Original Article

Diet quality score and survival rate in patients with colorectal cancer

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Background and Objectives: Results regarding associations between specific-food and prognosis of colorectal cancer (CRC) are limited and inconsistent, and few studies have examined this issue in Asian population. This study examined the association between diet and prognosis of CRC, and developed a diet quality score for prognosis of CRC. **Methods and Study Design:** 352 participants who provided completed dietary information were recruited during 2004 to 2014, and there are 154 death case documented with 10-year follow-up. Cox regression models were used to examine associations between food groups and survival rate, and to develop the diet quality score for prognosis of CRC. **Results:** Intake of whole grain, fruit and coffee consumption habitus were associated with higher survival rate (HR 0.56 [95% CI 0.35, 0.89] for whole grain; HR 0.62 [95% CI 0.40, 0.97] for fruit; HR 0.46 [95% CI 0.24, 0.87] for coffee), whereas intake of red meat and frequency of grilled food were associated with lower survival rate (HR 1.68 [95% CI 1.08, 2.61] for red meat; HR 1.78 [95% CI 1.05, 3.02] for grilled food). The overall diet quality based on these nutritional factors was negatively associated with survival rate (HR 1.60 [95% CI 1.07, 2.39] with adjustment for age, sex, BMI, smoking, drinking, energy intake, UICC stage, chemotherapy, postoperative adjuvant radiotherapy, tumor size, carcinoembryonic antigen and carbohydrate antigen 19-9 levels. **Conclusions:** Whole grain, fruit, red meat, coffee consumption habitus and frequency of grilled food were significantly associated with survival rate in Chinese population. The diet quality score may be useful for Chinese healthcare providers to advise patients on the optimal diet.

Key Words: colorectal cancer, dietary factors, diet quality score, prognosis, survival rate

INTRODUCTION

Colorectal cancer (CRC) is the third prevalent cancer in men and the second in women globally.[1] Incidence of CRC has remarkably increased in Asia during past decades.[2] In China, CRC has been reported to be one of the rapidly increasing malignant tumors, and its mortality persistently increased from 4.06/105 in the 1970s to 7.52/105 in 2005.[3]

The role of diet in the prevention of CRC has been abundantly investigated, which has led to a better understanding of its etiology.[4] High intake of whole grain, fruit, vegetable and dietary fiber have been consistently associated with lower risk of CRC,[5,6] whereas high intake of meat, alcohol showed opposing direction.[7,8] Despite this, it is still largely unknown about whether diet is associated with recurrence and mortality of CRC. Current studies regarding this issue are scarce, and results were inconsistent. One study has reported that higher red meat and processed meat was associated with higher mortality of CRC,[9] whereas the other study did not found such association.[10] Two systemic review studies also indicated that no consistent association between individual dietary components and CRC outcome was detected in the survival studies.[11,12] Diet, as a mixture of food and nutrients, frequently acts its physiological effect as a whole, and health impacts of individual dietary components frequently varied with different dietary patterns, which is likely a possible reason for these inconsistent results.

In addition to the above inclusive conclusions regarding association of individual dietary components with recurrence and mortality of CRC, there is still no relevant study based on the Chinese population although it is important for Chinese healthcare providers to advise patients on the optimal diet after treatment of CRC. Therefore, to fill this gap, this study intended to develop a diet quality score, which can be included the overall effect of diet, and examined associations between diet quality score and survival rate of CRC in a 10-year CRC cohort.

METHODS

Study population

The 369 CRC patients, who were diagnosed based on pathology at the Third Affiliated Hospital of Harbin Medical University, were recruited during from June 2004 to May 2005 and May 2007 to January 2008. All patients were in stages I-IV CRC with histological confirmation

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Manuscript received 17 April 2019. Initial review completed 29 April 2019. Revision accepted 06 May 2019.
doi:

and 17 patients were excluded due to the lack of questionnaires. Thus, a total of 352 CRC patients were included in the final analysis. For each patient, demographic, clinicopathological and treatment information was extracted from the electronic medical record system. All surgical operations were performed by the same surgical oncologist, and all patients had negative surgical margins. The extent of surgical resection was categorized as radical resection or palliative resection. All participants were Chinese and provided written informed consent. This study was approved by the Ethics Committee of Harbin Medical University.

