

Clinical and biological significance of precursor lesions of intrahepatic cholangiocarcinoma

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Abstract

Cholangiocarcinoma (CC) is primarily a malignant tumor of older adults most prevalent in Southeast Asia, where liver fluke infestation is high. However the etiology in western countries is unknown. Although the incidence of extrahepatic cholangiocarcinoma has remained constant, incidence of intrahepatic CC (ICC) which differs in

morphology, pathogenesis, risk factors, treatment and prognosis is increasing. While this increase is associated with hepatitis C virus infection, chronic nonalcoholic liver disease, obesity, and smoking, the pathogenesis of ICC and molecular alterations underlying the carcinogenesis are not completely elucidated. Benign biliary lesions such as biliary intraepithelial neoplasia, intraductal papillary neoplasm of the bile duct, von Meyenburg complex or bile duct hamartoma, and bile duct adenoma have been associated with ICC. For each of these entities, evidence suggests or supports a role as premalignant lesions. This article summarized the important biological significance of the precursor lesions of ICC and the molecular mechanisms that may be involved in intrahepatic cholangiocarcinogenesis.

Key words: Intraepithelial neoplasia; Von Meyenburg complex or bile duct hamartoma; Bile duct adenoma; Intrahepatic cholangiocarcinoma; Intraductal papillary neoplasm of the bile duct

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Core tip: This manuscript highlights the important development in the research field of intrahepatic cholangiocarcinogenesis, and summarizes some key points related to progression from the precursor lesions to the intrahepatic cholangiocarcinoma, including their molecular genetics. Each individual precursor or potential precursor is linked to the cancer by the clinical, histological and molecular association.

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INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is responsible for 10%-20% of primary liver cancers worldwide^[1]. ICCs are classified as perihilar or peripheral type. The perihilar type, involving the large bile ducts, is composed of a large tubular component or papillary proliferation of tall columnar epithelium with mucin production. The peripheral type, involving the smaller ducts and segmental branches, is composed of a proliferation of relatively small, tubular, closely packed cord-like structures or ductular pattern lined by small cuboidal epithelium^[2]. Grossly, both perihilar and peripheral ICC are firm and white to tan^[1]. Another classification scheme divides ICCs into conventional ductal carcinoma, bile ductular type, intraductal neoplasm and rare variants^[3], highlighting similarities between intraductal neoplasms and pancreatic intraductal papillary-mucinous neoplasms, and differences between bile ductular type and the conventional type on the origin of tumor cells. These classification schemes reflect the postulated cells of tumor origin with similarities between the perihilar type, conventional ductal carcinoma, bile duct type and mucin-producing type, and between the peripheral, bile ductular, cholangiolar and cholangiolocellular types^[2].

ICCs may evolve from two types of premalignant biliary lesions: Biliary intraepithelial neoplasia (BilIN) and intraductal papillary neoplasm of the bile duct (IPNB)^[3] as in the case of perihilar large duct type ICCs^[4]. ICC may also evolve without definite premalignant lesions. No intraepithelial or intraductal preneoplastic, dysplastic or neoplastic lesions have been demonstrated in the small bile ducts or ductules^[5]. Von Meyenburg complex (VMC) is suggested to be a possible premalignant lesion of ICCs due to the occasional association of VMC with ICCs and reports of VMC-like cystic ICCs^[6-8]. Progression of bile duct adenoma (BDA) to ICC has also been reported^[9]. The major clinical and histological characteristic features of above lesions are summarized in Figure 1 and Table 1. In addition to these precursor lesions, incidence is also increased in patients with risk factors such as chronic viral hepatitis, infection with parasites such as clonorchis and opistorchis, and hepatolithiasis^[1].

