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Research Article

Association between Diet and Tumor Progression in Patients with Colorectal Cancer

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Abstract

We recruited potential participants between 2006 and 2009. A food frequency questionnaire (FFQ) was used to assess each participant's habitual diet during the previous year and to record their experience with food items and their components associated with colorectal cancer. We designed a 90 - 60 (participants-food items) metric to measure participants' consumption of food items relative to the Taiwan food and nutrition-database guidelines. Exploratory factor analysis was used to determine the types of diets. There was a significant difference in the consumption of 17 food items between the two study groups. The levels of fatty acids, fiber, and calcium explained 92.1% of the variance. The consumption of the fatty acid intake is associated with the risk of colorectal cancer (OR = 1.09; 95% CI = 1.01 - 1.18; $p < 0.05$). The fruit fiber can reduce the risk of developing cancer (OR = 0.84; 95% CI = 0.74 - 0.95; $p < 0.05$). The calcium consumption such as milk intake can be helpful to people preventing from colorectal cancer. Colorectal cancer patients should be concerned about their daily diet because high-fat, low-fiber, and low-calcium diets might be a risk factor for tumor progression.

Keywords: Colorectal Cancer; Food Frequency Questionnaire; Dietary Fiber; Fatty Acid; Calcium

Abbreviations

BMI: Body Mass Index; CI: Confidence Interval; CRC: Colorectal Cancer; DC: Dimension Coefficient; EFA: Exploratory Factor Analysis; FFQ: Food Frequency Questionnaire; OR: Odds Ratio

Introduction

Colorectal cancer (CRC) is a malignant neoplasm of the large intestine (colon and rectum). It is reported [1] to be the third most common cancer in males and the second in females. The estimated new cases of colon cancer and rectal cancer in United States were 106,100 and 40,870, respectively, in 2009 [2]. About 40,340 new cases of rectal cancer were diagnosed and as the second leading cause of cancer deaths in the United States in 2013 [3,4]. Countries such as Australia, New Zealand, Canada, the United States, and parts of Europe have the highest incidence rate of CRC, whereas China, India, and parts of Africa and South America have the lowest in the world [5]. CRC is the third leading cause of cancer-related death worldwide, with over 900,000 diagnoses and 639,000 deaths each year [6].

Since 1950, the CRC incidence rate has sharply and steadily increased in Japan. Until 2005, it increased 9.5 times for males and 7.5 times for females. It is estimated to have reached a high peak of 12.3 times for males and 10.5 times for females in 2010 [7]. Many studies [8-10] have focused on the association between habitual diet and CRC.

Traditional Asian diets have been substantially westernized in many countries. One study [11] on cancer trends in Taiwan reported that CRC occurred between the ages of 50 and 70 years old.

Studies on the association between CRC and food intake consider diet an environmental factor that affects CRC. Vegetables and fruits high in fiber and micronutrients can reduce the risk of CRC

[12-14]. Willett., *et al*. [15] reported that females with high animal fatty acid intake have 2.5 times more CRC than do females with low fatty acid intake. Chao., *et al*. [16] found a high correlation between red meat intake and CRS (RR: 1.71; 95% CI: 1.15 - 2.52; p = 0.007). Cross., *et al*. [17] reported that overeating food high in iron, such as red meat with heme, is a core cause of CRC because the toxins produced by heme remain in the colon and increase the N-nitrous compound in excrement, which leads to CRC [16,17].

Increasing daily dietary fiber by 5% reduced the risk of CRC by 41% (OR: 0.59; 95% CI: 0.41 - 0.86); by 67% (OR: 0.83; 95% CI: 0.67-1.04) for eating 100 g vegetables every day; by 82% (OR: 0.92; 95% CI: 0.82 - 1.03) for eating 100 g of fruit every day in one study [18].

Furthermore, the micronutrients contained in calcium and vitamin D reduced the risk of CRC by using bile acid sequestrants to inhibit the level of bile acid and, therefore, its opportunities to damage the colon mucosa [19,20]. McCullough., *et al*. [21] suggested that people take compound supplements with vitamin D to reduce the risk of CRC by about 29%.

