

## Precancerous conditions of biliary tract cancer in patients with pancreaticobiliary maljunction: reappraisal of nationwide survey in Japan

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**Abstract** It is widely known that pancreaticobiliary maljunction (PBM), an anomalous arrangement of the pancreaticobiliary ductal system, is frequently associated with biliary tract cancer in patients with or without bile duct dilatation. In 1985, we surveyed patients with PBM who had been operated on at 133 Japanese institutions. A close relationship was shown between biliary tract carcinogenesis and PBM, according to the type of maljunction and age distribution: PBM patients with cystic dilatation had a high risk of bile duct cancer, even in those who were young (aged less than 20 years); the incidence of gallbladder cancer increased markedly in PBM patients over 40 years old with cystic dilatation, while it gradually increased with age in the PBM patients without cystic dilatation. Therefore, we recommend surgical treatment for patients with PBM even if they have no symptoms.

**Key words** Pancreaticobiliary maljunction · Biliary tract cancer

### Introduction

The incidence of biliary tract cancer in patients with congenital dilatation of the bile duct (CDB) who do not have pancreaticobiliary maljunction (PBM) has been reported to be 8.4% to 16.7% in the Japanese literature<sup>1-5</sup> (Table 1). On the other hand, in patients with PBM who do not have CDB, the incidence has been reported to 16.1% to 39.4%<sup>6-15</sup> (Table 2). It is generally

accepted that the incidence of biliary tract cancer in patients with CDB or PBM is high. However, it is uncertain whether the incidence is really higher than that of control subjects who have no CDB or PBM, because it is difficult to estimate the incidence of biliary tract cancer in control subjects. In the general Japanese population, the incidence of death from biliary tract carcinoma was 0.02% to 0.04% in the population over 70 years old.<sup>16</sup> In 1985, we had the opportunity to survey patients with PBM treated at 133 Japanese institutions whose representatives attended the Eighth Annual Meeting of the Japanese Study Group on Pancreaticobiliary Maljunction. This was the first and only nationwide survey of patients with PBM who underwent biliary tract surgery in Japan. This study revealed a correlation between the pathophysiology of PBM and the incidence of biliary tract malignancy, biliary tract stones, and pancreatitis according to age distribution. We have reported the results of this survey previously.<sup>8-10</sup> In the present report, we discuss the precancerous conditions of biliary tract cancer in patients with PBM by reviewing this nationwide survey in Japan.

### Incidence of PBM in patients who underwent biliary tract surgery in Japan

We surveyed patients with PBM who underwent hepatobiliary tract surgery at 133 Japanese institutions between 1980 and 1984. Among the 12399 patients, 414 (3.3%) had PBM, and 11985 patients (96.7%) had no PBM (control group). The incidence of PBM was 4.4% (32/735), 10.4% (80/769), and 9.1% (1/11) in patients with bile duct cancers, gallbladder cancers, and biliary tract cancers of unknown origin (cancers originating from bile duct or gallbladder), respectively. These percentages were significantly higher than that in patients with benign biliary tract disease (2.8%; 301/10884).

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**Table 1.** Incidence of biliary tract cancer in patients with CDB reported in the Japanese literature

Author (year)	<i>n</i>	Biliary tract cancer (incidence %)			Reference numbers
		Bile duct cancer (%)	Gallbladder cancer (%)	Total (%)	
Tadokoro et al. (1980)	466	46 (9.9)	4 (0.9)	50 (10.7)	1
Uchimura et al. (1982)	36	4 (11.1)	2 (5.5)	6 (16.7)	2
Komi et al. (1985)	645	38 (5.9)	16 (2.5)	54 (8.4)	3, 4
Todani et al. (1985)	877			127 (14.5)	5

CDB, Congenital dilatation of the bile duct

**Table 2.** Incidence of biliary tract cancer in patients with PBM reported in the Japanese literature

Author (year)	<i>n</i>	Biliary tract cancer (incidence %)			Reference numbers
		Bile duct cancer (%)	Gallbladder cancer (%)	Total (%)	
Hanyu et al. (1981)	50	9 (18.0)	9 (18.0)	18 (36.0)	6
Nagakawa et al. (1985)	33	2 (6.1)	11 (33.3)	13 (39.4)	7
Todani et al. (1985)	1062	111 (10.5)	137 (12.9)	248 (23.4)	5
Aoki et al. (1987); Hasumi et al. (1995, 1997)	569	31 (5.4)	93 (16.3)	124 (21.8)	8–10
Uchimura et al. (1991)	59	3 (5.1)	19 (32.2)	22 (37.3)	11
Tanaka et al. (1993)	31	2 (6.5)	8 (25.8)	10 (32.3)	12
Chijiwa et al. (1995)	45	2 (4.4)	6 (13.3)	8 (17.8)	13
JSPBM (1999)	1168	40 (3.4)	148 (12.7)	188 (16.1)	14
Funabiki (2000)	64	5 (7.8)	9 (14.1)	14 (21.9)	15

