World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v19.i43.7561

World J Gastroenterol 2013 November 21; 19(43): 7561-7568
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease

Has the risk of colorectal cancer in inflammatory bowel disease decreased?

Nynne Nyboe Andersen, Tine Jess

Nynne Nyboe Andersen, Tine Jess, Department of Epidemiology Research, Statens Serum Institut, DK-2300 Copenhagen, Denmark
Author contributions: Andersen NN collected the material and drafted the manuscript; and Jess T discussed the topic and revised the manuscript.
Correspondence to: Nynne Nyboe Andersen, MD, Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen, Denmark. nyna@ssi.dk
Telephone: +45-32-683139 Fax: +45-32-683165
Received: August 28, 2013 Revised: October 20, 2013
Accepted: November 1, 2013
Published online: November 21, 2013

Abstract

The association between inflammatory bowel disease (IBD) and colorectal cancer (CRC) has been acknowledged for almost a century and is assumedly promoted by a chronic inflammation-driven carcinogenic process in the intestine in combination with a genetic predisposition. The magnitude of the risk of CRC in IBD remains a continuing subject of debate. The early, high risk estimates for CRC in IBD were most likely overestimated due to selected patient populations originating from tertiary referral centers with a disproportional high percentage of patients with severe disease. Later population-based studies calculating risk estimates from a broad spectrum of IBD patients have found the risk to be significantly lower. At present, there is evidence that IBD patients with longstanding and extensive disease with uncontrolled inflammation are those at increased risk. Additional, other recognized risk factors include early age at onset, family history of CRC, and concomitant primary sclerosing cholangitis. A significant amount of effort is put into identifying potential preventive factors of CRC in IBD, including surveillance programs and chemopreventive agents but the individual effect of these remains uncertain. Interestingly, recent studies have reported a decline in risk of CRC over time. Surveillance programs and the new treatment strategies, particular biological treatment might be part of the reason for the observed decline in risk of CRC in IBD over time but future studies will have investigate this assumption.

Key words: Inflammatory bowel disease; Colorectal cancer; Risk; Ulcerative colitis; Crohn's disease

Core tip: The increased risk of colorectal cancer in inflammatory bowel disease is well established. But what is the true magnitude of this increased risk, does the risk of colorectal cancer differ between ulcerative colitis and Crohn's disease and what are the significant risk factors? Further, recent studies have indicated that the risk of colorectal cancer in patients with inflammatory bowel disease is decreasing over time, potentially due to improved treatment options that lower the inflammatory burden. These are some of the subjects that will be elucidated and discussed in this review.

Andersen NN, Jess T. Has the risk of colorectal cancer in inflammatory bowel disease decreased? *World J Gastroenterol* 2013; 19(43): 7561-7568 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i43/7561.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i43.7561

INTRODUCTION

In almost a century it has been recognized that the risk of developing colorectal cancer (CRC) is increased in patients with longstanding inflammatory bowel disease (IBD), and it is estimated that one out of six deaths in ulcerative colitis (UC) patients and one out of 12 of all deaths in patients with Crohn's disease (CD)[1,2] is caused

by colorectal cancer. Together with the hereditary syndromes of familial adenomatous polyposis and hereditary non-polyposis colorectal cancer, IBD is in the top-3 high risk conditions for CRC. Both UC and CD carry an increased risk of CRC; however the risk is most extensively studied in UC. The augmented risk of CRC in IBD is assumedly promoted by a chronic, inflammation-driven carcinogenic process in the intestine in combination with a genetic predisposition[3]. The prognosis of sporadic CRC and IBD-related CRC is similar with a 5-year survival of 50%[4] whereas IBD-related CRC affect younger patients than sporadic CRC (60 years *vs* 70 years)[4,5].

In 1925, Crohn and Rosenberg[6] were the first to elucidate the relation between CRC and UC and in 1928, Bargen[7] further described 20 cases of colorectal cancer in patients with UC from the Mayo clinic in the United States. In 1971, de Dombal[8] reported a cumulative risk of CRC in a population from Leeds with extensive UC to be 5% after 10 years and as high as 41.8% after 25 years. These findings led to the suggestion of cancer prophylactic colonic surgery in UC patients with extensive disease and a disease course of more than 10 years, but this proposal has never been carried out in practice. Since then, substantial effort has been made to elucidate the supposed risk of CRC in IBD and has presented a considerable variety in risk estimates, leading to an ongoing debate concerning the true magnitude of the risk of CRC in IBD. Additionally, novel population-based studies have suggested a decline in risk of IBD-related CRC over time, potentially due to a shift in treatment strategies from the era of sulfasalazine, 5-aminosalicylic acid and corticosteroids, to the era of immunomodulators, such as thiopurines and tumor necrosis factor (TNF)-α antagonists[5,9].

RISK OF COLORECTAL CANCER IN ULCERATIVE COLITIS

A landmark meta-analysis including 116 studies published by Eaden *et al*[1] in 2001, found that the cumulative risk of CRC for UC patients was 2% at 10 years, 8% at 20 years, and 18% at 30 years. However as an important weakness of the meta-analysis the underlying studies were of very different methodology and many factors may have biased results. A main subject, primarily in early studies, has been the selective collection of IBD patients from tertiary referral centers with a high percentage of patients with disproportionately severe disease, thereby potentially introducing referral bias with an overestimation of the risk. This is in line with the findings in a Dutch study, comparing a cohort of 121 IBD patients with CRC from referral centers with a cohort of 160 IBD patients with CRC from general hospitals and confirmed that IBD patients from referral centers represent a subgroup with a more severe IBD-phenotype[10].