We explored what food ingredients were significantly associated with CRC. Two research questions were raised: (1) what food ingredients are significantly associated with the risk of developing or exacerbating CRC? (2) how many types of food to identify food ingredients that might reduce the risk of developing or exacerbating CRC?

Material and Methods

Participants

We recruited 90 potential participants between 2006 and 2009 through the Nutrition Department of Chi Mei Medical Center in southern Taiwan. Patients with a clear consciousness who had been diagnosed with CRC and had undergone a surgery in the previous one month were assigned to the CRC group, and an equal number of age- and gender-matched patients without CRC were assigned to the Control group. CRC patients with cardiac or renal diseases, overt diabetes, or active intravenous drug abuse were excluded. Patients in the Control group were purposively sampled from a data bank of patients who had undergone a health examination.

Patients with severe illness or who were unwilling to accept a survey regarding food intake frequency withdrew from the study. Informed consent was secured from all study participants. The protocol was approved by the Chi Mei Medical Center Institutional Review Board (IRB #: 9410-002).

Risk factors and diet assessment

Within one week after the diagnosis of CRC and before treatment in scheduled consultations, patients were asked to complete questionnaires about their medical history, dietary habits, and body mass index (BMI): = weight (kg)/height (m^2). Demographic data, and information about their exercise, smoking, and drinking habits were recorded. Experienced dietitians helped patients complete a semiquantitative food frequency questionnaire (FFQ) developed in our laboratory and validated [22-24] to assess their habitual food intake for the previous year.

The FFQ contains food names, intake frequency, and the quantity in units of 20g for a meal. The names of 106 different foods are included: valley roots (11 items), fish and seafood (3 items), meat and processed meat products (8 items), visceral and intestinal foods (2 items), eggs and milk (11 items), nuts (1 item), vegetables (50 items), and fruits (20 items). Patients were requested to tell how often they ate which foods every day, week, month, or year, and then say how much they ate at each meal, and how frequently they ate every day. The quantity of an ingredient, e.g. Vitamin C(in column) with a value of 40 in a cell will correspond to a specific food, e.g. Vegetable (see reference [25] for demonstration), via a look-up request.

The formula for calculating the quantity of an ingredient for a person on a food intake is:

$$\text{Intake}(k) = \text{Intake}(k) + \text{Unit\_gram}(i) / 100 \times \text{Dish\_q}(k,i) \times \text{Quantity}(i,j) \quad \text{.....(Eq. 1)}$$

where Dish_q (k,i) = (year / 365 + month / 30 + week / 7 +day) × Dish_proportion (k,i); Quantity (i,j) = value extracted from the coordination of the food and the ingredient; Dish_proportion = 1, usually showing a dish (k,i) that contained 100 grams of a specific food (i).

Intake (k) is the summed quantity of an ingredient (j) from all food the patient has eaten, and Unit_gram (i) is a unit of food equal to the Quantity (i,j) of an Ingredient (j).

For instance, if one patient responds to a specific food (e.g., Vegetables) with 0, 3, 0, 0 for year, month, week, and day, respectively, we obtain Dish_q = (0 / 365 + 3 / 30 + 0 / 7 +0) × 1 = 0.1

We then look up the Quantity (i,j) (e.g. 40 for Vitamin C) for a food (i) according to the Unit_gram (i) (e.g. 20 g) and the Ingredient (j) in the data bank. The result for the patient's (k) food (Vegetables) intake of the ingredient (j) (Vitamin C) is 0.8 (= Unit_gram (i) / 100 × Dish_q (k,i) × Ingredient (j) = 20/100 × 0.1 × 40).

Following the formula, the total Vitamin C (j) for the patient (k) is the intake summation (Σ Quantity (k,i,j) for Vitamin C) in all food eaten during the previous year.

Data transformation

Sixty food ingredients [22-24] were extracted from a Taiwan Government Department of Health food-ingredient data bank. We designed a rectangular ingredient consumption metric for our 90 patients and the 60 food ingredients based on their responses to the FFQ. All patient ingredient intakes (i.e. Quantity (k,i,j) shown in the previous subsection) were filled using the FFQ formula above in reference [25].

Any significant differences in the means between the CRC and Control groups, based on independent t tests, are combined for additional assessment using exploratory factor analysis (EFA). The first research question, i.e. what food ingredients are significantly associated with the risk of developing or exacerbating CRC, can be answered.

