Small bowel cancer risk in Lynch syndrome

K Schulmann, C Engel, P Propping and W Schmiegel

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LETTERS

Authors' reply

It is now evident that both forms of inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis, are highly heterogeneous, not only at the clinical and pathogenetic level, but also in regard to time of appearance. In fact, early- and late-onset IBD are increasingly recognised as distinct entities that can be differentiated in regard to the underlying mechanism of inflammation and response to therapy, both in human patients and in experimental animal models.[1–3] While this differentiation is real, early and late IBD ostensibly result from the combined action of the same factors—that is, genetic predisposition, environmental changes and a disregulated immune response. On this background scenario, Damen and collaborators (*Gut* 2008;**57**:1480) ask the very pertinent question of what determines the development of specific effector T cells involved in early gut tissue damage: the expression of specific cell surface receptors or the production of specific cytokines by antigen-presenting cells? Based on the study of monocyte-derived dendritic cells from children with CD and UC, they found a clear dose response between the amount of the microbial ligands used to stimulate dendritic cells and the production if interleukin 12 (IL12) and IL23, and also found that the levels of these two cytokines varied independently of each other. They concluded that production of Th1- and Th17-inducing cytokines is independent of the type or stage of IBD, and the type of effector T cells depends on the amounts of particular microbial products and the presence of cell surface receptors for IL12 or IL23. While this conclusion is reasonable and plausible, it is also likely to be only part of the answer, considering the still numerous "unknowns" that afflict the investigation of IBD pathogenesis.

Children with CD or UC display unique phenotypic and genetic characteristics related to early-onset disease.[4] IBD at a young age is associated with a stronger family history of IBD, CD-affected children are more likely than adults to have colonic involvement, and UC-affected children are more likely than adults to have extensive colitis. With regard to genetic predisposition, genome-wide association (GWA) scans performed to date have been almost exclusively performed in adult CD patients, and the genetic variants reported so far do not account for the entire IBD genetic risk. Thus, it seems probable that future GWA scans may identify novel genes linked to early-onset IBD, as has been the case for other early-onset conditions such as Alzheimer disease, type 2 diabetes and breast cancer. Therefore, it is entirely possible that the cytokine patterns produced when dendritic cells encounter gut bacteria may differ in quantity or quality depending on what segment of the bowel the flora is sampled from and the genetically predetermined immune response of the host. It is also possible that the future IBD patient's genetic make-up may affect not only the antigen recognition process, but also the overall T cell function and the subsequent adaptive immune response.[5]

In regard to the environment, we are still at a loss in trying to figure out how to identify and analyse the myriad of factors besieging the newborn that will sooner or later develop IBD. Even though the diet and its components, starting with milk products, have been proposed as possibly culprits of IBD pathogenesis for decades, presently they receive essentially no attention from mucosal immunologists, which seem to be interested only in learning how the mucosal immune system deals with the intestinal microbiota. After all, the all-powerful dendritic cells that determine the fate of the gut immune response by shaping cytokine patterns and T cell repertoires see both dietary and bacterial antigens, and not exclusively the latter. Thus, the intense attention given to bacterial immunity in IBD may be a consequence of fashion and convenience in addition to reason, but perhaps it is time to think immunologically also of "food" and not exclusively "bugs". After all, the type of bacteria present in the intestine depends in a major way on the type of ingested food, and different diets go along with distinct types of microbial colonisation and variable frequency of IBD in separate parts of the world.

In a sea of questions and uncertainties, one thing is undeniable: early-onset paediatric IBD has come of age and it is finally receiving the attention that was long overdue.[6] Even though the efforts to understand its unique pathogenesis still seem too few or too simplistic at the moment, asking specific question in a specific paediatric setting is the way to go, as Damen *et al* have shown us.

S Kugathasan,[1] L J Saubermann,[2] L Smith,[3] D Kou,[4] J Itoh,[4] D G Binion,[5] A D Levine,[4] R S Blumberg,[2] C Fiocchi[4]

[1] Division of Pediatric Gastroenterology and Nutrition, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin, USA; [2] Gastroenterology Division, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [3] Apollon, Wyeth-Lederle Vaccines & Pediatrics, One Great Valley Parkway, Malvern, Philadelphia, USA; [4] Division of Gastroenterology, University Hospitals of Cleveland, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA; [5] Division of Gastroenterology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

