Furthermore, the association of coeliac disease and IBS symptoms is biologically plausible with many mechanisms being reported—for example, autonomic dysfunction, intussusception, exocrine pancreatic disease, small intestinal ulceration, and associated microscopic colitis. Our own group found an increased prevalence of coeliac disease in patients referred with surgical abdominal pain, notably in those with unexplained or non-specific abdominal pain.⁹ The association between IBS and coeliac disease appears to operate in both directions, as patients with coeliac disease (on a gluten-free diet) may describe IBS symptoms.¹⁰ Similarly, abdominal pain, diarrhoea, or constipation were associated with an increased risk of coeliac disease in a large multicentre study.¹¹ All of these symptoms can overlap with IBS.

From a clinical perspective, is investigating IBS patients for coeliac disease a valid approach? It is recognised that the majority of patients with coeliac disease have significant delays in diagnosis and once established on the gluten-free diet they derive symptomatic benefit. Case finding for coeliac disease in patients with IBS symptoms is both cost-effective and beneficial in terms of quality of life years gained, even at prevalence values of 1.1–2%.¹² We accept that further multicentre studies in both primary and secondary care are required to resolve this debate. In such studies assessment of quality of life and symptom resolution (when individuals are established on a gluten-free diet) is imperative. Despite the existing evidence, investigating for coeliac disease in patients fulfilling the Rome II criteria is still not widely accepted (although recommended in UK guidelines). Why should this be? Is this a clash of ideological dogma when considering possible mechanisms for IBS?

J S Leeds, D S Sanders

Gastroenterology and Liver Unit, Royal Hallamshire Hospital, Glossop Road, Sheffield, UK

Correspondence to: Dr John S Leeds, Gastroenterology and Liver Unit, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK; john.leeds@sth.nhs.uk

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Risk of pancreatic cancer in patients with cystic fibrosis

About 5–10% of pancreatic cancers have been linked to an underlying genetic disorder, usually inherited in an autosomal dominant manner. We have previously studied the risk of cancer in patients with cystic fibrosis and found that, although the overall risk of cancer was not increased, there was a fivefold increase in the risk of digestive tract cancer.^{1,2} Because

only four patients developed pancreatic cancer, it was difficult to estimate the risk accurately. Since the publication of these reports we have obtained information on additional patients with both cystic fibrosis and pancreatic cancer from the US cystic fibrosis patient registry, from published reports, and by querying fibrosis surgeons, pathologists, and cystic fibrosis physicians in the USA, Canada, and Europe.

We now describe nine patients with cystic fibrosis and pancreatic cancer identified during the study period (1985 to 2006), including four from our original reports (table 1). Based on age, sex, race, and calendar-year-specific incidence rates obtained from the Surveillance, Epidemiology, and End Results (SEER) programme, we previously estimated the number of expected pancreatic cancers in the USA cystic fibrosis population (n = 28 858) for the 10 year period 1990 to 1999 to be 0.4.² Assuming that the cystic fibrosis population in Europe is approximately equal to that in the USA, then the expected number of pancreatic cancers in the combined USA and European populations during the period 1985 to 2005 is 1.7, yielding a risk ratio of 5.3 (95% confidence interval, 2.4 to 10.1).

There were four women and five men with a median age of 35 years (range 18 to 58). Five patients had known cystic fibrosis mutations: four were $\Delta F508$ homozygotes and one was a $\Delta F508$ heterozygote. Five patients had pancreatic exocrine insufficiency, five had mild or moderate lung disease, and two had potential risk factors that might have increased their risk of pancreatic cancer. One patient had received six years of immunosuppressive treatment following lung transplantation before developing pancreatic cancer; this patient had also received growth hormone for three years. Another patient developed pancreatic mucinous cystadenocarcinoma in a cyst that had been present for 13 years.