Follow-up and outcomes

The primary outcome was overall survival (OS) from diagnosis to death and disease-free survival (DFS) from diagnosis to disease recurrence or metastasis or death, whichever came first. Outcomes were observed via an established protocol during the follow-up period through March 15, 2014. Patients were followed up postoperatively at a 6-month interval for the first year and annually thereafter. We used a telephone follow-up questionnaire to collect information on the date and cause of death of CRC patients. Among the 352 eligible CRC patients in the survival analysis, 158 patients were still alive, 154 patients died, 40 patients were lost to follow-up.

Dietary survey

Dietary habitus was evaluated by the validated food frequency questionnaire (FFQ) containing data regarding usual dietary intake over the past 12 months, including 103 food items from 14 food groups, which were rice, wheaten food, potato and its products, beans and its products, fresh vegetables, fresh fruits including apple, pear, orange, banana, melon, peach and strawberry, livestock and its products, poultry and its products, milk and dairy products, eggs and its products, fish and its products, snack, beverage and ice cream. For each food item, participants are asked to choose their usual rate of consumption frequency categories from “per day”, “per week”, “per month” and “never” and then answered the number of times for the corresponding frequency categories. The question regarding the amount of food intake consumed in lians (a unit of weight equal to 50 g) or mL (for liquid food item) for the corresponding frequency was measured by using molds of photographs of standard potion sizes. Each food items were quantified in g/d with multiplying the frequency by the amount of the food item. The energy intake per day was estimated by the Food Nutrition Calculator (V1.60, Chinese Center for Disease Control [CDC], Beijing, China).

Covariates

Height was measured without shoes to the nearest 0.2 cm using a portable SECA stadiometer (SECA, Hamburg, Germany). Weight was measured without shoes and in light clothing to the nearest 0.1 kg using a calibrated beam scale. Body mass index (BMI) was calculated, and was used as a continuous variable. Current smokers were defined as those who smoked at least 100 cigarettes in a lifetime or smoked every day or currently smoked some days. Current drinkers were defined as those who consumed ≥1 alcoholic drink each month in the 12 months prior to the survey. International Union Against Cancer (UICC) stage was categorized as I to IV levels. Chemotherapy was categorized as yes or no. Postoperative adjuvant radiotherapy was categorized as yes or no. Tumor size and preoperative carbohydrate antigen (CA19-9) were used as continuous variables.

Statistical analysis

Means and standard deviations or counts and frequencies are reported for the continuous or categorical variables, respectively. Generalized linear models were performed to test differences in baseline characteristics of continuous variables between alive and death cases with adjustment for age and sex. χ^2 test was used to measure differences in baseline characteristics of categorical variables. Cox regression models were used to estimate associations of food groups and diet quality score with survival rate. HRs and 95% CI were calculated. After the associations between food groups and survival rate were identified, these specific food groups were further included in the cox regression model without setting reference groups, and the correspondence coefficients were used for the score allocation.

Diet quality score was developed based on the magnitude of cox regression coefficient.[13] Overall diet quality score was calculated based on summing these points for each participant. A two-sided p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of studying variables

Characteristics of the studying variable of this study by outcomes are presented in the Table 1. Age, sex, BMI, tumor size did not differ significantly between alive and death cases. Whole grain in the alive group was significantly higher than that in the death group. Intake of fruit, vegetable, beans and coffee habitus showed a non-significant higher trend, whereas refined grain, red meat and high frequency of grilled food showed a non-significant lower trend in the alive group than that in the death group.

