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ORIGINAL RESEARCH

Incidence and distribution of advanced colorectal adenomas in patients undergoing colonoscopy for screening, surveillance, and symptoms

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Purpose: The aim of the study was to determine the frequency and distribution of advanced colorectal adenomas (ACAs) in Chinese population.

Methods: The patients who were referred to receive a colonoscopy were divided into three subgroups of screening, surveillance, and symptomatic, and then they were selected based on their indications. The symptomatic subgroup was further broken down into the alarm and non-alarm categories. The location and morphology of all colorectal lesions were both investigated and recorded.

Results: There were significantly more patients with ACAs in the symptomatic subgroup compared to the screening or surveillance subgroup (11.0% vs 4.1%, P<0.001; 11.0% vs 4.6%, P=0.006). No differences were found in the ACA frequency between the alarm and non-alarm categories (11.7% vs 9.7%, P=0.056). One observation was that in the symptomatic subgroup, distal lesions were more likely to contain ACAs than proximal ones (OR 1.50, 95% CI 1.05–2.15, P=0.024). It was also noted that nonpolypoid lesions had significantly higher amounts of ACAs in the symptomatic subgroup (OR 2.09, 95% CI 1.48–2.94, P<0.001) than the other groups.

Conclusion: The incidence of ACAs was higher in patients undergoing a colonoscopy due to their symptoms, compared to the incidence in those who underwent the procedure for screening or surveillance purposes. Additionally, more attention should be focused on distal and nonpolypoid lesions to improve the detection rate of ACAs.

Keywords: advanced colorectal adenomas, incidence, colonoscopy

Introduction

Colorectal carcinoma (CRC) is the second most prevalent cancer worldwide.[1] Most CRCs arise through the adenoma–carcinoma sequence, which takes, on average, 10–20 years to develop; this fact alone makes the screening and prevention of CRCs by colonoscopic examination and polypectomy feasible.[2] Advanced colorectal adenomas (ACAs; adenoma ≥10 mm or ≥25% villous features, or high-grade dysplasia), proposed by Atkin et al in 1992, are considered to be dangerous, precancerous lesions.[3] In the past 2 decades, the prevalence of ACAs has steadily increased.[4–6] It shows that the prevalence of ACAs has great relevance regarding a patient's indications for a colonoscopy and that other factors, such as age, sex, and diet, could not be neglected.[7–9] In many studies, the indications, such as screening, surveillance, or symptoms, had been taken into account.[5–7] There is still paucity of data to investigate the prevalence of ACAs when the three indications are analyzed at one time. Moreover, the distribution of ACAs, stratified by location and morphology of colorectal lesions, has not yet been extensively investigated. The risk of an adenoma becoming malignant or CRC is the greatest for ACAs, highlighting the importance of identifying adenoma patients with high risk

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for close surveillance after initial polypectomy. Therefore, we designed a cross-sectional study of local patients, so that the prevalence and distribution of ACAs could be assessed.

Materials and methods

Study population

Patients who were consecutively enrolled in the study were referred to receive a colonoscopy after obtaining written informed consent documentation. The study subjects were divided into three groups referred to as the screening subgroup, the surveillance subgroup, and the symptomatic subgroup, according to their indications. Asymptomatic patients were those who underwent a colonoscopy as a precautionary measure to screen for colorectal cancer (CRC) (the screening subgroup), as well as those who had a surveillance colonoscopy for having a medical history of colorectal neoplasm or a family history of CRC in a first-degree relative (the surveillance subgroup). Symptomatic patients (the symptomatic subgroup) were those who experienced hematochezia, melena, diarrhea, constipation, anemia, weight loss, or abdominal pain. The symptomatic patients were then further divided into two groups. The patients in alarm symptomatic category experienced anemia, hematochezia, melena, or weight loss, and the patients in non-alarm symptomatic category experienced constipation, diarrhea, or abdominal pain.

