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# Medical Radiology

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Andrea Laghi (Ed.)

# New Concepts in Diagnosis and Therapy of Pancreatic Adenocarcinoma

Foreword by
Albert L. Baert

Springer

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# Foreword

The prognosis of patients with adenocarcinoma of the pancreas remains poor notwithstanding the enormous progress achieved in the imaging of this disease during the past two decades by the introduction of the cross-sectional new imaging modalities including Pet-CT

Because this disease remains an important cause of death, due to oncological cause in men and women, big efforts have been made to clarify its epidemiology and pathology genetics as well as to develop new strategic concepts for therapy. Moreover the large spectrum of available modern imaging methods requires critical scrutiny of their cost-effectiveness.

The editor has adopted a new and original view on the problem of pancreatic adenocarcinoma. On the base of new discoveries in the area of molecular biology the book develops a multidisciplinary approach on the best strategies for diagnosis and therapy of this disease.

Andrea Laghi is an internationally leading academic radiologist, well-known and recognized for his original research and his numerous publications mainly related to abdominal CT and MRI. For this volume he is surrounded by an impressive group of Italian and International experts in the field. The text is concise, well written, and easy to read. The volume is completed by the judiciously selected and numerous up-to-date superb illustrations

I would like to thank Andrea Laghi for his outstanding performance as the editor of this work. I would like to congratulate him as well as all contributing authors for their outstanding contributions offering the latest in our knowledge on the topic.

This book offers an excellent update of our actual insights on the diagnosis and multidisciplinary management of pancreatic carcinoma and can be warmly recommended to certified radiologists and radiologists in training as well as to all other medical and surgical specialists involved in the care of patients with this disease.

Together with the two previous volumes on the pancreas, published earlier in this series, this “trilogy” offers one of the best comprehensive overviews on modern imaging of the pancreas.

I am convinced that this work will encounter the same success as previous volumes published in this series.

Leuven — Albert L. Baert

# Preface

Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death in the USA and the fifth in Europe. It is an insidious disease, with the vast majority of patients presenting at an incurable stage at the time of diagnosis. In practice, despite the enormous progress in imaging and therapy, patient prognosis is still very poor; with a 5-year survival rate, which does not exceed 20% even in those suitable for radical surgery.

Patient management is usually complex and typically involves multiple clinical specialists during the course of the disease, namely gastroenterologists, radiologists, pathologists, surgeons, and oncologists. Only a multidisciplinary approach can guarantee the best diagnosis, treatment, and ultimately, care for patients.

For this reason, when Prof. A. Baert asked me to edit this book, I strived to involve leading experts from these different fields in order to provide the readers with a comprehensive and multidisciplinary overview of pancreatic adenocarcinoma. I would like to express my sincere appreciation and gratitude to all the authors, who in their respective discipline made the effort to summarize the immense amount of knowledge in order to provide immediate, concise, and extremely up to date information for the benefit of a larger audience.

The book as we intended it, is recommended for different specialists as well as general practitioners who are eager to keep up to date on new diagnostic techniques as well as treatment options for Patients presenting with pancreatic adenocarcinoma.

The book is divided into three sections. The first is devoted to analyze epidemiology, clinical aspects, and risk factors. In particular, the perspective of potential primary and secondary (in patients at high risk) prevention strategies will be discussed. While pathological aspects, (with the description of the recognized precursors of disease), and genetics, will be presented in a synthetic but exhaustive chapter. The second section focuses on critically exploring the new advances of different imaging techniques: from contrast-enhanced ultrasound to multidetector-row CT, MR Imaging (including the additional value of new sequences), PET-CT and Endoscopic Ultrasound. Cost-effective considerations are also included as a way to propose to readers the most cost-effective and efficient diagnostic pathway to undertake according to the clinical conditions of the Patients. Finally, in the third section, different modern treatments are presented according to Patient status: surgery in those presenting with resectable disease; chemotherapy, chemoradiation therapy, or percutaneous ablative techniques in those with a locally advanced nonmetastatic disease; and systemic chemotherapy for those with

metastatic disease. The role of interventional endoscopy in the management of biliary obstruction and pancreatic pain will be discussed as well as the new frontiers represented by drug-eluting stents and brachytherapy.

It is my personal hope that readers will appreciate the efforts made by the authors and find this book useful for their clinical practice.

