, vegetables, and fiber and risk of colorectal cancer according to molecular subtypes: a pooled analysis of 9 studies. Cancer Res. 2020;80(20):4578–90. doi:10.1158/0008-5472.CAN-20-0168

68. Oh H, Kim H, Lee DH, Lee A, Giovannucci EL, Kang SS, Keum N. Different dietary fibre sources and risks of colorectal cancer and adenoma: a dose-response meta-analysis of prospective studies. Br J Nutr. 2019;122(6):605–15. doi:10.1017/S0007114519001454

69. Bahrami A, Houshyari M, Jafari S, Rafiei P, Mazandaranian M, Hekmatdoost A, Hejazi E. Dietary patterns and the risk of colorectal cancer and adenoma: a case control study in Iran. Gastroenterol Hepatol Bed Bench. 2019;12(3):217–25.

70. Chang H, Lei L, Zhou Y, Ye F, Zhao G. Dietary flavonoids and the risk of colorectal cancer: an updated meta-analysis of epidemiological studies. Nutrients. 2018;10(7):950. doi:10.3390/nu10070950

71. Bars-Cortina D, Martínez-Bardaji A, Macià A, Motilva M-J, Piñol-Felis C. Consumption evaluation of one apple flesh a day in the initial phases prior to adenoma/adenocarcinoma in an azoxymethane rat colon carcinogenesis model. J Nutr Biochem. 2020;83:108418. doi:10.1016/j.jnutbio.2020.108418

72. Romaneiro S, Parekh N. Dietary fibre intake and colorectal cancer risk: weighing the evidence from epidemiologic studies. Top Clin Nutr. 2012;27(1):41–7. doi:10.1097/TIN.0b013e3182461dd4

73. Zeng H, Lazarova D, Bordonaro M. Mechanisms linking dietary fiber, gut microbiota and colon cancer prevention. World J Gastrointest Oncol. 2014;6(2):41–51. doi:10.4251/wjgo.v6.i2.41

74. Barry EL, Lund JL, Westreich D, Mott LA, Ahnen DJ, Beck GJ, Bostick RM, Bresalier RS, Burke CA, Church TR, et al. Body mass index, calcium supplementation and risk of colorectal adenomas. Int J Cancer. 2019;144(3):448–58. doi:10.1002/ijc.31803