Prospective Study

Colorectal cancers in ulcerative colitis from a low-prevalence area for colon cancer

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Abstract

AIM: To determine the incidence and risk factors for colorectal cancer (CRC) in patients with ulcerative colitis from a low prevalence region for CRC.

METHODS: Our prospective database yielded a cohort of 430 patients [age: 44 ± 14.6 years; 248 men (57.7%)] with ulcerative colitis (median disease duration 6, range: 1-39 years) for analysis. Of these, 131 (30.5%) had left-sided colitis and 159 (37%) extensive colitis. Patients with histologically confirmed CRC within the segment with colitis were compared with those without CRC, to determine the risk factors for the development of CRC.

RESULTS: Twelve patients (2.8%) developed CRC. The overall incidence density was 3.56/1000 patient-years of disease - 3/1000 in the first 10 years, 3.3/1000 at 10 to 20 years, and 7/1000 at > 20 years. Three of our 12 patients developed CRC within 8 years of disease onset.

CONCLUSION: CRC occurred in 2.8% of patients with ulcerative colitis in our population - an incidence density similar to that in Western countries in spite of a low overall prevalence of colon cancer in our population.
The risk increased with extent and duration of disease.

**Key words:** Colon cancer; Dysplasia; Epidemiology; Inflammatory bowel disease; Malignancy

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**Core tip:** From an area with low prevalence of colon cancer, the risk of colorectal cancer (CRC) in patients with ulcerative colitis was as high as in those with high risk of CRC. Some patients developed CRC before the recommended commencement of colonoscopic surveillance for CRC.

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**INTRODUCTION**

The risk of development of colorectal cancer (CRC) in patients with ulcerative colitis varies in literature. A meta-analysis by Eaden et al[1] in 2001 concluded that the cumulative probability of CRC was 2% by 10 years, 8% by 20 years, and 18% by 30 years. The meta-analysis by Lutgens et al[2] shortlisted eight studies from 1988 to 2009 and reported that the risk of CRC is increased in inflammatory bowel disease but is not as high as reported in earlier studies; the pooled standardized incidence rate (SIR) was 1.7 (95%CI: 1.2-2.2).

These studies come from regions where the prevalence of CRC itself is high. India has an incidence of CRC that is approximately a tenth of that in the Western world[3]. It would be interesting to see whether the intrinsically lower risk in the population would translate to a lower overall risk in patients with ulcerative colitis. Previous studies from India do indeed point to a lower risk[4,5,6], however, the duration of ulcerative colitis in the patient population evaluated has been low, with only a small percent exceeding 10 year follow up. The recent Asia-Pacific consensus statement on ulcerative colitis highlighted the paucity of data on CRC in the Asian population[6].

In an attempt to diagnose CRC early, various societies have proposed surveillance guidelines[6-8]. Survival benefit from colonoscopic surveillance programmes in ulcerative colitis has not been conclusively established, but there seem to be fewer deaths in patients undergoing surveillance[9-10]. Surveillance guidelines in an otherwise low-risk population should depend on the risk increase of CRC with ulcerative colitis.

We therefore analysed the incidence of CRC in our cohort of patients with ulcerative colitis, in order to identify risk factors and also to determine whether standard recommendations for time-to-surveillance are reasonable for low-risk populations.

**MATERIALS AND METHODS**

This is an analysis of a prospectively maintained database of a cohort of patients with ulcerative colitis presenting to the Division of Gastroenterology since 2005. The data include demography, history, examination findings, laboratory investigations, colonoscopy (patients with disease proximal to splenic flexure were considered to have extensive colitis) and histology findings, imaging findings, diagnosis, therapy (medical and surgical), duration of disease and therapy, compliance with therapy (taking more than 85% of the prescribed dose of medications was considered “compliant with treatment”), response to treatment, course, complications of disease, and extra-intestinal manifestations.

Currently, colonoscopic surveillance is advised routinely to our patients with more than 8 years’ history of ulcerative colitis, irrespective of extent of disease. Follow up was recorded during their hospital visits, failing which they were contacted by telephone, e-mail or post, for update on their disease status. Patients with less than one-year duration of ulcerative colitis and those with less than one year of follow up were excluded from analysis in this study. Disease control was considered good when bowel frequency was normal, and there was no blood in stool and no systemic symptoms; when they were symptomatic, Truelove and Witt’s criteria[10] were used to assess disease severity; mild and moderate activity was considered as average control and severe activity was considered as poor control.

