Cancer Association of South Africa (CANSA)

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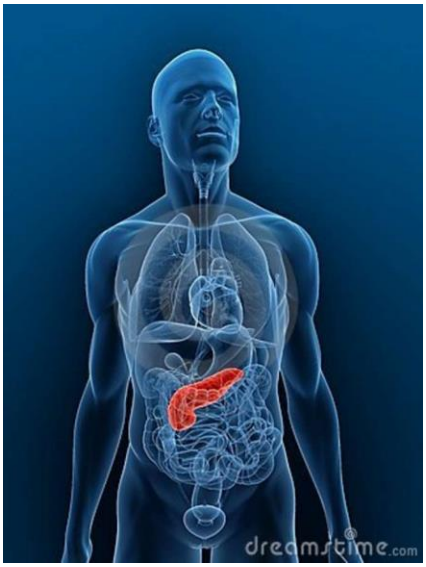
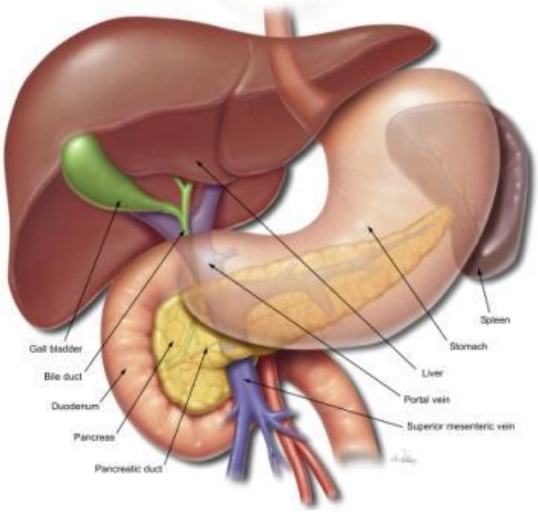
Fact Sheet
on
Pancreatic Cancer

Introduction

The pancreas is a glandular organ in the digestive and endocrine systems of vertebrates including humans. It is both an endocrine gland producing several important hormones, including insulin, glucagon, somatostatin and pancreatic polypeptide, as well as a digestive organ it secretes pancreatic juice which contains digestive enzymes that assist in the absorption of nutrients and digestion in the small intestine. These enzymes help to further break down the carbohydrates, proteins and lipids in the contents of the small intestine.



[Picture Credit: Pancreas Picture 1]



[Picture Credit: Pancreas Picture 2]

Pancreatic Cancer

Pancreatic cancer is a disease in which malignant (cancerous) cell are found in the tissues of the pancreas that are multiplying in an uncontrolled manner.

All types of pancreatic cancer begin when abnormal cells grow out of control within the pancreas. There are two types of cells in the pancreas, the exocrine cells (which produce digestive juices) and endocrine cells (which produce hormones). These cells also have different functions.

More than 95% of pancreatic cancers are classified as exocrine tumours. These tumours start in the exocrine cells that make pancreatic enzymes that help in digestion. In this category, the vast majority of tumours are adenocarcinomas.

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Incidence of Pancreatic Cancer in South Africa

According to the outdated National Cancer Registry (2014), known for under reporting, the following number of pancreatic cancer cases was histologically diagnosed in South Africa during 2014:

Group - Males 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	167	1:869	0,45%
Asian males	9	1:349	1,00%
Black males	46	1:2 505	0,42%
Coloured males	27	1:580	0,64%
White males	85	1:358	0,41%

Group - Females 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	175	1:1 125	0,46%
Asian females	3	1:1 890	0,26%
Black females	63	1:2 297	0,39%
Coloured females	21	1:760	0,50%
White females	89	1:431	0,54%

The frequency of histologically diagnosed cases of pancreatic cancer in South Africa for 2014 was as follows (National Cancer Registry, 2014):

Group - Males 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	0	0	2	22	47	57	29	9
Asian males	0	0	0	1	0	4	4	0
Black males	0	0	2	13	13	13	1	2
Coloured males	0	0	0	2	6	13	3	2
White males	0	0	1	3	28	24	24	2

