

Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis and the risk of developing malignancies. A large prospective study

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Acta Gastroenterol Latinoam 2008;38:26-33

Summary

Background/aim: primary sclerosing cholangitis (PSC) is associated with ulcerative colitis (UC) and seems to be a risk factor for colon cancer. However, taking into account that no data are available in South American population, we analyzed the prevalence of PSC in 1.333 patients with UC and the risk for developing colon cancer. **Material:** patients with persistent increases of alkaline phosphatase were studied by cholangiography and liver biopsy. To assess the risk of colon cancer, each patient with PSC and UC was matched with two control patients with UC without PSC of the same age, gender, extent and duration of UC. **Results:** the whole prevalence of PSC was 2.9% (39 patients) reaching 6.2% in extensive colitis. Seven (18 %) out of 39 patients with PSC developed colorectal carcinoma compared with 2 out of 78 (2.6%) in the control group ($p=0.006$). The cumulative risk of colorectal carcinoma was 11% and 18% after 10 and 20 years in the PSC group compared with 2% and 7% in the control group, respectively ($p=0.002$). **Conclusion:** this is the first prospective study performed in Latin America showing that the prevalence of PSC in patients with UC is similar to that reported in the Anglo-Saxon population. Patients with UC and PSC have a high risk of colorectal cancer.

Key words: Chronic biliary disease; Colorectal cancer; Inflammatory bowel disease.

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Prevalencia de colangitis esclerosante primaria en pacientes con colitis ulcerosa y el riesgo de desarrollar malignidades. Un extenso estudio prospectivo

Resumen

Introducción/objetivos: la colangitis esclerosante primaria (CEP) se asocia a colitis ulcerosa (CU) y parece ser un factor de riesgo para cáncer de colon. Sin embargo, teniendo en cuenta que no existen datos disponibles en población de Sudamérica, nosotros analizamos la prevalencia de CEP en 1.333 pacientes con CU y el riesgo de desarrollar cáncer de colon. **Material:** los pacientes con fosfatasa alcalina persistentemente elevada fueron estudiados con colangiografía y biopsia hepática. Para determinar el riesgo de cáncer de colon cada paciente con CEP y CU fueron apareados con dos pacientes controles con CU sin CEP de la misma edad, sexo, extensión y duración de la CU. **Resultados:** la prevalencia total de CEP fue de 2.9% (39 pacientes), alcanzando una prevalencia del 6.2% en colitis extensa. Siete (18%) de 39 pacientes con CEP desarrollaron cáncer colorectal comparado con 2 de 78 en el grupo control ($p=0.006$). El riesgo acumulado de cáncer colorectal fue 11 y 18% después de 10 y 20 años en el grupo con CEP comparado con 2 y 7% en el grupo control, respectivamente ($p=0.002$). **Conclusión:** este es el primer estudio prospectivo realizado en Latinoamérica mostrando que la prevalencia de CEP en pacientes con CU es similar a la reportada en población anglosajona. Los pacientes con CU y CEP tienen un alto riesgo de cáncer colorectal.

Palabras claves: La colangitis esclerosante primaria, prevalencia, colitis ulcerosa.

Primary sclerosing cholangitis is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the biliary ducts and is associated with UC in about 70-80 % of cases. Prevalence of PSC in patients with UC has been reported to range between 2.5 and 5.6% in series from Scandinavia, England and North America.¹⁻⁶ However, no data are available regarding the prevalence of PSC in patients with ulcerative colitis in South America.

Patients with PSC have a variable clinical course but most of them develop a progressive disease leading to liver transplantation or death by liver failure. In addition, PSC patients have an increased risk of developing cholangiocarcinoma.^{7,8} Recently, several studies have reviewed the role of PSC in the development of colorectal cancer in patients with UC.⁹⁻¹⁷ Although the results of these studies are controversial, critical examination of these data suggests that colorectal cancer is more frequent in patients with UC and PSC than in patients with UC without PSC.

We report the result of a study conducted in a single center to analyze: a) the prevalence of PSC in a large series of argentine patients with ulcerative colitis by means a prospective protocol carried out in our Center to detect and follow the cases with the association UC and PSC and b) the absolute cumulative risk of developing colorectal cancer in patients with PSC and UC compared to patients with UC without PSC.

