Hypothesis: Pancreaticobiliary maljunction (PBM) is a high-risk factor for biliary tract carcinogenesis because of a continuous reflux of pancreatic juice into the biliary tract. It remains to be disclosed whether we should perform prophylactic excision of gallbladders and bile ducts.

Design: A person-year method.

Setting: A university hospital.

Patients: We studied 68 patients with PBM treated between August 1, 1974, and December 31, 1999.

Main Outcome Measures: Relative risks (observed number–expected number ratios) of gallbladder and bile duct carcinomas according to type of bile duct dilation (ie, cystic dilation, diffuse dilation, and nondilation).

Results: Observed number–expected number ratios of gallbladder carcinomas were high: 291.3 in 43 patients with cystic dilation, 167.2 in 16 patients with diffuse dilation, and 419.6 in 7 patients with nondilation. Observed number–expected number ratios of bile duct carcinomas were 194.2 in 43 patients with cystic dilation before surgery and 142.8 in 39 patients with cystic dilation after long postsurgical follow-up. All these values were statistically significant (P<.01).

Conclusions: The gallbladder carries a high risk for carcinogenesis in all types of dilation in patients with PBM. The bile duct carcinomas of PBM were exclusively identified by the type of cystic dilation. Prophylactic cholecystectomy should be recommended for all dilation types, and prophylactic excision of bile ducts including cholecystectomy should be performed in patients with PBM and cystic dilation. Complete excision of extrahepatic dilated bile ducts and careful follow-up for carcinogenesis in residual dilated bile ducts should be recommended for patients with PBM and cystic dilation.

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IT IS WELL KNOWN that choledochal cysts are frequently associated with biliary tract carcinoma.1,2 Choledochal cysts are usually accompanied by anomalous pancreaticobiliary ductal junction, for which the term “pancreaticobiliary maljunction” (PBM) is commonly used in Japan. As a clinical entity, PBM has commonly been accepted as the cause and pathogenesis of carcinoma of the biliary tracts.3,4 Reflux of pancreatic juice into the biliary tract due to PBM has been considered a major risk factor for the development of biliary tract carcinogenesis in patients with PBM.3

Some patients with PBM have normal common bile ducts (nondilation type), and it is still unclear whether bile duct carcinoma develops even in those nondilation bile ducts.4 In this study, we classified patients with PBM into 3 types according to the complication of choledochal dilation: cystic dilation, diffuse dilation, and nondilation. Although the Todani classification of types of bile duct dilation has been widely accepted, we applied the simple classification described in the previous sentence, which is frequently used in Japan.

See Invited Critique at end of article

The aims of this study were to clarify the frequent carcinogenic sites of biliary tracts according to the type of bile duct dilation present and to disclose the significance of prophylactic excision of gallbladders and bile ducts in patients with PBM.

RESULTS

INCIDENCES OF GALLBLADDER AND BILE DUCT CARCINOMAS

Three (7%) of 43 patients with cystic dilation, 5 (31%) of 16 patients with diffuse dilation, and 6 (86%) of 7 patients with nondilation had gallbladder carci-
PATIENTS AND METHODS

PATIENTS

We studied 68 patients with PBM who underwent excision of extrahepatic bile ducts by hepaticojejunostomy or cholecystectomy between August 1, 1974, and December 31, 1999, at the Second Department of Surgery, Chiba University Hospital, Chiba, Japan. Pancreatobiliary maljunction is defined in Japan as a congenital anomaly in which the union of the pancreatic and biliary ducts is outside the duodenal wall, with an obviously long common channel, or exists in an apparently anomalous form.7 Confirmation is usually made by endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography.

