Assessment of the presence of pancreatic intraepithelial neoplasia in various diseases of this organ

Zińczuk J.[1 A,C,D], Zaręba K.[2 B,C], Konarzewska-Duchnowska E.[3C], Guzińska-Ustymowicz K.[1A], Kędra B.[2B], Kemona A.[1E], Pryczynicz A.[1E,F]

1. Department of General Pathomorphology, Medical University of Białystok, Poland
2. 2nd Department of General and Gastrointestinal Surgery, Medical University of Białystok, Poland
3. Department of Emergency Medicine and Disasters, Medical University of Białystok, Poland

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ABSTRACT

Purpose: Pancreatic intraepithelial neoplasia (PanIN) is one of the most commonly occurring precancerous lesions in the pancreas that leads to the development of pancreatic ductal adenocarcinoma (PDAC). We assessed the presence and grade of pancreatic intraepithelial neoplasia in the course of various diseases of the pancreas and its correlations with chosen clinicopathological parameters.

Materials and methods: We reviewed postoperative tissue samples and clinicopathologic data of patients who were diagnosed due to different pancreatic lesions from January 2008 to June 2014 at the Department of General Pathomorphology of the Medical University in Białystok (Poland). All slides were reviewed by two independent pathologists for the presence and grade of PanIN lesions.

Results: A total of 276 foci of PanIN were identified in 94 patients. The most common lesions were PanIN 1a and PanIN 1b, which together constituted 68.2 % of all lesions; whereas PanIN 2 was present in 21.7%, and PanIN 3 in 10.1% of patients. No statistical differences were observed in sex tendency for the development of PanINs. There was a correlation between patient age and degree of PanIN ($p>0.05$). There was no statistical difference in the PanIN frequency among patients with pancreatic ductal adenocarcinomas, neuroendocrine tumors, chronic pancreatitis, and pancreatic cysts.

Conclusions: Our study showed that age is an important factor in the development of pancreatic intraepithelial neoplasia, and the presence of PanIN in non-neoplastic diseases in older people should be included to the group with increased risk of cancer development.

Keywords: Pancreatic intraepithelial neoplasia, PanIN, pancreatic ductal adenocarcinoma, pancreatic cancer, chronic pancreatitis

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***Corresponding author:**
Justyna Zińczuk
Department of General Pathomorphology, Medical University of Białystok
ul. Jerzego Waszyngtona 13, 15-269 Białystok, Poland
E-mail: j.zinczuk@wp.pl; Fax: +48 (85) 7 48 59 96

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers in the world, with an average survival time of less than six months and an overall 5-year survival rate of less than 6%, and is related with aggressive growth and a high rate of metastasis. During the past several decades, the incidence of pancreatic cancer has significantly increased and is associated with a change in lifestyle, smoking, environmental pollution, and prolonged life expectancy, because pancreatic cancer is primarily a disease of old age [1]. The number of deaths in Europe due to pancreatic cancer in 2012 was 52600 men and 51900 women, which allowed classifying it at fourth and fifth place as the most frequent cause of cancer deaths [2]. The number of pancreatic cancer deaths in Poland in 2012 was 2397 in women and 2397 in men and was classified at fifth and sixth leading cause of cancer deaths [3].

It is expected that in 2017 the number of deaths of men and women with this cancer will amount to 22300 and 20790, respectively [4]. Currently, the only chance for a cure is surgical resection of the pancreas, but only 15-20% of changes are resectable at diagnosis [5]. This is caused by the fact that pancreatic cancer is usually diagnosed at an advanced stage due to the lack of symptoms in early stages and resection of an advanced tumor is not possible. In order to reduce the mortality rate in patients suffering from pancreatic cancer, tests that detect precancerous lesions should be developed [6, 7].

