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The Diverse Involvement of Cigarette Smoking in Pancreatic Cancer Development and Prognosis

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Abstract: Despite extensive research in the pathogenesis, early detection, and therapeutic approaches of pancreatic ductal adenocarcinoma (PDAC), it remains a devastating and incurable disease. As the global incidence and prevalence of PDAC continue to rise, there is a pressing need to place strong emphasis on its prevention. Although it is widely recognized that cigarette smoking, a potentially modifiable risk factor, has been linked to PDAC development, its contribution to prognosis is still uncertain. Moreover, the mechanistic pathways of PDAC progression secondary to smoking are various and lack a summative narration. Herein, we update and summarize the direct and indirect roles cigarette smoking plays on PDAC development, review literature to conclude the impact cigarette smoking has on prognosis, and postulate a comprehensive mechanism for cigarette smoking–induced PDAC.

Key Words: pancreatic ductal adenocarcinoma, cigarette smoking, diabetes, obesity, genetics

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Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related mortality in the United States (US) and the seventh worldwide.¹ Despite it not being among the most common cancers, PDAC causes almost 10% of all cancer-related deaths in both men and women.¹ In addition, the approximately US \$5 billion annual impact of the disease in the US presents a major economic concern.² Frighteningly, the overall incidence of PDAC continues to increase at an alarming rate.³ There are more than 40,000 new PDAC diagnoses annually and nearly that number die of the disease each year in US.⁴ Being that PDAC leads to a near 100% mortality rate, in addition to the further investigation of the crucial countermeasures, there is a strong need to place an emphasis on disease prevention, namely, on its established risk factors.⁵

Chronic pancreatitis, diabetes, obesity, genetic makeup, intraductal pancreatic mucinous neoplasm (IPMN), and excessive alcohol consumption are all risk factors that have been documented to contribute to PDAC initiation with contributions of each ranging from 3% to 10% of the cases.^{6–9} Cigarette smoking

has been determined, a major risk factor for PDAC, as it contributes to development of up to 25% of the cases.^{5,10,11} Moreover, elucidation of the underlying mechanistic action of smoking is paramount, as it can directly contribute to the prevention of PDAC, and perhaps mediate an important role in patient prognosis. Apart from disease stage, few prognostic factors have been identified. In particular, cigarette smoking and survival among patients with PDAC remain an unsettled and poorly characterized field.¹¹ Hence, cigarette smoking deserves particular attention, and as an avoidable risk factor, the mechanistic unraveling would lead to a considerable reduction in the number of PDAC cases diagnosed annually.

Despite enormous research efforts at early diagnosis and treatment, PDAC continues to be a significant global health care burden. Lack of early detection in combination with its unresponsiveness to nearly all treatment modalities to date accounts for 1- and 5-year survival rates of merely 25% and 5%, respectively, in PDAC patients.¹² For the past few years, multiple phase 3 trials of chemotherapeutic agents for advanced PDAC have failed, likely reflecting the refractory and complex nature of disease progression.^{3,13,14} Although the relationship between PDAC initiation and cigarette smoking has been extensively studied, the mechanism by which smoking acts to promote carcinogenesis, promote disease progression, and influence prognosis is yet to be revealed.⁵ Considering the above, knowledge and the methodology of PDAC prevention are still a major initiative given the highly malignant nature of this tumor. Herein, we summarize the current literature on the considerable involvement of cigarette smoking in PDAC development and review the relationship between cigarette smoking and the prognosis of patients with PDAC, as well as the mechanistic hypotheses presented for this association.

CIGARETTE SMOKING AS A RISK FACTOR FOR PDAC DEVELOPMENT

Over half a century ago, numerous studies determined a relationship between smoking and PDAC progression. These survey-based studies showed a 70% greater risk of developing PDAC in cigarette smokers compared with nonsmokers.^{5,15,16} More recently, a large meta-analysis found that current smokers have a 1.74-fold increased risk of developing PDAC in comparison with nonsmokers.¹⁷ In a large pooled analysis, cigarette smoking was associated with a staggering twofold increase for a risk of PDAC.¹⁸ Notably, even exposure to environmental tobacco smoke was found to be associated with an increased risk of PDAC.¹⁹ Current smokers were found to have a markedly elevated risk of PDAC development compared with nonsmokers with greater intensity, duration, and cumulative smoking dose.²⁰ Smoking has also been associated with an earlier onset of PDAC development, and in certain scenarios, this can be as much as 20 years earlier than nonsmokers.^{5,21–23} Although various studies have established smoking as an undeniable risk factor for the initiation of PDAC, its role in patient prognosis has not been concluded. In addition, detailed studies on how smoking affects the survival of patients with PDAC are inconsistent

