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REVIEW

Could the burden of pancreatic cancer originate in childhood?

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Abstract

The presence of pancreatic cancer during childhood is extremely rare, and physicians may be tempted to overlook this diagnosis based on age criteria. However, there are primary malignant pancreatic tumors encountered in pediatric patients, such as pancreatoblastoma, and tumors considered benign in general but may present a malignant potential, such as the solid pseudo-papillary tumor, insulinoma, gastrinoma, and vasoactive intestinal peptide secreting tumor. Their early diagnosis and management are of paramount importance since the survival rates tend to differ for various types of these conditions. Many pediatric cancers may present pancreatic metastases, such as renal cell carcinoma, which may evolve with pancreatic metastatic disease even after two or more decades. Several childhood diseases may create a predisposition for the development of pancreatic cancer during adulthood; hence, there is a need for extensive screening strategies and complex programs to facilitate the transition from pediatric to adult

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healthcare. Nevertheless, genetic studies highlight the fact the specific gene mutations and family aggregations may be correlated with a special predisposition towards pancreatic cancer. This review aims to report the main pancreatic cancers diagnosed during childhood, the most important childhood diseases predisposing to the development of pancreatic malignancies, and the gene mutations associates with pancreatic malignant tumors.

Key Words: Pancreatic cancer; Pancreatic metastasis; Childhood; Adult; Screening; Transition

Core Tip: Pancreatic malignant tumors are rarely found during childhood, their prognosis being linked to the type of tumor and its capacity to evolve towards metastasis. Also, there are types of cancer diagnosed in pediatric patients which may present with pancreatic metastasis later, during adulthood. Various conditions, when diagnosed during childhood, may be associated with the later onset of pancreatic cancer. Also, several genetic mutations have been linked to the development of pancreatic malignancies. We discuss here the above-mentioned topics in the context of a comprehensive literature review.

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INTRODUCTION

In spite of technological, economic and healthcare progress, pancreatic cancer remains correlated with high mortality rates, its diagnosis at an early stage being of paramount importance for a favorable outcome, but this objective has proven exceedingly difficult to achieve. Researchers in the field have attempted to correlate the appearance of malignant pancreatic tumors with various local or systemic diseases and/or genetic mutations. The preventive management in cases of high risk for pancreatic cancer begins during childhood, by assessing and, whenever possible, treating the predisposing factors[1].

Pancreatic tumors are rarely found among the pediatric population; therefore, their study is limited to isolated case reports or case series. From a histological point of view, pancreatic tumors differ during childhood and adulthood, with a tendency for a better prognosis and clinical outcome at younger ages[2].

This review aims at reporting the primary pancreatic malignant tumors encountered during childhood, the pediatric cancers with the capacity to evolve towards pancreatic metastatic disease, the conditions diagnosable at a pediatric age that may predispose to pancreatic cancer during adulthood, and the most important gene mutations correlated with a predisposition towards pancreatic cancer (Table 1).

PANCREATIC MALIGNANT TUMORS IN CHILDREN

In general, pancreatic tumors are divided into epithelial (exocrine, of acinar, ductal, or undetermined cell origin; or endocrine) and non-epithelial types. The most frequent pancreatic tumor among children is of acinar cell origin, pancreatoblastoma. Solid pseudo-papillary tumors present a low malignant potential and are mostly encountered in young female patients. Rare types of pancreatic cancer may be found in children, such as acinar cell carcinoma and the extremely rare ductal adenocarcinomas. In rare cases, neonatal hypoglycemia can be caused by a focal or diffuse neuroendocrine adenoma of the gland[3].

Table 1 Pediatric pancreatic cancers

Pediatric pancreatic malignant tumors
Pancreatoblastoma
Solid pseudo-papillary tumors
Insulinoma
Gastrinoma
VIPoma
Acinar cell carcinoma
Ductal adenocarcinoma
Mucinous cystic neoplasm
Lymphoma: Hodgkin lymphoma, large cell lymphoma, Burkitt's lymphoma
Germ cell tumors
Primitive neuroectoderma tumors: extraosseous Ewing's sarcoma
Mesenchymal tumors: rhabdomyosarcoma, leiomyosarcoma, schwannoma
Pediatric cancers evolving with pancreatic metastatic disease
Renal cell carcinoma
Sarcomas
Colorectal carcinoma
Neuroblastoma
Diseases (diagnosable) in pediatric patients predisposing to pancreatic cancer at adult age
Obesity
Diabetes mellitus, glucose metabolism disturbances and insulin resistance
Chronic and hereditary pancreatitis
Cystic fibrosis
McCune Albright syndrome
Multiple endocrine neoplasia type I
Von Hippel Lindau disease
Li Fraumeni syndrome

The pancreas may be also involved into neoplastic processes arising from the adjacent structures, such as lymphomas, teratomas, rhabdomyosarcomas and primitive neuroectodermal tumors. Secondary involvement may be seen during metastatic disease originating from neuroblastomas[4].

The study based on the data provided by the United States' National Cancer Institute for the Surveillance, Epidemiology and End Result (SEER) Database confirmed the scarcity of malignant pancreatic tumors in the pediatric population; data collected from a 30-year period of time identified only 58 patients aged under 20 years suffering from malignant pancreatic tumors[4].

