

Advanced Colorectal Neoplasm Screening in First-Degree Relatives is Better Understanding as Cruciform Screening

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Abstract

Aim: Colonoscopy screening of colorectal neoplasm in first-degree relatives is reported frequently, and is recommended in guidelines. However, data from China is limited. This observation study is to evaluate the current situation in Dongguan, China.

Methods: All first-degree relatives were recommended to perform colonoscopy screening when a proband is found in a family. They were divided into 3 groups, the down, up and crossing screening group (children, parents and siblings of proband). Control group rolled in healthy people who underwent colonoscopy while medical examination in our hospital. All subjects ranged from 30-80 (not included) years old. Advanced colorectal neoplasm is defined as: high-grade adenoma, villioustublar adenoma, adenoma with diameter ≥ 1 cm and colorectal cancer. Colonoscopy findings of lesions, site and size of the ACNs and polyp, pathology results of all subjects were recorded. Statistical analysis was run with SPSS 19.0.

Results: In 52 subjects of the Down screening group, 6 were found to be CANs, 9 were adenoma, the overall morbidity in the group is 28.8%. 8 out of 43 subjects in up screening group were found CANs, 7 were adenoma, making the overall morbidity is 34.9% of the group. There were 3 subjects in crossing screening group out of 28 found to be ACNs, 5 subjects were adenoma, overall morbidity of the group is 28.6%. Comparing to the control group, there were 176 subjects involved, 15 of them were found to be ACNs, 9 were found adenoma, overall morbidity is 13.6% in control group. Statistical analysis indicates that there were significant statistical differences when comparing the down, up and crossing screening group to control group (all $p < 0.05$).

Conclusion: First-degree relatives of proband in Dongguan have a high incidence of colorectal neoplasm, it is recommended to run colonoscopy screening. And it is better understanding as 'Cruciform screening' while screening of first-degree relatives.

Keywords: Colonoscopy; Screening; First-degree relatives; Cruciform screening; Colorectal neoplasm; Advanced Colorectal Neoplasm (ACN)

Core Tips

Screening for asymptomatic population is an important way for colorectal cancer preventing, methods for screening include fecal occult blood tests (FOBT), blood tumor maker test, sigmoidoscopy screening, colonoscopy screening. First-degree relatives of probands are one of the most important groups of population. The misunderstanding of the two terms 'direct relatives' and 'first-degree relatives' leads to inappropriate screening performed during clinical practice. If screening between first-degree relatives changed into cruciform screening (Down-Up-Crossing screening), it will be much easier for patients and doctors to understand and make it much more acceptable in patients. Outcome from this study showed that screening for first-degree relatives is better understanding as Cruciform screening.

Introduction

There are 30,000 newly diagnosed cases of colorectal cancer in England and Welsh each year [1], the American Cancer Society estimates that 136,830 people would be diagnosed with colorectal cancer and 50,310 people would die from the disease in 2014 [2]. Evidence shows the morbidity of colorectal in America and Europe is decreasing, one of the possible reasons is that the wide use of colonoscopy screening and removal of polyp under colonoscopy [1-3]. Report in Shanghai indicated that morbidity of colorectal cancer had raised rapidly, making it the third of all malignance cancer in Shanghai, China [4]. The morbidity of colorectal cancer had reached the top 3 from No.5 during the two decades since 1981 to 2000 [5]. A recently

large-scale multicenter research including 157,943 cases of colonoscopy results analysis indicated that, the incidence rate of advanced colorectal neoplasm had rose by 1.88 times, and 0.66 times for colorectal cancer, since 1990 till now [6]. These data all shows the urgency of colorectal neoplasm screening in China [7]. Research showed that, morbidity increased of first-degree relative of colorectal cancer probands [8], first-degree relative of adenomatoid polyp also had the same tendency, especially first-degree relatives of those who had developed advanced adenoma before 60 [8,9]. First-degree relatives of colorectal cancer and advanced adenoma propositus is one of the most important group of population for screening [9-11].

Currently, the cognition of the term 'first-degree relative' in China is uneven. Our study is based on the screening of first-degree relative of colorectal cancer or advanced adenoma probands in Dongguan city, and reveals the value in colorectal cancer screening. We modified it into an easy understanding, simply and practicable way which we called cruciform screening (up-down-cross screening).