Data of patients with confirmed diagnosis of CRC on endoscopic biopsy and/or operative specimens were analysed with regard to details of location of malignancy, whether it occurred in the segment with macroscopic colitis, stage of disease, presence of metastatic disease, and outcome. These patients were compared to those without malignancy to identify possible risk factors for development of malignancy.

**Statistical analysis**

Qualitative data are represented as frequency and percentage. Association between qualitative variables was assessed by \( \chi^2 \) test or Fisher’s exact test. \( P \) value less than 0.05 was taken as significant. All analyses were done using SPSS Version 13.0.1, IBM, New York. The study was approved by institutional review board.

**RESULTS**

Of the 461 patients with ulcerative colitis in our database, 31 were excluded from analysis (less
than one year of duration of disease). Of the 430 patients analysed [age: 44 ± 14.6 years; 248 males (57.7%), 38 (8.8%) had proctitis, 95 (22.1%) procto-sigmoiditis, 131 (30.5%) left-sided colitis, and 159 (37%) extensive colitis; disease extent was not recorded in 7 patients but all these had extent beyond the rectum. The duration of ulcerative colitis was 1 to 10 years in 301 (70%) patients, 11 to 20 years in 107 (24.9%), and 21 or more years in 22 (5.1%) patients. The median duration of disease was 6 (range: 1–39 years; interquartile range 7) years.

All except three patients received 5-aminosalicylic acid (5-ASA) formulations; 109 (25.3%) patients also received azathioprine. Two hundred forty-four patients were compliant with medications. Disease control was good in 156 (36.3%), poor in 55 (12.8%), and average in the remaining. Thirty-two (7.4%) patients underwent proctocolectomy for suboptimal disease control.

**Development of CRCs**

Twelve patients (2.79%) developed CRC and six developed non-colorectal malignancies (one each with acute myeloid leukaemia, carcinoma breast, cholangiocarcinoma, endometrial carcinoma, laryngeal cancer and non-Hodgkin lymphoma). The risk of CRC was higher in patients with pancolitis (9/159; 5.6%) than with the other extents of disease (3/130; 2.3%) (P = 0.0125). One CRC was detected during surveillance at 11 years whereas others were detected during work-up for symptoms. The overall incidence density of CRC was 3.6 per 1000 person-year disease (PYD): 2.3/1000 PYD in the first 10 years, 3.3/1000 PYD in the second decade, and 7/1000 PYD thereafter. Three of 12 patients developed CRC within 8 years of disease onset (one patient had lung metastases). Associated primary sclerosing cholangitis was present in four patients - one developed cholangiocarcinoma and one CRC. No patient reported the occurrence of CRC in a first-degree relative.

**Analysis of factors affecting the development of CRC**

Table 1 compares patients with and without CRC. For univariate analysis, age, gender, duration of disease, extent of colitis, history of smoking, family history of inflammatory bowel disease, medication compliance, and disease control were included. Pancolitis (P = 0.012), longer duration of disease (P = 0.00001), and poor control of disease (P = 0.007) were associated with development of CRC. On multivariate analysis, longer duration of disease (P = 0.01) and pancolitis (P = 0.027) were significant factors for development of malignancy.

**Details of CRCs**

Table 2 shows details of the patients with CRC. Malignancy developed at a median of 18 (range: 6–27 years; IQR 8) years after the onset of ulcerative colitis. Tumours were located in the rectum in six patients, recto-sigmoid junction in one, descending colon in one, ascending colon in two, and left colon in one patient. Two patients had multifocal tumours: one had 3 tumours (one each in the ascending, transverse and descending colon), and the other patient had 2 tumours (one each in the ascending colon and at the hepatic flexure).