Pancreatoblastoma

Pancreatoblastoma was described for the first time in a 15-mo-old male patient in 1957, and was originally termed "infantile adenocarcinoma of the pancreas"[5]. Later, histological similarities were found between the newly discovered type of tumor and the undifferentiated or incompletely differentiated fetal acini at 7-8 wk of gestation in the embryo, and the term "pancreatoblastoma" was imposed[6].

Most cases of pancreatoblastomas are sporadic but there have been cases of congenital nature associated with Beckwith-Wiedemann syndrome (macrosomia, macroglossia, visceromegaly, omphalocele and an increased risk for embryonal tumors, such as nephroblastoma, hepatoblastoma, rhabdomyosarcoma and mostly cystic pancreatoblastoma)[7].

Mostly encountered in pediatric patients aged 0 to 9-years-old, pancreatoblastomas are exceptionally rare in adults.

Pancreatoblastoma usually appears as a large well-defined solitary mass, with lobulated margins ranging between 1.5 cm and 20 cm, and with half of the cases arising from the cephalo-pancreatic region. It may present as a cystic mass accompanied by necrosis, especially when associated with Beckwith-Wiedemann syndrome[3].

Although it has been mostly cited in the male population, Rasalkar *et al*[8] reported two cases of pancreatoblastoma in 2 girls, aged 9-years-old and 11-years-old. The symptomatology included pain and discomfort in the epigastric region, accompanied by a local lump and food intolerance. In both cases, the mass had disordered the local anatomy by displacing the splenic vessels, right kidney, the renal veins and the inferior vena cava. The tumor was located on the head of the pancreas in the first case and on the distal body and pancreatic tail in the second case.

Other symptoms associated with pancreatoblastomas include weight loss, anorexia, fatigue, lethargy, and jaundice in rare cases. Local invasion has been cited, mostly involving the adjacent pancreas, biliary tree, and the local vessels, including the portal and the mesenteric veins. The most common sites of metastases are the liver and abdominal lymph nodes, but there have been case reports of rarely located metastasis, such as to the lungs, brain, omentum, colon, spleen and adrenal glands[9].

Solid pseudo-papillary tumors

Pseudo-papillary tumors of the pancreas are rarely encountered tumors of exocrine origin, having a strong female predilection and being diagnosed during childhood in half of the cases[3]. The literature suggests that they present no preference regarding location on the pancreas, a low-grade malignant potential and a favorable long-term prognosis after surgical treatment[10].

The histological origin of these tumors is not yet clear but it has been linked to ductal cells, endocrine or multipotent stem cells. One important issue is the possibility of recurrence and, hence, the mandatory imaging follow-up. Authors have reported cases of metastasis in the liver, regional lymph nodes, omentum, mesentery and peritoneum[11].

In a 15-year retrospective study, the authors found 11 patients with pseudo-papillary tumors presenting with abdominal pain or palpable abdominal mass, digestive intolerance, and 1 case of traumatic tumor rupture leading to hemoperitoneum; two cases were diagnosed incidentally during medical examinations for other diseases. In this lot, preoperative serum tumor markers were assessed as follows: α-fetoprotein, carcinoembryonic antigen, carbohydrate antigen (CA) 125 were within normal ranges, whereas elevated levels of CA 19-9 were found in 3 of 10 patients[10].

Insulinoma

Insulinomas are particularly rare in children, either the sporadic form or when associated with multiple endocrine neoplasia type 1 (MEN1). Although more than 90% of insulinomas are benign, there have been cases of malignant insulinomas, characterized by the World Health Organization (WHO) according to their metastatic potential and risk of recurrence and mortality. A tumor size larger than 2 cm as well as the presence of cytokeratin 19 and tumor staging and grading with Ki 67 > 2% are reported predictors for the metastatic disease. The most common sites of metastasis are the regional lymph nodes, the liver and bone[12].

The clinical manifestations include symptoms associated with neuroglycopenia, such as loss of consciousness, confusion, dizziness and lethargy, or with adrenergic stimulation, such as hunger, weight gain, tachycardia, palpitations and arterial hypertension; hypoglycemia may be difficult to recognize in neonates and small children up to 2 years of age because of the poor adrenergic symptoms. In these cases, the symptomatology associates with seizures, apnea and lethargy[13].

In a 20-year retrospective study, the fact that metastatic liver disease may appear years after the initial diagnosis and presumed curative surgical treatment of insulinomas was highlighted. In these cases, the metastatic liver disease manifested as recurrent, severe hypoglycemic episodes leading to coma[14].

Gastrinoma

Pancreatic gastrinomas are, in frequency, the second mostly encountered pancreatic neuroendocrine tumors (pNETs) after insulinomas. In children, this is an uncommon tumor, its diagnosis being based on complex biological and imagistic investigations. Because of its rarity, many cases of pediatric gastrinomas remain undiagnosed for

years; evidence of digestive ulcers associated with elevated levels of fasting gastrin is usually diagnostic for a gastrinoma associated with Zollinger-Ellison syndrome, but these findings have to be correlated with advanced imaging investigations in order to assess tumor localization and invasion. In the pediatric population, the malignancy rate is close to 30%, poor prognosis being associated with tumor size (> 3 cm), metastatic disease (especially hepatic, lymph nodes and bone metastasis), female gender, inadequate gastric hypersecretion control as well as the histopathological features[15].