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Variables	Gender		Age					Lesions			
	M	F	30~	40~	50~	60~	70~79	ACN	Adenoma	Polyp	Normal
Down group	28	24	8	31	15	0	0	6	9	10	27
Up group	22	21	0	0	4	23	16	8	7	8	20
Crossing group	15	13	4	5	10	5	4	3	5	7	13
Study group	65	58	12	40	29	28	16	17	21	25	60
Control group	109	67	16	57	34	38	31	15	9	16	136

Table 1: Characterization of all groups.

Variables	Down group	Up group	Crossing group	Study group	Control group
Male	28	22	15	65	109
Female	24	21	13	58	67
Total	52	43	28	123	176

Note: Comparing study group to control group, $\chi_1^2=2.457$, $P_1=0.074$; comparing all subgroups to control group, $\chi_2^2=2.535$, $P_2=0.472$.

Table 2: Comparing on gender of all groups.

Variables	Maximum age (year)	Minimum age (year)	Mean age (year)	SD (year)
Study group	79	30	54.07	12.063
Control group	79	30	55.04	12.572

Note: $F=0.442$, $P=0.506$

Table 3: Comparing on age of study group and control group.

Variables	Maximum age (year)	Minimum age (year)	Mean age (year)	SD (year)
Down group	59	30	45.77	6.998
Up group	79	51	66.72	6.196
Crossing group	79	30	54.07	12.575
Control group	79	30	55.04	12.572

Note: $F=28.275$, $P<0.01$

Table 4: Comparing on age of all subgroups and control group.

Materials and Methods

Study population and data collection

The study started on December 1st, 2013, and ended on 31st December 2015. All cases enrolled were from Dongguan Kanghua hospital. The study was designed to comparing the morbidity between first-degree relatives group, which was divided into 3 subgroups, down screening group (down group), up screening group (up group), cross screening group (cross group), and control group. Down group is to screen the children whose parent was found to be colorectal cancer or advanced adenoma patient, up group is to screening parents of colorectal cancer or advanced adenoma patient while cross group is to screening siblings of colorectal cancer or advanced adenoma patient, control group involved all cases who underwent colonoscopy for general health check-up at Dongguan Kanghua hospital from 1st to 31st December 2015. All participants enrolled were aged from 30 (include) to 80 (not include). Cases matched the following criteria were exclude: A. Data was incomplete. B. Those whom were clearly diagnosed of polyp and were prepared for polypectomy. C. Follow up patients of post polypectomy.

During the colonoscopy screening, the site, size, number and pathology result were all recorded when colorectal eminence lesions were found. Primary observation marker was advanced colorectal neoplasm and secondary observation marker was colonic adenomatous polyp with a size larger than 0.5 cm in diameter. Advanced colorectal neoplasm was defined as high-grade adenoma, tubulovillous adenoma, adenoma with a diameter more than 1 cm and colorectal cancer [12].

There were 123 cases involved in the first-degree relative group, 65 of them were male and the rest 58 were female. Dividing into subgroups is as follows. There were 52 cases in Down group, with 28 males and 24 females involved. Up group included 43 cases, with 22 males and 21 females. Crossing group involved 15 cases of male and 13 cases of female, adds a total of 28 cases. There were 176 cases in the control group, 109 of them were male and the rest 67 were females. The characterization of all groups and screening results were demonstrated in Table 1.

Statistical analysis

All results were statistical analyzed using SPSS 19.0. Enumeration data such as gender, lesions of the intestinal, were analyzed using Chi-square test. Quantitative data such as age were reported as means \pm standard deviation. If analysis showed that there is significant difference between first-degree relative group and control group, subgroup analysis was proceed. One-way ANOVA was used to compare difference between subgroups and control group. Criterion for statistical significance was $P<0.05$.

Results

187 cases were found to be probands of colorectal cancer or advanced colorectal neoplasm, a total of 565 cases of first-degree relatives were supposed to undergo colonoscopy screening. Only 65 cases of probands considered colonoscopy screening of first-degree relatives under doctors' advices. At the final data collection, 146 cases of first-degree relatives from 58 families actually underwent colonoscopy screening, only 25.8% of them took doctors' suggestion (146/565). Eventually, there were 123 cases of first-degree relatives involved in the study, 23 of them were ruled out due to incomplete data collected.

