World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i12.3644

World J Gastroenterol 2015 March 28; 21(12): 3644-3649
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Prospective Study

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

Devendra Desai, Sudeep Shah, Abhijit Deshmukh, Philip Abraham, Anand Joshi, Tarun Gupta, Ramesh Deshpande, Varun Khandagale, Siji George

Devendra Desai, Abhijit Deshmukh, Philip Abraham, Anand Joshi, Tarun Gupta, Varun Khandagale, Siji George, Division of Gastroenterology, P.D Hinduja Hospital, Mumbai 400016, India
Sudeep Shah, Division of Gastrointestinal surgery, Department of Surgery, P.D Hinduja Hospital, Mumbai 400016, India
Ramesh Deshpande, Division of Pathology, Department of Pathology, P.D Hinduja Hospital, Mumbai 400016, India
Author contributions: Desai D contributed to concept of the database on inflammatory bowel disease and this study, data collection and analysis, drafting and revision of the article; Deshmukh A collected and analyzed the data; Abraham P contributed to conceptualization of this study, drafting and revision of the article; Joshi A, Gupta T and Khandagale V contributed to data collection, drafting and revision of the article; Shah S contributed to data collection, drafting and revision of the article, and surgical input; Deshpande R review the pathology slides, collected the data and revised the article; and George S collected the data and drafted the article.
Ethics approval: The study was reviewed and approved by the National Health and Education Society (P D Hinduja Hospital) Institutional Review Board.
Conflict-of-interest: The study received no financial support from any source. None of the authors has any conflict of interest to declare.
Data sharing: No additional data is available.

Correspondence to: Devendra Desai, MD, Division of Gastroenterology, P D Hinduja Hospital, DNB (Gastroenterology) Room No 1106, OPD Block, Veer Savarkar Marg, Mahim, Mumbai 400016, India. devendracdesai@gmail.com
Telephone: +91-22-24447106
Received: August 31, 2014
Peer-review started: September 1, 2014
First decision: September 27, 2014
Revised: October 11, 2014
Accepted: January 8, 2015
Article in press: January 8, 2015
Published online: March 28, 2015

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. On univariate analysis, extensive colitis, longer duration of disease, and poor control of disease were associated with development of CRC. On multivariate analysis, duration of disease and extent of colitis remained significant.

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

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.

Desai D, Shah S, Deshmukh A, Abraham P, Joshi A, Gupta T, Deshpande R, Khandagale V, George S. Colorectal cancers in ulcerative colitis from a low-prevalence area for colon cancer. *World J Gastroenterol* 2015; 21(12): 3644-3649 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i12/3644.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i12.3644

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]; 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[7-9]. 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 χ^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

Table 1 Comparison of ulcerative colitis patients with and without colorectal cancer

	No malignancy	CRC	*P* value
Number of patients (males)	418 (242)	12 (5)	0.375[1]
Age (mean ± SD, yr)	44.5 ± 14.6	49.6 ± 10.1	0.23[2]
Median duration of disease (interquartile range)	6 (7)	18 (8)	0.00001[3]
History of smoking	31	0	1.0
Family history of IBD	24	2	0.15
Pancolitis	159	9	0.01
Left-sided colitis	129	2	1.0
No. of patients on azathioprine	108	2	0.738[1]
Poor compliance with therapy	144	6	0.23
Poor disease control	50	5	0.007[1]

[1]Fisher's exact test; [2]Unpaired *t* test; [3]Mann Whitney test. CRC: Colorectal cancer; IBD: Inflammatory bowel disease.

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.