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and poorly represented throughout literature, hence demanding further examination.⁵

RECENT INSIGHTS INTO THE MECHANISMS OF SMOKING-INDUCED CARCINOGENESIS BY THE OTHER RISK FACTORS

Patients with chronic pancreatitis, largely due to smoking and alcohol abuse, carry up to a 10% risk of developing PDAC, with an eightfold increased risk 5 years after diagnosis.^{8,24,25} Nevertheless, chronic pancreatitis accounts for approximately only 3% of PDAC cases.⁶ The long-standing, unresolved inflammation of chronic pancreatitis is thought to underlie PDAC development. Disorders of the process of autophagy, or the process by which proteins and organelles are recycled via lysosomes, are common to both chronic pancreatitis and PDAC, arguing common features and interrelatedness of chronic pancreatitis and PDAC.²⁶ In addition, the induction of pancreatic inflammation was found to accelerate oncogenic *KRAS*-induced fibrosis and PDAC development in mouse models.²⁷ Importantly, pancreatitis has been shown to affect PDAC prognosis.²⁸ The *Nr4c* gene may provide another connection between pancreatitis and PDAC development. The deletion of *Nr4c* resulted in spontaneous chronic pancreatitis concomitant with acinar-to-ductal conversion and pancreatic deletion of *Nr4c* dramatically accelerated *KRAS*-driven PDAC development in mice.²⁹ The transforming growth factor- β 1/Smad pathway has also been shown to connect both pancreatitis and PDAC.³⁰ Galectin-1 expression, a common intermediate in the Smad pathway, in activated pancreatic satellite cells was found to promote fibrosis leading to both pancreatitis and PDAC development.²⁰ Interestingly, infection with *Enterococcus faecalis* may be involved in chronic pancreatitis progression, ultimately leading to PDAC development.³¹

Patients with diabetes have an increased risk of developing PDAC by at least 2 times that of nondiabetic patients.³² Notably, a correlation between diabetes and prognosis of patients with PDAC has been established.³³ Of recent, several mechanisms regarding the association between PDAC and type 2 diabetes were postulated. It was established that the phosphoinositide 3-kinase and nuclear factor kappa B pathway play an integral role in this process and the expression of polo-like kinase 1 enables insulin to promote the proliferation of pancreatic ductal epithelial cells, leading to PDAC development via both these pathways.³⁴ Li et al³⁵ postulated that the worse prognosis associated with diabetes-associated PDAC is due to the effect of hyperglycemia on the pancreatic microenvironment causing a transient hypoxia, ultimately responsible for promoting the metastatic ability of PDAC.

Not surprisingly, obesity was found to play a strong role in PDAC development. There even was a correlation between every unit increase in body mass index (BMI) to an increase in the risk of PDAC.³⁶ The cellular defense mechanisms of inflammation and autophagy, thought to play an important role in PDAC, are dysregulated by visceral obesity. Therefore aside from a high-fat diet intake, the physiologic impact of being obese, even on a cellular level, has been shown to be as a risk factor for PDAC initiation.²⁶ In addition, a connection between BMI and overall survival of PDAC patients was identified.³⁷ However, other studies found conflicting evidence and could not prove an association between BMI and survival of patients with PDAC.³⁸ In vivo studies revealed that adiponectin suppresses leptin-induced signal transducer and activator of transcription 3 (STAT3) signaling in PDAC.³⁹ Inhibition of STAT3 signaling via activating the adiponectin receptor provides a potentially important approach to inhibit PDAC development.³⁹ Mechanistically, a study revealed that obesity-driven PDAC exhibits accelerated growth and a striking transcriptional benefit for pathways regulating nitrogen metabolism—more specifically

arginase 2.⁴⁰ Importantly, a loss-of-function mutation, which acts as a silencing agent on arginase 2, has shown to reduce PDAC development.⁴⁰ Furthermore, a number of obesity-sensitive pathways that manipulated by transcription activators such as *YAP* and *TAZ* reinforce *KRAS* signaling and mutation leading to prolonged *KRAS* activation and eventual PDAC progression.⁴¹

