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Review

Molecular epidemiology and biology of pancreatic cancer among Iranian patients: an updated preliminary review

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Abstract: Pancreatic cancer is one of the deadliest cancers, with a very poor prognosis and survival. The incidence and mortality of pancreatic cancer are increasing among the Iranian population. Pancreatic cancer is a multifactorial disease, and various genetic and environmental factors are involved in its pathogenesis. Genetic changes and epigenetic alterations feature prominently in the development of this disease; nevertheless, it is still not well defined for the Iranian population. According to these, the early detection of tumors is needed to reduce mortality in pancreatic cancer patients. This review aims to summarize the current knowledge about pancreatic cancer by focusing on cellular and molecular processes which have been observed among Iranian patients to elucidate the molecular pathobiology of pancreatic cancer. It is reported that immunity and inflammation, apoptosis, oxidative DNA damage and the development of diabetes mellitus are the most common cellular mechanisms, associated with pancreatic cancer. Moreover, this review introduces different factors including epigenetic (miRNAs, long non-coding RNAs and DNA methylation patterns) and genetic factors (DNA polymorphisms) as well as environmental and chemical factors that can serve as potential diagnostic, prognostic and/or therapeutic biomarkers to manage pancreatic cancer patients in the Iranian population.

Keywords: Pancreatic cancer, Tumor biomarker, LncRNA, Risk factor, DNA methylation

Introduction

Cancer is one of the leading causes of death in the world and the third leading cause of death among the Iranian population [1]. Pancreatic cancer (PC) is the seventh deadliest cancer in men worldwide, with a five-year survival rate of less than 7% [2, 3]. Moreover, PC is one of the most common malignancies worldwide, with a poor prognosis. Reportedly, the incidence and mortality rate of PC in Iran, as in Western countries, are higher in males than in females [4]. Various studies demonstrate the increasing incidence rate and mortality of PC in different regions of Iran [5-7]. The incidence rate of PC is heterogeneous in overall Iran. The highest incidence rate of females is recorded in the provinces of North Khorasan (2.26%) and Chaharmahal

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and Bakhtiari (1.24%), while the highest incidence rate in males is detected in the Semnan (1.17%), Markazi (1.12%), Ilam (1.03%) and Kohkiloueh and Boyerahmad (1.01%) provinces [8]. Consanguineous marriage is common in many regions of Iran, especially in rural areas. This may lead to the accumulation of genetic defects that cause PC [8]. The reasons for high mortality rates in PC are not completely known yet; however, it may be due to a lack of appropriate diagnosis in the early stage of cancer. Early detection of PC is difficult because the pancreas is located in a relatively inaccessible area in the abdominal cavity, and patients rarely exhibit symptoms in the early stages, so most patients are not diagnosed until cancerous cells have spread to another organ [9]. Usually, a set of different tests, including blood test, medical imaging and examination of tissue samples, are used for PC diagnosis. Radiotherapy, chemotherapy and surgery are treatment options that are chosen according to the cancer stage. Because PC is highly resistant to chemotherapy and radiotherapy, the mortality rate of this tumor is essentially as high as its morbidity [10]. Therefore, to increase the survival of patients with PC, identifying people at high risk for this disease can have a significant effect on reducing the complications and mortality. There is no screening test, molecular test or reliable imaging technique to diagnose PC in asymptomatic individuals. In recent years, few studies have been performed on PC in Iran. Besides, the Iranian population has its own specific ethnicity. Hence, clinical research has focused on discovering novel diagnostic biomarkers for personalized cancer therapy [11]. It is necessary to develop new molecular diagnostic and screening methods based on the population for the early detection of PC. This study is a review of the molecular epidemiology and biology of PC, including cellular and molecular processes such as immunity and inflammation, apoptosis, oxidative DNA damage and the development of diabetes mellitus, as well as all the risk factors, such as environmental, genetic, epigenetic and chemical factors reported among Iranian patients so far (Figure 1, Table 1 and Table 2).

