Journal of Crohn's and Colitis (2011) 5, 19–23

available at www.sciencedirect.com

Prevalence of inflammatory bowel disease related dysplasia and cancer in 1500 colonoscopies from a referral center in northwestern Greece

Konstantinos H. Katsanos [a], Paraskevi Stamou [a], Athina Tatsioni [b], Vasileios E. Tsianos [a], Stefanos Zoumbas [a], Spyridoula Kavvadia [a], Anna Giga [a], Ioannis Vagias [a], Dimitrios K. Christodoulou [a], Epameinondas V. Tsianos [a,*], on behalf of the Northwest Greece IBD Study Group [b,1]

[a] 1st Department of Internal Medicine & Hepato-Gastroenterology Unit, University Hospital of Ioannina, Greece
[b] Department of General Medicine, University Hospital of Ioannina, Greece

Received 2 March 2010; received in revised form 31 August 2010; accepted 1 September 2010

KEYWORDS
Inflammatory bowel disease;
Ulcerative colitis;
Crohn's disease;
Dysplasia;
Cancer;
Follow up

Abstract

Background and aim: To report on the prevalence of inflammatory bowel disease (IBD) related intestinal dysplasia and cancer in northwestern Greece.
Patients and methods: Single referral center retrospective study. The policy among all gastroenterologists of the area regarding medical treatment, patient follow up and bowel surveillance strategies including risk factors is the same.
Results: We analyzed 1494 colonoscopies from 696 consecutive IBD patients (494 UC). The follow up time [median, IQR] was 16 [8–23] years and the age at diagnosis was 28 [21–49] years. The number of patient years at risk was 16.219. Disease location for UC was: pancolitis 761 (59%), left sided colitis 455 (35%), and proctitis 69 (6%). Disease location for CD was: colitis 142 (66%), ilieitis 45 (22%) and ileocolitis 21 (10%). Disease activity was in remission in 1240 (83%) of them. In total, 498 (72%) patients were on mesalazine, 169(24%) on immunosuppression and 29 (4%) on biologicals. Biopsies were taken randomly in 1429 (96%) endoscopies and were targeted in 65 (4%) of them. We recorded 69 (9.4%) cases with dysplasia and 10 (1.4%) cases with intestinal cancer (9 in UC). No difference was found for dysplasia and cancer in patients who followed up for 10–20 years or for more than 20 years.

Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IC, Indeterminate colitis; IQR, interquartile range.

* Corresponding author. 1st Department of Internal Medicine, Medical School,University of Ioannina, Leoforos Stavrou Niarxou, 451 10 Ioannina, Greece. Tel.: +30 26510 07501; fax: +30 26510 07016.
E-mail address: etsianos@cc.uoi.gr (E.V. Tsianos).
[1] Northwest Greece IBD Study Group: E.V. Tsianos, K.H. Katsanos, D. Christodoulou, G. Baltayiannis, N Tzambouras, M. Papadopoulos, K. Dabos, V. Theopistos, A. Papathanasopoulos, C. Zois, P. Manousou, D. Sigounas, A. Germanopoulos, A. Vlachopoulos, K. Kistis, K. Masalas, S. Filis, P. Aggeli, T. Passas, S. Georgiou, N. Monastiriotis, S. Katsaros, A. Kogevinas, N. Kostas, D. Kourtessas.

doi:10.1016/j.crohns.2010.09.001

Conclusions: The prevalence of dysplasia and cancer is increased in UC compared to CD but the prevalence of high-grade dysplasia is comparatively low. Intestinal cancer prevalence is increasing after the first decade and then practically remains stable.

1. Introduction

Inflammatory bowel disease (IBD) is classically subdivided into ulcerative colitis and Crohn's disease, but in some instances, these diseases have overlapping clinicopathologic features. Patients with both ulcerative colitis (UC) and Crohn's disease (CD) have been reported as having an increased risk for colorectal cancer.[1,2] The concept that IBD patients have an altered risk factor for cancer is not new. In 1928, Bargen first reported an association between ulcerative colitis and colorectal cancer.[3] This association has been confirmed in many studies since then and by 1987 the causality of the association has been generally accepted and further supported.[4–6]

The risk of colorectal cancer in inflammatory bowel disease has varied widely among different studies.[7] This variation probably results because during cancer risk assessment of in IBD there is some bias: relatively low prevalence and clinically heterogeneous nature of inflammatory bowel disease in the population. In addition, there is also conflicting evidence between retrospective case-control and population-based data. Furthermore a significant number of inflammatory bowel disease patients have previously had their colon and rectum removed.

