Association of Hepatitis B Virus Infection and Risk of Pancreatic Cancer: A Review

Hafiz Khawar[1], Hubba Chaudhary[2], Saba Abbas[3*], Warda Munir[4], Madiha Akram[5], Hafiza Nida Shehzadi[6], Ali Raza Nawab[7]

[1,2,4,7]Institute of Industrial Biotechnology, Government College University Lahore,
[3,*5,6] School of Medical Laboratory Technology, Minhaj University Lahore.

***Correspondence:** Saba Abbas
*School of Medical Laboratory Technology, Minhaj University Lahore.
Email: sabaabbas786786@gmail.com

Abstract
According to an estimate, approximately, 350 million people frequently suffer with the hepatitis B virus (HBV), which can be spread by sexual promiscuity, working in the medical sector, undergoing dialysis, receiving transfusions of unscreened blood, getting tattoos, having a close relationship with an HBV carrier, and reusing injections by intravenous drug users. A chronic HBV infection can develop into pancreatic cancer due to the key risk factor for pancreatic cancer in patients suffering from hepatitis B, which is primarily genetic. Genetic variables take precedence over other criteria, such as the patient's blood type. Additionally, factors including smoking, being overweight, drinking alcohol, and H. *pylori* infection all have a significant effect. However, even if none of these factors apply to a patient, their risk of developing pancreatic cancer is still quite high if their family has a history of the disease. This review suggested that pancreatic cancer was given a new diagnosis in 196,000 people globally in 1990. 441,000 cases were discovered in 2017 across the globe. Pancreatic cancer is ranked 11th among the most frequently occurring cancer causing mortalities throughout the globe. Pancreatic cancer had 45,918 new cases of diagnosis in 2018, and it claimed 432,242 lives worldwide. In America in 2019, there were more than 45,000 deaths from pancreatic cancer and 56,000 new cases. The death rate associated with this illness is predicted to have doubled in both Europe and America by 2030.

Keywords: Hepatitis B Virus (HBV), Genetic Variables, Pancreatic Cancer, Infections

INTRODUCTION

Hepatitis is defined as the inflammation of the liver caused by various viral and non-infectious sources. Viral infections and parasitic infections are the primary infectious agents that can induce hepatitis to persist. The medications and perilous substances are classified as non-infectious factors. Viral hepatitis can result from viral infection of the liver and its cells. There are five different hepatitis virus types in total, including A, B, C, D, and E, that are responsible for related hepatitis infections. Viral hepatitis is declared as a public health risk throughout the globe (Gheorghe *et al*,. 2022). One study observed that approximately, 350 million folks are chronically infected by Hepatitis B virus. According to reports, in the United Kingdom (U.K), the United States (U.S), and Scandinavia, the transmission frequencies of hepatitis B surface antigen (HBsAg) range from 0.1- 0.2% to much more than 3% in Southern Italy and Greece. According to another research, the transmission rate reaches upto 10%–15% in the Far East and Africa. The two end-stage chronic liver diseases are significantly linked with Hepatitis B virus and Hepatitis C virus such as cholangiocarcinoma and hepatocellular carcinoma (HCC) which are also hepatotropic by nature (Hassan *et al*,. 2008).

The different risk factors for hepatitis B virus infection are extended interaction with some HBC carrier as well as sharing and reusing needles among the intravenous drug users along with medical field employment, sexual promiscuity, unscreened blood transfusion, renal dialysis and tattoos. The chance of developing cancer is doubled for smokers. A high-fat meal, decreased serum folate concentrations, long-term diabetes, chronic pancreatitis, and obesity are additional important risk factors. HBV is globally a threat for public health associated with various clinical symptoms (Wang *et al,.* 2012).

Survival rate

The most fatal malignant neoplasm, pancreatic cancer is reported to have a 5-year survival rate in the United States. The disease does not manifest its symptoms until it reaches a progressive stage. The poor prognosis is due to slow growth, variable non-specific symptoms, and a lack of sensitive and specific methods to identify the disease at an early stage (Gheorghe *et al,.* 2022). Pancreatic cancer is among the fourth most widespread cancer in the United States, inflicting 227,000 annual deaths worldwide. (Vincent *et al,.* 2011). People with a previous record of hepatitis B cancer have higher probability to get pancreatic cancer than people without any history. Hepatitis B infection has been shown to enhance the incidence of pancreatic cancer by up to 24%. (Desai *et al,.* 2018). When curative surgery fails to help the patients, it leads to the diagnosis of stage IV pancreatic cancer in almost 80% to 85% of the cases. In a limited number of cases, surgical

treatment is advised given that the disease is discovered at a localized stage. The 5-year survival rate will therefore rise by up to 20% as a result. (Gheorghe *et al,.* 2022).
Pancreatic cancer is the principal cause of cancer-associated mortalities across the globe. It can also be brought on by environmental factors such exposure to mutagenic nitrosamines, heavy metals, smoking, chlorinated hydrocarbon solvents and many more. Despite the fact that tailored therapy exists to treat pancreatic cancer, it is still neither generally accessible nor effective in its purpose (Li *et al,.* 2004)

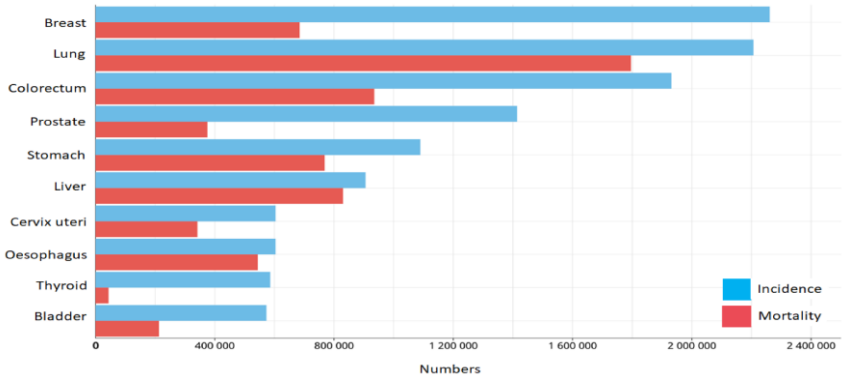

Figure 1. Estimated global number of new cancer cases in 2020, for both sexes and all age groups (Effer *et al*,. 2023).