According to the WHO classification, gastrinomas present with different potential of malignization corresponding to the degree of differentiation, as follows: Well differentiated gastrinomas with benign/uncertain behavior; well-differentiated gastrinomas with low-grade malignant behavior; and, poorly differentiated gastrinomas with high-grade malignant potential[16].

Massaro *et al*[17] reported a case of a gastrinoma with hepatic metastasis in a child investigated for Zollinger-Ellison syndrome who eventually underwent orthoptic liver transplant.

The symptomatology of sporadic pancreatic gastrinomas includes epigastric pain due to severe peptic ulcer disease, heartburn, chronic diarrhea, gastrointestinal (GI) bleeding, nausea and vomiting. There are pancreatic gastrinomas associated with *MEN1* mutation, which may manifest clinically at younger ages, before hyperparathyroidism; hence, complex management including assessment of ionized calcium and serum parathormone levels is important[16].

Vasoactive intestinal peptide secreting tumors

The vasoactive intestinal peptide secreting tumors (VIPomas) gather together a group of neuroendocrine tumors characterized by the secretion of the vasoactive intestinal peptide, resulting in the "WDHA" syndrome (featuring achlorhydria, hypokalemia and watery diarrhea). The literature suggests that 60%-80% of VIPomas have malignant potential and present with metastasis at first diagnosis. During childhood, VIPomas are usually diagnosed between 2-4 years of age, but there have been cases at younger age (Reindl *et al*[18] start their series with a 2-mo-old patient).

Metastasis are mostly located in the liver, but rare case of lymph node, lung and kidney metastasis have been described[19].

Acinar cell carcinoma

Carcinoma originating from the acinar cells represents a rare type of pancreatic cancer, although it is more frequently encountered during childhood compared to ductal cell adenocarcinoma. Even though the acinar cells represent the most commonly found cells in the pancreas, their malignant transformation accounts for only 1% of pancreatic exocrine tumors[20].

The histological differentiation between acinar cell carcinoma and pancreatoblastoma may be difficult in children, as their macroscopic and microscopic features tend to be similar. Other distinct characteristics include the presence of calcifications in one-third of the cases and the tendency for intratumoral hemorrhage[21].

Illyés *et al*[22] report the particular case of a 10-year-old male who presented with clinical and biological manifestations associated with Cushing's syndrome and was later diagnosed with pancreatic acinar cell carcinoma invading the retroperitoneum which evolved with multiple metastasis.

Ductal adenocarcinoma

Ductal adenocarcinomas are exceptionally rare entities in childhood. In spite of some case reports before 1993 and considering the current advancements in medicine and immunohistochemistry, these cases are no longer considered ductal adenocarcinomas [23].

The literature suggests that ductal adenocarcinomas appearing at a young age may present with a tendency for poor differentiation and a high degree of metastasis. The 5-year survival rate is similar to that in adults (2%-4%), although there have been authors who supported a lower survival rate due to delayed diagnosis in children and young adults[3].

Mucinous cystic neoplasms

Pancreatic cystic lesions usually present with a good prognosis in children, but rare cases of malignant (high grade dysplasia) or premalignant (low or intermediate grade dysplasia) course have been described. Recent studies suggest that mucinous cystic neoplasm is asymptomatic and discovered incidentally, and the malignant potential has to be considered, especially in tumors larger than 4 cm[24].

Lymphoma

Lymphomas may originate from the pancreatic tissue itself or may involve the pancreas with the true origin lying in the peripancreatic lymph nodes. During childhood, the most common type of lymphoma involving the pancreas is non-Hodgkin lymphoma; pancreatic and peripancreatic invasion can be seen in cases of large cell lymphoma and Burkitt's lymphoma. The pancreas involvement may be suggested by the presence of the mass itself or by a diffuse infiltration of the gland accompanied by local edema due to a process of acute pancreatitis or tumor lysis syndrome. There have been case reports of primary pancreatic lymphomas at a pediatric age manifested with obstructive jaundice, misleading the diagnosis towards a false acute cholestatic hepatitis[25,26].

Intrinsic pancreatic lymphomas usually affect female patients and manifest with nonspecific symptoms associated with the mass effect (abdominal pain, digestive intolerance). Imaging studies do not offer specific information and in order to make a definitive differential diagnosis from other pancreatic masses, a histological exam remains mandatory[27].

The literature reports less than 10 cases of pancreatic lymphoma manifesting as acute pancreatitis at debut. Athmani *et al*[28] report the case of a 6-year-old female with a rapidly progressive jaundice; in that case, abdominal imaging showed an important increase in the pancreatic size, homogeneous hepatomegaly and intra- and extrahepatic biliary ducts' dilatation. Ultimately, the histopathological examination set the diagnosis of Burkitt's lymphoma.

Standard diagnostic criteria for primary pancreatic lymphoma include absence of superficial lymphadenopathy, no enlargement of mediastinal lymph nodes visible on chest radiography, normal leukocyte count, the main mass located in the pancreas with peripancreatic lymph nodes involvement, and the absence of hepatic or splenic involvement[29].

Germ cell tumors

Extragonadal germ cell tumors represent 1%-3% of all childhood tumors. Even though their occurrence, originating from an upper abdominal organ, is exceedingly uncommon, they have been described on the head of the pancreas and causing biliary dilatation and mass-effect related symptoms. Based on the morphological characteristics and on the degree of differentiation, the WHO classifies teratomas as mature and immature[30].