Although intraductal papillary mucinous neoplasms (IPMNs) are benign and make up only approximately 20% of the cystic lesions of the pancreas, they are the most extensively studied that this is secondary to their innate ability to transform into malignant lesions.⁴² In addition, the development and recent advances in endoscopic ultrasonography have largely influenced our understanding of IPMN and its subsequent risk for PDAC development. Intraductal papillary mucinous neoplasm with high-grade dysplasia has been shown to increase the risk of the subsequent development of PDAC.⁴³ The presence of a mural nodule during endoscopic ultrasonography is the most reliable indicator for malignancy potential.⁴⁴ Size greater than 3 cm, though once thought to be a major predictor of malignancy, has been shown to not be a significant factor leading to cancer development.⁴⁵ The frequency of malignancy in main pancreatic duct lesions is close to 80%, whereas the frequency of malignancy in branch duct lesions is lower with an average of approximately 20%.^{46,47}

Although mild drinking is not a risk factor for PDAC, excessive alcohol consumption has been found to be associated with PDAC development.⁴⁸ However, as alcohol consumption is the leading cause of pancreatitis, which has been identified as a strong risk factor for PDAC development, it is debatable whether pancreatitis acts as the confounding factor. Further studies regarding mechanistic analyses of alcohol consumption and PDAC development would be required.

Hereditary factors contribute to somewhere between 5% and 10% of PDAC cases.⁸ Compared with individuals without a family history of PDAC, patients with a family history of PDAC have nearly a twofold increased risk for developing this lethal cancer.⁴⁹ Although hereditary conditions and specific genes shown to induce PDAC are difficult to discern from each other, as they overlap greatly, the previously mentioned environmental factors play a central role in promoting these specific genes. Thus, aside from the hereditary nature patients with these genes possess, having an environmental factor increases the risk of PDAC by virtue of enhancing those genetic expression patterns. It also possible that genetics in its entirety is a risk factor outside the realm of the other environmental risk factors, although future studies are needed to establish its precise role. *TP53* is one of the most frequently mutated genes in numerous cancers. Specifically, the role in PDAC is staggering, as it has been found mutated in 70% of PDAC cases.⁵⁰ A study suggests that *TP53* could be used as a biomarker for prognosis and perhaps even to guide therapy.⁵¹ Another major player identified to be involved with PDAC is the tumor suppressor protein *SMAD4*, which has been found to occur in approximately 50% of PDAC cases.⁵⁰ It has also been suggested that *SMAD4* inactivation could be used as a prognostic biomarker in PDAC.⁵² Numerous germ-line mutations including *BRCA2*, *FANC-C*, *FANC-G*, and *PALB2* were found to be closely associated with PDAC development.⁵³ Despite this, genetic disorders, which may involve some of these mutations, concur the highest risk for PDAC development. Oncogenic *KRAS* mutation is perhaps the most important trigger for PDAC initiation and is classically thought to play a vital role in disease progression as well. This signature genetic event has been found to be present in nearly 95% of PDAC cases.⁵⁴ Importantly, the ability of *KRAS* to alter metabolic pathways, reroute glucose transportation, influence autophagy, and drive the cellular macropinocytosis (the uptake of extracellular nutrients) of materials has furthered our understanding of PDAC initiation and

development.⁵⁵ The elucidation of this connection has opened up new attempts at understanding the mechanistic driving force of PDAC and has orchestrated a new era of clinical investigation.⁵⁴

THE RELATIONSHIP BETWEEN RISK FACTORS FOR PDAC AND CIGARETTE SMOKING

As illustrated in Figure 1, apart from its direct affects, cigarette smoke has indirect impacts on PDAC development, namely by activating and influencing its other risk factors. Exposure to tobacco smoking was found to be associated with an earlier diagnosis of chronic pancreatitis and predisposition to the development of pancreatic calcifications.⁵⁶ It also has been identified as an independent risk factor for chronic pancreatitis.⁵⁷ Numerous studies describe a strong relationship between cigarette smoking and the pathogenesis of diabetes. The development of complications, on both a microvascular and macrovascular level, has been proven to be modulated by cigarette smoke.⁵⁸ In addition, smoking cessation limits microvascular disease and may also facilitate tighter glycemic control.⁵⁹ A number of studies found that the odds of being obese increased progressively with smoking, such that male heavy smokers were more obese than male light smokers.⁶⁰ Although smokers weigh less than nonsmokers, upon cessation their weight returns to that observed in nonsmokers, with some smokers, gaining even more weight.⁶¹ Furthermore, smoking plays an important indirect role in PDAC carcinogenesis by its ability to induce DNA methylation as well as create DNA adducts.^{5,62} These adducts collectively aggregate and can even activate *KRAS* mutations thus hastening PDAC development.⁶³ Uniquely, having a smoking history is also one of the few valuable predictive factors for malignant IPMN that would thus warrant surgical resection.⁶⁴ Cumulative pack-years were higher in patients who had PDAC concomitant with IPMN than in patients with just IPMN, arguing a strong role for smoking induced malignant IPMN.⁶⁵ In a study by Zhang et al⁶⁶ only patients who were both cigarette smokers and alcohol drinkers were associated with reduced survival from PDAC and the 2 risk