Numerous investigations have demonstrated that the hepatitis B virus may replicate in human pancreatic tissues, and those who suffer from this infection experience reduced pancreatic function. The liver and pancreas share blood arteries and ducts which makes the pancreas a possible organ for hepatitis virus infections. Additionally, it was shown that bile and pure pancreatic juice both contained HBsAg, a marker of persistent HBV infection. The first ever evidence of pancreatic HBV replication was identified in the pancreatic secretions of patients with confirmed HBV cases. (Gheorghe *et al,.* 2022). It was established that the pancreatic metastases to the liver and the integration of HBV-DNA in the tissues of the infected patients' pancreas were due to the discovery of HBsAg and hepatitis B virus core antigen in the cytoplasm of the pancreatic acinar cells. HBV reinfection following liver transplantation and its reappearance are pointers of extrahepatic virus reservoirs (Hassan *et al,.* 2008).
A demonstration of the infection caused by the hepatitis B virus and that it can lead to illnesses of the liver was carried out in the animal models. In earlier studies, congenitally infected Pekin ducks were discovered to have several different forms of viral nucleic acids that were unique to replication as well as duck HBsAg and HBV core antigen in their pancreatic cells (Halpern *et al*,. 1983).

Hepatocellular Carcinoma
Chronic HBV and HCV are the chief reason of hepatocellular carcinoma (HCC). Although authorities hold the records of every patient diagnosed with HBV or HCV infection in Sweden, population-based national registries in Sweden are utilised to study the connection between pancreatic cancer risk and HBV and HCV infections (Huang *et al,.* 2013).
According to Annika Bergquist's research, Primary sclerosing cholangitis patients had a 161-fold enhanced probability of developing hepatobiliary malignancies than those without the condition. Within a year of diagnosis, there is a higher risk of 37% of doing this, as well as a 14-fold elevated chance of getting pancreatic cancer. Cholangitis is a significant risk factor for the emergence of pancreatic cancer. Previous epidemiological studies have shown that if the HBV infection is determined, the danger of extra-hepatic malignancies, such as gastric and pancreatic cancer and the capacity to cause cholangiocarcinomas is increased (Lee *et al,.* 2022).

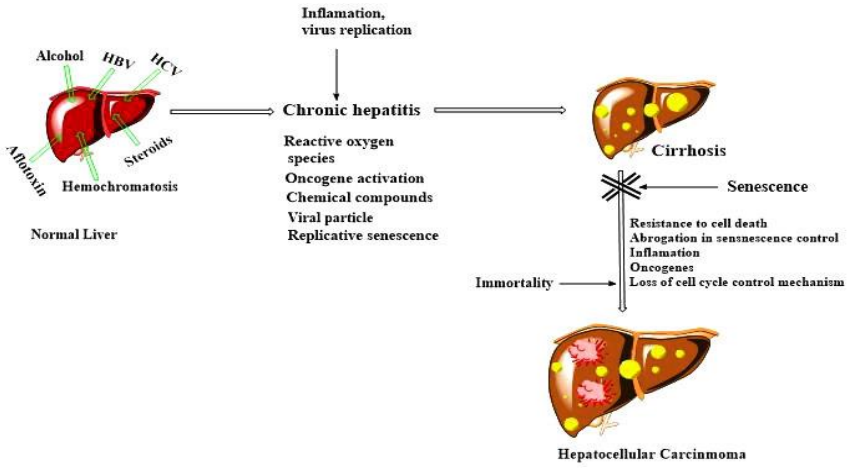

Figure 2. The proposed model of hepatocellular carcinoma development (Singh *et al*,. 2018).

Prevalence of Pancreatic Cancer

The wide variations in pancreatic cancer prevalence among various groups and geographical areas demonstrate the importance of behavioral, environmental, and hereditary factors. Because pancreatic cancer is highly dependent on age, if longevity increases, we will see a considerable
increase in pancreatic cancer cases globally in the next decade (Maisonneuve *et al,*. 2015).

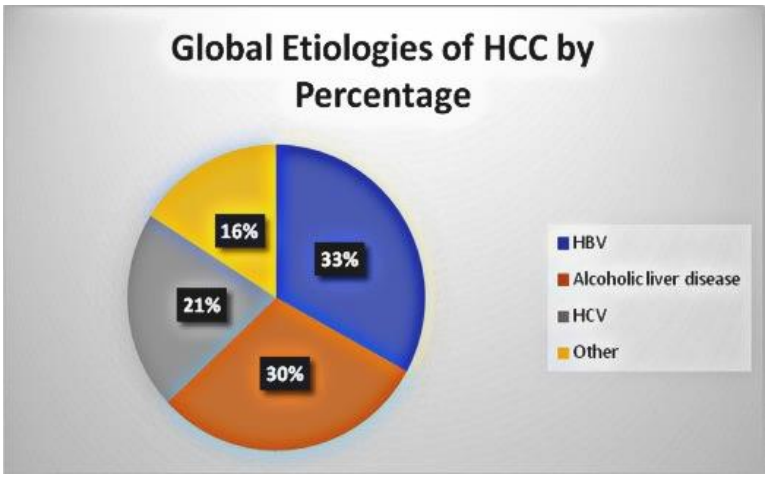

Figure 3. Global etiologies of HCC by percentage (Caines *et al*. 2020).

Incidences of Pancreatic Cancer

A reasonably well-known risk factor for the development of pancreatic cancer is the use of tobacco. Furthermore, the body of research indicates that this specific cancer is 100% related with characteristics including advanced age, hereditary pancreatitis, family history, chronic pancreatitis, and diabetic mellitus. Recent epidemiological studies have shown that some infections, including diabetes, H. pylori and HBV exposure, and improper oral health, may be linked to an elevated risk of pancreatic cancer (Huang *et al,*. 2013).

In countries with high affluence, pancreatic cancer was more common and had higher mortality rates. This demonstrates the connection between pancreatic cancer and lifestyle. Extrinsic and intrinsic variables make up two major categories of pancreatic cancer risk factors. There are other variable extrinsic risk factors. Tobacco, alcohol use, and obesity are the key risk factors that may be altered, and they are the reason why pancreatic cancer develops more in industrialized countries. Only 30% of the risk factors for the disease's variables have been recognized thus far. The most prevalent factor was smoking cigarettes. Other risk factors can also be considered important in the development of the disease because smoking only accounts for 20% of the cause of the disease (Klein *et al,*. 2021).

The discovery of a connection between pancreatic cancer and chronic hepatitis B virus infection is not shocking because patients suffering with chronic viral infections were already previously observed clinically and discovered to have a weakened function of the pancreatic exocrine. Acute pancreatitis may imply acute, fulminant, or chronic viral hepatitis. since persons with a chronic HBV infection have elevated levels of pancreatic enzymes in their urine and serum. Acute pancreatitis and acute viral hepatitis were both diagnosed in 7.7% of the 72 participants in a recent research (Hassan *et al,*. 2008).

