More Right-sided IBD-associated Colorectal Cancer in Patients with Primary Sclerosing Cholangitis

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Background: Patients with inflammatory bowel disease (IBD) and concurrent primary sclerosing cholangitis (PSC) have a higher risk of developing colorectal cancer (CRC) than IBD patients without PSC. The aim of this study was to investigate potential clinical differences between patients with CRC in IBD and those with CRC in IBD and PSC, as this may lead to improved knowledge of underlying pathophysiological mechanisms of CRC development.

Methods: The retrospective study from 1980–2006 involved 7 Dutch university medical centers. Clinical data were retrieved from cases identified using the national pathology database (PALGA).

Results: In total, 27 IBD-CRC patients with PSC (70% male) and 127 IBD-CRC patients without PSC (59% male) were included. CRC-related mortality was not different between groups (30% versus 19%, $P = 0.32$); however, survival for cases with PSC after diagnosing CRC was lower (5-year survival: 40% versus 75% $P = 0.001$). Right-sided tumors were more prevalent in the PSC group (67% versus 36%, $P = 0.006$); adjusted for age, sex, and extent of IBD, this difference remained significant (odds ratio: 4.8, 95% confidence interval [CI] 2.0–11.8). In addition, tumors in individuals with PSC were significantly more advanced.

Conclusions: The right colon is the predilection site for development of colonic malignancies in patients with PSC and IBD. When such patients are diagnosed with cancer they tend to have more advanced tumors than patients with IBD without concurrent PSC, and the overall prognosis is worse. Furthermore, the higher frequency of right-sided tumors in patients with PSC suggests a different pathogenesis between patients with PSC and IBD and those with IBD alone.

(*Inflamm Bowel Dis 2009;00:000–000)*

Key Words: colorectal cancer, primary sclerosing cholangitis, inflammatory bowel disease

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disorder characterized by inflammation and fibrosis of the intra- and extrahepatic bile ducts.[1,2] Up to 90% of the patients with PSC have inflammatory bowel disease (IBD) as well, usually ulcerative colitis (UC), while IBD is accompanied by PSC in only 5% of IBD patients.[3] Patients with IBD have an increased risk of developing colorectal cancer (CRC). Recent meta-analyses show 10-year and 20-year risks of 1%–2% and 4%–8%, respectively.[4,5]

Several studies have shown that in patients with IBD concurrent PSC increases the risk of developing colitis-associated CRC.[6,7] Our group[8] found 10-year and 20-year risks of 14% and 31%, respectively, of developing CRC in such individuals. An explanation for this high CRC risk is not available. Several hypotheses have been postulated, such as an abnormal bile acid composition in patients with PSC resulting in an increased concentration of secondary bile acids, which may have a carcinogenic effect on the colonic mucosa.[9,10] Another explanation may be the altered course of IBD in PSC patients. A more extensive colitis with at the same time a mild or even asymptomatic course, resulting in diagnostic delay and a lower colectomy rate, may contribute to an increased risk of developing CRC.[11]

The aim of this study was to compare patients with CRC and IBD with and without PSC with respect to clinical characteristics, endoscopic and histological findings, and prognosis. Potentially, the results may help to define improved clinical management strategies for individuals with

Received for publication December 23, 2008; Accepted December 31, 2008.

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M.M.H. Claessen is supported by an unrestricted grant from Janssen-Cilag, Tilburg, The Netherlands.

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DOI 10.1002/ibd.20886

Published online in Wiley InterScience (www.interscience.wiley.com).

PSC and IBD and guide future research in pathophysiological mechanisms in PSC–IBD-associated CRC.