All ingredients extracted using the t test method were additionally assessed using EFA to identify how many types of food could be classified from the study data. Using EFA, the second research question, i.e. how many types of food to identify food ingredients that might reduce the risk of developing or exacerbating CRC, can be answered. Interested readers are recommended to see the visual demonstration [25] and figure 1 for detailed information about the FFQ matching process.

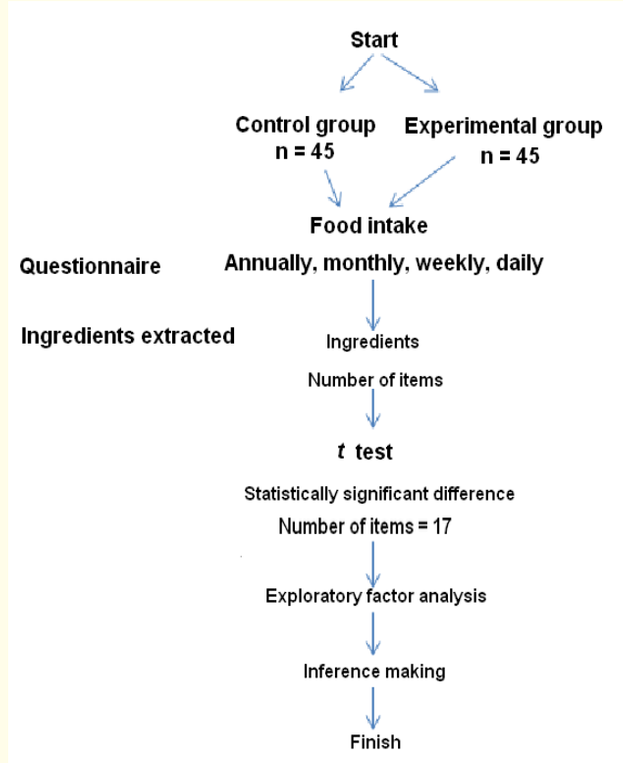

Figure 1: Flowchart of this study.

Statistical tools and analyses

The mean differences in the food ingredients between groups were examined using independent t tests. The number of components that could be extracted and retained was determined using EFA and confirmed using the dimension coefficient (DC)(26). The DC can be obtained using the first three eigenvalues (θ1, θ2, θ3) extracted from the EFA with equation 2 and equation 3:

$Z = (\theta 1/\theta 2)/(\theta 2/\theta 3)$ (Eq. 2)

$DC = Z/(1 + Z)$ (Eq. 3)

The value of the DC is between 0 and 1.0. A higher DC means a stronger tendency toward unidimensionality for a scale. When the DC is > = 0.70, the confidence interval (CI) is > 95%, which shows that the data can be measured using a unidimensional scale [26]. Otherwise, values < 0.70 show that there are at least two domains that refer to the DC value.

SPSS 15.0 for Windows (SPSS Inc., Chicago, IL) and MedCalc 9.5.0.0 for Windows (MedCalc Software, Mariakerke, Belgium) were used to (1) calculate Cronbach's α, (2) compute dimension coefficients (DCs) [26], (3) draw the scree and pyramid plots and (4) perform EFA. Independent t tests were used to compare (5) the mean difference between the two groups and to determine (6) which food ingredients had a significant effect on patients with CRC.

$\chi 2$ and Fisher's exact tests were used to examine different patterns associated with gender, and with exercise, smoking, and alcohol drinking habits. We used t tests to examine mean age differences between groups. Logistic regression analysis with food ingredients as independent variables was used to estimate odds ratios (ORs) and 95% CIs to predict the dependent variable: CRC.

Results and Discussion

Demographic characteristics of the sample

Each study group had 45 age- and gender-matched patients. Twenty-one CRC-group patients had CRC, 15 had distal colon cancer, and 9 had proximal colon cancer (Table 1). Four women in the CRC group had stage 0 cancer; 8 patients had stage I, 8 had stage II, 13 had stage III, and 12 had stage IV. There were significant differences between the groups for regular exercise ($p = 0.002$), alcohol drinking ($p < 0.001$), and smoking ($p < 0.001$).