PBM, Pancreaticobiliary maljunction; JSPBM, proceedings of the Japanese Study Group on Pancreaticobiliary Maljunction (1993–1999)

### Incidence of biliary tract cancer in patients who underwent biliary tract surgery, evaluated according to presence of PBM and age distribution

The incidence of bile duct cancer in patients without PBM was 0% in younger patients (those less than 20 years old), but increased with age for those over 20 years old, reaching 11.0% in older patients (those more than 70 years old). On the other hand, in patients with PBM, some of those who were younger developed bile duct cancers; the incidence of bile duct cancers ranged from 9.5% to 13.0% (5 to 14 times more than in the control group) in patients who were 20 to 59 years old, with the peak incidence occurring for patients in their forties. However, in patients who were older than 60 years, the incidence was lower than that in the control group (Fig. 1a).

The incidence of gallbladder cancer in the control group was 0% in younger patients; the incidence increased with age more than 20 years, reaching 11.3% in older patients. On the other hand, the incidence in patients with PBM was 0% in younger patients, but increased markedly with age for those more than 20 years old. The incidence among these patients ranged from 12.3% to 40.0% (3 to 16 times more than in the control group) in patients aged 30 to 70 years (Fig. 1b).

### Incidence of biliary tract cancer in patients with PBM according to shape of dilatation of bile ducts and pattern of union of pancreatic and bile ducts

We analyzed 569 patients with PBM (414 patients who underwent hepatobiliary tract surgery and additional 129 patients). The incidence of biliary tract cancer was 23.0% (131 patients): 5.4% (31 patients) had bile duct cancers; 16.3% (93 patients) had gallbladder-derived cancers; and 1.2% (7 patients) had biliary tract cancers of unknown origin. We further analyzed 543 patients with PBM according to the shape of the dilatation of the bile ducts (i.e., cystic type, non-cystic type: no dilatation, fusiform or cylindrical dilatation), as well as the pattern of the union between the pancreatic and the bile ducts according to the classification of Kimura et al.<sup>17</sup> (i.e., common bile duct enters pancreatic duct [CP] union type, non-CP union type: pancreatic duct enters common bile duct [PC] union type, and others).

