

# Epidemiology of Pancreatic and Periampullary Cancer

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**Abstract** Pancreatic cancer is an important public health problem, although infrequent but with an exceptionally high mortality rate worldwide. Given that the majority of cancers occur in association with smoking, diabetes, pancreatitis, genetic factors, and others and with a growing population worldwide in mind, more cases would be expected in the near future giving further impetus to investigating prevention and treatment strategies to this international issue. The representative data on epidemiology of carcinoma of pancreas in India and Nepal are very poor. While there are many questions to be resolved, it is apparent that many facets of pancreatic cancer are becoming increasingly understood, and prospects for prevention are becoming apparent. Hence, screening research, recommendations, and implementation is an obvious priority. Although previous studies have contributed to the knowledge of carcinoma of pancreas epidemiology, such association needs to be further verified with proper epidemiological work. A new and global approach to the study of carcinoma of pancreas epidemiology is required if the disease prevention and treatment strategies are to be adequately directed and supported in the coming years. The collection and analysis of epidemiologic carcinoma of pancreas data will play a critical role in guiding future disease prevention strategies and optimizing patient management.

**Keywords** Carcinoma of pancreas · Epidemiology · Risk factors

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## Introduction

Worldwide, carcinoma of the pancreas causes more than a quarter of a million deaths annually, being the 13th most common cancer, the eighth most frequent cause of death from cancer. Survival rates are among the worst for any tumor, being the mortality to incidence ratio of 98 %. It is among the tumors with worst survival rates [1].

Resectional surgery does lead to about a 20 % 5-year survival, but because of the presence of widespread local disease or metastasis, only 10–20 % of patients undergo pancreatic resection. As current therapeutic results are so dismal, it is essential to review the epidemiologic factors that influence the development of this disease in order to implement preventive and screening strategies that can reduce the burden of this lethal cancer [2].

With the exception of the small bowel, the pancreas is less likely to develop cancer than any other gastrointestinal organ. Nevertheless, the remote location of the organ, the lack of any specific diagnostic markers, the difficulty in establishing a tissue diagnosis, and the aggressive nature of pancreatic adenocarcinomas, which respond poorly to both chemotherapy and radiotherapy, contribute to the exceptionally high mortality associated with this type of cancer. At present, inherited disorders explain only a small part of the total burden of pancreatic cancer. Environmental factors seem to account for a large proportion of pancreatic cancer cases. Known preventive strategies are limited to reducing smoking exposure and maintaining normal body weight. Consuming adequate quantities of fruits and vegetables might also have a preventive effect, although strong epidemiological evidence is lacking. Promising areas for additional research include the substantial racial differences in pancreatic cancer frequency, the surprising link with blood groups, the possible relationship of pancreatic cancer to oncogenic viruses, and validation of the many putative

gene polymorphisms that have been tentatively identified as risk factors.

### Global Trends

According to SEER data based on 2008–2012, the number of new cases of pancreatic cancer was 12.4 per 100,000 men and women per year, and approximately 1.5% of men and women will be diagnosed with pancreatic cancer at some point during their lifetime [3]. Despite its low incidence in developed countries, pancreatic cancer is associated with poor survival and ranks as the fourth or fifth most common cause of cancer mortality. The incidence of pancreatic cancer in India is 0.5–2.4 per 100,000 men and 0.2–1.8 per 100,000 women [4]. Recent data shows a decreasing trend in both incidence and mortality of pancreatic cancer in the UK, though a study done in over 51 countries across the world (Europe, 33 countries; America, 8 countries; and Asia, 10 countries) between 1992 and 2002 revealed that the age-standardized mortality (world) rates (ASR (W)) for pancreatic cancer have been static [5].

#### *Family History and Genetic Disorders (Are Some People Genetically More Prone to Pancreatic Carcinoma?)*

A family history of pancreatic cancer in a first-degree relative is associated with an increased risk of pancreatic cancer of between 2.5 and 5.3 times. The risk increases as more relatives are affected. The increased risk in family members could be owing to genetic factors and/or lifestyle habits that may be similar in different generations, such as smoking. Genetic predisposition is regarded as one of the major risk factors in the development of cancer. The development of pancreatic cancer may be associated with inherited mutations in specific genes. These mutations are therefore the cause of various familial cancer syndromes. These germline disorders account for 5–10 % of pancreatic cancer cases. It is considered that activation of the oncogene K-ras with simultaneous inactivation of the tumor suppressor genes (p53, DPC4, p16, and BRCA2) results in pancreatic cancer. Ninety percent of all cases of pancreatic cancer have p16 mutations, 75 % have p53 mutations, and 55 % have DPC4 mutations. Of the remaining sporadic pancreatic cancers, some could be attributable to somatic polymorphic mutations in genes encoding tobacco and food metabolizing enzymes, as well as to DNA repair genes. A small fraction may evolve due to the dysfunction of the various DNA mismatch repair genes (microsatellite instability (MSI)) [5].

A number of genetic disorders are associated with an increased risk of pancreatic cancer, although no common genetic abnormality has been identified in all these conditions. These include hereditary pancreatitis, familial adenomatous polyposis, familial atypical multiple mole, melanoma, Peutz–Jeghers syndrome, hereditary non-polyposis colorectal cancer, familial breast cancer, ataxia-telangiectasia, and cystic

fibrosis [6]. A paternal inheritance pattern and long duration of onset of hereditary pancreatitis have shown to have higher risk [7] and those with Peutz–Jeghers syndrome the relative risk is very high for gastrointestinal and other non-gastrointestinal tumors [8].