Rome, Italy
September 2010

Andrea Laghi

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# Part I

# Epidemiology, Clinical Aspects and Pathology

# Epidemiology, Risk Factors and Clinical Presentation

Gabriele Capurso, Cesare Hassan,
Gianfranco Delle Fave, and Emilio Di Giulio

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## Abstract

- Pancreatic cancer (PDAC) is a deadly disease. It has an incidence ranging 8–12 per 100,000 per year, with a similar mortality, as more than 95% of patients diagnosed with PDAC will ultimately die.
- Prevention policies are therefore particularly important and they should be distinguished in: (1) Primary prevention, aimed at reducing risk factors for PDAC and possibly favouring protective habits. (2) Secondary prevention, aimed at the early diagnosis through appropriate screening tests in subjects with a particularly high risk.
- The most important risk factors for pancreatic cancer are family history of pancreatic cancer, smoking, obesity, diabetes, alcohol and chronic pancreatitis. Diabetes of recent onset should be considered a possible alarm symptom. In patients with defined genetic syndromes such as "familiar pancreatic cancer", and Peutz–Jeghers syndrome screening for pancreatic cancer as a part of research protocols are performed in selected Centres. There are no sufficient data to suggest that vitamins or aspirin may have a role for PDAC chemoprevention.

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## 1 Epidemiology and Disease Presentation

Pancreatic ductal adenocarcinoma (PDAC) is not one of the commonest cancer types, with an incidence ranging

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8–12 per 100,000 per year, but it is now the fourth leading cause of cancer-related death in the United States, with an estimate of some 35,000 deaths per year, and the fifth in Europe. Up to 80–85% of patients have incurable disease at the time of diagnosis (Jemal et al. 2007; Ferlay et al. 2007). The peak incidence is in the seventh and eighth decades with the average age at diagnosis being 60–65 years of age, with some 10% of cases, indicated as "early onset" occurring in people aged <50 years. The incidence of PDAC is slightly higher in males than females (relative risk 1.35), although this difference is decreasing, and the risk seems higher in black males.

The disease presents in a subtle way, with symptoms including weight loss, fatigue, abdominal pain, newly diagnosed diabetes mellitus, jaundice and nausea, which are non-specific and typically occur late in the course of the disease.

As a result, at the time of diagnosis some 50% of patients have metastatic disease, and only some 20% are considered for potentially radical surgery. The median survival of unresectable pancreatic cancer is 4–6 months, and not surprisingly more than 95% of patients diagnosed with PDAC will ultimately die from the disease (Berrino et al. 2007), and even in these receiving potentially radical surgery the 5-year survival rate is well below 20%. Unfortunately, there have been few progresses in the treatment of the disease either with chemotherapy, and radiotherapy. Prevention policies are therefore particularly important and they should be distinguished in:

1. Primary prevention, aimed at reducing risk factors for PDAC and possibly favouring protective habits.
2. Secondary prevention, aimed at the early diagnosis through appropriate screening tests in subjects with a particularly high risk.

As PDAC is a relatively rare disease, and tests are invasive and expensive, screening of the general population cannot be recommended and a better understanding of the role of genetic and environmental risk factors is particularly important.

## 2 Risk Factors

Several risk factors have been identified that increase an individual's risk of developing PDAC. They can be distinguished in "genetic (familial)" and "non-genetic (environmental)" factors.

### *2.1 Genetic Risk Factors*

#### 2.1.1 Family History of Pancreatic Cancer

A percentage of PDAC patients ranging from 5 to 10% reports family history of PDAC. A family history of PDAC in a first-degree relative is associated with an increased risk of developing PDAC between 2.5 and 5.3 times. The risk increases if more relatives are affected (see familial pancreatic cancer (FPC)), with a risk of 6.4 in subjects with two affected relatives, increasing to more than 30 if three relatives are affected (Brand et al. 2007). Accordingly, the risk of dying of PDAC is around 4% in relatives of PDAC patients, increasing to 7% if the relative with PDAC was aged under 60 at diagnosis (Del Chiaro et al. 2007).
These data highlight the importance of the genetic component of the disease. However, unfortunately, a specific "familial pancreatic cancer" gene has not been identified, but apart from other genetic syndrome, criteria for this condition have been defined in the last few years. These conditions and the related risk of developing PDAC are summarized in Table 1.

#### 2.1.2 Familial Pancreatic Cancer

FPC is defined as a clinical syndrome in which a family has at least two first-degree relatives affected with pancreatic cancer without accumulation of other cancers or familial diseases (Klein et al. 2004). It accounts for 1–3% of all PDAC cases (Brand et al 2007), and apart from single reports (Pogue-Geile et al. 2006) not confirmed in other families, a definite gene has not been identified, although the transmission is known to be autosomal dominant. These families are characterized by an early onset of disease and by the high lifetime risk of developing PDAC, therefore are now considered for screening as a part of research protocols in highly specialized Centres in the US (Brentnall et al. 1999; Canto et al. 2006) and Europe (Langer et al. 2009).