Food ingredients significantly associated with CRC

Food fiber, Calcium, and Vitamin C were significantly more present in the diets of Control-group patients (Table 2). Finally, there were differences in the intake of 17 food ingredients.

Three diet types significantly associated with CRC

EFA was used to examine whether the 17 food ingredients could be used to construct a unidimensional scale if both coefficients of internal consistency and dimension are greater 0.70. As a result, Cronbach's α was 0.52, which indicates that there was a low internal consistency among the 17 food ingredients. A DC of 0.39 confirms that this is a multidimensional construct. A scree plot (Figure 2) shows that the eigenvalue of each of the three domains is > 1. These three domains-I: fatty acid, II: fiber, and III: calcium-explain a total of 92.1% of the variance. t values > 2.0 in table 3 mean that significant differences exist between groups across these 17 items.

Characteristics	Colorectal group		Control group		*p*
	n = 45		n = 45		
	Male	Female	Male	Female	
Number of patients	25	20	25	20	
Age (years) (continuous variable)					
Mean	60.9	63.6	60	62.9	> 0.05
Standard Deviation	10.8	12.6	9.7	9	
Diagnosis					
Proximal colon cancer	4	5			
Distal colon cancer	8	7			
Colorectal cancer	13	8			
Cancer stage					
0		4			
I	4	4			
II	4	4			
III	8	5			
IV	9	3			
Body Mass Index (continuous variable)	25.6	22.9	23.5	22.3	
Regular exercise					
No	17	13	7	5	0.002
Yes	8	7	18	15	
Alcohol drinker					
No	6	19	16	20	< 0.0001
Yes	19	1	9	0	
Smoker					
No	11	20	16	20	< 0.0001
Yes	14	0	9	0	

Table 1: Demographic characteristics of participants.

Daily nutrient intake	Colorectal group	Control group	*t*
	Mean ± Standard Deviation	Mean ± Standard Deviation	
Energy (kcal)	1877.7 ± 742.4	1754.9 ± 617.6	
Protein (g)	73.4 ± 35.4	68.9 ± 25.8	
Carbohydrate (g)	244.6 ± 98.7	250.2 ± 95.3	
Fat (g)	67.0 ± 48	54.7 ± 28.5	
Fiber (g)	16.2 ± 6.8	20.5 ± 9.9	-2.3
Cholesterol (mg)	261.2 ± 176.2	226.7 ± 121.9	
Sodium (mg)	794.7 ± 530	694.2 ± 389.0	
Potassium (mg)	2127.1 ± 919	2528.6 ± 1237.1	
Calcium (mg)	387.8 ± 265.7	538.0 ± 362.0	-3.3
Magnesium (mg)	220.7 ± 82.8	258.7 ± 126.9	
Phosphorus (mg)	958.7 ± 375	1027.5 ± 452.8	
Iron (mg)	9.2 ± 5.2	9.7 ± 4.6	
Zinc (mg)	9.0 ± 3.3	8.6 ± 3.2	
Folate (mg)	282.1 ± 184.9	326.1 ± 225.0	
Vitamin A (mg RE)	1812.3 ± 2330.1	1949.8 ± 1395.0	
Vitamin E(mg α-TE)	2.0 ± 1.1	2.2 ± 1.5	
Vitamin B_1 (mg)	1.2 ± 0.9	1.9 ± 3.6	
Vitamin B_2 (mg)	1.4 ± 0.7	1.5 ± 0.7	
Vitamin B_6 (mg)	1.4 ± 0.8	1.3 ± 0.5	
Vitamin B_{12} (mg)	11.8 ± 22	8.5 ± 7.1	
Vitamin C (mg)	157.9 ± 94.8	231.7 ± 155.1	-2.3
Niacin (mg NE)	21.2 ± 10.6	21.8 ± 9.1	

Table 2: Comparison of daily nutrient intake of participants.

RE: Retinol; α-TE: Alpha-Tocopherol; NE: Niacin Equivalent; $p < 0.05$.