BILIN

BilIN is an epithelial lesion and a precursor to both ICCs (the intrahepatic bile ducts and peribiliary gland) and to extrahepatic cholangiocarcinoma (the extrahepatic bile ducts and gallbladder)^[10,11]. BilIN is characterized by epithelial cells with nuclear pseudostratification and atypia, often with micropapillary projections into the bile duct lumen^[10]. It is not grossly identifiable^[10]. BilIN has often been described as the biliary counterpart to pancreatic intraepithelial neoplasia (PanIN), partially due to the similar embryonal development and morphology of the pancreatic and biliary duct systems^[12]. Grading of BilIN follows a similar 3-tiered pattern to that of PanIN, which has proven similar in several morphologic and

immunohistochemical respects^[13]. BilIN is subdivided into BilIN-1, BilIN-2 and BilIN-3 according to consensus criteria proposed in 2005 and accepted by an international group in 2007^[14,15]. BilIN-1 shows relatively uniform, mildly irregular nuclei confined to the lower two thirds of the epithelium. In BilIN-2, nuclei are full-thickness and can be found apically, and loss of cellular and nuclear polarity is present but not diffuse. Nuclear irregularity is increased compared to BilIN-1, but mitoses remain rare. BilIN-3 is notable for marked cellular and nuclear atypia and loss of polarity, with cytological resemblance to invasive cholangiocarcinoma albeit without basement membrane invasion. Cribriforming and budding of cell clusters as well as mitoses are often seen^[11,15]. Macroscopic and radiologic identification of these lesions is not possible^[11].

BilIN has been associated with several conditions which can predispose to cholangiocarcinoma. There is no solid datum about the prevalence of BilIN. While estimates of overall prevalence of BilIN are difficult to determine, one study for margin status in biliary carcinomas showed that 4 of 19 ICCs had BilIN at the margin^[16].

BilIN is frequently diagnosed in cases of hepatolithiasis^[17], and primary sclerosing cholangitis and choledochal cyst have also been associated with BilIN^[15,18]. BilIN has also been shown to arise in autoimmune pancreatitis, chronic hepatitis B and C, and alcoholic cirrhosis^[19-21].

BilIN shares several molecular alterations with cholangiocarcinoma, and study of BilIN alongside cholangiocarcinoma has helped to elucidate several of the key molecular mechanisms in cholangiocarcinogenesis. Many of these molecular changes accumulate in conjunction with increasing grade of BilIN^[11]. KRAS has been shown to occur early in cholangiocarcinogenesis and is present in approximately 33% of BilIN lesions including in 25% of cases of BilIN-1^[22]. Also, p21, p53, cyclin D1 and EZH2 expression has been shown to increase and expression of Dcp4 and p16^{INK4A} decreases in tandem with increasing grade of BilIN^[3]. Importantly, p53 overexpression has been shown in BilIN-3 but reports show no increased expression in BilIN-1/2^[17,22]. Overexpression of EZH2 has been related to hypermethylation of the p16 promoter, which could explain the correlating increase in EZH2 expression and decrease of p16 expression with increasing grade of BilIN^[23]. Overexpression in EZH2 and decreased p16 expression are associated with deregulation of cellular senescence, and deregulation of autophagy has been shown through *in vitro* studies to precede cellular senescence^[24,25]. Related to these findings, it is notable that a recent study of expression of autophagy-related proteins showed that light chain 3 β (LC3), beclin-1 and p62 showed increased expression in BilIN-1, BilIN-2 and BilIN-3, suggesting that deregulated autophagy plays a role in occurrence and development of BilIN^[17]. Decreased membranous expression of β -catenin similarly correlates with increasing grade of BilIN, while E-cadherin is decreased in some cases of BilIN but in a smaller proportion of cases compared to

Table 1 Summary of the clinical and pathological features of intrahepatic cholangiocarcinoma and its precursor lesions