Patients and methods

We included 1333 patients with ulcerative colitis treated at the Hospital de Gastroenterología Dr Bonorino Udaondo in Buenos Aires from January 1990 to September 2003. There were 710 women and 623 men, including 613 patients (46%) with extensive colitis, 413 (31%) with left-side colitis and 307 (23%) with proctitis. Mean age was 40.4 years (range 13-91). All of them had 2 different liver tests determinations at least 2 months apart. Ulcerative colitis diagnosis was based on colonoscopic features and changes in rectocolonic biopsies compatible with UC. The extent of colonic disease was defined by endoscopic appearance and by maximal extent during follow-up, using similar classification system to that proposed by the Working Party of the 2005 Montreal World Congress of Gastroenterology.¹⁸

Extensive colitis was defined if the disease progressed beyond the splenic flexure; left-side colitis was defined when the disease did not reach beyond the splenic flexure and proctitis if the disease involved the rectum up to 15 cm from the anus. Duration of colitis was calculated from the time of diagnosis (estimated by the first presentation of signs and symptoms compatible with UC or the date of endoscopic and histological findings compatible with UC) until death, proctocolectomy, or until last total colonoscopy with biopsies performed in our Center before September 2003. Patients with extensive and left side colitis either diagnosed in our Center or referred were encouraged to undergo annual colonoscopy. All patients included had been studied by at least a colonoscopy in our Center. Total colonoscopies were carried out taken usually 1 to 2 biopsy samples per colorectal segment from areas without abnormalities suspicious for malignancy. These evaluations were performed as part of the diagnostic and treatment procedure to study the severity and extent of inflammation or to assess mucosal healing. It was similar to the procedure used in a published cohort study from Copenhagen County where the cancer risk in UC was also investigated¹⁹ Therefore, systematic extensive sampling method with 33 random biopsies as was proposed by Rubin et al.²⁰ for regular surveillance colonoscopy has not been performed as a protocol basis in our study. However, as a routine practice of colonoscopists with expertise in IBD in our Center, additional biopsies were taken in all patients from endoscopically visible suspicious lesions (polypoid elevated or slightly raised or finely nodular). Therefore, targeted biopsies, analogous to recent studies that showed its value in UC surveillance, were performed.²¹⁻²²

All surgical specimens from colectomy were systematically studied.

Patients with persistent increase of alkaline phosphatase (>1.5 fold above normal values in at least two liver tests performed eight weeks apart) underwent endoscopic retrograde cholangio-pancreatography (ERCP) or magnetic resonance cholangiography (MRC). Liver tests included ALT, AST, ALP, serum bilirubin, prothrombine time and serum albumin were performed, except during periods of exacerbation of colitis. Liver biopsy was performed in almost all patients with cholangiographic diagnosis of PSC for disease staging. Liver biopsy was also performed in all patients with persistent alkaline phosphatase

increase but without characteristic PSC findings on cholangiography. Diagnosis of PSC was based on a combination of cholangiographic and histological criteria. Cholangiographic criteria included the presence of strictures and dilatations of the intra or extrahepatic biliary ducts. Histological findings compatible with PSC were ductal damage, concentric periductal fibrosis or pericholangitis.

The mean follow-up of colonic disease was 8.4 ± 8.5 years.

Each patient with PSC and UC was matched with two control patients with UC without PSC to assess the risk of colon cancer. Patients and controls were randomly selected and matched for age and gender and duration and extension of ulcerative colitis. Patients who had undergone colectomy prior to a diagnosis of PSC or previously to be referred were excluded of this study, as well as those cases referred for colorectal neoplasia.

Protocol was approved by the Ethic Committee of Gastroenterology Hospital Bonorino Udaondo. Statistical Analysis

Comparisons between groups were performed using the Student's t test for quantitative data and the X² test with Yates correction or Fisher's exact test for qualitative data. All results are expressed as mean \pm SD. Cumulative risk of colorectal life development in PSC and controls were calculated by Kaplan–Meier life table analysis and difference estimated by Log Rank test.

Results

Clinical presentation of PSC

From the whole number of patients, thirty-nine (14 female) met the criteria for the diagnosis of PSC (2.9%). However, the prevalence of PSC reached 6.2% in patients with extensive colitis.

