International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 31, Issue 12, December 2025 **ijppr.humanjournals.com** ISSN: 2349-7203

Pancreatic Cancer: A Review

M.Poovarasan*, P. Mano, V. Abinaya, P. Durgadevi, M. Kaviya

Department of Pharmacy, Sree Bhavani College Of Pharmacy, India.

Received: 25 October 2025 Revised: 05 November 2025 Accepted: 26 November 2025

1. ABSTRACT:

Pancreatic cancer is an aggressive malignancy with one of the poorest prognoses among solid tumors. It ranks as a leading cause of cancer-related mortality worldwide, largely due to its asymptomatic early course and late-stage diagnosis. The most common type, pancreatic ductal adenocarcinoma, arises from precursor lesions through a series of genetic and molecular alterations, with KRAS, TP53, CDKN2A, and SMAD4 mutations playing key roles. Risk factors include smoking, chronic pancreatitis, obesity, diabetes mellitus, and hereditary cancer syndromes. Clinical presentation often involves jaundice, abdominal pain, weight loss, and new-onset diabetes. Diagnosis relies on a combination of laboratory markers, advanced imaging techniques, and histopathological confirmation, with staging guiding treatment planning. Surgery remains the only curative option, but is feasible in a minority of patients; multimodal approaches incorporating chemotherapy, radiotherapy, targeted therapy, and immunotherapy are increasingly used. Despite advances in molecular profiling and emerging targeted agents, overall survival rates remain low. Future progress depends on earlier detection, precision medicine strategies, and novel therapies that can overcome the tumor's dense stroma and immunosuppressive microenvironment.

Keywords: Pancreatic cancer, malignancy, solid tumors

2.INTRODUCTION:

Pancreatic cancer is a highly lethal malignancy of the digestive system, accounting for a significant proportion of global cancer-related deaths despite its relatively low incidence. It ranks among the top causes of cancer mortality, with a 5-year survival rate of approximately 10%, reflecting its aggressive nature and late presentation. The disease most commonly arises from the exocrine component of the pancreas, with pancreatic ductal adenocarcinoma (PDAC) representing over 90% of cases.

A major challenge in pancreatic cancer management is the lack of specific symptoms in its early stages. By the time patients present with clinical manifestations—such as painless jaundice, abdominal or back pain, unexplained weight loss, or new-onset diabetes—the disease is often locally advanced or metastatic. Established risk factors include cigarette smoking, chronic pancreatitis, obesity, diabetes mellitus, certain occupational exposures, and hereditary cancer syndromes. At the molecular level, mutations in KRAS, TP53, CDKN2A, and SMAD4 are common drivers of tumorigenesis.

3.EPIDEMIOLOGY:

Pancreatic cancer is a relatively uncommon malignancy compared to other gastrointestinal cancers, yet it ranks among the leading causes of cancer-related mortality worldwide due to its aggressive nature and late-stage diagnosis. Globally, it is the seventh leading cause of cancer death in both men and women, with more than 495,000 new cases and 466,000 deaths reported in 2020 according to GLOBOCAN data. The global incidence rate is rising, partly due to population aging, increased prevalence of risk factors such as obesity and diabetes, and improved diagnostic capabilities.

Incidence and Mortality Rates:

Globally, there were approximately 458,918 new cases of pancreatic cancer in 2018, with an age-standardized incidence rate of 4.8 per 100,000 people.

The incidence rates are highest in Eastern Europe (9.9 per 100,000), Western Europe (9.5 per 100,000), and North America (8.7 per 100,000) for males, and in Western Europe (7.2 per 100,000), Northern America (6.5 per 100,000), and Northern Europe (6.4 per 100,000) for females.

In 2022, the countries with the highest number of pancreatic cancer cases were China, the US, and Japan.

Risk Factors:

1.Smoking: Tobacco smoking is a significant risk factor, increasing the risk of pancreatic cancer by 75% compared to non-smokers.

2.Obesity: Being overweight or obese increases the risk of pancreatic cancer, with a relative risk of 2.08 for obese individuals.

3.Diabetes: Type 2 diabetes has been linked to an excess risk of pancreatic cancer, with a 1.8-fold increased risk.

4.Family History: Having a family history of pancreatic cancer increases the risk, especially in individuals with hereditary pancreatitis or certain genetic syndromes.

Survival Rates:

The 5-year survival rate for pancreatic cancer is approximately 9%, with little difference between developed and developing countries.

Survival rates vary depending on the stage of diagnosis, with 29.3% for localized disease and 2.6% for distant metastasis.