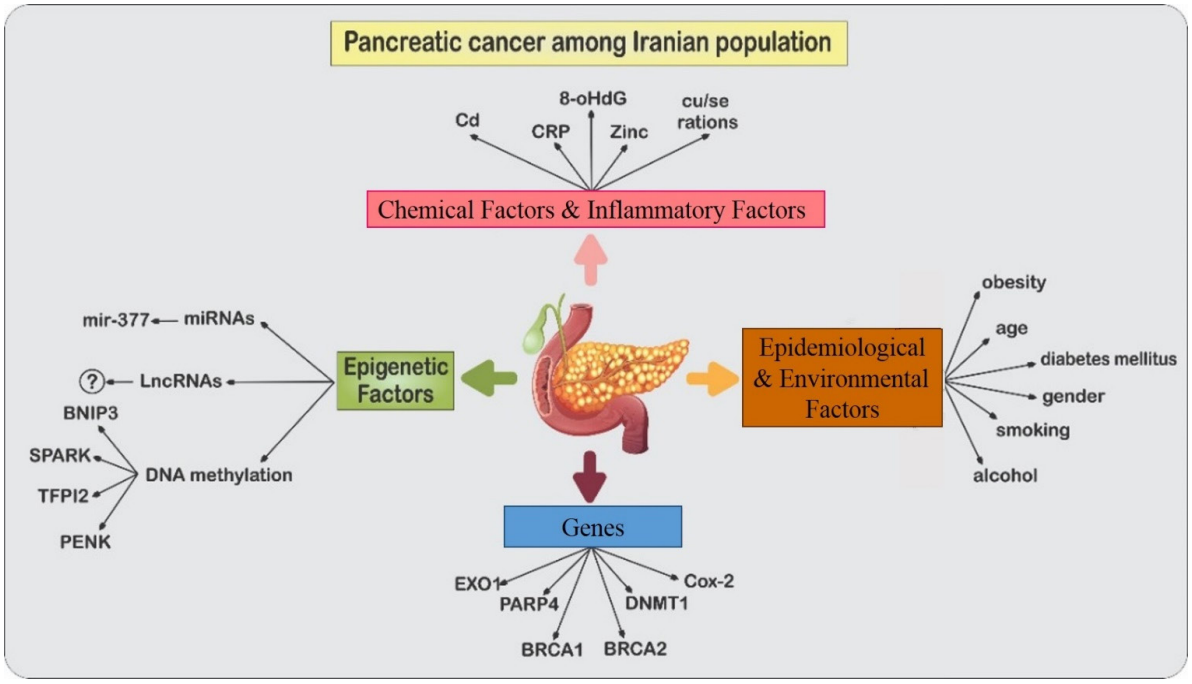

Figure 1. Different genetic, epigenetic, chemical and environmental factors involved in pancreatic cancer progression among Iranian cases. There is still no study on lncRNAs in pancreatic cancer in the Iranian population. 8-OHdG: 8-hydroxy-2'-deoxyguanosine, CRP: C-reactive protein, Zn: zinc, Cd: cadmium, Se: selenium, Cu: copper, Pb: lead.

Table 1. Risk Factors Which Are Associated With Pancreatic Cancer Among The Iranian Population

Risk Factor	Results	Cancer subtype	Number of clinical samples					References
			Total	Cases	Controls	Risk factor: N (%)		
						Cases	controls	
Smoking	The prevalence of smoking is 21.4%. The risk of PC increases with smoking.	PC	131	131	-	28 (21.4%)	-	[9]
Smoking	There is no association between smoking and PC risk.	PC	685	357	328	123(34.5%)	84 (25.6%)	[15]
Smoking	The risk of PC significantly increases with smoking.	PC	996	470	526	113 (24%)	90 (17%)	[14]
Opium use	Opium use is significantly associated with PC risk.	PC	54	54	-	17 (31.48%)	-	[16]
Opium use	The risk of PC significantly increases with opium use.	PC	996	470	526	75 (16%)	59 (11.2%)	[14]
Opium use	Opium use is significantly associated with an increased risk of PC.	PC	685	357	328	57 (16%)	21 (6.4%)	[15]
Alcohol consumption	Alcohol consumption is significantly associated with an increased risk of PC.	PC	685	357	328	39 (10.9%)	8 (2.4%)	[15]
Gender	The prevalence of PC is higher in men compared with women.	PC	131	131	-	80 males and 51 females	-	[9]
Gender	The prevalence of PC is higher in men compared with women.	Pancreatic adenocarcinoma	55	55	-	33 males and 22 females	-	[34]
Age	The incidence of PC increases steadily	PC	131	131	-	24-97 years (mean age: 63)	-	[9]
with age.	PC	131	131	-	24-97 years (mean age: 63)	-	[9]	[34]
Age	Age in operated patients is	PC	996	470	526	70 (14.9%)	47 (8.9%)	[14]
a prognostic factor.	Pancreatic adenocarcinoma	55	55	-	16-76 years (mean age: 57)	-	[34]	
Diabetes	T2D is associated with an increased risk of PC.	PC	996	470	526	70 (14.9%)	47 (8.9%)	[14]

Table 2. Molecular Factors Which Are Associated With Pancreatic Cancer Among The Iranian Population