factors interact with each other to promote the development of PDAC. Hence, taken collectively, aside from its direct effects, cigarette smoking yields indirect effects on PDAC development, namely, by modulating a number of its prominent risk factors.

THE IMPACT OF CIGARETTE SMOKING ON PDAC PROGNOSIS

To date, more than 7000 chemicals have been identified in tobacco smoke.⁴ Of these, 250 are known to be harmful, and 60 are classified as carcinogens containing extensively studied metabolites.^{4,67} Cigarette smoking might be the strongest environmental risk factor for PDAC development. In fact, cigarette smoking is associated with a reduced quality of life after diagnosis.⁶⁸ A detrimental effect of smoking on prognosis in patients with malignancies that are etiologically associated with tobacco use, such as lung cancer, esophageal cancer, and squamous cell carcinoma of the head and neck has already been established.^{11,69} Furthermore, tobacco usage in other cancers, such as colon, gastric, cervical, prostate, and renal cell carcinoma has also been associated with worse survival outcomes in comparison to nonsmokers.^{70–74} However, evidence as to whether cigarette smoking accelerates disease progression, is associated with a harsher disease course, and thus affects prognosis in patients with PDAC is inconsistent and remains poorly concluded. Although limited, various study designs including retrospective analyses, prospective cohorts, case controls, and others, aimed at determining if in fact cigarette smoking affects PDAC prognosis (Table 1). The results were inconsistent and the topic is in desperate need of a conclusive edge. While some studies show no correlation, others show a statistically significant relationship between smoking and PDAC prognosis.

In a hospital-based case-control study by Olsen et al⁷⁵ looking at 475 patients, no correlation between cigarette smoking and survival in patients with PDAC was found. However, the patient population identified had a large proportion (34%) of patients with resected disease; thus, overall survival may have been longer than

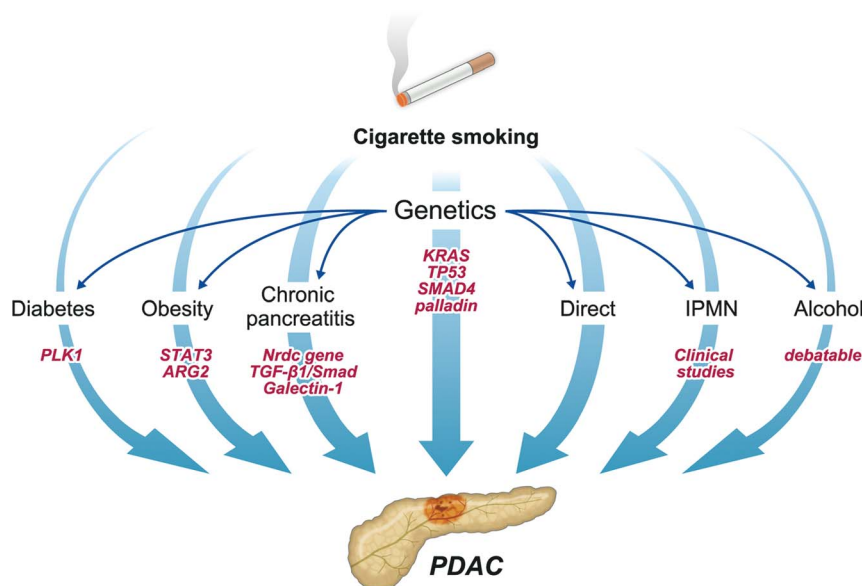


FIGURE 1. The diverse involvement of cigarette smoking in PDAC development and progression is illustrated in this diagram. Both the direct and indirect roles smoking plays in PDAC development are included. The direct affects are numerous, whereas the indirect affects occur through the modulation and/or activation of the various risk factors, namely, having a history of diabetes, IPMN, chronic pancreatitis, obesity, genetic mutations, and alcohol consumption. In addition, as illustrated, genetic factors (as effected by smoking) influence PDAC directly, as well as indirectly by modulating other risk factors.