The most common and the best defined in the literature precursor lesion leading to pancreatic ductal adenocarcinoma is pancreatic intraepithelial neoplasia (PanIN). Pancreatic intraepithelial neoplasia is defined as microscopic papillary or flat and non-invasive epithelial lesions arising in pancreatic ducts in which the diameter does not exceed 5mm. They are not grossly visible and clinically detectable. According to the degrees of architectural and cytological atypia in pancreatic ducts, PanINs are classified into three grades: PanIN 1, which is low grade PanINs and is divided into flat (PanIN 1a) and micropapillary (PanIN 1b) types; PanIN 2 – intermediate grade PanINs; and high grade PanIN - PanIN 3, which may be transformed into an invasive form of cancer, pancreatic ductal adenocarcinoma [8]. Many authors described a higher frequency of pancreatic intraepithelial neoplasia in patients with pancreatic ductal adenocarcinoma, but also reported that it may be present in patients with the following disorders of the pancreas: mucinous cystic neoplasms, neuroendocrine tumors, chronic pancreatitis, serous cystadenomas, acinar cell tumors, and pseudopapillary tumors [9].

The aim of the study was to assess the presence and grade of pancreatic intraepithelial neoplasia in various diseases of the pancreas.

MATERIALS AND METHODS

We reviewed samples from 94 patients (47 men, 47 women) aged 23-84 years that had been diagnosed due to different pancreatic lesions at the Department of General Pathomorphology of the Medical University in Białystok (Poland) between January 2008 and June 2014. From the above 94 diseases, 39 patients suffered from chronic pancreatitis, 45 had pancreatic ductal adeno-carcinomas, 6 neuroendocrine tumors, and 4 pancreatic cysts. For all cases, we reviewed the pathology reports and recorded the demographic parameters (age, sex), and also the location of the resected pancreatic tissue (head, body or tail). All slides were reviewed by two independent pathologists for the presence and grade of PanIN lesions, which were then classified according to the most recently published consensus statement [10]. Briefly, PanIN 1A is an epithelial flat lesion, whereas PanIN-1b is a papillary or micropapillary lesion composed of tall columnar cells with basally located nuclei of a round to oval shape and abundant supranuclear mucin without cytology atypia. PanIN 2 is a mucinous, epithelial flat, or papillary lesion with some nuclear abnormalities, including loss of polarity, crowding, enlargement, nuclear stratification, and hyperchromatism. PanIN 3 usually has a papillary or micropapillary architecture with abnormal cribriforming, budding, and luminal necrosis with cytologic abnormalities, such as loss of nuclear polarity, dystrophic goblet cells, atypical mitotic figures and macronucleoli. The presence of PanINs was evaluated on slides of normal pancreatic tissue at least 5 mm away from the carcinoma, while in non-neoplastic lesions it was evaluated in place of an ongoing disease process. The grade of PanINs was compared with the clinicopathological findings such as age, sex, location, and type of disease. Representative examples of four PanIN grades - 1a, 1b, 2, and 3 are shown in Figure 1.

We classified PanINs according to two methods: first, we evaluated and counted all the lesions in each case. Next, according to the Andea's classification [14], we assigned to each case the highest grade of PanIN lesion that was identified, irrespective of whether lower grade lesions were present. Briefly, a case of a given PanIN grade could also contain lesions of lower grade. For example, a case classified as PanIN 3 might also contain PanIN 1A, 1B, or PanIN 2 (Table 1).