Associations between food groups and survival rate

The associations between specific food groups and survival rate, and diet quality score system were presented in the Table 2. Intake of whole grain, fruit, red meat, coffee consumption habitus and frequency of grilled food were significantly associated with survival rate, whereas other food groups were not significantly associated with survival rate and they were not shown in the data. Compared to the lowest intake of whole grain and fruit, the highest intake was significantly with lower survival rate (HR 0.56 [95% CI 0.35, 0.89] for whole grain; HR 0.62 [95% CI 0.40, 0.97] for fruit) with adjustment for age, sex, BMI, smoking, drinking and energy intake. Compared to non-coffee consumption habitus, survival rate in participants who have coffee consumption habitus was significantly lower (HR 0.46 [95% CI 0.24, 0.87] with adjustment for covariates. Compared to the lowest intake of red meat and frequency of grilled food consumption, the highest intake and highest frequency were significantly with higher sur-

Table 1. Baseline characteristics regarding study variables

	Alive N=158	Death N=154	*p* for difference
Age (years)	59.0 (10.0)	57.9 (11.6)	0.388
Men (n [%])	98 (62.0)	90 (58.4)	0.563
BMI (kg/m^2)	23.3(3.44)	23.5(3.7)	0.649
Smoking (n [%])	42 (26.6)	44 (28.6)	0.706
Drinking (n [%])	45 (28.5)	48 (31.2)	0.622
UICC stage at I (n [%])	107 (67.7)	49 (31.8)	<0.001
Tumor size (mm)	168.7 (363.9)	150.3 (207.0)	0.583
CEA (mmol/L)	10.6 (16.9)	26.2 (48.4)	<0.001
Energy intake (kcal/d)	2007.5 (363.1)	2067.6 (383.0)	0.173
Refined grain (g/d)	118.8 (28.8)	123.3 (28.2)	0.173
Whole grain (g/d)	13.4 (6.9)	10.7 (5.2)	<0.001
Fruit (g/d)	327.3 (166.2)	297.3 (168.6)	0.115
Vegetable (g/d)	336.5 (147.5)	335.1 (142.9)	0.931
Beans (g/d)	247.2 (68.7)	243.2 (70.5)	0.622
Dairy (g/d)	15.0 (9.3)	15.7 (9.1)	0.494
Eggs (g/d)	20.9 (7.5)	21.8 (7.1)	0.281
Red meat (g/d)	97.7 (71.1)	114.1(80.5)	0.057
Poultry (g/d)	27.5 (30.7)	32.4(38.7)	0.249
Fish (g/d)	13.0 (6.3)	13.9 (6.3)	0.221
Coffee habitus (n [%])	10 (6.5)	4 (2.5)	0.106
Tea (n [%])	47 (31.8)	40 (27.2)	0.444
Frequency of grilled foods (n [%])			0.111
Once per month	31 (19.6)	17 (11.0)	
1 to 3 times per week	32 (20.3)	26 (16.9)	
4 to 6 times per week	27 (17.1)	34 (22.1)	
7 times per week	68 (43.0)	77 (50.0)	

UICC: International Union Against Cancer; CEA: carcinoembryonic antigen.
Continuous data was mean (SD); Generalized linear models adjusted for age and sex and $\chi 2$ test were used to probe for differences in continuous variables and categorical variables.