In order to approach a more unbiased risk estimate the use of population-based studies is essential with unselected cohorts of patients representing the complete and broad spectrum of disease. An early Swedish population-based study by Ekbom *et al*[11] including a cohort of 3117 patients with UC and followed from 1922-1983 found 91 cases of colorectal cancer, corresponding to a standardized incidence ratio (SIR) of 5.7 (95%CI: 4.6-7.0). A matched population-based cohort study by Bernstein *et al*[12] from 2000 revealed an increased risk of CRC in 2672 UC patients (RR = 2.75; 95%CI: 1.91-3.97) compared with a non-IBD population. In accordance, Söderlund *et al*[13] conducted a population-based study of 7607 IBD patients from Sweden diagnosed between 1954 and 1989 and found, for UC patients, a more than 2-fold increased risk of CRC compared to the background population (SIR = 2.7; 95%CI: 2.3-3.2). A Hungarian, population-based study by Lakatos *et al*[14] followed 723 UC patients for 8564 person-year from 1974 to 2004 and revealed a cumulative risk of CRC in UC of 0.6% after 10 years, 5.4% after 20 years and 7.5% after 30 years disease duration. Conversely, data from population-based studies originating from Scandinavia, Italy and the United States have reported lower risk estimates. A population-based study from Olmsted County, United States from 2006 found no overall increase in CRC in 378 UC patients (SIR = 1.1; 95%CI: 0.4-2.4), but in the subgroup of patients with extensive colitis the risk was increased 2-fold, although not reaching statistically significance (SIR = 2.4; 95%CI: 0.6-6.0)[15]. Winther *et al*[16] followed a population-based cohort of UC patients from Copenhagen County, for a median of 19 years and found no increased risk of CRC (standardized morbidity ratio: 1.05; 95%CI: 0.56-1.79). In accordance with this, a population-based study from Italy and a very recent population-based study from Northern Jutland, Denmark, did not find a significant increase in CRC in UC patients[17,18]. A recent meta-analysis[19], solely including population-based studies in order to approach an unbiased, general estimate of CRC risk in UC, found that an average of 1.6% of UC patients was diagnosed with CRC during 14 years of follow-up. This corresponds to a 2.4 (95%CI: 2.1-2.7) fold increased risk of CRC in UC. Looking at absolute risk the cumulative risk of CRC was 1.15% after 15 years, 1.69% after 20 years and 2.61% after 25 years disease duration. With 5 out of 8 studies originating from the Nordic countries the low risk has been suggested to be explained by high surgery rates and a high percentage of patients with proctitis in these countries, but this is not supported by the fact that the 3 non-Scandinavian studies revealed similar of even lower risk estimates than the Scandinavian studies. Beaugerie *et al*[20] recently published a prospective cohort study on risk of colorectal high-grade dysplasia and CRC among nearly 20000 patients with IBD enrolled in the French observational cohort CESAME (Cancer et Surrisque Associé aux Maladies Inflammatoires Intestinales En France) between May 2004 and June 2005. The authors found a 2-fold higher risk of CRC in IBD patients compared to the general population; a risk that was similar for both UC and CD. Sub-analyses revealed that this increased risk was driven by the relatively small percentage (14.6%) of patients with long-standing extensive colitis (>

10 years disease and > 50% of colon affected) with a SIR of 7 (95%CI: 4.4-10.5) compared with a non-significant increased risk in patients without long-standing extensive colitis (SIR = 1.1; 95%CI: 0.6-1.8). These risk estimates are higher than those originating from population-based studies and it is of importance to notice that data from the CESAME cohort arise from a selected IBD population. The difference in risk estimates from selected population *vs* unselected populations was addressed in a novel meta-analysis stratifying between study design and revealed a 4-fold greater risk of CRC in IBD patients when data originated from referral centers with selected patients compared with data from unselected patients from population-based studies[9].

RISK OF COLORECTAL CANCER IN CD

In contrast to the risk of CRC in UC patients, which has been comprehensively investigated, the risk of CRC in CD patients remains less explored. As with the risk of CRC in UC, studies on risk of intestinal cancer in CD have revealed inconsistent results with a variation in reported relative risk estimates from 0.8 to 20.0[21].

A meta-analysis from 2005 by Jess *et al*[22] exclusively including population-based studies and representing populations from North America, Scandinavia and Israel, estimated a pooled overall SIR for CRC in CD of 1.9 (95%CI: 1.4-2.5). Separate risk estimates for cancer in the colon and rectum resulted in a significant increased risk for colon cancer (SIR = 2.5; 95%CI: 1.7-3.5), whilst a slightly, non-significant increased pooled risk was estimated for rectum cancer (SIR = 1.4; 95%CI: 0.8-2.6). The risk of CRC cancer was significantly increased in CD patients with colonic involvement (SIR = 4.3; 95%CI: 2.0-9.4), non-statistically increased in patients with ileocolonic CD (SIR = 2.6; 95%CI: 0.8-8.2) and not increased in CD patients with pure ileal disease (SIR = 0.9; 95%CI: 0.2-4.1). Another meta-analysis from 2005, by Canavan *et al*[21] including both selected and unselected patient series studies, on risk of CRC in CD, reported similar results with an overall pooled RR of 2.5 (95%CI: 1.3-4.7) and only a significant increased risk for CD patients with colonic disease (RR = 4.5; 95%CI: 1.3-14.9). In subgroup analyses on site-specific CD the RR estimate increased for patients with colonic involvement whereas combined RR of CRC in CD patients with ileal disease was not increased (RR = 1.1; 95%CI: 0.8-1.5). A retrospective study by Herrinton *et al*[23] calculated risk of CRC cancer in a more recent IBD cohort from the Kaiser Permanente database from 1998 to 2010 and identified 29 incident CRC patients among persons with CD corresponding to a 1.6-fold higher risk of CRC compared with the general Kaiser Permanente population. In the up-dated meta-analysis from 2013 by Lutgens *et al*[9] the pooled risk estimate for CRC in CD was slightly increased (SIR = 1.6; 95%CI: 1.2-2.0) when data originated from population-based studies. Yet again, the risk was only increased in patients with colonic involvement, though not reaching statistical significance (pooled SIR = 2.0; 95%CI: 0.3-3.7).

