World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v18.i31.4091

World J Gastroenterol 2012 August 21; 18(31): 4091-4094
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

FIELD OF VISION

Colorectal cancer in patients with inflammatory bowel disease: Can we predict risk?

Vibeke Andersen, Jonas Halfvarson, Ulla Vogel

Vibeke Andersen, Medical Department, Sygehus Sønderjylland Aabenraa, DK-6200 Aabenraa, Denmark
Vibeke Andersen, Institute of Regional Health Services Research, University of Southern Denmark, DK-5000 Odense, Denmark
Jonas Halfvarson, Department of Internal Medicine, Örebro University Hospital, Örebro University, Örebro 70185, Sweden
Ulla Vogel, National Research Centre for the Working Environment, DK-2100 Copenhagen, Denmark
Author contributions: Andersen V collected the material and wrote the manuscript; Halfvarsson J discussed the topic; and Vogel U supervised the manuscript.
Correspondence to: Vibeke Andersen, Consultant, Specialist, Medical Department, Sygehus Sønderjylland Aabenraa, Kresten Philipsens Vej 15, DK-6200 Aabenraa, Denmark. vandersen@health.sdu.dk
Telephone: +45-2-1157790 Fax: +45-8-8834488
Received: June 27, 2012 Revised: July 10, 2012
Accepted: July 18, 2012
Published online: August 21, 2012

Abstract

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), may be complicated by colorectal cancer (CRC). In a recent population-based cohort study of 47 347 Danish patients with IBD by Tine Jess and colleagues 268 patients with UC and 70 patients with CD developed CRC during 30 years of observation. The overall risk of CRC among patients with UC and CD was comparable with that of the general population. However, patients diagnosed with UC during childhood or as adolescents, patients with long duration of disease and those with concomitant primary sclerosing cholangitis were at increased risk. In this commentary, we discuss the mechanisms underlying carcinogenesis in IBD and current investigations of genetic susceptibility in IBD patients. Further advances will depend on the cooperative work by epidemiologist and molecular geneticists in order to identify genetic polymorphisms involved in IBD-associated CRC. The ultimate goal is to incorporate genotypes and clinical parameters into a predictive model that will refine the prediction of risk for CRC in colonic IBD. The challenge will be to translate these new findings into clinical practice and to determine appropriate preventive strategies in order to avoid CRC in IBD patients. The achieved knowledge may also be relevant for other inflammation-associated cancers.

Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Colorectal cancer; Inflammation-associated cancer; Genetics; Preventive strategies

Peer reviewers: Andrzej S Tarnawski, Professor, Gastroenterology Section, VA Medical Center, University of California, Irvine, CA 90822, United States; Ferruccio Bonino, Professor, Liver and Digestive Division, Department of Internal Medicine, University of Pisa, Lungarno Bruno Buozzi 13, 56125 Pisa, Italy

Andersen V, Halfvarson J, Vogel U. Colorectal cancer in patients with inflammatory bowel disease: Can we predict risk? *World J Gastroenterol* 2012; 18(31): 4091-4094 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i31/4091.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i31.4091

INVITED COMMENTARY ON HOT ARTICLES

Incidence of colorectal cancer in inflammatory bowel diseases

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), may be complicated by colorectal cancer (CRC). In a new population-based cohort study encompassing 47 347 Danish patients with IBD, 268 patients with UC and 70 patients with CD developed CRC during 30 years of observation[1]. The authors concluded that the overall risk of CRC among patients with UC was comparable with that of the general