The mean age at diagnosis of PSC was 30.8 ± 12.4 years. The mean time from the beginning of UC to the diagnosis of PSC was 10.1 ± 9.1 years and the follow-up of patients from the diagnosis of PSC was 4.9 ± 4.7 years. Diagnosis of PSC was performed by cholangiography in 37 cases. It was defined as extrahepatic in 10 patients (26%), intra and extrahepatic in 20 (51%) and intra-hepatic in 7 (18%). Two patients (5%) had normal cholangiography with histological findings compatible with PSC and diagnosis of small ducts PSC was made. Three patients with extrahepatic compromise had associated autoimmune chronic pancreatitis.

Patients with PSC had a significant higher extension of ulcerative colitis compared to patients without PSC: 94% versus 44% ($p < 0.0001$) respectively.

In addition, the beginning of UC in PSC patients was earlier than in patients without PSC. The mean age in patients with PSC was 20.8 ± 11.3 (range 3-59) versus 32.3 ± 14.6 years (range 12-60) in patients without PSC ($p < 0.0001$). (Figura 1)

While 53% of PSC patients began UC within the two first decades of life, only 19% of patients without PSC started the disease in this period. (Figura 2)

Seventeen patients (44%) were asymptomatic at the diagnosis of PSC. Jaundice and pruritus were the most frequent symptoms in the remainders. Five patients showed some evidence of late stage PSC with splenomegaly, ascites and gastrointestinal bleeding for variceal rupture.

Sixty-one patients had transient increases in transaminases with normal ALP, but only in twelve of them these high levels remained for more than 6 months. In these patients liver biopsies showed fatty liver in 8 patients, chronic hepatitis related to HCV in 2 and non-specific changes in 2 cases.

Four patients were referred to liver transplantation. It was performed in only three because the fourth patient died on the waiting list due to colorectal carcinoma. An incidental cholangiocarcinoma was found in one of the explanted liver.

Eight patients (20%) died during follow-up. Causes of death were cholangiocarcinoma ($n=2$), liver failure ($n=2$), colorectal carcinoma, ovarian cancer, sepsis due to pouchitis and mesenteric arterial thrombosis in each one.

Clinical presentation of UC

Twelve patients with PSC (37.5%) and 23 out of 64 (35.9%) matched controls with UC without PSC underwent colectomy due to the severity of the UC ($p = ns$).

When the total casuistic is analysed, in spite of no different rates of colectomy and /or immunosuppression in both groups, the requirement of some of these procedures due to aggressive disease activity was earlier in the UC only group (median [IQ range]): 3.4 years [1.4-8] than in the UC with PSC: 12 years [5-15]).

Liver histology and biochemical data

Liver biopsy was performed in 32 patients (82%) and 11 (34%) of them had cirrhosis. Two patients had small bile ducts PSC defined by normal cholangiography and histological changes compatible with PSC. The most significant biochemical data

Figure 1. Mean age at ulcerative colitis onset in patients with primary sclerosing cholangitis and without primary sclerosing cholangitis. The difference between both groups were statistically significant ($p < 0.0001$).