#### 2.1.3 Other Genetic Syndromes Associated with PDAC

Familial atypical multiple mole melanoma (FAMMM) syndrome, is an autosomal dominant condition characterized by multiple atypical naevi, familial clustering

**Table 1** Major genetic syndromes associated with the risk of developing pancreatic ductal adenocarcinoma (PDAC)

| Syndrome | Gene | Cumulative PDAC risk at age 70 (%) | Other cancers |
|---|---|---|---|
| Familial pancreatic cancer<br>Two first degree relatives<br>>3 first degree relatives | ? | <br>3<br>16 | |
| Familial atypical multiple mole melanoma | CDKN2A/p16 | 17 | Melanoma<br>Breast |
| Peutz–Jeghers syndrome | LKB1/STK11 | 60 | GI tract<br>Breast |
| Familial adenomatous polyposis | APC | 2 | Colon<br>Ampulla |
| Hereditary non-polyposis colorectal cancer | MSH2, MLH1, MSH6… | 2–4 | GI tract, biliary<br>Ovary, urinary<br>endometrium… |
| Breast and ovarian cancer syndromes | BRCA2<br>BRCA1 | 5<br>1 | Breast, ovary, prostate… |
| Cystic fibrosis | CFTR | 2–3 | GI tract |
| Hereditary pancreatitis | PRSS1 | 40 | – |

of cutaneous malignant melanoma and an increased incidence of other malignancies, particularly of PDAC . The mutated gene is the tumour suppressor gene (TSG) p16, and the estimated cumulative risk of developing PDAC in carriers of the p16-Leiden mutation by 75 years of age is above 15% (Vasen et al. 2000; Borg et al. 2000).

Peutz–Jeghers syndrome (PJS) is a rare, autosomal dominant disease with characteristics features of hamartomatous GI polyps and labial mucocutaneous pigmentation which is associated to a high lifetime risk of developing cancers, including PDAC. The risk of PDAC in PJS has been reported to be as high as some 130 times, with a lifetime risk reported to range from 30 to 60% (Giardiello et al. 2000). Most cases are associated with mutation of the TSG LKB1/STK11. Screening for PDAC in patients with PJS is performed in different Centres, with a relatively high incidence of significant findings.

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease caused by germline mutations of the adenomatous polyposis coli (APC) gene, and characterized by thousands of adenomatous polyps in the GI tract. There are few reported cases of PDAC in FAP.

Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant condition characterized by the development of colon cancers, which are usually of the proximal colon, at an early age. HNPCC is caused by mutations in one of the DNA mismatch repair genes. PDAC cases have been described, but are not common in HNPCC patients (Lynch et al. 1985).

Familial ovarian and breast cancer (FOBC) is an important syndrome mainly caused by germline mutations in the BRCA1 or BRCA2 genes. The BRCA2 gene is mutated in sporadic PDAC cases, and, at higher rates, in subjects with important family history (Couch et al. 2007). On the other hand, the risk of PDAC is increased significantly in FOBC families, especially when BRCA2 is mutated (Lal et al. 2000; van Asperen et al. 2005).

Hereditary pancreatitis is a rare disorder characterized by recurrent idiopathic acute pancreatitis episodes which usually start at a paediatric age. The disease is autonomic dominant, and most cases are associated with mutations of the cationic trypsinogen gene, PRSS1. The lifetime risk of developing PDAC is pretty high, with reported percentages around 40% (Lowenfels et al. 1997). Smoking further increases the risk (Lowenfels et al. 2001).

Cystic fibrosis (CF) is one of the most common life-threatening autosomal recessive disorders in the Western World, affecting about 1/2,000–3,000 Caucasian newborns. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The main consequence for the pancreas is pancreatic insufficiency, but heterozygous mutations in the CFTR gene may result in CP. As a result, a slightly increased risk of PDAC has been reported

(Maisonneuve et al. 2003). Interestingly, the CFTR carrier status has also been linked with early onset of PDAC (McWilliams et al. 2005).

## 2.2 Non-genetic Risk Factors for Pancreatic Cancer

Most cases of PDAC are caused by non-genetic (environmental) risk factors, as summarized in Table 2. Many of them, such as smoking and overweight, may be controlled by definite health politics, with the potential of saving lifes, and eventually reducing the costs due to PDAC cure.