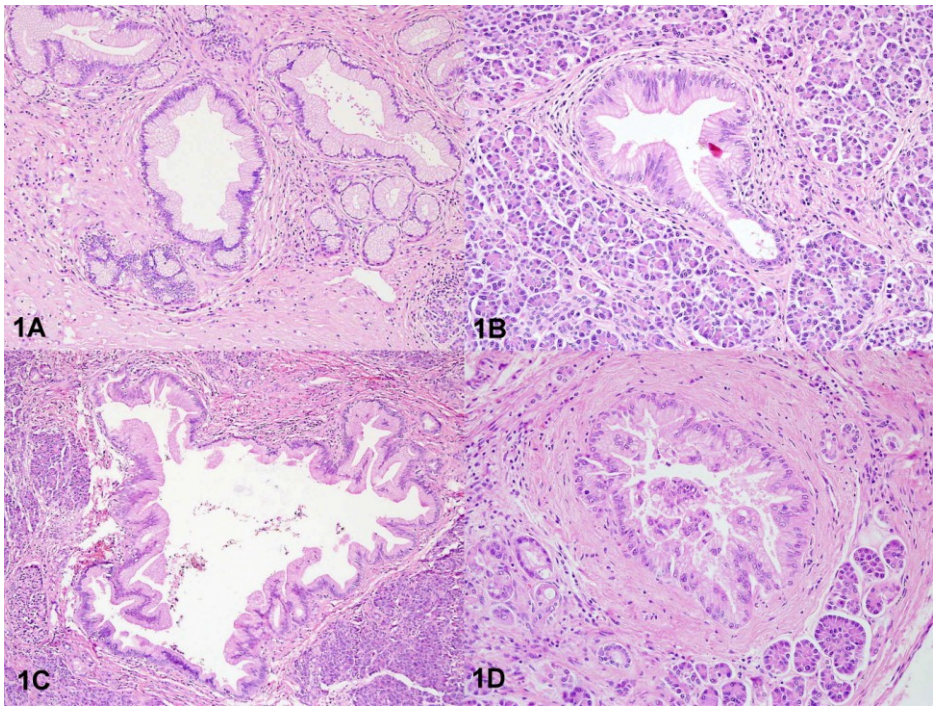

Figure 1. Histological features of PanIN 1a (A), PanIN 1b (B), PanIN 2 (C), PanIN 3 (D).

Table 1. Methodology used for grading the cases by Andea [12]

	PanIN lesions identified in a given case				
PanIN grade assigned to the case		**1A**	**1B**	**2**	3
	1A	Present	Absent	Absent	Absent
	1B	May be present	Present	Absent	Absent
	2	May be present	May be present	Present	Absent
	3	May be present	May be present	May be present	Present

PanIN grade assigned to a given case represented the grade of the highest PanIN lesion identified in that case.

Statistical analysis

All calculations were carried out using Statistica 10.0 software. Statistical analyses were performed with Spearman's correlation coefficient test. A *p-value* of <0.05 was considered to be statistically significant.

RESULTS

PanIN frequency and grade

A total of 276 foci of PanIN were identified in 94 cases, and were graded according to criteria established at the meeting of the Pancreas Cancer Think Tank in 1999 [6]. The patient clinicopathologic data are listed in Table 2. The total number of PanIN 1a was 100, PanIN 1b – 88, PanIN 2 – 60 and PanIN 3 – 28, which implies that the most frequently occurring lesions were PanIN 1a and PanIN 1b, and their percentage of the total number of PanINs was 68.2 %. According to the highest grade of PanINs, 94 patients were categorized as having PanIN 1A (n = 15), PanIN 1B (n = 25), PanIN 2 (n = 32), or PanIN 3 (n = 21) (Table 3).

Correlation of age and sex with the presence of PanIN

The average age of patients with pancreatic ductal adenocarcinoma, neuroendocrine tumors, chronic pancreatitis, and pancreatic cysts was 66 (range 44-84), 63 (range 55-74), 53 (range 23-76), and 65 (range 46-76), respectively (Table 2). Both in patients under and over 60 years of age the most frequently occurring lesions were low grade PanINs - 1a and 1b. In patients under 60 years of age, low grade PanINs constituted 70.8%, and in patients after 60 years of age 66.3% (Table 4). Simultaneously, we observed a higher percentage of intermediate and high grade lesions in

patients over 60 years (32.7% vs 29.2% in patients under 60 years of age). Moreover, in patients under 60 years of age, the total number of different degree lesions was 113, whereas, in patients over 60 years of age 163, suggesting that age plays an important role in the development of PanINs ($p<0.05$) (Table 4).

Figure 2 shows the age distribution of patients with PanIN 1a, 1b, 2, and 3. There was also no sex tendency for the development of PanINs, and both, men and women showed a similar frequency of PanINs, regardless of its grade ($p=0.301$) (Table 4, 5).

