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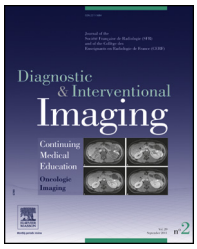

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Predisposing factors for pancreatic adenocarcinoma: What is the role of imaging?

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Abstract Early detection of pancreatic adenocarcinoma is the goal of imaging, enabling curative surgery. The identification of high-grade dysplastic precursor lesions is even more beneficial. Two forms are now better known: pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN). To detect these lesions with imaging, we need to know the patterns associated with them. A screening program could then be used to pinpoint them. This program could not be applied to the entire population. Identifying patients with an increased risk of pancreas adenocarcinoma is the first step of such screening.

Predisposing factors for pancreatic adenocarcinoma: what is the role of imaging?

In cases of pancreatic adenocarcinoma, patients often present with unresectable disease, and even in early-stage cancer recurrence is relatively high. However, genomic sequencing has shown that a fifteen-year interval is observed from initiation to the metastatic stage, suggesting a sufficient window for early detection [1]. Yet screening cannot be offered to the entire population due to its cost.

Screening is primarily offered to patients when there is evidence of increased risk, rather than evidence of the screening's effectiveness.

A better understanding of the natural history of this cancer could lead to better tailored screening. The aim of this article is to describe the different patterns of precancerous pancreatic diseases.

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Description of precancerous lesions at pathology

There are two main precancerous pancreatic lesions: pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN) [2]. Their pathologies are different, as described below (Fig. 1).

Pancreatic intraepithelial neoplasia (PanIN)

Amongst all the risk factors for pancreatic cancer, the latest to be described is PanIN. PanIN as a precursor of pancreatic cancer is a concept proposed by the 2000 WHO classification [3,4]. This new lesion may be associated with many pancreatic diseases, including diffuse conditions such as chronic pancreatitis, but also any type of tumor [5]. PanIN is a microscopic papillary or flat noninvasive epithelial neoplasm occurring in the pancreatic ductal epithelium with no or less than 5 mm of ductal dilatation [6,7]. It is characterized by columnar to cuboidal cells with varying amounts of mucin and different degrees of cytological and architectural atypia. Based on the degree of cellular and nuclear atypia, the lesions progress from PanIN-1 (low-grade dysplasia), which is probably indolent in nature and characterized by hyperplastic columnar ductal atypia, through PanIN-2 (moderate dysplasia) to PanIN-3 (carcinoma in situ), which shows high-grade dysplasia [6]. This grade is frequently associated with genetic abnormalities [6]. PanIN is rare in normal pancreatic tissue and are of low-grade dysplasia [7].

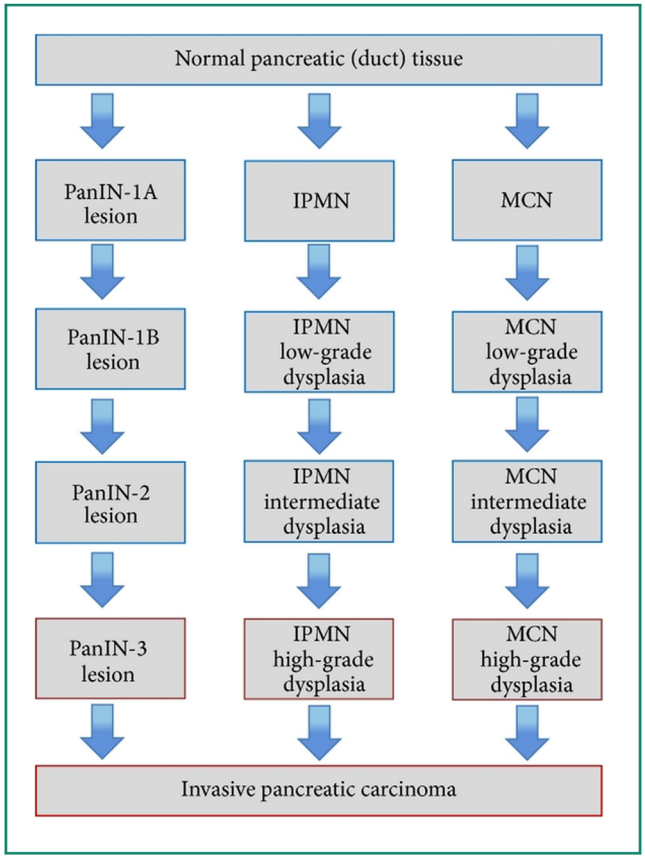

Figure 1. Pancreatic lesions known to be at risk of adenocarcinoma.

Intraductal papillary mucinous neoplasm (IPMN)

IPMN of the pancreas originates from a mucinous epithelium of the pancreatic duct (main duct or branch ducts) characterized by papillary growth and variable amounts of mucinous secretion causing ductal dilatation [8]. Depending on the degree of dysplasia, IPMNs may be benign or malignant. Malignancy can occur in 30% to 88% of patients, as in situ or invasive carcinomas according to the WHO classification [8]. In situ carcinoma (or high-grade ductal dysplasia) is characterized by a ductal epithelium with irregular projections lacking fibrovascular stalks. Invasive carcinoma is defined as the presence of single infiltrating cells or malignant infiltrative glands with an accompanying desmoplastic stromal reaction.

In situ carcinoma is confined to the ductal structure and appears as an intraductal nodule or lesion surrounded by a sharp margin created by the ductal wall. Invasive carcinoma infiltrates the pancreatic parenchyma and appears as a poorly circumscribed infiltrated parenchymal lesion [9].

Mucinous cystadenoma

The lesion may have a malignant form, i.e. mucinous cystadenocarcinoma. This malignancy appears in a mucinous cystadenoma, the lesions being nodular inside the unilocular cyst or focally invasive. The risk of malignancy is related to the size of the previous mucinous cystadenoma (the cutoff is over 4 cm), with focal nodules developing inside the wall of the cyst or thick septa [10,11]. A malignant lesion could progress to invasive adenocarcinoma if it is not resected.

No relationship between pancreatic parenchymal dysplasia and mucinous cystadenoma has been reported. Mucinous cystadenoma is often not mentioned in screening strategies addressing the predisposing factors for pancreatic carcinoma.

Risk factors

General extrinsic factors

Established risk factors for PC include smoking, diabetes, family history of PC, and obesity. They also apply to early-onset PC, i.e. before the age of 60 [12].

Tobacco

Cigarette smoking has been associated with over 30% of pancreatic adenocarcinoma-related deaths. Studies show a 100% to 200% increase in the risk of developing the disease correlated with the number of smoked cigarettes and smoking years. Nicotine, but not cigarette smoke, increases pancreatic carcinogenesis in mice [13].

Fatty pancreas

Fat replacement (also known as lipomatosis, adipose atrophy or fat infiltration) of the pancreas is pathologically

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