	ICC	BilIN	IPNB	VMC/BDH	BDA
Incidence/prevalence	10%-20% of primary liver cancers ^[1]	No published data	9%-38% of bile duct carcinomas ^[28]	5.6% of adults, 0.9% of children (autopsy series) ^[40]	0.0008%-0.006% of patients (autopsy series) ^[52,53]
Risk factors	Chronic viral hepatitis, clonorchis, opistorchis, hepatolithiasis ^[1]	Hepatolithiasis, primary sclerosing cholangitis, choledochal cyst, autoimmune pancreatitis, chronic viral hepatitis, alcoholic cirrhosis ^[15,17-21]	Hepatolithiasis, clonorchis ^[31,32]	Congenital hepatic fibrosis, polycystic liver disease ^[40]	No known risk factors
Gross appearance	Firm, white to tan ^[1]	Not grossly identifiable ^[10]	Dilated bile ducts filled with soft, papillary white to red to tan lesions without invasion ^[10]	Well-circumscribed unencapsulated nodules, < 5 mm ^[1]	Subcapsular, well-circumscribed unencapsulated gray to white, yellow or tan firm nodules, ≤ 2 cm ^[47,48]
Histologic appearance	Perihilar type: Involves large bile ducts, composed of large tubules or papillae lined by columnar epithelium. Peripheral type: Involves smaller ducts and segmental branches, composed of small, tubular cords or ductular pattern lined by cuboidal epithelium ^[2]	Epithelium with nuclear pseudostratification and atypia (increasing from BilIN-1 to BilIN-2 to BilIN-3), often with micropapillary projections into the bile duct lumen ^[10]	Noninvasive papillary or villous biliary neoplasm covering delicate fibrovascular stalks (subtypes pancreatobiliary, intestinal, gastric, oncocytic) ^[10]	Irregular dilated to branching low cuboidal epithelium-lined ductules within fibrous stroma, often adjacent to portal areas ^[1]	Small uniform cuboidal epithelium-lined ductules within fibrous stroma ^[47,48]
Molecular alterations	Activating mutations in KRAS (22%) occurs early in cholangiocarcinogenesis ^[63]	Activating mutation of KRAS present in approximately 33% of BilIN lesions including in 25% of cases of BilIN-1 ^[22]	Increased expression of Cyclin D1 and p21 ^[26,35]	Loss of heterozygosity at key loci (5q21, 9p21, 10q23, 17p13) harboring APC, p53, p16, and PTEN ^[44]	BRAF V600E mutation (53%) ^[46]
	Loss-of-function mutations in TP53 (15%), BRAF and EGFR mutation (7% and 2%) ^[55,61,65,67]	Increased expression of p21, p53, cyclin D1 and EZH2 ^[3,17,22-25]	Aberrant expression of p16 ^[30]		
	Rare NRAS and PI3K mutations have been ^[55,61-72]	Decreased expression of Dcp4 and p16INK4A. Loss of SMAD4/DPC4 associated with higher grade ^[3,30,35]	Inactivation of p53 associated with increasing grade of dysplasia and invasion ^[30]		
	IDH1 and IDH2 mutations co-occurring with increased TP53 expression and associated with DNA hypermethylation ^[62,66]	Decreased membranous expression of β-catenin with increasing grade of BilIN ^[26]	C-myc mutations in over 50% of cases ^[26]		
	Chromosomal aberrations including gains at 7p and 8q and losses at 1p, 4q and 9p ^[68,69,73-76]	Decreased expression of E-cadherin in some cases of BilIN ^[26]	Loss of SMAD4/DPC4 associated with higher grade ^[30,35]		
	Aberrant methylation of p16INK4a/CDKN2 (47%), RASSF1A (56%) and APC (29%) ^[70,71,76]	S100P: Increased immunohistochemical expression in BilIN-2 and BilIN-3 ^[27]			

BilIN: Biliary intraepithelial neoplasia; IPNB: Intraductal papillary neoplasm of the bile duct; VMC: Von Meyenburg complex; BDH: Bile duct hamartoma; BDA: Bile duct adenoma; ICC: Intrahepatic cholangiocarcinoma.

invasive cholangiocarcinoma^[26]. S100P also showed increased immunohistochemical expression in BilIN-2 and BilIN-3 as compared to reactive benign epithelium and BilIN-1^[27]. The S100P immunohistochemical marker is of particular interest as it has been suggested for use in clinical diagnosis and grading of BilIN^[11].

