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A Rule for Determining Risk of Colorectal Cancer in Patients With Inflammatory Bowel Disease

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BACKGROUND & AIMS: **Surveillance guidelines for inflammatory bowel disease–associated colorectal cancer (IBD-CRC) are based on findings from retrospective studies. We aimed to create and validate a prediction rule to assist clinicians in identifying patients with IBD who are at low and high risk for CRC.**

METHODS: **We performed a retrospective case-control study of 2 cohorts of patients from tertiary care centers (the University Hospital of Leuven, Belgium, and 7 University Medical Centers in The Netherlands). Multivariate Cox regression was used to select independent risk factors for CRC in the Leuven cohort. Based on their regression coefficients (β), we created a rule to predict risk for CRC. In validation studies, the predictive strength was tested by C-statistic analysis and then validated externally in the Dutch cohort.**

RESULTS: **In total, we identified 50 patients with IBD-CRC (cases) and 136 patients with IBD without CRC (controls) in Leuven, and 138 cases and 206 controls in the Dutch cohort. From the Leuven cohort we created the CRC risk prediction rule based on 4 risk factors: IBD-type ulcerative colitis ($\beta = 1.2$), primary sclerosing cholangitis ($\beta = 1.1$), extent of colonic disease ≥50% ($\beta = 1.1$), and postinflammatory polyps ($\beta = 0.8$). The prediction rule consisted of a total score for each individual patient calculated from the presence or absence of these 4 risk factors. For example, a score of 13 represented patients who had extensive Crohn's disease without PSC or postinflammatory polyps, who had a 15% likelihood of CRC in the Leuven cohort and a 24% likelihood of CRC in the Dutch cohort. Scores of 0, 13, 23, 27, and 37 represented patients with Crohn's disease, and scores 15, 25, 28, 38, 42, and 52 represented patients with ulcerative colitis. The total score per patient had a C-statistic of 0.75. In the Dutch cohort this score had a C-statistic of 0.67.**

CONCLUSIONS: **Ulcerative colitis, primary sclerosing cholangitis, disease extent ≥50%, and postinflammatory polyps were found to determine risk for CRC in patients with IBD. A surveillance guideline that incorporates the relative weights of these risk profiles would identify patients at risk for CRC more accurately than algorithms in current guidelines.**

Keywords: Colon Cancer; Inflammation; Screening; UC.

The risk of colorectal cancer (CRC) in inflammatory bowel disease (IBD) colitis patients is known to be increased,[1] although not as much as previously reported.[2] It is clear that the majority of IBD patients will never develop this complication. The challenge lies in identifying patients at particularly high risk by using established and reliable risk factors. Generally accepted factors are a previous diagnosis of colonic dysplasia,[3] disease duration,[2,4] disease extent,[4] and primary sclerosing cholangitis (PSC).[5,6] Endoscopic features also can assist in identifying high-risk patients. Both the presence of postinflammatory polyps[7,8] and colonic strictures[7] have been shown to be associated with an increased cancer risk in ulcerative colitis. Conversely, a normal endoscopic appearance reduces the risk to the same level as

Abbreviations used in this paper: BSG, British Society of Gastroenterology; CRC, colorectal cancer; DALM, dysplasia-associated lesion or mass; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; TNF, tumor necrosis factor.

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the background non-IBD population.[7] The recently updated British Society of Gastroenterology (BSG) guideline[9] also includes family history of CRC as a risk factor based on the study by Askling et al.[10] Despite the confirmed association of these predictive and protective factors with regard to CRC development in IBD, their combined value in predicting which patients are at a low or high risk of CRC has never been validated. Therefore, current recommendations on risk groups and intervals in the BSG and American Gastroenterology Association guidelines[9,11] are based on expert opinion. The aim of the present study was to discriminate reliably between low and high risk of IBD-associated CRC based on combined risk factors. To achieve this we created an internally and externally validated, easy-to-use prediction rule for IBD-associated CRC.

