Review

Risk factors for biliary tract carcinogenesis

R.W. Chapman
Dept of Gastroenterology, Oxford Radcliffe Hospital, Headley Way, Headington, Oxford 0X3 9DU, UK

Summary
Cholangiocarcinoma has a worldwide distribution which accounts for about 10-15% of all cases of primary hepatobiliary malignancy. Although, in the majority of cases, no aetiological factor can be identified, a number of risk factors have been shown to be important in the development of cholangiocarcinoma; most of these factors share long standing inflammation and chronic injury of the biliary epithelium. Primary sclerosing cholangitis is an uncommon disease, characterized by stricturing, fibrosis and inflammation of the biliary tree which is closely associated with chronic inflammatory bowel disease, particularly ulcerative colitis. It is commonly associated with cholangiocarcinoma and between 10-20% of patients with primary sclerosing cholangitis will go on to develop a cholangiocarcinoma. The rare congenital fibro-polyectytic diseases of the biliary system are associated with increased risks of cholangiocarcinoma, particularly choledochal cysts and Caroli's disease. Choledochal cysts are associated with a 10% overall incidence of cholangiocarcinoma; there is a 1% cumulative risk which plateaus after 15-20 years. However, the risk is diminished in children who present under the age of 10 years where the over all risk is 0.7%. This compares with the 14% over all risk of patients presenting over the age of 20 years. In the Far East, other forms of chronic inflammation associated with cholangiocarcinoma include infestation with liver flukes, Clonorchis sinensis and Opisthorchis viverrini. Cholangiocarcinoma is also rarely seen in association with cirrhosis and has been weakly linked to hepatitis C infection.

Key words: biliary tract, carcinogenesis, cholangiocarcinoma, risk factors

Introduction
Biliary tract cancer account for approximately 10-15% of all primary hepatobiliary cancers. The number of new cases in the United States is estimated at 1,500 to 3,000 per year compared with 30,000 cases per year of pancreatic cancer. The types of cancer which can occur are shown in Table 1, however, over 95% of cases are due to adenocarcinoma. The median age of presentation is in the mid-50's, but with a wide range, approximately one third of cases occur in patients less than 50 years old. In contrast to gall bladder cancer, cholangiocarcinomas occur more commonly in males, with a ratio of 1:3 to 2:4 to females. In the majority of elderly cases the aetiology remains unclear. However, in patients under 50 the number of risk factors have been shown to be important which are listed in Table 2.

Table 1: The histological types of biliary tract malignancies

- Adenocarcinoma (>95%)
- Squamous cell carcinoma
- Mucoepidermal carcinoma
- Rhabdomyosarcoma
- Leiomyosarcoma
- Cystadenocarcinoma
- Granular cell carcinoma
- Lymphoma
- Carcinoid

Table 2: Aetiological factors in the development of cholangiocarcinoma

**Chronic inflammatory bile duct diseases**
- Sclerosing cholangitis
- Cystic liver diseases
  - Caroli's disease
  - Choledochal cyst
  - Congenital hepatic fibrosis
  - Von Myerberg complexes
  - Intrahepatic calculi (hepatolithiasis)
  - Liver fluke infestation

**Chemicals & carcinogens**
- Thorotrast
- Oxymethalone
- Aromatic hydrocarbons

**Miscellaneous**
- Ulcerative colitis
- Chronic liver disease
  - Cirrhosis
  - Hepatitis C

**Primary sclerosing cholangitis**
Primary sclerosing cholangitis is a chronic cholestatic liver disease characterized by an obliterative inflammatory stricturing fibrosis which usually involves the whole biliary tree. The changes may sometimes be localized to either the extra or intra-hepatic bile ducts and the degree of involvement varies considerably from patient to patient. Approximately 70% of patients with primary sclerosing cholangitis have co-existing inflammatory bowel disease,
usually ulcerative colitis and primary sclerosing cholangitis if the most common form of liver disease found in ulcerative colitis [1]. Primary sclerosing cholangitis is found in between 5-10% of patients with total colonic involvement with inflammation [1,2]. Primary sclerosing cholangitis has a strong male predominance, with a male:female ratio of 2:1 which is in contrast to the slight female predominance of ulcerative colitis in isolation. An increased prevalence of cholangiocarcinoma in patients with ulcerative colitis has been well recognized for many years, with cholangiocarcinoma being reported in 0.5% of patients with ulcerative colitis, and in whom the relative risk of developing a cholangiocarcinoma has been estimated as being over 31 times that of the general population [3]. However, with the increased recognition that cholangiocarcinoma is closely associated with primary sclerosing cholangitis, it seems likely that the increased risk of developing cholangiocarcinoma in ulcerative colitis occurs as a consequence of co-existing primary sclerosing cholangitis.