MATERIALS AND METHODS

Patients

The Dutch nationwide network and registry of histo- and cytopathology reports (PALGA) was used to select patients with IBD-associated CRC.[12] A search in this database from January 1990 until June 2006 for cases diagnosed, in Dutch university medical centers, with synchronous or metachronous diagnoses of IBD and CRC was performed.[13] Patients with PSC-IBD and CRC were also selected from this search and from a long-term cohort study containing all PSC patients followed in the period 1980–2006 in 2 university medical centers (University Medical Center Utrecht and Erasmus Medical Center Rotterdam).[8]

The diagnosis PSC was based on typical findings on cholangiography[14] or the presence of characteristic histological liver abnormalities (pericholangiolar "onion-skin" fibrosis), in combination with elevated serum alkaline phosphatase levels and the presence of IBD.[15] The onset of PSC was designated as the date of the first abnormalities on cholangiography or liver histology. Patients with bile duct abnormalities attributable to other causes such as bile duct surgery, ischemia, portal vein thrombosis, or autoimmune pancreatico-cholangitis were excluded.

The diagnoses IBD and CRC were based on a combination of endoscopic and histological findings.[16] Patients with mere dysplasia were not eligible. Colonic surveillance was based on the American Gastroenterological Association (AGA) or British Society of Gastroenterology (BSG) guidelines and defined as surveillance after 8–10 years of disease in cases of Crohn's disease (CD) or extensive UC, after 15–20 years of disease in cases of left-sided UC, and directly after diagnosing PSC.[17,18]

Data Collection

Data were retrieved from medical records and computerized hospital databases and completed by contacting the patient's physician. Collected data included date of diagnosis of IBD, PSC, and CRC, time of onset of symptoms, medical history, location and stage of the CRC, cause of death, use of 5-aminosalicylic acid (5-ASA) and/or ursodeoxycholic acid (UCDA), and information on phenotype of IBD (extent, duration, and type). Extensive colitis was defined as a colitis proximal of the splenic flexure in patients with UC or >50% involved colonic mucosa in patients with CD. End of follow-up was the end of the study (June 2006), death, or time of last visit in case patients were lost to follow-up. Apart from location and stage of the CRC, information on synchronous and metachronous tumors was collected as well. Right-sided or proximal tumors were defined as tumors located proximally of the splenic flexure. Tumor stages were defined according to the American Joint Committee on Cancer (AJCC).[19]

Statistical Analysis

Follow-up started at the time when CRC was diagnosed. Differences between patients with PSC and IBD and those with IBD alone were analyzed using Student's *t*-test and the chi-square test, when appropriate. A separate analysis was performed, excluding the patients with CD to rule out that possible differences were based on the underlying type of IBD. Multivariate analysis was done using binary logistic regression to determine whether there were independent risk factors for tumor location. These variables included age at diagnosis CRC, gender, presence of PSC, and extent of colitis. Survival analyses were performed using the Kaplan–Meier method; differences between groups were analyzed with the log-rank test. SPSS 12.0 Statistical Software (Chicago, IL) was used for all statistical analyses. The Kaplan–Meier plots were created in MedCalc for Windows, v. 9.3. (MedCalc Software, Mariakerke, Belgium). *P*-values < 0.05 were considered statistically significant.

RESULTS

Clinical Characteristics

Twenty-seven IBD-CRC patients with PSC (70% male) and 127 IBD-CRC patients without PSC (59% male) were included. Median age at diagnosis of IBD was 33 years (range 3–46) and 28 years (range 6–82) in the groups with and without concurrent PSC, respectively ($P = 0.5$) (Table 1). Median age at diagnosis of PSC was 39 years (range 11–59). The majority of patients had extensive colitis, i.e., 89% and 71% of patients with and without PSC, respectively ($P = 0.1$). UC was diagnosed in 89% of the patients with PSC, and in 56% of the patients without PSC ($P = 0.003$). All patients with CD had colonic involvement; an extensive colitis (>50% inflammation) was found in 100% and 63% of the patients with and without PSC, respectively. Sixty-nine percent ($n = 31$) of the non-PSC patients with CD also had ileitis compared to 33% ($n = 1$) of the CD patients in the PSC group. The majority (86%) of all patients used 5-ASA. UCDA was used by 15 PSC patients (56%) and by 1 patient without PSC. The latter patient used it for cholelithiasis.

