Correlation Between Late-stage Schistosoma Infection and Colorectal Cancer: a Colorectal Cancer Screening Among Elderer in the Qingpu District of Shanghai

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Research Article

Keywords: schistosoma infections, Early screening, risk assessment, colorectal cancer

Posted Date: May 25th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-537627/v1>

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Abstract

Cancer monitoring of Shanghai showed a rapid increase in the incidence of colorectal cancer. Colorectal cancer risk assessment allows for rapid screening of high-risk populations. The colorectal cancer screening of elderly residents is ongoing since 2013 in Shanghai. This initiative screened 85,525 people from 11 communities of the Qingpu District. Screening included a questionnaire-based risk assessment and two Fecal Occult Blood Tests (FOBTs). We conducted a retrospective case study of patients with positive screening results that underwent fibro-colonoscopy examinations to investigate their histories of schistosoma infection, smoking, alcohol consumption, and dietary habits. A total of 85,525 people were screened in this study. Colorectal cancer was resulted in a prevalence of 59.84/100,000. And the prevalence of schistosoma infection was 400/100,000. Among patients with schistosoma infection, the positive rate of FOBT was 67.01%, in contrast to an overall positive rate of FOBT among all subjects of 17.00% [(Pearson $\chi^2=672.42$, $P < 0.0001$, OR = 3.94 (3.67,4.23)]. The prevalence of colorectal cancer among patients with schistosoma japonicum infections was 4,155.84/100,000, while the prevalence of colorectal cancer among all subjects was 44.15/100,000 [Pearson² = 980.62, $P < 0.001$, OR = 94.12 (53.05, 166.97)]. Our study found a high degree of correlation between late stage schistosoma infection of the intestinal tract and the occurrence of colorectal cancer and colonic adenoma. For patients with lesions caused by schistosoma infections of intestinal tract, the risk of colorectal cancer was higher than that of patients without intestinal schistosoma infections. Early screening and risk assessment can facilitate early diagnosis and treatment of colorectal cancer and colonic adenoma.

Introduction

Colorectal cancer tumors occur in the colonic segment of the digestive tract. Colorectal cancer includes tumors of the colon and rectum. Monitoring data obtained from the Shanghai Municipal Center for Disease Control and Prevention showed that the incidence and mortality of colorectal cancer has been significantly increasing. In Shanghai, mortality attributable to colorectal cancer has jumped from the seventh largest in the 1970s to the fourth largest in 2013, while the associated morbidity rate has become the third largest. The monitoring data obtained from the Qingpu District were similar to those for the entire city of Shanghai. The prevalence of colorectal cancer in the Qingpu District was 21.36/100,000. In addition, the prevalence rate of colorectal cancer was higher among males than females¹. In the Qingpu District, the mortality rate of colorectal cancer was 14.17/100,000, with a slightly higher mortality rate among females compared to males.

Previous studies have shown that the incidence of colorectal cancer was associated with lifestyle factors such as a high fat diet², smoking³, alcohol consumption⁴, family history⁵, and a history of gastrointestinal surgery⁶. Since 2013, Shanghai has organized colorectal cancer screening of elder residents within its communities. Through questionnaire-based risk assessments, fecal occult blood tests, and fibro-colonoscopy, Shanghai aims to achieve earlier diagnosis and treatment of colorectal

cancer. The colorectal cancer screening project in Qingpu District was completed over three years of phase I screening, from May 2013 to December 2015.

Materials And Methods

Target population. Shanghai residents who lived in Shanghai for more than six months and had access to Shanghai's social security benefits were eligible for study inclusion, provided that female subjects were 50–74 years old and male subjects were 60–74 years old. All subjects participated in the community colorectal cancer screening project on a voluntary basis and provided written informed consent.

Assessments. Screening involved a questionnaire-based risk assessment and fecal occult blood test (FOBT). The risk assessment questionnaire was designed by the Shanghai Municipal Center for Disease Control and Prevention, and collected basic information and information related to the main known risk factors for colorectal cancer. The results of risk assessment were automatically determined by a computer system. At the same time, all subjects underwent two FOBTs, with results determined by an immunological method. If positive results were obtained from any one of the above procedures, the overall results were deemed “positive” and the patient was required to undergo a fibro-colonoscopy examination.