The increased relative risk of pancreatic cancer in the cystic fibrosis population compared with the general population is an age related finding: pancreatic cancer is rare in younger individuals. However, although we observed an excess risk of pancreatic cancer within the cystic fibrosis population compared with the background population, we were able to identify only nine patients in North America and Europe over a 21 year period. This translates into an incidence of approximately 1/100 000/year (nine pancreatic cancers in 1.2 million person-years). Therefore, although the

Table 1 Pancreatic cancer in cystic fibrosis patients

Report	Population, year of diagnosis of pancreatic cancer (type)	Patient characteristics	Remarks
Petrowsky ³	Switzerland, 2005 (adenocarcinoma)	18 year old female, $\Delta F508$ /unknown; pancreas insufficient	Lung transplantation followed by immunosuppression $\times 6$ years and growth hormone $\times 3$ years before pancreatic adenocarcinoma
Oermann ⁴	USA, 2004 (mucinous cystadenocarcinoma)	19 year old female, $\Delta F508$ / $\Delta F508$; pancreas insufficient	Mucinous cystadenocarcinoma within cyst diagnosed at age 6
Davis ^{5*}	UK, 1985 (adenocarcinoma)	23 year old female, unknown genotype	Mild lung disease
McIntosh ^{6*}	USA, 1987	26 year old male, unknown genotype; diabetic pancreas insufficient	Moderate lung disease
Tummler	Germany, 2003	35 year old male, $\Delta F508$ / $\Delta F508$; diabetic pancreas insufficient	Personal communication
Tsongalis ⁷	USA, 1993 (adenocarcinoma)	39 year old male, $\Delta F508$ / $\Delta F508$; pancreas insufficient	Mild lung disease
Tedesco ⁸	USA, 1986	42 year old male, unknown genotype	Mild lung disease
Maisonneuve ²	USA, 2000 (ductal adenocarcinoma)	49 year old female, $\Delta F508$ / $\Delta F508$; diabetic	
Sheldon ^{9*}	UK, 1991 (carcinoma)	58 year old male, unknown genotype	Mild lung disease

*Also described in the report by Neglia.[1]

relative risk is increased, the chance of any single cystic fibrosis patient developing pancreatic cancer is extremely low. Physicians who treat cystic fibrosis patients are unlikely ever to encounter one with pancreatic cancer. However, as the life span of people with cystic fibrosis increases, the absolute risk of pancreatic and other types of digestive tract cancer is likely to increase. At present, screening cystic fibrosis patients for this cancer or other gastrointestinal tumours is not indicated.

As there is an excess risk of early onset pancreatic cancer in patients with cystic fibrosis, perhaps other modifying genes or environmental factors are important. Mucin genes, which are found in both cystic fibrosis and pancreatic cancer, may be important.¹⁰ Patients with cystic fibrosis can have nutritional deficiencies, another possible risk factor for cancer.

Although case ascertainment in the USA relies on a national cystic fibrosis registry and is likely to be complete, it is possible that we missed some cases of pancreatic cancer in the European cystic fibrosis patients. This potential deficit would be limited, as similar numbers of cases were reported in the USA and Europe, which have populations of roughly similar size.

In summary, the estimated risk of pancreatic cancer in cystic fibrosis is five to six times greater than in the general population, but compared with other causes of mortality, the absolute risk of pancreatic cancer in patients with cystic fibrosis is negligible.

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P Maisonneuve

European Institute of Oncology, Milan, Italy

B C Marshall

The USA Cystic Fibrosis Foundation, Bethesda, USA

A B Lowenfels

New York Medical College, Valhalla, USA

Correspondence to: Patrick Maisonneuve, Division of Epidemiology and Biostatistics, European Institute of Oncology, via Ripamonti 435, 20141 Milan, Italy; Patrick.Maisonneuve@ieo.it

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Glucocorticoid receptor isoform expression does not predict steroid treatment response in IBD

The occurrence of glucocorticoid dependent or refractory disease courses is a major clinical problem not only in inflammatory bowel disease (IBD) but also in other chronic inflammatory conditions such as asthma and rheumatoid arthritis.¹ It would be of great value if the responsiveness of patients to glucocorticoids could be evaluated before their administration to avoid ineffective treatment.