In a review of the literature in 1989 where almost all UC patients so far reported were included, there was a great variability in cumulative cancer incidence.[8] At 10 years of follow up the hospital studies a reported cancer incidence between 0.4% and 5% while in population studies cancer incidence ranged between 0.2% and 0.8%. This difference between data from hospital and population studies became even greater when comparing numbers after 30 years of follow up (cancer risk up to 40% in hospital studies and up to 13.5% in population-based studies). For total and extensive colitis, the cumulative cancer rates were even greater (up to 50% for hospital studies and 16.5% for population studies). This variation probably resulted from the smallness of the samples and the questionable validity of results from studies of selected patients group at referral centers.

Data seem to be more complicated as it has been suggested that IBD phenotype seems to be milder in South Europe comparing with IBD profile in Northern Europe and North America.[9]

In this study we aimed to describe the prevalence of IBD related dysplasia and intestinal cancer in biopsies from a series of colonoscopies from IBD patients followed in a referral center of northwestern Greece. Of interest, in this region of Greece UC is more frequent compared to CD and according to a retrospective survey in our area for the years 1982–1997, of 400 IBD patients, 334 were diagnosed with ulcerative colitis, 43 with Crohn's disease and 23 with indeterminate colitis.[10] In addition, in our area IBD generally presents with a mild profile and low prevalence of extra-intestinal manifestations.[11,12]

2. Patients and methods

2.1. Single referral center study

Northwestern Greece is a well-defined geographical region with very low rate of immigrates and a homogeneous population of nearly 500,000 inhabitants. Northwestern Greece has 6 hospitals and 22 specialized gastroenterologists. Since 1981, the University Hospital of Ioannina is an IBD referral hospital in this region with endoscopy, clinic and outpatient clinic facilities.

IBD diagnosis in all patients is based on clinical, endoscopic, histologic and radiologic criteria. The policy among all gastroenterologists of the area regarding medical treatment, patient follow up and bowel surveillance strategies in IBD patients is the same. All northwestern Greece gastroenterologists see all patients during every endoscopy but also on regular follow up and on demand in cases of emergency. The dysplasia/cancer registry has been established the same period as the IBD registry, almost thirty years ago.

2.2. Endoscopy and biopsy protocol

The policy among all gastroenterologists of the area regarding patient follow up and bowel surveillance strategies in IBD patients is the same. Patients underwent endoscopies either on scheduled or on emergency basis according to the treating physician's decision. All patients with pancolitis are invited for endoscopy after 10 years of disease. The beyond 10-year follow up endoscopy is scheduled according to a 10-year endoscopy and biopsy and also on individual basis according to patient risk factors and other co-morbidities; it is usually performed within two years time from the baseline 10-year endoscopy.

According to our policy multiple biopsies are taken in all patients either from visible lesions or in a random manner from all parts of the examined bowel in order to assess disease activity and any possible underlying dysplasia.

According to the protocol followed in the department of pathology, every biopsy is evaluated for IBD activity, for possible occurrence of any type of dysplasia (low grade, high grade) or cancer and is signed independently by two pathologists.

2.3. Dysplasia and cancer registry

A registry of dysplasia and cancer was created. This registry was possible by an overview of all endoscopy and biopsy records of our Hepato-Gastroenterology Unit and was conducted by four members of our IBD team (P.S, S.Z, S.K, and A.G).

2.3.1. Statistical analysis

Percentages were calculated for binary and categorical variables while continuous variables were described with median and interquartile range (IQR). For each binary outcome, odds ratios were calculated with 95% confidence intervals. Comparison between groups was performed using chi-square and Fisher's exact test for binary variables and Kruskal Wallis for categorical variables. A two tailed p value<0.05 was considered to be significant and for calculations we used the SPSS 13.0 (SPSS Inc., Chicago, IL) and StatXact 3.0.