For inclusion in the study, subjects were required to have undergone a colonoscopy for screening, surveillance, or symptomatic. Exclusion criteria for the study subjects were as follows: having undergone a previous surgical resection of any part of the colon; having a history of CRC, inflammatory bowel disease, polyposis syndrome, or hereditary nonpolyposis colon cancer; being in poor physical condition; and insufficient bowel preparation. The study protocol was approved by the institutional ethical committee of the Second Affiliated Hospital of Nantong University (China) and was in accordance with the revised Helsinki Declaration of 1983.

Patients received an orally administered glucose–electrolyte solution containing polyethylene glycol 4–6 hours before the examination. All colonoscopies were performed by an expert endoscopist using a high-resolution Olympus endoscope (CF-H260AZL; Olympus, Tokyo, Japan).

The size, location, and morphology of all lesions were recorded. The sizes of the lesions were visually estimated using standard biopsy forceps. The distal colon was defined as the rectum, the sigmoid colon, and the descending colon, which also included the splenic flexure. Similarly, the proximal colon was defined as the transverse colon, the ascending colon, and the cecum. This information is based on the standard classification system described by the Paris endoscopic classification of superficial neoplastic lesions.[10] The morphology of colorectal lesions was divided into polypoid and nonpolypoid types. The former consists of pedunculated (0-Ip), semipedunculated (0-Isp), and sessile (0-Is) lesions, and the latter consists of slightly elevated (0-IIa), completely flat (0-IIb), and slightly depressed (without ulcer; 0-IIc) lesions.

All identified lesions were removed via biopsy, endoscopic resection (polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection), or conventional surgery for histological evaluation. The pathologist independently identified the colorectal lesions, according to the Vienna classification of gastrointestinal epithelial neoplasm, without oral or written communication with the endoscopist.[11] ACAs can be defined as the presence of adenomas that are ≥10 mm in size, have more than 25% villous features, and have high-grade dysplasia.[3] The ACAs included in this study were defined by experienced endoscopists and pathologists.

Statistical analysis

Statistical analysis was performed with SPSS software (version 16.0; SPSS Inc, Chicago, IL, USA). Continuous variables were summarized as mean and SD. Categorical variables were summarized using percentages, and 95% CIs were calculated. Continuous variables were compared using the Student's *t*-test or ANOVA. Categorical data were compared to the Pearson chi-squared test or the Fisher's exact test. The OR indicated a 95% CI. Differences were considered significant if the two-tailed *P*-value was <0.05.

Results

Between July 2009 and June 2011, a total of 2,876 patients were enrolled in the study, and they underwent colonoscopies that were performed by an experienced endoscopist. However, 66 patients did not complete the entire colonoscopy. The cecal intubation process was completed in 2,810 cases (97.7% of the time). Of these 2,810 patients, 565 were in the screening subgroup, 813 were a part of the surveillance subgroup, and 1,432 were in the symptomatic subgroup. Overall, 514 patients were in the alarm symptomatic category, and 918 patients were in the non-alarm symptomatic category. Moreover, 869 patients with 1,342 colorectal lesions were detected in the complete cohort, including 57 cases of advanced carcinoma. Finally, 1,285 colorectal lesions were analyzed in total. The target population demographics are depicted in Table 1, and the clinicopathological features of the 1,285 colorectal lesions are indicated in Table 2.

Table 1 Demographic and clinicopathological data of the study population

Characteristics	All	Indications for colonoscopy		
		Screening	Surveillance	Symptomatic
Subjects	2,810	565	813	1,432
Age, years, mean (SD)	59.8 (11.0)	56.7 (10.5)	59.6 (10.1)	61.2 (11.9)
Men, n (%)	1,533 (54.6)	301 (53.3)	426 (52.4)	806 (56.3)
BMI >25, n (%)	1,358 (48.3)	269 (47.6)	398 (48.9)	692 (48.3)
Family history of colorectal cancer, n (%)	238 (8.5)	46 (8.2)	66 (8.1)	126 (8.8)
Urban areas, n (%)	2,172 (77.3)	436 (77.2)	626 (77.0)	1,110 (77.5)
Colorectal lesions, n	1,285	223	225	837

Abbreviation: BMI, body mass index.