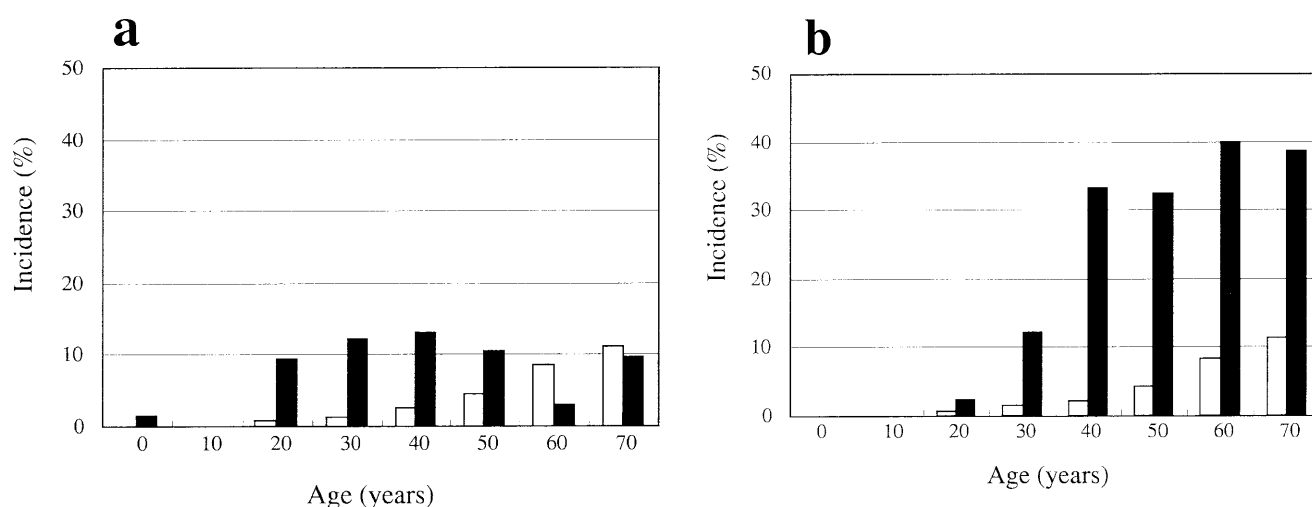
#### *Incidence of bile duct cancer*

The incidence of bile duct cancer in patients with PBM associated with cystic type dilatation of the bile duct was 7.3% for the CP union type lesions and 11.3% in the non-CP union type lesions — incidences that were

significantly higher than those noted in patients without PBM (i.e., the control group; 5.9%). The incidence of bile duct cancer in patients with non-cystic type dilatation was 2.6% in the CP union type and 3.2% in the non-CP union type — percentages that were considerably lower than those observed in the control group. Except for two patients with cystic type dilatation, no patients younger than 19 years old developed cancer. In patients 20 to 49 years old, 10.6% to 15.8% of the patients with cystic type dilatation developed cancer; this percentage was higher than that in patients with non-cystic type dilatation (3.0% to 4.5%) and higher than the incidence noted in the control group (1.9%). Moreover, in patients older than 50 years, the incidence was 14.3% to 16.7%, 3.8% to 4.8%, and 7.6% in patients with cystic type dilatation, those with non-cystic type dilatation, and the control group, respectively (Table 3).

### Incidence of gallbladder cancer

The incidence of gallbladder cancer in patients with PBM associated with cystic type dilatation of the bile duct was 4.2% in the CP union type and 1.9% in the non-CP union type, and these percentages were lower than that in the control group (5.7%). On the other hand, in patients with non-cystic type dilatation, the incidence was 11.5% and 31.8% in the CP union type and the non-CP union type, respectively. Both of these incidences were significantly higher than that in patients with cystic type dilatation or that in patients in the control group. No patients younger than age 19 years developed gallbladder cancer. In patients between 20 and 49 years of age, 0 to 4.3% of patients with cystic type dilatation, and 31.3% of patients with non-cystic type dilatation and with the non-CP union type, developed gallbladder cancer. In patients more than 50 years



**Fig. 1a,b.** Age distribution of **a** incidence of bile duct cancer and **b** incidence of gallbladder cancer in patients who underwent biliary tract surgery in Japan ( $n = 12399$ ) according to

the presence of pancreaticobiliary maljunction (PBM). *Black bars*, Patients with PBM; *white bars*, patients without PBM

**Table 3.** Incidence of bile duct cancer in patients with PBM ( $n = 543$ ) according to shape of dilatation of the bile ducts and pattern of union of pancreatic and bile ducts

Age (years)	Cystic type <sup>a</sup>		Non-cystic type <sup>b</sup>		Control <sup>c</sup> (no PBM)
	CP <sup>d</sup>	Non-CP <sup>e</sup>	CP	Non-CP	
≤19	0/74 (0%)	2/27 (7.4%)	0/30 (0%)	0/48 (0%)	0/57 (0%)
20–49	10/94 (10.6%)	3/19 (15.8%)	1/22 (4.5%)	2/67 (3.0%)	69/3547 (1.9%)
≥50	4/24 (16.7%)*	1/7 (14.3%)	1/26 (3.8%)	5/105 (4.8%)	634/8381 (7.6%)
Total	14/192 (7.3%)	6/53 (11.3%)	2/78 (2.6%)	7/220 (3.2%)	703/11985 (5.9%)

\*  $P < 0.05$  vs non-cystic type, non-CP

<sup>a</sup> Cystic dilatation of the bile duct

<sup>b</sup> No dilatation, or fusiform, cylindrical dilatation

<sup>c</sup> Patients who underwent hepatobiliary tract surgery at 133 Japanese institutions between 1980 and 1984

<sup>d</sup> Common bile duct enters pancreatic duct (CP) union type<sup>17</sup>

<sup>e</sup> Non-CP union type: pancreatic duct enters common bile duct (PC) union type or other form of maljunction<sup>17</sup>

**Table 4.** Incidence of gallbladder cancer in patients with PBM ( $n = 543$ ) according to shape of dilatation of bile ducts and pattern of union of pancreatic and bile ducts