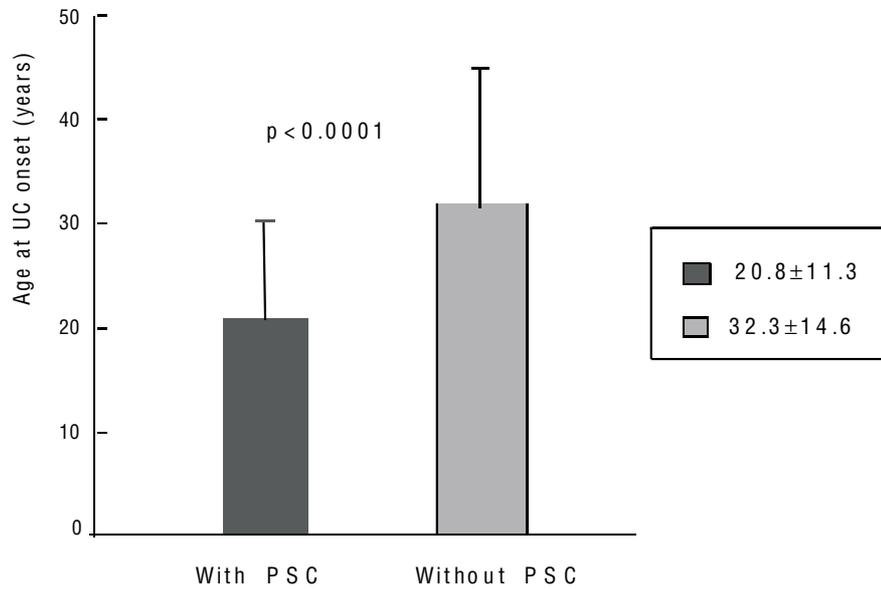
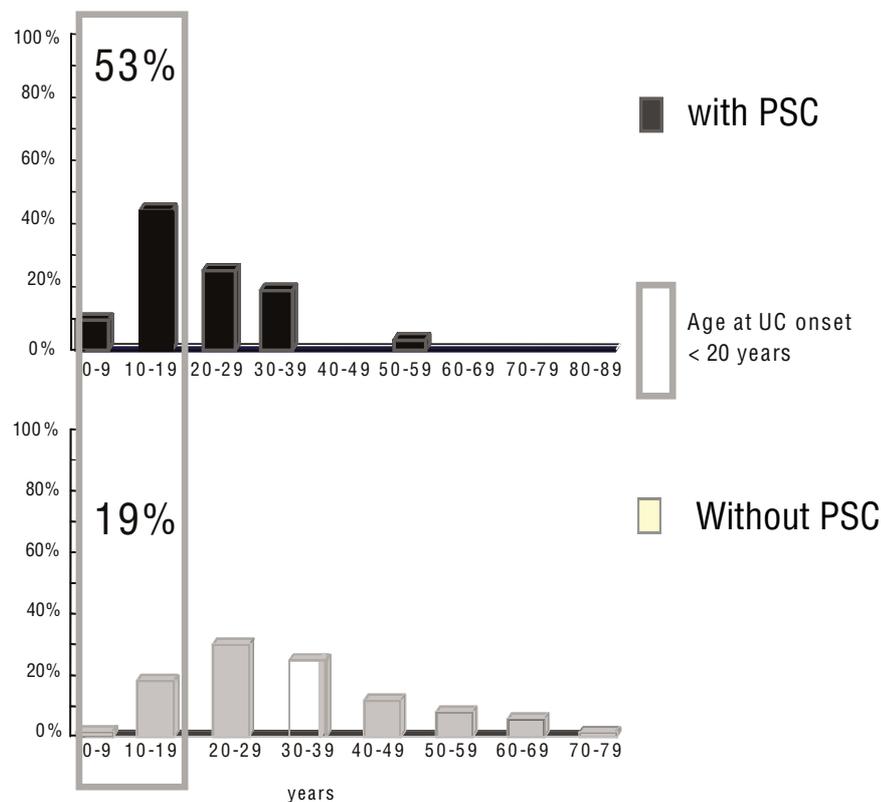


Figure 2. Age by decade at ulcerative colitis onset in patients with primary sclerosing cholangitis (PSC) and without primary sclerosing cholangitis. Whereas 53% of patients with PSC started before 20 years old, only 19% of patients without PSC started before 20. The difference was statistically significant ($p < 0.0026$).



from PSC patients included alkaline phosphatase increase in all patients, moderate increase in ALT and AST in 24 patients and high serum bilirubin level in 18 patients. Perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) were evaluated in twenty-five patients. Seventeen of them (68%) were positive.

Risk of malignancies

Colorectal cancer

As we described above, UC patients with PSC were matched with two UC controls without PSC in order to evaluate the risk of colorectal cancer. Seven UC patients with PSC developed colorectal carcinoma compared with only two patients in the control group. ($p=0.006$).

Confirmatory histology was available before surgery in six patients. In a case of a UC with a double surgical indication (treatment refractoriness and a 3 cm polipoid lesion DALM (dysplasia-associated lesion or mass) a high-degree dysplasia was detected prior to surgery and CRC was confirmed, as expected, in the analysis of colectomy specimen.

None of the patients with PSC and colorectal cancer had previously a liver transplantation. The absolute cumulative risk of developing colorectal carcinoma in the UC / PSC group was 11% and 18% after 10 and 20 years of disease, respectively. In

the UC without PSC group, the corresponding risk was 2% and 7% respectively ($p=0.002$). (Figura 3)

Other malignancies

Five UC patients with PSC developed other malignancies: three of them had cholangiocarcinoma (one was found in the explanted liver) and none of them was associated to colorectal neoplasia; one patient developed ovarian cancer and another gastric adenocarcinoma and colorectal cancer. No malignancies were found in the control group.

