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REVIEW

# Biliary carcinogenesis in pancreaticobiliary maljunction

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**Abstract** Pancreaticobiliary maljunction (PBM) is a congenital malformation in which the pancreatic and bile ducts join anatomically outside the duodenal wall. Because of the excessive length of the common channel in PBM, sphincter action does not directly affect the pancreaticobiliary junction, which allows pancreatic juice to reflux into the biliary tract. According to the results of a nationwide survey, bile duct and gallbladder cancers were found in 6.9 and 13.4 % of adult patients with congenital biliary dilatation, respectively, and in 3.1 and 37.4 % of those with PBM without biliary dilatation, respectively. Biliary tract cancers develop about 15–20 years earlier in patients with PBM than in individuals without PBM; they sometimes develop as double cancers. Carcinogenesis is strongly associated with stasis of bile intermingled with refluxed pancreatic juice. Epithelial cells in the biliary tract of PBM patients are under constant attack from activated pancreatic enzymes, increased secondary bile acids, or other mutagens. This can result in hyperplastic change with increased cell proliferation activity, and in turn, oncogene and/or tumor suppressor gene mutations in the epithelia, leading to the biliary tract carcinogenesis. The carcinogenesis of biliary tract cancer accompanying PBM is considered to involve a hyperplasia–dysplasia–carcinoma sequence induced by chronic inflammation caused by the reflux of pancreatic juice into the biliary tract, which differs from the adenoma-carcinoma sequence or the de novo carcinogenesis associated with biliary tract cancers in the population without PBM. Patients with a relatively long common channel have a similar, albeit slightly lower, risk for gallbladder cancer compared with PBM patients.

**Keywords** Pancreaticobiliary maljunction · Congenital biliary dilatation · Gallbladder cancer · Bile duct cancer · Pancreatobiliary reflux

## Introduction

Pancreaticobiliary maljunction (PBM) is a congenital malformation in which the pancreatic and bile ducts join anatomically outside the duodenal wall. For the diagnosis of PBM, an abnormally long common channel and/or an abnormal union between the pancreatic and bile ducts should be demonstrated on direct cholangiography (endoscopic retrograde cholangiopancreatography, transhepatic cholangiography, or intraoperative cholangiography) or magnetic resonance cholangiopancreatography (MRCP). PBM is also diagnosed when the pancreaticobiliary junction is observed outside the duodenal wall on endoscopic ultrasonography (US) or multidetector-row computed tomography and multi-planar reconstruction [1, 2].

PBM is classified as either PBM with biliary dilatation (congenital biliary dilatation, which involves local dilatation of the extrahepatic bile duct, including the common bile duct) or PBM without biliary dilatation. For the assessment of biliary dilatation, the maximum diameter of the bile duct is measured by non-pressure imaging modalities such as US or MRCP. As the standard diameter of the bile duct is correlated with age, the diagnosis of

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dilatation should be based on the upper limit of the bile duct diameter in each patient [3, 4].

The sphincter of Oddi, which regulates the outflow of bile and pancreatic juice, is typically located at the distal end of the pancreatic and bile ducts. In PBM, because of the excessive length of the common channel, sphincter action does not directly affect the pancreaticobiliary junction, and because the hydropressure in the pancreatic duct is usually greater than that in the bile duct, pancreatic juice frequently refluxes into the biliary tract (pancreatobiliary reflux). Persistently refluxed pancreatic juice injures the epithelium of the biliary tract and promotes the development of cancer, resulting in higher rates of carcinogenesis in the biliary tract of PBM patients. In some situations, bile refluxes to the pancreatic duct, and this biliopancreatic reflux may lead to pancreatitis (Fig. 1) [1, 2, 5].

## Clinical features of biliary cancer associated with PBM

In a nationwide survey in Japan ($n = 2561$) [6], biliary tract cancers were detected in 21.6 and 42.4 % of adult PBM patients with and without biliary dilatation, respectively. Furthermore, among patients with biliary tract cancers in association with PBM, bile duct and gallbladder cancers were found in 32.1 and 62.3 % and in 7.3 and 88.1 % of those with and without biliary dilatation, respectively. In other words, bile duct and gallbladder cancers were found in 6.9 and 13.4 % of adult patients with congenital biliary dilatation, and in 3.1 and 37.4 % of adult patients with PBM without biliary dilatation. Biliary tract cancer was only found in one pediatric patient with congenital biliary dilatation. The mean age at which PBM patients developed biliary tract cancers was 60.1 and 52.0 years for gallbladder and bile duct cancer, respectively, in patients with congenital biliary dilatation, and 58.6 years for gallbladder cancer in PBM patients without biliary dilatation. These patients developed biliary tract cancer about 15–20 years earlier than those without PBM [7].