After excluding all patients with CD, 24 UC-CRC patients with PSC (67% male) and 72 UC-CRC patients without PSC (67% male) remained. No changes in age at diagnosis IBD or PSC were found. Almost all patients in the PSC-UC-CRC group had an extensive colitis (92%) compared to 79% in the UC-CRC group ($P = 0.2$).

Follow-up

The median follow-up period after diagnosing CRC was 2.3 years (range 0–17.3) and 2.7 years (0–19.5) for the

TABLE 1. Patient Characteristics of 27 PSC-IBD-CRC Patients and 127 IBD-CRC Patients

	PSC-IBD-CRC (n = 27)	IBD-CRC (n = 127)	P-value
Gender, (% male)	19 (70)	75 (59)	0.4
Median age at diagnosis IBD, yrs (range)	33 (3–46)	28 (6–82)	0.5
Median age at diagnosis PSC, yrs (range)	39 (11–59)	NA	NA
Median age at diagnosis CRC, yrs (range)	47 (27–67)	49 (20–84)	0.06
Maximal extent of IBD (%)			
Extensive	24 (89)	80 (71)	0.1
Type of IBD (%)			
- Ulcerative colitis	24 (89)	71 (56)	0.003
- Crohn's disease	3 (11)	55 (43)	
Median IBD-CRC interval, yrs (range)	13 (0–35)	17 (0–43)	0.2

PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; CRC, colorectal cancer.
NA : not applicable

PSC and non-PSC group, respectively (P = 0.09). Sixty percent (n = 16) of the patients in the PSC group died versus 25% (n = 32) in the non-PSC group (P = 0.002). CRC-related mortality was not different between the 2 groups, i.e., 30% and 19% in the PSC-IBD-CRC and IBD-CRC group (P = 0.324). Other causes of death are shown in Table 2. Twenty-one percent of all patients were lost to follow-up. Differences in mortality rates remained statistically significant after excluding the CD patients (63% and 23% in the PSC-UC-CRC patients and UC-CRC patients, respectively).

TABLE 2. Causes of Death in 16 PSC-IBD-CRC Patients and 32 IBD-CRC Patients

	PSC-IBD-CRC n = 16	IBD-CRC n = 32
Colorectal carcinoma	8 (50)	24 (75)
Cholangiocarcinoma	2 (13)	0 (0)
Other malignancy	0 (0)	3[a] (9)
Colectomy	2 (13)	3 (9)
Liver failure	1 (6)	0 (0)
Other causes	1[b] (6)	2[c] (6)
Unknown	2 (13)	0 (0)

[a]Gastric, urothelial, and renal cell cancer.
[b]Ileus.
[c]Sepsis and gastrointestinal bleeding of unknown cause.
IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; CRC, colorectal cancer.

In the PSC-UC-CRC group 47% of the deaths were CRC-related versus 81% in the UC-CRC group (P = 0.044).

Three patients with PSC had undergone liver transplantation before developing CRC. These patients were not enrolled in a surveillance program, but underwent colonoscopy at an irregular basis without taking the required number of biopsies. The median interval between liver transplantation and detection of CRC was 13 months (range 2–20). Liver transplantation following a prior diagnosis of CRC was not performed.

The estimated overall 5-year survival rate after the diagnosis CRC was lower for patients with PSC (40%) than for those without PSC (75%, $P \leq 0.001$) (Fig. 1a,b). CRC-related mortality was not statistically significant different, with a 5-year survival of 62% and 82% for patients with and without PSC, respectively (P = 0.1) (Fig. 2a,b).

