Pancreas Divisum: A Retrospective Review to Evaluate the Risk of Biliary Tract Neoplasms

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**Background**—Congenital anomalies of the biliary tree are established risk factors for cholangiocarcinoma (CCA). This review was done to assess the association of pancreas divisum (PD) with biliary tract neoplasms. **Methods**—A retrospective review of prospectively collected, computer data of all patients who had undergone endoscopic retrograde cholangiopancreatography (ERCP) at the Indiana University Hospital (IUH). **Results**—A total of 10,339 ERCPs were performed on 7,809 patients between 1994 to 2001. Out of these, 5,570 patients underwent pancreatograms. The remaining were excluded from the review. Of the total sampled patients 875 (15.7%) had pancreas divisum. Out of all the ERCPs in both patients with or without divisum, a total of 73 cholangiocarcinomas, 46 ampullary carcinomas (ACA) and 42 ampullary adenomas were found. Of the total 73 CCA, 10 had PD (13.7%), of the 46 ACA, 8 had PD (17.4%), and of the total number of biliary tract malignancies, 18 had PD (15.1%). These figures did not differ significantly when compared to the number of biliary tract malignancies seen in patients without PD. On analysis, there was no statistically significant association found between biliary tract malignancies and PD. Sub-analysis was done after adding the 42 patients with ampullary adenomas in the cases. There was again no difference noted between the cases and the controls. **Conclusions**—There is no definite association between pancreas divisum and causation of biliary malignancies.

**INTRODUCTION**

Pancreas divisum is the most common congenital pancreatic anomaly; occurring in approximately 7.5% of the general population. It is recognized as a potential risk factor for recurrent acute pancreatitis, and possible chronic pancreatitis. Pancreas divisum results from the failure of fusion of the ventral and dorsal ductal system. The hypothesis of our study was that pancreas divisum predisposes to biliary tract malignancies, namely cholangiocarcinoma (CCA) and ampullary carcinoma (ACA). This hypothesis budded from the known association of biliary tract malignancies with congenital anomalies of the biliary tract as elaborated below.

Cholangiocarcinoma is an uncommon cancer developing in the epithelial cells of the intrahepatic and extrahepatic bile ducts and/or periductular glands of the biliary tract. It accounts for around 3% of all gastrointestinal malignancies (1), and incidence increases with age. Greater than 95% are adenocarcinomas, and a majority...
of the rest are squamous cell carcinoma. Incidence of CCA is reported to be one-to-two cases per 100,000 patients in the U.S.A, and most of the patients are more than 65 years of age (2); two-thirds of all cases present between the ages of 50 and 70 years (3). The estimated incidence in the USA was 3,000 cases in 2002 (4).

The majority of CCA occurs at the hilum and typically present at advanced stages with unresectable disease. The majority of patients with unresectable disease have a survival between six months to one year (5). The cure rates are low even when aggressive therapy is used. Progressive biliary obstruction causes liver failure or infection, leading to death. The five-year survival rate for extrahepatic CCA was found to be 26.8% for localized tumors, 12.4% for regional spread, 1.2% for distant spread and 7.2% for unstaged tumors, with the mean 5-year survival being 12.9% regardless of stage (2).

Most cases are sporadic; however several risk factors have been established. The most common risk factor is primary sclerosing cholangitis (PSC) with a reported incidence of CCA between 8%–40% (6, 7). The prevalence has been reported to be as high as 23% in the explants from patients undergoing liver transplantation for PSC (8). In an autopsy series, CCA has been shown in 30%–42% of patients with PSC (9). Congenital choledochal cysts are an established risk factor for CCA (10). The overall incidence of CCA with choledochal cysts is 10%–20% with a 1% per year cumulative risk (11,12). If cysts are not excised until the third decade of life, the risk of malignant transformation is up to 15%–20% (11).

Ulcerative colitis, with associated PSC, presents another risk factor with prevalence of CCA being 0.5% with estimated risk being more than 31 times that of the general population (13). Risk is greater in cases of pancolitis. Stones in the gallbladder are a risk factor for gallbladder cancer but are not a risk factor for CCA; intrahepatic ductal stones are strongly associated with CCA in Asia (14–17). Bile duct adenoma and multiple biliary papillomatosis are also associated with CCA. Liver flukes are also associated with this disease. The greatest association is with the species Opisthorchis viverrini, while Clonorchis sinensis infection is also a clear risk factor (18,19). Other risk factors include, thorotrast dye (20,21), dioxin exposure (7) and nitrosamines (7,22).