Group - Females 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	1	1	5	18	39	551	39	19
Asian females	0	0	0	0	0	0	0	0
Black females	1	1	4	8	16	17	10	2
Coloured females	0	0	1	2	8	6	3	0
White females	0	0	0	7	14	25	23	17

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

According to **Bruni, *et al*.,** (2019), the burden of Pancratic cancer for South Africa for 2018 is estimated as (based on Globocan estimates):

- Annual number of cervical cancer cases 2 051
- Annual number of cervical cancer deaths 2 028

Risk Factors for Pancreatic Cancer

A risk factor is anything that affects one's chance of getting a disease such as cancer. Different cancers have different risk factors. Some risk factors, like smoking, can be changed. Others, like a person's age or family history, cannot be changed. Having a risk factor, or even several risk factors, does not mean that one will get the disease. Many people who get the disease may not have had any known risk factors.

Researchers have found several factors that affect a person's chance of getting cancer of the pancreas. Most of these are risk factors for exocrine pancreatic cancer.

- Age - the risk of developing pancreatic cancer increases as people age. Almost all patients are older than 45.
- Gender - men are 30% more likely to develop pancreatic cancer than women. This may be due, at least in part, to increased tobacco use in men.
- Race - African Americans are more likely to develop pancreatic cancer than whites.
- Cigarette smoking - the risk of getting pancreatic cancer is at least twice as high among smokers compared to those who have never smoked. Scientists think this may be due to cancer-causing chemicals in cigarette smoke that enter the blood and damage the pancreas. About 20% to 30% of exocrine pancreatic cancer cases are thought to be caused by cigarette smoking. Cigar and pipe smoking also increase risk. Quitting smoking helps lower risk – 10 years after quitting, former smokers have the same risk as those who never smoked. People who use smokeless tobacco are also more likely to get pancreatic cancer.
- Obesity and physical activity - very overweight (obese) people are more likely to develop exocrine pancreatic cancer. Studies looking at the link between physical activity and the risk of pancreatic cancer have had mixed results.
- Diabetes - exocrine pancreatic cancer is more common in people who have diabetes. The reason for this link is not known. Most of the risk is found in people with type 2 diabetes. This type of diabetes most often starts in adulthood. It is often related to being overweight or obese.
- Chronic pancreatitis - chronic pancreatitis is a long-term inflammation of the pancreas. This condition is linked with an increased risk of pancreatic cancer, but most patients with pancreatitis never develop pancreatic cancer. The link between chronic pancreatitis and pancreatic cancer is strongest in smokers.
- Cirrhosis of the liver - cirrhosis is a scarring of the liver. It develops in people with liver damage from things like hepatitis and alcohol use. People with cirrhosis seem to have an increased risk of pancreatic cancer.
- Occupational exposure - heavy exposure at work to certain pesticides, dyes, and chemicals used in metal refining and the petroleum products may increase the risk of developing pancreatic cancer.
- Family history - pancreatic cancer seems to run in some families.
- Genetic syndromes - inherited gene mutations are abnormal copies of certain genes that can be passed from parent to child. These abnormal genes may cause as many as 10% of pancreatic cancers and can cause other problems as well.
- Stomach problems - infection of the stomach with the ulcer-causing bacteria *Helicobacter pylori* (*H. pylori*) may increase the risk of getting pancreatic cancer. Some researchers believe that excess stomach acid might also increase the risk.
- Diet - some studies linked pancreatic cancer and diets high in fat, or those that include a lot of red meat, pork, and processed meat (such as sausage and bacon). Some studies have found that diets high in fruits and vegetables may help reduce the risk of pancreatic cancer. Diets high in

meats, cholesterol fried foods and nitrosamines may increase the risk, while diets high in fruits and vegetables may reduce the risk of pancreatic cancer.