TABLE 1. Clinical Studies Investigating the Relationship Between Cigarette Smoking and PDAC Prognosis

Studies	Study Type	No. Patients	Correlation to PDAC Prognosis
Olsen et al, 2010 ⁷⁵	Case control	475	No
Dandona et al, 2011 ⁷⁶	Retrospective study	355	No
Allison et al, 1998 ⁷⁷	Prospective cohort	96	Not statistically significant
Trichopoulos et al, 1990 ⁷⁸	Prospective study	44	Not statistically significant
Park et al, 2006 ⁷⁹	Prospective cohort	348	Not statistically significant
Yu et al, 1997 ⁸⁰	Hospital-based registry study	25,436	Statistically significant
Pelucchi et al, 2014 ⁸¹	Follow-up from 2 case controls	648	Statistically significant
Yuan et al, 2017 ¹¹	Follow-up from 2 prospective studies	1037	Statistically significant

typical scenarios.⁷⁵ Similarly, a retrospective analysis including 355 patients spanning 14 years by Dandona et al⁷⁶ concluded that cigarette smoking has no impact on PDAC patient survival after pancreaticoduodenectomy.

In a study looking at numerous prognostic factors for PDAC patients after resection, Allison et al⁷⁷ found an association between prognosis and cigarette smoking. Although not statistically significant, the authors demonstrated that smoking does indeed affect patient survival. In a similar vein, Trichopoulos et al⁷⁸ examining α 1-antitrypsin concluded a nonstatistical association between PDAC survival and smoking. A well-crafted prospective cohort of 348 Korean men by Park et al⁷⁹ demonstrated findings consistent with the above. Current smokers had a hazard ratio of 1.20 (95% confidence [CI], 0.84–1.72). In addition, they correlated smoking amount to prognosis as well.

Not surprisingly, cigarette smoking has also been shown to reduce survival in PDAC patients whom are diagnosed in advanced disease stages, namely, those whom have liver metastasis.⁸² A hospital-based registry study by Yu et al⁸⁰ was one of the first large studies showing a significant correlation between cigarette smoking and PDAC prognosis. In a follow-up study containing data of PDAC patients enrolled in 2 Italian case-control studies, Pelucchi et al⁸¹ established a strong correlation between smoking and PDAC prognosis. For persons who ever smoked, the hazard ratio was 1.37 (95% CI, 1.14–1.65), for ex-smokers, the hazard ratio was 1.30 (95% CI, 1.03–1.65), and for current smokers, the hazard ratio was 1.42 (95% CI, 1.16–1.73). Even more importantly, increasing amount of smoking was associated with reduced survival. The hazard ratios of death were 1.26 (95% CI, 1.02–1.55) for smoking up to 19 cigarettes per day and 1.57 (95% CI, 1.26–1.96) for 20 or more cigarettes smoked per day.⁸¹ Moreover, increasing duration of smoking was associated with reduced survival with hazard ratios of 1.24 (95% CI, 0.98–1.57) for duration of smoking less than 30 years and 1.49 (95% CI, 1.22–1.83) of 30 or more years, as compared with never smokers. In addition, short-term ex-smokers had a higher mortality than did long-term ex-smokers.⁸¹ These results give further support to the detrimental role of smoking on patient's survival after PDAC diagnosis. A more recent study by Yuan et al¹¹ examined more than 1000 patients from 2 large US prospective cohorts. While accounting for comorbid factors that smokers generally have, such as obesity, diabetes, and heart disease, there results maintained statistical significance. The multivariable-adjusted hazard ratio for death in current smokers was 1.37 (95% CI, 1.11–1.69) to that of never smokers.¹¹ A significant negative trend in survival was observed for increasing pack-years of smoking with a hazard ratio for death of 1.49 (95% CI, 1.05–2.10) for 60 pack-years, and the authors found that regardless of time since quitting, survival among former smokers was similar to that for never smokers.¹¹

Altogether, it conclusively seems that cigarette smoking plays an imperative role, in not only the etiology of PDAC but also its prognosis as well. Hence, groups at high risk for PDAC need to be educated continually to quit smoking not only to prevent cancer but also to improve survival rates. However, understanding how smoking effects the pancreas on a cellular level is of great importance as it can lead to a better mechanistic understanding for further prevention strategies for PDAC.