The results and information from the two types of researches stated above raise the question about the extent of occurrence of pancreatic cancer due to persistent HBV infection. Patients with positive anti-HBV and negative HBsAg status are considered to be at an enhanced risk, which raises the chance of a latent HBV infection as well as a chronic, long-lasting viral infection. Infection with the occult hepatitis B virus is clinically significant (Munoz *et al,*. 2002).

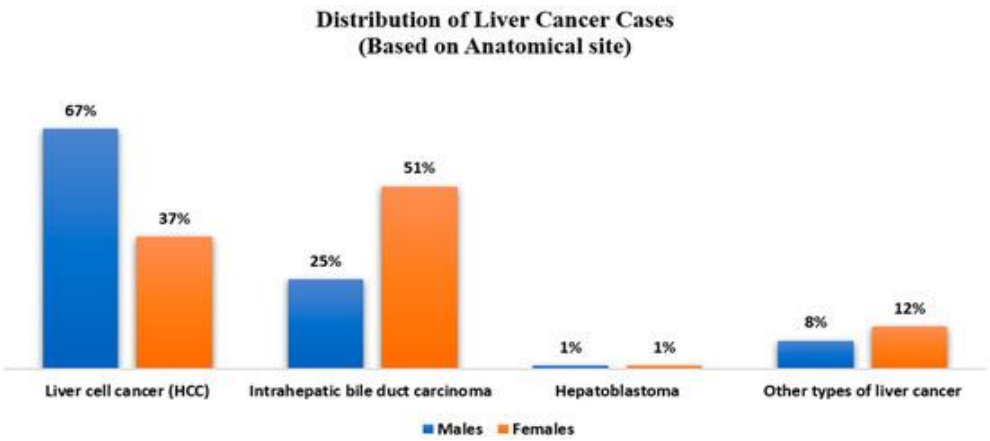

Figure 4. Distribution of Liver Cancer Cases based on anatomical site (Mani *et al*,. 2023).

Occult HBV Infection

In addition to patients who had an infection due to HBV, those who are undergoing hemodialysis, those who are drug addicts, and patients who had previously been introduced to HBV and then cure from chronic or acute infection and were now negative for HBsAg, occult HBV infection is also reported in them. The chief cause of the lack of detectable HBsAg in patients suffering with occult HBV infection is uncertain. Now-a-days, it is generally accepted that HCC is more likely to develop in individuals with occult HBV infection who do not possess serological evidence of the virus. (Hassan *et al,.* 2008).

Antigens

The ABO blood group's antigens can be found circulating in large quantities in the body and are broadly circulated all the way through the body besides being on the surface of red blood cells. According to the most recent studies, genetic blood group antigens and the likelihood of getting pancreatic cancer are related. Patients suffering from pancreatic cancer may not yet had the effects of HBV infection thoroughly evaluated. Pancreatic cancer is linked with the deletion of A, H, B, or Lewis antigens besides the expression of incompatible A and B antigens, according to Wang *et al*,. 2012. The mismatch between the expression of blood group-related antigens in pancreatic cancer cells and the patient's blood group type demonstrates that the expression of Lewis antigen does not require blood group phenotype and can be employed as a diagnostic biomarker. To illustrate that Lewis antigen, which is not dependent on the blood group phenotype and can be utilized as a tumor marker, is present in pancreatic cancer cells, it was revealed that the blood group-related antigens expressed by pancreatic cancer cells differ from the blood group type of the patient. Pancreatic cancer and a location on 9q34 that is suggested by a single nucleotide polymorphism termed rs505922 were connected, according to a recent study based on genome-wide association. The first intron of the ABO blood type gene is connected to this specific single-nucleotide polymorphism. However, this association is not well-known in China (Wang *et al,.* 2012).

HBV Infection

HBV infection has a systemic effect. When the findings of a prior study were analyzed, it was discovered that the kidneys, epidermis, and pancreas all contained HBV DNA sequences, demonstrating that these particular organs were infected with or by HBV. The pancreas is a possible target organ for HBV infection because it physically shares blood vessels and ducts with the liver. However, the epidemiological studies looking into the connection between pancreatic cancer and HBV infection have produced contradictory findings. Furthermore, no investigation has been conducted in China on association between the risk of pancreatic cancer triggered by HBV infection. (Wang *et al,.* 2012).

Hepatitis B reactivation has been reported in a few cases in persons who had either lung or breast cancer or choriocarcinoma. After receiving cytotoxic chemotherapy, several patients with metastatic pancreatic cancer who tested positive for HBsAg also suffered from a swift and temporary drop in their liver function tests. This was mostly caused by the reactivation of hepatitis B (Oksuzoglu *et al,.* 2002).

Pancreatic cancer or pancreatic ductal adenocarcinoma (PDAC), is a condition with a high death rate and is of great medical concern. As a result, distant metastases is identified in 50% of patients, and the 5-year survival rate is only 8%. Surprisingly, HBV was found to flourish in pancreatic tissues of PDAC patients no matter if a tumor is present or not. Experiments reveal that HBV may play a role in PDAC given that pancreatic cancer cells exhibit a limited HBV replication. Even if the treatment has significantly improved in last two decades, the survival rates for PDAC patients have only slightly increased (Dumitrascu *et al,.* 2018).

It has been predicted that the virus will have a minor role in the epidemiology of HCC because HBV infection has been significantly reduced in other countries as a result of vaccination. The dearth of research on this particular topic is due to the difficulty in identifying the HBV in extra-hepatic tissues. The best technique to demonstrate the existence of the virus in these tissues is through the recognition of HBV DNA, and Dejean and colleagues at the Institut Pasteur were the first to extract HBV DNA from the pancreatic tissues (Dejean *et al,.* 1984).

Unexpectedly, in PDAC patients, HBV not only replicates but also infects non-tumorous and tumor-free pancreatic tissue. If we seek long-term survival with PDAC, the only choice is pancreatic resection, but only a select few patients are suitable for surgery soon after diagnosis. Long-term survival is relatively uncommon in PDAC patients, on the other hand among those who had their tumors removed, the survival rate for 5 year was noticeably greater (10.1%) as cpmpared to those who had their tumors removed locally (0.5%) or had metastatic PDAC (0.1%) (Dumitrascu *et al,.* 2018).