Correspondence to: Dr C Fiocchi, The Cleveland Clinic Foundation, Lerner Research Institute, Department of Pathobiology/NC22, 9500 Euclid Avenue, Cleveland, OH 44195, USA; fiocchc@ccf.org

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Small bowel cancer risk in Lynch syndrome

We read with great interest the article by ten Kate *et al* (*Gut* 2007;**56**:1198–201) from the Dutch HNPCC group regarding the risk of small bowel cancer (SBC) in patients with hereditary non-polyposis colorectal cancer (HNPCC). The study confirms our data from 2005[1] regarding the localisation of tumours and the absence of identifiable risk factors for SBC in patients with HNPCC (ie, gender, mutation, family history, personal cancer history). The authors additionally calculated a lifetime risk of 4.2% for SBC using Kaplan–Meier statistics. Ten Kate *et al* recommend a non-invasive surveillance strategy. However, the authors argue that the lifetime risk for gastric cancer (GC) may influence a surveillance strategy for SBC regarding upper intestinal endoscopy.

In our previous studies[1 2] cumulative cancer risks were not provided. We therefore updated our data (census date, 15 August 2007) and calculated the age-dependent cumulative risks of SBC and GC for mutation carriers. We restricted the analysis to pathogenic germline mutation carriers (total n = 1295; proven 1138; obligatory 157; HNPCC cancer-affected n = 910; healthy n = 350, non-HNPCC cancer-affected n = 35). Among 1295 mutation carriers we observed a total of 36 patients with SBC (2.8%) and 29 patients with GC (2.2%).

Regarding SBC, the median age at diagnosis was 44 years (range 30–73 years). Six (17%) of 36 SBCs occurred before the age of 35 years. The distribution of tumours in the small bowel was as follows: duodenum 45%, jejunum 29%, ileum 12%, not specified 14%. Underlying germline mutations were MLH1 17, MSH2 18, MSH6 1, PMS2 0. The cumulative risk for SBC was significantly higher in men than in women (hazard ratio (HR) 2.673; 95% confidence interval (CI) 1.274 to 5.609; p = 0.009), but was not significantly associated with the affected mismatch repair (MMR) gene. In 13 patients SBC was the first HNPCC-associated tumour. Three out of 36 patients had synchronous or metachronous SBCs. In the families of three patients at least one member also had a SBC. The cumulative risks at age 70 years for SBC and GC were 7.8% (95% CI 3.9 to 11.6%) (fig 1) and 6.8%

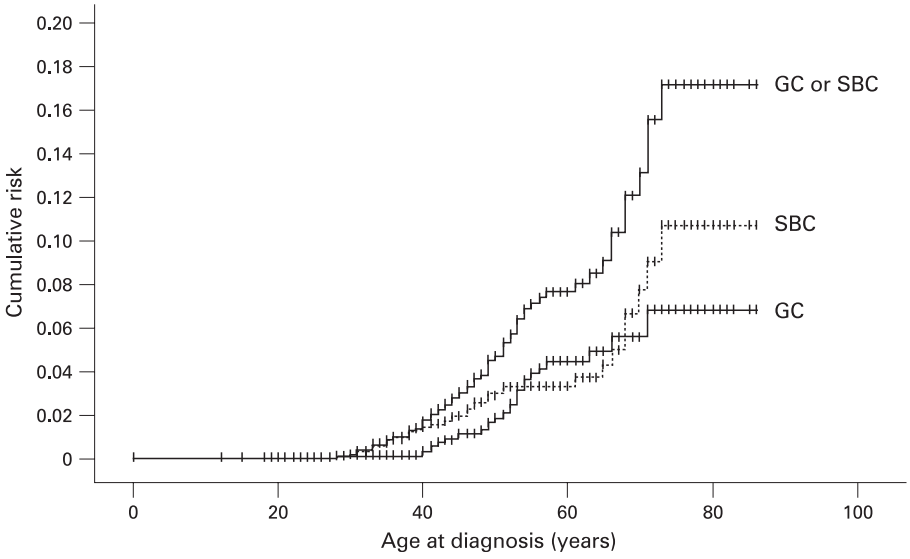

Figure 1 Cumulative lifetime risks for small bowel cancer (SBC) and gastric cancer (GC).

(95% CI 3.4 to 10.2%), respectively. The combined risk for GC and SBC was 13.2% (95% CI 8.8 to 17.5%).

