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• BRIEF REPORTS •

Meta analysis of risk factors for colorectal cancer

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Abstract

AIM: To study the risk factors for colorectal cancer in China.

METHODS: A meta-analysis of the risk factors of colorectal cancer was conducted for 14 case-control studies, and reviewed 14 reports within 13 years which included 5034 cases and 5205 controls. Dersimonian and Laird random effective models were used to process the results.

RESULTS: Meta analysis of the 14 studies demonstrated that proper physical activites and dietary fibers were protective factors (pooled OR<0.8), while fecal mucohemorrhage, chronic diarrhea and polyposis were highly associated with colorectal cancer (all pooled OR>4). The stratified results showed that different OR values of some factors were due to geographic factors or different resourses.

CONCLUSION: Risks of colorectal cancer are significantly associated with the histories of intestinal diseases or relative symptoms, high lipid diet, emotional trauma and family history of cancers. The suitable physical activities and dietary fibers are protective factors.

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INTRODUCTION

Meta-analysis named by Glass, is generally defined as a quantitative summary of studies in a particular area, which has addressed the same research question, and an overall summary obtained by statistically aggregating the results of the reviewed studies. It is used to improve the statistical efficiency, to evaluate the disadvantages of formulated researches, and hypothesis and to reach reliable conclusions from the mixed assortment of the potentially relevant studies to determine the most promising directions for future researches. It has been gradually applied in medicine since it was adopted in 1970s.

Colorectal cancer is one of the most malignant cancers in China and has been steadily increasing in frequency in large or middle cities[1]. Thus, in order to provide the overall information on colorectal cancer risk factors, we performed a meta analysis of the results of 14 case-control studies in China.

MATERIALS AND METHODS

Materials

The published Chinese literatures of case-control studies related to colorectal cancer risk factors from 1988 to 2000 were collected by bibliographic searches through Index of Chinese Science and Technology Data. The selection criteria of literature were as follows: The independent case-control studies were published in Chinese magazines from 1988 to 2000, each study should have the synthetic statistical index: odds ratio (*OR*), the similar research goal with the identical study method. The overall results of literature should be presented with the corresponding statistical index, the latest articles were chosen among several ones with the same sample size. Duplicated, poor quality reports or those with little information on colon cancer were discarded. Thus, 14 papers were chosen by screening, and 5 034 cases and 5 205 controls were accumulated.

Methods

Different stratified studies were performed, including studies on prevalence/death cases (CD) versus incidence cases (ND) according to different cases, studies on general population (PB) and on patients in hospital (HB). The studies were classified in rural or urban areas in the north (NOR) and those in the south (SOU) separated by the Yangtze River as the boundary. Studies were divided into colon cancer (Jca) and rectal cancer (Zca) according to the sites of cancer.

Statistical treatment

Test of equal variance was conducted before statistical analysis, and the index odds ratio (OR) was performed using the model established by Dersimonian and Laird. The fundamental principle was as follows: $y_i=lnOR_i$, with its variance: $S_i=[P_{1\,i}(1-P_{1\,i})/y_in_{1i}]+[P_{2i}(1-P_{2i})/n_{2i}]$, ($P_{1i}$ and n_{1i} are the exposing rate of the case group and the sample size, respectively; P_{2i} and n_{2i} are the corresponding parameters in control group). OR could be calculated with the confidence limit, standard error or Chi-squared value in some way if the basic data could not be acquired. If the total comprehensive effect was $\bar{y}^*$, then $\bar{y}^*=\sum(W_i^*\cdot y_i)/\sum W_i^*$, with 95 % confidence interval $\bar{y}^*\pm1.96\cdot SE(\bar{y}^*)$.

$$SE(\bar{y}^*)=1/\sum W_i^*$$
$$W_i^*=(W_i^{-1}+\Delta^2)^{-1}$$
$$W_i=S_i^{-1}$$
$$\Delta^2=max\{0,Q-(k-1)/\sum W_i-(\sum W_i^2/\sum W_i)\}$$
$$Q=\sum[W_i(y_i-\bar{y})^2]$$
$$\bar{y}=\sum(W_i\cdot y_i)/\sum W_i$$

RESULTS

The papers used in the studies are shown in Table 1. The number of literature in Zhejiang accounted for a half of the total in this country since Zhejiang had a high incidence of colorectal cancer.

Meta analysis showed that all the risk factors of colorectal cancer except alcohol drinking were significant (P<0.05), (Table 2), while proper physical activities and dietary fibers were protective factors (pooled OR was 0.6-0.8). Histories of fecal mucohemorrhage and bowel polyps were more

significantly associated with colorectal cancer (pooled OR>4) than other ones (pooled OR was 1-4).