IPNB

IPNB, defined as a precursor to cholangiocarcinoma according to the World Health Organization 2010 classification, has been described as the biliary counterpart

to the intraductal papillary mucinous neoplasm (IPMN) of the pancreas^[10,28]. Similarly to IPMN, the neoplasm is characterized by thin fibrovascular cores lined with noninvasive papillary or villous epithelium and filling a dilated bile duct lumen^[10]. Grossly, IPNB shows dilated, fusiform to cystic bile ducts with soft papillary lesions ranging from white to tan to red. Histologically, the aforementioned fibrovascular cores are lined by any of four cell types: Pancreatobiliary, intestinal, gastric and oncocytic types, parallel to those defined in IPMN^[10]. However, there are important differences between IPNB and IPMN. Only approximately 1/3 of IPNB show

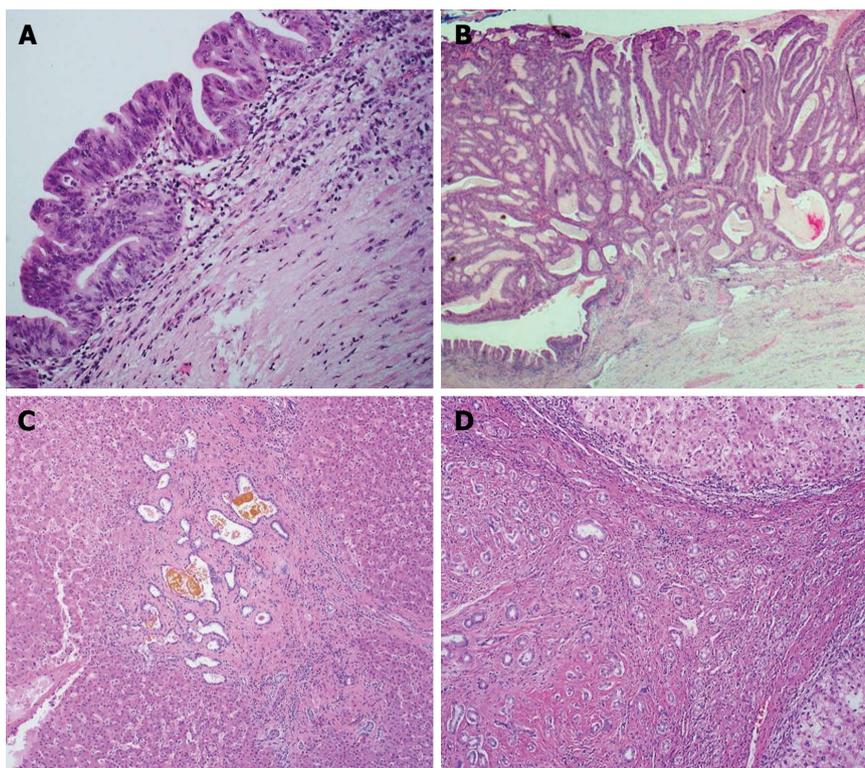


Figure 1 Premalignant biliary lesions. A: Biliary intraepithelial neoplasia. Biliary epithelium with nuclear pseudostratification and atypia; B: Intraductal papillary neoplasm of the bile duct. Papillary proliferation of neoplastic cells lining thin fibrovascular cores; C: Von Meyenburg complex. Small well-circumscribed lesion consisting of dilated irregular bile ducts embedded within dense collagenous stroma; D: Bile duct adenoma. Well-circumscribed proliferation of small uniform tubules surrounded by fibrous stroma.

macroscopic mucin production, while only rare IPMNs are not associated with mucin hypersecretion^[28,29]. Also, pancreatobiliary type epithelium is most common and gastric type epithelium is rare in IPNB, whereas IPMN least commonly shows pancreatobiliary differentiation^[10] and gastric is among the more common patterns^[30]. Just as grading of BilIN parallels that of PanIN, grading in IPNB follows that of IPMN. Low, intermediate and high grade are assigned based on cytologic and architectural characteristics, where low- and intermediate-grade tumors comprise one diagnostic entity, high-grade tumors another, and IPNB with associated invasive carcinoma a final separate entity^[10]. Studies of histomorphologic, molecular and other features of these tumors have shown disparate results to some extent due to the different features of IPNB with different etiology.