Quality control. Quality control of questionnaire-based risk assessment and FOBT tests was carried out by the Center for Disease Control and Prevention at the district and municipal level. The District Center for Disease Control and Prevention carried out a 10% quality control procedure in writing for questionnaire-based risk assessment, while 3% of the results were entered into a computer system for a secondary quality control procedure. For the interpretation of FOBT results, parallel samples were used in conjunction with a quality control procedure based on the chemical method. In addition, the Shanghai Municipal Center for Disease Control and Prevention also arranged for oncology experts to carry out secondary interpretation and quality control for pathological specimens.

Data entry. The results of risk assessment and FOBTs were entered into the Community Colorectal Cancer Screening System of the Shanghai Municipal Center for Disease Control and Prevention by doctors in community health service centers. Quality control for 20% of data entry was carried out by the District Center for Disease Control and Prevention, so as to ensure a data conformance higher than 95%. The screening data were then exported to Access2013 by the District Center for Disease Control and Prevention and analyzed.

Results

Early screening for colorectal cancer among community residents of the Qingpu District.

Over the course of three years, a total of 85,525 people in the Qingpu District, aged 50–74 years old, were screened for colorectal cancer. Among them, 56 people presented with advanced colorectal cancer. The prevalence rate was 59.84/100,000. In addition, 65 people showed tumor *in situ* with an associated

prevalence rate of 76.27/100,000, whereas the prevalence of adenoid tumors was 1,134.64/100,000, as shown in Table 1.

Table 1
Results of early screening for colorectal cancer among community residents of the Qingpu District

Age	No. of screened subjects	No. with colorectal cancer	Prevalence per 100,000	No. of patients with tumor <i>in situ</i>	Prevalence per 100,000	Adenomas	Prevalence per 100,000
50–54	6058	3	49.52	1	16.51	40	660.28
55–59	12419	4	32.21	5	40.26	93	748.85
60–64	23022	11	43.44	16	69.50	257	1116.32
65–69	20311	17	78.78	17	83.70	287	1413.03
70–74	15488	12	71.02	17	109.76	210	1355.89
75–	7927	9	88.31	9	113.54	80	1009.21
total	85225	56	59.84	65	76.27	967	1134.64

Analysis of risk factors in patients with advanced colorectal. The diagnosis rate of tumors and early-stage tumors *in situ* was twice rate observed in clinical practice. In addition, the prevalence of adenoid tumor was as high as 1,134.64/100,000.

As shown in Table 2, we used single factor analyses to conduct risk assessment of the 56 patients diagnosed with advanced colorectal cancer. After subjecting the positive results to multivariate logistical regression analysis, we found that the risk factors for advanced colorectal cancer included age, mucus, and bloody purulent stool [OR = 4.388, 95%CI (1.285, 14.988)]. In addition, a history of chronic appendicitis or appendectomy [OR = 2.058, 95%CI (1.081, 3.916)] and other tumors [OR = 4.795, 95%CI, (1.463, 15.711)] were also risk factors for advanced colorectal cancer, while the correlations with other risk factors were not significant.

Table 2
Logistical regression analysis of risk factors in patients with advanced colorectal cancer

