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• COLORECTAL CANCER •

Nested case-control study on the risk factors of colorectal cancer

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Abstract

AIM: To investigate the risk factors of colon cancer and rectal cancer.

METHODS: A nested case-control study was conducted in a cohort of 64 693 subjects who participated in a colorectal cancer screening program from 1989 to 1998 in Jiashan county, Zhejiang, China. 196 cases of colorectal cancer were detected from 1990 to 1998 as the case group and 980 non-colorectal cancer subjects, matched with factors of age, gender, resident location, were randomly selected from the 64 693 cohort as controls. By using univariate analysis and mutivariate conditional logistic regression analysis, the odds ratio (OR) and its 95 % confidence interval (95 %CI) were calculated between colorectal cancer and personal habits, dietary factors, as well as intestinal related symptoms.

RESULTS: The mutivariate analysis results showed that after matched with age, sex and resident location, mucous blood stool history and mixed sources of drinking water were closely associated with colon cancer and rectal cancer, OR values for the mucous blood stool history were 3.508 (95 %CI: 1.370-8.985) and 2.139 (95 %CI: 1.040-4.402) respectively; for the mixed drinking water sources, 2.387 (95 %CI: 1.243-4.587) and 1.951 (95 %CI: 1.086-3.506) respectively. All reached the significant level with a *P*-value less than 0.05.

CONCLUSION: The study suggested that mucous blood stool history and mixed sources of drinking water were the risk factors of colon cancer and rectal cancer. There was no any significant association between dietary habits and the incidence of colorectal cancer.

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INTRODUCTION

Colorectal cancer is one of the most common malignant tumors[1-6]. During the past decades, the incidence of colorectal cancer was increased all around the world, more than 500 000 cases were diagnosed as colorectal cancer per year. In the east of China, there has been a higher incidence of colorectal cancer. In Jiashan County, the mortality rate of colorectal cancer was the highest among China, which is about 20/100 000 per year[7].

The causes of colorectal cancer are generally regarded as two aspects: heredity and environment[8-10]. The former includes family history of cancer, intestinal polyp history, and so on. The later includes particularly dietary habit and physical activity.

Nested Case-Control Study (NCCS), an analytical epidemiological study method, was first presented by Mantel N, an American epidemiologist, in 1973[11], and it was widely used after 1980' s[12-21]. All the subjects in such study are selected from a whole cohort, which is generally called cohort set. Compared with the cohort study, NCCS has the privilege of time-saving, money-saving, and trouble-saving; while compared to case-control study, since the exposure data are collected before the incident of disease, it is certain of the causes and time consequences relationship, and observational bias could be controlled efficiently. All of these characteristics of NCCS are suitable to the study of chronic disease, such as cancer.

There are many reports on the risk factors of colorectal cancer using classical case-control study method, however, few studies used nested case-control study method[22-29]. The purpose of this study is to explore the risk factors of colorectal cancer, providing evidence for the prevention of colorectal cancer.

MATERIALS AND METHODS

Selection of cases and controls

A colorectal cancer screening program beginning on 1st May 1989 and ending on 30th April 1990 was conducted in ten countries which belonged to Jiashan county, Zhejiang province, China, including Weitan town, Yangmiao country, Xiadianmiao country, *et al*. From 75 842 eligible subjects aged 30 years and over, 64 693 subjects were enrolled as the base cohort set, the respondence rate was 85.3 %. Moreover, Jiashan county has founded cancer registration system and colorectal cancer report system, monitoring new cancer cases, including colorectal cancer. The cases in this study, who had participated in the 1989-1990 screening program, were the new colorectal cancer patients reported by Institute of Cancer Research and Prevention of Jiashan county. Up to 1998, the total number was 196 cases. Of which, 151 cases were pathological diagnosed, account for 77.1 %, 20 cases were diagnosed in the operation, 10.2 %, 23 cases were diagnosed by endoscopy, 11.7 %. Under the principle of same-country or town, same-sex, and no more than 3 years age disparity, 980 non-colorectal cancer subjects in the cohort set were selected as controls, resulting the final study subjects of 196 cases and 980 controls.

Contents of the study

The study contents composed of three parts as follow: (1). General characteristics: including age, sex, job types, educational levels, address *et al*; (2). Personal habits: including dietary habits, drinking water sources, alcohol consumption and cigarette smoking, *et al*; (3). Symptoms and disease history related with colorectal cancer: including changes of stool status, abdominal operation history, intestinal disease history, asthma history and allergy history, family cancer history, ancylostomiasis history, drug using history, psychic stimulation history, and so on.