In our series of 129 PBM patients, bile duct and gallbladder cancer occurred in eight (11 %) and 15 (21 %) of 73 patients with congenital biliary dilatation, and in two (4 %) and 43 (77 %) of 56 patients with PBM without biliary dilatation. These included metachronous ($n = 1$) and simultaneous ($n = 2$) multiple biliary cancers (Table 1). In other studies, 19 (51 %) of 37 patients with simultaneous double or multiple biliary tract cancers suffered from concurrent PBM [8–12]. The prevalence of gallstone detection in our 43 PBM patients without biliary dilatation who developed gallbladder cancer was only 9 %, which is significantly lower than the 62 % reported among the gallbladder cancer population without PBM [13].

## Carcinogenesis in the biliary tract of PBM patients

### Pathophysiology

The mechanism of carcinogenesis in PBM appears to be related to the persistence of pancreatic juice refluxed into the biliary tract. Owing to the increase of intraductal pressure of the bile duct or bacterial infection, refluxed

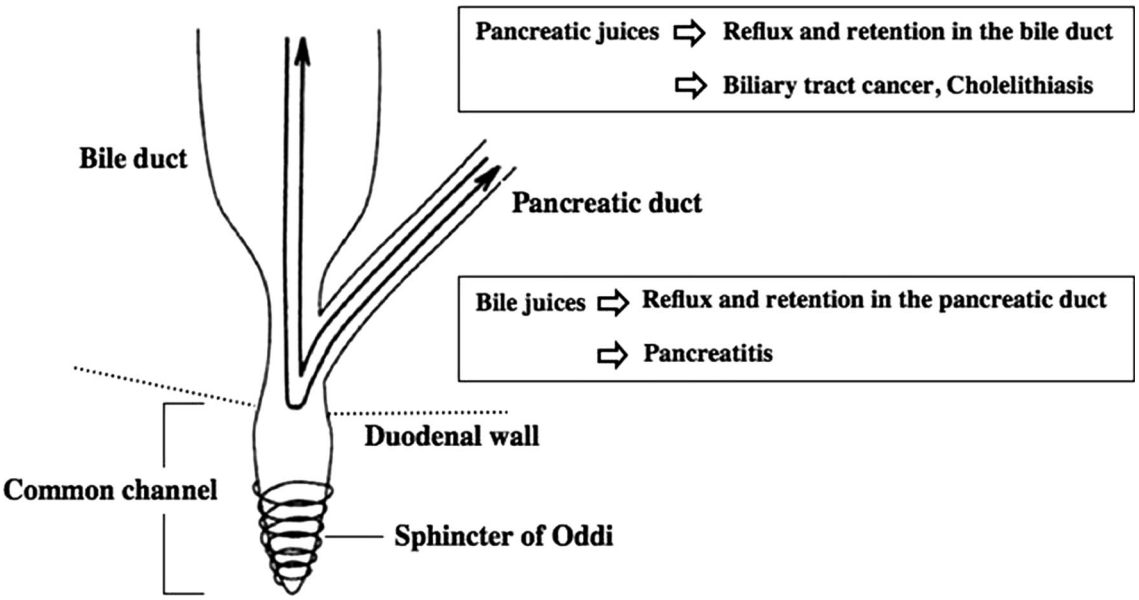


**Fig. 1** Pathophysiology of pancreaticobiliary maljunction [1]

**Table 1** Occurrence rates of associated biliary cancer in Tokyo Metropolitan Komagome Hospital

| | Congenital biliary dilatation ($n = 73$) | PBM without biliary dilatation ($n = 56$) |
|---|---|---|
| Male:female | 1:3.4 | 1:3.3 |
| Bile duct cancer | 8 (11 %) | 2 (4 %) |
| Gallbladder cancer | 15 (21 %) | 43 (77 %) |

proteolytic pancreatic enzymes and phospholipase $A_2$ are easily activated in the biliary tract. Phospholipase $A_2$ has a powerful destructive action and converts lecithin within the bile to lysolecithin, which has a strong damaging effect on the cell membrane [14]. In the bile of PBM patients, increased levels of secondary bile acids, especially taurodeoxycholic acid, have been found [15], as have mutagenic substances that damage DNA, both clinically and in experimental animal models [16, 17]. Exposure to harmful substances accelerates the cell cycle, which adversely affects the epithelium and damage DNA.