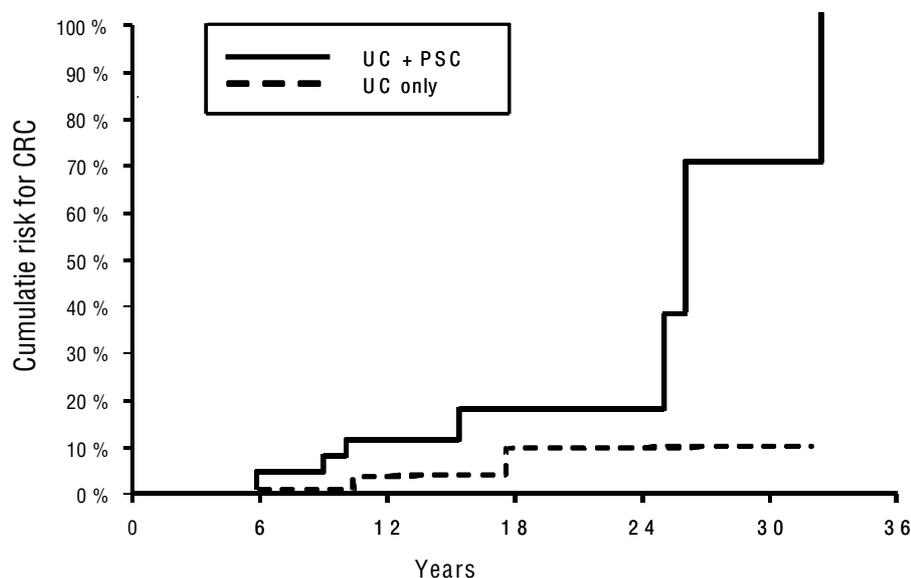
Discussion

Primary sclerosing cholangitis has been considered to be a rare disease associated with inflammatory bowel disease, mainly ulcerative colitis. The current study is, to the best of our knowledge, the first one performed in South America to assess the prevalence of primary sclerosing cholangitis in a large series of patients with ulcerative colitis.

Studies from Scandinavian countries, England and North America have shown that 2 to 3.7% of patients with ulcerative colitis have, or will have, primary sclerosing cholangitis.¹⁻⁶

Interestingly, the prevalence of PSC in the current study was similar to that observed in series from those countries.

Figure 3. Survival curves showing the time (years) until colorectal cancer of UC in patients with UC only and UC plus primary sclerosing cholangitis. Cumulative risk of developing colorectal cancer and statistical differences were estimated by Kaplan-Meierlife table analysis and log-rank test ($p=0.002$).



In a similar, but retrospective study, performed in the general population in five areas of Sweden, estimated in about 1 million inhabitants, 1500 individuals were identified as presenting ulcerative colitis. Patients with high alkaline phosphatase levels were studied by endoscopic cholangiography and PSC was diagnosed in 55 patients (3.7%).¹ In another study, 29 (2.3%) of 1274 patients with UC studied in the county of Stockholm developed primary sclerosing cholangitis.² In addition, the prevalence of PSC was 2% in 534 patients with UC in Finland³ and 3.6% in 305 patients with UC at the Aalborg Hospital in Denmark.⁴ A study from England showed a prevalence of 2.4% of PSC in patients with UC⁵ while in North America the prevalence of PSC was 3% in men with UC in a population-based study of the University of Manitoba, Canada.⁶

Furthermore, as it was mentioned in previous studies, 94% of our PSC patients had extensive colitis. It is remarkable that our prevalence of PSC in extensive colitis is 6%, similar to the 5.5% rate reported in a population study performed in Sweden.¹

A serum alkaline phosphatase increase appears to be a good marker to select patients to perform ERCP or MRC for the diagnosis of PSC. Although our prevalence rates may underestimate the true prevalence of PSC based on the fact that alkaline phosphatase would be normal in some patients with PSC, this situation is very unusual.²³ Taking into account that we did not perform ECRP to patients with normal ALP, it is possible that a small number of patients with PSC were misdiagnosed. Most of our patients were first studied by endoscopic cholangiography. However, a recent study showed that MRC could be the initial procedure to identify patients with PSC.²⁴

