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Features of Adenoma and Colonoscopy Associated With Recurrent Colorectal Neoplasia Based on a Large Community-Based Study

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BACKGROUND & AIMS: We investigated adenoma and colonoscopy characteristics that are associated with recurrent colorectal neoplasia based on data from community-based surveillance practice. **METHODS:** We analyzed data of 2990 consecutive patients (55% male; mean age 61 years) newly diagnosed with adenomas from 1988 to 2002 at 10 hospitals throughout The Netherlands. Medical records were reviewed until December 1, 2008. We excluded patients with hereditary colorectal cancer (CRC) syndromes, a history of CRC, inflammatory bowel disease, or without surveillance data. We analyzed associations among adenoma number, size, grade of dysplasia, villous histology, and location with recurrence of advanced adenoma (AA) and nonadvanced adenoma (NAA). We performed a multivariable multinomial logistic regression analysis to estimate odds ratios (ORs) and 95% confidence intervals (CIs). **RESULTS:** During the surveillance period, 203 (7%) patients were diagnosed with AA and 954 (32%) patients with NAA. The remaining 1833 (61%) patients had no adenomas during a median follow-up of 48 months. Factors associated with AA during the surveillance period included baseline number of adenomas (ORs ranging from 1.6 for 2 adenomas; 95% CI: 1.1−2.4 to 3.3 for ≥5 adenomas; 95% CI: 1.7−6.6), adenoma size ≥10 mm (OR = 1.7; 95% CI: 1.2−2.3), villous histology (OR = 2.0; 95% CI: 1.2−3.2), proximal location (OR = 1.6; 95% CI: 1.2−2.3), insufficient bowel preparation (OR = 3.4; 95% CI: 1.6−7.4), and only distal colonoscopy reach (OR = 3.2; 95% CI: 1.2−8.5). Adenoma number had the greatest association with NAA. High-grade dysplasia was not associated with AA or NAA. **CONCLUSIONS: Large size and number, villous histology, proximal location of adenomas, insufficient bowel preparation, and poor colonoscopy reach were associated with detection of AA during surveillance based on data from community-based practice. These characteristics should be used jointly to develop surveillance policies for adenoma patients.**

Keywords: Metachronous Adenoma; Polypectomy; Predictors.

Colorectal cancer (CRC) is one of the leading causes of cancer-related death in the Western world.[1,2] Detecting and removing (early-stage) cancers and precursor lesions (adenomas) can reduce CRC incidence and mortality.[3–5] Individuals in whom adenomas are detected have an increased risk of CRC developing compared with the average population, even after the adenoma has been removed.[4,6–9] Therefore, it is recommended that adenoma patients undergo regular surveillance colonoscopy.[10–14] Surveillance colonoscopy currently presents a considerable burden for individuals and demand on endoscopy units. To increase the efficacy of surveillance, risk stratification based on advanced adenoma (AA) recurrence rates with well-allocated surveillance intervals is needed. Patients with high-risk adenomas, so-called "advanced adenomas," or with >2 adenomas are especially known for higher advanced adenoma recurrence rates.[4,9,15,16] Advanced adenomas are usually defined as adenoma(s) with at least one of the following characteristics: size ≥10 mm, high-grade dysplasia (HGD), and (tubulo)villous histology.

Currently recommended surveillance intervals differ between countries and institutions, and are predominantly based on adenoma multiplicity and categorization of an adenoma as advanced or nonadvanced.[11–13] None of the surveillance guidelines have incorporated recommendations when specific combinations of the various aspects (ie, size ≥10 mm, villousness, HGD) of advanced adenomas are present. Previous studies suggested that these adenoma characteristics are independent predictors of adenoma recurrence, but these studies were often small or assessed the adenoma predictors one at a time.[17–19] Two meta-analyses explored the predictive effect of individual adenoma characteristics on AA recurrence.[9,19] These stud-

Abbreviations used in this paper: AA, advanced adenoma; CI, confidence interval; CRC, colorectal cancer; HGD, high-grade dysplasia; IQR, interquartile range; NAA, nonadvanced adenoma; OR, odds ratio.

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ies included data from clinical trials performed in the United States, often with high-quality examinations and per-protocol surveillance intervals. Most studies included patients with prior adenomas and without certain medical conditions, and approximately half of the population included also underwent a dietary or chemopreventive intervention. The aim of the present study was to determine independent adenoma-related and colonoscopy-related predictors and their associated odds ratios for (advanced) colorectal adenomas during clinical surveillance practice in a large community-based study.