RISK FACTORS

It is essential, in a clinical aspect to obtain knowledge of potential cancer predictive factors in order to identify subgroups of patients who need closer surveillance or more intense treatment. Known risk factors for CRC in IBD patients include young age at diagnosis, duration and anatomic extent of disease, family history of CRC, concurrent primary sclerosing cholangitis and persisting inflammation of the colon.

AGE AT ONSET

Young age at onset of colitis has been reported to be an independent risk factor for CRC. Interpretation of existing evidence is complicated as children tend to have more extensive and severe colitis compared with those diagnosed in adult age, and further have a potential for longer disease duration, a risk factor in itself.

The impact of early age at onset of IBD as a risk factor for CRC was assessed in a Danish cohort study by Jess *et al*[5]. They found that the risk of CRC varied markedly by age at diagnosis of UC; those diagnosed at childhood or adolescence (age 0-19 years) had the greatest risk (RR = 43.8; 95%CI: 27.2-70.7) followed by those diagnosed in young adulthood (age 20-39 years) with a RR of 2.65 (95%CI: 1.97-3.56). Those diagnosed with UC at the age period from 60-79 years had a risk of CRC that was below that of the background population (RR = 0.76; 95%CI: 0.62-0.92). However, as pointed out by the authors, the absolute risk of CRC was limited even in those diagnosed in young age[24]. Patients diagnosed with UC at age 0-19 had an absolute risk of CRC of 1.64% (95%CI: 0.25%-3.00%) after 25 years disease duration and for the group diagnosed at 20-39 years of age this risk was 0.80% (95%CI: 0.39%-1.20%). In matched controls the corresponding 25-year risk estimates were 0.05 (95%CI: 0.03%-0.07%) and 0.47% (95%CI: 0.43%-0.50%), respectively for the two age-groups. These data are supported by a population-based meta-analysis which showed that the standardized CRC incidence ratio was 4 times higher in IBD patients diagnosed at young age (< 30 years) compared with a non-significantly increased risk patients diagnosed at the age of 30 years or older[9], but the meta-analysis did not report absolute risks.

DISEASE EXTENT AND DURATION

UC patients with pancolitis are at highest risk, left-sided colitis carries a moderate risk, and patients with proctitis and protosigmoiditis are at similar risk of CRC as the background population. Ekbom *et al*[11] found that UC patients with pancolitis had a nearly 15-fold increased risk of CRC (SIR = 14.8; 95%CI: 11.4-18.9) as compared to the background population, in contrast to an increased risk of 2.8 for those with left-sided colitis and a non-significant increased risk of 1.7 for those with proctitis. A smaller risk was found in the population-based study by Söderlund *et al*[13] exploring the significance of site-

specific inflammation for both UC and CD, on risk of CRC. Within the cohort and compared with UC proctitis the risk of CRC cancer was 2.0 (95%CI: 1.3-3.0) for UC pancolitis, 1.2 (95%CI: 0.7-1.9) for left-sided UC, 0.9 for colonic CD (95%CI: 0.5-1.6) and 0.7 (95%CI: 0.4-1.1) for non-colonic CD. A risk of 5.6 (95%CI: 4.4-7.0) was found for UC pancolitis, compared to an overall risk for UC of 2.7 (95%CI: 2.3-3.2) when comparing with the general population. In accordance, the population-based meta-analysis by Jess *et al*[19] reported an overall risk of 4.8 (95%CI: 3.9-5.9) for UC patients with extensive disease. Backwash ileitis in UC, theoretically representing the greatest extent of disease due to ileal involvement, has been reported to carry an additional increased risk of CRC[25], but this has not been confirmed by others[26].

In addition to extent of disease, longer duration of disease is associated with an augmented risk of CRC in IBD. In a Danish, nationwide cohort study by Jess *et al*[5] the relative risk of CRC in IBD was low in the first years after diagnosis (except for an implausible high RR the first year after diagnosis, assumedly as a result of differential diagnostic problems or cases of coincidental detection of recent onset IBD in patients diagnosed with CRC), then progressively increasing with duration of IBD reaching the level of the non-IBD population after 8 years. After disease duration of 13 years the RR was significantly higher than the background population, reaching a level around 50% increase with longer follow-up. These results are consistent with the current surveillance guidelines defined by the American Gastroenterological Association[27] and the British Society for Gastroenterology[28] recommending initiation of surveillance after 8-10 years disease duration for CD and extensive UC and after 15-20 years for patients with left-sided UC. Nevertheless, studies have shown that up to a third of IBD patients develop CRC prior to the initial point of surveillance[5,20,29], thus questioning the efficacy of the present surveillance strategy.

PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease present in 3%-8% of patients with UC and 1%-3% of patients with CD[30-32], whereas 60%-80% of patients with PSC have IBD[33]. In 1992, Broomé *et al*[34] were the first to suggest that IBD patients with PCS potentially had an increased risk of CRC. A later study by the same group revealed an absolute cumulative risk of CRC in patients with UC and PSC of 9% after 10 years disease duration, 31% after 20 years and as high as 50% after 25 years; compared with 2%, 5% and 10% in patients with UC alone[35]. A meta-analysis published in 2002, including 11 studies concerning risk of CRC in patients with concomitant UC and PSC, revealed that 21% of UC-PSC patients developed CRC compared to 4% of UC patients without PSC, thus giving an odds ratio of 4.8 (95%CI: 3.6-6.4)[36]. The risk of CRC in CD patients with PSC is uncertain. A British case control study by Braden *et al*[37] studied risk of CRC in colonic CD/PSC patients and concluded that the presence of PSC did not increase the risk of CRC in patients with colonic CD. Thackeray *et al*[38] conducted a retrospective study in order to determine the time-interval between diagnosis of IBD, PSC and CRC and found that IBD-PSC patients developed cancer or dysplasia relatively soon after diagnosis of both IBD and PSC. Interestingly, patients with PSC and IBD typically have mild or asymptomatic pancolitis with prolonged remission and an inactive cause[39-41]. Further, studies have reported a more frequent location of cancer in the right colon in patients with IBD-PCS[42]. This could suggest a different pathogenesis in the subgroup of IBD patients with PSC compared to IBD patients in general, but these mechanisms remains unidentified.

Due to the high cumulative risk of CRC in IBD patients with PSC, the short time-interval between PSC diagnosis and CRC progression, and the predominately right-sided cancer location, it is recommended that patients with IBD-PSC should initiate an annual surveillance colonoscopy, rather than sigmoidoscopy, program already at time of PSC diagnosis[43].

FAMILY HISTORY OF COLORECTAL CANCER

Healthy individuals, with a family history of CRC, carry a near 2-fold increased risk of CRC. Few studies have assessed the significance of familial CRC, or IBD on risk of CRC in patients with IBD. A population-based study from Sweden found that a family history of CRC in IBD patients resulted in a doubling of the already increased risk of CRC in IBD, irrespectively of type and extent of IBD[44]. Further, sub-analyses revealed that IBD patients with a 1st-degree relative diagnosed with CRC before the age of 50 had an even higher risk (RR = 9.2; 95%CI: 3.7-23). A family history of IBD did not increase the risk of CRC.

SEVERITY OF INFLAMMATION

Under the assumption that inflammation is the promoting factor in development and progression of CRC in IBD it seems evident that the relationship between degree of inflammation and risk of CRC would be comprehensively investigated. Paradoxically, data are sparse. Rutter *et al*[45] conducted a retrospective case-control study, using data on histological and endoscopic grade of inflammation from a well-established cancer surveillance program for patients with long-standing, extensive UC from the United Kingdom and found a highly significant correlation between severity of inflammation and the risk of CRC; both when using colonoscopic scores (OR = 2.5, $P = 0.001$) and histological scores (OR = 5.1, $P < 0.001$). These findings were replicated in another retrospective case-control study from Finland, concluding that the risk of dysplasia or CRC is strongly associated with the degree of inflammation in patients with UC[46].

IS THE RISK OF COLORECTAL CANCER DECREASING?

The management of IBD has changed markedly in the last decades[47] not only with advancement in medical treatments, *e.g.*, new biological therapies, surgical treatment options and improved diagnostic tools leading to early detection, but also with implementation of surveillance programs and awareness of the need of adherence to medication from a patient perspective. These factors could potentially reduce the long-term inflammation in IBD patients and thereby reduce the risk of CRC.

Eaden *et al*[1] reported in their meta-analysis an increase in incidence of IBD-related CRC over time from 1955 to 2001 by plotting cancer risk against the midpoint of 41 studies, but the result did not reach statistical significance (slope: 0.003, $P = 0.80$). Another meta-analysis reported a decline in risk over time, by pooling results on risk estimates classified by the publication year. They found an incidence rate of 4.29/1000 pyrs in the 1950s compared to an incidence rate of 1.09/1000 pyrs from 2000-2011[48]. Several other studies have shown a declining trend in risk over time. Söderlund *et al*[13] conducted a population-based study showing time-trends in incidence and mortality of CRC from 1960 to 2004 in 7607 Swedish IBD patients and reported adjusted relative risks of 1.7 (95%CI: 0.6-4.4) from 1960 to 1969, 1.3 (95%CI: 0.7-2.6) from 1970 to 1979, 1.2 (95%CI: 0.7-2.2) from 1980 to 1989, 1.1 (95%CI: 0.7-1.8) from 1990 to 1999, and 1 (reference) from 2000 to 2004, revealing a non-significant, declining trend. Compared to the general population the relative risk declined from a 5-fold increased risk of CRC in IBD in the 1960s to a 2-fold increased risk in the period from 2000 to 2004 (P for trend = 0.06). The risk of death from CRC decreased significantly during the same time period, both when comparing patients within the cohort and with the general population. Whether this decline in mortality is due to surveillance, better surgical management, better follow-up, or other changes is unanswered. Results from other studies are diverse. Herrinton *et al*[23] used data on IBD and CRC from the United States health insurance Kaiser Permanente database to report time-trends over a 14.5 year study period from 1998 to 2010. Results showed no time-trend with incidence rates of CRC per 100000 pyrs, varying from 87.9 in 1998-2001, to 67.0 in 2002-2006 and to 73.9 in 2007-2010 (P trend = 0.98) but one could argue that this time-interval is too short to reveal any trend over time. In contrast to the results from the United States, a nation-wide cohort study from Denmark revealed a decrease in risk of CRC in IBD over 30 years from 1979 to 2008[5]. During 178 million person-years of follow-up, relative risk estimates of CRC in IBD were calculated, adjusted by sex, age and calendar period and subdivided into three time-periods of 10 years from 1979 to 2008. Compared to the general population the overall RR of CRC in UC decreased from 1.34 (95%CI: 1.13-1.58) in 1979-1988 to 1.09 (95%CI: 0.90-1.33) in 1989-1998 and further to 0.57 (95%CI: 0.41-0.80) in 1999-2008. It has been argued that the observed decreased risk could be explained by the initiation of screening of CRC in the general population but first of all there is no systematic screening program for CRC in Denmark before year 2014 and further relative risks compared within the cohort, using the RR in the intermediate period from 1989-1999 as reference (hence enabling adjustment for shorter length of follow-up in recent cohorts) the risk was still significantly reduced (RR = 0.59; 95%CI: 0.39-0.90) in the late period from 1999-2008. When analyzing time-trends in CD no significant changes were observed. Likewise, a study on mortality within the same population revealed a decrease in mortality in UC patients from 1982 to 2010, largely due to a reduction in mortality from gastrointestinal orders and CRC[49]. In addition to the mentioned original studies, an updated meta-analysis by Lutgens *et al*[9] found a similar decreasing trend in risk of CRC in IBD over time in meta-regression analyses from 9 population-based studies, but the trend did not reach statistical significance, most likely due to a type Ⅱ error as only few studies were available for analysis. Overall, there may be a declining risk of CRC in IBD over time and the reason for this observation needs to be studied further.