4.ETIOLOGY OF PANCREATIC CANCER:

The etiology of pancreatic cancer is multifactorial, involving genetic, environmental, and lifestyle factors. Some of the key risk factors include:

1. Genetic Mutations: Germline mutations in genes such as BRCA2, PALB2, and CDKN2A increase the risk of pancreatic cancer. Somatic mutations in genes like KRAS, TP53, and SMAD4 are also common in pancreatic cancer.

2. Family History: Having a first-degree relative with pancreatic cancer increases the risk.

3. Smoking: Tobacco smoking is a significant risk factor, increasing the risk of pancreatic cancer by 75% compared to non-smokers.

4. Obesity: Being overweight or obese increases the risk of pancreatic cancer.

5. Diabetes: Type 2 diabetes has been linked to an increased risk of pancreatic cancer.

6. Chronic Pancreatitis: Chronic inflammation of the pancreas increases the risk of pancreatic cancer.

7. Diet and Lifestyle: A diet high in red meat, processed meat, and low in fruits and vegetables may increase the risk.

Pathology of Pancreatic Cancer:

Pancreatic cancer is a complex and heterogeneous disease, with various subtypes and histological features. Some of the key pathological features include:

1. Adenocarcinoma: The most common type of pancreatic cancer, accounting for about 85% of cases.

2. Ductal Adenocarcinoma: The most common subtype of pancreatic adenocarcinoma, arising from the ductal epithelium.

3. Pancreatic Intraepithelial Neoplasia (PanIN): A precursor lesion to pancreatic cancer, characterized by dysplastic changes in the pancreatic ducts.

4. Tumor Microenvironment: The tumor microenvironment plays a crucial role in pancreatic cancer progression, with cancer-associated fibroblasts, immune cells, and extracellular matrix components contributing to tumor growth and metastasis.

5. Histological Features: Pancreatic cancer is characterized by glandular or ductal structures, with varying degrees of differentiation and cellular atypia.

Molecular Pathology:

Pancreatic cancer is characterized by a complex molecular landscape, with various genetic and epigenetic alterations. Some of the key molecular features include:

1. KRAS Mutations: Mutations in the KRAS gene are common in pancreatic cancer, leading to constitutive activation of the MAPK signaling pathway.

2. TP53 Mutations: Mutations in the TP53 gene are also common, leading to loss of tumor suppressor function.

3. SMAD4 Mutations: Mutations in the SMAD4 gene can lead to disruption of the TGF-β signaling pathway.

4. Epigenetic Alterations: Epigenetic changes, such as DNA methylation and histone modification, can contribute to pancreatic cancer development and progression.

5.HISTOPATHOLOGICAL AND CLASSIFICATION:

Pancreatic cancer can be classified into several histopathological subtypes based on the cell of origin, morphology, and molecular characteristics. The main types of pancreatic cancer are:

1. Ductal Adenocarcinoma: This is the most common type of pancreatic cancer, accounting for about 85% of cases. It arises from the ductal epithelium and is characterized by glandular or ductal structures.

2. Acinar Cell Carcinoma: This type of cancer arises from the acinar cells of the pancreas and accounts for about 1-2% of cases.

3. Pancreatic Neuroendocrine Tumors (PNETs): These tumors arise from the neuroendocrine cells of the pancreas and can be benign or malignant.

4. Solid-Pseudopapillary Neoplasm: A rare type of pancreatic cancer that typically affects young women.

5. Intraductal Papillary Mucinous Neoplasm (IPMN): A type of tumor that grows in the pancreatic ducts and can progress to invasive cancer.

Histological Grading:

The histological grade of pancreatic cancer is based on the degree of differentiation and cellular atypia. The most commonly used grading system is:

1. Well-differentiated (Grade 1): Tumors with a high degree of differentiation and minimal cellular atypia.

2. Moderately differentiated (Grade 2): Tumors with a moderate degree of differentiation and some cellular atypia.

3. Poorly differentiated (Grade 3): Tumors with a low degree of differentiation and significant cellular atypia.

TNM Staging:

The TNM staging system is used to classify pancreatic cancer based on the extent of the tumor (T), the presence of lymph node metastases (N), and the presence of distant metastases (M). The stages are:

1. Stage I: Tumor limited to the pancreas, with no lymph node or distant metastases.

2. Stage II: Tumor extends beyond the pancreas, with or without lymph node metastases.

3. Stage III: Tumor involves major blood vessels or has extensive lymph node metastases.

4. Stage IV: Distant metastases are present.

6.DIAGNOSIS:

The diagnosis of pancreatic cancer involves a combination of imaging tests, laboratory tests, and biopsy. Here are some of the common diagnostic methods:

Imaging Tests:

1. Computed Tomography (CT) Scan: A CT scan is often the first imaging test used to diagnose pancreatic cancer. It can help identify the tumor and determine its size and location.