Association of PanINs with location and diseases

PanINs were accompanied by all diseases presented in this paper, such as pancreatic ductal adenocarcinomas, neuroendocrine tumors, chronic pancreatitis, and pancreatic cysts. We counted the number of PanIN lesions in each disease. There was no statistical difference in PanIN frequency among patients with pancreatic ductal adenocarcinomas, neuroendocrine tumors, chronic pancreatitis, or pancreatic cysts ($p=0.592$). In 52% of the cases, the examined pancreatic tissue originated from the head of the pancreas, whereas in 18.5% of the cases it was obtained from the tail, and 9% derived from the body of the organ. A total of 21.5% of the cases originated both from body and tail of the pancreas. We did not show a statistically significant relationship.

Table 2. Demographics of 94 patients

	Number of cases	Sex		Age	
		Female	Male	Range	Median
PDA	45	23	22	44-84	66
Neuroendorcine tumors	6	4	2	55-74	63
Chonic pancreatitis	39	18	21	23-76	53
Pancreatic cysts	4	2	2	46-76	65

Table 3. Number of PanIN lesions

	PanIN 1A n (%)	PanIN 1A n (%)	Total PanIN 1 n (%)	PanIN 2 n (%)	PanIN 3 n (%)	Total n (%)
Total number of lesions	100 (36.3)	88 (31.9)	188 (68.2)	60 (21.7)	28 (10.1)	276 (100)
Number of highest degree of lesions	15 (16.0)	25 (26.6)	40 (42.6)	32 (34.0)	22 (23.4)	94 (100)

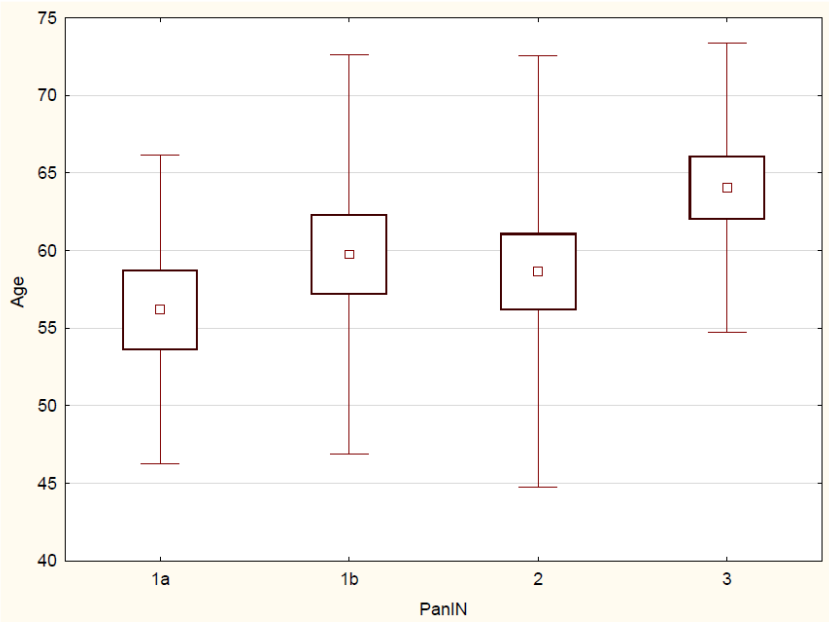

Figure 2. Age distribution of patients with PanIN 1a, 1b, 2, and 3. Age distribution (in years) of patients with PanINs was analyzed and plotted in a box plot. The square in the boxes represents median age.

Table 4. Correlations between clinicopathological parameters and all degrees of PanIN.