Table 2. Associations between food and survival rate in CRC patients

	Case/N	Survival rate	
		Model 1	Model 2
		HR (95% CI)	HR (95% CI)
Whole grain			
Q1 (≤7.1 g/day)	45/78	1 (Ref.)	1 (Ref.)
Q2 (7.1 g/day to 10.7 g/day)	45/78	0.96 (0.64-1.46)	0.96 (0.63-1.45)
Q3 (10.7 g/day to 17.9 g/day)	34/77	0.75 (0.48-1.17)	0.73 (0.46-1.15)
Q4 (≥17.9g/day)	30/79	0.57 (0.36-0.90)	0.56 (0.35-0.89)
p for trend		0.063	0.050
Fruit			
Q1 (≤181.4 g/day)	47/79	1 (Ref.)	1 (Ref.)
Q2 (181.4 g/day to 283.4 g/day)	40/80	0.72 (0.47-1.09)	0.70 (0.46-1.07)
Q3 (283.4 g/day to 500.0 g/day)	31/78	0.56 (0.35-0.88)	0.55 (0.35-0.87)
Q4 (≥500 g/day)	36/75	0.65 (0.42-0.99)	0.62 (0.40-0.97)
p for trend		0.059	0.049
Red meat			
Q1 (≤35.7 g/day)	44/100	1 (Ref.)	1 (Ref.)
Q2 (35.7 g/day to 107.1 g/day)	39/83	1.16 (0.75-1.78)	1.19 (0.77-1.84)
Q3 (107.1 g/day to 142.8 g/day)	28/58	1.18 (0.74-1.90)	1.24 (0.76-2.02)
Q4 (≥142.8 g/day)	43/71	1.60 (1.05-2.43)	1.68 (1.08-2.61)
p for trend		0.176	0.144
Coffee habitus			
No	144/298	1 (Ref.)	1 (Ref.)
Yes	4/14	0.47 (0.25-0.89)	0.46 (0.24-0.87)
p for trend		0.020	0.018
Grilled food			
Once per month	17/48	1 (Ref.)	1 (Ref.)
1 to 3 times per week	26/58	1.32 (0.72-2.44)	1.34 (0.73-2.47)
4 to 6 times per week	34/61	1.74 (0.97-3.12)	1.73 (0.97-3.10)
7 times per week	77/145	1.75 (1.04-2.96)	1.78 (1.05-3.02)
p for trend		0.139	0.136

CRC: colorectal cancer. Data was HR (95% CI); Model 1 was crude model; Model 2 was further adjustment for age, sex, BMI, smoking, drinking and energy intake.

Table 3. The points allocation and diet score system

	β-coefficient	Points allocations
Whole grain	-0.229	-2.3
Fruit	-0.173	-1.7
Red meat	0.162	1.6
Coffee habitus	-0.783	-7.8
Grilled food	0.174	1.7

β-coefficients were derived based on cox regression models using these variables without setting reference groups. Diet quality score was calculated with summing the points allocates.

vival rate (HR 1.68 [95% CI 1.08, 2.61] for red meat; HR 1.78 [95% CI 1.05, 3.02] for frequency of grilled food;) with adjustment for covariates. The diet quality score of CRC prognosis was further developed based on the points allocated (Table 3).

Associations between diet quality score of CRC prognosis and survival rate

Association between diet quality score of CRC prognosis and survival rate was presented in the Table 4. After adjustment for age, sex, BMI, smoking, drinking, energy intake, UICC stage, tumor size, chemotherapy, postoperative adjuvant radiotherapy compared to the highest diet quality, the lowest was significantly associated with lower survival rate (HR 1.63 [95% CI 1.09, 2.43]). After further adjustment for biomarkers (CEA and CA19-9) for CRC prognosis, the lowest diet quality was still significantly associated with lower survival rate (HR 1.60 [95% CI 1.07, 2.39]). The survival curve across tertiles of diet quality score was presented in the Figure 1. The survival rate gradually decreased across the tertiles of diet quality score, which was consistent with results documented in the Table 3.

DISCUSSION

In this study, using longitudinal data with 10-year follow-up, we observed that intake of whole grain, fruit and coffee were significantly associated with lower risk of mortality, whereas red meat and grilled food were significantly associated with higher risk. Based on these foods, we developed a diet quality score for CRC prognosis, and such diet quality score was associated with the survival of CRC patients independent of BMI, CEA, CA19-9 and UICC stage.