We currently recommend annual oesphagogastroduodenoscopy (EGD) starting at age 35 years irrespective of family history of GC for the surveillance of GC. This is supported by our findings as all but one GC in mutation carriers occurred at an age of 40 years or above. With respect to SBC the lifetime risk seems even higher. A screening strategy which allows surveillance of GC and SBC at once thus seems warranted. SBC occurred at an age of 30 years or above. Since 45% of SBCs occurred in the duodenum and nearly one-third in the jejunum, push enteroscopy starting at age 30 years might be a reasonable approach.

We agree that the feasibility, value and optimal interval of different small bowel surveillance strategies (EGD only, push enteroscopy, capsule enteroscopy, magnetic resonance (MR) enteroclysis, double ballon enteroscopy) needs to be determined prospectively. This should be performed in an international cooperative study to enable enrolment of a sufficient number of patients within a reasonable study period. In addition, a non-invasive molecular stool test should be evaluated in this high-risk group. We have previously shown that the spectrum of frameshift mutations of mononucleotide repeats in the coding region of HNPCC-associated SBC is similar to MSI-H or HNPCC-related colorectal cancer (CRC)[1] and these might be attractive targets for a molecular stool test in HNPCC patients.

K Schulmann,[1] C Engel,[2] P Propping,[3] W Schmiegel[1]

[1] Ruhr-University Bochum, Knappschaftskrankenhaus, Bochum, Germany; [2] University of Leipzig, Institute for Medical Informatics, Statistics and Epidemiology, Leipzig, Germany; [3] University of Bonn, Institute of Human Genetics, Bonn, Germany

Correspondence to: Dr K Schulmann, Ruhr-University Bochum, Medical Department, Knappschaftskrankenhaus, Reference Centre Gastroenterology of the German HNPCC Consortium, Bochum, Germany; karsten.schulmann@rub.de

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The non-invasive diagnosis of cirrhosis using the Fibroscan must be performed with cause-specific stiffness cut-offs

We read the article by Fraquelli *et al* (*Gut* 2007;**56**:968–73) with great interest. In addition to the Fibroscan's excellent reproducibility, the authors reported stiffness cut-offs for the non-invasive diagnosis of liver fibrosis with, notably, a value of 11.9 kPa for cirrhosis. This choice is arguable because the study population was heterogeneous, with cases of chronic viral hepatitis C (78%) and B (8%), alcohol-related liver disease (ALD) (2%) and non-alcoholic steatohepatitis (NASH) (7%). Previous studies have reported cut-off values of 12.5 kPa for the diagnosis of viral hepatitis C cirrhosis.[1] However, data from other series in the field of ALD feature significantly higher cut-offs for the diagnosis of alcoholic cirrhosis, at between 19 kPa [2] and 21.5 kPa.[3] In this latter study, the cut-offs differed according to whether the condition had a viral or alcoholic aetiology.[3] Furthermore, a value of 17.5 kPa[4] has been recommended for the diagnosis of cirrhosis in NASH, with 17.3 kPa for cirrhosis secondary to primary sclerosing cholangitis or primary biliary cirrhosis.[5] The nature of the cause of cirrhosis is thus primordial in the choice of a stiffness cut-off for the diagnosis of this condition using the Fibroscan, since the distribution of hepatic fibrosis differs for viral liver disease, ALD, NASH and biliary tract conditions. The cut-off for cirrhosis reported by Fraquelli *et al* is thus non-specific and could conceivably lead to overdiagnosis of cirrhosis if applied to non-viral liver diseases. We believe that readers should be made aware of this aspect.

E Nguyen-Khac,[1] D Capron,[1] A Braillon,[2] J L Dupas[1]

[1] Service d'Hépato-Gastroentérologie, Amiens University Hospital, Amiens, France; [2] Service de Santé Publique, Amiens University Hospital, Amiens, France

Correspondence to: Dr E Nguyen-Khac, Service d'Hépato-Gastroentérologie, Amiens University Hospital, Place Victor Pauchet, F-80054 Amiens, France; nguyen-khac.eric@chu-amiens.fr

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Authors' response

We fully agree with the comments by Dr Nguyen-Khac who cautions against the extension of the cut-off value of 11.9 kPa for transient elastography (TE) which identifies cirrhosis in hepatitis C-infected patients compared with other patients with hepatitis B, alcohol-related liver disease, non-alcoholic steatohepatitis (NASH) or cholestasis. We wish to remind you, however, that our study primarily dealt with the assessment of TE reproducibility,[1] even though we acknowledge that the cut-off for cirrhosis was obtained in a patient population that was skewed toward hepatitis