CLASSIFICATION OF PBM

We classified PBM into 3 types—cystic dilation, diffuse dilation, and nondilation—according to the complication of choledochal dilation using endoscopic retrograde cholangiopancreatographic or percutaneous transhepatic cholangiographic findings. Although the Todani classification of bile duct dilation types has been widely accepted, it includes rare types such as types II, III, IV-B, and V. Therefore, we applied the simple classification, which had been commonly used in Japan. The nondilation type was defined as having a maximum choledochus diameter of less than 10 mm and the other 2 types were defined as having a maximum diameter greater than 10 mm. The cystic dilation type was defined as having a ratio of maximum to portal minimum choledochus diameter greater than 2 and the diffuse dilation type was defined as having a ratio of less than 2. The diffuse dilation type included 16 patients with spindlelike or cylinderlike choledochus (Todani type 1c). Of 68 patients with PBM, 43 had cystic dilation (Todani type 1a [n=23] or IV-A [n=20]), 16 had diffuse dilation (Todani type 1c), 7 had nondilation, and 2 had unknown types.8

INCIDENCES OF CARCINOMAS AND STATISTICAL ANALYSES

We analyzed the relative risk of bile duct carcinoma (gallbladder and bile duct carcinomas) in patients with PBM using the person-year method.9,10 Relative risk was calculated as the observed number–expected number (O/E) ratio, where the expected number was obtained from the standardized morbidity rate (SMR) and the observation period.11 The observation periods were the intervals between birth and the operation for the presurgery group and between the operation and the final day of observation for the postsurgery group. These periods were recorded between January 1, 1974, and December 31, 1999. Therefore, the beginning point of observation in the presurgery group was January 1, 1974, or birth day after January 1, 1974, and the ending point in the postsurgery group was the final day of observation, including day of death, before December 31, 1999, or during December 31, 1999. The SMR was obtained in each sex and age class for every 5 years for the general population in the central area of Chiba Prefecture in Japan (from the Annual Report of the Cancer Registration Project of Chiba Prefecture). The expected numbers were calculated as follows: product = (total observation period of each observed PBM patient in each sex and age class) × (the SMR of biliary tract carcinoma in the central area of Chiba Prefecture in each corresponding sex and age class). Because gallbladder and bile duct carcinomas were registered together in one category in the Annual Report, the SMR and expected numbers were calculated as biliary tract carcinoma involving gallbladder carcinoma and bile duct carcinoma, and the SMR and expected numbers were the same values in every dilation group. The expected number is considered to be the number of patients with biliary tract carcinoma (gallbladder carcinoma plus bile duct carcinoma) if patients with PBM had the same morbidity rate as the general population. The significance of the relative risk to the general population was tested by Poisson distribution. The level of statistical significance was defined as P<.05.

PATHOHISTOLOGIC STUDIES OF BILIARY TRACTS

Pathohistologic examinations of excised gallbladders and bile ducts were performed in all patients. Confirmation of bile duct carcinoma was made by pathologists at our hospital (Chiba University Hospital, Chiba, Japan) using surgical or autopsy specimens. We classified the pathological stages of gallbladder carcinoma according to the 1997 TNM classification of malignant tumors of the International Union Against Cancer.12

GALLBLADDER CARCINOMA

Table 1 shows the pathological stages, operative methods, and prognoses in 14 patients with gallbladder carcinoma. In the cystic dilation group, 2 of 3 patients had gallbladder carcinoma as highly advanced as stage IVB and died within 2 years 2 months of surgery because of

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tumor growth. In the diffuse dilation group, 3 of 5 patients had gallbladder carcinoma as advanced as stages III and IVA; 2 of them died within 2 years of surgery because of tumor growth. On the other hand, in the non-dilation group, 5 of 6 patients had gallbladder carcinoma at the relatively early stage II. Two patients underwent cholecystectomy alone and remain free from recurrence.

**CHOLECYSTECTOMY**

**Table 2** shows the prognoses of 4 patients who underwent cholecystectomy only.

**BILE DUCT CARCINOMA**

All patients other than those who underwent cholecystectomy only underwent bile duct excision with cholecystectomy. **Table 3** shows the cancer stages and sites in 5 patients with bile duct carcinoma. Patient 1, a 30-year-old woman, developed carcinoma in the middle of the common bile duct (stage II [T2]) and also in the gallbladder (patient 1 in Table 1). Because of cancer surface spreading for intrapancreas bile duct, pancreaticoduodenectomy was carried out with hepaticojejunostomy. The postoperative pathohistologic examination revealed adenosquamous cell carcinoma of the common bile duct and gallbladder. Patient 2, a 55-year-old woman, generated carcinoma in the upper segment of the common bile duct that invaded the intrahepatic bile duct wall. Multiple liver and peritoneal metastases were revealed during surgery, and the patient died 4 months later (stage IVB [M1]).