- Alcohol - some studies have shown a link between heavy alcohol intake and pancreatic cancer.
- Ethnic Background - pancreatic cancer is proportionally more common in Jews than the rest of the population. This may be the result of a particular inherited mutation in the BRCA2 breast cancer gene which runs in some Jewish families.

Lu, Y., Gentiluomo, M., Lorenzo-Bermejo, J., Morelli, L., Obazee, O., Campa, D. & Canzian, F. 2020.
BACKGROUND: Observational studies have reported multiple risk factors for pancreatic ductal adenocarcinoma (PDAC). Some are well established, like tobacco smoking, alcohol drinking, obesity and type 2 diabetes, whereas some others are putative, such as allergy and dietary factors. Identifying causal risk factors can help establishing those that can be targeted to contribute to prevent PDAC.
OBJECTIVE: We sought to investigate the possible causal effects of established and putative factors on PDAC risk.
METHODS: We conducted a two-sample Mendelian randomisation (MR) study using publicly available data for genetic variants associated with the factors of interest, and summary genetic data from genome-wide association studies of the Pancreatic Cancer Cohort Consortium (PanScan) and the Pancreatic Cancer Case-Control Consortium (PanC4), including in total 8769 cases and 7055 controls. Causality was assessed using inverse-variance weighted, MR-Egger regression and weighted median methods, complemented with sensitivity and radial MR analyses.
RESULTS: We found evidence for a causal effect of body mass index (BMI) on PDAC risk (OR 1.43, 95% CI 1.20 to 1.71, $p=8.43\times10^{-5}$). Fasting insulin (OR 2.84, 95% CI 1.23 to 6.56, p=0.01), low-density lipoprotein cholesterol (OR 1.16, 95% CI 1.02 to 1.32, p=0.03) and type 2 diabetes (OR 1.09, 95% CI 1.01 to 1.17, p=0.02) were also causally associated with PDAC risk. BMI showed both direct and fasting insulin-mediated causal effects.
CONCLUSION: We found strong evidence that BMI is causally associated with PDAC risk, providing support that obesity management may be a potential prevention strategy for reducing pancreatic cancer risk while fasting insulin and type 2 diabetes showed a suggestive association that should be further investigated.

Signs and Symptoms of Pancreatic Cancer
Signs and symptoms of pancreatic cancer can be summarised as follows:

Pancreatic cancer doesn't usually give rise to any symptoms or signs in the early stages. This is the main reason why it is so difficult to detect and diagnose. As the cancer grows, the symptoms caused, will depend on the type of pancreatic cancer and where it is in the pancreas. Any symptoms people do have can be quite vague and may come and go at first. An example is abdominal pain, which may start off as occasional discomfort before becoming more painful and more frequent. The symptoms can also be a sign of other more common, less serious illnesses. This means that people may end up seeing their medical practitioner several times or being sent for a number of different tests before pancreatic cancer is even considered.

Abdominal pain - pain is a symptom in about 70% of pancreatic cancer cases. It often starts as general discomfort or pain in the abdomen (tummy), which can spread to the back. It can be worse

after eating or when lying down. Sitting forward can sometimes relieve the pain. At first the pain may come and go, but over time it may become more constant. If any of the organs (pancreas, liver or gall bladder) in the abdomen are inflamed or enlarged the area may also be tender to touch.

Other common symptoms of pancreatic cancer:
Bowel problems - a condition called steatorrhoea (stools that are large, pale, oily, floating and smelly) is a common symptom of diseases of the pancreas. It happens because the cancer affects the production of the enzymes needed to digest food, particularly high fat food. Undigested food passing quickly through the body can also cause diarrhoea and subsequent weight loss.

Nausea and vomiting - nausea (feeling sick) and vomiting can occur for several different reasons. A tumour can block the bile duct or press on the duodenum, which obstructs digestion. It may also cause inflammation in the pancreas, or jaundice. Both of these can lead to a chemical imbalance in the body which can make people feel sick.

Fever and shivering - if the pancreas is inflamed or the ducts are blocked because of a tumour, this can cause a high temperature and shivering.