Investigation methods and quality control

In the 1989-1990 screening investigation, a well-built *Investigation Manual* as the uniform criteria for inquiring the subjects and filling up the constructed questionnaire was used. All interviewers were trained focusing on the skills of inquiring. No subjects refused to be interviewed except that they were out of towns. For building the database, the questionnaires were coded and put into computer twice to control bias. The data used in this study were taken from this database.

Statistical analysis

Classical analysis methods of case-control study can be used to NCCS data, usually calculating OR value. In this study, Chi-square test was used in the univariate analysis of the data; conditional logistic regression was used in the multivariate analysis. The SPSS 10.0 for windows and the SAS system for windows, version 6.12, were used for completing all the statistical analyses.

RESULTS

General information

In this study, there were 196 cases (84 colon cancer, 112 rectal cancer) and 980 controls. The distribution of age between cases and controls for male and female was shown in Table 1.

Table 1 The distribution of subjects by age and sex

age	male		female	
	case	control	case	control
30-	3	15	7	35
35-	9	49	3	15
40-	14	69	3	19
45-	11	52	14	66
50-	21	110	14	78
55-	24	114	22	104
60-	11	57	13	63
65-	11	54	3	15
70-	2	10	5	26
75-	2	10	3	14
80-	0	0	1	5
Total	108	540	88	440

The average age of case group was 54.5±10.6 years, while that of the control group was 54.3±10.6 year, there was no statistically significant difference (t=0.127, P=0.899).For sex, there was also no difference statistically (χ^2=0.001, P=0.979).

Univariate analysis

In order to control the possible confounding bias the age, sex and resident location were matched in the study design. Given that the risk factors of colon cancer might be different from that of rectal cancer, the analysis of the risk factors were separated into colon cancer and rectal cancer, instead of colorectal cancer. The OR and its 95 % confidence intervals (95 %CI), χ^2 and P values in the univariate analysis were showed respectively in Table 2 and Table 3 (the variables showed P>0.20 were excluded).

Table 2 Results of univariate analysis for colon cancer (cases n=84, controls n=420)

factors	OR	95 % CI		χ^2	P
pork eating(y=1,n=0)	1.481	0.846	2.593	1.890	0.169
drining mixed water source* (y=1,n=0)	2.273	1.255	4.117	7.332	0.007
drining gutter water (y=1,n=0)	1.639	0.777	3.457	1.680	0.195
drining well water (y=1,n=0)	0.542	0.338	0.870	6.445	0.011
chronic diarrhea history(y=1,n=0)	2.018	1.003	4.060	3.871	0.049
constipaton history(y=1,n=0)	0.483	0.171	1.363	1.888	0.169
appendicitis history(y=1,n=0)	1.697	0.966	2.981	3.386	0.066
appendix operating history(y=1,n=0)	1.707	0.873	3.334	2.446	0.118
intestinal polyps history(y=1,n=0)	6.503	2.009	21.049	9.762	0.002

*drinking mixed water source refers to the subjects drinking different type of water sources through his / her lifetime ,mostly drinking river water and gutter water. So is Table 2,3 and 4

Table 3 Results of univariate analysis for rectal cancer (cases n=112, controls n=560)

factors	OR	95 % CI		χ^2	P
drining mixed water source (y=1,n=0)	2.021	1.170	3.491	6.363	0.011
mucious blood history (y=1,n=0)	2.138	1.122	4.072	5.335	0.021
defaecation drug using (y=1,n=0)	2.280	0.711	7.312	1.923	0.166
cholecyst excision history (y=1,n=0)	2.294	0.715	7.352	1.195	0.163

In Table 2, it was showed that four variables, well water drinking, mixed water source drinking, chronic diarrhea history and intestinal polyp history, were significantly associated with colon cancer (P<0.05). The factor of appendicitis history showed an OR value close to significant level (P=0.066). For rectal cancer in Table 3, there were two variables reached the significant level of P=0.05, which were mixed water source drinking (OR=2.02) and mucous blood stool history (OR=2.14).

Mutivariate analysis

The variables showing associations with the risk of colon cancer and rectal cancer at P<0.15 level were further tested in forward stepwise conditional logistic regression models. The final model consisted of those variables showing a significant association with the risk of colorectal cancer at P<0.05 level. Results were showed in Table 4 and Table 5 for colon and rectal cancers, respectively.