Given the association of CCA with congenital biliary abnormalities, we hypothesized that presence of pancreas divisum may also predispose to the development of this rare cancer. Hence we undertook this study to demonstrate an association. In addition, the incidence of CCA has risen over the past three decades. The incidence and mortality from intrahepatic CCA in the USA increased by about 9% from 1973 to 1997 (23). There has been a similar increase in incidence of intra- and extrahepatic CCA seen in Crete between 1992 and 2000 (24). This makes it more relevant to look into the role for cancer surveillance. This in turn would require identification of any new risk factors, in this case possibly pancreas divisum, which would define high-risk patients. A preliminary analysis from our institution showed an association between pancreas divisum and CCA and this study is a larger cohort.

**PATIENT SELECTION AND METHODOLOGY**

The study was designed as a retrospective case control study. The proposal was submitted to and accepted by the Institutional Review Board Committee at Indiana University.

The pre-existing, prospectively collected computer database of all patients who had undergone endoscopic retrograde cholangiopancreatography (ERCP) for various indications was reviewed. First duplicate entries for patients undergoing multiple procedures were eliminated. This was followed by exclusion of all patients who had unattempted or failed pancreatograms. Data including patient demographics, indication of procedure, diagnosis, cholangiogram and pancreatogram findings and histopathologic diagnosis (if available/applicable) was recorded.

Cases were patients with CCA or ACA as evidenced by malignant appearance of biliary strictures by ERCP as well as pathologic evidence of malignancy, in the absence of other cancers like pancreatic or metastatic adenocarcinoma as a cause for the malignant biliary strictures. Indeterminate strictures were followed for a minimum of one year. Repeated tissue sampling was done with each stent change. A deteriorating clinical course with death within one year was considered cancer even in the absence of tissue confirmation. The con-
control group was comprised of all patients without CCA or ACA, with or without biliary strictures due to any other etiology (benign or malignant) who underwent ERCP (with pancreatograms) at Indiana University Hospital between the time period from 1994 to 2001. The presence or absence of pancreas divisum as demonstrated by pancreatograms was noted. Pancreatic divisum was diagnosed 1) if a small ventral ductal system was filled via the major papilla (care was taken to differentiate duct cut-off from chronic pancreatitis or neoplasms) or 2) if a dorsal ductogram via the minor papilla showed no communication back to the major papilla or 3) if incomplete pancreas divisum seen via either major or minor papilla. Magnetic resonance cholangiopancreatography was not used in this study.

The data was then analyzed using Epi Info to see if pancreas divisum predisposes to the development of biliary tract malignancies and P values and confidence intervals were calculated.

RESULTS

A total of 7,809 patients underwent a total of 10,339 ERCPs for various clinical reasons over the time period between 1994 to 2001. Of these 5,570 (71%) patients had ERCPs done with pancreatograms performed by the major and/or minor papillae and this constituted our study population. Ninety percent of these patients had completed cholangiograms. The mean age of the patients was 50 years, 65.6% were females and 34.4% were males.

Amongst these, 875 subjects (15.7%) had endoscopic retrograde pancreatography (ERP) which identified pancreas divisum. The various anomalies by numbers and percentages are shown in Table 1.

Of the 5,570 study patients, 73 (1.3%) had CCA and 46 (0.82%) had ACA by endoscopic radiographic and/or histological evidence. These patients (total of 119) were considered as the cases whereas those without any biliary malignancy were regarded as controls. The mean age of the cases was 67.6 years and male to female ratio was 1.24:1. The demographics and comparisons of the cases and controls are illustrated in Table 2.

Two of the 73 CCA were squamous cell on pathology (2.7%), whereas 71 (97.3%) were adenocarcinomas. Of the 46 ACA, 43 (93.5%) were adenocarcinomas, 3 (6.5%) were invasive carcinoid. There were also 42 ampullary adenomas (papillary adenomas); of these 30 were tubular adenomas, seven were tubulovillous adenomas and five were villous adenomas.