Patients 3, 4, and 5 developed carcinomas in the residual dilated bile ducts 19 years 6 months, 8 years 8 months, and 2 years 5 months after surgery, respectively. These 3 patients had no history of abdominal surgery. Patient 3, a woman aged 35 years at the time of hepaticojejunostomy, was admitted to the hospital 19 years 6 months after Roux-en-hepaticojejunostomy with symp-
Gallbladder carcinoma is frequently detected in patients with PBM with and without choledochal dilation. In the present study, the incidence of gallbladder carcinoma in patients with PBM was 291.3 times higher in the cystic dilation, 167.2 times higher in the diffuse dilation, and 419.6 times higher in the nondilation group than in the general population. Because of the high frequency of gallbladder carcinoma, we should affirm the necessity of prophylactic cholecystectomy for patients with PBM. The incidence of gallbladder carcinoma was high in the nondilation group (6 of 7 patients) and 419.6 times higher than in the general population, perhaps because PBM could be diagnosed in most patients in the cystic dilation and diffuse dilation groups by means of identification of dilated choledochus, using ultrasonography and after endoscopic retrograde cholangiopancreatography, whereas, in all patients in the nondilation group in this study, PBM was detected by the findings of elevated lesions in gallbladders and after endoscopic retrograde cholangiopancreatography. The remaining patient had adenomyomatosis in the gallbladder, and we have never primarily detected PBM in patients with nondilation. There might have been latent PBM cases of nondilation without elevated lesions in the gallbladder, which could not be identified by screening tests such as ultrasonography. Therefore, the actual number of patients with PBM and nondilation would be higher.

In this study, all 5 bile duct carcinomas were identified in patients with PBM and cystic dilation, which were classified as type IV-A dilation according to the Todani classification (Table 3). The frequency of bile duct carcinoma in PBM of a cystic dilation type was 194.2 times as high as in the general population. Pancreaticobiliary maljunction with cystic dilation is prone to complications such as cholangitis, biliary cirrhosis, portal hypertension, lithiasis, rupture, and pancreatitis. For these reasons, we should accept the necessity for the excision of extrahepatic bile ducts in PBM with cystic dilation. A reflux of pancreatic juice into the biliary tract due to PBM has been considered an important factor in the development of biliary tract carcinogenesis in patients with PBM.

In conclusion, first, we should affirm the necessity for prophylactic cholecystectomy in all PBM cases with or without cystic dilation. We excised extrahepatic bile ducts with hepaticojejunostomy mainly in cases of choledochal dilation with PBM. We consider this surgery valuable as a separation operation to terminate mixture of the bile and pancreatic juice. However, as we previously reported, the incidence of bile duct carcinoma is still high, even after the excision of extrahepatic bile ducts in patients with PBM and cystic dilation. The refluxed pancreatic juice might have played an important role in the histological change of cystic-dilated walls to the precancerous stage, leading to bile duct carcinoma after long-term dormancy. In the present study, the postoperative incidence of bile duct carcinoma was 142.8 times higher in patients with PBM and cystic dilation than in the general population.

As presented in Table 3, the bile duct carcinoma of patients with PBM developed in the cystic-dilated walls. It is possible to excise extrahepatic bile ducts in primary prophylactic surgery. Therefore, we should completely excise extrahepatic dilated bile ducts in patients with PBM and cystic dilation. However, in patients such as patient 5 (Table 3) who develop cancer in the intrahepatic dilated bile duct of the left lobe, it is impossible for us to resect the hepatic lobe as a prophylactic operation. Long-term careful follow-up is necessary in such patients.