2. Magnetic Resonance Imaging (MRI): MRI can provide detailed images of the pancreas and surrounding tissues, helping to determine the extent of the tumor.

3. Endoscopic Ultrasound (EUS): EUS involves inserting an endoscope with an ultrasound probe into the stomach or small intestine to obtain images of the pancreas.

4. Positron Emission Tomography (PET) Scan: A PET scan can help identify areas of high metabolic activity, which can indicate cancer.

Laboratory Tests:

1. CA 19-9: This tumor marker is often elevated in pancreatic cancer, but it is not specific and can be elevated in other conditions as well.

2. Liver Function Tests: These tests can help identify liver damage or dysfunction, which can be associated with pancreatic cancer.

3. Pancreatic Enzyme Tests: These tests can help identify pancreatic damage or dysfunction.

7.TREATMENT:

The treatment of pancreatic cancer depends on the stage of the disease, the location of the tumor, and the patient's overall health. Here are some of the common treatment options:

Surgery:

1. Whipple Procedure (Pancreaticoduodenectomy): This is a complex surgery that involves removing the tumor, part of the pancreas, and other surrounding tissues.

2. Distal Pancreatectomy: This surgery involves removing the tail of the pancreas, where the tumor is located.

Chemotherapy:

1. Gemcitabine: This is a common chemotherapy drug used to treat pancreatic cancer.

2. FOLFIRINOX: This is a combination chemotherapy regimen that includes fluorouracil, leucovorin, irinotecan, and oxaliplatin.

Radiation Therapy:

1. External Beam Radiation Therapy (EBRT): This involves delivering radiation from outside the body to the tumor site.

2. Stereotactic Body Radiation Therapy (SBRT): This involves delivering high doses of radiation to the tumor site with precision.

Immunotherapy:

Checkpoint Inhibitors: These are immunotherapy drugs that inhibit the programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) pathway.

8. PREVENTION:

While there is no surefire way to prevent pancreatic cancer, there are some lifestyle changes and strategies that may help reduce the risk. Here are some of them:

Lifestyle Changes:

1. Don't smoke: Smoking is a significant risk factor for pancreatic cancer. Quitting smoking can help reduce the risk.

2. Maintain a healthy weight: Being overweight or obese increases the risk of pancreatic cancer. Maintaining a healthy weight through a balanced diet and regular exercise can help reduce the risk.

3. Exercise regularly: Regular physical activity can help reduce the risk of pancreatic cancer.

4. Eat a balanced diet: A diet rich in fruits, vegetables, and whole grains may help reduce the risk of pancreatic cancer.

Dietary Factors:

1. Fruits and vegetables: A diet rich in fruits and vegetables, particularly those high in antioxidants and fiber, may help reduce the risk of pancreatic cancer.

2. Whole grains: Whole grains, such as brown rice, quinoa, and whole-wheat bread, may help reduce the risk of pancreatic cancer.

3. Omega-3 fatty acids: Omega-3 fatty acids, found in fatty fish, flaxseeds, and walnuts, may help reduce inflammation and the risk of pancreatic cancer.

9. FUTURE PRESPECTIVE:

The future perspective of pancreatic cancer treatment looks promising, with ongoing research and advancements in various therapeutic areas. Some potential future directions include [1 2]:

1.Targeted Therapies: Researchers are exploring targeted therapies that can specifically attack cancer cells with certain genetic mutations, such as KRAS G12C and G12D inhibitors. Adagrasib and MRTX1133 are examples of targeted therapies being investigated.

2.Immunotherapy: Immunotherapy has shown potential in treating pancreatic cancer, particularly in patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) tumors. Pembrolizumab is an immune checkpoint blocker approved for use in such cases.

3.PARP Inhibitors: PARP inhibitors, such as olaparib and rucaparib, are being studied for their potential in treating BRCA-mutated pancreatic cancer.

4.Neoadjuvant Therapy: Neoadjuvant therapy, which involves chemotherapy and/or radiation therapy before surgery, is becoming increasingly popular. This approach has shown promise in improving survival rates and increasing the number of patients eligible for surgery.

10. CONCLUSION:

Pancreatic cancer is a complex and challenging disease with a poor prognosis. Despite advances in medical technology and treatment options, the 5-year survival rate remains low. Early detection and diagnosis are critical for improving treatment outcomes and survival rates.

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How to cite this article:
M.Poovarasan et al. Ijppr.Human, 2025; Vol. 31 (12): 256-261.
Conflict of Interest Statement: All authors have nothing else to disclose.