Variable (Ingredient)	Factor			*t*	Eigenvalue	Variance Expl. (%)
	1	2	3			
Redmeat_ Oleic acid (g/day)	0.99			2	10.4	60.9
Redmeat_ Monofat (g/day)	0.99			2.04		
Redmeat_ Total fat (g/day)	0.99			2.13		
Redmeat_ Satfat (g/day)	0.99			2.14		
Redmeat_ Linoleic acid (g/day)	0.99			2.13		
Redmeat_ Polyfat (g/day)	0.99			2.14		
Red meat (g/day)	0.99			2.14		
Red meat (Ex/day)	0.98			2.13		
Linoleic acid (g)	0.98			2		
Medium-high-fat meats (Ex/day)	0.89			2.17		
Medium-high-fat meats (g/day)	0.86			2.22		
Dietary fiber		0.93		−2.32	4.2	85.9
Vitamin C		0.93		−2.32		
Fruit fiber		0.85		−2.32		
Fruit		0.82		−2.65		
Milk			0.91	−3.04	1.1	92.1
Calcium			0.73	−3.29		

Table 3: Variance extracted from study data using exploratory factor analysis

Expl.: Explained; Monofat: Monounsaturated Fat; Satfat: Saturated Fat; Polyfat: Polyunsaturated Fat; Ex: Exchange; DC: Dimension Coefficient = 0.39.

Diet was significantly associated with CRC

Fatty acid (OR = 1.09; 95% CI = 1.01 - 1.18; $p < 0.05$), fruit fiber (OR = 0.84; 95% CI = 0.74 - 0.95; $p < 0.05$), and calcium (OR = 0.94; 95% CI = 0.89 - 0.99; $p < 0.05$) intake were all positively or negatively significantly associated with the development of CRC (Figure 3).

Figure 2: Exploratory factor analysis-derived scree plot for the 17 food ingredients.

Figure 3: Comparisons of the two study groups across ingredients.

Discussion

We found that the consumption levels of 17 food ingredients were significantly different between the CRC and Control groups. We determined that there were three types of diets based on these ingredients: diets high in fatty acids, low in fruit fiber, and low in calcium. These three types of diets explain 92.1% of the variance in results. Fatty acids are positively associated with the development and exacerbation of CRC, and fruit fiber and calcium are negatively associated.

We also found that three lifestyle choices-habitual exercise, habitual alcohol drinking, and habitual smoking-are similarly associated with the development and exacerbation of CRC: negatively [27], positively [28] and positively [29], respectively.

We found that a diet high in fatty acids is positively associated with the development and exacerbation of CRC, which is consistent with the literature [18,30], which shows a high risk (OR = 1.2, 95% CI = 0.71 - 2.04) for people who eat a great deal of red meat (e.g. beef, lamb, pork, and related processed red meat products) and a low risk (OR = 0.43, 95% CI = 0.19 - 0.95) for people who, instead, eat a great deal of white meat (e.g., poultry, fish, seafood, and related processed white meat products).

Many studies [31-33] have reported that eating fiber and calcium help prevent the development and exacerbation of CRC. Drinking milk and eating dairy products was also recently [34] reported to be inversely associated with the development and exacerbation of CRC. Chau., *et al*. [35] indicated that intake of multivitamin and calcium supplements might be associated with a decreased risk of CRC.

Our study has some limitations. First is the relatively small sample size, which reduces the statistical power for subgroup analysis. Second is the possibility of error associated with dietary assessments using the recall FFQ. Participants might misreport their periodic food intake or underestimate portion sizes, particularly when ill. Third is the inherent deficiencies associated with retrospective study designs, which do not allow us to conclude that our findings about the associations of diets high in fatty acids, or low in fiber, and calcium with the development and exacerbation of CRC.

Despite these limitations, our study provides several implications for CRC management. To help prevent the development and exacerbation of CRC and to reduce its incidence rate, dietitians and other healthcare personnel should advise CRC patients to increase their habitual exercise and the fiber and calcium in their daily diet, and to decrease or eliminate their habitual smoking and alcohol drinking and reduce the amount of fatty acids in their diet.

Using the FFQ and EFA to analyze the association between diet and the development and exacerbation of CRC is a novel methodology. We believe that it is a fruitful one as well.

Conclusion

We suggest that people avoid eating high-fat low-fiber diets. Further longitudinally designed and interventional studies with large sample sizes might help confirm our findings using the method in this study to improve the nutrition of CRC patients.

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