3. Results

3.1. IBD cohort characteristics

All patients were either followed by our IBD outpatient clinic or were referred from Northwest Greece gastroenterologists to our hospital either for diagnosis or for a second opinion. A flow chart of patient selection is presented in Fig. 1. All these consecutive endoscopies were included in analysis. We analyzed in total the results of 1494 consecutive colonoscopies and subsequent biopsies from 696 consecutive IBD patients. The clinical and demographic characteristics of this IBD patient cohort are presented in Table 1.

As expected from our previous studies, the majority of patients were finally diagnosed with ulcerative colitis. The duration of IBD follow up (median [IQR]) was 16 years [8–23] and the age at IBD diagnosis (median [IQR]) was 28 [21–49] years.

The disease location for UC endoscopies was as follows: pancolitis 761 (59%), left sided colitis 456 (35%), and proctitis 69 (6%). The disease location for CD endoscopies was as follows: colitis 142 (66%), ileitis 45 (22%), and ileocolitis 21 (10%).

Disease activity at the time of UC and CD endoscopies was remission in 1240 (83%) and relapse in 254 (17%) of them. In total, 498 (72%) patients were on mesalazine, 169(24%) on immunosuppression and 29 (4%) on biologicals.

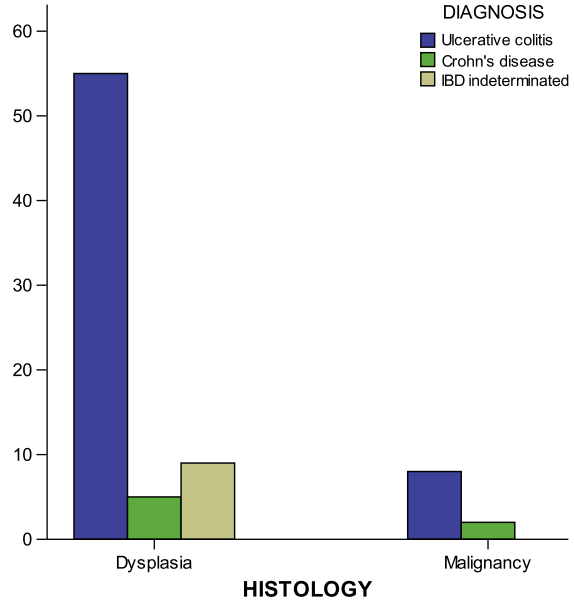

Figure 1 Prevalence of dysplasia and intestinal cancer in histology reports in IBD patients from northwestern Greece (values on the Y-axis represent absolute number of patients).

Table 1 Clinical and demographic characteristics of the Northwest Greece IBD patient cohort [UC = ulcerative colitis, CD = Crohn's disease, and IC = indeterminate colitis].

Total number of patients	696
Ulcerative colitis	474 [68%]
Crohn's disease	112 [16%]
Indeterminate colitis	110 [16%]
Follow up time/Duration of IBD in years [median, IQR]	16 [8–23]
Patient age in years [median, IQR]	33 [24–62]
The age at IBD diagnosis [median, IQR]	28 [21–49]
Males/Females	396 [57%]/300 [43%]
Total number of endoscopies	1494
Disease location per endoscopy (UC/CD/IC)	
Pancolitis	903 (60.5%)
Left sided colitis	456 (30.5%)
Proctitis	69 (5%)
Ileocolitis	21 (1%)
Ileitis	45 (3%)
Number of endoscopies per patient [median, IQR]	1 [1–3]
Number of endoscopies in UC patients	1045 (70%)
Number of endoscopies in CD patients	278 (18.5%)
Number of endoscopies in IC patients	171 (11.5%)
Number of endoscopies with dysplasia [UC/CD]	69 (9.4%) [57/12]
Number of endoscopies with cancer [UC/CD]	10 (1.4%) [9/1]

In total 62 (4%) endoscopies were performed in resected (any type of resection) bowels. Five UC patients were colectomized (total colectomy and ileoanal anastomosis) for reasons other than intestinal malignancy (i.e. disease activity) and another 3 patients underwent colectomy because of high-grade dysplasia in their bowel specimens.