Methods

Data Collection

We used the nationwide registry of histopathology and cytopathology (PALGA) to select patients with newly diagnosed adenoma between 1988 and 2002 from 10 hospitals (3 academic and 7 nonacademic) in The Netherlands. Participating hospitals were selected on the basis of long-term availability of electronic medical records and geographical distribution throughout The Netherlands. Years of inclusion of adenoma patients depended on the availability of electronic medical records per hospital. Local hospital medical records, mainly endoscopy and pathology reports, were reviewed until December 1, 2008 to collect information on patient characteristics and adenoma characteristics at index colonoscopy and surveillance endoscopies. Patients with any of the following criteria were excluded: age at index colonoscopy younger than 40 years; (suspected) hereditary CRC syndromes, such as Lynch syndrome (hereditary nonpolyposis colorectal carcinoma), familiar adenomatous polyposis, Peutz-Jeghers syndrome, juvenile polyposis, or mutYH-polyposis; personal history of CRC or CRC at index colonoscopy; inflammatory bowel disease; hyperplastic polyps (nonadenomatous polyps) only; (partial) colonic bowel resections before or at the time of index colonoscopy; acromegaly; uretero-sigmoidostomy; index endoscopy was a sigmoidoscopy; missing pathology or endoscopy report at index colonoscopy; and no surveillance endoscopy.

The study was approved by the Institutional Review Board at the Erasmus MC University Medical Center and confirmed by the local Institutional Review Board of each participating hospital.

Measures and Definitions

Index colonoscopy was defined as the colonoscopy with first adenoma diagnosis. Repeat endoscopy examinations performed within 6 months were considered as one examination and histological findings were combined. In case of combining results from endoscopies, date of last colonoscopy was used.

The adenoma characteristics collected at index and surveillance endoscopies were number of adenomas, and per adenoma found: size (measured by endoscopist and pathologist), presence of HGD and villous histology, and location. For the analysis, we coded the number of adenomas as 1 to 5+ and used endoscopic size of the largest adenoma categorized as <10 mm or ≥ 10 mm. Histological characteristics (HGD and villous histology) in any adenoma were coded as present or absent. Adenoma location was considered proximal if at least 1 adenoma was located proximal to the splenic flexure or if location was not specified when located at an endoscope insertion of ≥ 60 cm. The colonoscopy-related characteristics collected at index colonoscopy were colonoscopy reach (coded as full [to cecum], proximal colon, or distal colon), and index bowel preparation (coded as good, moderate, or insufficient).

The 2 outcomes of interest were presence of at least 1 AA and presence of nonadvanced adenoma (NAA) only at surveillance endoscopy. We defined an AA as an adenoma with at least 1 of the following characteristics: size ≥ 10 mm (either on endoscopic description or pathology), villous histology ($\geq 75\%$ villous architecture), or HGD (including intramucosal carcinoma or carcinoma in situ), or CRC. In contrast, we defined NAA as size <10 mm, with tubular or tubulovillous histology, and with low-grade dysplasia. In cases where more than 1 adenoma was found, patients were categorized according to most advanced features. We present absolute numbers and percent with AA and NAA at surveillance colonoscopy.

Statistical Analysis

Missing values. We coded missing values as negative for presence of HGD, villous histology, and a proximal location. We assumed "a good bowel preparation" and "a full colonoscopy," respectively, when bowel preparation and completeness of colonoscopy were not explicitly documented ($n = 2141$ and $n = 58$, respectively). For missing values concerning endoscopic adenoma size at index colonoscopy ($n = 584$) and sex ($n = 2$), we used a statistical imputation technique.[20] Imputations were based on correlations with patient characteristics at index colonoscopy: age and sex; adenoma characteristics at index colonoscopy: number of adenomas (1−5+), presence of HGD, (tubulo)villous histology (villous, tubulovillous, tubular), proximal location, and adenoma size (pathology); year of index colonoscopy; outcome (AA, NAA, or no adenoma during surveillance); and surveillance interval, using the aregImpute function in R v2.11 software (R foundation for statistical computing, Vienna, Austria). It is good methodological practice to include the outcome variable in the imputation of predictor variables to avoid biased imputations.[21] The outcome is related to the predictor values; by omitting the outcome in the imputation, the association between the predictor and outcome will falsely be weakened. Imputing missing outcomes was not considered.[21] For adenoma size at surveillance colonoscopy, we used either endoscopic size or size at pathology (size ≥ 10 mm) if available and otherwise we assumed that the adenoma size was <10 mm.

Strength of the association. Multinomial logistic regression analysis was used to assess odds ratios (OR) of predictors of AA and NAA during surveillance. We used a modulated renewal method[22] to make full use of the available follow-up data. For this purpose, we included further surveillance data when available, in those patients with a (consecutive) negative surveillance endoscopy (no AA or NAA) until AA or NAA was observed, or until the last negative surveillance endoscopy, with a maximum of the fifth surveillance period. For these patients, multiple records were included in the dataset, one for each included surveillance event. For each record, the time of surveillance was calculated from the index date (date of colonoscopy with first adenoma diagnosis) to the date of the surveillance endoscopy and the end point was the finding at that particular surveillance endoscopy (AA/CRC, NAA, no adenoma). For example, if a patient had 2 negative surveillance endoscopies and at the third surveillance examination a NAA detected, this patient was included 3 times in our database. This modulated renewal method leads to analysis of all first NAAs and AA/CRCs that occur during follow-up. It enhances the efficiency of the estimation with smaller standard errors of the estimated parameters.