In three patients, CRC developed with disease duration of less than 8 years. The first patient (aged 51 years) with pancolitis developed CRC after 6 years of disease and had 3 tumours. The second patient (aged 42 years), also with pancolitis, had adenoma in the rectum but refused surgery for 2 years. Two years later (7 years’ disease duration) he agreed to surgery when biopsy showed adenocarcinoma in the adenoma. The third patient (aged 40 years) with left-sided colitis was incidentally detected to have lung metastases when she underwent high-resolution CT scan of the chest (at disease duration of 6 years) as part of a
The prevalence of colorectal cancer (CRC) in ulcerative colitis (UC) varies widely across populations, with higher rates reported in Western countries compared to Asia. In a study from Vellore, India, the prevalence of CRC in UC was 2.79%. This is comparable to other studies from India and the United States, where the prevalence is around 1-3% in Indian patients with UC. However, the prevalence is much lower in Asian populations, such as South Asians in the United States, where the prevalence is reported to be 0.7% to 3.3%.

In a cohort study of 430 patients with UC from Vellore, India, the prevalence of CRC was 2.8%. This is higher than the general population prevalence in India, which is around 0.78/100000 in men and 0.91/100000 in women. The risk of CRC in UC is higher in UC patients with pancolitis and longer disease duration. In a study of UC patients from Vellore, India, the prevalence of CRC was 2.79%, higher than the general population prevalence.

In a recent study by Venkataraman et al., the prevalence of CRC in UC patients was 2.8%, similar to the prevalence in the general population in India. However, in a study by Venkataraman et al., the prevalence of CRC in UC patients was 2.79%, higher than the general population prevalence.

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patients with ulcerative colitis developed CRC before the recommended surveillance. A recent analysis from Surveillance, Epidemiology and End Result (SEER) data suggested an increased rate of missed CRC in older patients with inflammatory bowel disease. It is not clear if this can be applied to patients in other age groups with ulcerative colitis but it has relevance to surveillance strategy. Thus, although a strong body of literature suggests that few patients develop CRC with ulcerative colitis disease duration less than 10 years, it appears that approximately 10% to 20% of cancers may occur earlier during the course of the disease.

In summary, 12 (2.8%) patients with ulcerative colitis in our study developed CRC during a mean follow up of 7.8 years. The overall incidence density of cancer was 3.6 per 1000 person-year disease, with the incidence increasing with each decade. Extensive disease and duration of disease were significant risk factors for the development of CRC. Two patients had multifocal tumours; four of nine patients had nodal involvement, and one had metastases at presentation. A fourth of our patients developed cancer with disease duration less than 8 years. This study points to a significant increase in the incidence of colon cancer in ulcerative colitis over the population incidence and supports the recommendation for screening patients with ulcerative colitis even in a low-endemicity zone for colon cancer.

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COMMENTS
Background
This study presents the prevalence of colorectal cancer (CRC) ulcerative colitis from an area with low prevalence for colon cancer.

Research frontiers
The epidemiology of CRC in ulcerative colitis is changing with many studies suggesting lower CRC rates. This study suggests that CRC prevalence in ulcerative colitis patients from an area with low prevalence for CRC is equivalent to that in the areas with high prevalence for CRCs. The disease extent, severity and other factors do not explain this fully.

Applications
To study the differences in epidemiology in CRC in patients with ulcerative colitis in different parts of and to look at the innovative ways of colonoscopic surveillance in ulcerative colitis.

Peer-review
In this manuscript, the authors assessed the incidence and risk factors for CRC in patients with ulcerative colitis from a low prevalence region for CRC. They concluded that an incidence density of CRC in population with a low overall prevalence of colon cancer similar to that in Western countries, and the risk increased with extent and duration of disease. Their conclusions are reliable. Similar article however, the context lacks of novelty and can not provide new insights into CRC.