No patient had a family history of inherited bowel premalignant conditions (i.e. polyposis) nor any evidence of Lynch type I or type II syndromes. None of the patients had a two-parent history of colorectal cancer and no patient had any evidence of cancer before diagnosis of IBD was made with the exception of a young male patient in whom CD and small bowel adenocarcinoma diagnosis were simultaneously made.[13] In this IBD patient cohort, no patient had concomitant PSC.

3.2. Prevalence of dysplasia and intestinal cancer

Biopsies were taken randomly in 1429 (96%) endoscopies and were targeted (taken from visible abnormalities) in 65 (4%) of them. We recorded 69 (9.4%) patient cases with evidence of dysplasia (3 high grade). Intestinal dysplasia was more prevalent in UC compared to IC and CD patients [57 UC vs 12 CD/IC] patients (Fig. 1) and more prevalent to patients with pancolitis (52 cases). The number of patient years at risk was 16.219. We recorded 10 (1.4%) patients with intestinal cancer (1 lymphoma). Intestinal cancer was more prevalent in UC compared to IC and CD patients [9 UC vs 1 CD/IC] patients (Figs. 1 and 2).

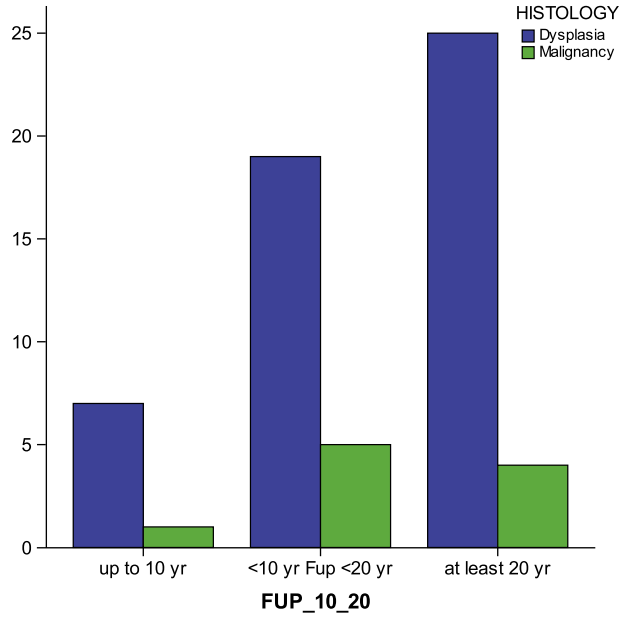

Figure 2 Follow up time related prevalence of dysplasia and intestinal cancer in histology reports in IBD patients from northwestern Greece (values on the Y-axis represent absolute number of patients).

3.3. Follow up time related prevalence of dysplasia and intestinal cancer

We recorded 15 cases of dysplasia (1 high grade) and 1 intestinal cancer at the follow up period from 0–10 years and 54 cases of dysplasia (2 high grade) and 9 intestinal cancers at follow up exceeding the 10-year period ($p = 0.02$). The age of CRC development (median, range) was 47 [38–69] years. No significant difference was found for the occurrence of dysplasia and cancer in the groups of patients that were followed up for 10–20 years or more than 20 years.

4. Discussion

We presented herein a clinical observational single referral center study on intestinal dysplasia and cancer during long-term follow up of IBD patients in northwestern Greece.

According to the results of this study the occurrence of dysplasia in IBD and especially in UC patients, is not infrequent. By contrast, the prevalence of high-grade dysplasia is comparatively low. Intestinal cancer prevalence is increasing after the first decade of follow up and is more prevalent in UC compared to CD patients.