Even though the malignant potential of pancreatic teratomas is yet to be established, 7%-10% of retroperitoneal teratomas with other localization are malignant[31]. For example, in other teratomas, the presence of yolk sac tumor microfoci may promote a malignant relapse after an incomplete surgical resection[32].

Primitive neuroectodermal tumors

Primitive neuroectodermal tumors usually originate in the bone and soft tissue, and there have been cases where they originated from solid organs containing neuroendocrine cells, like the pancreas, which accounts for 0.3% of primary pancreatic neoplasms at all ages[33].

In a literature review of extraosseous Ewing's sarcoma of the pancreas, Bose *et al*[34] pointed out the fact that the symptomatology usually associates with abdominal pain and jaundice; there were 2 particular cases in females of pediatric age where the tumor manifested with precocious puberty and 2 cases of GI bleeding and secondary iron deficiency anemia.

Primitive neuroectodermal tumors present an aggressive behavior, mostly due to the metastatic power; the most usual sites for metastasis are lungs, liver, bone and bone marrow.

Mesenchymal tumors

In children, the most common malignant mesenchymal tumor involving the pancreas is rhabdomyosarcoma. A percentage (specifically 15%) of rhabdomyosarcomas diagnosed during childhood originate from a site other than the head, neck, genitourinary tract and extremities. When situated in the abdomen, rhabdomyosarcomas can have originated from any part of the GI tract, including the extrahepatic biliary tract, pancreas and omentum; malignant ascites is an uncommon feature. An appreciable amount (specifically 14%) of these children present with metastatic disease at the initial diagnosis; the most common sites for metastasis are the lungs (36%), bone marrow (22%) and bones (7%)[35].

In rare cases, leiomyosarcomas may arise from the pancreatic duct and blood vessel walls within the pancreas; although rarely encountered, there have been cases of pancreatic leiomyosarcomas in children aged 14 and older[36].

Pancreatic schwannomas are rarely described in the literature, and more than 90% of them are benign tumors. However, there have been cases, mostly associated with von Recklinghausen disease, where the authors have described large schwannomas with malignant characteristics. Usually found on the pancreatic head and body, they usually manifest as nonspecific abdominal pain, weight loss, jaundice or GI bleeding [37].

Complete surgical resection is the treatment of choice in cases of pancreatic schwannomas, especially due to the fact that the character of malignancy cannot be established pre/during surgery and the fact that they do not respond to radiotherapy or chemotherapy[38].

Sheng *et al*[39] reported the first case of a low-grade malignancy pancreatic solitary fibrous tumor in a pediatric patient, a 14-mo-old male toddler.

PEDIATRIC CANCERS EVOLVING WITH PANCREATIC METASTATIC DISEASE

Metastatic pancreatic disease accounts for less than 2% of the entire pancreatic malignancies[40].

Pancreatic metastasis are rare entities that usually appear years after the diagnosis of the primary tumor. Following a topical literature review, authors reported that 62.6% of pancreatic metastasis appeared secondary to renal cell carcinoma, 7.2% secondary to sarcomas and 6.2% secondary to colorectal carcinoma[41]. Renal cell carcinoma is extremely rare in children, representing 1.8% to 6.3% of all types of renal cancers. Metastases originating from renal cell carcinomas usually present themselves as solitary or multiple masses inside the pancreas, which may occur even 20 years after the primary tumor manifestation. It is mandatory that the differential diagnosis of a pancreatic mass in patients with a history of renal cell carcinoma include secondary pancreatic metastasis[42].

Kim *et al*[43] reported the case of a 4-year-old male with stage 4 neuroblastoma, who presented with pancreatic metastasis manifesting as acute pancreatitis and rapidly progressive severe cholestasis. Farah *et al*[44] reported the case of a 15-year-old female who developed pancreatic metastasis due to an alveolar rhabdomyosarcoma located into the paranasal sinuses.

Pediatric pancreatic malignant tumors present with different degrees of aggressiveness and different potential for metastatic disease or local recurrences. The overall survival rates of pancreatic cancer diagnosed during childhood is not well established, but the 5-year survival rate for particular tumors ranges from more than 95% for some to as low as 2%-4% for ductal adenocarcinomas. For example, Bien *et al*[45] highlighted the fact that the 5-year survival rate of patients with pancreatoblastomas ranges between 30%-50%, despite surgical treatment and chemotherapy.

The 5-year survival rate for solid pseudo-papillary tumors has been reported between 95%-98% after complete surgical resection[46]. Primitive neuroectodermal tumors are highly aggressive and present with very poor prognosis; the 5-year survival rate is reported to be 50%[47].

Brecht *et al*[4] analyzed 5-year overall survival in a group of 228 patients under the age of 30 diagnosed with malignant pancreatic tumors (100 carcinomas, 85 endocrine tumors, 8 solid pseudopapillary neoplasms, 11 pancreatoblastomas). The data were extracted from the United States National Cancer Institute's SEER Public-use Database from 1973 to 2004. According to this study, 5-year overall survival (OAS) varied widely as follows: According to stage, it was 87%, 68%, 21 % for local (n = 54), regional (n = 42), distant metastatic disease (n = 108), respectively. According to histological types, OAS of patients with carcinoma was 33%, endocrine tumors 58%, solid pseudopapillary tumor of the pancreas 88%, pancreatoblastomas 66%. Following multivariate analysis, tumor stage, histology and age group are important and independent predictors for outcome.

