

Significance of the site of origin of pancreatic exocrine adenocarcinoma

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SUMMARY The pancreatic head and neck constitute less than half (mean $46 \pm 5\%$) of the whole pancreas. There is no difference in the concentration of ductal epithelium between the head and the body of the pancreas. The preponderance of pancreatic exocrine tumours which arise in the head of the pancreas compared to the body is not, therefore, due to a larger number of cells at risk in the pancreatic head. This suggests that there is a greater risk of exocrine adenocarcinoma developing from the cells within the head of the pancreas than in those within the body of the pancreas.

Studies of the distribution of the site of origin of pancreatic ductal-adenocarcinoma, carried out at necropsy, suggest that 60% of these tumours arise in the head or neck of the pancreas (Table). This apparently uneven distribution may be an important clue to the pathogenesis of this condition and it has prompted Wynder⁶ to suggest that it could be produced by pancreatic ductal reflux of carcinogens from the duodenum. However, Bouchier⁷ has pointed out that more tumours may appear to arise from the pancreatic head and neck because there is more pancreatic tissue in these areas than in the body and tail of the pancreas. This view has been supported by studies of experimental nitrosamine-induced pancreatic tumours in the hamster.⁸ In this animal model of the human disease, the distribution of pancreatic tumours corresponds to the distribution of pancreatic tissue between the three lobes of the hamster pancreas. The greatest incidence of tumour is in the largest splenic lobe.

Necropsy surveys have consistently suggested that a preponderance of pancreatic carcinomas arise in the head and neck of the pancreas

No of cases	% distribution of site of origin			Reference
	Head and neck	Body and or tail	Multiple or diffuse	
57	61.4	5.2	33.3	Mirallie C (1893) ¹
50	56	38	6	Duff GL (1939) ²
609	59.1	25.6	15.3	Bell ET (1957) ³
68	70.5	10.9	19.1	Parkash O (1972) ⁴
380	61	18	21	Cubilla A, Fitzgerald PJ (1978) ⁵

It is not clear, therefore, whether in man this uneven distribution of pancreatic tumours is due to a greater risk of neoplastic change in the ductal epithelium of the pancreatic head and neck or whether the risk of neoplastic change is the same but there is more ductal epithelium in the head and neck of the pancreas than in the body and tail. The purpose of this study was to discover the relative distribution in man of pancreatic tissue, in particular ductal epithelium, between the head and neck and the body and tail of the pancreas.

Material and methods

Pancreas was obtained at necropsy less than 48 h after death from non-pancreatic disease. After fixation in 10% formalin for five days it was sliced throughout its length at 1 cm intervals in the sagittal plane. The neck of the pancreas is the region where the uncinate process and superior mesenteric vein are posterior relations of the pancreas⁹ and this could be accurately identified by examination of the serial sagittal slices taken through this region. The weight of those slices making up the head and neck, and those from the body and tail of the pancreas were noted. Seventy-seven pancreases were examined.

Tissue removed from the head and from the body of eight pancreases was processed and stained by haematoxylin and eosin. Using a computerised microscope morphometer (Cambridge Electronic Design Ltd) the lengths of the perimeters of the inter and intralobular, and intercalary ducts seen in a 958 141 μm^2 field were measured; 25 fields in each section, a total area of 23.95 mm^2 per section were measured. The sum of the duct perimeters

measured in each section, and the frequency of occurrence of ducts by perimeter size were compared between sections taken from the head of the pancreas and those taken from the body.

Results

The mean weight of the head and neck of the pancreas (38 g) was significantly less ($t = 6.23$, $p < 0.001$) than the mean weight of the tissue from the body and tail (44 g). The proportion, expressed as a percentage, of the total pancreatic weight which is contributed by the head and neck of the pancreas (mean $46 \pm 5\%$) is shown in Fig. 1 for the specimens which were examined.

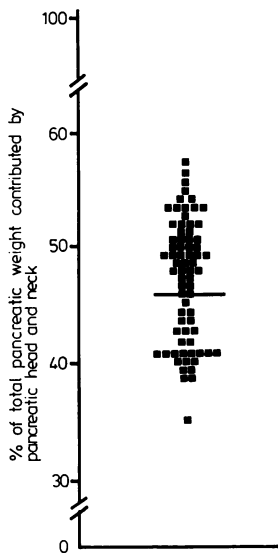


Fig. 1 The proportion of the total pancreatic weight (expressed as a percentage) which is contributed by the head and neck of the pancreas is shown for the specimens which were examined. The mean value is 46% and in only one specimen did the value approach 60% which is the proportion of tumours arising from the head and neck of the pancreas.

There was no significant difference in either the total perimeter of ductal epithelium measured per unit area (Fig. 2) or in the frequency of occurrence of ducts by perimeter size (Fig. 3) between the head and the body of the pancreas.