PDAC-Associated Factors

Many factors are related with the elevated risk of PDAC namely obesity, alcohol abuse, older age, smoking, diabetes and chronic pancreatitis. The risk of PDAC development is also associated with infections caused by H. *pylori*. In lots of countries, the prevalence of infection by HBV was lowered due to vaccination and the virus is expected to have a negligible impact on the spread of HCC. The goal of World Health Organization is the eradication of HBV from the world by the year 2030 (Dumitrascu *et al,.* 2018).

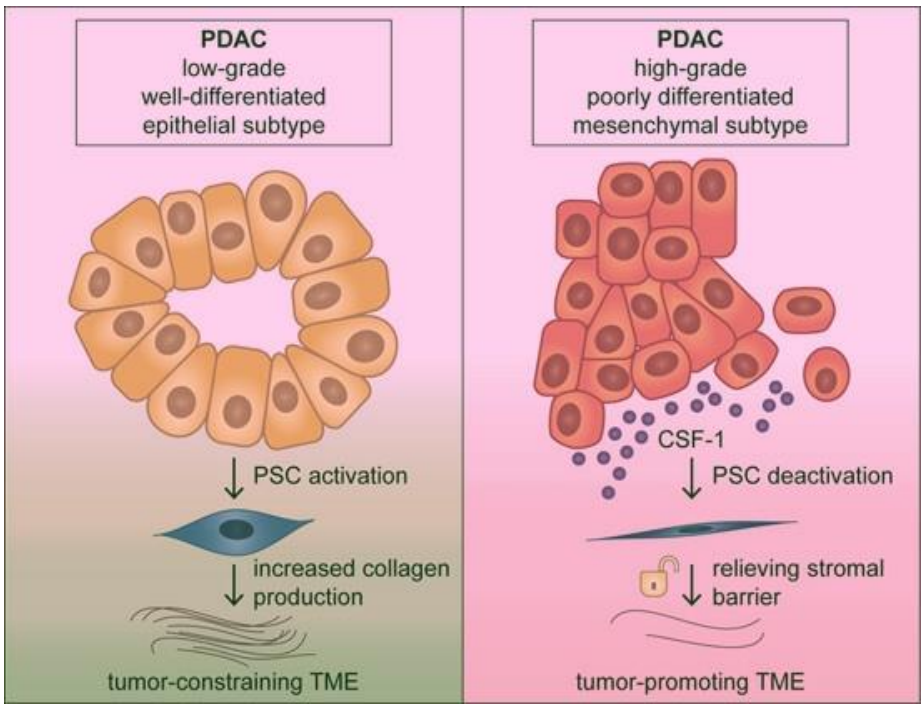

Figure 5. Comparison between high-grade and low-grade PDAC (Steins *et al*,. 2020).

Correlation between Hepatitis B, C & H. *pylori*

There is a positive correlation between the presence of hepatitis C, hepatitis B, H. *pylori* infection and the risk of pancreatic cancer. The results from the literature points towards a connection that is present between H. *pylori*'s colonization and all the blood groups apart from O. Patients with blood groups other than O had anti-H. *pylori* antibodies. The difference of the binding capability of H. *pylori* in the gastrointestinal tract is, at this level, influenced by the terminal binding agent present in the mucins as per a theory. Blood groups are responsible for determining the kind of terminal agents. Moreover, it has been revealed that H. *pylori* is responsible for the pathogenesis of gastric cancer and lymphoma that are termed as neoplasms (Gheorghe *et al,.* 2022).

Viral Infection

Viral infections also serve as a risk factors for pancreatic cancer. Because of this reason, there exists a big chance of the progression of pancreatic cancer in patients with chronic liver infections due to the HBV and HCV as per a 2013 meta-analysis of observational studies. Hepatitis B and C viruses have the capability to incorporate their viral DNA and RNA into the genomes of infected cells. (Xu *et al,.* 2013). A deep analysis was done by a few studies that suggested of a link between the risk factors that have been mentioned earlier and pancreatic cancer. They came forward with the view that there is a link between pancreatic cancer and smoking, excessive drinking, and consumption of coffee but were unable to recognize any relationship between the pancreatic cancer incidence and the latter two factors (Gheorghe *et al,.* 2022).

Chronic Pancreatitis

An inflammatory condition of the pancreas is called chronic pancreatitis which can lead to pancreatic cancer. Due to this, not taking into account the pancreatitis type, the patients of chronic pancreatitis had a risk of 1.8% of progressing towards pancreatic cancer in 10 years and 4% in 20 years. A research analysis conducted in 2012 revealed a risk reduction of 1.34% above two years following the diagnosis of patients with chronic pancreatitis. In 2017, a comprehensive review mentioned that it would be a better option to observe the patients of chronic pancreatitis in order to not miss the signs of progression of the pancreatic cancer. According to studies, the cationic trypsinogen gene (PRSS1) has been associated to the etiopathogenesis of chronic pancreatitis and pancreatic cancer. It is established that the somatic PRSS1 mutations are mostly responsible for the onset of cancer. (Gheorghe *et al,.* 2022).

The existence of a relationship between cystic fibrosis, a number of malignancies and pancreatic cancer has been confirmed. The most widespread autosomal recessive disease in Europe is cystic fibrosis which is manifested due to the biallelic inactivating germ-line mutations occurring in the CFTR gene which is deemed responsible to control the purpose of cystic fibrosis transmembrane conductance membrane (Gheorghe *et al,.* 2022).

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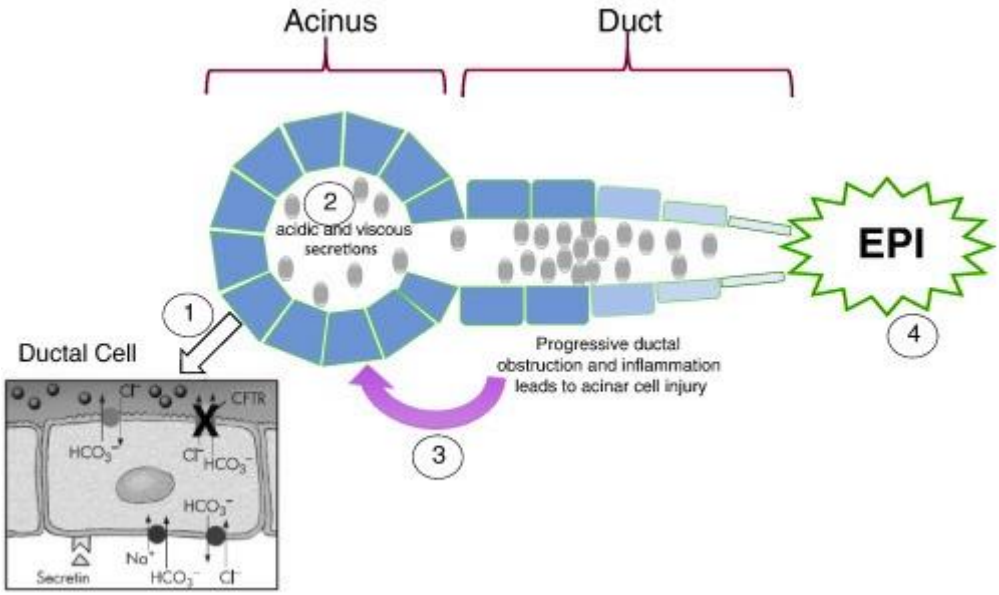