### 2.2.1 Smoking

Smoking is by far the major environmental risk factor for PDAC. Its role is biologically plausible, clear, and consistently reported in numerous case–control and cohort studies conducted worldwide, and related meta-analyses (Iodice et al. 2008). Smoking causes a 75% increase in the risk of developing PDAC, and explains at least 25% of all PDAC cases. The risk is dose and time related, with former smokers still at risk for at least 10 years after quitting smoking. It has been calculated that if all smokers would quit, the number of new cases of pancreatic cancer in the EU could be reduced by at least 15% (Mulder et al. 2002).

**Table 2** Non-genetic factors consistently associated with an increased risk of PDAC

| Risk factor for PDAC | Estimated OR compared to non-exposed[a] |
|---|---|
| Smoking | 1.75 |
| Overweight/obesity | 1.12 per increased 5 kg/m$^2$ |
| Heavy alcohol drinking | 1.2 |
| Type I diabetes | 2 |
| Long standing type II diabetes | 1.5 |
| New onset type II diabetes | 2 |
| Chronic pancreatitis | 14 |
| Occupational exposure to nickel | 1.9 |

[a]The reported odds ratio are estimates of data obtained from the literature, taking in account the highest quality evidence when available (i.e. meta-analyses or large cohort studies)

Smoking is also associated with an higher risk of cancer and a younger age of onset, in sporadic cases (McWilliams et al. 2006; Brand et al. 2009) in subjects with family history of pancreatic cancer (Rulyak et al. 2003), and those with hereditary or chronic pancreatitis (Howes et al. 2004; Talamini et al 1999). Smoking has also been reported to act synergistically with diabetes and family history of pancreatic cancer in a wide, well-designed recent case–control study (Hassan et al. 2007a). There is no evidence for passive smoking as a risk factor (Hassan et al. 2007b), while the risk for pipe or cigars smokers seems much lower, yet significant.

### 2.2.2 Overweight and Obesity

Overweight and obesity are also biologically plausible risk factors for pancreatic cancer (reviewed in Giovannucci and Michaud 2007). A recent meta-analysis of prospective studies reported a risk of some 12% per increase of 5 kg/m$^2$, and a risk exceeding 30% in obese subjects (Larsson et al. 2007). The risk has previously been reported to be slightly lower, and close to 20% for obese subjects in a meta-analysis of both retrospective and prospective studies (Berrington de Gonzalez et al. 2003). A case–control study conducted in Italy reported no significant relationship (Pezzilli et al. 2005). However, of course the risk may be underestimated in case–control studies due to recall bias, and to weight loss frequently occurring before diagnosis. Some data suggest that this risk is far more relevant in the US than in Europe, possibly due to the higher prevalence of obesity (Renehan et al. 2008). Moreover, it has recently been reported that the risk of PDAC is related with overweight and obesity throughout lifetime, particularly during early adulthood, with an earlier age of PDAC onset in subjects who have been overweight since adolescence (Li et al. 2009a). This is a very relevant issue, as public health politics deemed at reducing overweight and obesity in children and young adults may tackle this deadly disease.

### 2.2.3 Alcohol

The evidence for a causal association between alcohol intake and PDAC is much weaker than these reported

for smoking and overweight. A minority of the published cohort studies, and some case–control study suggest a moderate risk. However, as alcohol is a risk factor for chronic pancreatitis and diabetes, a "confounding" effect is likely. Moreover, heavy drinkers tend to be heavy smokers and to have a "unhealthy" diet, and most case–control studies are not corrected for these interferences. Accordingly, the risk of pancreatic cancer is not different in alcoholic and non-alcoholic chronic pancreatitis. Some recent well-conducted cohort studies, however, reported a moderately increased risk with heavy alcohol use, particularly for liquor (RR 1.62) (Jiao et al. 2009a), or a risk of 1.22, comparing subjects drinking more than 30 g of alcohol compared to non-drinkers, which is only significant among women, possibly suggesting that this topic deserves further attention. (Genkinger et al. 2009).

### 2.2.4 Other Dietary Factors and Lifestyle

A high consumption of red meat has inconsistently been reported as a risk factor. Cooking method may be a factor determining the different results (Anderson et al. 2002). Similarly fat intake cannot be considered a significant risk factor (Michaud et al. 2003). Most of these studies were performed in the US or Northern Europe, where consumption of fat and red meat is highly prevalent, possibly masking a small risk difference. However, it is more likely that the entire diet style, and its interaction with other habits, such as smoking and drinking may influence the risk of developing PDAC. Interestingly, a very recent study investigated the role of a "healthy lifestyle score", combining smoking, drinking, weight, diet and physical activity, and found that compared with the lowest combined score, the highest score was associated with a 58% reduction in risk of developing PDAC (Jiao et al. 2009b).