Discussion

The pancreatic head and neck constitute a mean of 46% of the total pancreatic weight, but are the site of origin of about 60% of pancreatic exocrine

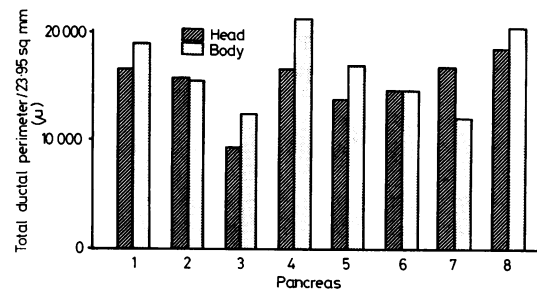


Fig. 2 The total ductal perimeter (μm) measured in an area of 23.95 sq mm taken from sections of the head compared to that from the same area of sections from the body of the same pancreas. There is no significant difference between the amount measured in each area from the same pancreas.

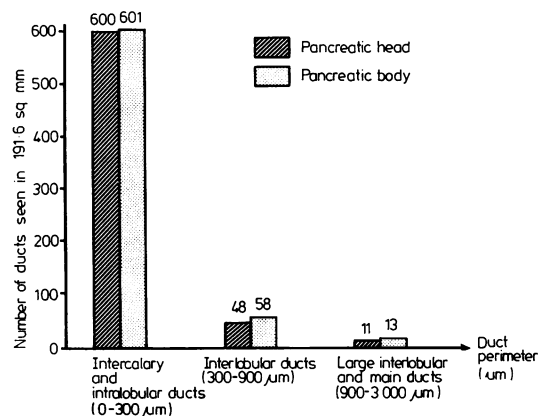


Fig. 3 The frequency of ducts, according to their perimeter size, measured in an area of 191.6 sq mm. There are fewer ducts as their perimeter size increases, but the number found in tissue from the head of the pancreas is similar to that in tissue from the body.

tumours. This difference is not explained by a change in the concentration of ductal epithelium or a difference in the incidence of ducts of a particular size between the pancreatic head and body. Differences between the amount of fat contained within the head and the body of the pancreas might influence these proportions. The head of the neonatal pancreas contains areas in which there is variation in the amount of intralobular fat present.¹⁰

However these differences in intralobular fat are small (of the order of 1-2% of the total pancreatic volume) and the mean for all areas of the head could not differ from the mean value for the pancreatic body by more than 1% of the total pancreatic volume. Any difference of this size would not have a significant effect on the findings described herein. Thus the incidence of pancreatic tumours in relation

to the amount of pancreas from which they arise is about $\times 1.8$ greater in the head and neck than in the body and tail of the pancreas.

Bates¹¹ has suggested that this increase could be due to earlier diagnosis of tumours in the head of the pancreas which would therefore be more localised than tumours of the body of the pancreas which often do not produce symptoms until the disease is more widespread. However, the estimate of 60% of pancreatic tumours originating from the head of the pancreas does not include diffuse tumours of the pancreas as it relates only to those localised at the time of necropsy to the pancreatic head. In fact, evidence from experimental pancreatic tumours in the rabbit suggests that a proportion of diffuse pancreatic tumours may originate in the head.¹² In this animal model those tumours originating in the head of the pancreas are more likely to spread to the tail because duct obstruction in the head with accompanying stasis predisposes to tumour spread towards the tail.

Willis¹³ has proposed that many cancers of the retropancreatic common bile duct are incorrectly ascribed to an origin from the pancreas thus spuriously increasing the incidence of tumours in the pancreatic head. In a typical necropsy survey Miller, Baggenstoss and Comfort¹⁴ found that the average diameter of a tumour of the head of the pancreas at necropsy was 4.2 cm. A tumour of the common bile duct would produce obstructive jaundice at a very much smaller size than this and would be an improbable source for such a large tumour which has the clinical reputation for being unresectable by the time jaundice has developed. It is more likely that tumours of the retropancreatic bile duct would be included in the category of "ampullary tumours" than pancreatic tumours.

There appears, therefore, to be a real increase in the risk of adenocarcinoma developing in the head of the pancreas compared to the body. The reason for this is not clear. It may be due to the effect of duodenopancreatic reflux of carcinogens in bile¹⁵ or gastroduodenal juice,¹⁶ or it may be due to an alteration in the pancreatic juice, as it passes along the pancreatic duct, affecting either the concentration or the activation of a pancreatic carcinogen so that it exerts a greater effect on the head than on the body of the pancreas. Although its significance is not understood this uneven distribution does appear to be one of the few clues to those factors which affect the development of carcinoma in the human pancreas.

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