### Diabetes

Diabetes mellitus (DM) being a complex metabolic condition defined by the level of hyperglycemia giving rise to risk of microvascular or macrovascular complications [9]. Diabetes is common in Nepal and India. The prevalence in India is around 10 % i.e., 31 million people which is predicted to increase to 80 million by year 2030. Asians have a strong genetic susceptibility for type II diabetes. Recent onset of diabetes can be associated with pancreatic cancer, an early symptom in nearly 75 % of all pancreatic cancer patients [10]. Huxley et al revealed the relationship of therapy for diabetes with carcinoma of pancreas in which they found that Metformin, an oral antidiabetic agent, is associated with a decreased risk of pancreatic cancer, whereas another study showed that insulin and insulin secretagogues increase the risk of pancreatic cancer [11]. Risk of pancreatic cancer increases up to 50 % in patients with long-term disease ( $\geq 10$  years) with type 2 DM [12].

### Chronic Pancreatitis

Chronic pancreatitis has a significant association with pancreatic cancer. A large, retrospective cohort study of patients with at least 5 years of chronic pancreatitis before being diagnosed with pancreatic cancer found a 14-fold increased risk of pancreatic cancer in patients with chronic pancreatitis [13]. A causative role for pancreatitis in carcinoma of pancreas in humans has been strongly suggested based on various similar studies [14]. The degree of association is very strong between rare autosomal dominant hereditary form of pancreatitis, which arises during or soon after childhood, risk being 50 times than that in the general population [15]. However, chronic pancreatitis is rare and is not a main cause of pancreatic cancer [16].

### Smoking

Nearly all studies published since 1966 have shown an association between smoking and pancreatic cancer. The risk of pancreatic cancer is raised by 75 % as compared to non-smokers, risk persisting minimum of 10 years after cessation of smoking when the risk gradually diminishes to the baseline [17]. Another study that included nearly 13,000 patients with pancreatic cancer showed that current smokers had an odds ratio of 2.2, compared with never smokers, and the odds ratio was 1.2 for ex-smokers. With cessation of smoking, risk gradually decreases but requires more than 10–20 years before the

smoking-related risk disappears [18]. Pipes, cigars, other tobacco products, and even oral tobacco products increase the risk of pancreatic cancer. Smokeless tobacco contributes to risk probably lower than that of smokers but higher than that of non-tobacco users [19]. Estimated prevalence of smoking is about 30 % in many parts of the world, and the risk of pancreatic cancer is doubled in smokers. Tobacco smoking releases many carcinogens. A recent study examined several detoxifying genes in 455 patients with pancreatic cancer [20]. Variants in genes such as CYP1B1-4390-GG and uridine 5'-diphosphoglucuronosyltransferase reduced the risk of pancreatic cancer, whereas variants in others, such as GSTM1, increased risk. Little is known about the mechanisms by which these genes affect cancer risk, but their products could affect the inflammatory response, fibrosis, cell proliferation, and other processes involved in carcinogenesis [21]. Various germline mutations, as in hereditary pancreatitis, familial atypical mole–multiple melanoma (FAMMM) syndrome, Li–Fraumeni syndromes, Peutz–Jeghers, cystic fibrosis, and BRCA1/BRCA2, were suggested to increase the risk of early onset pancreatic cancer in interaction with smoking suggesting the primary role of smoking in early onset pancreatic cancer [22].

### Age, Gender, and Race

Age is the strongest risk factor for pancreatic cancer. The risk is almost 20 times higher for individuals older than 50 years as compared to younger persons. As for other cancers, fewer than 10 % of cases of pancreatic cancer occur among individuals younger than 55 years old, and the median age of onset is 71 years. In all groups, men have higher incidence rates than women [23]. Few if any, gender-specific hormonal risk factors seem to have a causal role in pancreatic cancer and that carcinoma of pancreas is an estrogen dependent tumor at least in part. [24] Since smoking rates are higher in men than in women, smoking could be responsible for the higher rates observed in men.

Fifty to ninety percent higher incidence of pancreatic cancer in blacks compared with whites seen for decades is due to established risk factors (mainly cigarette smoking and diabetes) in men and less accepted risk factors (i.e., heavy alcohol drinking and elevated BMI) in women [25].

### Alcohol

Alcohol is a major risk factor for pancreatitis; however, studies have failed to support its association with pancreatic cancer including a recent large retrospective cohort study from Sweden [26] whereas only a weak relation has been reported by some studies [27]. As there is a strong relationship between smoking and alcohol consumption, confounding factor being

smoking could be the reason of weak association that could not be excluded.

### Diet

No strong link has been found between diet and pancreatic cancer [28]. However, study done by Ghorbani Z et al. [29] have shown in a well-matched case control study that increased frequency of intake of rice, bread and barbequed meat and deep fried vegetables can aggregate the risk while consumption of fish can decrease the incidence of pancreatic cancer. There has been no association between intake of fat and risk of pancreatic cancer [30] while exercise, which helps to maintain normal body weight, has been associated with a reduced risk of pancreatic cancer [31]. Non-steroidal anti-inflammatory drugs (NSAIDs), mainly aspirin, have shown to decrease risk of pancreatic cancer [32, 33]; however, other non-aspirin NSAIDs have not shown the benefit [34]. Similarly, lipid-lowering statins have a modest role in decreasing risk of pancreatic cancer [35].

### Conclusions

Type II diabetes, heavy alcohol drinking, cigarette smoking, excess body weight, chronic pancreatitis, a family history of pancreatic cancer, and known few germline mutations are some of the identifiable risk factors for pancreatic cancer. Chronic inflammation in the pancreas due to several reasons like chronic pancreatitis, alcohol, smoking, hyperlipidemia, etc. is probably involved in the development pancreatic cancer.

### Compliance with Ethical Standards

**Conflict of Interest** The author declares that he has no competing interests.

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