

• LARGE INTESTINAL CANCER •

Reduction of the incidence and mortality of rectal cancer by polypectomy: a prospective cohort study in Haining County

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Abstract

AIM: To reduce the incidence and mortality of rectal cancer and address the hypothesis that colorectal cancer often arise from precursor lesion(s), either adenomas or non-adenomatous polyps, by conducting a population-based mass screening for colorectal cancer in Haining County, Zhejiang, PRC.

METHODS: From 1977 to 1980, physicians screened the population of Haining County using 15cm rigid endoscopy. Of over 240000 participants, 4076 of them were diagnosed with precursor lesions, either adenomas or non-adenomatous polyps, which were then removed surgically. All individuals with precursor lesions were followed up and reexamined by endoscopy every two to five years up to 1998.

RESULTS: After the initial screening, 953 metachronous adenomas and 417 non-adenomatous polyps were detected and removed from the members of this cohort. Further, 27 cases of colorectal cancer were detected and treated. Log-rank tests showed that the survival time among those cancer patients who underwent mass screening increased significantly compared to that of other colorectal cancer patients ($P < 0.0001$). According to the population-based cancer registry in Haining County, age-adjusted incidence and mortality of rectal cancer decreased by 41% and 29% from 1977-1981 to 1992-1996, respectively. Observed cumulative 20-year rectal cancer incidence was 31% lower than the expected in the screened group; the mortality due to rectal cancer was 18% lower than the expected in the screened group.

CONCLUSION: Mass screening for rectal cancer and precursor lesions with proctoscopy in the general population and periodical following-up with routine endoscopy for high-risk patients may decrease both the incidence and mortality of rectal cancer.

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INTRODUCTION

Colorectal cancer is the second most common cause of death from cancer in the United States^[1,2] and the fifth in mainland of China^[3]. Dietary modification and non-steroidal anti-inflammatory drugs (NSAID) may reduce the risk of colorectal cancer^[4-6]. Nevertheless, few of the Chinese people have benefited from these chemoprevention strategies so far. Recently, the results of several randomized controlled trial showed that fecal occult blood testing (FOBT) based on mass screening might reduce the mortality caused by colorectal cancer in general population^[7-9]. Unfortunately, the incidence of colorectal cancer could not be reduced by this protocol.

As reviewed by Potter^[10-13], colorectal cancer is a result of accumulation of multiple genetic alterations within the epithelial cells. The concept of the adenoma-to-carcinoma is well accepted, and describes a stepwise progression from normal colorectal epithelium to adenoma, and to carcinoma^[14-16]. The adenomatous polyps, the precursor lesion resulted from epithelial cell hyperproliferation and crypt dysplasia, have malignant potential. Progression from precursor lesions to colorectal cancer is a multi-step process that requires ten to fifteen years^[15]. Approximately 30-60% of patients with a history of adenomas will develop a metachronous adenoma within three to five years after their initial polypectomy^[17,18]. Therefore, it has been hypothesized that removing colorectal polyps might change the natural history of colorectal cancer; mass screening and following up with endoscopy might reduce the incidence and mortality of colorectal cancer. Nevertheless, evidence for the effectiveness of colonoscopy is indirect, since no large trials with mortality endpoints have been conducted to evaluate the efficacy of screening for colorectal cancer with colonoscopy^[19-21].

According to census survey of death causes in 1970 in China, more than 66% of colorectal cancers were found in the rectum^[22-24]. It is suggested that about 60% of colorectal cancer could be effective by screening with proctoscopy in China. To prove above hypothesis, we conducted a population-based mass screening with 15cm rigid endoscopy in Haining County, PRC from 1977 to 1980. Results presented herein are based on findings at the initial screening as well as 20 years of follow-up examinations in those individuals with precursor lesions.