IPNB comprises 9%-38% of bile duct carcinomas and is most common in patients from far eastern countries in their 6th and 7th decades^[28]. In these patients who often have risk factors such as hepatolithiasis and clonorchiasis, intestinal subtype is most common (47% and 38% in two large series)^[31,32]. However, Western cohorts more commonly show pancreatobiliary type epithelium (36%, 69% and 45% of patients in three recent series from the United States and western Europe)^[30,33,34]. Series in all populations have shown uncommon oncocytic and gastric subtypes.

Molecular changes in IPNB remain poorly characterized, although several recent studies have begun

to explore various molecular mechanisms in these precursor neoplasms. Comparisons between IPNB and BilIN have shown conflicting results. Cyclin D1 and p21 expression increase occurs in IPNB just as it does in BilIN; a study by Itatsu *et al.*^[26] showed higher expression in IPNB than in BilIN while Nakanishi *et al.*^[35] did not find this differential expression. Another cell cycle protein, p16, has also shown aberrant expression in IPNB and this aberrant expression was shown to be more frequent in cholangiocarcinoma than in IPNB^[30]. Inactivation of p53 has been shown to increase with increasing grade of dysplasia and with invasion in one study^[30], while other studies have shown different results^[35,36]. C-myc mutations have been shown to be common as well with expression in over half of cases in one study^[26]. Similar to pancreatic neoplasms, loss of SMAD4/DPC4 has been shown in IPNB and BilIN with increased loss associated with higher grade^[30,35]. GNAS mutation has been seen mostly in intestinal subtype and mucin hypersecretion-associated cases, and has been recognized more frequently in studies involving Asian cohorts where intestinal subtype is more common^[30,37]. KRAS mutations on the other hand appear more common in early and low-grade lesions^[28,30].

VMC (BILE DUCT HAMARTOMA)

VMCs, also known variously as bile duct or biliary hamartomas or as biliary microhamartomas, are small

(generally < 5 mm), well-circumscribed unencapsulated nodules which consist of irregularly shaped, often dilated bile ducts lined by a low cuboidal epithelium, embedded within a dense collagenous stroma. VMCs are thought to result from persistence of the embryonic ductal plate and are generally adjacent to portal areas^[1]. Multiple case reports showed exist of VMCs with histologic evidence of transformation to cholangiocarcinoma, showing benign, hyperplastic and dysplastic epithelium with adjacent progression to invasive carcinoma^[7,8,38,39].

These lesions are fairly common with prevalence of 5.6% in adults and 0.9% of children in one autopsy series, and are especially prevalent in patients with adult polycystic kidney disease or congenital hepatic fibrosis^[40]. VMCs are generally considered benign, but several case reports suggest that these lesions are capable of transformation to cholangiocarcinoma, showing benign, hyperplastic and dysplastic epithelium with adjacent progression to invasive carcinoma, particularly in patients with multiple VMCs^[8,38,39,41-43]. This phenomenon has been corroborated with molecular evidence of mutations shared between cholangiocarcinoma and VMCs^[44]. Further suggesting this link is a radiologic study of 6 patients with multiple VMCs in which one of the six (17%) patients with initial imaging evidence of VMCs developed cholangiocarcinoma within 2 years^[45].

Specific molecular genetic changes for transformation of VMCs to cholangiocarcinoma have not been definitively established^[38]. In contrast to biliary duct adenomas, BRAF V600E mutations seen in a subset of ICC are not present in VMCs^[46]. However, recent studies have identified multiple findings suggestive of the sequential genetic changes required for transformation of benign VMCs to invasive cholangiocarcinoma^[38,44]. In one study of two patients with multiple VMCs and cholangiocarcinoma, loss of heterozygosity (LOH) was examined at 20 key genetic loci in the cholangiocarcinoma tumor, in VMCs distant from the tumor, and in intermediate lesions where VMCs showed transformation to cholangiocarcinoma. LOH was seen in VMCs at some of the same key loci as seen in cholangiocarcinoma, affecting oncogenes p16, p53, APC and PTEN which have been shown to play a role in the development of cholangiocarcinoma^[44]. In contrast, immunohistochemical expression of p16INK4A was shown to be lost in cholangiocarcinoma in one report while adjacent uninvolvement VMC ducts retained expression of p16INK4A^[38].