Similar results were recently reported by Picado *et al*[48] analyzing the Data from the National Cancer Database (2004-2014) which included 109 children with pancreatic tumors. The 5-year overall survival by tumor histology was 95% for pseudopapillary tumors, 75% for neuroblastomas, 70% for pancreatoblastomas, 51% for endocrine tumors, 43% for sarcomas, and 34% for adenocarcinomas. On multivariable analysis, the strongest predictor of survival was the surgical resection[48].

Another recently published study, performed on 65 patients under the age of 21 diagnosed with pancreatic neoplasms, who followed the outcome after pancreatico-duodenectomy, reported that the 5-year overall survival by tumor histology was 95% for pseudopapillary neoplasm, 75% for neuroblastomas, 70% for pancreatoblastomas, 51% for endocrine tumors, 43% for sarcomas, and 34% for adenocarcinomas. In this study, the outcome was primarily associated with histology[49].

The burden of a diagnosis such as pancreatic cancer is often associated with adulthood, and pediatricians are tempted to overlook this possibility, especially in a toddler or young child. Diagnostic delays/mistakes are not uncommon at this age and they lead to worse outcome due to the aggressiveness of the local mass and the metastatic character.

DISEASES (DIAGNOSABLE) IN PEDIATRIC PATIENTS PREDISPOSING TO PANCREATIC CANCER AT ADULT AGE

Obesity

Various studies have highlighted a connection between increased body mass index (BMI) and the risk for pancreatic cancer[50-52].

It has been observed that a BMI of at least 30 kg/m^{2}was associated with a significantly increased risk of pancreatic cancer compared with a BMI of less than 23 kg/m^2[relative risk (RR): 1.72, 95%CI: 1.19-2.48], while an inverse relationship was also highlighted for moderate physical activity when comparing the highest to the lowest categories (RR: 0.45, 95%CI: 0.29-0.70), particularly among those with a BMI of at least 25 kg/m^2[53].

Moreover, it has been suggested that obese individuals develop pancreatic cancer earlier in life compared to patients with a normal weight, while also having lower survival rates following the diagnosis of pancreatic cancer[51,54].

Recent studies have also shown that overweight status and obesity in late adolescence and early adulthood are associated with an increased risk of this type of cancer[55,56].

Taking these aspects into consideration, researchers also questioned whether increased body weight during childhood would also be associated with adult pancreatic cancer. A prospective Danish cohort study including over 293000 individuals for whom data on height and BMI between the ages of 7 and 13 years were available, linked this information with data from Danish Cancer Registry. This study highlighted that increased BMI at every age from 7-13 years was significantly and positively associated with pancreatic cancer in adulthood, diagnosed up until age 70 [57].

Furthermore, the American National Institutes of Health-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study Cohort and several pooled analyses of cohort studies also revealed that adolescent or early adulthood body size would be positively associated with pancreatic cancer[51,58].

BMI in children aged 7-13 was identified as being associated with the development of pancreatic cancer in adulthood[57].

These positive associations were not dependent of the evolution of BMI later in life, indicating that the risk was established to a certain extent in earlier life. Consequently, in the context of increased prevalence of childhood obesity, improved strategies for prevention and early management of childhood obesity should be considered to diminish the risk for developing pancreatic cancer in adulthood, but also for other various diseases including cardiovascular diseases and other types of neoplasia[59-61].

Diabetes mellitus, glucose metabolism, and insulin resistance

The relationship between diabetes and pancreatic cancer has been investigated extensively, since numerous epidemiologic studies have described an association between these two entities; a meta-analysis including 88 cohort and case-control studies identified an around 2-fold risk (RR: 2.08, 95%CI: 1.87-2.32) of pancreatic malignancy in diabetic patients compared to patients without diabetes[62-64].

However, the exact direction of this association is under debate, with some data suggesting that diabetes may be a consequence rather than a cause of pancreatic cancer, while others support the bidirectional relationship between the two entities, taking into account some pathophysiological background, such as the fact that insulin resistance, as well as obesity may be mediated by reduced levels of plasma adiponectin, a fat-derived hormone that has insulin-sensitizing and anti-inflammatory properties[65-67].

All these data have come from studies including adult populations and mainly focused on type 2 diabetes mellitus, with less data on type 1 diabetes mellitus. A systematic review of studies that assessed risk of pancreatic cancer in people with diabetes, specifically mentioning whether it was type 1 or type 2 diabetes, or a surrogate for type 1 diabetes, such as young age at onset, suggested that the risk of pancreatic cancer is comparably increased both for type 1 and type 2 diabetes. The results of this systematic review also underlined some causality within this relationship. With regard to type 2 diabetes, a bidirectional relationship can be called upon, meaning that insulin resistance and diabetes may be induced by undiagnosed cancer or precancerous conditions of the pancreas, but considering the increased risk of pancreatic cancer reported as 1.5- to 2-fold higher in type 2 diabetes even when impaired glucose tolerance is detected more than 10 years before onset of cancer, suggesting that reverse causality does not individually and exclusively explain the association[68,69].

