Association of distal hyperplastic polyps and proximal neoplastic lesions: a prospective study of 5613 subjects CME

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Background and Aims: Current evidence of whether distal hyperplastic polyps (HPs) are markers of proximal neoplasia (PN) is mixed. We evaluated the association between distal neoplasia and synchronous PN in asymptomatic subjects.

Methods: We recruited 5819 Chinese asymptomatic screening participants 50 to 70 years of age who underwent colonoscopy in Hong Kong from 2008 to 2014, of whom 206 subjects with distal advanced neoplasia or cancer were excluded. The association between distal pathology (tubular adenomas [TAs], HPs, no polyps) and proximal pathology (PN, proximal advanced neoplasia [PAN]) was assessed by multivariate regression models, overall and stratified by the Asia Pacific Colorectal Screening scoring system (scores of 4-7, high risk; scores of 0-3, lower risk).

Results: The prevalence of PN in the no distal polyps group, distal HPs group, and distal TAs group was 14.8%, 19.3%, and 29.4%, respectively. The corresponding prevalence of PAN was 1.8%, 3.2%, and 3.5%. Participants with distal HPs did not have significantly higher odds of PN (adjusted odds ratio [AOR] 1.24; 95% confidence interval [CI], 0.97-1.59; $P = .089$), and their association with PAN was marginally significant (AOR 1.77; 95% CI, 1.00-3.13; $P = .052$), except in lower risk subjects for whom the odds of PAN were marginally higher in the distal HPs group than the no distal polyps group (AOR 1.97; 95% CI, 1.01-3.85; $P = .048$). Overall, the distal polyps group had significantly lower odds of PN than the distal TAs group (AOR 0.55; 95% CI, 0.40-0.76; $P < .001$). The increased risk of PN and PAN among those with distal HPs was modest.

Conclusions: A direct association between distal HPs and PN is lacking, and this implies a need for a multivariate assessment of the risk of PAN. Recommending colonoscopy for every patient with distal HPs detected by screening sigmoidoscopy is not supported by this study. (Gastrointest Endosc 2016;83:555-62.)

Colorectal cancer (CRC) affects 1.2 million people globally, accounting for 10% of all malignancies and 8% of all cancer deaths.[1,2] Fecal occult blood tests, flexible sigmoidoscopy (FS), and colonoscopy could effectively reduce cancer-related mortality by up to 33%, 40%, and 68%, respectively.[3-8]

Compared with other screening modalities, use of FS is now becoming more widespread, especially in Europe and especially after the results of 4 landmark randomized, controlled trials were published.[8-12] FS is a cost-effective strategy to reduce both the incidence and mortality of CRC.[10,13] It also represents an attractive option in

Abbreviations: AOR, adjusted odds ratio; APCS, Asia Pacific Colorectal Screening; CI, confidence interval; CRC, colorectal cancer; FS, flexible sigmoidoscopy; HP, hyperplastic polyp; OR, odds ratio; PAN, proximal advanced neoplasia; PN, proximal neoplasia; TA, tubular adenoma.

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resource-deprived countries where screening colonoscopy and gastroenterologists are not widely available. Studies have demonstrated that adequately trained family physicians and nurse endoscopists can perform screening FS as safely and effectively as gastroenterologists or surgeons.[14-17]

Whereas it was widely recognized that subjects with distal advanced neoplasia have higher risks of proximal neoplasia (PN) and proximal advanced neoplasia (PAN),[18-20] whether distal hyperplastic polyps (HPs) are also markers of PN and PAN is under debate. Formal guidelines do not endorse distal HPs as markers of PN or PAN.[20-22] Fourteen of 17 published colonoscopy studies reported no association between HP, PN, and PAN.[23] However, recent pathology studies suggest that microvesicular HPs could develop into sessile serrated adenomas via microsatellite instability and MLH1 methylation pathways.[24] Of 4 meta-analyses,[23,25-27] 2 concluded that there was an association between distal HPs and PN,[23,25] 1 demonstrated an association between distal adenomatous polyps and PN,[26] and 1 showed no association between distal HPs and PN/PAN.[27] The interpretation of these meta-analyses is mixed because the heterogeneity of the methodologies used by the original articles varied substantially. Treating distal HPs as normal colonoscopy findings has not been unanimously agreed on, as reflected by many physicians still referring patients with distal HPs alone for colonoscopy.[28] There are thus far fewer large-scale colonoscopy studies that were prospectively conducted in asymptomatic individuals in Asia. Hence, the generalizability of the existing evidence to Eastern Asian populations is uncertain.