Of the patients with CCA, 13.7% had pancreas divisum, whereas, of those without CCA, 15.7% had divisum. On the other hand, pancreas divisum was found in 17.4% of the patients with ACA and 15.7% without ACA. Considered cumulatively, of all the cases with biliary malignancy (either CCA or ACA), 15.1% had pancreas divisum whereas 15.7% of the controls had pancreas divisum. Hence there was no difference in the rates of developing biliary tract malignancies in patients with pancreas divisum as compared to those without pancreas divisum (P value = 0.86). Further analysis was done after adding the 42 patients with ampullary adenomas in the cases. The justification of

<table>
<thead>
<tr>
<th>Pancreatic anomaly</th>
<th>Types</th>
<th>Numbers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divisum</td>
<td>Complete</td>
<td>788 (90.1)</td>
</tr>
<tr>
<td>(875)</td>
<td>Incomplete</td>
<td>87 (9.9)</td>
</tr>
<tr>
<td>Non-divisum</td>
<td>None</td>
<td>4669 (99.4)</td>
</tr>
<tr>
<td>(4695)</td>
<td>Ansa</td>
<td>18 (0.4)</td>
</tr>
<tr>
<td></td>
<td>Annular</td>
<td>8 (0.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics of cases and controls</th>
<th>Cases</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>66 (55.4%)</td>
<td>1851 (34%)</td>
<td>0.000001</td>
</tr>
<tr>
<td>Females</td>
<td>53 (44.5%)</td>
<td>3600 (66%)</td>
<td></td>
</tr>
<tr>
<td>M:F ratio</td>
<td>1.2:1</td>
<td>0.5:1</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>67.6</td>
<td>49.6</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Cases = Patients with cholangiocarcinoma or ampullary carcinoma (continued on page 28)
adding these to the cases was the known adenoma-carcinoma sequence for these lesions. There was again no difference noted between the cases and the controls (P value = 0.88). These results are summarized in Table 3.

Looking from another aspect, 10 out of 875 patients with pancreas divisum (1.14%) had CCA, and 8 (0.91%) had ACA. In comparison, 63 out of 4,695 patients without pancreas divisum (1.34%) had CCA and 38 (0.81%) had ACA. In total 18 (2.06%) of patients with pancreas divisum had either CCA or ACA versus 101 (2.15%) of the patients without pancreas divisum. Hence there was no difference in the frequency of biliary malignancies in patients with or without pancreas divisum. All these malignancies represent presence at one point in time and do not signify development of cancers over a period of follow-up. We are aware of no patient with pancreas divisum in our series who developed a CCA while being followed for long term.

Sub-analysis was also done sequentially, only including patients above 50, 55 and 60 years of age, however p values were still not significant (0.9, 0.6 and 0.4 respectively).

Risk factors for CCA include primary sclerosing cholangitis (PSC), anomalous pancreato-biliary junction (PBJ), choledochal cyst and intrahepatic stones. The frequencies of these risk factors were equally distributed amongst the cases and the controls, hence eliminating any confounders contributing to the development of biliary tract malignancies. These were demonstrated on cholangiogram findings which are illustrated in Table 4.

Other types of cancers seen in the sample of 5,570 subjects undergoing ERCP included pancreatic cancer in 264 (4.7%), intraductal papillary mucinous tumor (IPMT) in 77 (1.4%), gall bladder carcinoma in 10 (0.2%), lymphoma in 9 (0.2%) and hepatocellular carcinoma in 4 (0.1%). Chronic pancreatitis was seen in 1,145 (20.6%) of the total sample. Biliary strictures were demonstrated in a total of 855 patients. Some of these were caused by primary biliary tract malignancies, although not all biliary tract

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**Table 3**

<table>
<thead>
<tr>
<th>Hepatobiliary malignancies</th>
<th>Odds Ratio</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholangiocarcinoma (CCA) only</td>
<td>0.85</td>
<td>0.64</td>
<td>0.41 &lt; OR &lt; 1.73</td>
</tr>
<tr>
<td>Ampullary carcinoma (ACA) only</td>
<td>1.13</td>
<td>0.75</td>
<td>0.48 &lt; OR &lt; 2.55</td>
</tr>
<tr>
<td>CCA and ACA</td>
<td>0.96</td>
<td>0.86</td>
<td>0.55 &lt; OR &lt; 1.63</td>
</tr>
<tr>
<td>CCA, ACA and ampullary adenomas</td>
<td>1.03</td>
<td>0.88</td>
<td>0.66 &lt; OR &lt; 1.62</td>
</tr>
<tr>
<td>Pooled CCA and ACA data *</td>
<td>1.19</td>
<td>0.39</td>
<td>0.79 &lt; OR &lt; 1.78</td>
</tr>
</tbody>
</table>