REFERENCES
1 Eaden JA, Abrams KR, Mayherry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001; 48: 526-535 [PMID: 11247898 DOI: 10.1136/gut.48.4.526]
2 Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. Inflamm Bowel Dis 2013; 19: 789-799 [DOI: 10.1097/MIB.0b013e31828029c0]
3 Mohandas KM. Colorectal cancer in India: controversies, enigmas and primary prevention. Indian J Gastroenterol 2011; 30: 3-6 [DOI: 21222189]
4 Kochhar R, Goenka MK, Kaushik SP, Gupta NM, Nagi B, Mehta SK. Colorectal carcinoma in Indian patients with idiopathic ulcerative colitis. Eur J Cancer Prev 1992; 1: 293-296 [PMID: 14677777 DOI: 10.1007/00008469-199206000-00003]
5 Venkataraman S, Mohan V, Ramakrishna BS, Peter S, Chacko A, Chandry G, Kuriyan G, Kuriyan S, Mathan M, Mathan VI, Patra S, Pulimood A, Rolston DD. Risk of colorectal cancer in ulcerative colitis in India. J Gastroenterol Hepatol 2005; 20: 705-709 [PMID: 15853982]
6 Cui JJ, Fock KM, Makharia GK, Goh KL, Ling KL, Hilmi I, Lim WC, Kelvin T, Gibson PR, Geetray RB, Ouyang Q, Sollano J, Manatsahtit S, Rerknimit R, Wei SC, Leong WK, de Silva HJ, Leong RW. The Asia-Pacific consensus on ulcerative colitis. J Gastroenterol Hepatol 2010; 25: 453-468 [PMID: 20370724 DOI: 10.1111/j.1440-1746.2010.06241.x]
7 Farrayre FA, Odze RD, Eaden J, Izkowitz SH, McCabe RP, Dassopoulos T, Lewis JD, Ultnan TA, James T, McLeod R, Burgart LJ, Allen J, Brill JV. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology 2010; 138: 738-745 [PMID: 20141808 DOI: 10.1053/j.gastro.2009.12.037]
8 Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, Eaden JA, Rutter MD, Akinp 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: 666-668 [PMID: 20427401 DOI: 10.1136/gut.2009.179804]
9 Van Assche G, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, Beaugerie L, Tompkins D, Huerlim K, Oldenburg B, Panes J, Portela F, Rogler G, Stein J, Tilg H, Travis S, Lindsay JO. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. J Crohns Colitis 2013; 7: 1-33 [PMID: 23040453 DOI: 10.1016/j.crohns.2012.09.005]
10 Truedove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955; 2: 1041-1048 [PMID: 13260656 DOI: 10.1136/bmj.2.4947.1041]
11 Stewénius J, Adherl E, Anderson H, Ekelund GR, Florin CH, Fork FT, Janzon L, Lindström C, Ognren M. Incidence of colorectal cancer and all cause mortality in non-selected patients with ulcerative colitis and indeterminate colitis in Malmö, Sweden. Int J Colorectal Dis 1995; 10: 117-122 [PMID: 7636371 DOI: 10.1007/BF00341210]
12 Winther KV, Jess T, Langholz E, Munkholm P, Binder V. Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. Clin Gastroenterol Hepatol 2004; 2: 1088-1095 [PMID: 15626564 DOI: 10.1016/S1542-3565(04)00543-9]
13 Palli D, Trallori G, Bagnoli S, Saieva C, Tarantino O, Cerori M, d’Albisso G, Pacini F, Amorosi A, Masala G. Hodgkin’s disease risk is increased in patients with ulcerative colitis. Gastroenterology 2000; 119: 647-653 [PMID: 10982757 DOI: 10.1053/gast.2000.16487]
14 Bernstein CN, Blanchard JF, Kliever E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer 2001; 91: 854-862 [PMID: 11241255 DOI: 10.1002/1097-0142(20010215)91:4<854::AID-CNCR1073-3.0.CO;2-Z>3.0.CO;2-Z]
15 Wadland EP, Daniker P, Möller Pedersen F, Wilson B, Schaffalitzky de Muckadell OB. Survival and incidence of colorectal cancer in patients with ulcerative colitis in Funen county diagnosed between 1973 and 1993. Scand J Gastroenterol 2000; 35: 312-317 [PMID: 10766327 DOI: 10.1080/003655200750024209]
Desai D et al. Colorectal cancer in ulcerative colitis

16 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 [PMID: 16618397 DOI: 10.1053/j.gastro.2005.12.037]

17 Giltat T, Fireman Z, Grossman A, Hacohen D, Kadish U, Ron E, Rozen P, Lilos P. Colorectal cancer in patients with ulcerative colitis. A population study in central Israel. Gastroenterology 1988; 94: 870-877 [PMID: 3345886]

18 Chang DK, Kim YH, Byeon JS, Yang SK, Chung YW, Han DS, Kim SG, Kim TI, Kim WH, Jeen YT, Eun CS, Choi H, Choi KY, Song IS. The current status of ulcerative colitis-associated colorectal cancer in Korea: a KASID study. Korean J Gastroenterol 2005; 46: 276-282 [PMID: 16247271]