	B	Se	Wald	d.f.	P	Exp (B)	Exp (B) 95%CI	
							Lower limit	Upper limit
Intercept	-8.398	0.450	347.946	1	0.000			
Age group	0.185	0.106	3.028	1	0.082	1.203	0.977	1.481
Hx of chronic diarrhea	0.760	0.494	2.362	1	0.124	2.138	0.811	5.634
Hx of chronic constipation	-17.497	3676.490	0.000	1	0.996	2.517E-08	0.000	. ^b
Mucus or bloody stool	1.479	0.627	5.567	1	0.018	4.388	1.285	14.988
Hx of chronic appendicitis or appendectomy	0.722	0.328	4.833	1	0.028	2.058	1.081	3.916
Hx of chronic cholecystitis or cholecystectomy	0.261	0.393	0.442	1	0.506	1.299	0.601	2.806
Hx of trauma	-17.554	5698.599	0.000	1	0.998	2.378E-08	0.000	. ^b
Hx of cancer	1.568	0.606	6.702	1	0.010	4.795	1.463	15.711
Hx of intestinal polyps	-17.334	0.000		1		2.963E-08	2.963E-08	2.963E-08
Hx of first-degree relatives with colorectal cancer	0.800	0.731	1.198	1	0.274	2.226	0.531	9.334

After regression analysis of risk factors in patients with early-stage colorectal cancer and cancer *in situ* that were discovered during screening, the risk factors of early carcinoma in situ included age [OR = 1.303, 95%CI (1.083, 1.567)], a history of chronic cholecystitis or gallbladder resection [OR = 2.482, 95%CI (1.393, 4.424)], and a history of intestinal cancer in first-degree relatives [OR = 3.674, 95%CI (1.310, 10.300)]. However, the correlation of early stage colorectal cancer with other risk factors was not significant, as shown in Table 3.

Table 3
Multivariate Logistic regression analysis of risk factors for early-stage carcinoma in situ

	B	SE	Wald	df	P	Exp(B)	Exp(B) 95%CI
							Lower limit Upper limit
Intercept	-8.441	.412	419.370	1	.000		
Age group	.264	.094	7.841	1	.005	1.303	1.083 1.567
Hx of chronic diarrhea	.098	.534	.033	1	.855	1.103	.387 3.142
Hx of chronic constipation	.525	.476	1.218	1	.270	1.691	.665 4.296
Mucus or bloody stool	.587	.747	.618	1	.432	1.799	.416 7.770
Hx of chronic appendicitis or appendectomy	– .302	.382	.625	1	.429	.740	.350 1.563
Hx of chronic cholecystitis or cholecystectomy	.909	.295	9.507	1	.002	2.482	1.393 4.424
Hx of trauma	.972	.618	2.471	1	.116	2.642	.787 8.872
Hx of cancer	– .286	1.029	.077	1	.781	.751	.100 5.640
Hx of intestinal polyps	.888	1.033	.739	1	.390	2.430	.321 18.395
Hx of first-degree relatives with colorectal cancer	1.301	.526	6.120	1	.013	3.674	1.310 10.300

The multivariate logistic regression analysis of patients with adenoid tumors that were discovered during screening revealed that the main risk factors for colonic adenoma included age [OR = 1.116, 95%CI (1.065, 1.169)], chronic diarrhea [OR = 1.507, 95%CI (1.161, 1.954)], a history of mucus and/or bloody stool [OR = 1.782, 95%CI (1.172, 2.711)], a history of chronic cholecystitis or gallbladder resection [OR = 1.383, 95%CI (1.156, 1.655)], and a history of intestinal cancer in first-degree relatives such as parents, children and siblings [OR = 2.307, 95%CI (1.643, 3.238)], as shown in Table 4.

Table 4
Multivariate Logistic regression analysis of factors related to colonic adenoma

	B	Se	Wald	df	P	Exp(B)	Exp(B) 95%CI	
							Lower limit	Upper limit
Intercept	-4.985	.098	2598.481	1	0.000			
Age group	.110	.024	21.006	1	.000	1.116	1.065	1.169
Hx of chronic diarrhea	.410	.133	9.526	1	.002	1.507	1.161	1.954
Hx of chronic constipation	– .014	.161	.008	1	.930	.986	.719	1.352
Mucus or bloody stool	.578	.214	7.287	1	.007	1.782	1.172	2.711
Hx of chronic appendicitis or appendectomy	.163	.089	3.408	1	.065	1.178	.990	1.401
Hx of chronic cholecystitis or cholecystectomy	.325	.091	12.583	1	.000	1.383	1.156	1.655
Hx of trauma	– .540	.341	2.517	1	.113	.583	.299	1.136
Hx of cancer	– .013	.284	.002	1	.963	.987	.566	1.722
Hx of intestinal polyps	.416	.387	1.157	1	.282	1.516	.710	3.236
Hx of first-degree relatives with colorectal cancer	.836	.173	23.312	1	.000	2.307	1.643	3.238

