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BRIEF ARTICLE

Relationship of human rectal aberrant crypt foci and formation of colorectal polyp: One-year following up after polypectomy

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Abstract

AIM: To clarify the relationship of human rectal aberrant crypt foci and formation of colorectal polyp.

METHODS: Eighty-nine subjects were recruited from the population of Japanese individuals who underwent polypectomy at Yokohama City University Hospital. All patients had baseline adenomas removed at year 0 colonoscopy. Aberrant crypt foci (ACF) were defined as lesions in which the crypts were more darkly stained with methylene blue than normal crypts and had larger diameters, often with oval or slit-like lumens and a thicker epithelial lining.

RESULTS: A total of 366 ACFs were identified in 89 patients; all had baseline adenomas removed at the first examination (year 0) colonoscopy and returned for the second (year 1). ACF in the lower rectum were assessed at year 0 and study group were divided into two groups depend on ACF numbers, 0-3 or over 3. All participants were examined in the number and maximum size of adenoma. There was no statistical difference in number and maximum size of ACF at year 0, however, maximum size of adenoma was larger in over 3 group than 0-3 group at year 1.

CONCLUSION: The number of ACF may be a predictive factor of relatively large adenoma incidence in the pilot phase study.

Key words: Aberrant crypt foci; Colorectal carcinogenesis; Visceral fat; Adiponectin

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INTRODUCTION

Colorectal cancer (CRC) has high mortality and morbidity rates, and its prevalence has been increasing[1,2]. The development from normal colonic epithelium to small adenomas is little understood. In experimental models of colonic carcinogenesis, aberrant crypt foci (ACF) are the earliest detectable abnormality and precede adenomas. ACF was first discovered in mice treated with azoxymethane[3], have been clearly shown to be precursor lesions of CRC, and are now established as a biomarker of the risk of CRC in azoxymethane-treated mice and rats[4]. In humans, ACF can be detected using magnifying colonoscopy[5]. Recent advances in magnification chromoendoscopy now allow these lesions to be identified *in vivo* and their natural history ascertained. It would be very useful, to clarify the relationship of ACF incidence to established risks for colorectal tumors. We have reported the relation between number of ACF and visceral fat obesity[6]. In this study, human ACF in the lower rectum were assessed and subjects returned 1 year later to evaluate the natural history of the lesions. Herein, we wanted to determine the adenoma incidence over a 1-year period after polypectomy.

MATERIALS AND METHODS

Study population

We prospectively evaluated 89 subjects recruited from the population of Japanese individuals who underwent polypectomy at Yokohama City University Hospital. All patients had baseline adenomas (over 5 mm) removed at year 0 colonoscopy. The exclusion criteria included: presence of contraindications to colonoscopy; current or past non-steroidal anti-inflammatory drug use including aspirin; or family history of CRC; or history of carcinoma, familial adenomatous polyposis, inflammatory bowel disease, radiation colitis and diabetes mellitus. Written informed consent was obtained from all the subjects prior to their participation. The study protocol was approved by the Yokohama City University Hospital Ethics Committee.

Magnifying colonoscopy for identification of ACF

Participants' bowel preparation for the colonoscopy was carried out using polyethylene glycol solution. A Fujinon EC-490ZW5/M colonoscope was used to perform the magnifying colonoscopy (Fujinon Toshiba ES Systems Co., Ltd, Tokyo, Japan). Total colonoscopy was performed before imaging of lower rectal ACF. Subsequently, 0.25% methylene blue was applied to the mucosa with a spray catheter. Aberrant crypts were distinguished from normal crypts by their deeper staining, larger diameter, must be < 2 mm raised and the number of ACF in the lower rectum was counted. This counting was conducted in the lower rectal region, extending from the middle rectal fold to the dentate line, based on the results of a previous study[5]. ACF were defined as lesions in which the crypts were more darkly stained with methylene blue than normal crypts and had larger diameters, often with oval or slit-like lumens and a thicker epithelial lining[7-10]. All ACF were recorded photographically by one endoscopist and evaluated by two independent observers who were unaware of the subjects' clinical histories.