MATERIALS AND METHODS

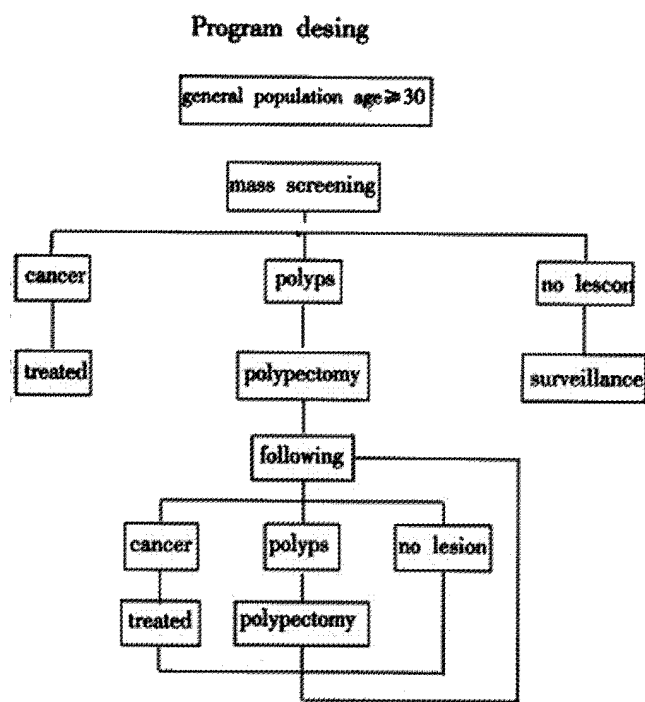
Study design was described in Figure 1. The high-risk population with rectal polyps was identified by proctoscopy through a general population-based mass-screening program, and followed with endoscopy periodically. All detectable polyps including adenomatous or non-adenomatous polyps were removed.

As previously described in detail^[25,26], population-based screenings with 15cm rigid endoscopy was conducted from 1977 to 1978 in Haining County, a rural community located in the eastern part of China. Only residents in Haining County who were at least 30 years old were eligible for the screenings. The screening team includes

epidemiologist, physician, pathologist, surgeon and investigators, who had been trained before starting the program. We screened 186234 of the 223866 eligible individuals (83% response rate), of which 2815 were found carrying polyps and/or adenomas. The detectable adenoma and/or polyp were surgically removed thereafter. All individuals with precursor lesions were eligible for follow-up endoscopic screenings, which were performed in the years of 1979-1980, 1981, 1983, 1987, 1993 and 1998. In addition, of the 53987 volunteers who aged 30 or over screened during 1979-1980's following-up, polyps and/or adenomas were detected and removed in 1,261 individuals. These patients were eligible for follow-up endoscopic screenings in 1982, 1984, 1988, 1994 and 1998. Due to technological advances in screening methods during this time period, all screenings after 1985 were performed with 60cm flexible sigmoidoscopy rather than 15cm rigid endoscopy.

Pathologic material was reviewed independently by three senior pathologists using standard criteria developed by the World Health Organization (WHO). A final diagnosis was made when at least two of the pathologists agreed on the patient's diagnosis. The age distribution of patients from both screenings is presented in Table 1. Table 2 lists the pathologic features of the initial polyp or adenoma for each patient; for patients with more than one adenoma or polyp, the most advanced lesion is listed.

Cancer mortality data was collected since 1974, and Cancer incidence data was available since 1977 by the population-based cancer registry in Haining County. The International Classification of Disease (ICD-9) was employed by the registry for site-specific histologic classification. Population estimates were based on the periodic censuses, with age-and sex-specific annual estimates derived by linear inter- and extrapolation for the remaining years. Rates for each period are age-adjusted to the world standard population using the direct method for each 5-year age group. From 1974 to 1976, before mass screening program carried out, the adjusted mortality of colon and rectum cancer was 2.66 and 4.20 per 100000 respectively. From 1977 to 1996, histologic confirmation was available for 94.4% of the 1005 incident colorectal cancer cases and 92.3% of the 735 deaths due to colorectal cancer.



Note: Polyps include adenomatous polyps and non-adenomatous polyps All polyps would be removed when detected by endoscopy examiner
Figure 1 Design for mass screening and following-up with endoscopy

Table 1 Age distribution of two groups of high-risk populations with polyps

Age Group	1 ^a		2 ^b		Total(%)
	Male(%)	Female(%)	Male(%)	Female(%)	
30-	644(36.6)	440(41.6)	287(34.4)	181(37.2)	1 552(38.1)
40-	452(25.7)	270(25.6)	226(27.1)	100(23.7)	1 049(25.8)
50-	434(24.7)	237(22.4)	204(24.4)	99(23.5)	974(23.9)
60-	164(9.3)	89(8.4)	99(11.9)	37(27.2)	389(9.6)
70-	64(3.7)	21(2.0)	19(2.3)	5(1.2)	109(2.7)
Total	1758	1057	835	422	4072