In Japan, there has been discussion about the excision of extrahepatic bile ducts in PBM without choledochal dilation because of the low frequency of its coexistence with bile duct carcinoma, despite the reflux of pancreatic juice into the biliary tract due to PBM. In this study, we could not find enough evidence to support the propriety of excision of extrahepatic bile ducts in patients without cystic dilation because we did not observe bile duct carcinoma cases other than the cystic dilation type of PBM. Four patients with PBM underwent cholecystectomy only (Table 2). One patient had the diffuse dilation type and the other 3 had the nondilation type. One year 6 months, 3 years 7 months, 7 years 2 months, and 12 years 3 months passed without any tumorigenesis or symptoms in these patients after the primary cholecystectomy, although cholecystectomy on its own does not terminate the reflux of pancreatic juice. The results show that there were no cases of bile duct carcinoma in patients with PBM and diffuse dilation or nondilation and that postoperative PBM cases after cholecystectomy did not provide us with a positive approach to the excision of bile ducts in patients with PBM without cystic dilation. Complications are not unusual in the hepaticojejunostomy of normal choledochus, and most patients with PBM are relatively young. Therefore, cholecystectomy might be applicable for PBM without bile duct dilation, given enough information about the importance of follow-up. If minimally invasive imaging modalities such as magnetic resonance cholangiopancreatography are further developed to reveal anomalous PBM, more PBM cases of nondilation will be found, even in patients without any clinical symptoms or findings. Cholecystectomy, especially laparoscopic cholecystectomy, might be recommended for patients with newly detected PBM of nondilation type to decrease the incidence of gallbladder carcinoma. Prognoses of gallbladder carcinoma are poor.

In conclusion, first, we should affirm the necessity of prophylactic cholecystectomy in all PBM cases with or without cystic dilation. Second, we should excise extrahepatic bile ducts in all PBM cases with choledochal dilation. Third, we must perform aggressive surgery in patients with newly detected PBM of nondilation type.
Corresponding author and reprints: Susumu Kobayashi, MD, Second Department of Surgery, Chiba University School of Medicine, 1-8-1 Inohana, Chuoh-ku, Chiba 260-8670, Japan.

REFERENCES


Otabayashi et al present a retrospective review of 68 patients with pancreaticobiliary maljunction. Pancreaticobiliary maljunction or anomalous junction of the pancreaticobiliary ducts is a concept that has received considerable attention over the last 5 to 10 years, particularly from Japanese authors. Various articles have addressed the anatomic anomalous junction of the pancreatic duct and bile duct, the presence or absence of choledochal cyst, and the question of whether reflux of pancreatic juice into the biliary tract increases the likelihood of carcinogenesis in the biliary epithelium. This present study is carefully done and classifies the lesions studied very well. The authors do not specify the definition of PBM, which in the literature is accepted as a common channel between the pancreatic duct and the bile duct of at least 1.5 mm as measured with either percutaneous transhepatic cholangiography or endoscopic retrograde cholangiopancreatography. The authors conclude that in patients with PBM and no evidence of choledochal cyst, the finding of gallbladder carcinoma is extremely high and much greater than expected. The question that is not addressed is how to define the high-risk patient who might have this type of pancreaticobiliary configuration. One article referenced by the authors suggests that patients who have no obvious cause for acute pancreatitis be assessed for anomalous PBM and be considered for cholecystectomy.

One of the questions that also begs to be asked is whether the same conditions that apply to the Japanese population apply to American patients. Is there a familial pattern here that might suggest a high-risk group of patients? The authors do not provide any leads in terms of how to screen patients for this particular anomaly. The use of endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography, or even endoscopic ultrasound, which all have high sensitivity in detecting this abnormality, cannot be used broadly in the routine general population. Another question that is not answered is whether cystic dilation of the bile duct without PBM predisposes patients to bile duct carcinoma.

An important finding of the authors is that there was a high incidence of metachronous bile duct carcinoma in patients who underwent previous incomplete resection of a choledochal cyst. The occurrence of metachronous cancer has been suggested in several other studies, but the present study supports the need to perform total excision of the abnormal bile duct.

In summary, the article raises an issue that needs further study in American patients with biliary tract disease. Patients with anomalous connection of the pancreatic and bile ducts appear to be at higher risk for gallbladder cancer, and if cystic dilation of the bile duct is present, there appears to be higher risk for bile duct cancer as well. Determining who should be screened for these abnormalities is still undetermined.

William E. Strodel, MD
San Antonio, Tex

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