Measurement of the visceral and subcutaneous fat areas

Body mass index (BMI) was calculated using the following equation: body weight (kg)/[height (m)^2]. Intra-abdominal adipose tissue was assessed, as previously described by measuring the visceral fat area (VFA), subcutaneous fat area (SFA), total fat area (TFA) and waist circumference from computed tomography (CT) images at the level of the umbilicus[6]. All CT scans were carried out with the subjects in the supine position. The borders of the intra-abdominal cavity were outlined on the CT images, and the VFA was quantified using Fat Scan software (N2 System Corporation, Kobe, Japan).

Statistical analysis

We examined the associations between clinical characteristics and number of ACF (0-3 *vs* over 3), because this criteria divided into almost same volume two groups. All data were expressed as mean ± SD, unless otherwise indicated. Non-parametric tests were used to test differences. Statistical analyses were determined using the Stat View software (SAS Institute Inc., Cary, NC, United States). $P < 0.05$ were considered to denote statistical significance.

RESULTS

Patient characteristics

A total of 366 ACFs were identified in 89 patients; all had baseline adenomas (over 5 mm) removed at the first examination (year 0) colonoscopy and returned for the second examination (year 1). ACF in the lower rectum were assessed at year 0 and study group were divided into two groups depend on ACF numbers, 0-3 or over 3. Table 1 summarizes the clinical characteristics of study participants of the first examination. The mean age was 63.4 years and 69% were male. A total of 8% had advanced adenoma, 61% had non advanced adenoma and 31% had no adenoma. There was no statistical difference between 0-3 and over 3 numbers of ACF, in waist circumference, BMI, total cholesterol, triglyceride, hemoglobin A1c, TFA, VFA and SFA.

Natural history of ACF one year follows up after polypectomy

The mean number of observed ACF was 4.1 ± 3.7 at year 0, 4.0 ± 4.6 at year 1. This result shows natural history of ACF, and there was no statistical difference in number of ACF. The typical magnifying colonoscopic features of ACF at year 0 and 1 are shown in Figure 1.

Adenoma incidence and size one year after polypectomy

All participants were assigned two groups, 0-3 or over 3 with number of ACF, and examined in the number and

Table 1 Clinical characteristics of study participants at year 0

	Number of ACF			*P* value
	Total	0-3	> 3	
No. of subjects	89	41	48	
Age (yr)	63.4 ± 11.1	62.6 ± 12.9	64.1 ± 9.5	0.52
Gender (male:female)	61:28:00	28:14:00	33:15:00	
Waist Circumference (cm)	85.9 ± 11.5	84.7 ± 8.1	86.7 ± 13.6	0.57
BMI (kg/m^2)	23.2 ± 3.1	22.6 ± 2.3	23.8 ± 3.6	0.09
Total cholesterol (mg/dL)	210.7 ± 34.9	208.7 ± 32.6	212.2 ± 36.9	0.69
Triglyceride (mg/dL)	146.2 ± 77.1	125.9 ± 64.1	161.5 ± 83.2	0.06
Hemoglobin A1c (%)	5.9 ± 1.3	5.6 ± 1.2	6.2 ± 1.4	0.13
TFA (cm^2)	198.9 ± 95.2	177.0 ± 55.6	215.5 ± 115.2	0.19
VFA (cm^2)	90.4 ± 53.5	75.6 ± 41.1	101.6 ± 59.7	0.11
SFA (cm^2)	108.5 ± 58.1	101.4 ± 45.7	113.9 ± 66.4	0.49

Data are expressed as mean ± SD. ACF: Aberrant crypt foci; BMI: Body mass index; VFA: Visceral fat area; SFA: Subcutaneous fat area; TFA: Total fat area.

Table 2 Endoscopic results of adenoma at year 0 and year 1

No. of aberrant crypt foci at year 0	0-3	> 3	0-3 *vs* > 3
No. of subjects	41	48	
No. of adenoma at year 0	1.4 ± 1.2	1.6 ± 1.8	0.71
Maximum size of adenoma at year 0	6.0 ± 4.6	6.3 ± 7.2	0.81
No. of adenoma at year 1	1.0 ± 1.0	1.5 ± 1.4	0.08
Maximum size of adenoma at year 1	3.5 ± 3.5	5.5 ± 5.8	0.03[1]

Data are expressed as mean ± SD. [1]$P < 0.05$.

maximum size of adenoma (Table 2). There was no statistical difference in number and maximum size of ACF at year 0, however, maximum size of adenoma was larger in over 3 group than 0-3 group at year 1.