^a1: high-risk population with history of polyps identified during 1977-1978; ^b2: High-risk population identified in 1980. The age of 4 participants is unknown

Table 2 Pathologic features of initial polyps of two groups of high-risk populations

Pathologic Diagnosis	First group		Second group		Total	
	n	%	n	%	n	%
Adenoma	1485	52.88	876	69.47	2361	58.02
Tubular	1352	48.15	843	66.85	2195	53.94
Tubulovillous	104	3.70	31	2.46	135	3.32
Villous	19	0.68	2	0.16	21	0.52
Non-adenomatous	1326	47.22	382	30.29	1708	41.98
Mucosal	596	21.23	95	7.53	691	16.98
Juvenile	183	6.52	95	7.53	278	6.83
Hyperplastic	113	4.02	72	5.71	185	4.55
Inflammatory	90	3.21	4	0.32	94	2.31
Schistosomiasis	326	11.61	115	9.12	441	10.84
Lymphoid	10	0.36	1	0.08	11	0.27
Other	8	0.28	0	0.00	8	0.20
No pathologic diag	7	0.25	3	0.24	10	0.25
Total	2815		1261		4076	

RESULTS

From 1979 to 1998, patients diagnosed with adenomas and/or polyps during the first screening have been followed up six times. Of 2815 cases with polyps, 20.5% of them participated whole six times endoscopy examination, and 89.6% finished at least three times. While those patients diagnosed at the group of volunteers have been re-screened five times, and 82.5% of them were re-examined at least two times. Table 3 summarizes the expected and observed incidence rates of adenomas, polyps and colorectal cancer for both groups. After the initial screening, 953 metachronous adenomas and 417 non-adenomatous polyps were detected and removed from members of this cohort. Further, 27 cases of colorectal cancer were detected and treated, we analyzed data collected by the cancer registry of Haining County, Zhejiang Province, PR China. Both rectum cancer incidence and mortality were decreased steadily from 1977 to 1996 (Table 3). The age and sex adjusted incidence rates of rectal cancer decreased from 7.27 per 100000 (1977-1981) to 3.71 per 100000 (1992-1996), and mortality was decreased from 4.20 per 100000 (1974-1976) to 2.98 per 100 000 (1992-1996). Thus, age-adjusted incidence and mortality of rectal cancer decreased by 41% and 29% respectively. Nevertheless, both adjusted incidence rates and mortality of colon cancer increased slightly at the same period.

Table 3 Output of following with endoscopy among high-risk population with history of polyps

Year	Expected n	Observed n (%)	Adenoma n (%)	Non-adenomatous n (%)	Colorectal cancer (1/100000)
1st group					
1979	2803	2197(78.38)	178(8.10)	104(4.73)	6(273.10)
1981	2763	1592(57.62)	61(3.83)	27(1.70)	4(251.26)
1983	2719	2147(78.96)	108(5.03)	33(1.54)	2(93.15)
1987	2689	2408(89.52)	191(7.93)	96(4.00)	4(166.11)
1993	2388	1475(61.77)	121(8.20)	52(3.53)	4(271.19)
1998	2207	1020(46.22)	95(9.31)	17(1.67)	4(392.16)
2nd group					
1982	1253	461(36.79)	17(3.69)	6(1.30)	0(0.00)
1984	1235	1056(85.51)	49(4.64)	26(2.46)	0(0.00)
1988	1183	931(78.70)	64(6.87)	20(2.15)	0(0.00)
1994	1097	479(43.66)	33(6.68)	17(3.55)	3(626.30)
1998	1040	486(46.73)	36(7.41)	17(3.50)	0(0.00)
Total		1425	2953(6.68)	417(2.93)	27(189.45)

^{*}Following with 60cm flexible sigmoidoscopy since 1987

Cumulative 20-year incidence and mortality caused by colon and rectal cancers are presented in Figures 2,3 and table 4. Figure 2 shows the incidence of colon and rectal cancers in those individuals aged 30 years and older in the mass screening in 1977. Figure 3 shows mortality caused by colon and rectal cancer in the screened population (those aged 30 years and older in 1977). According to incidence and mortality of age and sex sub-group during 1977 to 1981, we calculated the annual expected rate of sub-group for this cohort population from 1977 to 1996, and then 20-year cumulative incidence and mortality. Observed cumulative 20-year rectal cancer incidence was 31% lower than expected in the screened group; mortality caused by rectal cancer was 18% lower than expected in the screened group. There is no significant difference of incidence and mortality of colon cancer almost between observed and expected. Results showed incidence and mortality were only reduced in the rectal cancer, but not colon cancer.