Colorectal Carcinoma

Patients were younger at CRC diagnosis in the PSC group than in the non-PSC group (median age: 47 years (range 27–67) versus 49 years (range 20–84, P = 0.064)). The median interval between the diagnosis IBD and the development of CRC was not different, i.e., 13 years (range 0–35) in the PSC group and 18 years (range 0–43) in the non-PSC group (P = 0.2). Patients with PSC had significantly more tumors with an AJCC tumor stage of 3A or higher compared to patients with IBD alone (61.5% and 38.5%, P = 0.003) (Table 3). Eleven patients (9%) in the non-PSC group had a synchronous CRC and 3 (2.4%) patients had 3 tumors diagnosed at the same time. Synchronous tumors were not detected in the PSC group. No statistically significant differences were found in the AJCC tumor stages when comparing PSC-UC-CRC to UC-CRC patients (tumor stage of 3A or more: 61% of the PSC-UC-CRC patients and in 41% of the UC-CRC patients, respectively, P = 0.091).

The tumors were located proximally of the splenic flexure in 18 (67%) patients with PSC and in 52 (36%) patients without PSC (P = 0.006). After excluding patients with CD, this difference remained statistically significant (P = 0.02). Multivariate analysis, including age at diagnosis of CRC, gender, and extent of colitis showed that PSC was an independent risk factor for (right-sided) tumor location with an odds ratio of 4.8 (95% confidence interval [CI] 2.0–11.8).

Only a small number of patients underwent colonic surveillance according to the AGA/BSG guidelines, i.e., 33% and 17% patients with and without PSC, respectively. No difference in AJCC tumor stage was found between patients with or without colonic surveillance (P = 0.128).

DISCUSSION

This study shows a significantly higher prevalence of right-sided CRCs in patients with PSC and IBD compared to patients with IBD alone. These findings are in line with

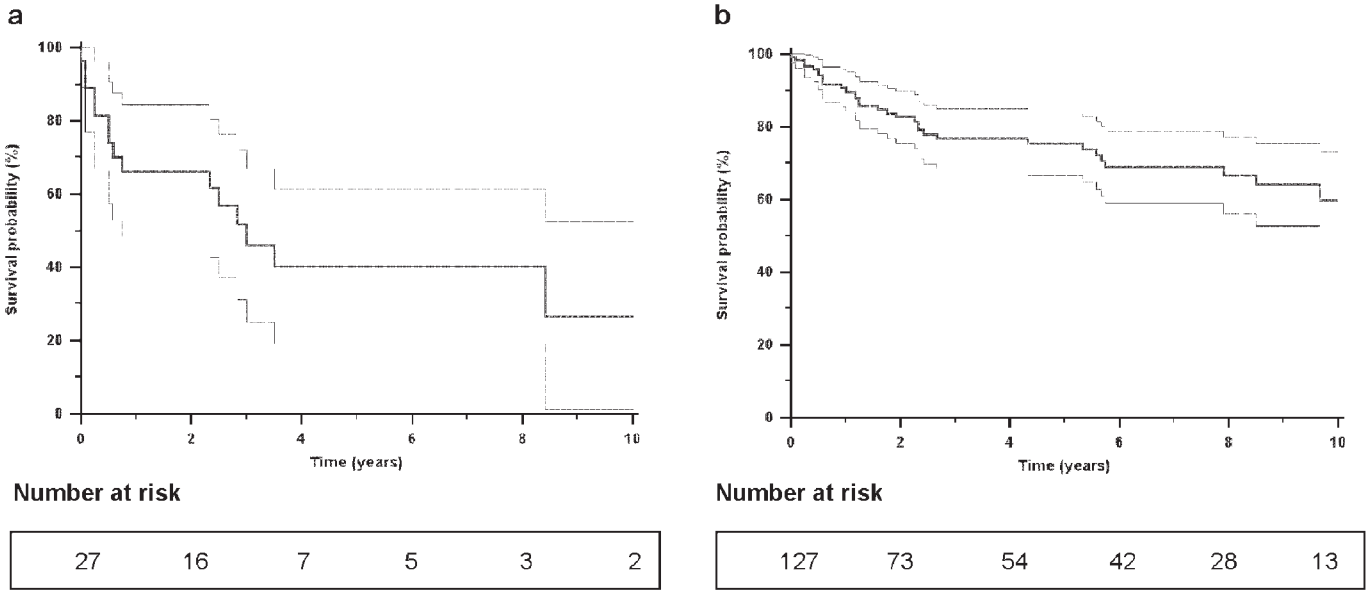

FIGURE 1. Kaplan–Meier plot of survival (+95% CI) after diagnosing CRC of 27 patients with PSC and concurrent IBD (a) and 127 patients with IBD alone (b) ($P = 0.002$, log-rank test).