population [relative risk (RR), 1.07; 95% confidence interval (CI): 0.95-1.21]. The observed risk estimate persisted even after exclusion of patients with hemorrhagic proctitis (RR, 1.04; 95% CI: 0.91-1.18). When adjusted for age at diagnosis and duration of UC, a decreased risk of CRC among UC patients diagnosed in 1999-2008 was observed compared to UC patients diagnosed in 1989-1998 (RR, 0.59; 95% CI: 0.39-0.90). However, patients diagnosed with UC during childhood or adolescents (age 0-19 years; RR, 43.8; 95% CI: 27.2-70.7, age 20-39 years; RR, 2.65; 95% CI: 1.97-3.56) may be at increased risk as well as those with long duration of disease. Thirteen years after diagnosis, the CRC risk was significantly increased over background, and with longer follow-up the risk remained 50% above the risk in non-IBD individuals. The risk of CRC in patients with CD was similar to that of the non-IBD population. RR for CRC was 0.85 (95% CI: 0.67-1.07) among patients with CD and 0.80 (95% CI: 0.43-1.49) among patients with colonic CD.

Risk of CRC in IBD has been assessed previously in a Swedish population-based study[2]. In agreement with the present study there was a trend towards lowered risk with shorter observation period[2]. During 198 227 person-years follow-up for 7607 IBD cases, 188 cases of CRC were observed from 1954 to 2004[2]. After adjusting for sex, age, duration of disease, type and extent of IBD, the authors found a decline in relative risk from a 5-fold increased risk in the 1960s to a doubled risk of CRC in the time-period 2000-2004 (*P* for trend 0.006). The overall risk of CRC among the patients with IBD, UC and CD colitis was found to be increased compared with the general population (standardized incidence ratio 2.3; 95% CI: 2.0-2.6, 2.7; 95% CI: 2.3-3.2, and 2.1; 95% CI: 1.2-3.4, respectively). The CRC risk among patients with colonic CD has also been estimated in hospital-based or community-based case-control studies[3-5] and the overall relative risk estimate over the past 30 years was found to be 4.5 (range: 1.3-14.9) in a meta-analysis, with declining risk estimate over the past 30 years[3]. On the other hand, a recent study by Herrington *et al*[6] which was also published in Gastroenterology assessed time changes in risk of CRC within the Kaiser Permanente Medical Care Program, a community-based health care delivery system, from 1998 to 2010. The authors identified 29 and 53 CRC cases among CD and UC patients, respectively, corresponding to an incidence of CRC in patients with IBD which was 60% higher than in the general population. Furthermore, the incidence was found to be essentially constant over time. The study design may have some drawbacks such as missing detailed data on the study participants, selection bias, and too short observation period to detect the impact of optimizing IBD management on CRC risks which were discussed in the Editorials[7].

There is general agreement that patients with UC diagnosed at a young age, with primary sclerosing cholangitis, and with long disease duration are at increased risk of CRC[8-10]. Most cancers arise in extensive colitis and pancolitis and there is little or no increased risk associated with proctitis while left sided colitis is associated with an intermediate cancer risk[11,12]. The Danish study found no risk associated with having UC even after excluding cases with proctitis compared to the general population[1].

According to the British Society of Gastroenterology (BSG) "It is now widely accepted that patients with ulcerative colitis have a similar risk to those with Crohn's colitis for a similar extent and duration of colonic involvement"[13]. The Danish population-based study covered 30 years follow-up of all UC and CD patients and is by far the largest study to date on IBD and CRC risk[1]. This study found no risk of CRC among patients with colonic CD compared to the general population which the authors speculated could be due to the medical treatment and follow-up leading to control of the intestinal inflammation[1].

Surveillance colonoscopy is considered to be the gold standard in diagnosing early dysplastic alterations. The recent years new and emerging endoscopic imaging techniques have improved neoplasia detection rate[14]. The existing recommendation is, however, based on evidence level IV: Evidence obtained from expert committee reports, opinions or clinical experiences of respected authorities[13]. The study by Jess and colleges constitutes a basis for future evidence-based guidelines.

Understanding the mechanism(s) of CRC in IBD

The relationship between inflammation and cancer has been well established in the gastro-intestinal system. Colitis-associated cancer has been investigated in mouse models[15-17]. These studies have highlighted the role of toll-like receptors (TLR) and tumour necrosis factor-α (TNF-α) in the activation of nuclear factor κB (NFκB), which induces transcription of genes involved in tumorigenesis, including COX-2[15-17]. Defect signalling via p53 may be an early event in the progression of colitis-induced dysplasia to cancer[18]. Without p53-induced apoptosis, aberrant cells are not eliminated and cancer may ensue[18]. Probiotic bacteria may prevent carcinogenesis in mouse models of cancer by producing conjugated linoleic acid which activates PPARγ, inhibits COX-2 and induces apoptosis[19,20].