The prevalence of cholangiocarcinoma in patients with primary sclerosing cholangitis has been estimated in different series to range from 5-15% (Table 3) [1,4,5,6]. However, these figures may substantially underestimate the true prevalence of cholangiocarcinoma in PSC as it is clear that many cases of cholangiocarcinoma are only diagnosed either at laparotomy for liver transplantation at autopsy or by histological examination of explant livers from transplant recipients.

It has proved to be extremely difficult to diagnose cholangiocarcinoma in the setting of primary sclerosing cholangitis. Clinical features are not helpful, imaging is unreliable and tumour markers such as CA19-9 and CEA have not proved to be specific or sensitive enough to be clinically useful in the majority of cases [7]. The best data comes from a large study of 305 Swedish patients with PSC who were followed for a median time of 63 months [6]. Histological examination of the explant livers of transplant recipients revealed a prevalence of cholangiocarcinoma in PSC of 12/34 (35.3%) [6]. Moreover, cholangiocarcinoma was the main cause of death in 12/45 (26.7%) patients who had died without receiving a liver transplant [6]. The authors found that amongst the 79 patients who died or underwent liver transplantation, cholangiocarcinoma had developed in 24 (30.4%). It is clear from this data that primary sclerosing cholangitis is the major risk factor in the USA and Europe for the development of cholangiocarcinoma.

The high rate of cholangiocarcinoma in PSC has lead to a search to identify which patients are at high risk of developing cholangiocarcinoma with a view to expediting liver transplantation before this has occurred. Although some authors have suggested that tumor is more likely to develop in patients with end-stage disease, most studies have indicated that neither age, gender, the known duration of primary sclerosing cholangitis, the intra or extra-hepatic distribution of PSC, histological stage or the presence and duration of inflammatory bowel disease are of no predictive value [4,5]. However, two studies from Huddinge Hospital, in Sweden, have helped to elucidate the problem. In the first small study it was found that patients with PSC who smoked appeared to be at higher risk of cholangiocarcinoma, although the numbers involved were very small [8]. This is interesting, as smoking is clearly a major risk factor for pancreatic cancer and also both PSC and inflammatory bowel disease are found to be significantly more common in non-smokers. In a second important study, Broome et al have demonstrated that cholangiocarcinoma is significantly more prevalent amongst a sub-group of patients with ulcerative colitis complicated by colorectal dysplasia or cancer 7/16 (43.8%) than in those without colorectal neoplasia 2/24 (8.3%) [9]. Previous studies have shown that patients with ulcerative colitis and PSC are at higher risk of developing colorectal dysplasia than ulcerative colitis patients without PSC for reasons which are unclear. However, it does appear that patients in this group have an increased risk of both colonic and biliary malignancy. The mean interval between the first detection of the neoplastic lesions in the bowel and the development of cholangiocarcinoma was 8 years (range 0-22 years) [9]. In ulcerative colitis the development of colonic cancer is often preceded the development of low and then high grade dysplasia which has established the concept of surveillance in these patients to reduce the risk of colonic malignancy by performing colectomy in those patients in whom high grade dysplasia is established. Although biliary dysplasia had been reported previously in PSC the concept that it may anti-date the development of cholangiocarcinoma was put forward by Martins et al. [10]. This study suggested that the presence of dysplastic biliary epithelium in liver biopsy sections may have prognostic significance, as biliary dysplasia preceded the appearance of cholangiocarcinoma by at least 18 months in two patients. This concept has been confirmed and extended by a multicentre study by the European PSC Group [11]. This group found that 13% of patients had evidence of biliary dysplasia on a liver biopsy performed two years before the diagnosis of confirmed cholangiocarcinoma [11]. Thus, it may prove possible to either by a biliary tract cytology or by liver biopsy to consider biliary surveillance. However, these studies need to be confirmed by other groups, and proven by prospective studies.