CHEMOPREVENTION

Instead of focusing on early detection of neoplasia in IBD, the ideal would be to prevent neoplasia from ever developing. In light of the theory of an inflammation-driven carcinogenic process as a causative factor of IBD-related CRC, medical therapies reducing the inflammatory burden could potentially lower the risk of CRC in IBD. Hence, there has been an increasing interest in detecting chemopreventive agents that can reduce the overall risk of dysplasia and cancer and serve as a complement to current surveillance programs.

5-aminosalicylic acid (5-ASA) is the first line agent for maintenance therapy in mild to moderate UC and it has been shown in *in vitro* studies to have antineoplastic properties by inhibiting the nuclear kappa-B pathway which is involved in tumor progression[50]. However, the evidence of a potential chemoprophylactic effect of 5-ASA is contradictory. In 2005 Velayos *et al*[51] published a meta-analysis of 9 observational studies (3 cohort, 6 case-control) on effect of 5-ASA in preventing IBD related CRC. Pooled analysis revealed a protective effect of 5-ASA use on risk of IBD-related CRC with an odds ratio of 0.51 (95%CI: 0.37-0.69). Since then several case-control and population-based studies have not been able to detect any chemopreventive effect of 5-ASA[52-54]. Recently, Nguyen *et al*[55] published a meta-analysis solely including non-referral studies; thereby potentially reducing bias and presenting evidence that is more generalizable. The meta-analysis revealed a pooled adjusted OR of 0.95 (95%CI: 0.66-1.38) for CRC in patients with IBD treated with 5-ASA and based on these results the authors concluded that there does not seem to be a protective effect

of 5-ASA on risk of CRC in IBD.

In addition to 5-ASA, an increasing number of patients are treated with the thiopurine drugs, azathioprine and 6-mercaptopurine. Existing data on the potential chemopreventive effect of thiopurines in IBD are, however, conflicting. In the French CESAME clinical based cohort study the authors investigated the impact of thiopurines on risk of CRC in IBD[20]. Almost half of the 19.484 IBD patients had been exposed to thiopurines and among current users the adjusted hazard ratio for CRC was 0.57 (95%CI: 0.24-1.32) thereby revealing no significantly protective effect of thiopurine use on CRC risk in the general IBD population. However, in subanalysis confined to IBD patients with long-standing extensive colitis, current treatment with thiopurines reduced the risk of advanced colorectal neoplasia significantly (CRC and high grade dysplasia combined; HR = 0.28; 95%CI: 0.09-0.89). A Dutch cohort study by van Schaik *et al*[56] have further evaluated the effect of thiopurines on risk of CRC in an IBD cohort of 2578 IBD patients of whom 770 were exposed to thiopurines. They found that thiopurine exposure were associated with significantly decreased risk of developing advanced neoplasia (high grade dysplasia and colorectal cancer combined; adjusted HR = 0.10; 95%CI: 0.01-0.75). In a Danish nationwide population-based study by Pasternak *et al*[57] from 2013, the effect of thiopurine exposure on risk of CRC was assessed among 43969 IBD patients of whom 12% had been exposed to thiopurines. In contrast to the more selected French study, no difference in risk of CRC was observed among thiopurine exposed *vs* non-exposed patients (adjusted RR = 1.00; 95%CI: 0.61-1.63). Similar results were reported in another large population-based study from the United Kingdom[58].

Recent data from models of experimental colitis have indicated that TNF-α has a tumor promoting effect[59]. Few studies have been able to evaluate the effect of the new biological treatments, as TNF-α blockers, on risk of CRC due to the relatively short existence of these agents relative to the latency of CRC. In a Dutch nested case-control study by Baars *et al*[60] risk factors for IBD-related CRC were identified by comparing 173 cases of IBD-related CRC (collected from 1990 to 2006) with 393 non-CRC IBD controls. The authors found that use of TNF-α antagonist was a protective factor for the development of CRC (OR = 0.09; 95%CI: 0.01-0.68). In a Danish, nationwide population-based cohort study, the risk of CRC was compared between IBD patients exposed to TNF-α antagonist *vs* non-exposed and revealed no impact of TNF-α antagonist on risk of CRC (adjusted RR = 1.06; 95%CI: 0.33-3.40)[61]. The association between TNF-α antagonists and cancer is two-edged with hypotheses on both a tumor-promoting and a tumor preventing effect and future studies are necessary to clarify this aspect.