Current strategies to identify genetic predictors of CRC in IBD

It is increasingly recognized that CRC consists of many entities having similar phenotypic appearance. This heterogeneity may at least in part be due to differences in genetic susceptibility which may act in combination with various environmental factors such as diet and intestinal microbes. Patients with IBD and CRC constitute 1%-2% of all cases of CRC[21]. As a group, patients with IBD-associated CRC are characterized by intestinal inflammation and may thus represent a model with a relatively homogeneous mechanism for developing CRC. Indeed, distinct characteristics have been found for IBD-associated CRC. For example, a Norwegian study found that cancer was more often widespread than localized at diag-

nosis, age at diagnosis of CRC was lower, and prognosis poorer in IBD-associated CRC compared to CRC in the background population[22]. Thus, "IBD-associated cancer serves as an excellent model of inflammation-associated cancer and might provide many important clues to understanding the pathogenesis of sporadic colorectal cancer"[23]. On the other hand, a Swedish population-based study of more than 30 000 IBD cases identified 560 CRCs cases among first-degree relatives, giving no increased risk of CRC among first-degree relatives[24]. The authors concluded that the study did not suggest a common cause of IBD and CRC in general and the risk of CRC in IBD seemed to be the result of the disease rather than genetic predisposition[23].

The International IBD Genetics Consortium is a network of researchers working on the genetics of IBD[25]. This group has initiated a case-control study to determine if genetic polymorphisms associated with IBD and other immune disorders related to IBD are more prevalent in patients with colonic IBD and CRC/dysplasia than in patients with colonic IBD alone. For each case with IBD-associated CRC/dysplasia, two IBD non-cancer cases from the same centre will be included. Analyses are carried out using the Immunochip, an Illumina Infinium genotyping chip containing 196 524 polymorphisms (718 small insertion deletions, 195 806 SNPs). The Immunochip was initiated by the Wellcome Trust Case-Control Consortium and designed to perform deep replication of major autoimmune and inflammatory pathways[26]. Phenotypic information includes age at IBD and CRC/dysplasia diagnosis, gender, disease location, family history of CRC/dysplasia, medication, history of hospitalizations, and smoking habits.

Another approach may be based on utilizing existing pathological samples. For example, in Denmark, individual-based registration-systems have been developed along with the introduction of information technology and since 1978 nation-wide reporting of clinical diagnosis has been implemented[27]. Due to the introduction of DNA changes (e.g., mutations and polyploidy) during carcinogenesis, pathological samples with signs of CRC should be avoided. Samples with signs of IBD which precede CRC development, may be used for DNA extraction and assessment of genetic polymorphisms[28-31]. Furthermore, data may be linked to other registers such as Danish National Patient Register and The Danish Prescription Database for further investigations[32]. The validity of the diagnoses of IBD and CRC, respectively, in the Danish National Patient Register are more than 90%[33,34]. Thereby, candidate gene analyses of genetic polymorphisms in inflammatory pathways and associations found by genome-wide association studies may be performed and sought replicated.

Future research directions to predict the risk for CRC in IBD

A major challenge is now to identify the patients who would benefit from preventive strategies. Large and well-designed cohorts, such as population-based cohorts, with prospectively recorded data are required for the assessment of patients at risk. Provided that genetic susceptibility contributes to the risk of CRC in IBD, investigating genetic susceptibility in IBD patients may be particularly rewarding due to the expected relatively homogeneous biological mechanism(s) of action in this group. This may imply that associations may be identified in relatively small groups of well-characterized patients. The further advance will depend on the cooperative work of e.g., epidemiologists and molecular geneticists. The ultimate goal is to incorporate genotypes and clinical parameters into a predictive model that will refine the risk for CRC in colonic IBD. The challenge will be to translate these new findings into clinical practice and to determine appropriate preventive strategies in order to avoid CRC in IBD patients.