results from previous series. However, the studies of Marchesa et al,[20] Lindberg et al,[21] and Shetty et al[10] were all based on relatively small numbers of CRC patients with IBD with or without concomitant PSC. In addition, we found that CRC in patients with PSC and IBD was associated with a decreased survival compared to patients with IBD alone. The difference in CRC-related 5-year survival (62% versus 82%) between the 2 groups, however, was not statistically significant.

The high frequency of right-sided colorectal tumors in PSC patients fits well with the hypothesis that an altered bile acid composition is implicated in the increased frequency of CRCs in these patients.[10] In this respect, an increased concentration of secondary bile acids and higher serum and bile levels of deoxycholic acid and lithocholic acid both might play a role.[22–24] Interestingly, specific binding sites for deoxycholic acid were identified in 31% of the sporadic CRCs compared to only 3% of normal mucosa samples (*P*

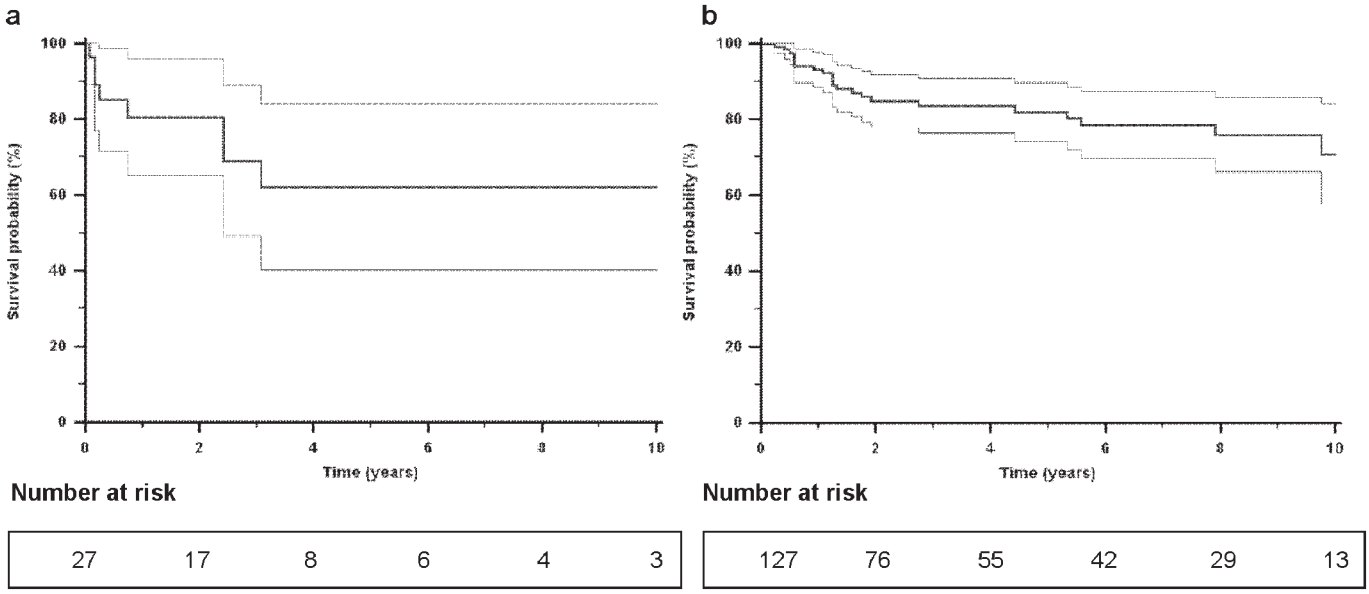

FIGURE 2. Kaplan–Meier plot of the CRC-related mortality (+95% CI) for 27 patients with PSC and concurrent IBD (a) and 127 patients with IBD alone (b) ($P = 0.324$, log-rank test).