Multivariate analysis of risk factors for colorectal cancer. Among patients with colonic lesions, 385 showed calcified schistosoma eggs under fibro-colonoscopy. After examining their disease histories, the rate of schistosoma infection among subjects who underwent colorectal cancer screening was 400/100,000, indicating a relatively high rate of schistosoma infection. Since the eradication of *Oncomelania hupensis* in the Qingpu District in 1983, there have been no new cases of schistosoma infection. The survey showed that the shortest history of schistosoma infection in a patient with colonic lesions was 34 years, while the longest history was 48 years. The average duration of infection was 38.60 ± 2.77 years. The results of this screening showed that 67.01% of FOBTs were positive in individuals who had exhibited schistosoma japonicum infections, while the positive rate for FOBT in all subjects was 17.00% [Pearson $\chi^2=672.42$, $P < 0.0001$, OR = 3.94 (3.67, 4.23)]. In addition, among patients with schistosoma japonicum infection, the prevalence rate of colon cancer was 4155.84/100,000, while the prevalence rate in all subjects was 44.15/100,000 (corrected $\chi^2=980.62$, $P < 0.001$, OR = 94.12 (53.05, 166.97)], as shown in Table 5.

Table 5
Multivariate analysis of risk factors for colorectal cancer

		B	se	Wald	Df	P	Exp(B)	Exp(B) 95%CI	
								Lower limit	Upper limit
1	Intercept	-7.856	.172	2097.638	1	0.000			
	Smoking	-.261	.488	.286	1	.593	.771	.296	2.004
	Second-hand smoking	-.365	.456	.642	1	.423	.694	.284	1.696
	Milk consumption	-.030	.550	.003	1	.957	.970	.330	2.852
	Vegetable intake	3.505	.600	34.090	1	.000	33.278	10.261	107.924
	Fruit intake	-.135	.469	.083	1	.773	.873	.348	2.191
	Schistosoma infection	1.585	.523	9.185	1	.002	4.880	1.751	13.604

After investigating the behavioral risk factors associated with colorectal cancer, the multivariate logistical regression analysis suggested that *Schistosoma japonicum* infection was an important risk factor in the Qingpu District. In addition, insufficient vegetable intake was an important behavioral risk factor for colorectal cancer. There were statistically significant between-group differences in these two factors.

Discussion

Early symptoms of colorectal cancer. The early symptoms of colorectal cancer, such as mucus, bloody purulent stool, and chronic diarrhea are not obvious and are often overlooked. The results of this screening showed that the presence of early symptoms, such as a history of the aforementioned early symptoms, were positively correlated with the onset of colorectal cancer, suggesting that such symptoms were closely related to colorectal cancer^{7,8}. Therefore, in cases where there is a change in defecation habits that is greater than two weeks in duration, the possibility of colorectal cancer or adenoma should be investigated.

The risk factors for early-stage colorectal cancer. The risk factors for early-stage colorectal cancer and colonic adenoma included a history of chronic appendicitis, appendectomy, chronic cholecystitis and gallbladder surgery^{9,10}. The possible mechanisms of tumorigenesis may be reactive intestinal lesions induced by appendectomy and gallbladder surgery, which can cause digestive disorders and fat metabolism deregulation¹¹. Therefore, patients with a history of gallbladder and appendix diseases should pay attention to the possibility of colonic lesions. On the other hand, early screening and colonoscopy can be used to discover and prevent colorectal diseases.

The results of this screening. The results of this screening also showed that a history of intestinal cancer in first-degree relatives was a high risk factor for colorectal cancer and adenoma, suggesting the presence of a certain familial aggregation in colorectal cancer. Therefore, the history of colonic tumors in a family will significantly increase the possibility of colorectal cancer in *other* family members.