*Combined data from current study and previous abstracts from Ruffolo, et al (33) and Nugent, et al (34)

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**Table 4**

<table>
<thead>
<tr>
<th>Cholangiogram Findings</th>
<th>Cases n = 119</th>
<th>Controls n = 5451</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stricture</td>
<td>116 (97.5%)</td>
<td>739 (13.6%)</td>
<td>0.00</td>
</tr>
<tr>
<td>Bile duct dilation</td>
<td>94 (79%)</td>
<td>1518 (27.8%)</td>
<td>0.00</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>8 (6.7%)</td>
<td>559 (10.3%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>3 (2.5%)</td>
<td>93 (1.7%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Anomalous PBJ</td>
<td>0 (0%)</td>
<td>22 (0.4%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Choledochal cyst</td>
<td>0 (0%)</td>
<td>42 (0.8%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Intrahepatic stone</td>
<td>1 (0.8%)</td>
<td>36 (0.7%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cystic duct stone</td>
<td>0 (0%)</td>
<td>58 (1.1%)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
malignancies led to strictures. The other causes of these strictures are divided into two categories, benign and malignant and are outlined in Table 5.

**DISCUSSION**

The diagnosis of pancreas divisum at ERP is made by visualization of a small short terminally arborizing ductogram via the major papilla which does not cross the spine. Alternatively, minor papilla cannulation and dorsal ductography may establish the diagnosis by visualization of a long ductal system which connects to the tail but does not connect to the major papilla (except in incomplete pancreas divisum). Incomplete pancreas divisum is similar to the above except the dorsal and ventral systems connect via a tiny communicating branch. Incomplete pancreas divisum were classified as pancreas divisum in our series.

Acquired pancreas divisum occurs when a neoplastic or inflammatory process obstructs communication between the dorsal and ventral systems. Usually, the main ventral duct is of normal (large) caliber and a “cut-off” obstruction is seen per ductogram. The endoscopist’s judgment along with ERCP colleague review was used to make this final judgment for diagnosis classification in cases with uncertainty.

Our ERCP technique routinely includes cannulation of the minor papilla whenever cannulation of the major papilla failed to identify the pancreatic duct. This way, a more accurate diagnosis of pancreas divisum was made. The diagnosis of CCA was made by the appearance of a typical malignant type stricture as seen on ERCP, complemented by brush cytology and biopsy. Ampullary carcinoma was diagnosed similarly, with the location being in the ampullary/papillary segment.

ERP was not done in 29% of our patients in the ERCP database. In these cases, pancreas divisum could have been missed. When pancreatography was thought to be clinically relevant (including patients with CCA) minor papilla ductography was done.

The percentage of patients with pancreas divisum in our sample was 15.7%. The prevalence in the general population (mostly Caucasian) is usually quoted to be approximately 7%. It occurs in approximately 7% of subjects in autopsy series (range 1% to 14%) (25, 26). In one retrospective series of ERCPs, pancreas divisum was found in 7.5% (27). Similarly, about 1.3% had CCA and the reported prevalence in autopsy series is 0.01 to 0.46% (1). This is because our sample consisted of symptomatic and usually sick patients undergoing ERCP and therefore is not representative of the general population.

There is an increased incidence of extrahepatic bile duct cancers in patients with ulcerative colitis, primary sclerosing cholangitis and choledochal cysts (28–30). It is suspected that these cause chronic biliary inflamma-

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiology</th>
<th>Numbers</th>
<th>Percentages</th>
<th>Divisum</th>
<th>Non-divisum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>Pancreatic carcinoma</td>
<td>245</td>
<td>28.7%</td>
<td>14</td>
<td>231</td>
</tr>
<tr>
<td></td>
<td>Metastatic carcinoma</td>
<td>48</td>
<td>5.6%</td>
<td>2</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Intraductal papillary mucinous tumor</td>
<td>11</td>
<td>1.3%</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Gall bladder carcinoma</td>
<td>9</td>
<td>1.1%</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
<td>9</td>
<td>1.1%</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Hepatocellular carcinoma</td>
<td>3</td>
<td>0.4%</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Benign</td>
<td>Chronic pancreatitis</td>
<td>276</td>
<td>32.3%</td>
<td>61</td>
<td>215</td>
</tr>
<tr>
<td></td>
<td>Primary sclerosing cholangitis</td>
<td>42</td>
<td>4.9%</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Orthotopic liver transplant</td>
<td>38</td>
<td>4.4%</td>
<td>4</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic (post cholecystectomy)</td>
<td>31</td>
<td>3.6%</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous (GVH, PTLD)</td>
<td>2</td>
<td>0.2%</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