CONCLUSION

The absolute risk of CRC in IBD is limited. However, subgroups of IBD patients with severe, long-standing active disease who do not undergo colectomy and patients with PSC carry a greater risk of CRC than the background population. Overall, it seems evident that to prevent CRC from occurring in IBD, the goal is to minimize severity and extent of inflammation, whereas the methods used to do this (regular follow-up, medical treatment, surgery, and surveillance) act in common and not as single cancer-preventive factors. Whether new treatment strategies, particular biological treatment might be part of the reason for the observed decrease in risk of CRC in IBD over time needs further investigation.

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 **Jess T**, Winther KV, Munkholm P, Langholz E, Binder V. Intestinal and extra-intestinal cancer in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. *Aliment Pharmacol Ther* 2004; **19**: 287-293 [PMID: 14984375 DOI: 10.1111/j.1365-2036.2004.01858.x]

3 **Kraus S**, Arber N. Inflammation and colorectal cancer. *Curr Opin Pharmacol* 2009; **9**: 405-410 [PMID: 19589728 DOI: 10.1016/j.coph.2009.06.006]

4 **Rhodes JM**, Campbell BJ. Inflammation and colorectal cancer: IBD-associated and sporadic cancer compared. *Trends Mol Med* 2002; **8**: 10-16 [PMID: 11796261 DOI: 10.1016/S1471-4914(01)02194-3]

5 **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 DOI: 10.1053/j.gastro.2012.04.016]

6 **Crohn BB,** Rosenberg H. The sigmoidoscopic picture of chronic ulcerative colitis (non-specific). *Amer J Med Sci* 1925; **170**: 220-228 [DOI: 10.1097/00000441-192508010-00006]

7 **Bargen JA**. Chronic ulcerative colitis associated with malignant disease. 1928. *Dis Colon Rectum* 1994; **37**: 727-730 [PMID: 8026242 DOI: 10.1007/BF02054420]

8 **de Dombal FT**. Ulcerative colitis. Epidemiology and aetiology, course and prognosis. *Br Med J* 1971; **1**: 649-650 [PMID: 4926950 DOI: 10.1136/bmj.1.5750.649]

9 **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]

10 **Mooiweer E**, Baars JE, Lutgens MW, Vleggaar F, van Oijen M, Siersema PD, Kuipers EJ, van der Woude CJ, Oldenburg B. Disease severity does not affect the interval between IBD diagnosis and the development of CRC: results from two large, Dutch case series. *J Crohns Colitis* 2012; **6**: 435-440 [PMID: 22398065 DOI: 10.1016/j.crohns.2011.09.014]

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 [PMID: 2215606 DOI: 10.1056/NEJM199011013231802]

12 **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]