Although higher intakes of whole grain, fruit and coffee have been consistently reported to be associated with lower incidence of CRC in previous studies, studies that examined their associations with survival of CRC are relative scarce. Results of this study indicated that higher intake of whole grain was significantly associated with 44% reduced risk of mortality, intake of fruit with 38% reduced risk, and coffee consumption habitus associated with 52% reduced risk, respectively. A few previous observational studies regarding this issue may support these findings. Recent studies have reported that higher intake of dietary fiber or low quality of carbohydrate diet was significantly associated with lower mortality caused by CRC,[14,15] and according to alternative health eating index characterized by high whole grain, fruit and vegetables was also demonstrated to be associated with lower risk of mortality.[16] For coffee, two previous studies have consistently documented the positive association between coffee intake and survival rate of CRC,[17,18] which supported the observations of this study. Cell and animal studies may provide the potential mechanisms for these associations. First, intake of whole grain was reported to be associated with improved insulin sensitivity and reduced inflammation,[19,20] which have been linked to decreased mortality in nonmetastatic CRC patients.[21] Second, animal studies indicated that high-fiber diets promote apoptosis and suppress colorectal tumor development.[22] Third, polyphenol caffeic acid found in coffee may inhibit colon cancer metastasis through targeting mitogen-activated protein kinases and T-cell-originated protein kinase,[23] and a coffee-specific diterpene, had the potential to inhibit metastasis by disruption of STAT3-mediated transcription of the pro-metastatic genes.[23] Further, although tea has been reported to be associated with incidence and survival rate of CRC in previous studies, this study did not find such association and tea consumption rate did not differ significantly between alive and death groups. The possible reason for the non-significant results probably is that tea is a popular beverage in China, which may lead to increased consumption rate in the two groups of this study population, attenuating the association between tea consumption and survival rate of CRC. Further studies are still needed to examine this association.

In addition to the above protective food in relation to

Table 4. Association between diet quality score of CRC and survival rate

Score	Case/N	Survival rate			
		Model 1	Model 2	Model 3	Model 4
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Tertile 1 (≤-9.4)	43/104	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Tertile 2 (-9.4 to -5.5)	45/100	1.17 (0.77-1.78)	1.19 (0.78-1.82)	1.24 (0.81-1.90)	1.29 (0.84-1.97)
Tertile 3 (≥-5.5)	66/108	1.88 (1.28-2.76)	1.93 (1.31-2.86)	1.63 (1.09-2.43)	1.60 (1.07-2.39)
p for trend		0.003	0.002	0.049	0.070
			Survival rate with DFS		
Tertile 1 (≤-9.4)	43/104	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Tertile 2 (-9.4 to -5.5)	45/100	1.09 (0.72-1.64)	1.15 (0.76-1.75)	1.35 (0.88-2.08)	1.42 (0.92-2.19)
Tertile 3 (≥-5.5)	66/108	1.77 (1.20-2.60)	1.85 (1.25-2.74)	1.64 (1.10-2.45)	1.63 (1.09-2.43)
p for trend		0.006	0.004	0.053	0.057

Data was HR (95%CI); Model 1 was crude model; Model 2 was further adjustment for age, sex, BMI, smoking, drinking and energy intake; Model 3 was further adjustment for UICC stage, tumor size, chemotherapy and postoperative adjuvant radiotherapy; Model 4 was further adjustment for CA19-9 and CEA. DFS, disease-free survival time.