## Pathological findings

Bile stasis accompanied by refluxed pancreatic juice induces various histopathological changes, including inflammation, hyperplasia, metaplasia, and dysplasia. The characteristic finding in the gallbladder of PBM patients is hyperplastic change of the epithelium [18]. In our series, the thickness of the gallbladder mucosa was significantly higher in PBM patients than in controls (6.3 vs. 3.2 mm, respectively; $p < 0.01$), and the incidence of epithelial hyperplasia of the gallbladder was significantly higher in PBM patients than in controls (73 vs. 0 %, respectively; $p < 0.01$). The Ki-67 labeling index, a marker of cell proliferation activity, was significantly higher in the gallbladder epithelium of PBM patients than in that of controls (8.1 vs. 1.4 %, respectively; $p < 0.01$) [5, 19, 20]. Furthermore, hyperplastic change of the gallbladder epithelium has been found in 39–91 % of patients with PBM [21, 22]. Tokiwa et al. reported finding gallbladder epithelial hyperplasia in 50 % of 28 pediatric patients with PBM [23]. A hyperplastic polyp of the gallbladder was reported in a 9-year-old girl with PBM [24]; however, the incidence of high-grade hyperplasia increases with age, and dysplasia or metaplasia of the gallbladder epithelium is typically detected only from adolescence onwards [22, 25]. Dysplasia is frequently observed in the mucosa around the gallbladder cancer. Hyperplastic epithelium can be present from the early stages of infancy or at birth, while dysplasia or metaplasia appears with age. In consideration of these facts, a hyperplasia–dysplasia–carcinoma sequence can be suggested in the carcinogenesis process in PBM [25, 26].

Overexpression of cyclooxygenase-2 and vascular endothelial growth factor [27] and mucin core protein [28] were reported in the hyperplastic biliary epithelia of PBM patients.

## Gene mutation

Point mutation of *K-ras* oncogene is frequently observed in gallbladder and bile duct cancers. However, in PBM patients, in addition to biliary tract cancers, *K-ras* mutation is detected in the noncancerous epithelium of the gallbladder and bile duct. Matsubara et al. reported that in PBM patients without biliary carcinoma, *K-ras* mutation was detected in 33 and 40 % of the gallbladder and bile duct epithelium, respectively [29]. Iwase et al. reported that *K-ras* mutation was detected in 36 % of hyperplastic gallbladder lesions in PBM patients [30]. *K-ras* mutation was reportedly detected in 64, 28, and 17 % of PBM patients with hyperplastic, metaplastic, and dysplastic gallbladder epithelium, respectively [31]. In our series, *K-ras* mutation was detected in the noncancerous gallbladder epithelium of 36 % of the PBM patients [5, 19]. Since *K-ras* mutation is often detected in the hyperplasia and noncancerous gallbladder epithelium of gallbladder of PBM patients, these epithelia could be considered to be in a genetically precancerous state and therefore represent an early event in multistep carcinogenesis.

Mutation of suppressor gene *p53* is frequently detected in biliary tract cancer. Matsubara et al. reported that mutation of the *p53* gene was detected in 39 % of the noncancerous biliary epithelium of PBM patients [32], while Nagai et al. reported that *p53* gene mutation was not detected in the noncancerous gallbladder epithelium of PBM patients [33]. Therefore, although it remains unclear whether *p53* gene mutation is present in the noncancerous biliary epithelium of PBM patients, because it is regarded as a late event in carcinogenesis within the adenoma-carcinoma sequence of cancer, it may occur in relatively late stages of the carcinogenetic process in PBM.

Microsatellite instability (MSI), an important factor in carcinogenesis, is reflected in abnormalities of DNA repair genes. Nagai et al. reported that although MSI was undetected in hyperplasia, it was detected in 85.7 % of dysplasia of the biliary epithelium involving PBM patients [33]. Therefore, similar to *p53* gene mutation, MSI might play a role as a late event in the carcinogenetic process in PBM.

*Bcl-2* expression and increased telomerase activity in the gallbladder epithelium of PBM patients were also reported [34].

Epithelial cells of the biliary tract of PBM patients are under constant attack from activated pancreatic enzymes, increased secondary bile acids, and other mutagens, which leads to hyperplastic change with increased cell proliferation activity. This leads to oncogene and/or tumor suppressor gene mutation in the epithelia, and subsequently biliary tract carcinogenesis. Therefore, the carcinogenesis of biliary tract cancer accompanying PBM appears to involve the hyperplasia–dysplasia–carcinoma sequence caused by the chronic inflammation induced by pancreatic juice refluxed into the biliary tract, which differs from the adenoma-carcinoma sequence or the de novo carcinogenesis associated with biliary tract cancers in the population without PBM [1, 4] (Fig. 2).