Another important finding of the current study was the high number of asymptomatic patients. Forty-one percent of the PSC patients were diagnosed in the asymptomatic period and some of them had advanced liver disease in the liver biopsy. To date, no effective treatment for PSC has been found.²⁵ It is unknown, if an early diagnosis and treatment could improve the prognosis of these patients. Preliminary studies suggested that high doses of ursodeoxycholic acid can improve histology, biochemistry and prognosis of patients with PSC.^{26,27} However, a recent study performed in 219 patients with PSC randomized to receive 17 to 23 mg/kg body weight per day of ursodeoxycholic acid

or placebo for 5 years, did not find any difference between groups regarding survival, prevention of cholangiocarcinoma or quality of life.²⁸

Following the study by Broome and colleagues,²⁹ several studies have been conducted to answer if primary sclerosing cholangitis associated with ulcerative colitis increases the risk of colorectal cancer. Despite the fact that most of these studies suggest a positive answer, these clinical studies seem to have different methodological problems. The control group appears to be one of the most relevant problems. In this sense, it is well-known that risk factors for malignant transformation are the duration and the extent of ulcerative colitis. Our matched control group with ulcerative colitis without PSC was carefully randomized for each patient with PSC with similar extension and duration of ulcerative colitis.

Furthermore, cumulative incidence of colorectal cancer in patients with ulcerative colitis without PSC in different series ranges between 2 and 4% at 10 years of follow-up, similar to that found in the current study.¹²⁻¹⁴

The risk of colorectal cancer as well as the probability of developing this complication was significantly higher in patients with UC and PSC. Our data are similar to those presented by Broome et al.¹⁴ At 10 years of follow-up, the probability of developing colorectal cancer was 9% in the study from Broome and 11% in our study, whereas at 20 years the probability was 31% and 18% respectively.

We have not included in this paper information about dysplasia in flat mucosa due to a potential drawback in our study method to detect dysplasia. We have not taken 33 non-targeted biopsies, which has been published as the estimated number of specimens along the colon to detect dysplasia with 90% confidence.²⁰ However the more accuracy method to detect dysplasia, is currently controversial. Two recent studies have shown that targeted biopsies of macroscopic lesions during surveillance colonoscopy are superior in the detection of neoplasia (dysplasia and/or cancer) compared with current standard techniques of random segmental biopsies every 10 cm throughout the length of the colon.^{21,22} As far as we know efficacy of endoscopic techniques potentially better for early detection of cancer or dysplasia as dye-spray targeted biopsies were not still reported in the follow-up of UC patients with PSC. Follow-up of an infrequent disorder through a large period involves imperfect patient's adherence and modifications in the consensued criteria for disease

control and management. Similarly to our study, the results of a cohort investigated at the Mayo Clinic and published in *Gastroenterology*, were limited to provide information about relative risk of colorectal cancer in PSC but no about dysplasia in prevention of a possible weakness in the surveillance procedure.¹² Also likewise our reporting, in a population-based cohort of 1160 patients with UC from Demark, the colonoscopy procedures used to inform colorectal cancer risk have been performed only as part of the diagnostic therapeutic regimen and not for the purpose of cancer surveillance, on the hypothesis that this policy theoretically may allow a possible accumulation of patients to detected colonic cancer.¹⁹ We think that, in spite of possible methodology limitations due to the lack of entirely homogeneous procedures for data collection, it is important that the risk of colorectal cancer in diverse predisposing diseases be reported worldwide.

In conclusion, the results of the first investigation performed in South America showed that the prevalence of PSC in patients with UC is similar to that reported in North-Western countries. Finally, another important fact shown in this study is that the risk of developing colorectal cancer in patients with PSC and UC seems to be independent of geographical differences.