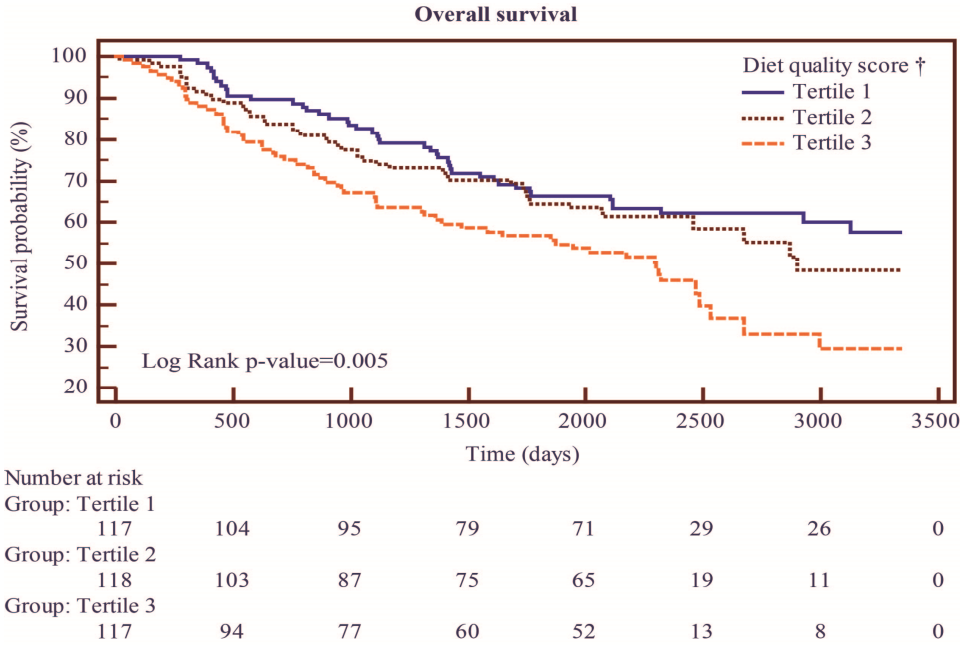

Figure 1. Kaplan-Meier survival curve of CRC patients across tertiles of diet quality score. †The cut-off value of tertile 1-3 were <-9.4, -9.4 to -5.5 and > -5.5, respectively.

survival rate of CRC, this study also found that high red meat intake and grilled food habitus was associated with 68% and 78% increased risk of mortality in CRC patients, respectively. These observations are consistent with previous studies, which have reported that high intake of red meat or the western dietary pattern characterized by high meat intake were associated with lower survival rate of CRC patients.[24] High red meat intake has been reported to be associated with tumour growth and the inhibition of apoptosis, probably leading to the low survival rate.[25,26] For grilled food habitus, prognosis of CRC studies regarding this issue is still very limit, however, association between intake of grilled food and incidence of CRC has been documented in previous studies. N-nitroso compounds, heterocyclic amines and polycylic aromatic hydrocarbons are frequently found in smoked, fried or high-temperature grilled meat, which are likely possible mechanism for the observed associations.[26,27] Moreover, grilled food habitus has been found to be associated with intestinal microbiota, and some intestinal microbiota was associated with colonic polyp formation and with the risk of developing CRC.[28,29]

Diet, as a complex mixture of nutrients and foods, frequently plays its health impacts as a whole, and recent dietary guidelines emphasized the importance of the whole diet quality rather than individual food or nutrient. Therefore, this study further developed a diet quality score for 10-year prognosis of CRC based on the above five food groups. The diet quality score was significantly associated with survival rate of CRC with adjustment for multiple covariates, and higher diet quality score was associated with lower survival rate of CRC. These observations indicated that diet quality may play important roles in relation to the prognosis of CRC, independent of stage of UICC, tumor size, chemotherapy, postoperative adjuvant radiotherapy and biomarkers indices including CEA and CA19-9. Compared to previous studies regarding this issue, few studies have examined association between the overall diet quality and prognosis of CRC, and only one study has reported that western dietary pattern is associated with lower survival rate, which partially supported the observations of this study.

This study is the first on this subject area conducted in an Asian population with long follow-up duration. However, it does have certain limitations. First, this study included only Chinese participants, which is likely to limit the generalisability of our findings to other ethnic populations. Second, as in any observational study, it is limited by the possibility of residual confounding and measurement error, such as the determinants of alcohol consumption, the presence of which would affect the accuracy of estimates in this study. Third, this study only included dietary information before the surgery, this may influence the results because patients probably changed their dietary habitus after the CRC surgery;[30] however, previous studies have reported that cancer patients frequently do not changed their diet after surgery, we may therefore expect that this limitation influence our results slightly. Fourth, the sample size was not very large, and the proportion of death cases was relative high in this study. This may result in overestimated the association between diet and survival rate of CRC. Future studies with large sample size are still warrant to validate these observations.

In conclusion, this study examined food groups and survival of CRC, five food groups regarding whole grain, fruit, red meat, grilled food and coffee consumption habitus were identified to be associated with survival rate in Chinese population. A diet quality score based on these food was also developed, and demonstrated that diet played important roles in relation to the prognosis of CRC.

AUTHOR DISCLOSURES

This work was supported by the National Natural Science Foundation of China (grant numbers 81473055, 30972539). The authors declare that they have no competing interests.

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