Diabetes - diabetes can develop if a tumour stops the pancreas from functioning properly. This is because the pancreas produces the hormone insulin which the body needs to regulate the amount of sugar in the blood. People with diabetes often feel extremely thirsty, pass more urine than normal, lose weight and feel weak and lacking in energy. Diabetes is particularly associated with pancreatic cancer in older people. If someone develops late onset diabetes with no other explanation a diagnosis of pancreatic cancer should be considered.

Diagnosis of Pancreatic Cancer
Pancreatic cancer may go undetected until it's advanced. By the time symptoms occur, diagnosing pancreatic cancer is usually relatively straightforward.

A doctor may conduct the following:

- By taking a medical history, a doctor learns the story of the illness, such as the time of onset, nature and location of pain, smoking history, and other medical problems
- Lab tests may show evidence that bile flow is being blocked, or other abnormalities
- Based on a person's physical examination, laboratory results and description of symptoms, a doctor often orders an imaging test:
  - Computed tomography (CT scan): A scanner takes multiple X-ray pictures, and a computer reconstructs them into detailed images of the inside of the abdomen. A CT scan helps doctors make a pancreatic cancer diagnosis
  - Magnetic resonance imaging (MRI): Using magnetic waves, a scanner creates detailed images of the abdomen, in particular the area around the pancreas, liver, and gallbladder
  - Ultrasound: Harmless sound waves reflected off organs in the belly create images, potentially helping doctors make a pancreatic cancer diagnosis

- Positron emission tomography (PET scan): Radioactive glucose injected into the veins is absorbed by cancer cells. PET scans may help determine the degree of pancreatic cancer spread
- If imaging studies detect a mass in the pancreas, a pancreatic cancer diagnosis is likely, but not definite.
- Only a biopsy - taking actual tissue from the mass - can diagnose pancreatic cancer.

Lo, W., Morris, M.C., Ahmad, S.A. & Patel, S.H. 2019.
"Pancreatic cancer remains a leading cause of cancer-related death in the United States. Patients with familial pancreatic cancer, hereditary pancreatitis, known genetic mutations, and syndromes are deemed high risk for the development of pancreas cancer. Guidelines have been made to help facilitate early diagnosis and treatment for these patients and these will be reviewed. The exact timing of initial screening depends not only on the individual risk factors but consists of endoscopic ultrasound and magnetic resonance cholangiopancreatography. The frequency of screening depends largely on the findings of initial imaging and the patient's clinical status. We suggest that providers make themselves knowledgeable of current screening recommendations and appropriately apply them. Further critical evaluation of ongoing research is necessary to amend these recommendations as more data and genetic testing becomes available."

Sandrasegaran, K., Lin, Y., Asare-Sawiri, M., Taiyini, T. & Tann, M. 2019.
OBJECTIVES: We investigated the value of CT texture analysis (CTTA) in predicting prognosis of unresectable pancreatic cancer.
METHODS: Sixty patients with unresectable pancreatic cancers at presentation were enrolled for post-processing with CTTA using commercially available software (TexRAD Ltd, Cambridge, UK). The largest cross-section of the tumour on axial CT was chosen to draw a region-of-interest. CTTA parameters (mean value of positive pixels (MPP), kurtosis, entropy, skewness), arterial and venous invasion, metastatic disease and tumour size were correlated with overall and progression-free survivals.
RESULTS: The median overall and progression-free survivals of cohort were 13.3 and 7.8 months, respectively. On multivariate Cox proportional hazard regression analysis, presence of metastatic disease at presentation had the highest association with overall survival ($p = 0.003$-0.05) and progression-free survival ($p < 0.001$ to $p = 0.004$). MPP at medium spatial filter was significantly associated with poor overall survival ($p = 0.04$). On Kaplan-Meier survival analysis of CTTA parameters at medium spatial filter, MPP of more than 31.625 and kurtosis of more than 0.565 had significantly worse overall survival ($p = 0.036$ and 0.028, respectively).
CONCLUSIONS: CTTA features were significantly associated with overall survival in pancreas cancer, particularly in patients with non-metastatic, locally advanced disease.
KEY POINTS: • CT texture analysis is easy to perform on contrast-enhanced CT. • CT texture analysis can determine prognosis in patients with unresectable pancreas cancer. • The best predictors of poor prognosis were high kurtosis and MPP.