Inflammatory bowel disease mortality and colectomy rates in Northwest Greece are remarkably low and, overall, the contribution of IBD related dysplasia and cancer to IBD mortality, is extremely low and does not practically differ from this of general NW Greece population.[14]

In 1990 Ekbom et al.[1] in order to provide more accurate estimates of risk of colorectal cancer among patients with ulcerative colitis, investigated a population-based cohort and demonstrated that the incidence of colorectal cancer in this cohort was increased. Less extensive disease at diagnosis was associated with a lower risk. Age at diagnosis was also an independent risk factor for colorectal cancer.[15,16]

In this study the prevalence of dysplasia and cancer was very low in CD patients. Until 1969 Crohn's disease was not associated with gastrointestinal cancer. At that time J.H. Jones[17] reported on 15 cases of such an association. Between 1973 and 1980 several studied have supported the theory of an increased colorectal cancer risk in Crohn's disease.[18–25] In the review of the literature by Hordijk and Shivananda[8] on risk of cancer in inflammatory bowel disease, the cumulative cancer incidence for Crohn's disease patient was again increased but there was also a marked variation. Several other studies or cases, however, have found no association between Crohn's disease cancer.[26–29]

The low prevalence of bowel cancer among our cohort of IBD patients has to be studied more extensively.[28,30] We must underline that all UC patients were on uninterrupted maintenance treatment since diagnosis. A reduced risk for colorectal cancer in ulcerative colitis patients actively treated with anti-inflammatory drugs has been reported.[29,31] It has also been reported that patients with ulcerative colitis who were not on long-term sulphasalazine or 5-aminosalicylic acid therapy were significantly more likely to develop colorectal cancer than their compliant counterparts.[32] On the other hand hepatic transplantation in ulcerative colitis patients seems to increase the risk for colorectal neoplasia.[33] So the benefits from life-long therapy in these patients have to be studied.[34–36]

In this study, in the separate analysis per decade of follow up we clearly demonstrated that a beyond 20-year follow up does not seem to influence dysplasia and cancer prevalence figures that were noticed after the 10-year follow up.

The association between ulcerative colitis and colorectal cancer has led to two major approaches to prevent the development of fatal malignancy: the prophylactic colectomy and colonoscopic surveillance[37,38] especially in patients with concomitant sclerosing cholangitis[39] and positive family history[40,41] which was not the case in this study.

Although the most effective strategy to prevent colorectal cancer in high-risk patients with ulcerative colitis is prophylactic colectomy,[42] the most widely accepted strategy is colonoscopic surveillance[43] combined with histology and immunohistopathology.[44]

Despite of its retrospective nature this study demonstrated that the prevalence of high-grade dysplasia and intestinal cancer is low in our IBD patients.

However, the very descriptive aspect of our results need to be emphasized as, ideally, in such studies we have to consider more in detail possible confounding factors, for example the higher prevalence may be confounded by the fact that UC patients referred to this tertiary center are older and/or with more active disease or more difficult to diagnose and treat. Then our prevalence estimate could be biased by "confounding by indication" – indication to perform the colonoscopy – more strongly in UC than in CD. These results are suggestive of a mild profile of IBD in our region, which may contribute in prolonging malignancy formation procedures. In addition to this, this study clearly showed that dysplasia and cancer are increasing after the first decade of diagnosis and then practically remain stable beyond the second decade of follow up. This data may prove of great importance in designing efficient follow up strategies for our patients in the future.