13 **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 in-

flammatory bowel disease. *Gastroenterology* 2009; **136**: 1561-1567; quiz 1818-1819 [PMID: 19422077 DOI: 10.1053/j.gastro.2009.01.064]
14 **Lakatos L**, Mester G, Erdelyi Z, David G, Pandur T, Balogh M, Fischer S, Vargha P, Lakatos PL. Risk factors for ulcerative colitis-associated colorectal cancer in a Hungarian cohort of patients with ulcerative colitis: results of a population-based study. *Inflamm Bowel Dis* 2006; **12**: 205-211 [PMID: 16534422 DOI: 10.1097/01.MIB.0000217770.21261.ce]
15 **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]
16 **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]
17 **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]
18 **Jess T,** Horváth-Puhó E, Fallingborg J, Rasmussen HH, Jacobsen BA. Cancer Risk in Inflammatory Bowel Disease According to Patient Phenotype and Treatment: A Danish Population-Based Cohort Study. *Am J Gastroenterol* 2013 Aug 27; Epub ahead of print [PMID: 23978954 DOI: 10.1038/ajg.2013.249]
19 **Jess T**, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol* 2012; **10**: 639-645 [PMID: 22289873 DOI: 10.1016/j.cgh.2012.01.01]
20 **Beaugerie L**, Svrcek M, Seksik P, Bouvier AM, Simon T, Allez M, Brixi H, Gornet JM, Altwegg R, Beau P, Duclos B, Bourreille A, Faivre J, Peyrin-Biroulet L, Fléjou JF, Carrat F. Risk of colorectal high-grade dysplasia and cancer in a prospective observational cohort of patients with inflammatory bowel disease. *Gastroenterology* 2013; **145**: 166-175.e8 [PMID: 23541909 DOI: 10.1053/j.gastro.2013.03.044]
21 **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 [PMID: 16611269 DOI: 10.1111/j.1365-2036.2006.02854.x]
22 **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 [PMID: 16393226 DOI: 10.1111/j.1572-0241.2005.00287.x]
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 **Langholz E**. Relative or relevant risk? *Gastroenterology* 2012; **143**: e20, author reply e20-e21 [PMID: 23000225 DOI: 10.1053/j.gastro.2012.09.039]
25 **Heuschen UA**, Hinz U, Allemeyer EH, Stern J, Lucas M, Autschbach F, Herfarth C, Heuschen G. Backwash ileitis is strongly associated with colorectal carcinoma in ulcerative colitis. *Gastroenterology* 2001; **120**: 841-847 [PMID: 11231938 DOI: 10.1053/gast.2001.22434]
26 **Haskell H**, Andrews CW, Reddy SI, Dendrinos K, Farraye FA, Stucchi AF, Becker JM, Odze RD. Pathologic features and clinical significance of "backwash" ileitis in ulcerative colitis. *Am J Surg Pathol* 2005; **29**: 1472-1481 [PMID: 16224214]
27 **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]
28 **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]
29 **Baars JE**, Kuipers EJ, van Haastert M, Nicolaï JJ, Poen AC, van der Woude CJ. Age at diagnosis of inflammatory bowel disease influences early development of colorectal cancer in inflammatory bowel disease patients: a nationwide, long-term survey. *J Gastroenterol* 2012; **47**: 1308-1322 [PMID: 22627504 DOI: 10.1007/s00535-012-0603-2]
30 **Fausa O**, Schrumpf E, Elgjo K. Relationship of inflammatory bowel disease and primary sclerosing cholangitis. *Semin Liver Dis* 1991; **11**: 31-39 [PMID: 2047887 DOI: 10.1055/s-2008-1040420]
31 **Olsson R**, Danielsson A, Järnerot G, Lindström E, Lööf L, Rolny P, Rydén BO, Tysk C, Wallerstedt S. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. *Gastroenterology* 1991; **100**: 1319-1323 [PMID: 2013375]
32 **Rasmussen HH**, Fallingborg JF, Mortensen PB, Vyberg M, Tage-Jensen U, Rasmussen SN. Hepatobiliary dysfunction and primary sclerosing cholangitis in patients with Crohn's disease. *Scand J Gastroenterol* 1997; **32**: 604-610 [PMID: 9200295 DOI: 10.3109/00365529709025107]
33 **Molodecky NA**, Kareemi H, Parab R, Barkema HW, Quan H, Myers RP, Kaplan GG. Incidence of primary sclerosing cholangitis: a systematic review and meta-analysis. *Hepatology* 2011; **53**: 1590-1599 [PMID: 21351115 DOI: 10.1002/hep.24247]
34 **Broomé U**, Lindberg G, Löfberg R. Primary sclerosing cholangitis in ulcerative colitis--a risk factor for the development of dysplasia and DNA aneuploidy? *Gastroenterology* 1992; **102**: 1877-1880 [PMID: 1587406]
35 **Broomé U**, Löfberg R, Veress B, Eriksson LS. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology* 1995; **22**: 1404-1408 [PMID: 7590655]
36 **Soetikno RM**, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. *Gastrointest Endosc* 2002; **56**: 48-54 [PMID: 12085034 DOI: 10.1067/mge.2002.125367]
37 **Braden B**, Halliday J, Aryasingha S, Sharifi Y, Checchin D, Warren BF, Kitiyakara T, Travis SP, Chapman RW. Risk for colorectal neoplasia in patients with colonic Crohn's disease and concomitant primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2012; **10**: 303-308 [PMID: 22037429 DOI: 10.1016/j.cgh.2011.10.020]
38 **Thackeray EW**, Charatcharoenwitthaya P, Elfaki D, Sinakos E, Lindor KD. Colon neoplasms develop early in the course of inflammatory bowel disease and primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2011; **9**: 52-56 [PMID: 20920596 DOI: 10.1016/j.cgh.2010.09.020]
39 **Marchesa P**, Lashner BA, Lavery IC, Milsom J, Hull TL, Strong SA, Church JM, Navarro G, Fazio VW. The risk of cancer and dysplasia among ulcerative colitis patients with primary sclerosing cholangitis. *Am J Gastroenterol* 1997; **92**: 1285-1288 [PMID: 9260790]
40 **Shetty K**, Rybicki L, Brzezinski A, Carey WD, Lashner BA. The risk for cancer or dysplasia in ulcerative colitis patients with primary sclerosing cholangitis. *Am J Gastroenterol* 1999; **94**: 1643-1649 [PMID: 10364038]
41 **Sokol H**, Cosnes J, Chazouilleres O, Beaugerie L, Tiret E, Poupon R, Seksik P. Disease activity and cancer risk in inflammatory bowel disease associated with primary scle-