With regard to type 1 diabetes, it is likely, considering the early age at its onset, that it precedes pancreatic cancer rather than the other way round; therefore, type 1 diabetes should be considered a risk factor for pancreatic cancer[70].

Large cohort studies indicated that cancer risk in type 1 diabetes is rather low, but other authors reported that this risk is comparable between type 1 and type 2 diabetes. As older studies report, type 1 diabetes associates an overall modestly increased cancer risk[71].

Both epidemiological and genetic studies have tried to prove the association between type 2 diabetes and pancreatic cancer. Pierce *et al*[72] analyzed the 37 risk alleles attributed to type 2 diabetes and found a significant positive association between 2 of these alleles and pancreatic cancer.

However, the currently available data is limited and further studies including large type 1 and 2 diabetes and nondiabetic cohorts are needed.

Chronic pancreatitis

Chronic pancreatitis is a risk factor for pancreatic adenocarcinoma, independent of etiology[73,74].

Although the exact pathophysiology is not yet clear, several signaling pathways have been identified as activated during pancreatic inflammation, in the context of repeated DNA damage, error-prone repair mechanisms, and the progressive accumulation of genetic mutations, ultimately stimulating the development of pancreatic cancer[75]. Pancreas precancerous histologic changes are associated with a sequential accumulation of genetic defects, namely pancreatic intraepithelial neoplasms, which are present in sporadic pancreatic adenocarcinomas and also in patients with a history of chronic pancreatitis. Mutations found in the early stages involve the *kRas* gene, followed by *p16/CDKN2A*, *TP53* and *SMAD4/DPC4* genes[76]. Mutations in all four genes have been recognized as driver mutations that trigger neoplastic transformation and tumor progression[77].

Non-hereditary chronic pancreatitis is also an important risk factor for pancreatic cancer[73,74]. Reports from the International Pancreatitis Study Group identified a cumulative risk of 1.8% at 10 years and 4% at 20 years for pancreatic cancer, independent of the etiology of chronic pancreatitis[78]. More recent data included in a meta-analysis has suggested that the risk of pancreatic cancer was elevated 16-fold in patients with more than 2 years since their diagnosis of chronic pancreatitis, and even though this risk declines over time, it persists even after long-term follow-up. After at least 9 years of follow-up from the time of diagnosis of chronic pancreatitis, this patient category still had an over 3-fold increased risk of pancreatic cancer compared to patients without chronic pancreatitis[79].

Although these data were obtained from an adult population, they raise concern regarding the pediatric population, especially when considering patients with hereditary pancreatitis. Pancreatitis is rare in the pediatric population and frequently reported as idiopathic pancreatitis, showing gaps in the identification of the etiology. Recently, it was shown that genetic factors play a far more important role in the development of chronic pancreatitis in infancy and childhood than previously thought [80].

Hereditary pancreatitis is defined as two first-degree relatives or at least three second-degree relatives in two or more generations with chronic pancreatitis for which there is no other etiology. Several mutations have been associated with hereditary pancreatitis, from the initial description of the mutation in the cationic trypsinogen gene (*PRSS1*) by Whitcomb *et al*[81] to mutations in the *SPINK1*, *CPA1* and *CFTR* genes[82-85].

Due to a lack of specific signs and even to a sometimes quiet presentation, hereditary pancreatitis is frequently diagnosed at an advanced stage[86].

In some sporadic cases, mutations compatible with hereditary pancreatitis can be found without a corresponding family history, which could be explained by inheritance from unaffected carrier parents or even spontaneous *de novo* mutations[75,87].

Although progress has been made in diagnosing hereditary pancreatitis, the therapeutic pathway for this entity in children is still under debate[80]. Furthermore, counseling in patients with hereditary pancreatitis and their families should cover several aspects, from highly penetrant childhood-onset disease to a predisposition for pancreatic cancer in adulthood[88].

Studies are suggesting that *PRSS1* and *CFTR* gene mutations may not be directly linked with the development of pancreatic cancer. The onset of hereditary pancreatitis during childhood or early adulthood favors the perpetual exposure to chronic inflammation. The link between inflammation and cancer may not be limited to a subset of tumors but may be present within different types of cancer including lung, bladder, digestive, skin, and vulvar cancer. Hence, even though mutations in the *PRSS1* and *CFTR* genes are not directly associated with pancreatic cancer, chronic inflammation may favor tumor formation[89].

Beyond hereditary pancreatitis, other genetically determined conditions, including exocrine pancreatic insufficiency could evolve towards chronic pancreatitis and therefore potentially associate an increased risk for pancreatic cancer. Among these, Shwachman-Diamond syndrome is included. This a rare multi-organ recessive disease, mainly characterized by bone marrow failure leading to increased risk of transformation to myelodysplastic syndrome, skeletal defects, short stature, and pancreatic insufficiency contributing to the failure to thrive[90].

Cystic fibrosis

The cystic fibrosis phenotype results from mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator protein encoded by the *CFTR* gene and is among the most common autosomal recessive disease in White people having an increased risk of pancreatic cancer[91].

A meta-analysis investigating the risk for various cancers in cystic fibrosis patients identified a standardized incidence ratio of 6.18 (95%CI: 1.31-29.27), which is 2-fold to 5-fold higher in patients who had undergone lung transplantation in this setting[92]. Since there is an excess risk of early-onset pancreatic cancer in patients with cystic fibrosis, interventions for avoiding this setting should be identified. These could range from tackling environmental factors to gene therapy targeting mucin genes. Considering that nutritional deficiencies represent another possible risk factor for cancer, appropriate nutritional interventions to avoid or correct deficits should also be considered[93].