## Treatment of PBM

Once PBM is diagnosed, prophylactic surgery is recommended before malignant changes can take place in the biliary tract. The treatment of choice for congenital biliary dilatation is excision of the extrahepatic biliary tract with biliary reconstruction (flow-diversion surgery). As remnant bile duct mucosa preceding progression to cancer might advance over time, extended or total excision of the biliary tract is necessary. The hepatic side should be transected at the confluence of the right and left hepatic ducts, and the pancreatic side should be transected just above the junction of the bile and pancreatic ducts [1, 4, 26].

The treatment of PBM without biliary dilatation remains controversial. As most biliary tract cancers that develop in patients with PBM without biliary dilatation are gallbladder cancers, only prophylactic cholecystectomy is performed in many institutions. However, in some institutions, because of a perceived risk of bile duct cancer, the extrahepatic bile duct is excised together with the gallbladder [1, 4, 26, 35].

## Risk of gallbladder cancer in regard to a relatively long common channel

The frequency of common channel formation ranges from 55 to 91 %, and the mean length of the common channel has been reported to be 4.5 mm [36, 37]. To investigate the clinical significance of a relatively long common channel, we defined a high confluence of pancreaticobiliary ducts (HCPBD) as a disease state in which the common channel length was $\geq$6 mm and communication was occluded during contraction of the sphincter [36]. Among HCPBD patients, reflux of contrast medium into the pancreatic duct during postoperative T-tube cholangiography (biliopancreatic reflux) and elevation of amylase levels in the bile (pancreatobiliary reflux) were frequently observed. Gallbladder cancer was observed in 12 % of HCPBD patients. Similar to PBM patients, hyperplastic change with increased epithelial cell proliferation activity and *K-ras* mutation was also detected in the non-cancerous epithelium of the gallbladder of HCPBD patients. Itoi et al. also reported that Ki-67 labeling index in non-cancerous epithelium of gallbladder was significantly higher in

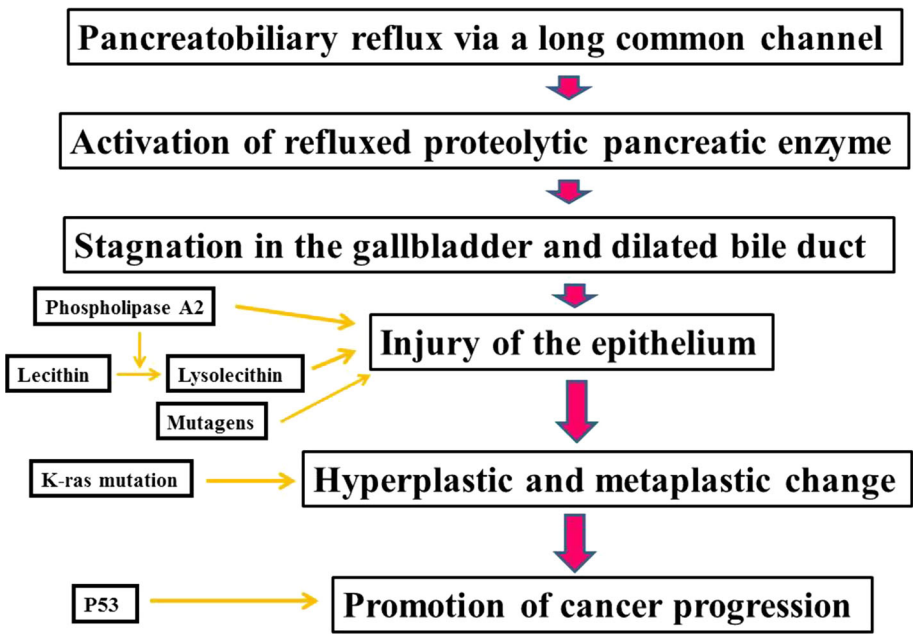


**Fig. 2** Mechanism of biliary carcinogenesis in pancreaticobiliary maljunction

patients with occult pancreatobiliary reflux than those with low biliary amylase levels [38]. A relatively long common channel also appears to be an important risk factor for the development of gallbladder cancer, although the risk is lower than that in relation to PBM [19, 20, 36, 39].

## Conclusions

Activated proteolytic pancreatic enzymes and other cytotoxic substances constantly injure the epithelia of the biliary tract of PBM patients, leading to hyperplastic and dysplastic changes with increased cell proliferation activity. This causes the mutation of oncogenes and/or tumor suppressor genes in the epithelia, which can lead to biliary tract carcinogenesis. Therefore, the carcinogenesis of biliary tract cancer accompanying PBM is considered to involve the hyperplasia–dysplasia–carcinoma sequence resulting from chronic inflammation induced by refluxed pancreatic juice.

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