19 Kim BJ, Yang SK, Kim JS, Jeen YT, Choi H, Han DS, Kim HJ, Kim WH, Kim YJ, Chang DK. Trends of ulcerative colitis-associated colorectal cancer in Korea: A KASID study. J Gastroenterol Hepatol 2009; 24: 667-671 [PMID: 19378391]

20 Kekilli M, Dagli U, Kalkan IH, Tunç B, Disibeyaz S, Ulker A, Sahin B. Low incidence of colorectal dysplasia and cancer among patients with ulcerative colitis: a Turkish referral centre study. Scand J Gastroenterol 2010; 45: 434-439 [PMID: 20085438 DOI: 10.3109/00365520903540830]

21 Gong W, Lv N, Wang B, Chen Y, Huang Y, Pan W, Jiang B. Risk of ulcerative colitis-associated colorectal cancer in China: a multi-center retrospective study. Dig Dis Sci 2012; 57: 503-507 [PMID: 21938485 DOI: 10.1007/s10620-011-1890-9]

22 Jess T, Simonsen J, Jorgensen 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; quiz e13-14 [PMID: 2252090]

23 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 [PMID: 22609382 DOI: 10.1053/j.gastro.2012.04.054]

24 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917 [PMID: 21351269 DOI: 10.1002/(jic.25516]

25 Yeole BB. Trends in cancer incidence in esophagus, stomach, colon, rectum and liver in males in India. Asian Pac J Cancer Prev 2008; 9: 97-100 [PMID: 18439085]

26 Sood A, Midha V, Sood N, Bhatia AS, Avasthi G. Incidence and prevalence of ulcerative colitis in Punjab, North India. Gut 2003; 52: 1587-1590 [PMID: 14570727 DOI: 10.1136/gut.52.11.1587]

27 Thia KT, Loftus EV, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. Am J Gastroenterol 2008; 103: 3167-3182 [PMID: 19086963 DOI: 10.1111/j.1572-0241.2008.02158.x]

28 Probert CS, Jayanthi V, Pinder D, Wicks AC, Mayberry JF. Epidemiological study of ulcerative protocotitis in Indian migrants and the indigenous population of Leicestershire. Gut 1992; 33: 687-693 [PMID: 1307684 DOI: 10.1136/gut.33.5.687]

29 Probert CS, Jayanthi V, Hughes AO, Thompson JR, Wicks AC, Mayberry JF. Prevalence and family risk of ulcerative colitis and Crohn’s disease: an epidemiological study among Europeans and south Asians in Leicestershire. Gut 1993; 34: 1547-1551 [PMID: 8244142 DOI: 10.1136/gut.34.11.1547]

30 Walker DG, Williams HR, Kane SP, Mawdsley JE, Arnold I, McNeil I, Thomas HJ, Teare JP, Hart AL, Pitcher MC, Walters JR, Marshall SE, Orchard TR. Differences in inflammatory bowel disease phenotype between South Asians and Northern Europeans living in North West London, UK. Am J Gastroenterol 2011; 106: 1281-1289 [PMID: 21577243 DOI: 10.1038/ajg.2011.85]

31 Mukewar S, Mukewar S, Limaye K, Lopez R, Wu X, Shen B. Environmental Factors Impact the Natural History of Ulcerative Colitis (UC): Indian-Americans With UC Have a Higher Risk for Colorectomy Than Asian Indian Counterparts (abstract). Gastroenterol 2012; 142 Suppl 1: S784

32 Lutgens MW, Vleggaar FP, Schipper ME, Stokkers PC, van der Woude CJ, Hommes DW, de Jong DJ, Dijkstra G, van Bodegraven AA, Oldenburg B, Samsom M. High frequency of early colorectal cancer in inflammatory bowel disease. Gut 2008; 57: 1246-1251 [PMID: 18373222 DOI: 10.1136/gut.2007.143453]

33 Wang YR, Cangemi JR, Loftus EV, Picco MF. Rate of early/missed colorectal cancers after colonoscopy in older patients with or without inflammatory bowel disease in the United States. Am J Gastroenterol 2013; 108: 444-449 [PMID: 23295277 DOI: 10.1038/ajg.2012.429]

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