CIGARETTE SMOKING–MEDIATED MORPHOLOGICAL DAMAGE

Autopsy specimens have allowed us to gain a great wealth of knowledge regarding the distinct histopathological alterations pancreatic cells undergo as a result of cigarette smoking–induced insult to the pancreas.⁸ Pancreatic acinar cells, being the principal cells affected, were found to undergo marked hyperplasia and even dysplasia as a result of cigarette smoking.⁸³ Laboratory rats exposed to environmental tobacco smoke also developed acinar cell damage similar to what was found in humans.⁸⁴ Thus, it suggested that this may be a precursor lesion to acinar cell carcinoma.⁸ Nuclear atypia of both pancreatic ductal and acinar cells were seen secondary to cigarette smoking.⁸ The atypical nuclei demonstrated were different in shape, size, and staining character than normal pancreatic cells.⁸⁵ In a study examining the immunohistochemical effects of cigarette smoke on laboratory rats, the Langerhans islet cells showed a marked decrease in insulin expression, whereas the glucagon expression increased in the pancreas.⁸⁶ Hence, a possible diabetogenic effect of smoking can be observed by the increased glucagon-secreting cells and decreased insulin-secreting cells.⁸⁶ This is in line with the fact that chronic cigarette smokers when compared with nonsmokers are generally intolerant to glucose.⁸⁷

UNDERLYING MECHANISMS POSTULATING THE DIRECT IMPACT OF SMOKING ON PDAC

It is well established that exposure to cigarette smoke stimulates inflammatory cell infiltration including macrophages and mast cells leading to long-lasting fibrotic changes.⁶⁷ Hence, inflammation and fibrosis-mediated damage can explain how smoking induces morphological changes within the pancreas. Thus, cigarette smoking mediates enough damage on a cellular level to induce PDAC and alter pathways encouraging a harsher disease course. However, identifying the underlying mechanisms explaining how this occurs, to intervene at the appropriate pathological step therapeutically, is of critical importance.

A causal link between chronic inflammation and cancer has been well known. However, the exact molecular mechanism linking inflammation to cancer is unclear. Liu et al⁸⁸ posed that the *Src* family kinases are key players in this connection as they

have been demonstrated to be important in the activation of many cell types and also been shown to control production of cytokine tumor necrosis factor α in normal cells.^{89,90} Thus, an elevation and/or a dysregulation of the *Src* activity may play an integral role in the initiation of the invasive cell phenotype seen in precancerous cells.⁸⁸ The potent *Src*-mediated stimulatory effects on malignant cell proliferation as well as the ability to inhibit cellular death can potentially increase the total mass of the tumor leading to cancer progression.⁸⁸ Similarly, Wittel et al⁹¹ illustrated that exposure to cigarette smoke stimulated fibrosis and inflammation in the pancreas of rats.

Inflammation facilitates some of the important tenants of cancer cell survival. The inflammatory response acts via the production of inflammatory mediators, such as interleukin (IL)-6, IL-11, tumor necrosis factor α , and IL-1 α . These, as instructed by oncogenic *KRAS*, activate STAT3 and nuclear factor kappa B transcription factors to promote cell survival and proliferation, as well as invasion.²⁶ In addition, the surveillance immune system is suppressed by high inflammatory states.

The imbalance in protumor and antitumor immune cells as well as the absence of antitumor CD8⁺ killer T cells has been shown to promote PDAC development.²⁶ In addition, inflammation has been shown to inhibit oncogene-induced senescence which in mice was shown to accelerate carcinogenesis.²⁶ Elevated levels of inflammatory cells are closely associated with a stronger expression of vascular endothelial growth factor and basic fibroblast growth factor in human PDAC tissues compared with that of normal pancreatic tissues.⁶⁷⁻⁹² Collectively, these act as a key mediator in tumor angiogenesis. Moreover, inflammation promotes metastasis by stimulating the epithelial-mesenchymal transition that has been demonstrated to be a necessary precursor for tumor development.²⁶ Thus mechanistically, how carcinogenesis can be a by-product of inflammation secondary to cigarette smoke are elucidated.