Mccune-Albright syndrome

McCune-Albright syndrome (MAS) represents a rare disorder, characterized by variable phenotypic expressions, including fibrous dysplasia of bone, hyperfunctioning endocrinopathies, and café-au-lait macules, in the context of a somatic gain-of-function mutation in the *GNAS gene*, which encodes the cAMP-regulating protein $G\alpha_s$, taking place early in embryonic development[94]. These types of *GNAS* mutations were previously identified in various types of neoplasias (pituitary, thyroid, appendiceal, and gonadal tumors, and breast cancer)[95-99].

Since there is such a wide range of pathology associated with MAS, it is essential to define them all and to establish an optimal screening strategy and clinical management. The activating *GNAS* mutations have been identified as somatic driver mutations in sporadic intraductal papillary mucinous neoplasms (IPMNs) and various GI lesions, also suggesting a potential role in pancreatic and GI tumorigenesis[100].

In a cohort of patients with MAS, about 46% developed IPMNs, which have risk for malignant degeneration[100,101]. This can lead to IPMN-associated adenocarcinoma but also to developing concurrent or distinct ductal adenocarcinoma, a pattern which has been described in a 2%-9% of patients who are being followed for IPMN[102,103].

Consequently, GI manifestations in MAS are common and include precursory pancreatic lesions for pancreatic cancer; therefore, patients with MAS may benefit from evaluation for GI pathology. Even though the optimal care for pancreatic lesions in MAS is not clearly shaped, a thorough GI history-taking at every visit and consideration of imaging with abdominal magnetic resonance imaging/magnetic resonance cholangiopancreatography would be useful[100].

A small observational study describes the link between MAS and pancreatic cancer, liver adenoma and choledochal cysts *via* the cAMP pathway. Taking into consideration this association, the authors suggest that all patients suffering from MAS should benefit from routine screening by magnetic resonance imaging (MRI) and if no lesion is observed, surveillance MRI may be performed every 5 years[104].

MEN1

MEN1 mutations cause a rare hereditary tumor syndrome, with an autosomal dominant transmission and high degree of penetrance. MEN1 tumors are caused by inactivating mutations of the tumor suppressor gene *MEN1*, and is characterized by a predisposition to a multitude of endocrine and nonendocrine tumors[105]. The classical phenotype includes hyperplasia and/or tumors of parathyroid, enteropancreatic, and/or anterior pituitary origin, with 30%–70% of patients developing enteropancreatic tumors, either functional or non-functional pancreatic endocrine pancreatic tumors upon reaching middle age[106]. Germline *MEN1* mutations have also been noted in families with only a parathyroid disorder, namely familial isolated primary hyperparathyroidism, but this type of mutation has also been reported in some cases of "sporadic" pNETs[107-109].

Considering the pattern of transmission and variety of manifestations, the Endocrine Society's clinical practice guidelines for MEN1 recommend a complex surveillance scheme commencing at early pediatric age, aiming to detect early and manage optimally MEN1-associated manifestations and tumors[110]. Recommended screening for pancreatic tumors in this setting begins early, at age 5 for insulinoma, with recommendation for yearly evaluation of fasting glucose and insulin level; for other pNETs, screening is recommended beginning at age 10, with evaluation of chromogranin A, pancreatic polypeptide, glucagon, vasoactive intestinal peptide levels and annual imaging, comprising magnetic resonance imaging, computed tomography or endoscopic ultrasound, considering that large pancreatic tumors may develop between 10 and 20 years of age[105].

Von Hippel-Lindau disease

Von Hippel–Lindau (vHL) disease is an autosomal dominant syndrome which occurs secondary to germline mutations in the *VHL* tumor suppressor gene, with patients being at risk of developing visceral cysts and tumors throughout the body[111]. Most commonly, the pancreas and kidneys are involved, with development of cystic lesions, but there is also an increased risk of developing neoplasms, often with clear cell features, including cerebellar and retinal hemangioblastomas, adrenal pheochromocytomas, clear cell renal cell carcinomas, pancreatic neuroendocrine tumors and pancreatic serous cystadenomas.

Although the most frequent pancreatic lesions include pancreatic cysts, which are found in 75% of vHL patients, one-fifth of the vHL patients will present pNETs, arising earlier than in non-syndromic patients, mostly in the fourth decade of life[112, 113].

Considering the increased potential for metastatic disease of pNETs in vHL patients and also the risk for metastasis generally associated with pNETs, regardless of the histologic grade, surgical resection is typically recommended for all pNETs greater than 2 cm[114]. However, taking into account the possibility of recurrent pNETs in vHL patients, in the context of the particular genetic background, the therapeutic decision must be well considered[115]. Although these lesions most commonly present during adulthood, screening and surveillance should begin in the pediatric years for patients with vHL disease.

Li Fraumeni syndrome

Li Fraumeni syndrome (LFS) is inherited in an autosomal dominant manner, which implies an increased risk for multiple primary cancers in affected individuals[116]. The most frequently implied cancers include bone and soft tissue sarcomas, leukemia, breast cancer, and brain tumors; subsequent evidence highlighted a broader spectrum of neoplasia, including cancers of the lung, digestive tract, prostate, ovary and pancreas, as well as lymphoma and melanoma[117,118].