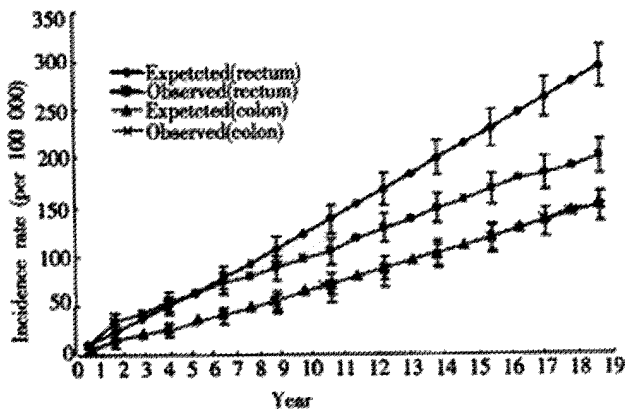


Figure 2 The Expected and Observed Twenty-year Cumulative Incidence of Colon and Rectum Cancer

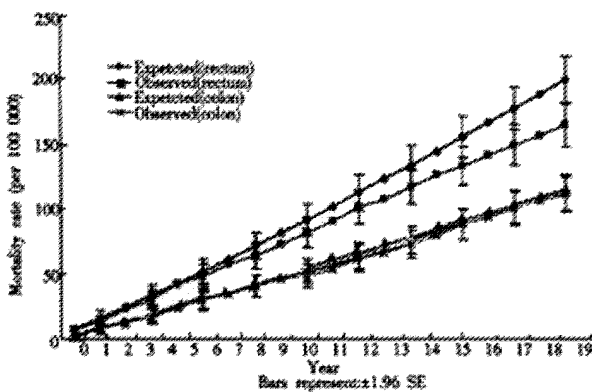


Figure 3 The Expected and Observed Twenty-year Cumulative mortality of Colon and Rectum Cancer

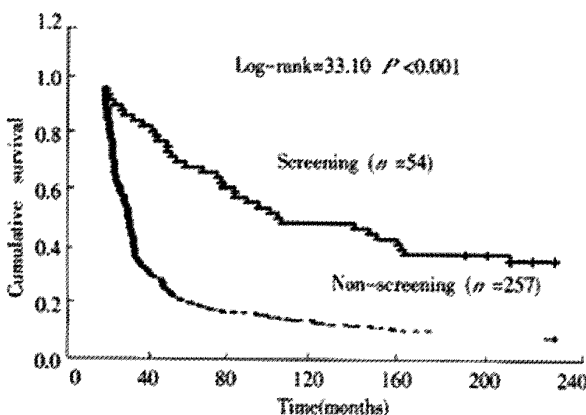


Figure 4 Survival curve (Kaplan-Meier) of rectal cancer diagnosed during 1977-1982

During the initial screenings, 54 cases of colorectal adenocarcinomas were detected and treated. Survival analyses showed that patients with rectal cancers detected during the screenings had significantly longer survival time than rectal cancers identified in patients who were not included in the mass screenings at the same period (log-rank=27.12; $P<0.001$) (See Figure 4). The mean age of screened rectal cancer patients was 57 years (SD=12.8) while the mean age of non-screened rectal cancer patients was 59 years (SD=12.1). The median survival time of screened patients was 133 months (95% CI=56-210mos.) compared with only 14 months (95% CI=11-15 mos.) in non-screened patients. Excluded the leading time bias, the median survival time for screened patients was prolonged by 7.9 years.