Table 2 Characteristics of colorectal cancer in ulcerative colitis

No.	Age (yr)	Sex	Extent of disease	Duration[1], yr	Location of CRC
1	59	M	Ext colitis	24	Recto-sigmoid
2	47	F	Left-sided colitis	10	Left colon
3	51	M	Ext colitis	6	Ascending, transverse, descending colon (multifocal)
4	42	M	Ext colitis	7	Rectum
5	64	F	Ext colitis	13	Ascending colon
6	41	F	Ext colitis	17	Descending colon
7	40	F	Left-sided colitis	6	Rectum
8	46	F	Ext colitis	20	Rectum
9	67	F	Left sided	27	Rectum
10	49	M	Ext colitis	22	Rectum
11	56	M	Ext colitis	17	Rectum
12	51	F	Ext colitis	13	Ascending colon

[1]Duration from onset of ulcerative colitis to detection of CRC. Ext: Extensive colitis; CRC: Colorectal cancer.

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

study protocol; she was then found to have rectal adenocarcinoma on colonoscopy.

The pathological stage of CRC was known in 10 patients (one patient underwent surgery at another centre and one patient refused surgery and was subsequently lost to follow up): 3 patients had T1 N0 M0 stage, one patient had T2 NO M0 disease, one had T3 N0 M0, and five had nodal involvement. One patient had lung metastases at presentation.

DISCUSSION

Our study found a prevalence rate of 2.8% for colon cancer in a cohort of 430 patients with ulcerative colitis. This is similar to that reported in previously published studies, predominantly from the Western world, where prevalence rates of CRC in ulcerative colitis varied from 0.7% to 3.3%[11-16].

The trend in Asia is not clear; studies have shown that the likelihood of CRC is low, ranging from 0.8% to 1.8%[4,5,17-21]. Our study, taken together with two others from India[4,5], provides insight into the risk of CRC in ulcerative colitis in India. Kochhar *et al*[4] reported that the risk of CRC in ulcerative colitis was 1.8%; Venkataraman *et al*[5] reported a lower rate of CRC (0.94%). Our study reports a higher rate (2.79%). This is possibly a result of having a greater number of patients with duration of ulcerative colitis greater than 20 years. The duration of ulcerative colitis has not been specified in the study by Kochhar *et al*[4], and the lower mean duration of follow up (6 years) in the study from Vellore[5] with no increase in incidence density between 10 and 20 years also suggests a shorter disease duration. Colectomy rates were similar in the two studies (8.8% in the Vellore study[5] and 7.4% in ours) and could not account for the difference.

Two recent studies from the West have reached different conclusions about the increased risk of colon cancer in ulcerative colitis. Jess *et al*[22], in a population-based study from Denmark, suggested that the risk of colon cancer in ulcerative colitis is not as high as previously reported and in fact may not be different than that in the general population. To the contrary, Herrinton *et al*[23], from California showed that the risk of CRC in ulcerative colitis is 60% higher than in age- and gender-matched cohorts of people without inflammatory bowel disease, and the risk remained the same throughout the study period of 14.5 years.

Recent data suggest that the age-adjusted rates of CRC in the general Indian population vary from 2.65 to 3.06/100000 in men and 3.40/100000 in women[3,24,25]. The low prevalence of colon cancer in the general population can be seen by the absence of a single case of colon cancer amongst first-degree relatives of our cohort of patients. The risk of CRC in Indian patients with ulcerative colitis thus appears much higher (900 times) than in the general population. This is a much larger risk factor than that in West, owing to the far lower prevalence of colon cancer in the Indian population. This supports the contention that ulcerative colitis is a risk factor for tumour and therefore requires surveillance. If we look at the reason for relatively high prevalence of CRC in an area with low prevalence for CRC, there are no clear answer but some questions arise: It may be related to prevalence of UC in India. A study from India has shown that the incidence and prevalence of UC (incidence 6.02/100000 and prevalence 44.3/100000) is comparable to the west[26]. The prevalence is higher that the rest of Asia[27]. The studies on migrant Indian in Leicestershire have suggested that Indian may be more susceptible to inflammatory bowel disease (IBD) than the caucasians (RR = 2.45)[28,29]. Secondly more than prevalence, it may be related to disease phenotypes in Indian patients. There is mixed literature on this. A study by Walker *et al*[30] compared the IBD disease phenotypes between South Asians (India, Paksistan and Bangladesh) and Northern Europeans living in London. The phenotype of ulcerative colitis differed significantly: higher number of of South Asian patients had extensive colitis as compared to Northern Eurpean patients (63% *vs* 42.5%, P = 0.0001); The colectomy rate was non significantly lower in migrant population; they did not study the cancer development. Another study reported in an abstract form compared UC phenotype in native (living in Nagpur, Central India) Indian, Indians migrated to the United States of America (Indian-American) and Caucasian Americans[31]. Proportion of patients with pancolitis was 34.7% in Indians, 65.9% in Indian Americans and 62.9% in Caucasian Americans. Indian Americans were more likely to have colectomy than Indian in India. So the prevalence and disease phenotypes do not seem to explain the high likelihood of CRC. Another factor like disease control may explain the high liklihood of cancer.

