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Lindgren, Stefan

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PO Box 117  
221 00 Lund  
+46 46-222 00 00

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## **The variable risk of colorectal cancer in patients with inflammatory bowel disease**

Patients with long-standing extensive ulcerative colitis and Crohn's colitis are at increased risk of developing colorectal cancer. There is, however, considerable variability in the cancer risk within this patient population. Although it is possible that some of the variability is genetic, the major risk factors are likely to be acquired. Further definition of high and low risk subgroups of patients is highly desirable since it would allow a more appropriate allocation of resources, particularly with regard to endoscopic surveillance. Most of our knowledge concerning risk factors for colorectal cancer is based on information from patients with ulcerative colitis. However, the majority of studies examining the incidence of colorectal cancer in Crohn's colitis, have also demonstrated an increased risk, of similar or slightly lower magnitude to that seen in ulcerative colitis.

A large population-based study reported a standardized incidence ratio of colorectal cancer of 5.7 for all patients with ulcerative colitis (1). Carcinoma also tends to occur at an earlier age in these patients, typically 15-20 years sooner than in the general population. The risk of developing colorectal cancer within 8-10 years of diagnosis is low, but thereafter increases by approximately 0.5 to 1 per cent per year for patients with extensive colitis (2, 3). Reported 20 year incidences in extensive colitis range from 5-14 per cent, rising to 15-25 per cent at 30 years (4, 5). The risk for patients with left sided colitis or proctitis is much lower. Thus, the anatomical macroscopical extension of colonic inflammation is a major risk factor for cancer development (1). Early age at onset of ulcerative colitis further increases the risk for later cancer development (6). Having a first degree relative with colorectal carcinoma increases the incidence twofold in patients with ulcerative colitis, and even more if the relative's cancer occurred before the age of 50 years (7). Primary sclerosing cholangitis appears to be an

additional independent risk factor (8). In contrast there are no data to support any link between ulcerative colitis, smoking and colitis-related cancer.

It is biologically plausible that the excess cancer risk mainly is secondary to chronic inflammation. However, this has been difficult to document and only recently a case-control study of patients with long-standing extensive ulcerative colitis unequivocally demonstrated the severity of colonic inflammation as an important determinant of the risk of colorectal neoplasia (9). These severe consequences of chronic colonic inflammation highlight the possible importance of treatment strategies for the risk of developing cancer. It is striking that studies from Denmark on both ulcerative colitis and Crohn's colitis revealed a cancer risk comparable to the normal population even after 25 years of extensive colitis (10, 11). This might very well be explained by the high rate of colectomy in treatment-failure and possibly also by the frequent use of 5-aminosalicylic acid (5-ASA) drugs as long-term maintenance treatment in this cohort. The latter explanation is particularly attractive since altered prostaglandin metabolism might promote carcinogenesis in long-standing inflammation (12). Several other authors have observed that patients on long-term maintenance treatment with mesalazine, and possibly also other anti-inflammatory drugs, tend to show reduced rates of colorectal cancer. However, since folate deficiency has been associated with dysplasia, the anti-inflammatory effect of sulfasalazine, which is a competitive inhibitor of folate absorption, appears to be out-weighted by the effect of folate deficiency (9, 13). Thus, it might be preferable for patients on long-term 5-ASA maintenance treatment to use non-sulfasalazine compounds. Overall, these data underline the importance of minimizing colonic inflammation as a primary treatment goal.

In this issue of the *Journal*, Katsanos and co-workers report a normal risk of developing cancer in a cohort of 215 patients with inflammatory bowel disease (IBD) compared to the general Greek population (14). The authors suggest that this might reflect that IBD phenotypes seem to be milder in South Europe compared to Northern Europe and North America. The mild profile refers both to the clinical presentation of IBD and to the relatively low incidence of extra-intestinal manifestations and might imply both genetic and environmental mechanisms. However, there are several important characteristics of the study population that must be considered before this conclusion is drawn. Most importantly, the mean follow-up of the Greek patients was only 7.5 years from the time of diagnosis, and it is well known that the risk of developing colorectal cancer is low during the first ten years and rises significantly only after 15-20 years duration. Secondly, the mean age of the patients was fairly high, 51 years, which also could reduce the risk of IBD related cancer development in this cohort. In addition, the number of patients with extensive colitis was small. Finally, although the overall prevalence of colectomy was low, all patients with ulcerative colitis were on uninterrupted maintenance treatment with mesalazine since diagnosis. It is therefore too early to conclude that the risk of colorectal cancer is lower in Greece than in other areas of the world. However, it will be of great interest to follow this cohort of patients for another 10-15 years to document whether the clinical impressions of mild IBD phenotypes and low incidence of extra-intestinal manifestations are truly reflected by a low incidence of dysplasia and colorectal cancer.

Current colonoscopic surveillance programmes that focus on patients with long-standing extensive disease only, are both labour intensive and expensive and furthermore associated with discomfort and reduced quality of life for IBD patients.. Further risk stratification according to severity of ongoing active inflammation and possibly also successful long-term

maintenance treatment would therefore be welcome. The paper from Katsanos and co-workers suggests that also geographical differences in risk might exist. Only time and further careful follow-up of IBD-patients will tell.

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Stefan Lindgren

Professor, M.D., Ph.D.

Gastroenterology and Hepatology Division

Department of Medicine

University Hospital MAS,

SE-205 02 Malmö, Sweden

e-mail address: [Stefan.Lindgren@medforsk.mas.lu.se](mailto:Stefan.Lindgren@medforsk.mas.lu.se)

Tel: +46 40 33 23 06

Fax: +46 40 92 32 72