Factor	PanIN 1A n=100 n (%)	PanIN 1B n=88 n (%)	Total PanIN 1 n=188 n (%)	PanIN 2 n=60 n (%)	PanIN 3 n=28 n (%)	*P value*
Age						**0.034**
<60	43 (38.1)	37 (32.7)	80 (70.8)	23 (20.4)	10 (8.8)	
>60	57 (35.0)	51 (31.3)	108 (66.3)	37 (22.7)	18 (11.0)	
Sex						0.301
M	45 (34.9)	39 (30.2)	84 (65.1)	29 (22.5)	16 (12.4)	
F	55 (37.4)	49 (33.3)	104 (70.7)	31 (21.1)	12 (8.2)	
Location						0.329
head	53 (37.6)	46 (32.6)	99 (70.2)	30 (21.3)	12 (8.5)	
body	9 (36.0)	7 (28.0)	16 (64.0)	6 (24.0)	3 (12.0)	
tail	19 (37.3)	16 (31.4)	35 (68.7)	11 (21.6)	5 (9.8)	
body and tail	19 (32.2)	19 (32.2)	38 (64.4)	13 (22.0)	8 (13.6)	
Disease						0.592
pancreatitis	43 (36.4)	37 (31.4)	80 (67.8)	26 (22.0)	12 (10.2)	
PDA	47 (34.3)	44 (32.1)	91 (66.4)	31 (22.6)	15 (11.0)	
neuroendocrine tumors	6 (46.1)	5 (38.5)	11 (84.6)	2 (15.4)	0 (0)	
pancreatic cysts	4 (50.0)	2 (25.0)	6 (75.0)	1 (12.5)	1 (12.5)	

Table 5. Correlations between clinicopathological parameters and the highest degree of PanIN (highest grade PanIN lesion used for assigning grade)

Factor	PanIN 1A n=15 n (%)	PanIN 1B n=25 n (%)	Total PanIN 1 n=40 n (%)	PanIN 2 n=32 n (%)	PanIN 3 n=22 n (%)	*P value*
Age						***0.020***
<60	10 (23.8)	12 (2.6)	23 (52.4)	14 (33.3)	6 (14.3)	
>60	5 (9.6)	13 (25.0)	18 (34.6)	18 (34.6)	16 (30.8)	
Sex						*0.920*
M	11 (23.4)	9 (19.2)	20 (42.6)	13 (27.7)	14 (29.8)	
F	4 (8.5)	16 (34.1)	20 (42.6)	19 (40.4)	8 (17.0)	
Location						*0.105*
head	8 (17.0)	13 (27.7)	21 (44.7)	16 (34.0)	10 (21.3)	
body	2 (25.0)	1 (12.5)	3 (37.5)	2 (25.0)	3 (37.5)	
tail	5 (23.8)	6 (28.6)	11 (52.4)	6 (28.6)	4 (19.0)	
body and tail	0 (0)	5 (27.8)	5 (27.8)	8 (44.4)	5 (27.8)	
Disease						*0.901*
pancreatitis	8 (20.5)	9 (23.1)	17 (43.6)	14 (35.9)	8 (20.5)	
PDA	4 (8.9)	12 (26.7)	16 (35.6)	16 (35.6)	13 (28.9)	
neuroendocrine tumors	1 (16.7)	3 (50.0)	4 (66.7)	2 (33.3)	0 (0)	
pancreatic cysts	2 (50.0)	1 (25.0)	3 (75.0)	0 (0)	1 (25.0)	

DISCUSSION

Pancreatic cancer is one of the worst and most aggressive type of human cancers with a very poor prognosis. Median survival time for patients with pancreatic ductal adenocarcinoma is only 3 to 6 months. This is associated with diagnosis at an advanced stage of the disease with distant metastasis. Only 15% of all patients are diagnosed when they have tumors smaller than 20 mm without lymph node metastases [11]. For these patients, complete surgical resection ensures a 5-year survival rate of 30–60%, but in the case of lesions smaller than 10 mm the survival rate increases to 75%. Greater understanding of the biology and mechanisms of pancreatic cancer may lead to possibly earlier detection, prevention, treatment, improved prognosis, and decreased risk of recurrence in the future.