Figure 6. Theorized mechanism for the progression of pancreatic damage resulting in pancreatic insufficiency in utero. Mutation inCFTR(1) impairs HCO_3^- secretion which leads to acidic and viscous pancreatic secretions (2). This results in progressive ductal obstruction and inflammation (3) that causes acinar cell injury and ultimately, exocrine pancreatic insufficiency (4) (Freeman et al,. 2017).

Intraductal Papillary Mucinous Neoplasms (IPMN)

Pancreatic cyst is one disorder which poses the danger of pancreatic cancer development with intraductal papillary mucinous neoplasms (IPMN) being the most prevalent one. A close observation is carried out on patients who have this disease in order to detect any possible deterioration of the malignant at an early stage. A surveillance plan was carried out for IPMN and it was found that 2%-9% of patients experienced pancreatic ductal adenocarcinoma irrespective in what way IPMN developed, hence proving the involvement of pancreatic tissues (Gheorghe *et al,*. 2022).

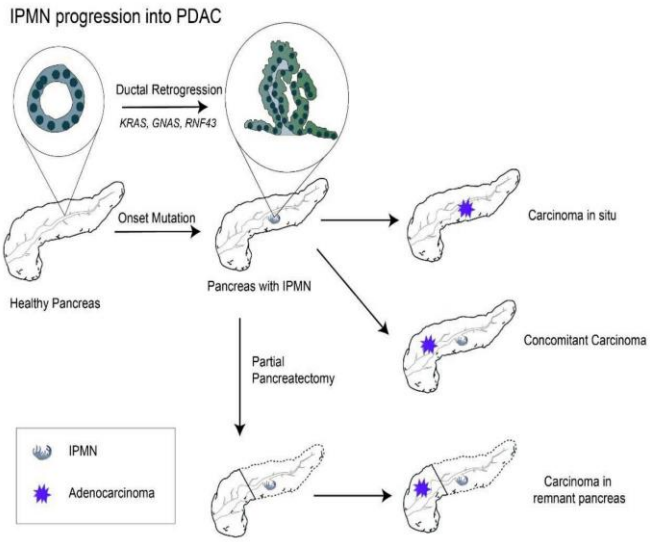

Figure 7. The remaining risks of PDAC progression in the remnant pancreas after partial pancreatectomy to remove the primary IPMN lesion. Abbreviations: IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma; GNAS, guanine nucleotide-binding protein-stimulating α subunit; and RNF43: ubiquitin E3 ligase ring finger 43 (Li *et al* ,. 2021).

Genetic Susceptibility

In almost 10% of the patients, pancreatic cancer was caused by genetic susceptibility. Many genes have been discovered by scientists that are related to the development of malignancy. *STK11, PALB2, BRCA2,* and *CDKN2A* are the genes with high penetration and the genes with a low penetrance include the ABO blood group locus. Based on the genetic risk of pancreatic cancer development, two groups were acknowledged. In the first category, those patients are included that have genetic syndromes and have a threat of the development of malignancies which includes pancreatic cancer with examples being Lynch II syndrome, Peutz-Jeghers syndrome, Li-Fraumeni syndrome etc. In the second category, those patients are included who are in a danger of developing the familial pancreatic cancer without any definite molecular basis (Gheorghe

et al,. 2022).

Patients who have the ALDH2*2 genotype has a larger possibility of developing pancreatic cancer even if they consume alcohol occasionally (30g daily) which is suggestive of alcohol usage connected strongly to the growth of pancreatic cancer in the East Asians owing to a high incidence of impaired acetaldehyde metabolism in them. Enough studies have not been done to know how the polymorphism of ALDH2 affects the link that exists between drinking and pancreatic cancer and so thus more study is required (Tsai *et al,.* 2019).

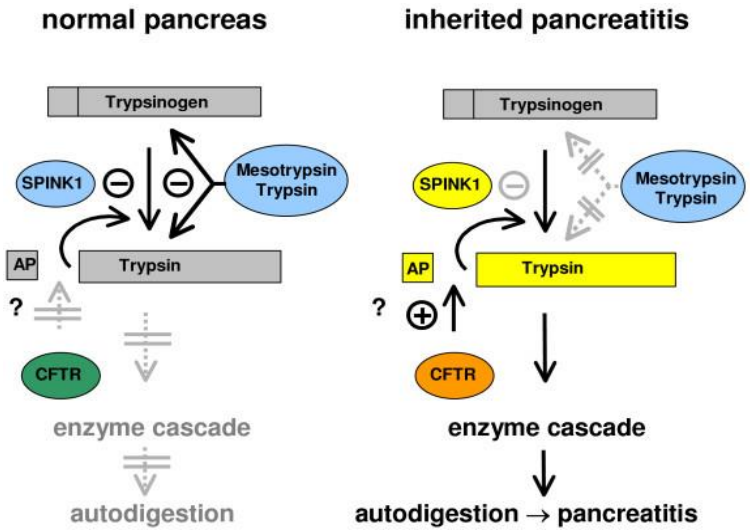

Figure 8. Model of inherited pancreatitis. In the normal pancreas (left) trypsin that is prematurely within the pancreas is inhibited by SPINK1 and in the second line by trypsin and mesotrypsin preventing autodigestion. In inherited pancreatitis (right) mutations in PRSS1 or SPINK1 lead to an imbalance of proteases and their inhibitors resulting in autodigestion. The role of CFTR is until now poorly understood. Abbreviations: AP= activation peptide (Rosendahl *et al*,. 2007).