TABLE 3. AJCC Tumor Stages

AJCC	Tumor Stage	PSC-IBD-CRC $n = 26$ (%)[a]	IBD-CRC $n = 122$ (%)[a]
0	T in situ	2 (8)	7 (6)
1	T1, T2. N0, M0	4 (15)	26 (21)
2A	T3, N0, M0	4 (15)	40 (33)
2B	T4, N0, M0	0 (0)	2 (2)
3A[b]	T1, T2, N1, M0	1 (4)	5 (4)
3B[b]	T3, T4, N1, M0	5 (19)	14 (12)
3C[b]	Any T, N2, M0	2 (8)	10 (8)
4[b]	M1	8 (31)	18 (15)

[a]Six tumors (1 in PSC-IBD-CRC group, 5 in IBD-CRC group) were not classifiable due to unknown tumor stages.
[b]PSC-IBD-CRC patients had statistically significant more advanced tumors (tumor stage: 3A, 3B, 3C, or 4) compared to the IBD-CRC group ($P = 0.03$).

< 0.05).[25] The same has been observed in colitis-associated carcinogenesis by Hill et al,[9] who reported an increased concentration of total fecal bile acids in UC patients with dysplasia or carcinoma as well. The promising results of UDCA as a chemoprotective agent in the development of CRC in UC patients with concurrent PSC also suggest a role for bile acids in colorectal carcinogenesis.[26,27] On the other hand, the sparse data available on bile composition in patients with PSC[28–31] do not corroborate this hypothesis: bile acid excretion in cholestatic patients, including PSC patients, is decreased[28,31] and serum concentration of secondary bile acids was not increased in patients with PSC when compared to healthy controls.[31,32] In addition, the risk of developing CRC remains increased after liver transplantation, which is likely to normalize bile acid composition.[33]

Another explanation for the predominance of right-sided CRCs in PSC may be offered by an alternative molecular pathogenesis.[34,35] A parallel might be drawn with patients with hereditary nonpolyposis colon cancer (HNPCC) in whom a high frequency of right-sided tumors occurring at a relatively young age is observed as well.[36] The pathophysiological mechanism of this hereditary disease is based on a defect in the DNA mismatch repair genes. In colitis-associated carcinogenesis, data regarding defects in DNA mismatch repair genes and the associated molecular phenotype of microsatellite instability (MSI) are conflicting. The frequency of MSI varies between 1% and 45%, depending on the types of tissue analyzed and, in particular, the number and choice of microsatellite markers.[37–41] The frequency of MSI in patients with IBD-associated CRC and concurrent PSC is presently unknown.

A remarkable observation of our study was that the IBD-CRC interval between patients with and without PSC did not differ. Although PSC is known to be an additional risk factor for CRC,[6–8] our results do not support an accelerated progression to CRC in these patients. However, as many PSC patients seem to have asymptomatic or mild colitis, the exact date of onset of IBD is difficult to establish.[11,42] This might have led to an underestimation of the duration of the colitis.

A minority of patients (20%) were enrolled in a strict surveillance colonoscopy program. During the 1980s and 1990s, the currently accepted guidelines[17,18] were not yet implemented, which might explain this low percentage. In addition, the fact that 3 patients developed CRC relatively soon after liver transplantation also illustrates that the current standard of surveillance before and after liver transplantation was not yet introduced at that time.

Patients with PSC had a decreased survival in comparison with the non-PSC group, although CRC-related mortality did not differ. Most patients in both groups died from CRC. Although statistically not significant, the difference in the 5-year survival rate of 62% and 82% for CRC patients with and without PSC, respectively, is noteworthy. The observed higher frequency of more advanced AJCC tumor stages in the PSC group may explain this lower survival rate. The lack of significance may be ascribed to the relatively small patient population (type II error).