BDA OR PERIBILIARY GLAND HAMARTOMA

BDA are small (< 2 cm) benign gray to white, yellow or tan lesions usually located directly beneath the liver capsule. They are firm, well-circumscribed and not encapsulated. Histologically, they are comprised of uniform tubular or curvilinear ductules within a fibrous stroma^[47,48]. The ductules are lined by cuboidal cells with bland, round to oval nuclei and without mitotic activity,

and sometimes show mucinous metaplasia, 1-antitrypsin droplets and neuroendocrine differentiation. Previously synonymous with bile duct hamartoma (BDH)^[49] - BDA and BDH have overlapping features - histological findings and immunohistochemical properties aid in distinguishing between the two. It has been reported that BDAs originate from peri-biliary glands and not bile ductules or ducts^[50]. This finding is supported by the monoclonal antibody identification of antigens D10 and IF6 and the presence of mucin cells; a shared profile amongst peribiliary glands and BDAs but not VMCs. Malignant transformation of BDA has not been unequivocally demonstrated. ICC in a background of BDA mixed with minor component of BDH is reported in the literature^[51] (also present in authors' unpublished case report). There has also been a report of progression of BDA to ICC^[9]. BDA is a rare lesion and has been found in 0.0008%-0.006% of patients in two large autopsy series^[52,53].

Molecular characterization of BDAs is incomplete. The BRAF V600E mutation was identified by PCR and immunohistochemistry in 53% (8/15) cases of BDA in one series^[46]. Interestingly, both wild-type BRAF and BRAF V600E lesions coexisted in patients with multiple BDAs. Identification of oncogenic mutations in BDA supports a benign neoplasm rather than reactive process and suggests that BDA may be an early lesion in the pathogenesis of ICC, which has been shown to harbor BRAF V600E mutations^[54,55]. Furthermore, the finding of coexistence of benign lesions, dysplastic lesions and carcinoma (authors' unpublished data) and progression of BDA to ICC^[9] strongly suggests an adenoma-dysplasia-carcinoma pathway, as seen in colorectal carcinogenesis. BRAF V600E mutation was not identified in von Meyenberg complexes, supporting distinct etiologies with different molecular and biological processes^[46].

BILIARY ADENOFIBROMA

Few cases of biliary adenofibroma^[56-59], a benign tumor with complex tubulocystic nonmucin secreting biliary epithelial and an abundant fibroblastic stromal components, have been reported to date. The immunohistochemical profile (cytokeratins 7, 8, 18, 19 and D10 positive, and 1F6 negative) suggests a large bile duct or interlobular duct origin^[59,60]. Malignant transformation of the epithelial component has been reported^[56].

MOLECULAR GENETICS OF ICCS AND PRECURSORS

Molecular alterations underlying ICC and the pre-malignant biliary lesions are not completely elucidated. Activating mutations in KRAS (22%), loss-of-function mutations in TP53 (15%), BRAF and EGFR mutation (7% and 2%), and rare NRAS and PI3K mutations have been reported^[55,61-72]. IDH1 and IDH2 mutations co-occurring

with increased TP53 expression and associated with DNA hypermethylation has also been reported, although the functional relevance is unknown. Chromosomal aberrations including gains at 7p and 8q and losses at 1p, 4q and 9p were identified by comparative genomic hybridization studies^[69,73-76]. Aberrant methylation of p16INK4a/CDKN2 (47%), RASSF1A (56%) and APC (29%) genes have been demonstrated in ICC although the exact role in the pathogenesis is also not delineated. Investigation of genetic and epigenetic alterations in benign intrahepatic biliary lesions will further highlight mechanisms of carcinogenesis.

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