Our study showed that pancolitis and duration of disease are significantly associated with increased likelihood of CRC, in keeping with previous literature. Age, gender, history of smoking, family history of inflammatory bowel disease, duration of 5-ASA therapy, azathioprine therapy and compliance with therapy were not significant associations.

Guidelines by various societies suggest that surveillance for CRC should begin after 8 to 10 years of disease duration[7-9]. However, if these recommendations are followed, CRC may be missed. Three of 12 patients with CRC in our study developed the malignancy at 6, 6 and 7 years; one of them had lung metastases at presentation. In another Indian study, by Kochhar *et al*[4], 2 of 8 patients with ulcerative colitis developed CRC at 7 and 8 years' disease duration. In the study by Gilat *et al*[17], 2 of 26 patients who developed CRC in ulcerative colitis had disease duration less than 10 years (6 and 9 years). In the study by Gong *et al*[21], cumulative risk of CRC in the first decade was 1.15 %, similar to the 1.6 % in the meta-analysis by Eaden *et al*[1], Lutgens *et al*[32] reported that 15% of their

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[33]. 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.

ACKNOWLEDGMENTS

The authors wish to acknowledge Ms Sangeeta Chhabria for secretarial help in maintaining the database.

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, Mayberry 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 [PMID: 23448792 DOI: 10.1097/MIB.0b013e31828029c0]

3 **Mohandas KM**. Colorectal cancer in India: controversies, enigmas and primary prevention. *Indian J Gastroenterol* 2011; **30**: 3-6 [PMID: 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: 1467777 DOI: 10.1097/00008469-199206000-00003]

5 **Venkataraman S**, Mohan V, Ramakrishna BS, Peter S, Chacko A, Chandy G, Kurian G, Kurian 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 **Ooi CJ**, Fock KM, Makharia GK, Goh KL, Ling KL, Hilmi I, Lim WC, Kelvin T, Gibson PR, Gearry RB, Ouyang Q, Sollano J, Manatsathit S, Rerknimitr R, Wei SC, Leung 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 **Farraye FA**, Odze RD, Eaden J, Itzkowitz SH, McCabe RP, Dassopoulos T, Lewis JD, Ullman 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, 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 [PMID: 20427401 DOI: 10.1136/gut.2009.179804]

9 **Van Assche G**, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, Beaugerie L, Gomollón F, Häuser W, Herrlinger 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 **Truelove 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**, Adnerhill I, Anderson H, Ekelund GR, Florén CH, Fork FT, Janzon L, Lindström C, Ogren 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: 15625654 DOI: 10.1016/S1542-3565(04)00543-9]

13 **Palli D**, Trallori G, Bagnoli S, Saieva C, Tarantino O, Ceroti M, d' Albasio 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, Kliewer 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]

15 **Wandall EP**, Damkier P, Møller 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]

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 **Gilat 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 JY, 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, Tunc 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, 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; quiz e13-14 [PMID: 22522090]
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/ijc.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.5211.1587]
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 proctocolitis 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 J, 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 Colectomy 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: 18337322 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]

P- Reviewer: Arasaradnam RP, Chen CN, Moldovan R, Uchiyama K, Zhu YL **S- Editor**: Ma YJ **L- Editor**: A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327