Molecular and genetic research confirms the claim that pancreatic ductal adenocarcinoma does not arise de novo, but may develop through stepwise progression from precursor lesions [6-8]. Many studies have identified three preinvasive lesions of pancreatic cancer: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMN), and mucinous cystic neoplasms (MCN), among which pancreatic intraepithelial neoplasia lesions are the most common and most well characterized. Pancreatic intraepithelial neoplasia, similarly to pancreatic ductal adenocarcinoma, reveals genetic abnormalities including mutations of *Kras*, inactivation of *p16* and *DPC4*, and abnormal expression of *p53*; however, the exact mechanism through which PanIN lesions lead to adenocarcinoma is yet unknown [15].

There are few studies describing the frequency of pancreatic intraepithelial neoplasia in patients with different pancreatic lesions: pancreatic ductal adenocarcinoma, serous cystadenoma, neuroendocrine tumors, chronic pancreatitis, and other pathologies [16-19]. In this paper we also evaluated the presence and frequency of PanIN lesions and its association with such parameters as: age, sex, location, and primary diseases such as: pancreatic ductal adenocarcinomas, chronic pancreatitis, neuroendocrine tumors, and pancreatic cysts. In our study, the most frequent lesions were PanIN 1a and PanIN 1b, which constituted 68,1% of total lesions, PanIN 2 occurred in 21,7%, whereas PanIN 3 represented only 10,1% of all found lesions. Counting only the highest degree of PanIN lesions using Andea's method, we obtained similar results: PanIN 1 – 43.5%, PanIN 2 – 33.95%, and PanIN 3 – 22.55%.

In the paper by Konstantinidis et al. [12], PanIN 1 was also the most frequent lesion and constituted half (50%) of all found lesions. PanIN 2 represented 41%, whereas PanIN accounted for only 8% of all lesions [12]. This enables concluding that regardless of age, sex, location of lesions in the pancreas, and primary diseases the most common changes were low grade PanIN.

Studies by Recavarren [18] and Andea [14] have shown that aging is a major factor leading to the development of pancreatic intraepithelial neoplasia and pancreatic cancer. Our study also showed that patient age correlated with PanIN frequency ($p=0.034$). Our results suggest that the frequency of pancreatic intraepithelial neoplasia increases with age, and in patients over 60 years of age the total number of lesions is higher than in patients under 60 years of age. Moreover, high grade lesions – PanIN 2 and PanIN 3 – occur more commonly in patients over 60 years of age compared with patients under 60 years of age. We did not find any statistically significant correlations between frequency of pancreatic intraepithelial neoplasia and sex ($p=0.301$). Both, men and women showed a similar frequency of PanINs. Similar results were obtained by Hassid [19], Recavarren [18], and Oda [13]. In their papers, they also did not observe a correlation between sex and PanIN frequency, which suggests that sex does not affect the development of pancreatic intraepithelial neoplasia.

There were no significant relationships between PanIN frequency with the location of these lesions ($p=0.329$) and types of primary diseases ($p=0.592$). Both Hassid [19] and Andea [14] did not show a correlation with PanIN and its locations, but Andea observed that more than half of the lesions (53%) originated from the head of the pancreas. This is probably related to the fact that the majority of neoplastic lesions derived from the pancreatic head.

Although, pancreatic intraepithelial neoplasia is considered a precursor lesion for pancreatic ductal adenocarcinoma, it may appear in non-neoplastic diseases such as acute or chronic pancreatitis [20]. In our paper PanINs were present in pancreatitis, pancreatic cysts, and neuroendocrine tumors. Others authors also observed the presence of PanIN with different pancreatic lesions such as: intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, serous cystadenomas, and finally neuroendocrine tumors, or chronic pancreatitis [9, 11-17]. This suggests that the presence of PanIN in non-neoplastic diseases in older people means an increased risk for future pancreatic cancer.

CONCLUSIONS

Our study showed that age is an important factor in the development of pancreatic intraepithelial neoplasia.

We described PanIN incidence in the various patient groups – both, in patients with pancreatic ductal adenocarcinoma and non-neoplastic diseases.

It would be useful for future research to design screening tests for the detection of precancerous lesions and a deeper understanding of the mechanisms responsible for cancer development.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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