GVH: Graft vs host disease; PTLD: Post transplant lymphoproliferative disorder
tion which may lead to the development of dysplasia and then carcinoma. For similar reasons, we hypothesized that pancreas divisum may also be associated with development of biliary tract malignancies. The proposed pathogenesis of development of CCA in the setting of pancreas divisum may be related to reflux of juices and sub-clinical inflammation of the bile ducts. Areas of dysplasia and carcinoma in situ have been demonstrated in the extrahepatic bile ducts, just adjacent to invasive carcinoma, suggesting the dysplasia-carcinoma sequence in the development of these tumors (31,32).

However, as per the results outlined above, we were not able to show any association between pancreas divisum and biliary tract malignancies, hence disproving our study hypothesis. There have been two other retrospective reviews done at our institution looking into such an association. Our sample in the current study did not include the patients from these previous abstracts. Both these studies reviewed data from different periods and included smaller sample sizes as compared to our study. The first study (33) reviewed data between 1986 and 1989 (n = 1,524). This study found that 9.35% of patients with pancreas divisum had CCA or ACA as compared to only 2.12% without pancreas divisum (p < 0.001). The second study (34) was from 1986 to 1992 and included the data from the previous study (n = 3,761). The results of these pooled data showed that the rate of biliary tract malignancy in patients with pancreas divisum was 4.4% whereas it was 2.3% in patients without pancreas divisum (p < 0.035). Both of these studies suggested the possibility that pancreas divisum can provide an environment for such malignancies to develop. When the 1986 to 1992 data are combined with the current 1994 to 2001 series, the rate of biliary tract malignancies in pancreas divisum was 2.62% and in controls was 2.21% (P value = 0.39).

Recently, a group from Japan concluded that there was a significantly higher prevalence of pancreatic cancers and lower prevalence of biliary tract cancer in pancreas divisum than in fused pancreas (35). This increased prevalence of pancreatic cancers could be due to the differences between Asian population and our patient population.

Bile duct carcinomas may also start as adenomas. Surveillance, epidemiology and end results (SEER) program reported such cases as 0.7%. One study had reported that 21% of bile duct carcinomas had arisen from adenomas (36). For this reason, we re-analyzed the data after including all the cases of ampullary adenomas and comparing them against the controls. However, this sub-analysis also failed to show any positive association between pancreas divisum and development of biliary tract neoplasms.

As mentioned above, the diagnosis of CCA is usually based on the appearance of a typical malignant type stricture seen on ERCP plus positive tissue sampling or a deteriorating course and death within one year. There were a number of limitations in the study. Since biliary strictures can be caused by a variety of different cancers, including metastatic and pancreatic cancers, malignant appearing strictures without associated pancreatic mass or other primary cancer were classified as CCA, based on exclusion. Diagnosis of CCA has improved significantly due to the availability of ERCP with brush cytology, fine needle aspiration and forceps biopsy (37), although interpretation may be difficult because many of these tumors are well differentiated (38–40). However, a negative test cannot rule out malignant disease. These limitations affect making the correct diagnosis and could underestimate the true prevalence of this disease. Twelve month minimal follow-up of clinical course is thought to likely identify all cancers. The cases were diagnosed by ERCP. Our one year minimal follow-up identified patients detected by other modalities. Our sample therefore, is probably representative of the true prevalence of biliary tract malignancies.

Cholangiocarcinomas have often metastasized when diagnosed and outcomes are poor. Tumor location is an important factor in prognosis. Cancers located in the lower third of the bile duct are surgically more successfully resectable than those at other locations (41). However, the majority of the tumors are located within the upper third of the bile ducts (42).

In conclusion, although two earlier studies suggested a possible association of pancreas divisum with biliary tract malignancies, this larger, more representative review negates such an association. No screening for CCA in pancreas divisum appears to be warranted. ■

(continued on page 34)
Acknowledgment
We thank Dr. Thomas Imperiale for his help in the statistical analysis.

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