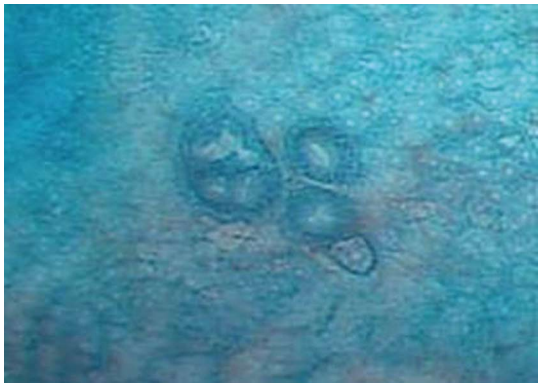

Figure 1 Typical features of aberrant crypt foci on magnifying colonoscopy.

DISCUSSION

Colorectal adenomas are considered to be a validated surrogate endpoint biomarker for sporadic CRC because removing adenomas by endoscopic polypectomy correlates with a decrease in CRC incidence[11]. Therefore, the opportunity of endoscopic polypectomy and needs of predictive colorectal tumor marker are in increasing. ACF have emerged as the putative precursor to colorectal adenomas. In numerous animal studies, ACF predict subsequent development of CRC[12,13]. Cross-sectional studies have shown that there is a higher rate of ACF in subjects with CRC and adenoma compared with those with normal colons[5,14,15]. Because of the epidemiologic and genetic association of ACF with colorectal neoplasia, ACF are a potential biomarker for CRC. Therefore, some chemopreventive studies were reported using ACF as a surrogate marker[16-24]. Natural history of human ACF was reported, however there was no significant change in number of ACF at one year observation[25]. ACF are small lesions and it is possible that the biopsy forceps missed or overwhelmed the lesion. More importantly, because of issues in biopsy orientation and the small number of crypts affected in comparison with the biopsy sample, pathologic diagnosis may not be reliable. Assessment of molecular abnormalities in histologically confirmed ACF and in endoscopically suspected ACF that are not pathologically confirmed will be an additional means of assessing the validity of the endoscopic classification of an ACF. Some studies measuring ACF by magnification chromoendoscopy found a high degree of association between the number of rectal ACF and the presence of synchronous adenomas and adenocarcinomas[26]. In this study, we demonstrated a correlation between the number of ACF 0-3 and over 3 in maximum size of adenoma at year 1. The meaning of the number of ACF is not elucidated, however the number of ACF may be a predictive factor of relatively large adenoma incidence in the pilot phase study.

COMMENTS

Background

Colorectal cancer (CRC) has high mortality and morbidity rates, and its prevalence has been increasing. The development from normal colonic epithelium to small adenomas is little understood. In experimental models of colonic carcinogenesis, aberrant crypt foci (ACF) are the earliest detectable abnormality and precede adenomas. In humans, ACF can be detected using magnifying colonoscopy.

Research frontiers

Recent advances in magnification chromoendoscopy now allow these lesions to be identified *in vivo* and their natural history ascertained. It would be very useful, to clarify the relationship of ACF incidence to established risks for colorectal

tumors.

Innovations and breakthroughs

The authors have reported the relation between number of ACF and visceral fat obesity, however the relation that human ACF and formation of colorectal polyp was unclear.

Applications

In this study, human ACF in the lower rectum were assessed and subjects returned 1 year later to evaluate the natural history of the lesions. Herein, the authors wanted to determine the adenoma incidence over a 1-year period after polypectomy.

Terminology

The meaning of human ACF is still unclear, however may be a surrogate marker of colorectal carcinogenesis. Therefore it is hoped that human ACF will be a surrogate marker of chemopreventive trials.

Peer review

The authors described the relationship of ACF with adenoma. In this study, the authors found maximum size of adenoma was larger in over 3 group than 0-3 group at year 1. It is a novel knowledge and nice to know for gastroenterologist. The authors reviewed their results by relevant high-integrity references. This report is a very interesting study and includes a novel finding. Furthermore, authors described and reviewed well.

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