The response to steroids is mediated by the glucocorticoid receptor (hGR) of which two isoforms exist, hGR α and hGR β . Both are products of alternative splicing of the primary transcript of GR messenger RNA (mRNA).² The hGR isoforms differ in their carboxyl termini: whereas hGR α is ligand activated, modulating the expression of glucocorticoid responsive genes by binding to specific glucocorticoid response elements (GREs), hGR β does not bind glucocorticoids and is transcriptionally inactive. Therefore it has been suggested that hGR β might be an endogenous inhibitor of glucocorticoid action and a negative regulator determining glucocorticoid sensitivity in the target tissues.³

In 2000 Honda and coworkers published a study indicating that hGR β mRNA was detectable in peripheral blood mononuclear cells (PBMC) in 9.1% of cases of glucocorticoid sensitive ulcerative colitis, 83.3% of cases of glucocorticoid resistant ulcerative colitis, and 10% of healthy volunteers.⁴ The authors concluded that the expression of hGR β mRNA in PBMC could serve as a novel predictor of glucocorticoid response in patients with ulcerative colitis or IBD in general.

As the prediction of steroid response is an important issue in the clinical management of IBD, we prospectively and retrospectively tested this hypothesis in a cohort of patients by quantitative polymerase chain reaction (PCR). Blood samples were collected from 21 healthy controls, 16 newly diagnosed steroid naive IBD patients, 35 IBD patients in remission treated with or without glucocorticoids, and 35 patients with active disease. RNA was isolated using the RNeasy[®] Mini Kit (Qiagen, Hilden, Germany). mRNA was reverse transcribed (Promega, Madison, USA) in a 15 minute reaction at 42°C. hGR α /GAPDH and hGR β /GAPDH mRNA ratio levels were determined from isolated PBMC using quantification of gene expression by Taqman PCR (hGR α probe: 5'-TTG GAT AAG ACC ATG AGT ATT GAA TTC C-3', hGR α forward: 5'-TCT CCT TAA CTA TTG CTT CCA AAC AIT-3', hGR α reverse: 5'-TGG TGA TGA TTT CAG CTA ACA TCT C-3', hGR β probe: 5'-TGG CGC TCA AAA AAT AGA ACT CAA TGA GAA AA-3', hGR β forward: 5'-TTA ATC TGA TTT TCA TCC CAA CAA TC-3', hGR β reverse: 5'-TTG ACA ACG AAG TGC ACA TAA TCT T-3'; human GAPDH: No 4310884E, Applied Biosystems, Warrington, UK). Clinical

response (disease course: remission, active disease; side effects) to steroid treatment was determined by medical record review and was correlated with hGR α and hGR β levels.

In the setting described, hGR β was detected in all samples investigated at similar levels, indicating that an expression or significant upregulation only in glucocorticoid refractory patients is unlikely (fig 1). The ratio between the systemic (PBMC) hGR α and hGR β levels of steroid treated IBD patients, IBD patients not receiving steroid treatment, and the control subjects did not differ significantly (fig 2). Steroid treatment was not inversely correlated with hGR mRNA expression, as it was supposed to be from earlier data on reduced glucocorticoid binding in treated patients.⁵ Obviously, glucocorticoid binding capacity cannot simply be estimated from mRNA expression of hGR. Ten of the patients who presented with active IBD could not be treated sufficiently with steroids and had to be switched to other immunosuppressive agents, indicating steroid refractory or steroid dependent disease. There was no significant difference in the other

Figure 1 hGR α (white bars) and hGR β (grey bars) mRNA expression in peripheral blood mononuclear cells from healthy staff members (control, n=21), newly diagnosed steroid naive IBD patients (n=16), IBD patients in remission treated with (rem +, n=15) or without glucocorticoids (rem -, n=20) and patients with active disease with (act +, n=16) or without glucocorticoids (act -, n=19). IBD, inflammatory bowel disease.

Figure 2 Ratio of hGR α to hGR β mRNA expression in peripheral blood mononuclear cells from healthy staff members (control, n=21), newly diagnosed steroid naive IBD patients (n=16), IBD patients in remission treated with (rem +, n=15) or without glucocorticoids (rem -, n=20) and patients with active disease with (act +, n=16) or without glucocorticoids (act -, n=19). IBD, inflammatory bowel disease.