REFERENCES

1 **Jess T**, Simonsen J, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. *Gastroenterology* 2012; **143**: 375-381.e1

2 **Söderlund S**, Brandt L, Lapidus A, Karlén P, Broström O, Löfberg R, Ekbom A, Askling J. Decreasing time-trends of colorectal cancer in a large cohort of patients with inflammatory bowel disease. *Gastroenterology* 2009; **136**: 1561-1567; quiz 1818-1819

3 **Canavan C**, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther* 2006; **23**: 1097-1104

4 **Ekbom A**, Helmick C, Zack M, Adami HO. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. *Lancet* 1990; **336**: 357-359

5 **Jess T**, Gamborg M, Matzen P, Munkholm P, Sørensen TI. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. *Am J Gastroenterol* 2005; **100**: 2724-2729

6 **Herrinton LJ**, Liu L, Levin TR, Allison JE, Lewis JD, Velayos F. Incidence and mortality of colorectal adenocarcinoma in persons with inflammatory bowel disease from 1998 to 2010. *Gastroenterology* 2012; **143**: 382-389

7 **Nguyen GC**, Bressler B. A tale of two cohorts: are we overestimating the risk of colorectal cancer in inflammatory bowel disease? *Gastroenterology* 2012; **143**: 288-290

8 **Baars JE**, Looman CW, Steyerberg EW, Beukers R, Tan AC, Weusten BL, Kuipers EJ, van der Woude CJ. The risk of inflammatory bowel disease-related colorectal carcinoma is limited: results from a nationwide nested case-control study. *Am J Gastroenterol* 2011; **106**: 319-328

9 **Rutter MD**, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology* 2006; **130**: 1030-1038

10 **Eaden JA**, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001; **48**: 526-535

11 **Ekbom A**, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med* 1990; **323**: 1228-1233

12 **Jess T**, Loftus EV, Velayos FS, Harmsen WS, Zinsmeister AR, Smyrk TC, Schleck CD, Tremaine WJ, Melton LJ, Munkholm P, Sandborn WJ. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from olmsted