The strong relationship between *KRAS* mutations and PDAC development begs explanation from a purely genetic perspective and is essential to understanding how carcinogenesis can be mediated via cigarette smoking.⁹³ Reactive oxygen species (ROS) is a potent detoxification molecule responsible for killing cells suspicious of harboring deficiencies or disease, and smokers have an increased propensity toward increased *KRAS* mutations and patients with *KRAS* mutations were found to have decreased levels of ROS.⁹³ With low levels of ROS, a permissive, proliferative, intracellular environment is established. This environment is one that has no stop to self-renewal and tumor cell growth.⁹³ Hence, based on the association by Kong et al,⁹³ it is conceivable how *KRAS* mutations secondary to smoking can directly contribute to PDAC initiation. As mentioned earlier, the formation of DNA adducts, transversions, and mutations as a result of the active metabolites present in cigarette smoke play a direct role in PDAC carcinogenesis.⁵

Pandol et al⁴ took the previously mentioned one step further that smoking acts in cooperation with activating *KRAS* to promote PDAC, based on the fact that treatment with 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone in *KRAS*-mutated mice resulted in advanced lesions that did not develop in control treated mice. These results indicate that smoking acts synergistically with *KRAS* to promote pancreatic carcinogenesis. Of note, the advanced lesions contained fibrotic stellate cells similar to human PDAC.⁹⁴

Cigarette smoke also plays a role in PDAC development by its ability to alter normal cellular signaling pathways. Cigarette smoke stimulates pancreatic cancer cell growth through adrenergic receptor activation of cyclooxygenase-2, intracellular cyclic adenosine monophosphate, as well as by stimulating extracellular

signal-regulated kinase phosphorylation in pancreatic ductal cells.⁹⁴⁻⁹⁶ Moreover, smoking compounds interact with pancreatic cells through nicotinic acetylcholine receptors (AChRs) such as through $\alpha 7$ AChR.^{4,97}

Cigarette smoking causes the aberrant expression of microRNA (miRNA) encoding genes, which in result effects protein synthesis.⁹⁸⁻¹⁰¹ Thus, their aberrant expression could lead to the initiation and progression of malignancies.^{101,102} Zhang et al¹⁰¹ identified a panel of aberrantly expressed miRNAs in pancreatic duct epithelial cells exposed to cigarette smoke. In particular, the *miR-25-3p* level was significantly higher in smokers than in nonsmokers and in PDAC than in nontumor tissues and elevated levels were correlated with shorter survival time of patients.¹⁰¹ Not surprisingly, this oncogenic *miR-25-3p* has been reported in various other types of human carcinoma.^{103,104}

There is an association between cigarette smoke exposure and the enzymatic levels of pancreatic cells illustrating that the alteration of enzyme levels may contribute to PDAC development and there was a ratio disturbance of trypsin, chymotrypsin, basal serum amylase, and pancreatic elastase expression in smokers.⁸ In addition, there was a decreased activity of pancreatic cell lysates in rats exposed to cigarette smoke.⁹¹

More recently, the direct effect cigarette smoke has on the microenvironment of tumor cells has become clear.¹⁰⁵ Pancreatic cancer cells have an environment characterized by an extremely dense desmoplasia that surrounds the cells of this tumor.^{45,105} The desmoplasia contains myofibroblastic pancreatic stellate cells, extracellular matrix proteins, numerous collagen subtypes, hyaluronic acid, and immune cells.^{45,105,106} These factors enable the growth of cancer by providing a scaffold of angiogenesis factors.¹⁰⁷ Evidence is emerging that there is a strong relationship between pancreatic cancer cells and stellate cells that results in rapid tumor growth and possibly metastasis.¹⁰⁷ Cigarette smoke activates the stellate cells leading to secretion of extracellular matrix proteins, growth factors, and cytokines.⁴ These then interact with integrins, which transactivate the insulin-like growth factor-1 receptor, which in turn mediates the intracellular events that promote cancer cell survival and growth.¹⁰⁸ In addition, they promote the survival of cancer cells through the activation of intracellular ROS-generating systems, which mediate prosurvival and proproliferative effects in cancer cells through their regulation of phosphatases and kinases.¹⁰⁹

Moreover, the immunomodulation of the microenvironment has shown to be a cause of PDAC as alluded to earlier. There is a restricted immune surveillance secondary to the high inflammatory levels created by the microenvironment.⁵⁵ In this environment, tumorigenesis is supported via paracrine cross talk between these immune cells and tumor cells.¹⁰⁹ This, by a process of immune cell recruitment, eventually leads to a block in T cell-mediated immunity.⁵⁵ Thus, the field of tumor immunology may be a potential therapeutic target to combat PDAC.