Several limitations of this study are worth considering. First of all, data were collected retrospectively. Second, the controls were not case-matched. Due to the asymptomatic course of IBD in patients with PSC it is difficult to match patients with regard to IBD duration and extent. In the multivariate analysis we corrected for the extent of the colitis as a potential confounder. Finally, in the IBD-CRC group more patients with CD were included compared to the PSC-CRC group, which may have affected the results. However, all patients with CD had colonic involvement and after excluding the patients with CD from analysis the differences remained statistically significant.

In summary, our study shows that CRCs develop predominantly in the proximal colon of PSC patients with IBD. Additional studies are needed to explore the underlying molecular mechanisms to explain these findings.

ACKNOWLEDGMENT

The authors thank Dr. M. Casparie (Prismant, Utrecht, the Netherlands) for help with the PALGA data search.

REFERENCES

1. Chapman RW, Arborgh BA, Rhodes JM, et al. Primary sclerosing cholangitis: a review of its clinical features, cholangiography, and hepatic histology. *Gut.* 1980;21:870–877.
2. Thorpe ME, Scheuer PJ, Sherlock S. Primary sclerosing cholangitis, the biliary tree, and ulcerative colitis. *Gut.* 1967;8:435–448.
3. Fausa O, Schrumpf E, Elgjo K. Relationship of inflammatory bowel disease and primary sclerosing cholangitis. *Semin Liver Dis.* 1991;11:31–39.
4. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut.* 2001;48:526–535.
5. Lutgens MW, van der Heijden GJ, Vleggaar FP, et al. A comprehensive