Table 4 Results of multivariate analysis for colon cancer

factors	OR	95 % CI		P
drining mixed source water (y=1,n=0)	2.387	1.243	4.587	0.009
mucous blood history (y=1, n=0)	3.508	1.370	8.985	0.009

Table 4 and Table 5 illustrated that, at P=0.05 level, both for colon cancer and rectal cancer, the final logistic regression model comprised two factors: mixed water source drinking and mucous blood stool history.

Table 5 Results of multivariate analysis for rectal cancer

factors	OR	95%CI		P
drinking mixed water source (y=1, n=0)	1.951	1.086	3.506	0.025
mucous blood history (y=1, n=0)	2.139	1.040	4.402	0.039
factors	2.870	1.117	7.371	0.029

DISCUSSION

It is generally believed that colorectal cancer is the combined outcome of heredity and environment[8-10,30]. Despite uncertainties regarding the underlying association between heredity and colorectal cancer, the genetic factors may affect the individual sensitivity to cancer[3,30-37]; many documents had reported that the environmental factors might also influence colorectal cancer[37-49]. On the secondary prevention for colorectal cancer, symptoms and/or disorders of pre-cancer, such as intestinal polyps, ulcerative colitis, should be considered[50,51].

Univariate analysis results of this study showed that drinking well water is a protective factor for colon cancer, OR value was 0.542, (P<0.05); drinking mixed water, mostly drinking river water and gutter water, was a risk factor both for colon cancer and rectal cancer, OR values were 2.387 (95 %CI: 1.247-4.587) and 1.951 (95 %CI: 1.086-3.506) in multivariate conditional logistic model, respectively. The association between drinking mixed water and colorectal cancer is consistent with former study. In this study, country subjects account for about 75 %, most of the mixed water drinking aggregated in country. In the local country, people usually were drinking river water and well water. It reflects that uncertainty of drinking water source, especially mixed drinking river water and gutting water would increase the incidence of colon cancer and rectal cancer. The findings in this study resembled other study reports[47,52].

Chronic diarrhea, mucous blood stool and constipation history are the pre-clinical symptoms of colorectal cancer[53-56]. This study has found the positive association between mucous blood stool history and colorectal cancer. In final colon cancer logistic model and rectal cancer logistic model, the OR values of mucous blood stool history were 3.508 (95 %CI: 1.370-8.985) and 2.139 (95 %CI: 1.04-4.402) respectively, both reached statistical significant level. Univariate analysis also showed that, for colon cancer, the OR value of chronic diarrhea history was 2.018 (95 %CI: 1.023-4.06), P<0.05, but did not enter the final logistic regression model.

Intestinal polyp history commonly regarded as a high risk factor for colorectal cancer[57-65]. Although the univariate analysis result showed a positive association between intestinal polyp history and colon cancer, OR=6.503 (95 %CI: 2.009-21.049), P<0.05, after being matched with age, sex and location, the factor did not enter the final logistic regression model. However, the association between intestinal polyp history and rectal cancer could not reach the significant level even in the univariate analysis.

Although the association between dietary habits and colorectal cancer has been reported[35,38,39,41,45,49, 66,67], this study was not able to confirm such a positive association. It was reported that increasing fat while reducing fibrous in diet would increase the incidence of colorectal cancer[68-70]. In this study, after merging the two variables, pork eating and vegetable eating, into one variable by cross-difference method, we got a negative association. Red meat eating, such as fish cooked with soy souse, was reported to be the risk factor of colorectal cancer[71], but the result of this did not agree with that. Moreover, recent reports were not consistent with each other about the association between cigarette smoking and colorectal cancer, nor does the alcohol consumption[71-76]. This study did not find any statistical association between cigarette smoking, nor was alcohol consumption and colorectal cancer.

Nested case control study, namely case control study within cohort, is based on a cohort set. After baseline investigation for the cohort set, including population structure, exposure factors and pertinent factors, the study subjects are divided into two groups: the disease individuals form the case group and the individuals of control group need to be randomly selected from the non-disease subjects. This kind of study can be analyzed statistically as a case-control study. The risk factors found in nested one are certain in cause and time consequence. In addition, the number of case in this study was abundance after ten years of follow-up; the controls were randomly selected from the whole disease-free cohort set and can represent the normal public population well. All of these endue the results with persuasion.

It should be noted that, after ten years of follow-up, some exposure factors may have changed, factors such as dietary habits, drinking water sources, intestinal disease history may be different from the primate investigation. All the changes may discount the preciseness of the conclusion. That the association between dietary habits and colorectal cancer could not be put forward any positive evidence might be explained by such changes.

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