Nutrition and Pancreatic Cancer

Numerous researches have examined for a link between the incidences of pancreatic cancer due to nutrition and have achieved varied levels of success. Generally, having a diet that is high in fruits, vegetables and other plant based products pose a reduced risk of pancreatic cancer but if the diet is high in meat and other animal products, then the chances are increased (Tsai *et al,.* 2019). According to the studies done on nutrition, plant-based foods for instance, vegetables, fruits, nuts and whole grains contain dietary fiber along with phytochemicals that help in lowering the chance of developing cancer. On the other hand, anti-cancer actions have been demonstrated by carotenoids, alkaloids, nitrogen containing compunds, phenolics and organosulfur containing compunds. The DNA damage repairing ability, antioxidant abilities, anti-inflammatory properties, and prevention of tumorigenesis, growth, and invasion are just a few of the pathways that are addressed by these anti-cancer activities (Casari *et al,.* 2015).

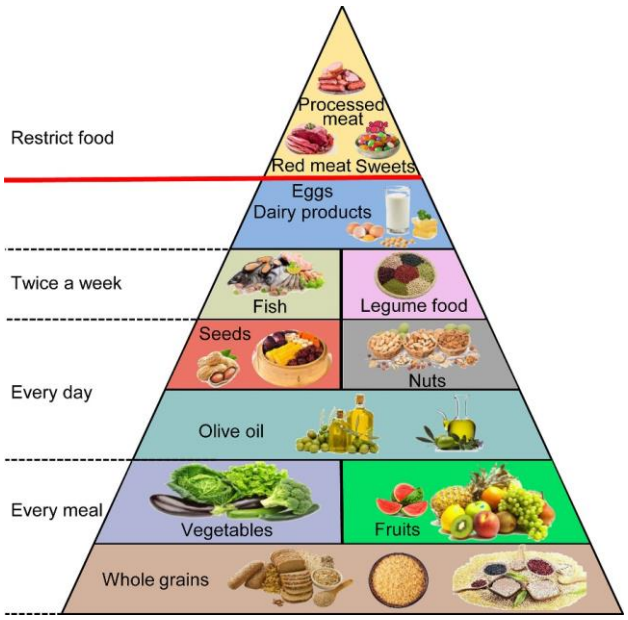

Figure 9. A balanced diet for pancreatic cancer patients (Zhang *et al*. 2021).

Physical Activity

A number of contradictory findings have been reported for the linkage between physical activity and pancreatic cancer have produced contradictory findings. A meta-analysis that pooled information from 28 research showed that exercise was linked to a reduced risk of pancreatic cancer. The association never demonstrated a dose-response connection. The occurrence of pancreatic cancer was revealed to be considerably lessened by light exercise (Bao *et al,.* 2008).

Three additional investigations also revealed contrary results. In a prospective American investigation, there was no link between exercise and pancreatic cancer. (Tsai *et al,.* 2019). Other study revealed no link between physical activity and a lower risk of pancreatic cancer in individuals around 60 (HR (hazard ratio) = 1.23, 95% confidence interval (CI): 0.96-1.57), but was associated with a lower risk in those under 60 (hazard ratio (HR) = 0.27, 95% confidence interval CI: 0.07-0.99) (Noor *et al,.* 2016). Physical activity is essential besides a healthy diet to avoid obesity, which is a known risk factor for pancreatic cancer. Additional studies must investigate at how food and exercise influence the likelihood of developing pancreatic cancer.

Obesity

According to multiple research, there is a correlation between obesity and an increased risk of pancreatic cancer. According to an analysis of approximately 2,170 patients with pancreatic cancer and 2,209 controls, those patients with BMIs in the maximum quartile have a increased r risk of the development of the disease than those patients in the lowermost quartile, (OR = 1.33, 95% CI: 1.12-1.58) (Arslan *et al,.* 2010). In an Israelian study conducted on 1.79 million youngsters , it was shown that teen obesity was linked with greater incidence of pancreatic cancer at a later stage in life in comparison with typical weight (5th - 85th percentile) for both men and women (HR = 3.67, 95% CI: 2.52-5.34). Hormonal imbalance and inflammatory responses are two possible mediators, even though the precise molecular pathways behind the relationship between obesity and pancreatic cancer are still not entirely understood. More research is needed on the molecular mechanisms that could explain the link between pancreatic cancer and obesity. (Tsai *et al*,. 2019).

Probability

Poor oral hygiene, particularly periodontal disorders and tooth loss, has commonly been related to amplified risk of pancreatic cancer. It was revealed in a meta-analysis that included data from eight trials that periodontitis was significantly linked to a increased incidence of pancreatic cancer (RR = 1.74, 95% CI: 1.41-2.15) (Maisonneuve *et al,.* 2017). The loss of teeth was associated with an enhanced risk of pancreatic cancer in forthcoming investigation involving 29,104 smoking men (HR = 1.63, 95% CI). CI: 1.09-2.46) (Stolzenberg-Solomon *et al,.* 2003A correlation between the likelihood of having pancreatic cancer and either tooth loss, periodontitis, or possibly both was discovered in a study including nearly 40,000 American African women. Despite the fact that the underlying pathway is currently poorly comprehended, studies have consistently found a link between reduced dental care and an elevated incidence of pancreatic cancer. (Tsai *et al,.* 2019).

Pathogens

When hazardous oral bacteria infect the mouth, it can result in periodontal disease, dental disorders, and other ailments that affect the mouth. According to reports, researchers are examining the role that oral flora plays in the growth of pancreatic cancer. After examining the blood antibody titer for oral bacteria in a stacked research that included approximately 405 patients with pancreatic cancer and approximately 416 controls, Michaud *et al*,. 2013 examined the link between mouth bacteria and pancreatic cancer incidence. The discovery of a relationship between increased serum antibody levels and the pancreatic cancer-causing bacterium P. *gingivalis* ATTC53978. Additionally, researchers found a link between higher levels of antibodies that are specific to friendly oral bacteria and a lower risk of pancreatic cancer, which can slow the growth of mouth cancer (Tsai *et al*,. 2019).

The oral bacterial patterns of approximately 58 healthy controls, 39 patients with intraductal papillary mucinous neoplasm (IPMN) and 40 patients with pancreatic cancer were surveyed in a study by Olson *et al*,. 2017. They revealed that the proportion of firmicutes was greater in pancreatic cancer patients in comparison with controls, but these bacterial patterns had no connection to evaluations of oral health. It is conceivable that an infection of the mouth could lead to systemic inflammation, which in turn might affect inflammation in another organ, such the pancreas. In turn, persistent inflammation may promote the growth of cancer (Tsai *et al,.* 2019).