Molecular Factor	Results	Cancer subtype	Number of clinical samples	Assessed cell line	Targets/ Regulators	Function	References
BRCA1/2	Two mutations in BRCA1 (c.301+1G > A), and BRCA2 (c.260_261delCT) were susceptibility mutations in PC patients.	Pancreatic adenocarcinoma	24 cases younger than 50 years (29-49 years, mean age: 43.9) including 12 male and 12 females	-	-	BRCA1/2 are involved in repairing damaged DNA.	[38]
PARP4	Mutation (c.3667-1G>A) was a potential candidate susceptibility factor for PC.	Pancreatic adenocarcinoma	24 cases younger than 50 years (29-49 years, mean age: 43.9) including 12 male and 12 females	-	-	PARP4 has a role in genome repair.	[38]
EXO1	Mutation (c.2212-1G>C) was a potential candidate susceptibility factor for PC.	Pancreatic adenocarcinoma	24 cases younger than 50 years (29-49 years, mean age: 43.9) including 12 male and 12 females	-	-	EXO1 is an Exonuclease 1, involved in DNA Mismatch Repair.	[38]
COX-2	There was a significant difference of intronic deletion c.724-10_724-7 (rs201231411) between PC cases and the control group.	PC	Blood samples from 96 PC patients and 96 healthy controls	-	-	COX-2 as an oncogene should be elevated for increasing cancer risk.	[54]
TP53	A higher frequency of R249 TP53 mutation in PC cases	PC	Blood samples from 133 PC patients and 85 healthy controls	-	-	The position of R249 residue is in the DNA-binding domain of p53 and is responsible for direct binding with Axin. p53 and Axin are tumor suppressors that regulate cell growth and apoptosis.	[53]
TGF-β1	There was no association between the rs1800469 and rs1800471 and PC risk.	PC	Blood samples from 78 PC patients and 94 healthy controls	-	-	-	[71]
TGF-β1	There was no association between the rs1800469 and rs1800471 and PC risk.	PC	blood samples from 78 PC patients and 94 healthy controls	-	-	-	[71]

miR-377	Decreased miR-377 levels in PC tissues in comparison with normal tissues	PC	PC tissues and adjacent normal tissues from 10 PC patients	MIA PaCa-2, PANC-1 and AsPC-1	DNMT1	The increased miR-377 expression can significantly suppress cell proliferation and promote apoptosis through DNMT1.	[96]
DNMT1	Increased DNMT1 levels in PC tissues in comparison with normal tissues	PC	PC tissues and adjacent normal tissues from 10 PC patients	MIA PaCa-2, PANC-1 and AsPC-1	-	DNMT1 controls tumor suppressor genes including SPARC, BNIP3, TFPI2 and PENK.	[96]
SPARC, BNIP3, TFPI2 and PENK	There was hypermethylation of these TSGs in PC tissues.	PC	PC tissues and adjacent normal tissues from 10 PC patients.	MIA PaCa-2, PANC-1 and AsPC-1	-	These genes are tumor suppressor genes.	[96]
CRP	Significant enhancement in PC patients	PC	Blood samples from 55 PC patients and 55 healthy controls	-	-	CRP is an inflammatory marker that is significantly increased in PC patients.	[52]
8-OHdG	Significant enhancement in PC patients	PC	55 PC patients and 55 healthy controls	-	-	There is a significant association between high 8-OHdG level and PC.	[52]
Zinc, cadmium	There was a significant difference in both Zn and Cd levels between the patient and control groups.	Pancreatic adenocarcinoma	Blood samples from 80 pancreatic adenocarcinoma patients and 100 healthy controls	-	-	Cd is an acceptable carcinogen in the pancreas. There is a significant association between Zn metabolism and PC.	[48]
Selenium, copper, lead	There was a non-significant difference in Se, Cu and Pb levels between PC cases and controls.	Pancreatic adenocarcinoma	Blood samples from 80 pancreatic adenocarcinoma patients and 100 healthy controls	-	-	-	[48]

Risk factors in PC

There are clear associations between PC and several risk factors including smoking, obesity, diabetes mellitus, alcohol, gender, age, PC family history, chronic pancreatitis and genetic factors [11]. The epidemiological correlation between cigarette smoking and the development of PC has been established, and cigarette smoking is recognized as an important risk factor for PC [11]. So far, there are a few research works about the correlation between cigarette smoking and PC development in the Iranian population. However, Hadizadeh et. al. (2014) found that the risk of PC increases with smoking in Iranian patients [9, 12]. Momayez Sanat et. al. reported a significant correlation between the increased risk of PC and smoking. They also found a remarkable association between opium use and the increased risk of PC in the Iranian population [13]. In contrast to Hadizadeh et. al. observation, Shakeri et. al. (2015) did not observe any association between cigarette smoking and the risk of PC in the Iranian population, but they found a significant relationship between opium use and PC risk [14]. Moreover, Moossavi et. al. (2018) have shown that contrary to cigarette smoking, opium use increases the risk of PC [15] (Table 1). In Iran, the rate of

smoking is lower than in Western countries, so the incidence of PC seems to be lower compared with that of Western countries [16].