Results of the stratified meta analysis including index cases, study area, location of cancer and origins of the controls are shown in Table 3. The pooled OR of family history of cancers differed significantly between prevalence/death cases (CD) and incidence cases (ND), which in the latter (pooled OR=3.73 [95 % confidence interval (CI) 3.14-4.44]) was one-fold more than that in the former (1.76 [1.71-1.81]). History of chronic diarrhea was more frequently significant among rectum cancers (pooled OR=4.02, $P<0.05$). However, no significant association was observed with colon cancer ($P>0.05$).

Table 1 Case-control studies on risk factors of colorectal cancer

No	Author	Area	Number of cases	Number of factors	Sources of references
1	JIAO Den-Ao	Jiashan	160	9	Zhonghua Liuxingbingxue Zazhi, 1988, 9(6): 354-357
2	WU Den-Ren	Jiashan	114	5	Shiyong Zhongliu Zazhi, 1990, 5(2): 95-99
3	YANG Gong	Shanghai	850	2	Zhonghua Liuxingbingxue Zazhi, 1992, 13(1): 30-33
4	ZHANG Cao	Beijing	250	5	Zhonghua Liuxingbingxue Zazhi, 1992, 13(6): 321-323
5	ZOU Run	Jiashan	41	10	Zhongguo Manxingbing Yufang Yu Kongzhi, 1993, 1(5): 213-215
6	MEN Fan-He	Guangdong	100	3	Diyi Junyi Daxue Xuebao, 1994,14(4): 281-283
9	LIU Xi-Yong	Jiashan	286	6	Zhongguo Manxingbing Yufang Yu Kongzhi, 1994, 2(3): 122-124
7	YANG Gong	Shanghai	1328	4	Zhonghua Liuxingbingxue Zazhi, 1994, 15(5): 299-303
8	YANG Gong			3	Zhongguo Zhongliu Linchuang, 1995, 22(6): 403-408
10	LAI Kuang-De	Dalian	129	3	Zhongguo Manxingbing Yufang Yu Kongzhi, 1995, 3(3): 106-109
11	HE Xi-Zhen	Shenyang	390	2	Shiyong Zhongliuxue Zazhi, 1996, 10(2): 64-65
12	YANG Gong	Shanghai	3166	3	Zhongliu, 1996, 16(2): 74-78
13	ZOU Run	Hangzhou	245	5	Zhejiang Yike Daxue Xuebao, 1996, 25(5): 204-206
4	LIU Ai-Zong	Hunan	153	7	Zhongguo Gonggong Weisheng, 1997, 13(4): 206-207

Table 2 Results from meta-analysis of risk factors of colorectal cancer

Factors	Number of references	Pooled *OR and* 95 % C.I.	Factors	Number of references	Pooled *OR and* 95% C.I.
(1) History of chronic diarrhea	7	4.80 (4.30~5.37)	(8) Pickled vegetables	3	1.86 (1.67~2.07)
(2) History of fecal mucohemorrhage	5	7.18 (5.06~10.21)	(9) High lipid food	3	3.16 (2.22~4.51)
(3) History of bowel polyps	5	12.69 (7.49~21.48)	(10) Proper physical activities	4	0.74 (0.72~0.77)
(4) History of constipation	4	2.23 (1.95~2.54)	(11) Alcohol drinking	5	1.06 (0.91~1.24)
(5) History of appendicitis	3	1.98 (1.71~2.28)	(12) Cigarette smoking	5	1.40 (1.10~1.77)
(6) Dietary fibers	5	0.79 (0.59~0.99)	(13) Emotional trauma	4	2.95 (2.81~3.09)
(7) Fish fry-cooked with soybean sauce	4	2.99 (2.69~3.35)	(14) Family history of cancers	7	2.27 (2.12~2.44)

(1) references: 1,2,5,7,9,13, 14 (2) references: 1,5,7,9,13 (3) references: 1,2,5,7,12
(4) references: 1,5,7,9 (5) references: 1,2,5 (6) references: 4,6,10,11,14
(7) references: 1,5,6, 7 (8) references: 2,6,14 (9) references: 4,5,14
(10) references: 4,10,13,14 (11) references: 2,5,8,13,14 (12) references: 2,5,6,8,14
(13) references: 1,4,5,7 (14) references: 1,3,4,5,6,7,14

Table 3 Results from stratified meta-analysis of risk factors of colorectal cancer