### 2.2.5 Diabetes

Diabetes is a significant risk factor for pancreatic cancer. Type I diabetes is associated with a significantly increased risk, with a RR = 2 in a recent meta-analysis of both case–control and cohort studies (Stevens et al. 2007). Type II diabetes is also a significant risk factor, but in the last few years it has become clear that the risk is different for long standing diabetes (some 50% increase in risk compared to non-diabetic subjects) and patients with recent onset diabetes in whom the risk is as high as 100% of that of healthy individuals, as reported in a meta-analysis of 36 studies (Huxley et al. 2005). More recent data have confirmed this association highlighting the diabetogenic nature of the neoplasm. Indeed, new onset diabetes, recognized by alterations found up to 3 years before PDAC diagnosis has a higher prevalence in PDAC patients than in controls, and is resolved by surgery in some 60% of patients (Pannala et al. 2008). For this reason a sudden onset of diabetes, especially in people aged > 60 requires particular medical attention (Pannala et al. 2009).

Moreover, amongst diabetic patients, a protective role has been recently reported for metformin, while diabetic patients treated with insulin or insulin secretagogues have an higher risk of PDAC (Li et al. 2009b).

### 2.2.6 Chronic Pancreatitis

Chronic pancreatitis is a risk factor for pancreatic cancer, while data about acute pancreatitis are scanty and inconsistent. The risk for chronic pancreatitis has been variably reported to range from some twofold to a figure as high as 19-fold (McKay et al. 2008). Initial misdiagnosis of chronic pancreatitis in patients with early cancer may be a confounder, but the risk is still elevated when cases of cancer diagnosed in the first years after chronic pancreatitis diagnosis are excluded (Talamini et al. 1999).

### 2.2.7 Occupational Exposure

As far as regards occupational exposure, a meta-analysis examining data from 92 studies suggests that exposure to chlorinated hydrocarbon solvents (OR 1.3) and nickel compounds (OR 1.9) is associated with an increase risk of PDAC (Ojajärvi et al. 2000).

### 2.2.8 Peptic Ulcer and *H. pylori*

Data regarding *H. pylori* infection as a risk factors for PDAC are conflicting, with some older studies reporting an excess risk (Stolzenberg-Solomon et al. 2001), not

confirmed subsequently (de Martel et al. 2008). The putative mechanism is also still unknown and speculative, as diseases associated either with acid hypersecretion (peptic ulcer) and hyposecretion (pernicious anaemia) have also been associated with PDAC. Interestingly, the risk after peptic ulcer is only elevated many years after surgery and not increased in unoperated (Luo et al. 2007) subjects, suggesting that an unbalance in the oxidative stress due to achlorhydria, may be the factor associated with an increased risk (Capurso et al. 2004).

### 2.3 Factors Associated with Decreased Risk and Potential Chemoprevention

Unfortunately, there are few protective factors for PDAC, and no chemoprevention policies are advisable. One of the few protective factors is atopy which amongst other allergic conditions, has been associated with the lowest risk (RR 0.7), in a well-conducted meta-analysis. (Gandini et al. 2005). As far as regards diet, a meta-analysis of pooled data from clinical trials employing vitamin supplement vs. placebo, reported no evidence for a benefit of either beta-caroten, vitamins A, C, E or their combinations (Bjelakovic et al. 2004). On the other hand, there is some evidence for a protective role of folates (Larsson et al. 2006).

Some in vitro data, and observational data also suggested a protective role for statins, which although biologically plausible, should be considered unproven, at least at the clinically employed doses, as suggested by a recent meta-analysis (Bonovas et al. 2008).

Finally, as for other cancers, reduction of inflammation through aspirin and NSAIDS has been considered as a possible therapeutic strategy for PDAC (Garcea et al. 2005). This is supported by findings of increased expression of COX-2 in PDAC and in pre-invasive ductal lesions (PanIn) compared with normal pancreatic ducts, and by in vitro data (Maitra et al. 2002). However, while the use of aspirin and NSAIDs is associated with a reduced risk of most gastrointestinal cancers (oesophagus, stomach, colorectal), this is not true for PDAC in a meta-analysis of case–control and cohort studies adjusted for different doses (Capurso et al. 2007), and some studies even reported an increased risk (Schernhammer et al. 2004).

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