Taken collectively, smoking-induced PDAC occurs through an array of mechanisms (Fig. 2). Besides, cigarette smoking affects differently on pancreatic cells and on signaling pathways in PDAC growth as shown in Table 2. The combination of interfering with physiologic pathways, stimulating inflammation and fibrosis, as well as the powerful interactions cigarette smoke has with DNA, enables cigarette smoke to disrupt all the major pathways a normal cell needs to transition into a cancerous one, namely, self-sufficiency, limitless replication, evasion of apoptosis, sustained angiogenesis, invasion, and metastasis. By altering enzymatic secretion, morphologically damaging ductal as well as acinar cells, distorting the microenvironment, disarming the natural immune system, inducing high inflammatory states, and causing epigenetic alterations, in combination to the DNA changes

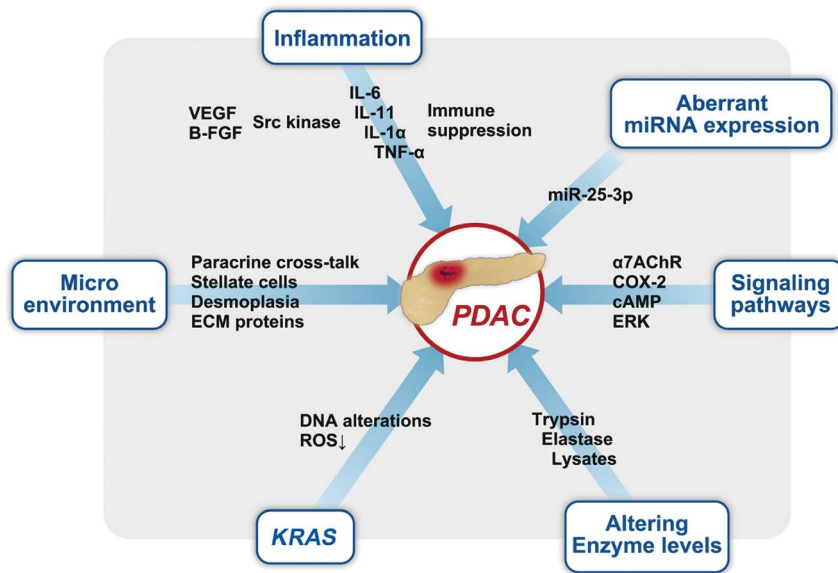


FIGURE 2. The summative mechanistic approach of cigarette smoking–induced PDAC is summarized in this diagram. It consists of the ability of cigarette smoke to change the microenvironment, cause long-standing inflammation, increase miRNA expression, induce *KRAS* mutations, affect signaling pathways, and alter enzyme secretion. Understanding the combined mechanistic pathway will yield positive outcomes in terms of drug discovery and reduced PDAC-related mortality.

seen, cigarette smoke is directly responsible for PDAC initiation and progression.

CONCLUSIONS

As PDAC continues to be a stealthy killer, because of it generally being diagnosed in its advanced stages, both primary and secondary methods of treatment are warranted. Although effective preventative screening methods are yet to be discovered, understanding the avoidable risk factors of its development will help lower the incidence of the disease. Hence, cigarette smoking, a major risk factor for PDAC, not only has both a direct and an indirect influence on PDACs etiology but also affects its prognosis.

Understanding this will hopefully aid in the promotion of cessation of smoking in patients across the globe and elucidating the mechanism of the disease will provide opportunities for the development of therapeutic strategies for PDAC patients. Furthermore, identifying key steps in the mechanism of smoking-induced disease will lead to a comprehensive understanding and potential treatments of all stages of PDAC development. As there still is a limited amount of research on the mechanistic pathogenesis of smoking-induced PDAC progression, further studies are still needed. Finally, as we are certainly getting closer to the crucial drug discovery to help prolong survival in patients with PDAC, the need of identifying the key steps in the mechanism, as laid out in this article, is essential.

TABLE 2. The Different Effects of Smoking on Cells and Pathways

Cells	DNA methylation (DNA adducts) Hyperplasia and dysplasia Acinar cell damage Nuclear atypia Inflammatory cell infiltration and fibrotic changes Alteration of enzyme levels Dense desmoplasia
Pathways	Adrenergic receptor activation of COX2 Intracellular cAMP ERK phosphorylation α7AChR miR-25-3p Activation of intracellular ROS-generating systems

cAMP indicates cyclic adenosine monophosphate; COX2, cyclooxygenase-2; ERK, extracellular signal-regulated kinase.

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