Review

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# Role of Inflammation in Pancreatic Carcinogenesis and the Implications for Future Therapy

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**Key Words**

Inducible nitric oxide · Interleukins · Pro-inflammatory cytokines · Cyclooxygenase-2 · NF-kappa B · Reactive oxygen species · DNA adducts · Lipoxygenases · Chemoprevention

**Abstract**

***Background:*** The link between inflammation and pancreatic cancer has been observed for a number of gastrointestinal neoplasms. This review examines the role of inflammation in pancreatic carcinogenesis and how it can be utilised to develop new therapies against pancreatic cancer. ***Methods:*** A literature review of Pubmed, Medline and Web of Science databases was undertaken using the key words, pancreatic cancer, inflammation, inducible nitric oxide, interleukins, pro-inflammatory cytokines, cyclooxygenase-2, NF-kappa B, reactive oxygen species, DNA adducts, lipoxygenases, chemoprevention. ***Results:*** Epidemiological evidence and molecular studies both in vitro and in vivo all support the hypothesis that inflammation plays an important in the initiation and progression of pancreatic tumours. ***Conclusion:*** Sustained damage caused by chronic inflammation may precede the onset of frank malignancy by a significant interval. As such, suppression of inflammatory changes and oxidative damage, may help delay or even prevent the inception of pancreatic neoplasia.



## Introduction

Pancreatic cancer is one of the most lethal cancers of the gastrointestinal tract, with a death to incidence ratio of 0.99 [1]. The poor prognosis of pancreatic cancer is attributable to its tendency for late presentation, aggressive local invasion, early metastases and poor response to chemotherapy [2]. The only curative treatment for pancreatic cancer is surgical resection, however, only 10–15% of patients will have localised disease at presentation [3]. Retrospective studies have revealed a global increase in the mortality rate from pancreatic cancer, reflecting a rising incidence of pancreatic tumours [4–7]. This trend of increasing incidence, coupled with the poor prognosis of pancreatic cancer, emphasises the need to elucidate the mechanisms underlying pancreatic carcinogenesis, in order to find new treatments against the disease.

Smoking remains one of the most important risk factors for pancreatic cancer. Smokers have a 2- to 3-fold increased risk compared to non-smokers [8]. The main carcinogens implicated in tobacco smoke are the tobacco-

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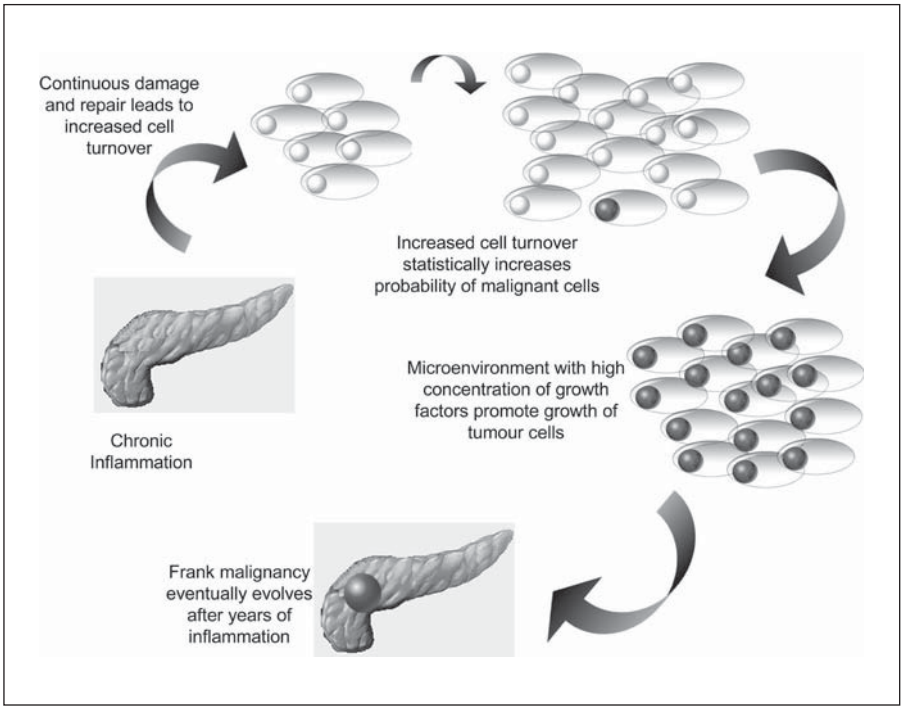


**Fig. 1.** Proposed mechanism between chronic inflammation and malignancy.

specific nitrosamines (TSNA). There is some evidence that exposure to occupational carcinogens such as chromium [9], DDT [10] and halogenated hydrocarbons [11] may increase the risk of pancreatic cancer. Furthermore, heterocyclic amines and polycyclic aromatic hydrocarbons, formed during the cooking of red meat, may also contribute to pancreatic cancer risk [12]. Other risk factors include familial inheritance [13, 14], with a 50-fold increase in the risk of pancreatic cancer if three family members are affected [15], and *Helicobacter pylori* seropositivity [16].

The possible causal relationship between inflammation and cancer has been observed in a number of gastrointestinal malignancies, such as inflammatory bowel disease with colorectal cancer, viral hepatitis with hepatocellular carcinoma and reflux oesophagitis with oesophageal adenocarcinoma. The exact link between chronic inflammation and carcinogenesis is unclear. It is possible that the drive for continued replication, due to continuous damage and subsequent repair, statistically increases the probability of cells accumulating enough 'genetic hits' for initiation to occur. The probability of cell initiation may be increased further by the formation of potential carcinogens produced during the inflammatory process, for example, reactive oxygen species, which can bind to DNA to form oxidative DNA adducts.

Once initiation has occurred, the microenvironment formed by inflammation in tissues, which has a high concentration of growth factors and cytokines, may enhance proliferation of initiated cells leading to promotion and eventually progression of a population of tumour cells (fig. 1). These changes may take many years to develop. Hence, interrupting the pro-carcinogenesis pathways associated with chronic inflammation could inhibit, retard or even prevent the onset of cancer. This review discusses the role of inflammation in pancreatic carcinogenesis, and how knowledge in this area could lead to new therapeutic possibilities in the treatment of pancreatic cancer.

## Chronic Pancreatitis and Pancreatic Cancer

Several studies have observed an increased incidence of pancreatic cancer in patients with chronic pancreatitis, when compared to the average population [17–20]. The increase in incidence varies across different studies. The Standardized Incidence Ratio has previously been reported from 3.8 [21] to as high 18.5 [22]. Some studies have found the increase in risk to be as high 16-fold in patients with chronic pancreatitis [23]. Familial pancreatitis accounts for less than 1% of all cases of pancreatitis and is