References

1. Ekbom A, Helmick C, Zack M, Adam H-O. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. *Lancet* 1990;**11**:357–9.
2. Denroede GJ, Taylor WF, Sauer WG, Jackman RJ, Stickler GB. Cancer risk and life expectancy of children with ulcerative colitis. *N Engl J Med* 1971;**285**:17–21.
3. Bargen JA. Chronic ulcerative colitis associated with malignant disease. *Arch Surg* 1928;**17**:561–76.
4. Summers RW. Is the risk of cancer in ulcerative colitis increasing. *Am J Gastroenterol* 1995;**90**:337.
5. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001 Apr;**48**(4):526–35.
6. Travis SPL. Insurance risks for patients with ulcerative colitis or Crohn's disease. *Alim Pharmacol Ther* 1997;**11**:51–9.
7. Palli D, Trallori G, Saieva C, Tarantino O, Edili E, D'Albasio G, et al. General and cancer specific mortality of a population based cohort of patients with inflammatory bowel disease: the Florence study. *Gut* 1998;**42**:175–9.
8. Hordijk ML, Shivananda S. Risk of cancer in inflammatory bowel disease. Why are the results in the reviewed literature so varied. *Scand J Gastroenterol* 1989;**24**:70–4.
9. Wolters FL, Russel MG, Sijbrandij J, Ambergen T, Odes S, Riis L, et al. On behalf of the European Collaborative Study Group on Inflammatory Bowel D: phenotype at diagnosis predicts recurrence rates in crohn's disease. *Gut* 2006;**55**:1124–30.
10. Tsianos EV, Katsanos KH, Christodoulou D, Dimoliatis I, Kogevinas A. Northwest Greece Inflammatory Bowel Disease Study Group. Continuing low incidence of Crohn's disease in Northwest Greece. *Dig Liver Dis* 2003;**35**:99–103.
11. Christodoulou DK, Katsanos KH, Kitsanou M, Stergiopoulou C, Hatzis J, Tsianos EV. Frequency of extraintestinal manifestations in patients with inflammatory bowel disease in Northwest Greece and review of the literature. *Dig Liver Dis* 2002;**34**:781–6.
12. Tsianos EV, Merkouropoulos M, Massalas K, Dalekos G, Logan RF. Incidence of inflammatory bowel disease in Northwest Greece; rarity of Crohn's disease in an area where ulcerative colitis is common. *Gut* 1994;**35**:369–72.
13. Christodoulou D, Skopelitou AS, Katsanos KH, Katsios C, Agnantis N, Price A, et al. Small bowel adenocarcinoma presenting as a first manifestation of Crohn's disease; report of a case and literature review. *Eur J Gastroenterol Hepatol* 2002;**14**:805–10.
14. Viscido A, Bagnardi V, Sturniolo GC, Annese V, Frieri G, D'Arienzo A, et al. Survival and causes of death in Italian patients with ulcerative colitis. A GISC nationwide study. *Dig Liver Dis* 2001;**33**:686–92.
15. Blomqvist P, Ekbom A. Inflammatory bowel diseases: health care and costs in Sweden in 1994. *Scand J Gastroenterol* 1997;**32**:1134–9.
16. Tsianos EV. Risk of cancer in inflammatory bowel disease. *Eur J Int Med* 2000;**11**:75–8.
17. Jones JH. Colonic cancer and Crohn's disease. *Gut* 1969;**10**:651–4.
18. Greenstein AJ, Gennuso R, Sachar DB, Heimann T, Smith H, Janowitz HD, et al. Extraintestinal cancers in inflammatory bowel disease. *Cancer* 1985;**56**:2914–21.
19. Solomon MJ, Schnitzler M. Cancer and inflammatory bowel disease. Bias, epidemiology, surveillance, and treatment. *World J Surg* 1998;**22**:352–8.
20. Bansal P, Sonnenberg A. Risk factors of colorectal cancer in inflammatory bowel disease. *Am J Gastroenterol* 1996;**91**:44–8.
21. Langholz E, Munkholm P, Krasilnikoff PA, Binder V. Inflammatory bowel diseases with onset in childhood. *Scand J Gastroenterol* 1977;**32**:139–47.
22. Lashner BA. Risk factors for small bowel cancer in Crohn's disease. *Dig Dis Sci* 1992;**37**:1179–84.
23. Ky A, Sohn N, Weinstein MA, Korelitz BI. Carcinoma arising in anorectal fistulas of Crohn' disease. *Dis Colon Rect* 1998;**41**:992–6.