References

- Olsson R, Danielsson A, Jarnerot G, et al. Prevalence of Primary Sclerosing Cholangitis in Patients with Ulcerative Colitis. *Gastroenterology* 1991;100:1319-1313.
- Broome U, Glaumann H, Hellers G, et al. Liver disease in ulcerative colitis: an epidemiological and follow up study in the county of Stockholm. *Gut* 1994;35:84-89.
- Aitola P, Karvonen AL, Matikainen M. Prevalence of hepatobiliary dysfunction in patients with ulcerative colitis. *Ann Chir Gynaecol* 1994;83:275-278.
- Rasmussen H, Fallingborg J, Mortensen P, et al. Primary sclerosing cholangitis in patients with ulcerative colitis. *Scand J Gastroenterol* 1992;27:732-736.
- Shephard H, Selby W, Chapman R, et al. Ulcerative colitis and persistent liver dysfunction. *Q J Med* 1983;52:503-513.
- Bernstein CN, Blanchard JF, Rawsthorne P, et al. The prevalence of extra intestinal diseases in inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2001;96:1116-1122.
- Leidenius M, Hockerstedt K, Broome U, et al. Hepatobiliary carcinoma in primary sclerosing cholangitis: a case control study. *J Hepatol* 2001;34:792-798.
- Rosen C, Nagorney D, Wiesner R, et al. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Ann Surg* 1991;213:21-25.
- Soetikno R, Lin O, Heindenreich P, et al. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis. A meta analysis. *Gastrointest Endosc* 2002;56:48-54.
- Jayaram H, Satsangi J, Chapman R. Increased colorectal neoplasia in chronic ulcerative colitis complicated by primary sclerosing cholangitis: fact or fiction? *Gut* 2001;48:430-434.
- Shety K, Rybicki L, Brzezinski A, et al. The risk for cancer or dysplasia in ulcerative colitis patients with primary sclerosing cholangitis. *Am J Gastroenterol* 1999;94:1643-1649.
- Loftus E, Sandborn W, Tremaine W, et al. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis. *Gastroenterology* 1996;110:432-440.
- Marchesa P, Lashner B, Lavery J, et al. The risk of cancer and dysplasia among ulcerative colitis patients with primary sclerosing cholangitis. *Am J Gastroenterol* 1977;92:1285-1288.
- Broome U, Lofberg R, Veress B, et al. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology* 1995;22:1404-1408.
- Brentnall T, Haggitt R, Rabinovich P, et al. Risk and natural history of colonic neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis. *Gastroenterology* 1996;110:331-338.
- Eaden J, Mayberry J. Colorectal cancer complicating ulcerative colitis: a review. *Am J Gastroenterol* 2000;95:2710-2719.
- Nuako K, Ahlquist D, Sandborn W. Primary sclerosing cholangitis and colorectal carcinoma in patients with chronic ulcerative colitis: a case-control study. *Cancer* 1998;82:822-826.
- Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. *Can J Gastroenterol*. 2005;19:5-36.
- 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.
- Rubin CE, Haggitt RC, Burmer GC, Brentnall TA, Stevens AC, Levine DS, et al. DNA aneuploidy in colonic biopsies. predicts future development of dysplasia in ulcerative colitis. *Gastroenterology* 1992;103:1611-1620.
- Rutter MD, Saunders BP, Wilkinson KH, Kamm MA, Williams CB, Forbes Most dysplasia in ulcerative colitis is visible at colonoscopy. *A Gastrointest Endosc* 2004;60:334-339.
- Marion JF, Wayne JD, Present DH, Israel Y, Bodian C, Harpaz N, Chapman M, Abreu MT, Ullman TA, Aisenberg J, Mayer L. Methylene Blue Dye-Spray Targeted Biopsies are Superior To Standard Colonoscopic Surveillance Biopsies For Detecting Dysplasia In Patients Ulcerative and Crohn's Colitis: A Prospective Endoscopic Trial. *Gastroenterology* 2007;132:A76

23. Balasubramaniam K, Wiesner R, LaRusso N. Primary sclerosing cholangitis with normal serum alkaline phosphatase activity. *Gastroenterology* 1988;95:1395-1398.
24. Angulo P, Pearce D, Johnson D, et al. Magnetic resonance cholangiography in patients with biliary disease: its role in primary sclerosing cholangitis. *J Hepatol* 2000;33:520-527.
25. Lindor K, for the Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. Ursodiol for Primary Sclerosing Cholangitis. *N Engl J Med* 1997;336:691-695.
26. Harnois D, Angulo P, Jorgensen R, et al. High-dose Ursodeoxycholic acid as Treatment for Patients With Primary Sclerosing Cholangitis. *Am J Gastroenterol* 2001;96:1558-1562.
27. Mitchell S, Bansi D, Hunt N, et al. A preliminary Trial of High-Dose Ursodeoxycholic acid in Primary Sclerosing Cholangitis. *Gastroenterology* 2001;121:900-907.
28. Olsson R, Boberg K, de Muckadell O, et al. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. *Gastroenterology* 2005;129:1464-1472.
29. Broome U, Lindberg G, Lofberg R. Primary sclerosing cholangitis in ulcerative colitis- a risk factor for the development of dysplasia and DNA aneuploidy?. *Gastroenterology* 1992;102:1877-1880.