Age (years)	Cystic type <sup>a</sup>		Non-cystic type <sup>b</sup>		Control <sup>c</sup> (no PBM)
	CP <sup>d</sup>	Non-CP <sup>e</sup>	CP	Non-CP	
≤19	0/74 (0%)	0/27 (0%)	0/30 (0%)	0/48 (0%)	0/57 (0%)
20–49	4/94 (4.3%)**	0/19 (0%)	1/22 (4.5%)	21/67 (31.3%)	64/3547 (1.8%)
≥50	4/24 (16.7%)**	1/7 (14.3%)	8/26 (30.8%)	49/105 (46.7%)	625/8381 (7.5%)
Total	8/192 (4.2%)	1/53 (1.9%)	9/78 (11.5%)	70/220 (31.8%)	689/11985 (5.7%)

\*\*  $P < 0.01$  vs non-cystic type, non-CP

<sup>a</sup> Cystic dilatation of the bile duct

<sup>b</sup> No dilatation, or fusiform, cylindrical dilatation

<sup>c</sup> Patients who underwent hepatobiliary tract surgery at 133 Japanese institutions between 1980 and 1984

<sup>d</sup> CP union type: common bile duct enters pancreatic duct<sup>17</sup>

<sup>e</sup> Non-CP union type: PC union type (pancreatic duct enters common bile duct) or other form of maljunction<sup>17</sup>

old, the incidence was higher than that in the 20- to 49-year-old group. In particular, in patients with non-cystic type dilatation, the incidence was 30.8% to 46.7%, which was considerably higher than that noted in patients with cystic type dilatation (14.3% to 16.7%) (Table 4).

#### Summary: precancerous conditions for biliary tract cancer in patients with PBM and their surgical treatments

Our nationwide survey of the incidence of biliary tract cancer in patients with PBM was summarized as follows. Patients with CDB associated with cystic dilatation of the bile duct and the CP union type tended to have had operations before age 20 years before the development of biliary tract cancers. However, if these patients grew up without any symptoms, they would develop biliary tract cancers because of the reflux, stasis, and chemical irritation of pancreatic juice within the dilated bile duct. The incidence of bile duct cancer increased with age; it was 11% in patients who were 20 to 49 years of age (5.6 times the incidence for age-matched patients without PBM), and 17% in patients who were more than 50 years old (2.2 times the incidence for age-matched patients without PBM). The incidence of gallbladder cancer also increased with age; the incidence was 4% in PBM patients who were 20 to 49 years old (2.4 times the rate seen in age-matched non-PBM patients), and 17% in PBM patients who were more than 50 years old (2.2 times the rate in control patients). The incidence of gallbladder cancer in patients with PBM associated with cystic type dilatation was lower than that in those patients with non-cystic type dilatation. It has been speculated that pancreatic juice, regurgitated into the bile duct, does not affect the gallbladder, because it remains within the

dilated bile duct. On the other hand, in patients with PBM associated with non-cystic type dilatation of the bile duct (and associated with the non-CP union type maljunction), the diagnosis of PBM tended to be overlooked before age 20. The incidence of biliary tract stones and gallbladder cancer, however, increased with age. Remarkably, patients with PBM associated with non-cystic type dilatation and the non-CP union type developed gallbladder cancers; the cancer occurred in 31% of patients between 20 and 49 years of age (17.4 times the rate noted in control patients), and in 47% of patients more than 50 years of age (6.2 times the rate noted in control patients). The incidence of bile duct cancer was 3% to 5%, which was lower than that in patients with cystic type dilatation, and similar to that in control patients. Our survey was based on the classification of PBM as at 1985; however, there is a report demonstrating that classifications such as CP or PC union type are inappropriate from the viewpoint of embryogenesis.<sup>18</sup> The significance of the classification of PBM according to the pattern of union of the pancreatic and the bile ducts, particularly in relation to the development of biliary tract cancer, remains to be elucidated.

Surgical treatments are reasonable for patients with PBM, because such patients are considered to have precancerous conditions that predispose them to biliary tract cancer. Recently, a wide variety of predisposing factors, such as the activation of oncogenes, the inactivation of tumor-suppressor genes, and the dysregulation of cell proliferation have been identified in the development of biliary tract cancer in patients with PBM.<sup>19–21</sup> In order to avoid the precancerous conditions, the recommended surgical procedures are: cholecystectomy and resection of the dilated bile duct, with reconstruction by an end-to-side hepaticoduodenostomy, for patients with PBM associated with cystic type dilatation and the CP union type of maljunction;

and cholecystectomy for patients with non-cystic type dilatation and the non-CP union type maljunction.

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