county, Minnesota. *Gastroenterology* 2006; **130**: 1039-1046
13 **Cairns SR**, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, Eaden JA, Rutter MD, Atkin WP, Saunders BP, Lucassen A, Jenkins P, Fairclough PD, Woodhouse CR. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010; **59**: 666-689
14 **Neumann H**, Vieth M, Langner C, Neurath MF, Mudter J. Cancer risk in IBD: how to diagnose and how to manage DALM and ALM. *World J Gastroenterol* 2011; **17**: 3184-3191
15 **Westbrook AM**, Szakmary A, Schiestl RH. Mechanisms of intestinal inflammation and development of associated cancers: lessons learned from mouse models. *Mutat Res* 2010; **705**: 40-59
16 **Goel GA**, Kandiel A, Achkar JP, Lashner B. Molecular pathways underlying IBD-associated colorectal neoplasia: therapeutic implications. *Am J Gastroenterol* 2011; **106**: 719-730
17 **McConnell BB**, Yang VW. The Role of Inflammation in the Pathogenesis of Colorectal Cancer. *Curr Colorectal Cancer Rep* 2009; **5**: 69-74
18 **Dirisina R**, Katzman RB, Goretsky T, Managlia E, Mittal N, Williams DB, Qiu W, Yu J, Chandel NS, Zhang L, Barrett TA. p53 and PUMA independently regulate apoptosis of intestinal epithelial cells in patients and mice with colitis. *Gastroenterology* 2011; **141**: 1036-1045
19 **Bassaganya-Riera J**, Viladomiu M, Pedragosa M, De Simone C, Hontecillas R. Immunoregulatory mechanisms underlying prevention of colitis-associated colorectal cancer by probiotic bacteria. *PLoS One* 2012; **7**: e34676
20 **Bassaganya-Riera J**, Viladomiu M, Pedragosa M, De Simone C, Carbo A, Shaykhutdinov R, Jobin C, Arthur JC, Corl BA, Vogel H, Storr M, Hontecillas R. Probiotic bacteria produce conjugated linoleic acid locally in the gut that targets macrophage PPAR γ to suppress colitis. *PLoS One* 2012; **7**: e31238
21 **Munkholm P**. Review article: the incidence and prevalence of colorectal cancer in inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; **18** Suppl 2: 1-5
22 **Brackmann S**, Aamodt G, Andersen SN, Roald B, Langmark F, Clausen OP, Aadland E, Fausa O, Rydning A, Vatn MH. Widespread but not localized neoplasia in inflammatory bowel disease worsens the prognosis of colorectal cancer. *Inflamm Bowel Dis* 2010; **16**: 474-481
23 **Rhodes JM**, Campbell BJ. Inflammation and colorectal cancer: IBD-associated and sporadic cancer compared. *Trends Mol Med* 2002; **8**: 10-16
24 **Askling J**, Dickman PW, Karlén P, Broström O, Lapidus A, Löfberg R, Ekbom A. Colorectal cancer rates among first-degree relatives of patients with inflammatory bowel disease: a population-based cohort study. *Lancet* 2001; **357**: 262-266
25 International inflammatory bowel disease genetics consortium (IIBDGC). Hinxton (UK): Trust Sanger Institute; [updated 2012 Jul 3; cited 2012]. Available from: URL: http://www.ibdgenetics.org/
26 **Cortes A**, Brown MA. Promise and pitfalls of the Immunochip. *Arthritis Res Ther* 2011; **13**: 101
27 The danish pathology data bank (Patologidatabank). [updated Jul 3 2009; cited 2012]. Available from: URL: http://www.patobank.dk/
28 **Vangsted AJ**, Klausen TW, Ruminski W, Gimsing P, Andersen NF, Gang AO, Abildgaard N, Knudsen LM, Nielsen JL, Gregersen H, Vogel U. The polymorphism IL-1beta T-31C is associated with a longer overall survival in patients with multiple myeloma undergoing auto-SCT. *Bone Marrow Transplant* 2009; **43**: 539-545
29 **Vangsted AJ**, Klausen TW, Gimsing P, Andersen NF, Abildgaard N, Gregersen H, Vogel U. A polymorphism in NFKB1 is associated with improved effect of interferon-{alpha} maintenance treatment of patients with multiple myeloma after high-dose treatment with stem cell support. *Haematologica* 2009; **94**: 1274-1281
30 **Vangsted AJ**, Klausen TW, Abildgaard N, Andersen NF, Gimsing P, Gregersen H, Nexø BA, Vogel U. Single nucleotide polymorphisms in the promoter region of the IL1B gene influence outcome in multiple myeloma patients treated with high-dose chemotherapy independently of relapse treatment with thalidomide and bortezomib. *Ann Hematol* 2011; **90**: 1173-1181
31 **Pikor LA**, Enfield KS, Cameron H, Lam WL. DNA extraction from paraffin embedded material for genetic and epigenetic analyses. *J Vis Exp* 2011; (**49**): 2763
32 **Pedersen CB**, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006; **53**: 441-449
33 **Fonager K**, Sørensen HT, Rasmussen SN, Møller-Petersen J, Vyberg M. Assessment of the diagnoses of Crohn's disease and ulcerative colitis in a Danish hospital information system. *Scand J Gastroenterol* 1996; **31**: 154-159
34 **Helqvist L**, Erichsen R, Gammelager H, Johansen MB, Sørensen HT. Quality of ICD-10 colorectal cancer diagnosis codes in the Danish National Registry of Patients. *Eur J Cancer Care* (*Engl*) 2012; Epub ahead of print

S- Editor Gou SX **L- Editor** A **E- Editor** Zhang DN