rosing cholangitis. *World J Gastroenterol* 2008; **14**: 3497-3503 [PMID: 18567077 DOI: 10.3748/wjg.14.3497]
42 **Claessen MM**, Lutgens MW, van Buuren HR, Oldenburg B, Stokkers PC, van der Woude CJ, Hommes DW, de Jong DJ, Dijkstra G, van Bodegraven AA, Siersema PD, Vleggaar FP. More right-sided IBD-associated colorectal cancer in patients with primary sclerosing cholangitis. *Inflamm Bowel Dis* 2009; **15**: 1331-1336 [PMID: 19229982 DOI: 10.1002/ibd.20886]
43 **Torres J**, Pineton de Chambrun G, Itzkowitz S, Sachar DB, Colombel JF. Review article: colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **34**: 497-508 [PMID: 21692821 DOI: 10.1111/j.1365-2036.2011.04753.x]
44 **Askling J**, Dickman PW, Karlén P, Broström O, Lapidus A, Löfberg R, Ekbom A. Family history as a risk factor for colorectal cancer in inflammatory bowel disease. *Gastroenterology* 2001; **120**: 1356-1362 [PMID: 11313305 DOI: 10.1053/gast.2001.24052]
45 **Rutter M,** Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, Williams C, Price A, Talbot I, Forbes A. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004; **126**: 451-459 [PMID: 14762782 DOI: 10.1053/j.gastro.2003.11.010]
46 **Nieminen U**, Jussila A, Nordling S, Mustonen H, Färkkilä MA. Inflammation and disease duration have a cumulative effect on the risk of dysplasia and carcinoma in IBD: A case-control observational study based on registry data. *Int J Cancer* 2014; **134**: 189-196 [PMID: 23797639 DOI: 10.1002/ijc.28346]
47 **Herrinton LJ**, Liu L, Fireman B, Lewis JD, Allison JE, Flowers N, Hutfless S, Velayos FS, Abramson O, Altschuler A, Perry GS. Time trends in therapies and outcomes for adult inflammatory bowel disease, Northern California, 1998-2005. *Gastroenterology* 2009; **137**: 502-511 [PMID: 19445944 DOI: 10.1053/j.gastro.2009.04.063]
48 **Castaño-Milla C**, Chaparro M, Gisbert JP. Has the risk of developing colorectal cancer in patients with ulcerative colitis been overstated? A meta-analysis. *Gastroenterology* 2013; **142**: s-251[abstract] Available from: URL: http://www.gastrojournal.org/article/S0016-5085%2812%2960944-5/abstract
49 **Jess T**, Frisch M, Simonsen J. Trends in overall and cause-specific mortality among patients with inflammatory bowel disease from 1982 to 2010. *Clin Gastroenterol Hepatol* 2013; **11**: 43-48 [PMID: 23022699 DOI: 10.1016/j.cgh.2012.09.026]
50 **Kaiser GC**, Yan F, Polk DB. Mesalamine blocks tumor necrosis factor growth inhibition and nuclear factor kappaB activation in mouse colonocytes. *Gastroenterology* 1999; **116**: 602-609 [PMID: 10029619]
51 **Velayos FS**, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. *Am J Gastroenterol* 2005; **100**: 1345-1353 [PMID: 15929768 DOI: 10.1111/j.1572-0241.2005.41442.x]
52 **Bernstein CN**, Nugent Z, Blanchard JF. 5-aminosalicylate is not chemoprophylactic for colorectal cancer in IBD: a population based study. *Am J Gastroenterol* 2011; **106**: 731-736 [PMID: 21407180 DOI: 10.1038/ajg.2011.50]
53 **Jess T**, Loftus EV, Velayos FS, Winther KV, Tremaine WJ, Zinsmeister AR, Scott Harmsen W, Langholz E, Binder V, Munkholm P, Sandborn WJ. Risk factors for colorectal neoplasia in inflammatory bowel disease: a nested case-control study from Copenhagen county, Denmark and Olmsted county, Minnesota. *Am J Gastroenterol* 2007; **102**: 829-836 [PMID: 17222314 DOI: 10.1111/j.1572-0241.2007.01070.x]
54 **Terdiman JP**, Steinbuch M, Blumentals WA, Ullman TA, Rubin DT. 5-Aminosalicylic acid therapy and the risk of colorectal cancer among patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2007; **13**: 367-371 [PMID: 17206695 DOI: 10.1002/ibd.20074]
55 **Nguyen GC**, Gulamhusein A, Bernstein CN. 5-aminosalicylic acid is not protective against colorectal cancer in inflammatory bowel disease: a meta-analysis of non-referral populations. *Am J Gastroenterol* 2012; **107**: 1298-304; quiz 1297, 1305 [PMID: 22751467 DOI: 10.1038/ajg.2012.198]
56 **van Schaik FD**, van Oijen MG, Smeets HM, van der Heijden GJ, Siersema PD, Oldenburg B. Thiopurines prevent advanced colorectal neoplasia in patients with inflammatory bowel disease. *Gut* 2012; **61**: 235-240 [PMID: 21602529 DOI: 10.1136/gut.2011.237412]
57 **Pasternak B**, Svanström H, Schmiegelow K, Jess T, Hviid A. Use of azathioprine and the risk of cancer in inflammatory bowel disease. *Am J Epidemiol* 2013; **177**: 1296-1305 [PMID: 23514635 DOI: 10.1093/aje/kws375]
58 **Armstrong RG**, West J, Card TR. Risk of cancer in inflammatory bowel disease treated with azathioprine: a UK population-based case-control study. *Am J Gastroenterol* 2010; **105**: 1604-1609 [PMID: 20104215 DOI: 10.1038/ajg.2009.745]
59 **Onizawa M**, Nagaishi T, Kanai T, Nagano K, Oshima S, Nemoto Y, Yoshioka A, Totsuka T, Okamoto R, Nakamura T, Sakamoto N, Tsuchiya K, Aoki K, Ohya K, Yagita H, Watanabe M. Signaling pathway via TNF-alpha/NF-kappaB in intestinal epithelial cells may be directly involved in colitis-associated carcinogenesis. *Am J Physiol Gastrointest Liver Physiol* 2009; **296**: G850-G859 [PMID: 19179628 DOI: 10.1152/ajpgi.00071.2008]
60 **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 [PMID: 21045815 DOI: 10.1038/ajg.2010.428]
61 **Andersen NN**, Basit S, Svanström S, Pasternak B, Caspersen S, Munkholm P, Hviis A, Jess T. Tumor necrosis factor-alpha antagonists and malignancy in inflammatory bowel disease [abstract]. *J Crohns Colitis* 2012 [DOI: 10.1016/S1873-9946(12)60451-6]

P- Reviewers: Capasso R, Gazouli M, Nielsen OH
S- Editor: Cui XM **L- Editor:** A **E- Editor:** Wu HL

百世登
Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327
4 3>
9 771007 932045