Table 2 Clinicopathological features of colorectal lesions analyzed in the study

Features	Number
All colorectal lesions	1,285
Size, mm, mean (SD)	3–45, 6.7 (1.6)
Morphology	
Polypoid	822
Nonpolypoid	463
Location	
Proximal colon	474
Distal colon	811
Pathological findings	
Intramucosal carcinoma	39
Submucosal carcinoma	9
Adenoma	675
Hyperplastic polyp	546
Others[a]	16

Notes: [a]There were eight hamartomatous polyps, one ectopic gastric mucosa, three granulation tissue, and four submucosal tumors.

As listed in Table 3, the prevalence of ACAs in patients who underwent colonoscopies for screening, surveillance, and\symptoms was 4.1% (95% CI, 2.5%–5.7%; n=565), 4.6% (95% CI, 3.2%–6.0%; n=813), and 11.0% (95% CI, 9.4%–12.6%; n=1,432), respectively. There were significantly more patients with ACAs in the symptomatic subgroup than in the screening or the surveillance subgroup (11.0% vs 4.1%, *P*<0.001; 11.0% vs 4.6%, *P*=0.006). In the surveillance subgroup, the prevalence of ACAs was found to be 4.6%; therefore, no statistical significance was concluded compared to the screening subgroup (4.6% vs 4.1%, *P*=0.346).

In the symptomatic subgroup, 68 of the patients were found to have 79 ACAs in the alarm category, and 89 of the patients were found to have 105 ACAs in the non-alarm category. The prevalence of ACAs in the alarm and non-alarm categories was 11.7% (95% CI, 8.9%–14.5%; n=514) and 9.7% (95% CI, 7.8%–11.6%; n=918), respectively. There was no statistical significance between the two groups (11.7% vs 9.7%, *P*=0.056).

The distribution of colorectal lesions and ACAs, stratified by location and morphology of the subgroups, is listed in Table 4. Furthermore, Tables 5 and 6 list the proportion of ACAs in colorectal lesions stratified by location and morphology.

In the symptomatic subgroup, distal lesions were more likely to contain ACAs than proximal ones (OR 1.50, 95% CI 1.05–2.15, *P*=0.024); however, no significant results were revealed in the screening subgroup (OR 0.66, 95% CI 0.37–1.38, *P*=0.322) or in the surveillance subgroup when comparing the likelihood of occurrence of ACAs (OR 0.60, 95% CI 0.31–1.18, *P*=0.139). The proportion of ACAs in the distal lesions was 24.4% (95% CI 20.8%–28.0%) in the symptomatic subgroup, 13.1% (95% CI 7.5%–18.7%) in the screening subgroup, and 15.4% (95% CI 9.2%–21.6%) in the surveillance subgroup. There were significantly more ACAs in the distal lesions of a part of the symptomatic subgroup, compared to their prevalence in the screening subgroup (24.4% vs 13.1%, *P*=0.005) or surveillance subgroup (24.4% vs 15.4%, *P*=0.028).

Nonpolypoid lesions with higher proportions of ACAs were also found in the symptomatic subgroup (OR 2.09, 95% CI 1.48–2.94, *P*<0.001), but no significant difference was detected in the screening subgroup (OR 1.93, 95% CI 0.92–4.02, *P*=0.078) or the surveillance subgroup (OR 0.61, 95% CI 0.31–1.23, *P*=0.165). The proportion of ACAs in the nonpolypoid lesion category was 31.5% (95% CI, 25.5%–37.5%) in the symptomatic subgroup, 20.2% (95% CI, 12.1%–28.3%) in the screening subgroup, and 14.7% (95% CI, 7.8%–21.6%) in the surveillance subgroup. A higher proportion of ACAs were categorized as nonpolypoid lesions in the symptomatic subgroup compared to the screening subgroup (31.5% vs 20.2%, *P*=0.041) or surveillance subgroup (31.5% vs 14.7%, *P*=0.001).

