Small bowel cancer risk in Lynch syndrome

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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.1,2 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 deregulated 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 clarify in what way to identify and analyse the myriad of factors besetting 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 not only 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, it seems possible that specific question in a specific paediatric setting is the difference? Dig Liver Dis 2008; 40:12–15.

Small bowel cancer risk in Lynch syndrome

We read with great interest the article by ten Kate et al (Gut 2007; 56:1195–201) from the Dutch HNPPC group regarding the risk of small bowel cancer (SBC) in patients with hereditary non-polyposis colorectal cancer (HNPPC). The study confirms our data from 20057 regarding the localisation of tumours and the absence of identifiable risk factors for SBC in patients with HNPPC (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,8 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 mutations of SBC and GC for mutation carriers. We included the authors argue that the lifetime risk for gastric cancer (GC) may influence a surveillance strategy for SBC regarding upper intestinal endoscopy.

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might be attractive targets for a molecular approach.

We currently recommend annual oesophago-gastro-duodenoscopy (EGD) starting at age 55 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 formation in an international cooperative strategy which allows surveillance of GC and SBC at once thus seems warranted. SBC occurred at an age of 50 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 balloon 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 framsih mutations of mononucleotide repeats in the coding region of HNPCC-associated SBC is similar to MSI-H or HNPCC-related colorectal cancer (CRC) and these might be attractive targets for a molecular stool test in HNPCC patients.

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**Competing interests:** None.

The cumulative lifetime risks for small bowel cancer (SBC) and gastric cancer (GC) are shown in Figure 1.

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3. **The German HNPCC Consortium is located at the Ruhr-University Bochum. The Central Database and Biometry of the German HNPCC Consortium is located at the University of Leipzig. PP is the spokesman of the German HNPCC Consortium, and WS is the co-spokesman of the German HNPCC Consortium.

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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, even though we acknowledge that the cut-off for cirrhosis was obtained in a patient population that was skewed toward hepatitis C cirrhosis. 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 and 21.5 kPa. In this latter study, the cut-offs differed according to whether the condition had a viral or alcoholic aetiology. Furthermore, a value of 17.5 kPa 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. 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.

**REFERENCES**