The objective of this study was to evaluate the association between distal HPs and PN/PAN among CRC screening participants who underwent colonoscopy. Because a recent study reported that the detection of proximal serrated lesions at screening colonoscopy was independently associated with the risk of synchronous advanced colorectal neoplasia,[29] we also examined the relationship between proximal serrated lesions and distal HPs.

METHODS

The study setting has been described elsewhere.[30-36] In 2008, a bowel cancer screening center was established in Hong Kong. It recruited eligible Hong Kong residents 50 to 70 years of age who were asymptomatic for CRC screening via media invitations. This study was approved by an ethics committee of the Chinese University of Hong Kong, and each participant provided informed consent.

Participant recruitment

We prospectively recruited self-referred screening participants for CRC screening via telephone, fax, e-mail, or walk-in. Enrolled subjects were eligible if they (1) were 50 to 70 years of age; (2) had no existing or previous symptoms suggestive of CRC such as rectal bleeding, melena, anorexia, change in bowel habits in the past 4 weeks, and weight loss of more than 5 kg in the past 6 months; and (3) had not undergone any CRC screening tests in the past. Exclusion criteria included personal history of CRC, colonic adenoma, diverticular disease, inflammatory bowel disease, prosthetic heart valve, or vascular graft surgery. Subjects with contraindications to colonoscopy, including medical conditions such as cardiopulmonary insufficiency and the use of dual antiplatelet therapy, were also excluded. The participants were offered either a yearly fecal occult blood test or a colonoscopy for CRC screening. This study included all participants who underwent a colonoscopy (years 2008-2014).

Colonoscopy procedure

A standardized bowel preparation regimen by using polyethylene glycol (Klean-Prep; Helsinn Birex Pharmaceuticals Ltd, Dublin, Ireland) was used. The colonoscopy was conducted at an endoscopy center in a major hospital, conducted by experienced colonoscopists. Before the colonoscopy, all subjects received a standard sedation regimen consisting of midazolam 2.5 mg (Groupe Panpharma, Beignon, France). Pethidine 25 mg (Martindale Pharma, Buckinghamshire, United Kingdom) was administered intravenously. A withdrawal time of at least 6 minutes was practiced for all subjects, which is in accordance with the current quality indicators for colonoscopy.[37] All lesions were removed and underwent biopsies, as deemed appropriate by the endoscopists. In this study, the colonoscopists attempted to remove and perform biopsies on all lesions including benign-appearing HPs, except lesions that were smaller than 2 mm. These small lesions were also regarded as HPs in this analysis. The biopsy specimens were examined by gross and microscopic evaluation in a certified laboratory by experienced histopathologists.

Outcome variables and covariates

The major outcome variable was the detection of PN and PAN. PAN is defined as any colorectal adenoma in the proximal colon 10 mm or greater in diameter having high-grade dysplasia and villous or tubulovillous histologic characteristics or any combination thereof. The secondary outcome variable was the detection of proximal serrated lesions, defined as HPs larger than 9 mm, those interpreted as sessile serrated adenomas or sessile serrated polyps, and traditional serrated adenomas in the proximal colon. The variables tested for association are distal tubular adenomas (TAs) and HPs, defined as TAs and HPs situated within the colonic mucosa in the rectum, the rectosigmoid junction, and the sigmoid colon. The covariates included participant age, sex, body mass index, smoking status, alcohol use, family history of CRC, concomitant comorbidities, and the use of aspirin and nonsteroidal anti-inflammatory drugs.