Discussion

The incidence and distribution data of ACAs described in this report identify several priority areas for CRC prevention. First, the incidence of ACAs was higher in the symptomatic

Table 3 Prevalence of ACAs in the subgroups

	Screening subgroup	Surveillance subgroup	Symptomatic subgroup
Patients	565	813	1,432
Total ACA number	34	42	184
Number of patients with ACAs	23	37	157
Prevalence of ACAs (%)	4.1	4.6	11.0

Abbreviation: ACA, advanced colorectal adenoma.

Table 4 Distribution of ACAs and colorectal lesions stratified by anatomic location and morphological appearance into subgroups

Subgroups	Lesion types	Location		Morphology	
		Proximal	Distal	Polypoid	Nonpolypoid
Screening subgroup	ACAs	16	18	15	19
	Colorectal lesions	86	137	129	94
Surveillance subgroup	ACAs	22	20	27	15
	Colorectal lesions	95	130	123	102
Symptomatic subgroup	ACAs	53	131	111	73
	Colorectal lesions	300	537	605	232

Abbreviation: ACA, advanced colorectal adenoma.

Table 5 Proportion of ACAs in subgroups stratified by location

Subgroups	Lesion types	Proximal	Distal	Distal vs proximal		
				OR	95% CI	*P*-value
Screening subgroup	ACAs (%)	16 (19.5)	18 (13.1)	0.66	0.37–1.38	0.322
	Colorectal lesions	86	137	–	–	–
Surveillance subgroup	ACAs (%)	22 (23.1)	20 (15.4)	0.60	0.31–1.18	0.139
	Colorectal lesions	95	130	–	–	–
Symptomatic subgroup	ACAs (%)	53 (17.7)	131 (24.4)	1.50	1.05–2.15	0.024
	Colorectal lesions	300	537	–	–	–

Abbreviation: ACA, advanced colorectal adenoma.

Table 6 Proportion of ACAs in subgroups stratified by morphology

Subgroups	Types	Polypoid	Nonpolypoid	Nonpolypoid vs polypoid		
				OR	95% CI	*P*-value
Screening subgroup	ACAs (%)	15 (12.6)	19 (20.2)	1.93	0.92–4.02	0.078
	Colorectal lesions	129	94	–	–	–
Surveillance subgroup	ACAs (%)	27 (22.0)	15 (14.7)	0.61	0.31–1.23	0.165
	Colorectal lesions	123	102	–	–	–
Symptomatic subgroup	ACAs (%)	111 (18.3)	73 (31.5)	2.09	1.48–2.94	<0.001
	Colorectal lesions	605	232	–	–	–

subgroup compared to that in the screening or surveillance subgroups and should be the focus for prevention. We also report high rates of distal lesions and nonpolypoid lesions in the symptomatic subgroup, indicating an important target for CRC prevention.

The incidence of ACAs and CRCs is increasing rapidly in both Asian and Western populations.[11] The high-risk factors for colorectal tumor in these populations are believed to be different, but the details are not yet known. Prior to our study, two previous studies focused on the prevalence of ACAs in a target group of asymptomatic Chinese subjects. Sung et al[5] enrolled 505 subjects in health exhibitions who were ≥50 years old and documented 12.5% of ACAs in a population of Hong Kong Chinese subjects. Another group of researchers, Liu et al,[6] detected 3.3% of ACAs in a group of asymptomatic Taiwanese Chinese subjects. In this study, 4.1%

of ACAs were detected among 565 asymptomatic subjects in mainland China. The high prevalence of ACAs in the first target subject groups may in part reflect the relatively large number of individuals who were older (>50 years old). In addition, as shown in Table 1, an inherent selection bias in terms of enrolled subjects, geography (mostly from urban areas), or dietary factors were among other plausible explanations.

Unlike previous studies that only examined asymptomatic subjects, this study also focuses on surveillance and symptomatic patients who might have a higher likelihood of having colorectal neoplasms. Subjects in the surveillance group showed a 4.6% prevalence for ACAs, with no significant differences compared to the screening subgroup. This result suggests that ACAs do progress to invasive cancer and that understanding the epidemiology of ACAs would predict the risk of CRC. Similarly, Costedio et al[12] note that family history does not predict an increase in ACAs. However, research by Armelao et al[7] indicates that patients having first-degree relatives with CRC hold an increased risk of ACAs compared to average-risk individuals.