A study that demonstrated how gut bacteria may promote the development of aberrant pancreatic cell cancer examined the intestinal microbiota profiles of approximately 85 patients with pancreatic cancer and 57 controls. They revealed that the microbial profiles from the gut of patients suffering from pancreatic cancer indicated a greater concentrations of several specific pathogens and bacterial species that produce lipopolysaccharides and small amounts of probiotics as well as bacterial species that produce butyral in comparison to normal participants (Ren *et al*,. 2017).

The research by Pushalkar *et al*,. 2018 suggested that intestinal bacteria can travel from the gut to the pancreas, suggesting a potential link between the microclimate of the pancreas and intestinal bacteria. Additionally, it has been noted that the malignant pancreatic has a higher pathogen density than the healthy pancreas. In the initial stages of pancreatic oncogenesis, microbial dysbiosis was seen in the mouse model of pancreatic cancer. This discovery aided in the quick identification of pancreatic cancer tumors using intestinal flora as tumor markers (Tsai *et al,.* 2019).

Coffee

Numerous researchers have examined the relationship between coffee consumption and development of pancreatic cancer, with various degrees of success. Majority of these studies utilized case-control techniques, which were subjected to bias by recall and control strategy. Later, larger prospective studies found no link between coffee drinking and pancreatic cancer. When Zhou *et al*,. 2019 prospectively observed 309,797 non-smokers over a mean follow-up of 13.7 years in the UK, they did not find any relationship between coffee drinking and the hazard of pancreatic cancer.

Drugs

Numerous studies have looked into the potential side effects of commonly used drugs like aspirin, various NSAIDS, statins, or drugs for diabetes like metformin. Metformin use appears to reduce the risk of pancreatic cancer in diabetics, in contrast to statins and aspirin, which either have no associations or shaky connections with pancreatic cancer risk. The majority of meta-analysis found that the protective relationship was only apparent in scientific investigations (RR 14 0.56), not in two controlled trials (RR 14 0.93). Five data reports on relationships with various anti-diabetic drugs have been analyzed. Recent insulin or insulin glargine use was linked with a higher incidence of pancreatic cancer but the interaction may be due to reverse causality (Maisonneuve *et al,*. 2015).

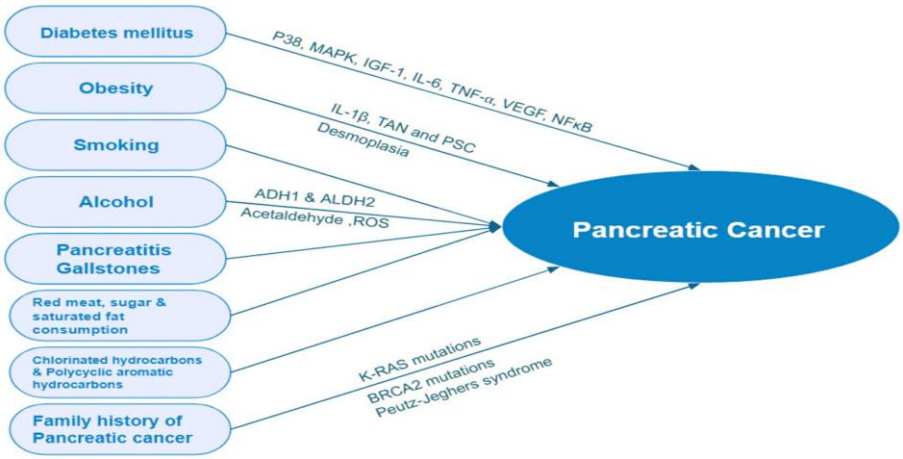

Figure 10. A schematic representation of some of the common risk factors for pancreatic cancer (George *et al*,. 2022).

Diagnostic risk factors linked with pancreatic cancer

Diabetes

Patients suffering from diabetes are at an elevated risk of developing pancreatic cancer. A higher danger of pancreatic cancer was linked with having diabetes for more than two years. (OR= 1.90, 95% CI: 1.72-2.09), and the increased threat persisted for more than 20 years of mellitus (OR = 1.30, 95% CI: 1.03-1.63), according to a meta-analysis of statistics from 15 case reports. Any previous incidence of hyperglycemia increased the risk of developing pancreatic cancer by approximately 52% (95% CI: 1.43-1.63), according to a pooled study of 23 prospective observations. According to studies, having chronic hyperglycemia elevates the risk of acquiring pancreatic cancer (Tsai *et al,*. 2019).

Chronic pancreatitis

According to studies, the frequency of chronic pancreatitis and pancreatic cancer are directly related. There was a substantial correlation between chronic pancreatitis and an elevated incidence of pancreatic cancer within 2 years of the condition's development (RR = 16.16, 95% CI: 12.59-20.73), according to a pooled examination of data from 13 samples; however, the association diminished when the gap between the two conditions was established at 5 to 9 years (RR = 3.53, 95% CI: 1.69-7.38) (Kirkegard *et al,*. 2017).

In certain instances, rather than being the consequence of a direct causative relationship, the association between chronic pancreatitis and pancreatic cancer may be the result of reverse causality. Experts estimate that those with pancreatitis have a 5% probability overall of establishing pancreatic cancer (Raimondi *et al,*. 2009).

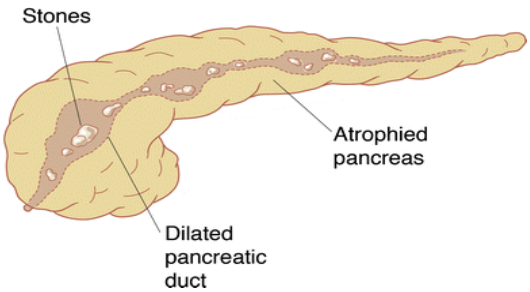

Figure 11. Anatomical changes in pancreatic cancer (Dua *et al*,. 2017).

Allergic reactions

An increased incidence of pancreatic cancer has been linked to allergic reactions, according to numerous research. According to a 2005 pooled analysis of data from 14 case-control studies, having any allergy signs was linked to a reduced incidence of pancreatic cancer (RR = 0.82, 95% CI: 0.68-0.99). A meta-analysis of 10 investigations revealed that having allergies was linked with a reduced risk of pancreatic cancer (OR = 0.79, 95% CI: 0.62-1.00), hay fever (OR = 0.74, 95% CI: 0.56-0.96), and allergies to pets (OR = 0.62, 95% CI: 0.41-0.94). According to the "immunosurveillance hypothesis", allergies are a mark of an autoimmune reaction that is particularly adept at identifying and eradicating cancer cells before actively working to prevent cancer from arising. On the other hand, the "prophylaxis hypothesis" contends that since the body uses allergies to remove carcinogens, they actually help the battle against cancer. To better understand how these two situations connect to the inverse link between allergies and pancreatic cancer, more research is required (Tsai *et al,.* 2019).