24. Munkholm P, Langholz E, Davidsen M, Binder V. Intestinal cancer risk and mortality in patients with Crohn's disease. *Gastroenterology* 1993;**105**:1716–23.
25. Lindgren A, Wallerstedt S, Olson R. Prevalence of Crohn's disease and simultaneous occurence of extraintestinal complications and cancer. *Scand J Gastroenterol* 1996;**31**:74–8.
26. Langholz E, Munkholm P, Krasilnikoff PA, Binder V. Inflammatory bowel diseases with onset in childhood. Clinical features, morbidity and mortality in a regional cohort. *Scand J Gastroenterol* 1997;**32**:139–47.
27. Gyde SN, Prior P, Macartney JC, Thompson H, Waterhouse JAH, Allan RN. Malignancy in Crohn's disease. *Gut* 1980;**21**:1024–9.
28. Tsianos EV. The risk of cancer in inflammatory bowel disease. *Eur J Int Med* 2000;**11**:75–8.
29. Katsanos KH, Christodoulou DK, Zioga A, Tsianos EV. Cutaneous nevi pigmentosus during infliximab therapy in a patient with Crohn's disease: fallacy or coincidence? *Inflamm Bowel Dis* 2003;**9**:279.
30. Greenstein AJ. Cancer in inflammatory bowel disease. *Mt Sinai J Med* 2000;**67**:227–40.
31. Itzkowitz SH. Cancer prevention in patients with inflammatory bowel disease. *Gastroenterol Clin North Am* 2002;**31**:1133–44.
32. Moody GA, Jayanthi V, Probert CSJ, Mac Kay H, Mayberry JF. Long-term therapy with sulphasalazine protects against colorectal cancer in ulcerative colitis: a retrospective study of colorectal cancer risk and compliance with treatment in Leicestershire. *Eur J Gastroenterol Hepatol* 1996;**8**:1179–83.
33. Christodoulou DK, Katsanos KH, Baltayannis G, Tzabouras N, Tsianos EV. A report on efficacy and safety of azathioprine in a group of inflammatory bowel disease patients in Northwest Greece. *Hepatogastroenterology* 2003;**50**:1021–4.
34. van der Eijk I, Stockbrugger RW, Russel MG. Influence of quality of care on quality of life in inflammatory bowel disease:literature review and studies planned. *Eur J Int Med* 2000;**11**:228–34.
35. Biasco G, Rossini FP, Hakim R, Brandi G, Di Battista M, Di Febo G, et al. Cancer surveillance in ulcerative colitis: critical analysis of long term prospective programme. *Dig liver Dis* 2002;**34**:339–42.
36. Moum B. Medical treatment:does it influence the natural course of inflammatory bowel disease? *Eur J Int Med* 2000;**11**:197–203.
37. Eaden JA, Mayberry JF. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. *Gut* 2002;**51**:V10–2.
38. Sharan R, Schoen RE. Cancer in inflammatory bowel disease. An evidence-based analysis and guide for physicians and patients. *Gastroenterol Cin North Am* 2002;**31**:237–54.
39. Kornfeld D, Ekbom A, Ihre T. Is there an excess risk for colorectal cancer in patients with ulcerative colitis and concomitant primary sclerosing cholangitis? A population based study. *Gut* 1997;**41**:522–5.
40. Nuako KW, Ahlquist DA, Mahoney DW, Schaid DJ, Siems DM, Lindor NM. Familial predisposition for colorectal cancer in chronic ulcerative colitis: a case-control study. *Gastroenterology* 1998;**115**:1079–83.
41. Askling J, Dickman PW, Karlén P, Broström O, Lapidus A, Löfberg R, et al. Family history as a risk factor for colorectal cancer in inflammatory bowel disease. *Gastroenterology* 2001;**120**:1356–62.
42. Rhodes JM. Surveillance for colitis-associated cancer: we cannot stop now. *Dig Liver Dis* 2002;**34**:319–21.
43. Karlen P, Kornfeld D, Brostrom O, Lofberg R, Persson P-G, Ekbom A. Is colonoscopic surveillance reducing colorectal cancer mortality in ulcerative colitis? A population based case control study. *Gut* 1998;**42**:711–4.
44. Skopelitou A, Katsanos KH, Michail M, Mitselou A, Tsianos EV. Immunohistochemical expression of FHIT gene product in inflammatory bowel disease;significance and correlation with clinicopathological data. *Eur J Gastroenterol Hepatol* 2003:665–73.