Factors	Strata	Pooled *OR and* 95% C.I.	Factors	Strata	Pooled *OR and* 95% C.I.
History of chronic diarrhea	CD[a]	6.04 (5.45~6.70)	Pickled vegetables	CD	1.58 (1.20~2.07)
	ND[a]	3.99 (2.81~5.66)		ND	2.30 (1.30~4.20)
	Jca[b]	7.01 (0.48~10.12)		Jca	1.70 (1.10~2.50)
	Zca[b]	4.02 (1.13~14.21)		Zca	1.50 (1.01~2.30)
	HB	6.60 (2.46~11.21)		HB	2.30 (1.30~4.20)
	PB	4.50 (3.90~5.17)		PB	1.58 (1.20~2.07)
Fecal muco-hemorrhage	CD[b]	9.81 (4.55~21.17)	Alcohol drinking	CD[b]	0.91 (0.71~1.17)
	ND[b]	3.60 (2.80~4.80)		ND[b]	1.65 (1.03~2.63)
	Jca[b]	2.80 (0.75-10.46)		HB[b]	1.65 (1.03~2.63)
	Zca[b]	4.56 (2.12~9.81)		PB[b]	0.91 (0.71~1.17)
History of bowel polyps	CD[a]	7.40 (4.13~13.28)	Cigarette smoking	CD[b]	0.74 (0.43~1.27)
	ND[a]	22.30 (12.40~40.01)		ND[b]	1.92 (1.49~2.47)
	Jca	17.42 (14.54~20.85)		HB[b]	1.92 (1.49~2.47)
	Zca	12.14 (3.07~28.00)		PB[b]	0.74 (0.43~1.27)
History of constipation	CD	2.53 (1.55~4.11)	Emotional trauma	Jca[b]	2.80 (1.51~3.28)
	ND	1.90 (1.50~2.40)		Zca[b]	1.63 (0.39~6.85)
	Jca[b]	3.4 (1.02~11.39)		NOR	3.36 (2.21~5.12)
	Zca[b]	0.89 (0.09~8.53)		SOU	2.53 (2.28~2.81)
Dietary fibers	CD[b]	0.43 (0.18~0.97)	Proper physical activities	CD	0.79 (0.77~0.81)
	ND[b]	1.02 (0.40~2.57)		ND	0.57 (0.35~0.90)
	NOR[b]	0.43 (0.18~0.97)		NOR[a]	0.69 (0.67~0.71)
	SOU[b]	1.02 (0.40~2.57)		SOU[a]	0.77 (0.70~0.85)
	HB[b]	0.86 (0.58~0.96)		HB	0.57 (035~0.90)
	PB[b]	0.37 (0.06~2.13)		PB	0.79 (0.77~0.81)
Fish fry-cooked with soybean	CD	2.84 (2.31~3.48)	Family history of cancers	CD[a]	1.76 (1.71~1.81)
	ND	3.20 (1.60~6.30)		ND[a]	3.73 (3.14~4.44)
	Jca[b]	7.01 (1.10~12.01)		Jca[a]	2.84 (2.58~3.13)
	Zca[b]	1.18 (0.30~8.01)		Zca[a]	1.52 (1.34~1.72)
	HB	3.20 (1.60~6.30)		HB[a]	3.73 (3.14~4.44)
	PB	2.84 (2.31~3.48)		PB[a]	1.76 (1.71~1.81)

[a]: No mutual involvement of OR by correspondent two ranges of 95 % CI was found. [b]: At least one 95 % CI of pooled OR was found including 1.00.

DISCUSSION

Environmental factors are the predominant contributors to colorectal cancer, and genetic factors show significant effects[1,3-5]. Meta analysis indicated that a variety of factors could contribute to colorectal cancer as follows.

1. **Intestinal disorders and colorectal cancer** Precancerous syndromes or diseases based on the review of Chinese literature included chronic diarrhea, fecal mucohemorrhage, polyposis, constipation, etc. Therefore, colorectal cancer should be suspected if chronic diarrhea, fecal mucohemorrhage or constipation of unknown cause occur in patients with a history of bowel polyps[2]. In addition, whether appendicitis is a risk factor of colorectal cancer remains plausible. However, it is considered as one of the risk factors since its pooled OR was 1.98 ($P<0.05$) demonstrated in this study. Because appendicitis weakens the immunological function of appendix and thus causes colorectal cancer.