Fibropolycystic diseases

Carolii's disease

Carolii's disease is a rare congenital disorder believed to be transmitted and to be autosomal recessive in most cases [12]. The disease consists of cystic dilatation of both intra-hepatic, and occasionally, the extra-hepatic bile ducts which maintain communication with the remainder of the biliary system [13]. The abnormalities may affect both hepatic lobes, and the segments as well as their secondary branches. Generally, it is localized in one lobe, and occasionally only one or two segments [12]. Carolii's disease is closely associated with congenital hepatic fibrosis and choledochal cysts have been reported in 21% of patients accompanying Carolii's and congenital hepatic fibrosis [14]. The clinical course is characterized by recurrent cholangitis with the formation of intra-hepatic calculi. Cholangiocarcinoma is a common complication. In the larger series 10/142 (7%) had developed malignancies of the liver or biliary tree, or which 8 comprised cholangiocarcinomas [15]. Although 8 of these 10 patients had previously undergone a biliary drainage operation, up to 14 years earlier, none had undergone hepatic resection [15]. Other authors have found
Cholangiocarcinoma in 11-14% of patients [16,17]. It seems likely, as in primary sclerosing cholangitis, malignancy develops in areas of severe dysplasia in the inflamed biliary tree.

In view of the high risk of cholangiocarcinoma, and the generally poor prognosis, liver transplantation has been advocated in patients who have generalized disease [12]. In patients with biliary disease confined in the minority of patients who have biliary disease confined to one hepatic lobe, hepatic resection may be indicated and this would appear to eliminate the risk of malignancy as there have been no reports of cholangiocarcinoma occurring after hepatic resection [12]. This concept is strengthened by the report of dysplastic biliary epithelium in a localized area of Caroli’s disease with no other abnormal findings in the surround normal biliary tree [18].

Choledochal cysts

Choledochal cysts, or congenital bile duct cysts, may be detected at any age, and in any portion of the bile duct. Although the classical symptoms and other patients may present late in adult life, and may even be picked up routinely as an unexpected finding on ultrasound scanning. The over all incidence of cholangiocarcinoma is 10% with a 1% per year cumulative risk plateauing after 15-20 years [19]. However, there is a decreased risk of cholangiocarcinoma in children presenting under 10 years who have a 0.7% over all risk [20]. In comparison the risk in patients presenting over the age of 20 is 14% [19]. In the light of these findings it has been suggested that all patients with choledochal cysts should be referred for complete resection, to prevent cholangiocarcinoma developing.

Liver flukes

In the Far East, lithiasis is caused more by major health problems. There are three bile duct flukes which are acquired by humans who eat raw fish; *Clonorchis sinensis*, *Opisthorchis viverrini* and *O. felineus*. The flukes are about 1cm in length and have a sucker which attaches to the intrabiliary hepatic duct epithelium, which then lives in the biliary system for approximately ten years. *C. sinensis* is mainly found in China and in East Asia [21]. *O. viverrini* is limited to North East Thailand, Laos and Cambodia. However, there is a high prevalence rate, particularly in North Eastern Thailand where approximately one third of the population is infected [22,23]. *O. felineus* infects cats and humans in areas of Eastern Europe, including Russia. There is strong epidemiological evidence to link infection with bile duct flukes with chronic biliary tract disease, and leading to the ultimate development of cholangiocarcinoma [24-26]. For example, in North East Thailand, a prevalence of 14.1% was found in male residents who had the highest intensity of *O. viverrini* infection and over 4% of the male population with more than 6,000 eggs per gm of faeces were found to have cholangiocarcinoma [24].

A hamster animal model has been developed which showed that the development of cholangiocarcinoma was related in *C. sinensis* infected hamsters to the simultaneous administration of the carcinogen dimethylnitrosamine [29,30]. Carcinogenic nitrosamines have also been implicated in man infected with *O. viverrini* [29,30].

The high rate of cholangiocarcinoma in endemic areas has lead to screening programmes and also attempts to modify dietary habits and eliminate existing infection with Praziquantel [31].

**Table 3: Prevalence of cholangiocarcinoma in patients with PSC.**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Location</th>
<th>Overall prevalence of cholangiocarcinoma (%)</th>
<th>Rate of detection cholangiocarcinoma at autopsy (%)</th>
</tr>
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<tbody>
<tr>
<td>Rosen <em>4</em></td>
<td>USA</td>
<td>5/70 (7.1)</td>
<td>5/12 (41.7)</td>
</tr>
<tr>
<td>Chapman <em>1</em></td>
<td>UK</td>
<td>3/29 (10.3)</td>
<td>3/11 (27.3)</td>
</tr>
<tr>
<td>Aadland <em>3</em></td>
<td>Sweden</td>
<td>4/45 (8.9)</td>
<td>4/12 (33.3)</td>
</tr>
<tr>
<td>Broome <em>6</em></td>
<td>Sweden</td>
<td>4/29 (13.8)</td>
<td>4/12 (33.3)</td>
</tr>
</tbody>
</table>

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Correspondence to:
Dr R W Chapman
Dept of Gastroenterology
Oxford Radcliffe Hospital
Headley Way
Headington
Oxford OX3 9DU
UK