Methods

Study Design

We performed a retrospective case-control study to identify predictive and protective factors for IBD-associated CRC. To validate findings in an external cohort we collected data from 2 separate cohorts, 1 from the University Hospital Leuven in Belgium and 1 from university hospitals in The Netherlands.[12] The Leuven cohort was used to build the prediction rule and the Dutch cohort served as an external validation.

Patient Selection: Leuven Cohort

We used an International Classification of Diseases, 9th revision, coding search for the diagnoses of IBD and CRC at the University Hospital Gasthuisberg, Leuven, which is a tertiary referral center in Flanders, North Belgium. Search results were available for the period from September 1999 to August 2009. The search yielded 99 results. After an initial check, we identified and excluded 3 patients with isolated ileal Crohn's disease, 21 patients with unconfirmed IBD, 7 patients with synchronous diagnoses of IBD and CRC, 10 patients with low-grade dysplasia but no CRC, 1 patient with high-grade dysplasia but no CRC, and 7 patients with cancers other than colorectal adenocarcinoma. To expand our cohort we cross-referenced the local electronic patient database with all local pathology reports from September 1990 through June 2011. This yielded 5 additional CRC cases between 1990 and 1999. Controls in Leuven were selected from the Leuven IBD biobank by generating a randomly ordered patient list. Controls then were selected consecutively from the top of the list. Crohn's patients with only ileal involvement were excluded ($n = 12$). In total, we collected data from 50 cases and 136 unmatched controls. We used unmatched controls to include as many modifiers of CRC risk as possible.

Patient Selection: Dutch Cohort

The cohort from The Netherlands included all IBD-associated CRC cases from 1990 to 2006 in tertiary referral centers. The cohort of Dutch patients with IBD-associated CRC has been reported previously.[12,13] These patients were selected using the nationwide pathology automated archive (known as PALGA).[14] Search terms for colitis and carcinoma with multiple synonyms were used to identify patients with IBD and CRC. Results were screened manually for confirmed IBD and CRC. By using this method we identified 149 IBD-associated CRCs in 7 Dutch university medical hospitals. Eleven patients were excluded because of synchronous diagnoses of IBD and CRC. We selected controls by using identical search terms, but this time we excluded neoplasia. A random number generator was used to select controls in a 1:2 ratio to cases. After manual screening, 94 selected controls were excluded because of isolated ileal Crohn's disease or an unconfirmed diagnosis of IBD. In total, we collected data from 138 cases and 206 unmatched controls.

Data Collection

The starting point of data collection and follow-up evaluation was the date of symptom onset that could be attributed to IBD. This was defined by a persistent change of bowel habits and/or bloody diarrhea and/or continuous abdominal pain followed by a diagnosis of IBD. If no clear onset of symptoms was recorded, the date of IBD diagnosis was used. The end of follow-up evaluation for cases was the date of CRC diagnosis. The end of follow-up evaluation for controls could be any of the following: (1) end of study date, which was October 15, 2011, for the Leuven data, and July 1, 2006, for the Dutch data; (2) date of death by any cause; (3) loss to follow-up evaluation defined by the date of the last known visit to the outpatient clinic; or (4) the date of total colectomy. The following variables were collected for both cohorts: sex; IBD type, defined as ulcerative colitis or Crohn's colitis (indeterminate colitis cases were analyzed with the ulcerative colitis group); smoking, defined as positive for active smoking at the end of the follow-up evaluation or a smoking history; family history of CRC, defined as any first-degree relative having a diagnosis of CRC; limited disease, defined as microscopic disease extent of less than 50%, and extensive disease, defined as microscopic disease extent equal to 50% or greater of the colonic surface; concurrent PSC; post-inflammatory polyps; dysplasia-associated lesion or mass (DALM); adenoma-like lesion; flat low-grade dysplasia; flat high-grade dysplasia; colonic stenosis; any mesalamine use; any thiopurine use; any anti–tumor necrosis factor (TNF)-α use; any methotrexate use; colonoscopic surveillance, defined as a dichotomous variable (as yes when random biopsy specimens were taken every 10 cm or chromoendoscopy was performed;