There was no significant difference comparing gender between study group and control group, nor did the subgroups and control group (Table 2).

The study group involved cases aged from 30 to 79, with a mean of 54.07 ± 12.063 , while the control group aged from 30 to 79, with a mean of 55.04 ± 12.572 . More details comparing age between study group, subgroups and control group were shown in Tables 3 and 4. There was no significant difference when comparing age of study group to control group and Cross group to control group. Data indicated that there were significant differences when comparing age of Down group to control group and Up group to control group. Pair-wised comparisons between subgroups and control group were shown at Table 5.

Fifty-two cases in Down group were from 25 families, the incidence rate of advanced colorectal neoplasm was 11.5% (6/52) including 1 case of colorectal cancer, incidence rate of adenoma was 17.3% (9/52), total incidence rate (include advanced colorectal neoplasm and adenoma) was 28.8% (15/52). There were 43 cases involved in up group, which were from 24 families, 8 of them were found to be advanced colorectal neoplasm patients including 3 colorectal cancer patients, morbidity

Variables	Mean difference	Std. error	p	95% Confidence interval	
				Lower bound	Upper bound
Down group vs. up group	-20.952	2.278	<0.01	-25.44	-16.47
Down group vs. crossing group	-8.302	2.591	<0.01	-13.40	-3.20
Down group vs. control group	-9.271	1.745	<0.01	-12.70	-5.84
Up group vs. crossing group	12.650	2.684	<0.01	7.37	17.93
Up group vs. control group	11.681	1.880	<0.01	7.98	15.38
Crossing group vs. control group	-0.968	2.249	0.667	-5.39	3.46

Note: Further pair-wised comparing on age of all subgroups and control group, comparing down group to up group, $p < 0.01$, shows significant statistic difference; comparing down group to crossing group, $p < 0.01$, shows significant statistic difference; comparing down group to control group, $p < 0.01$, shows significant statistic difference; comparing up group to crossing group, $p < 0.01$, shows significant statistic difference; comparing up group to control group, $p < 0.01$, shows significant statistic difference; comparing crossing group to control group, $p = 0.667$, shows no significant statistic difference.

Table 5: Further pair-wised comparing on age of all subgroups and control group.

Variables	ACN	Adenoma	Polyp	Normal	Total
Study group	17	21	25	60	123
Control group	15	9	16	136	176

Note: $\chi^2 = 27.850$, $P < 0.01$

Table 6: Comparing on intestinal lesions of study group and control group.

Variables	ACN	Adenoma	Polyp	Normal	Total
Down group	6	9	10	27	52
Up group	8	7	8	20	43
Crossing group	3	5	7	13	28
Control group	15	9	16	136	176

Note: $\chi^2 = 30.043$, $P < 0.01$

Further pair-wised comparing on intestinal lesions of all subgroups and control group, comparing down group to up group, $\chi^2 = 0.956$, $P > 0.05$, shows no significant statistic difference; comparing down group to crossing group, $\chi^2 = 0.409$, $P > 0.05$, shows no significant statistic difference; comparing down group to control group, $\chi^2 = 15.184$, $P < 0.002$, shows significant statistic difference; comparing up group to crossing group, $\chi^2 = 1.035$, $P > 0.05$, shows no significant statistic difference; comparing up group to control group, $\chi^2 = 16.686$, $P < 0.001$, shows significant statistic difference; comparing crossing group to control group.

Table 7: Comparing on intestinal lesions of all subgroups and control group.

was 18.6%, morbidity of adenoma was 16.3% (7/43), total incidence rate was 34.9% (15/43). 28 cases in 12 families were involved in Cross group, 9 of them were siblings of proband in Down group, 19 of them were siblings of proband in up group. Incidence rate of advanced colorectal neoplasm was 10.7% (3/28), including 1 case of colorectal cancer, morbidity of adenoma was 17.9% (5/28), and total rate was 28.6% (8/28). Consider all subgroups as a whole, the incidence rate of advanced colorectal neoplasm in study group was 13.8% (17/123), 5 of them were colorectal cancer patients, incidence of adenoma was 17.1% (21/123), total morbidity was 30.9% (38/123). There are 176 cases involved in control group, 15 of them, including 6 colorectal cancers, were found to be advanced colorectal neoplasm patients (incidence rate was 6.8%), incidence rate of adenoma was 5.1% (9/176), and total morbidity was 13.6% (24/176). There is significant difference when comparing results between first-degree relative group and control group ($p < 0.05$), details was showed were shown at Table 6. Pair-wised comparing between subgroups and control group were shown at Table 7.