Infections

There have been studies looking into the potential links between a number of diseases, including pancreatic cancer and H. *pylori* as well as hepatitis B and C. An analysis of eight researches found a relationship between hepatitis B and C viruses and an greater risk of pancreatic cancer (Xu *et al,.* 2013). According to an observational study conducted in Taiwan, hepatitis B considerably worsened the risk of emerging pancreatic cancer compared to hepatitis C. After optimizing factors for age, gender, diabetes, drinking, , smoking, etc a second Taiwanese study with 585 patients and 1,716 controls that analyzed the blood samples for hepatitis B and C infections found no association between the disease and the risk of pancreatic cancer (Chang *et al,.* 2014).

A significant increase in the incidence of pancreatic cancer was linked to the HCV in a prospective study of 12,126 people with chronic hepatitis. (Xu *et al*,. 2013). In general, studies showed a possible link between hepatitis B or C infection and a higher risk of pancreatic cancer. (Tsai *et al,.* 2019). The seropositivity for CagA-positive H. *pylori* was shown to have a link with a lower risk of pancreatic cancer (Odd ratio (OR)= 0.78, 95% Confidence interval (CI): 0.67-0.91), whereas seropositivity for CagA-negative H. *pylori* was associated with a higher risk (OR= 1.30, 95% CI: 1.02-1.65), according to a pooled analysis that combined data from 10 researchers. Verification of the various H. *pylori* strains' suspected impacts on pancreatic cancer will require additional research. In pooled studies that were released after the meta-analysis, it was discovered that seropositivities for H. *pylori* in general, for CagA-positive H. *pylori*, and for CagA-negative H. *Pylori* were all unrelated to the risk of developing pancreatic cancer (Schulte *et al,.* 2015).

PANCREATIC GLUCAGONOMA

Further research is needed to analyze the relations between the different strains of H. *pylori* and pancreatic cancer in order to substantiate the strain-specific association between H. *pylori* and pancreatic cancer. In contrast to cancer prevention, allergy is a sign of an overactive immune response which is particularly good at recognizing and eradicating cancer cells. Allergies are necessary for the body to get rid of the oncogene. (Huang *et al*,. 2017).

The risk prediction model (Pancreatic cancer)

Identifying high-risk patients for evaluation in order to improve timely diagnosis and increase life expectancy is one of the main objectives for the detection of disease risk factors (Klein *et al,.* 2013). Some researchers incorporated into their model variables such prior pancreatic inflammation, diabetes diagnosis, past cigarette smoking, present proton pump inhibitor use, Jewish heritage, and non-O ABO blood type. They calculated the 5-year risk of pancreatic cancer based on multiple combinations of risk factors; some of the five-year hazards above 5–10%, which may call for pancreatic cancer screening (Risch *et al,.* 2015). In the male's predicting model, the following factors were taken into account: age, height, mass index, skipping meals, urine sugar levels, smoking, and age at which smoking was first started. The prediction model for women involved factors like height, BMI, fasting, urine glucose, and alcohol intake. The models' Auc values for men and women of 0.813 and 0.804 respectively showed how effectively their systems discriminated against different racial and gender subgroups (Tsai *et al,.* 2019).

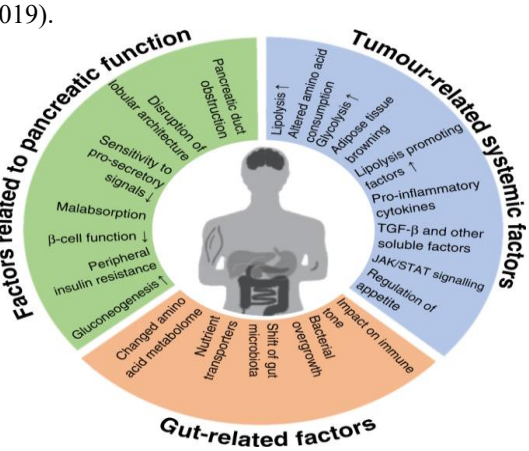

Figure 12. Conceptualisation of the three dimensions involved in the development of pancreatic cancer cachexia (Kordes *et al*,. 2021).

Nakatochi created two pancreatic cancer risk predicting models that take into account smoking, family history of the disease, and five single nucleotide polymorphisms using data from 664 Japanese people who had the disease and 664 sex- and age-matched controls. The complete model's AUC of 0.63, which was greater than the model's AUC of 0.61 for just the five Single Nucleotide Polymorphisms, suggests the usefulness of including both genetic and environmental components in risk prediction models (Nakatochi *et al*,. 2018). As a result, checking patients for newly developing hyperglycemia may present a wonderful, once-in-a-lifetime chance for the early detection of curable pancreatic cancer. According to this, pancreatic cancer-related diabetes may manifest up to three years before the disease is identified. However, because type-2 diabetes represents the majority of newly diagnosed diabetes patients, screening for pancreatic cancer would be prohibitively expensive in each case (Tsai *et al,*. 2019).

Besides clinically confirmed diabetes, medical proof is essential to increase the precision of the pancreatic cancer prediction model. In 2017, Boursi generated a pancreatic cancer prediction model utilizing statistics from 109,385 newly diagnosed diabetes. If the disease risk was kept at 1% over a three-year follow-up period, 6.2% of persons with newly identified mellitus required to be observed for pancreatic cancer. Therefore, the sensitivity ratio will estimated to be 44.7%, specificity 94%, and positive predictive value 2.6% (Boursi *et al,*. 2017).

CONCLUSION

The study concluded that the incidence of pancreatic cancer may increase by hepatitis B infection equal to 24% with a history of such infection than in patient without previous record of hepatitis B infection in patient with (P= 0.88). Pancreatic cancer has poor prediction mostly because of its late diagnosis in hepatitis B infected patient. Different approached are necessary for an earlier diagnosis to improve the prediction of patients that associate with pancreatic cancer. Other factors such as the blood group types of the patient that secondly come to genetic reasons. Moreover, smoking, obesity, alcohol consumption, and infection with H. *pylori* also play a very important role but if there is a history of pancreatic cancer in the patient's family, the chances of acquiring it are very high even if the patient is a non-smoker, non-alcoholic and not even obese.

Future prospects

Moreover, prospective research is needed to assess the best effective and cost-effective treatment option for those with chronic viral hepatitis with risk for developing pancreatic cancer. It's conceivable that the strategy for antiviral therapy treatment for virus clearance may play their part in reducing the pancreatic cancer risk.

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