Types of Pancreatic Cancer
The following are different types of pancreatic cancers

Non-Endocrine Adenocarcinomas This is the form of cancer that most people are talking about when they refer to 'cancer of the pancreas'. These tumours account for more than 75% of all pancreas cancers.

Endocrine (Islet Cell) Tumours

These tumours are far less common than the non-endocrine tumours listed above. They account for about 1% of pancreatic cancers. The endocrine tumours may produce highly active hormones and, therefore, have very dramatic symptoms.

Reducing the Risk for Pancreatic Cancer

- The number one way to prevent pancreatic cancer is not to smoke or, if smoking, to stop smoking.
- Other lifestyle choices that may lower one's chances of getting pancreatic cancer include:
- Avoid or restrict alcohol intake
- Eating a healthy diet consisting of at least five (5) vegetables and fresh fruit (in season) every day
- Maintaining a healthy weight
- Getting regular exercise

Staging of Pancreatic Cancer

Staging is a way of describing where the cancer is located, if or where it has spread and whether it is affecting the functions of other organs in the body. Doctors use diagnostic tests to determine the cancer's stage, so staging may not be complete until all the tests are finished. Knowing the stage helps the doctor to decide what kind of treatment is best and can help predict a patient's prognosis (chance of recovery).

Where Pancreatic Cancer May Spread to in the Body

Should pancreatic cancer spread (metastasise) in the body, it may spread as indicated below:

Cancer Type:	**Main Sites of Metastasis (Spread)**
Bladder	Bone, liver, lung
Breast	Bone, brain, liver, lung
Colon	Liver, lung
Colorectal	Liver, lung, peritoneum (lining of abdomen)
Kidney	Adrenal gland, bone, brain, liver, lung
Lung	Adrenal gland, bone, brain, liver, other lung
Melanoma	Bone, brain, liver, lung, skin, muscle
Ovary	Liver, lung, peritoneum (lining of abdomen)
Pancreas	Liver, lung, peritoneum (lining of abdomen)
Prostate	Adrenal gland, bone, liver, lung
Stomach	Liver, lung, peritoneum (lining of abdomen), ovaries
Thyroid	Bone, liver, lung
Uterus	Boner, liver, lung, peritoneum (lining of abdomen), vagina
Non-melanoma skin cancer	Very rare: lymph nodes, lung, bone (if in head/neck region)

Treatment of Pancreatic Cancer

When pancreatic cancer is diagnosed or even suspected, the doctor needs to know the extent (also known as the *stage*) of disease to plan the best treatment. Staging is a careful attempt to find out the size of the tumour in the pancreas, whether the cancer has spread and if so, to what parts of the body. At the time of diagnosis, only about 20% of pancreatic cancers can be removed by surgery.

- Surgery - the surgeon may remove all or part of the pancreas. Sometimes the cancer cannot be completely removed.
- Radiation therapy - when a pancreatic cancer is removed surgically, often additional treatments such as radiation therapy and chemotherapy may be recommended.
- Chemotherapy is the use of drugs to kill cancer cells. Doctors also give chemotherapy to help reduce pain and other problems caused by pancreatic cancer.

Cloyd, J.M., Tsung, A., Hays, J., Wills, C.E. & Bridges, J.F. 2020.