DISCUSSION

In the 1980's, it was suggested that population-wide screening with fecal occult blood test (FOBT) was not cost-effective^[27,28]. However, more recent analyses suggest that FOBT-based screening can reduce colorectal cancer mortality^[29-32]. Mandel and colleagues at the Mayo Clinic in Minnesota conducted a randomized screening of over 46,000 individuals^[33,34]. Participants were randomized to annual or biannual FOB test group and a control group. The cumulative 18-year colorectal cancer mortality was reduced by 33% in the annually screened group and 21% in the biennially screened group compared to the control group. It is important to note that although FOBT may be important in early detection of colorectal cancer, this test does not affect the underlying process of neoplastic transformation in the large bowel. In addition, the use of a rehydrated hemocult test instead of an unrehydrated hemocult test increased test sensitivity but decreased test specificity resulting in over 10% of participants undergoing colonoscopy exam at each screening. Moreover, a total of 38% of the screened group had at least one colonoscopy during the entire study period. It was proposed by Lang and colleagues that approximately one third to one half of the observed reduction in mortality found in Mandel's study was the result of chance selection for colonoscopy rather than the FOBT itself^[35-37]. Another two randomized screening trials using unrehydrated hemocult test every two years resulted in only 4% of the test group requiring colonoscopy, yet reduced colorectal cancer mortality by 15-18%^[39-43]. However, no evidence showed incidence rate has been reduced from colorectal cancer by FOBT-based mass screening.

The population-wide mass screenings were conducted from 1977-1980 among 246252 residents of Haining County aged 30 years or older. The overall participation rates were 83%. A total of 54 cases of rectal cancer were detected and treated. Overall survival in these patients was significantly increased compared to non-screened rectal cancer patients (log-rank=33.4; $P<0.0001$). Excluding leading time bias, the survival time was prolonged by almost 8 years in screened patients. In addition, 4076 patients with newly discovered adenomas and/or nonadenomatous polyps were treated by polypectomy and followed with periodic examinations through 1998. During follow-up, 953 metachronous adenomas and 417 nonadenomatous polyps were detected and removed; an additional 27 colorectal cancers, 12 of which were carcinoma in situ, were diagnosed and treated. According to the Haining County Cancer Registry, from 1977 to 1996 both age- and sex-adjusted colorectal cancer incidence and mortality decreased by 41% and 29% respectively. Further, cumulative 20-year observed incidence and mortality from rectal cancer in the screened population decreased by 31% and 18%, respectively. If interest, incidence rates of rectal cancer in Shanghai, PRC (located 120km from Haining) increased by 11.3% in males and 6.0% in females from 1972 to 1994^[44,45]. Chinese official data showed from 1973-1975 to 1990-1992, age and sex adjusted mortality caused by colorectal cancer increase by 3.61% in urban and decrease by 5.22% in rural population of China^[3]. Above evidence supported that

both incidence and mortality of rectal cancer decreased in Haining due to the population-wide mass screening and following-up with endoscopy to high-risk population.

Winawer and colleagues reported a 76-90% reduction in colorectal cancer incidence in 1418 adenoma patients who underwent periodic colonoscopy after initial polypectomy compared to age-, sex-, and polyp-size-adjusted control groups. Further, follow-up colonoscopy performed three years after initial colonoscopy detection and removal was found to be as effective as follow-up colonoscopy performed after only one or two years. Thus, it is suggested that a screening interval of three years is sufficient following colonoscopic removal of newly diagnosed adenomas^[15,16]. Anyway, our results showed only 31% reduction of incidence of rectal cancer through population-wide mass screening with proctoscopy. It is suggested that there are other pathways besides except of adenoma pathway.

These results suggest that colorectal cancer may be prevented by mass screening with FOBT or endoscopy. Further, removal of precursor lesions may slow or halt the natural history of rectal neoplasms. Our data suggest that mass screening by endoscopy can reduce the incidence and mortality of colorectal cancer. Screening guidelines for asymptomatic individuals suggest that all individuals aged 50 years or older may be benefited by periodic digital rectal examinations, stool guaiac and/or colonoscopy. For patients without adenomas or polyps, these exams should be repeated every three to five years, while patients with precursor lesions should be re-examined for new lesions after one year^[46-48]. Data from cancer statistics of United States indicated that approximately 60% of colorectal cancers are found in the distal colon or rectum^[49,50]. However, according to 1980's report by the Research Team in China, 80% of colorectal cancers are found in the distal colon or rectum, with up to 66% in the rectum alone^[24]. Therefore, it was suggested that mass screening and following up with sigmoidoscopy periodically might be more cost-effective than colonoscopy in China.

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