meta-analysis of the risk of colorectal cancer in ulcerative colitis and Crohn's disease. *Gastroenterology.* 2008;134:A33–A34.
6. Broome U, Lofberg R, Veress B, et al. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology.* 1995;22:1404–1408.
7. 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;41:522–525.
8. Claessen MMH, Vleggaar FP, Tytgat KMAJ, et al. High lifetime risk of cancer in primary sclerosing cholangitis. *J Hepatol.* 2008;50:158–164.
9. Hill MJ, Melville DM, Lennard-Jones JE, et al. Faecal bile acids, dysplasia, and carcinoma in ulcerative colitis. *Lancet.* 1987;25:185–186.
10. Shetty 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.
11. Loftus EV Jr, Harewood GC, Loftus CG, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. *Gut.* 2005;54:91–96.
12. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol.* 2007;29:19–24.
13. Lutgens MW, Vleggaar FP, Schipper ME, et al. High frequency of early colorectal cancer in inflammatory bowel disease. *Gut.* 2008;57:1246–1251
14. MacCarty RL, LaRusso NF, Wiesner RH, et al. Primary sclerosing cholangitis: findings on cholangiography and pancreatography. *Radiology.* 1983;149:39–44.
15. Ludwig J, Barham SS, LaRusso NF, et al. Morphologic features of chronic hepatitis associated with primary sclerosing cholangitis and chronic ulcerative colitis. *Hepatology.* 1981;1:632–640.
16. Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol.* 1983;14:931–968.
17. Eaden JA, Mayberry JF. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. *Gut.* 2002;51(suppl 5):V10–V12.
18. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. *Gastroenterology.* 2003;124:544–560.
19. AJCC Cancer Staging Manual. 6th ed. New York: AJCC; 2002.
20. Marchesa P, Lashner BA, Lavery IC, et al. The risk of cancer and dysplasia among ulcerative colitis patients with primary sclerosing cholangitis. *Am J Gastroenterol.* 1997;92:1285–1288.
21. Lindberg BU, Broome U, Persson B. Proximal colorectal dysplasia or cancer in ulcerative colitis. The impact of primary sclerosing cholangitis and sulfasalazine: results from a 20-year surveillance study. *Dis Colon Rectum.* 2001;44:77–85.
22. Nagengast FM, Grubben MJ, van Munster I. Role of bile acids in colorectal carcinogenesis. *Eur J Cancer.* 1995;31A:1067–1070.
23. Bayerdorffer E, Mannes GA, Ochsenkuhn T, et al. Unconjugated secondary bile acids in the serum of patients with colorectal adenomas. *Gut.* 1995;36:268–273.
24. Kishida T, Taguchi F, Feng L, et al. Analysis of bile acids in colon residual liquid or fecal material in patients with colorectal neoplasia and control subjects. *J Gastroenterol.* 1997;32:306–311.
25. Summerton J, Flynn M, Cooke T, et al. Bile acid receptors in colorectal cancer. *Br J Surg.* 1983;70:549–551.
26. Pardi DS, Loftus EV Jr, Kremers WK, et al. Ursodeoxycholic acid as a chemopreventive agent in patients with ulcerative colitis and primary sclerosing cholangitis. *Gastroenterology.* 2003;124:889–893.
27. Tung BY, Emond MJ, Haggitt RC, et al. Ursodiol use is associated with lower prevalence of colonic neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. *Ann Intern Med.* 2001;16:89–95.
28. Jazrawi RP, de Caestecker JS, Goggin PM, et al. Kinetics of hepatic bile acid handling in cholestatic liver disease: effect of ursodeoxycholic acid. *Gastroenterology.* 1994;106:134–142.
29. Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. *Hepatology.* 2002;36:525–531.
30. Rost D, Rudolph G, Kloeters-Plachky P, et al. Effect of high-dose ursodeoxycholic acid on its biliary enrichment in primary sclerosing cholangitis. *Hepatology.* 2004;40:693–698.
31. Stiehl A, Rudolph G, Sauer P, et al. Biliary secretion of bile acids and lipids in primary sclerosing cholangitis. Influence of cholestasis and effect of ursodeoxycholic acid treatment. *J Hepatol.* 1995;23:283–289.
32. Beuers U, Spengler U, Zwiebel FM, et al. Effect of ursodeoxycholic acid on the kinetics of the major hydrophobic bile acids in health and in chronic cholestatic liver disease. *Hepatology.* 1992;5:603–608.
33. Loftus EV Jr, Aguilar HI, Sandborn WJ, et al. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis following orthotopic liver transplantation. *Hepatology.* 1998;27:685–690.
34. Gervaz P, Bouzourene H, Cerottini JP, et al. Dukes B colorectal cancer: distinct genetic categories and clinical outcome based on proximal or distal tumor location. *Dis Colon Rectum.* 2001;44:364–372.
35. Sugai T, Habano W, Jiao YF, et al. Analysis of molecular alterations in left- and right-sided colorectal carcinomas reveals distinct pathways of carcinogenesis: proposal for new molecular profile of colorectal carcinomas. *J Mol Diagn.* 2006;8:193–201.
36. Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology.* 1999;116:1453–1456.
37. Brentnall TA, Crispin DA, Bronner MP, et al. Microsatellite instability in nonneoplastic mucosa from patients with chronic ulcerative colitis. *Cancer Res.* 1996;15:1237–1240.
38. Itzkowitz SH. Microsatellite instability in colitis associated colorectal cancer. *Gut.* 2000;46:304–305.
39. Lyda MH, Noffsinger A, Belli J, et al. Microsatellite instability and K-ras mutations in patients with ulcerative colitis. *Hum Pathol.* 2000;31:665–671.
40. Suzuki H, Harpaz N, Tarmin L, et al. Microsatellite instability in ulcerative colitis-associated colorectal dysplasias and cancers. *Cancer Res.* 1994;15:4841–4844.
41. Willenbucher RF, Aust DE, Chang CG, et al. Genomic instability is an early event during the progression pathway of ulcerative-colitis-related neoplasia. *Am J Pathol.* 1999;154:1825–1830.
42. Broome U, Lofberg R, Lundqvist K, et al. Subclinical time span of inflammatory bowel disease in patients with primary sclerosing cholangitis. *Dis Colon Rectum.* 1995;38:1301–1305.