Discussion

Screening for asymptomatic population is an important way for colorectal cancer preventing, methods for screening include fecal occult blood tests (FOBT), blood tumor maker test [2], sigmoidoscopy screening, colonoscopy screening [13-16]. First-degree relatives of probands are one of the most important groups of population. Screening of this group is a matter of considerable interest, it helps to increase the detection rate of advanced colorectal neoplasm, and to reduce the incidence of colorectal cancer [17-19].

Studies showed that detection rate of adenoma in this group of population is as high as 13.5% to 32.8%, and that rate of advanced colorectal neoplasm is 4.0%-10.8%, while rates of general population are 11% to 16% and 2% to 4.1% [17,19-22]. Screening for first-degree relatives of colorectal cancer patients is well accepted by doctors and medical associates, several country and regions had already listed in this in their guideline [1,23,24]. The term 'first-degree relatives' include biological parents, biological sons and daughters and siblings [25,26]. But this is not well understood by medical staffs in China, a lot of them got confused by terms such as direct relatives. We found that nearly 40% of medical staffs thought that siblings were not first-degree relatives in our questionnaire. And the recognition rate of that parents and children belong to first-degree relatives were only 93.1% and 85.6%. More details were showed in Table 8.

Due to the hereditary inclination in the incidence of colorectal cancer, if parent confirmed to be colorectal cancer patient, their biological children is 2-3 folds of risk to have the disease than general population [17,27,28]. Having endoscopy examination in this population as early as possible, especially when they were still young, were able to detective advanced colorectal neoplasm or polyps. Performing endoscopic intervention such as polypectomy helped to prevent progress and deterioration. Most of patients' children get benefits from doctors' advices of colonoscopy examination.

However, there are some young adults who were diagnosed advanced colorectal neoplasm or colorectal cancer before their parents got a chance to have colonoscopy. Did their parents get the risk of colorectal diseases like cancer? Since young sons and daughters were listed into high risk population when their parent was diagnosed colorectal cancer due to their highly chance of being diagnosed advanced colorectal neoplasm [29], parents of young diagnosed colorectal cancer patients should be listed into high risk screening population too, so did their siblings.

This study was designed to perform colonoscopy screening biological children of elderly advanced colorectal neoplasm patients, biological parents of young advanced colorectal neoplasm patients and siblings of advanced colorectal neoplasm patients. We defined down screening group as screening children when parent was diagnosed advanced colorectal neoplasm, up screening group as screening parents while child was diagnosed advanced colorectal neoplasm, crossing screening group as screening siblings of advanced colorectal neoplasm patients. The whole study was defined as Cruciform screening for the whole first-degree relatives. Our results indicated that incidence for down screening group, up screening group and crossing screening group were all higher when compared with control group.

Wong et al. reported that, in a prospective study covered 16 Asia-Pacific regions including China of colonoscopy screening between

Are these people first-degree relatives?	Parents		Children		Siblings		Recognition rate by occupations (%)		
	YES	NO	YES	NO	YES	NO	Parents	Children	Siblings
Doctors	85	6	80	11	55	36	93.4	87.9	60.4
Nurses	68	3	60	11	45	26	95.8	84.5	63.4
Other Medical staffs	9	3	9	3	4	8	75	75	33.3
Total	162	12	149	25	104	70	93.1	85.6	59.8

Note: Control group, $x^2=14.417$, $P=0.002$, shows significant statistic difference.