"Pancreatic ductal adenocarcinoma is an aggressive cancer with high recurrence rates following surgical resection. While adjuvant chemotherapy improves survival, a significant proportion of patients are unable to initiate or complete all intended therapy following pancreatectomy due to postoperative complications or poor performance status. The administration of chemotherapy prior to surgical resection is an alternative strategy that ensures its early and near universal delivery as well as improves margin-negative resection rates and potentially improves long-term survival outcomes. Neoadjuvant therapy is increasingly being recommended to patients with pancreatic ductal adenocarcinoma, however, patient-centered research on its use is lacking. In this review, we highlight opportunities to focus research efforts in the domains of patient preferences, patient-reported outcomes, patient experience, and survivorship. Novel research in these areas may identify relevant barriers and facilitators to the use of neoadjuvant therapy thereby increasing its utilization, improve shared-decision making for patients and providers, and optimize the experience of those undergoing neoadjuvant therapy."

Han, H., Hou, Y., Chen, X., Zhang, P., Kang, M., Jin, J. & Gao, M. 2020.

"Pancreatic ductal adenocarcinoma, as one of the most aggressive cancers, is characterized by rich desmoplastic stroma that forms a physical barrier for anti-cancer drugs. To address this issue, we herein report a two-step sequential delivery strategy for targeted therapy of pancreatic cancer with gemcitabine (GEM). In this sequential strategy, metformin (MET) was firstly administrated to disrupt the dense stroma, based on the fact that MET down-regulated the expression of fibrogenic cytokine TGF-β to suppress the activity of pancreatic stellate cells (PSCs), through the AMP-activated protein kinase (AMPK) path-way of PANC-1 pancreatic cancer cells. In consequence, the PSC-mediated desmoplastic reactions generating α-SMA and collagen were inhibited, which promoted the delivery of GEM and pH (low) insertion peptide (pHLIP) co-modified magnetic nanoparticles (denoted as GEM-MNP-pHLIP). In addition, pHLIP largely increased the binding affinity of the nanodrug to PANC-1 cells. The targeted delivery and effective accumulation of MET/GEM-MNP-pHLIP in vivo were confirmed by magnetic resonance imaging enhanced by the underlying magnetic nanoparticles. The tumor growth inhibition of the se-quential MET and GEM-MNP-pHLIP treatment were investigated on both subcutaneous and orthotopic tumor mice models. A remarkably improved therapeutic efficacy, e.g., up to 91.2% growth inhibition ratio over 30-day treatment, well exemplified the novel cascade treatment for pancreatic cancer and the innovative use of metformin."

Fan., J.Q., Wang, M.F., Chen, H.L., Shang, D., Das, J.K. & Song, J. 2020.
"Pancreatic ductal adenocarcinoma (PDAC) is an incurable cancer resistant to traditional treatments, although a limited number of early-stage patients can undergo radical resection. Immunotherapies for the treatment of haematological malignancies as well as solid tumours have been substantially improved over the past decades, and impressive results have been obtained in recent preclinical and clinical trials. However, PDAC is likely the exception because of its unique tumour microenvironment (TME). In this review, we summarize the characteristics of the PDAC TME and focus on the network of various tumour-infiltrating immune cells, outlining the current advances in PDAC immunotherapy and addressing the effect of the PDAC TME on immunotherapy. This review further explores the combinations of different therapies used to enhance antitumour efficacy or reverse immunodeficiencies and describes optimizable immunotherapeutic strategies for PDAC. The concordant combination of various treatments, such as targeting cancer cells and the stroma, reversing suppressive immune reactions and enhancing antitumour reactivity, may be the most promising approach for the treatment of PDAC. Traditional treatments, especially chemotherapy, may also be optimized for individual patients to remodel the immunosuppressive microenvironment for enhanced therapy."

Lifestyle Changes After a Diagnosis of Pancreatic Cancer
Lifestyle changes can be helpful. General Guidelines

- Stop smoking
- Avoid alcohol
- Prevent diabetes
- Follow a nutritious diet, including 5 portions of fresh fruits (in season) and vegetables
- Participate in a reasonable level of exercise
- Seek support
- Reduce the risk of infection
- Rest when tired

(Dankner, *et al*., 2018)

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.
Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Pancreas Picture 1
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