Review Article

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F. Holzinger
H.U. Baer
M.W. Büchler

Department of Visceral and Transplantation Surgery, Inselspital, University of Bern, Switzerland

Mechanisms of Biliary Carcinogenesis and Preneoplastic Lesions

Key Words
Biliary cancer
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Risk factors
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Prevention strategies

Abstract
Carcinoma of the intra- and extrahepatic biliary tract is a relatively rare cancer. In most cases, the etiology of these cancers is rather obscure. Depending on the location of the carcinoma there are some risk factors identified such as hepatolithiasis and biliary calculi, congenital cystic and dysplastic lesions of the biliary tract, inflammatory bowel disease, thorotrast application, activated biliary bile acids, reflux and stasis of pancreatic juice, infection with the liver flukes *Clonorchis sinensis* (CL) and *Opisthorchis viverrini* (OV) and long-standing cholangitis. Multiple studies suggest that carcinogenesis in biliary epithelia is a multiple and multistage process through hyperplasia, metaplasia, adenoma, dysplasia, adenocarcinoma in situ to invasive adenocarcinoma in most cases of biliary cancer. Biliary carcinogenesis is caused by different mechanisms such as DNA damage produced by nitric oxide and by reactive oxygen species in infected and inflamed tissue, specific mutation in proto-oncogenes and tumor suppressor genes, mechanically damaged tissue by biliary calculi or parasites, reflux and stasis of pancreatic enzymes with activation of biliary acids and some other unidentified factors. Furthermore, some epidemiological facts and prevention strategies in relation to biliary cancer will be addressed based on a review of the literature.

Introduction

Carcinoma of the biliary tract should be subdivided into (1) cholangiocarcinoma; (2) carcinoma of the gallbladder; (3) carcinoma of the extrahepatic bile duct – divided into (a) proximal to the junction of the cystic duct including the hilar region (Klatskin tumors); (b) the lower mid-region with the cystic duct, and (c) the lower end of the common bile duct –, and (4) carcinoma of the papilla of Vater because of different incidence, clinical importance, therapeutic modalities and prognosis (table 1). Prognosis is considered worst for lesions affecting the confluence of the bile ducts (Klatskin tumors), and best for lesions near the papilla of Vater. Different histomorphological studies suggest that the biliary epithelium undergoes hyperplastic, adenomatous and dysplastic transformation by different risk factors and multistage carcinogenesis, and the adenomatous and dysplastic epithelium in turn transforms into noninvasive adenocarcinoma and finally to invasive adenocarcinoma [1–3]. Thus, the hyperplasia-metaplasia-adenoma-dysplasia-noninvasive and invasive carcinoma sequence may be operative in biliary carcinogenesis as is generally accepted for cancer development in the gastrointestinal tract (stomach and colon) [4]. In the following, we will discuss the epidemiological aspects of biliary cancer, the supposed risk factors for biliary carcinogenesis, some proposed mechanisms of carcinogenesis, the histomorphological findings, and, finally, some prevention strategies in order to prevent biliary cancer development.

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Prof. Dr. M.W. Büchler
Department of Visceral and Transplantation Surgery
Inselspital
University of Bern
CH-3010 Bern (Switzerland)

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Epidemiological Aspects of Biliary Cancer

Biliary cancer is a relatively rare cancer (table 2). The frequency of cholangiocarcinomas, which strictly speaking are only tumors of the intrahepatic bile ducts, is reported to vary between 5 and 30% of all liver cancers showing an incidence rate of 0.1–0.5% with a very high incidence in northeast Thailand and Hong Kong because of the endemic presence of liver flukes in these regions [5]. It is estimated that worldwide there are 46,000 cases of cholangiocarcinoma each year. However, at least 80% of this world total is unrelated to opisthorchis (OV) infection [5]. Because of effective treatment of opisthorchiasis with Praziquantel, a reduction in the incidence of cholangiocarcinoma in the high-risk regions in Asia seems possible. A carcinoma of the gallbladder is known to be found in approximately 1–2% of all resected gallbladders giving risk/year for the development of a gallbladder carcinoma of 0.01% of patients with cholecystolithiasis [6]. Gallbladder cancer is the commonest form of biliary malignancy and represents the fifth most common gastrointestinal cancer. Extrahepatic bile duct cancer shows an incidence rate of 0.01–0.5% with the worst prognosis in the proximal (hilar) tumors [5]. Carcinoma of the papilla of Vater is found in 0.2–0.3% of general autopsy studies [7] and represents about 1% of all epithelial malignancies and about 5% of all gastrointestinal tumors. A neoplasm in the papilla of Vater can be diagnosed early and has a good prognosis after surgical therapy [1], compared with the prognosis of carcinoma of the gallbladder, the proximal bile duct and cholangiocarcinoma which are equally poor because of diagnostic delay in most cases [8].

Table 1. Classification of biliary cancer [35]

1	Cholangiocarcinoma (intrahepatic)
2	Carcinoma of the gallbladder
3	Bile duct cancer
	3.1 proximal (Klatskin)
	3.2 lower-mid region with cystic duct
	3.3 lower end
4	Carcinoma of the papilla of Vater

Table 2. Percent incidence of different biliary cancers in autopsy studies

1	Cholangiocarcinoma	0.1–0.5
2	Carcinoma of the gallbladder	1–2
3	Bile duct cancer	0.01–0.5
4	Carcinoma of the papilla of Vater	0.2–0.3

Table 3. Risk factors for biliary carcinogenesis

Proved	Possible
Hepatolithiasis	Cholecystolithiasis
Congenital cystic lesions	Choledocholithiasis
APBD	Nitrosamines
Cholecystitis	
Cholangitis (PSC)	
Chronic ulcerative colitis	
Familial adenomatous polyposis	
Thorotrast	
Parasites (OV and CL)	

Risk Factors for Biliary Carcinogenesis

There have been relatively few epidemiological studies of biliary cancer. Most of the information on risk factors (table 3) which are likely to be important in biliary carcinogenesis is derived from clinical series.

Congenital Cystic Lesions, Caroli's Disease and Anomalous Arrangement of the Pancreaticobiliary Ducts (APBD)

Congenital choledochal duct dilatation and cyst formation with often elevated amylase levels in the choledochal cysts as in APBD leads one to assume that the longstanding inflammation of the biliary tract caused by the reflux of pancreatic juice and formation of secondary bile acids (lithocholic acid) due to a lack of sphincter function often with bacterial degradation, might be one of the factors in carcinogenesis in the biliary tract, especially in the gallbladder and in poorly drained choledochal cysts [9, 10]. Nowadays, it is accepted that there is an etiological link between the formation of congenital choledochal cysts and APBD except in patients with Caroli's disease and choledochocele. Several clinical series have shown that congenital choledochal cysts are associated with APBD in over 90% with a distal common bile duct stenosis at the pancreaticobiliary junction [9]. Caroli's disease is also associated with the development of cholangiocarcinoma more frequently than in patients without this condition