Germline mutations in the tumor suppressor gene *TP53* are mainly incriminated for this syndrome; however, the absence of detectable germline *TP53* mutations in some LFS families suggests other genes are potentially involved in this syndrome[119].

There are various diagnostic criteria for the syndrome, such as the one included in the classical definition, which was afterwards extended for Li Fraumeni-like syndrome (an entity which shares some features of LFS but does not meet the strict LFS diagnostic criteria), in order to establish the criteria for *TP53* genetic testing[120]. Since

there is such a diversity of types of neoplasia which could arise in the context of LFS, we currently lack appropriate clinical surveillance strategies in this setting. Moreover, in the absence of a thorough knowledge on potential clinical benefits, psychosocial and economic impact of a comprehensive clinical surveillance protocol on early cancer detection, including pancreatic cancer screening, in asymptomatic *TP53* mutation carriers remains unknown.

OTHER GENE MUTATIONS ASSOCIATED WITH A PREDISPOSITION FOR PANCREATIC CANCER

Genetic risk factors play a major role in the development of pancreatic cancer, even if we are considering hereditary pancreatic cancer, familial pancreatic cancer or cases of pancreatic cancer associated with a familial cancer syndrome. The genetic predisposition for developing a particular malignancy has been of interest over the last decades, and several gene variants have been linked to an increased risk for pancreatic cancer, such as *BRCA1* and *BRCA2, STK11, PRSS1, PALB2, ATM, CDKN2A, APC, MLH1, MSH6, MSH2,* and *PMS2*[121].

However, this area of genetic research is still providing new information with the expectation to develop tests in order to assess the individual risk factors for pancreatic cancer, especially inside families with pancreatic cancer patients.

The definition of familial pancreatic cancer implies the existence of at least one pair of first-degree relatives suffering from pancreatic cancer, in the absence of a particular syndrome inside the family[122].

BRCA1 and *BRCA2* mutations are highly associated with inherited breast and ovarian cancer, but in carriers other types of cancer occur at higher rates than in the general population, including of pancreatic cancer. Brose *et al*[123] emphasize the fact that the general population risk of 1.3% transforms into a 2.8 RR for pancreatic cancer in people who carry the *BRCA1* mutation.

Familial atypical multiple mole melanoma syndrome is disease related to a cell cycle regulator gene for the p16 protein product, CDKN2A. Screening should begin early in childhood, in order to capture the early debut of both malignant melanoma and pancreatic cancer[124].

APC gene mutations are associated with the onset of familial adenomatous polyposis, a condition which, classically, increases the risk for colorectal cancer. Nowadays, evidence strongly suggests a correlation between inherited mutation of this gene and duodenal, thyroid, hepatic and pancreatic cancers[125].

The hereditary non-polyposis colorectal cancer known as Lynch syndrome also accounts for an increased risk for pancreatic cancer (1.3%-4%)[126]. Geary *et al*[127] pointed out the 30-fold increased risk for pancreatic cancer in patients with particular germline mutations in genes associated with the appearance of Lynch syndrome, such as *MLH1, MSH2, MSH6* and *PMS2.*

Complete family medical history is of paramount importance in assessing the particular risk for pancreatic cancer. In risk stratification, early molecular studies and germline mutation testing are mandatory.

CONCLUSION

Pancreatic cancer is generally considered an adulthood condition. In spite of this fact, its origins may lay in diseases or predisposing conditions which may be diagnosed at an early age, hence the need for rigorous screening strategies in patients with hereditary diseases connected with pancreatic cancer or familial aggregation of such conditions. Clinicians should be aware of rare conditions diagnosed during childhood, which may associate an increased risk for adult-onset pancreatic cancer. Also, the rare diagnosis of pancreatic cancer should be taken into consideration even at a pediatric age, especially when facing previously considered idiopathic acute pancreatitis or cholestatic hepatitis. The clinical features associated with pancreatic or peripancreatic masses may mimic other diseases and their management should include extensive imaging and histopathological examinations.

Malignant pancreatic tumors remain extremely rare in children and young adults and limited data on incidence and outcomes are available. Entities change over the age groups towards a predominantly increased number of carcinomas with worse outcome in older patients. The overall survival of pediatric patients with pancreatic

tumors is grim, and the survival rates tend to vary between different tumors. Given the rarity and aggressivity of many histological types of pancreatic tumors in children, in many instances it is difficult to assess whether there is any link between pancreatic cancer in childhood and adulthood.

International collaboration is needed to learn more about pediatric pancreatic tumors and to study the link between pancreatic tumors in childhood and adulthood.

Prophylaxis strategies should include weight control during childhood, screening for diabetes mellitus at younger ages, early routine imagistic investigations in cases with a predisposition towards pancreatic cancer or pancreatic metastasis. MRI and endoscopic ultrasonography are the recommended screening methods for pancreatic lesions. Also, screening strategies should include parents, siblings and children of patients with pancreatic cancer, especially in cases where there are more than 2 pancreatic cancer patients within the same biological family.

The implementation of transition programs from pediatric to adult healthcare services remains mandatory for these patients, namely childhood pancreatic cancer survivors or children with predisposing conditions for pancreatic malignancies.

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