The prevalence of advanced colorectal cancer. The prevalence of advanced colorectal cancer gradually increased with age. For example, in subjects over 75 years old, risk was twice that of subjects who were 50 years old¹². The prevalence rate of early stage carcinoma *in situ* has increased by more than 10 times, suggesting that age was an important factor in the occurrence and development of colorectal cancer¹². Thus, with the increasing age, risk in the elderly population also increases, suggesting a need for regular colorectal cancer screening in elderly populations.

Schistosoma japonicum infections are commonly in China and Southeast Asia. The historical research showed that the *Schistosoma* parasite lives in the liver and can easily cause liver lesions^{13,14}. In addition, schistosoma eggs calcify in colorectal regions. Historically, although schistosoma infections can cause splenomegaly and dwarfish pathological manifestations¹⁵, its involvement in colorectal cancer has not been shown. In this screening, calcified schistosoma eggs were detected in some patients with colonic lesions, usually accompanied by a history of schistosoma infection. Although Shanghai officially eliminated schistosoma in 1987, there are more than 1,000 patients with advanced schistosoma infections in the Qingpu District. This screening suggested that, following deposition and calcification in the colon, schistosoma eggs may induce colorectal inflammation and hence may lead to the occurrence of colorectal cancer. Nevertheless, the mechanisms of such a hypothesis should be further clarified. Colorectal cancer may also result from changes in the gene expression of colorectal cells¹⁶ upon mechanical and biological stimulation generated by schistosoma eggs in the intestine.

***Schistosoma japonicum* infections and colorectal cancer.** Approximately 1% of patients with colonic adenoma will undergo malignant transformation after several years or several decades. In this colorectal cancer screening, the prevalence rate of colonic adenoma reached 1134.64/100,000 suggesting that the incidence of colorectal cancer could be reduced through early detection and treatment. The results of this screening showed that the mean time for colonic lesions to occur after schistosoma infection was 38.60 ± 2.77 years and the shortest time prior to colonic lesion onset was 34 years, indicating that chronic schistosoma infection could lead to colonic lesions.

During proactive screening, the prevalence of advanced colorectal cancer was more than twice that observed in patients who were diagnosed due to clinical symptoms. In addition, proactive screening could be used to discover more early-stage carcinoma *in situ*. Through early treatment after screening, the mortality rate of colorectal cancer in the population could be effectively reduced. The results of this screening further showed that patients with *Schistosoma japonicum* infection had significantly more positive FOBTs, compared to the general population. This disparity was accompanied by a higher prevalence of colorectal cancer. Routine follow-up fibro-colonoscopy and FOBT tests should be performed for patients with schistosoma infections to discover early lesions.

Through organized community events and proactive colorectal cancer screening, patients with early colorectal cancer can be effectively diagnosed, potentially resulting in significant social benefits and reduced treatment costs. In addition, proactive colorectal cancer screening can effectively reduce the medical care and follow up costs incurred by society and families. The health and economic benefits of community colorectal cancer screening should not be overlooked.

Declarations

Acknowledgements

Thanks: thanks to the public health doctors of the community health service center participating in the project, and thanks to the public health doctors of the center for Disease Control and prevention of Qingpu District for their work for the project.

Ethics reputation

The study was conducted under the guidance of Shanghai Center for Disease Control and prevention, and community residents signed the informed consent. All the investigations and sampling of the study were approved by community residents. After the review of the ethics committee of Qingpu Center for Disease Control and prevention, it did not violate medical ethics. Ethics review No. (2013-01).

Conflict of Interest Statement

There is no potential conflict of interest in this article.

Author contributions

X.Y. designed and carried out the study. S. W. and G.F.L. conducted the research and performed statistical analysis. R.F.X., K.X. and J.Z. contributed to the data collection and preparation of study subjects. X.Y. wrote the paper.

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Figures

Figure 1

Flow chart of the screening