Table 8: Recognition rate of first-degree relatives in a 174 medical staffs questionnaire in Dongguan, China.

first-degree relatives, results shows that among first-degree relatives, siblings, parents and children have the same risk of being diagnosed colorectal tumor [30]. Our result gets us a similar conclusion. Incidence of advanced colorectal neoplasm is higher in study group or each subgroup when comparing control group. Indicating that once one of the family members was diagnosed colorectal cancer or advanced colorectal neoplasm, his/her first-degree relatives should accept colonoscopy screening as soon as possible. Further analyze shows that, among subgroups and control group, there is difference in ages. Subjects in down group is obviously younger than subjects in up group, but when comes to colorectal lesions, there is no statistical difference between the two groups. However, when comparing to control group, no matter down group, up group or crossing group, all showed significant difference in this aspect. This is not quite according to the acknowledge that people is at higher risk of malignance tumor with age growing in general population. We assumed that among all risks of colorectal advanced colorectal neoplasm, first-degree relatives as a risk is one more relevant than aging. Outcome from this study showed that screening for first-degree relatives is better understanding as cruciform screening (down-up-crossing screening).

Efficiency of population screening is relevant to the willing of participation in the population [25,31,32]. Our results showed that the willing for screening in first-degree relatives is poor, only 25.2% actually involved, this is much lower than that out from China [18,25,33]. Possibility reasons include: Firstly, there is no official guideline for colorectal cancer screening in China by now. Recommendations of expert groups just published not long ago, some experts still holding differing views, medical education to patients and their families were limited to doctor's personal opinion of the disease. Secondly, the awareness of disease preventing is weak for patients, they barely seek for medical assistance when alert symptom presents, not to mention initiative preventative health examine. Thirdly, most of clinical physicians in China were kept busy by overwhelming daily work; they only got time to deal with patients, no time were separate for preventing. Fourthly, the term of 'first-degree relative' is not well understood, it should include parents, children and siblings of the proband. It is not accurate understood by neither patients nor part of medical staffs. Reasons including but not limited to personal realization of family relationship; parents, children and spouse were listed as direct relatives according to law in China, a lot of people get confused by these two terms and thought that the two of them means the same thing. The misunderstanding of the two terms 'direct relatives' and 'first-degree relatives' is one of the most important reasons. If screening between first-degree relatives changed into cruciform screening (down-up-crossing screening), it will be much easier for patients and doctors to understand and make it much more acceptable in patients.

Our results strongly suggested that we should perform colonoscopy screening among first-degree relatives of colorectal cancer and advanced colorectal neoplasm patients in Dongguan city. Xu et al. reported that during a general population investigation involved 100,890 cases in Huizhou city, Guangdong Province, China; results

showed that the incidence of colorectal cancer is 46.5 per 100, 000 population in male and 37.2 per 100, 000 population in female after standardization [34]. This data is similar to that of America [3]. China is the largest population country in the world, according to the 5th nationwide population census, there is 1.37 billion people in China, twice the number of the entire Europe, more than triple of the number than America [35,36]. If we estimate it using the incidence of American colorectal cancer, there would be more than 500,000 new diagnosed colorectal cancer in China each year; this would be a huge population. If we do not pay attention to that now, as time goes by, in a future we can precede not far, gastroenterologist in China would be busy dealing with that. And medical fee for that would be a large burden for families of patients and society. Based on the fact that, newly diagnosed colorectal cancer patients is increased rapidly in China, however, that number in America is decreasing due to colorectal cancer screening; we strongly suggested that China should launch a wide-range screening program for colorectal cancer.

There is some deficiency in our study. Firstly, this study is a single centre study, it would be more convincing if it is a multicentre study. Secondly, sample in the study is not large enough, data would be closer to reality if we could get more sample in the study. Thirdly, Dongguan is a developed city, comparing to other not so developed cities in Guangdong province, incidence of advanced colorectal neoplasm and colorectal cancer is not quite the same. If we could bring more centers all over the province or even all over the country to join a national wide study, it will much more appropriate to the true incidence of the disease in first-degree relatives and data would be more persuasive.

Conclusion

To sum up, performing colonoscopy screening among first-degree relatives for advanced colorectal neoplasm in Dongguan is a great worth due to its high detection rate of advanced colorectal neoplasm. And we suggested that, screening in this population is better understanding as Cruciform screening. It is much simple, and easier to understand for patients and doctors.

Author contributions

The study was designed by Yu SP. Data were obtained by Wu GY, Cen XH, Huang XG, Zhang Fu and Huang MT. Endoscopy is performed by Wen ZQ, Yu SP, Cen XH, Lin XD, Li SH and Huang Xian-Guang. Data were analyzed by Wu GY. The report was mainly written by Yu SP and Wu GY. All authors approved the final version.

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