2. **Diet** High fat diet was the highest risk factor of colon cancer ($OR=3.16$), followed by fish fry-cooked with soybean sauce ($OR=2.99$) and pickled vegetables ($OR=1.86$). In contrast, dietary fibers played a protective role in colorectal cancer (pooled $OR=0.79$, $P<0.05$). Fried fish with soybean sauce may generate mutagenic heterocyclic amines as red meats[6,7]. The dietary fiber may shorten the transporting time of excrement in intestines, decrease the time of carcinogens affecting intestinal mucus and reduce the growth of bacterial strains that produce carcinogens in the colonic lumen. However, no evidence was reported to suggest that high dietary fiber could reduce the incidence or recurrence of adenomatous polyps during a two to four year period[8]. In addition, many experimental findings indicated an association between diet with high calcium and vitamin D and low risk for colorectal cancer, which deserve further study[9].

3. **Physical activity, cigarette smoking and alcohol** The relationship between physical activities and colorectal cancer has been noticed recently. Studies showed that people with proper physical activities had low incidence of colorectal cancer since appropriate physical activities could decrease the random segmentation without propulsion of the intestine, and increase effective vermiculation, thus shortening the transit time of excrement in the intestine and reducing the contact between intestinal mucosa and carcinogen. No significant association was found between alcohol and colorectal cancer in meta analysis, though other studies reported that significantly lower levels of serum cholesterol and triglycerides were found in daily alcohol drinkers with colorectal adenomas[10], while cigarette smoking was regarded as a risk factor since its OR exceeded 1($P<0.05$) although it is plausible whether smoking causes colorectal cancer.

Moreover, it was suggested that long-term emotional trauma and family history of cancers were related to the increased risk of colorectal cancer. However, further work is needed to clarify the mechanism.

Bias and confounding factors can also be found in meta analysis, and so we conducted the stratified analysis as follows: (1) Since studies on the prevalence or death cases could lead to bias due to selection and exposure misclassification, stratified analysis for the index cases was performed, which showed that there was a difference between studies on the prevalence or death cases and those on the incidence cases (Table 3). (2) The results of different strata suggested that studies on incidence cases based on the population should be conducted strictly in the future. (3) Risk factors of colorectal cancer in south and in the north may be different. (4) The cause of colon cancer may not be completely the same as that of cancer in the rectum. In this study, chronic diarrhea and fecal mucohemorrhage were more frequent in cancers of rectum, while complaint of constipation, fish fry-cooked with soybean sauce and emotional trauma were more frequently seen in colon cancer.

Meta means "more comprehensive, transcending"[11]. Meta analysis has extended quickly from social sciences to medical sciences. Incidence of colorectal cancer has increased over the last decade in China, and it is necessary to study its causes. Thus, synthetic analysis was performed on the etiology of colorectal cancer in China in 12 years with meta analysis. However, the potential confounding factors may not be well controlled due to the limited literature and therefore the result may be affected. Thus, further study is required.

REFERENCES

1 **Zhang ZS**, Zhang YL. Development of research on colorectal cancer in China. *Shijie Huaren Xiaohua Zazhi* 2001; **9**: 489-494
2 **Li SR**. Strategy for the early diagnosis of colorectal cancer. *Shijie Huaren Xiaohua Zazhi* 2001; **9**: 780-782
3 **Lai MD**. Related genes of generation and development of colorectal cancer in China. *Shijie Huaren Xiaohua Zazhi* 2001; **9**: 1227-1232
4 **Sheng JQ**, Chen ZM. Screening of colorectal cancer with the related genes. *Shijie Huaren Xiaohua Zazhi* 2001; **9**: 783-785
5 **Johns LE**, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risks. *Am J Gastroenterol* 2001; **96**: 2992-3003
6 **Sweeney C**, Coles BE, Nowell S, Lang NP, Kadlubar FF. Novel marker of susceptibility to carcinogens in diet: Associations with colorectal cancer. *Toxicology* 2002; **181-182**: 83-87
7 **Norat T**, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: dose-response meta-analysis of epidemiological studies. *Int J Cancer* 2002; **98**: 241-256
8 **Asano T**, Mcleod RS. Dietary fiber for the prevention of colorectal adenomas and carcinomas. *Cochrane Database Syst Rev* 2002; **2**: CD003430
9 **Lipkin M**. Update of preclinical and human studies of calcium and colon cancer prevention. *World J Gastroenterol* 1999; **5**: 461-464
10 **Fujimori S**, Kishida T, Mitsui K, Yonezawa M, Nagata K, Shibata Y, Tanaka S, Tatsuguchi A, Sato J, Yokoi K, Tanaka N, Ohaki Y, Sakamoto C, Kobayashi M. Influence of alcohol consumption on the association between serum lipids and colorectal adenomas. *Scand J Gastroenterol* 2002; **37**: 1309-1312
11 **Bailar JC**, Mosteller F. Medical uses of statistics. 2nd edition. *Waltham Mass: Nejm Books* 1992: 422-427

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