

## Sclerosing cholangitis, race and sex

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### Abstract

**Background**—Primary sclerosing cholangitis develops in 3–10% of patients with ulcerative colitis, and may be associated with an increased cancer risk. Ulcerative colitis is probably less common in people of African origin than in populations of European descent.

**Aims and methods**—To review the records of all patients under regular follow up for ulcerative colitis at St Bartholomew's Hospital (London, UK), a tertiary referral centre, prompted by discovering a cluster of cases with common features.

**Results and conclusions**—Among 166 patients with ulcerative colitis under regular follow up, only four (all women) are of African or Caribbean genetic origin, and three of these have developed sclerosing cholangitis within three years of presentation with colitis, compared with four of 162 patients of European or Asian descent (odds ratio 119, 95% confidence interval 8–3837;  $p=0.0002$ ). This cluster, which is not explained by common HLA DR or DQ type, suggests that Africans and Afro-Caribbeans, especially women, may be at increased risk of sclerosing cholangitis. This may reflect genetic influences on the development of enteric and hepatobiliary inflammatory disease.

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Keywords: sclerosing cholangitis; ulcerative colitis; genetics of inflammatory bowel disease; racial effects on disease

It is often stated that ulcerative colitis is rare in Africa, although the evidence for this is limited and based on a small number of good hospital based surveys<sup>1</sup> and on informal observation. Only a few surveys have been conducted using internationally accepted diagnostic techniques. There is much better evidence that ulcerative colitis is less common in people of African genetic origin living in Europe<sup>2,3</sup> or North America.<sup>4</sup> It has also been suggested that, although less common, ulcerative colitis may be more severe than in people of European descent,<sup>5</sup> although this may be a consequence of later diagnosis or presentation. Primary sclerosing cholangitis (PSC), a progressive obliterative fibrosis of the biliary tract, occurs in 3–10% of patients with ulcerative colitis; conversely, 70% of patients with PSC have ulcerative colitis.<sup>6</sup> However, our recent experience suggests that this association may be stronger in a subgroup defined by race and sex.

### Methods and Results

We have reviewed the records of all patients under regular follow up for ulcerative colitis in this institution, a tertiary referral centre, prompted by discovering a cluster of cases with common features. Since 1991, we have diagnosed PSC in three young black women. The first, aged 31 years, was born in the United Kingdom of black Caribbean parents and presented with a five year history of intermittent diarrhoea. An increased serum alkaline phosphatase concentration was noted at the time the diagnosis of ulcerative colitis was made by sigmoidoscopic biopsy. As itching began to dominate the clinical picture, PSC was diagnosed by endoscopic retrograde cholangiopancreatography (ERCP). Orthotopic liver transplantation was required three years after the initial presentation with ulcerative colitis, because of intractable itching. She is HLA DR 7, 15, 51, 53, DQ 1, 2, and serum is positive for antinuclear and cytoplasmic type (c-type) antineutrophil cytoplasmic antibodies (ANCA). The second patient, aged 18 at presentation, is of West African origin and birth, and a homozygote for the S haemoglobin gene, although with minimal symptoms of sickle disease. She was diagnosed as having ulcerative colitis in 1988 at the age of 12 years, found to have a notably raised alkaline phosphatase concentration in 1991, and diagnosed with PSC in 1996, with few symptoms attributable to the biliary dysfunction. She is HLA DR 0102(1), 0301(17), 52, DQ 2, 5, and serum is positive for antinuclear and c-type ANCA. The third patient, West African born and bred, was 32 years old at presentation with ulcerative colitis. Within two months her serum alkaline phosphatase concentration was notably raised. Further investigations were interrupted by semi-urgent colectomy, but in due course ERCP revealed severe changes of PSC with narrowed and beaded intrahepatic bile ducts. She is HLA DR 15, 51, 51, DQ 6, but her autoantibody status is unknown. In all three patients the diagnosis of PSC was made within three years of presentation of ulcerative colitis, and has run an aggressive course in two. In all three cases the ulcerative colitis extended throughout the colon. This cluster of cases is not explained by shared HLA DR genotype.

Of a total of 166 patients with ulcerative colitis currently under regular follow up at St Bartholomew's Hospital, only four are of African or Caribbean origin, and of these three (described earlier) have recently developed PSC. The other black woman still free of the disease has HLA DR type 1, 15, 51 DQ 5, 6, and is negative for ANCA. Four (three women, one man) of 162 patients of other racial origin

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TABLE 1 *PSC complicating ulcerative colitis according to racial classification*

Origin	PSC present	PSC absent
African/Caribbean	3	1
White/Indian	4	158

Odds ratio 119; 95% confidence interval 8–3837;  $p=0.0002$  by Fisher's exact test.

(all white European) have also been diagnosed as having PSC (table 1).

### Discussion

The cluster we describe may indicate an association which would be of interest in understanding genetic contributions to inflammatory bowel and hepatobiliary disease. Although based on few cases, the association in this institution between race and PSC is striking, and suggests that women of African genetic origin with ulcerative colitis are more likely to develop PSC. All of these women developed attributable symptoms while living in the United Kingdom. To our knowledge, only one previous report has specifically described PSC in people of African genetic origin.<sup>5</sup> In that study, PSC developed in 12% of black North American patients. The association in that study was not as strong as in the patients reported here. This might be at least partly explained if there has been greater racial mixing in American blacks than in the patients of African genetic origin seen in London. PSC has been associated with the HLA DR phenotypes B8, DR2, DR3, DR4, and Drw52a,<sup>7</sup> but there was no consistency in the HLA DR phenotype or genotype of our patients. None of these patients had HLA DR4, previously associated with rapid progression of the cholangitis.<sup>8</sup> Two of them had c-type ANCA

antibodies, rather than the perinuclear ANCA antibodies usually associated with PSC.<sup>9</sup>

It has recently been suggested that patients with PSC and ulcerative colitis have an increased risk of colorectal cancer compared with patients with ulcerative colitis but without PSC,<sup>10</sup> further emphasising the importance of the interaction of these inflammatory disorders. Although any association of race, sex and PSC in colitic patients could be due to exposure to an environmental factor or to an unrecognised selection bias, these three patients differ in their upbringing and there is a distinct possibility that any association is genetic.

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