Nevertheless, the prevalence of ACAs among patients in the symptomatic subgroup was 11.0%, which is significantly higher than that among patients in the screening or surveillance subgroup; this statistic corresponds with the results of a prior study conducted by Soetikno et al.[13] In another study, the prevalence of advanced neoplasms (including ACAs and cancer) was 9.4% in a total of 5,464 eligible patients who underwent colonoscopies due to their symptoms in Asia.[14] However, the prevalence of ACAs in alarm or non-alarm categories has not been explored in previous studies, creating a lack of data regarding this topic. Therefore, we further divided the symptomatic subgroup into alarm and non-alarm categories. No difference was determined between the prevalence of ACAs among patients in these two groups.

In this study, we further explored the distribution of ACAs stratified by anatomic location. There have been various discussions regarding the anatomic distribution of colorectal neoplasms. Proximal and distal colorectal neoplasms showed distinct epidemiological, clinical, and molecular characteristics.[15] The finding of a proximal shift in ACAs was demonstrated in several previous studies.[4,16,17] However, the study conducted by Friedenberg et al[18] lacks the topic of proximal shift in the distribution of ACAs. Recently, Rondagh et al[19] indicated that distal colorectal neoplasms are more likely to contain advanced histology than proximal colorectal neoplasms in a predominantly symptomatic population, which also corresponds with our findings. Prospective multicenter studies evaluating the proximal or distal shift of ACAs in large populations of Chinese subjects will be needed.

CRC is believed to evolve through the growth of polypoid adenoma over time.[20] It is believed that ACAs can be classified according to the growth pattern by observing the location and morphology. These classifications have prognostic significance. For instance, nonpolypoid lesions appeared to indicate a worse prognosis than polypoid ones.[21] However, nonpolypoid colorectal neoplasms (NP-CRNs) potentially explain the development of postcolonoscopy CRC. Soetikno et al[13] show that NP-CRNs were more likely to contain carcinoma than polypoid lesions, regardless of size. Whether they represented a distinct disease with a pathogenetic pathway different from the typical adenoma–carcinoma sequence in colorectal tumorigenesis and had higher malignant potential remained a matter of debate. In this study, we found that nonpolypoid lesions have a higher proportion of ACAs in the symptomatic subgroup. It is important for endoscopists to be aware of the presence and clinical significance of these nonpolypoid polyps. It has been reported that one of the potential mechanisms underlying the difference in incidence and pathogenesis between nonpolypoid and polypoid lesions is genetic change, including Ki-ras mutations, p53 mutation, and frameshift mutations.[22] Our results suggest that, in clinical practice, more attention should be given to nonpolypoid lesions since they appear to indicate worse prognosis than polypoid ones.

Limitations

There were several limitations in this study. First, this was a single-center study with small sample size, and all the procedures were performed by the same endoscopist. Second, another potential issue is that the polyp size might be misjudged by the endoscopist.[23] Due to the lack of standardization, the proportion of ACAs may not be accurately reflected in this study. A further limitation is the absence of data on the overall distribution of adenomas (advanced vs nonadvanced).

Conclusion

In patients who underwent a colonoscopy because of their symptoms, the prevalence of ACAs was higher compared to the prevalence in patients who underwent the examination for screening or surveillance purposes. Additionally, more attention should be focused on the distal colon and nonpolypoid lesions to improve the detection rate of ACAs.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55(2):74–108.

2. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med*. 1993;329(27):1977–1981.
3. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. *N Engl J Med*. 1992;326(10):658–662.
4. Chen HM, Weng YR, Jiang B, et al. Epidemiological study of colorectal adenoma and cancer in symptomatic patients in China between 1990 and 2009. *J Dig Dis*. 2011;12(5):371–378.
5. Sung JJ, Chan FK, Leung WK, et al. Screening for colorectal cancer in Chinese: comparison of fecal occult blood test, flexible sigmoidoscopy, and colonoscopy. *Gastroenterology*. 2003;124(3):608–614.
6. Liu HH, Wu MC, Peng Y, Wu MS, Mc W. Prevalence of advanced colonic polyps in asymptomatic Chinese. *World J Gastroenterol*. 2005;11(30):4731–4734.
7. Armelao F, Paternolli C, Franceschini G, et al. Colonoscopic findings in first-degree relatives of patients with colorectal cancer: a population-based screening program. *Gastrointest Endosc*. 2011;73534(3):527–534.
8. Gupta A, Samadder J, Elliott E, Sethi S, Schoenfeld P. Prevalence of adenomas and advanced adenomas in patients in the 40- to 49-year age group undergoing screening colonoscopy because of a family history of adenoma/polyp in a first-degree relative. *Gastrointest Endosc*. 2012;75(4):705–711.
9. Forsberg AM, Kjellström L, Agréus L, et al. Prevalence of colonic neoplasia and advanced lesions in the normal population: a prospective population-based colonoscopy study. *Scand J Gastroenterol*. 2012;47(2):184–190.
10. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc*. 2002;58(6 Suppl):S3–S43.
11. Sung JJ, Lau JY, Goh KL, Leung WK, Asia Pacific Working Group on Colorectal Cancer. Increasing incidence of colorectal cancer in Asia: implications for screening. *Lancet Oncol*. 2005;6(11):871–876.
12. Costedio M, Church J. Pathways of carcinogenesis are reflected in patterns of polyp pathology in patients screened for colorectal cancer. *Dis Colon Rectum*. 2011;54(10):1224–1228.
13. Soetikno RM, Kaltenbach T, Rouse RV, et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. *JAMA*. 2008;299(9):1027–1035.
14. Leung WK, Ho KY, Kim WH, et al. Colorectal neoplasia in Asia: a multicenter colonoscopy survey in symptomatic patients. *Gastrointest Endosc*. 2006;64(5):751–759.
15. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. *Ann Intern Med*. 1990;113(10):779–788.
16. Dinning JP, Hixson LJ, Clark LC. Prevalence of distal colonic neoplasia associated with proximal colon cancers. *Arch Intern Med*. 1994;154(8):853–856.
17. Fenoglio L, Castagna E, Comino A, et al. A shift from distal to proximal neoplasia in the colon: a decade of polyps and CRC in Italy. *BMC Gastroenterol*. 2010;10:139.
18. Friedenberg FK, Singh M, George NS, Sankineni A, Shah S. Prevalence and distribution of adenomas in black Americans undergoing colorectal cancer screening. *Dig Dis Sci*. 2012;57(2):489–495.
19. Rondagh EJ, Masclee AA, van der Valk ME, et al. Nonpolypoid colorectal neoplasms: gender differences in prevalence and malignant potential. *Scand J Gastroenterol*. 2012;47(1):80–88.
20. Saitoh Y, Waxman I, West AB, et al. Prevalence and distinctive biologic features of flat colorectal adenomas in a North American population. *Gastroenterology*. 2001;120(7):1657–1665.
21. George SM, Mäkinen MJ, Jernvall P, Mäkelä J, Vihko P, Karttunen TJ. Classification of advanced colorectal carcinomas by tumor edge morphology: evidence for different pathogenesis and significance of polypoid and nonpolypoid tumors. *Cancer*. 2000;89(9):1901–1909.
22. Kaneko K, Kurahashi T, Makino R, et al. Pathological features and genetic alterations in colorectal carcinomas with characteristics of nonpolypoid growth. *Br J Cancer*. 2004;91(2):312–318.
23. Johnson ME, Feinn R, Anderson JC. Clinical factors associated with non-polypoid colonic adenomas ≥6 mm: a prospective study in an asymptomatic population using a high-definition colonoscope. *Am J Gastroenterol*. 2011;106(11):2018–2022.