Obesity carries a modest risk for PC, however, nowadays the rate of obesity prevalence is increasing rapidly. Several lines of evidence indicate that there is a positive correlation between obesity and PC [17]. Also, obesity increases the risk of diabetes, which is associated with an increased risk of PC [18, 19]. Obesity induces the adipocyte to secrete inflammatory cytokine and leptin, which increases the incidence of PC [17, 18]. Pourshams et. al. (2018) showed a strong association between PC and obesity in the Iranian population [20].

It is well known that type 2 diabetes mellitus (T2DM) is related to an increased risk of various cancers in humans. After smoking and obesity, T2DM is probably the third modifiable risk factor for PC [12]. Several lines of evidence demonstrate about 50-80% of PC patients with present diabetes or impaired glucose tolerance [21, 22]. However, the link between diabetes and PC is complex. It is elusive whether diabetes is a predisposing factor in PC or a consequence of tumor progression. Although the mechanism of the link between diabetes and PC is not yet known, metabolic, hormonal and immunological changes can affect tumor growth [12]. Insulin resistance, hyperinsulinemia and insulin-like growth factors (IGFs) are the most important mechanisms linking T2DM to PC [21, 23]. Insulin resistance results in hyperinsulinemia and inflammation that have a possible role in the development of diabetes-associated PC [12]. In addition, needy glycemic control is related to increased levels of advanced glycation end products (AGEs) which activate RAGE (receptor for AGEs). Subsequently, the activation of RAGE contributes to the development of obesity and probably a higher PC incidence in T2DM [24, 25]. The increase of PC incidence in the diabetic populations has been frequently observed in epidemiological studies [26, 27]. A study in Taiwan reports that diabetic patients are more than three times prone to PC compared to non-diabetics [28]. Momayez Sanat et. al. (2018) reported that long-term diabetes is associated with an increased risk of PC in the Iranian population. In addition, they found that diabetes has a great impact on the development of PC in Iranian women [13]. Pourshams et. al. (2018) observed a strong association between PC and long-term diabetes mellitus in the Iranian population [20]. They reported that a sudden change in blood glucose levels in diabetic patients with controlled diabetes can be a sign of PC [20]. A significant association between diabetes and PC is reported in Japanese population studies [29]. Moreover, a study in Korea confirms the significant relationship between PC and diabetes [30], but Engin et. al. (2012) did not find any association between diabetes and the risk of PC in the Turkish population [31].

Alcohol is another risk factor for pancreatitis, and some studies have shown an association between alcohol consumption and increased PC risk. Since alcohol consumption is outlawed in Iran, estimates of the relationship between alcohol consumption and the risk of PC are subject to several biases. Shakeri et. al. (2015) concluded that alcohol consumption is significantly associated with the increased PC risk among Iranian cases [14].

Gender is another risk factor for PC. Several lines of evidence identify that PC is more common in men than in women [11]. Hadizadeh et. al. (2014) showed that PC occurs slightly more in males compared to females with a ratio of 1.56 in the Iranian population, which is similar to the situation in Western regions, and also the fatality rate is higher in men than in women [9]. Ahmadloo et. al. (2010) reported that in Iran, the higher incidence of PC in males is probably related to higher occupational risk factors, smoking, alcohol consumption and other risk factors [32].

Age has been reported in many studies as another important risk factor in the etiology of pancreatic malignancies. In Iran, PC is more common in elderly people and rare in adults under 40 years of age. As in Western countries, the morbidity of the disease peaks between the ages of 60 and 80, but patients are relatively younger at diagnosis [9]. In addition, Hadizadeh et. al. (2014) indicated that the incidence of PC rises steadily with age in the Iranian population [9]. This finding is nearly identical to those of other Iranian studies [32]. This may be related to the high familial marriage rate in Iran, particularly in the rural regions that contribute to the accumulation of genetic defects in these young patients.

PC, similar to most other cancers, has a relatively high clinical heritability. Positive family history is one of the risk factors for PC, although it is not discussed in Iran. First-degree relatives of patients with PC are at higher risk of developing the disease [33]. Also, genetic variation or mutation (germ-line mutation) plays an important role in increasing the risk of PC [34]. About 5 to 10% of PC patients are genetically predisposition such as gene variations or alterations in disease progression, such as *BRCA1, BRCA2, MSH2, MSH6, PMS2, PALB2, ATM, MLH1, APC, EPCAM, PRSS1, SPINK1, STK11/LKB1, CDKN2A* and *CFTR* [35-38]. These changes are transmitted via an autosomal dominant model that leads to familial clustering [39]. *BRCA1/2* genes are among the most common genes susceptible to mutated PC that should be considered in all cases with early-onset and in patients with a positive family history of cancer. Alimirzaie et. al. (2018) also confirmed the importance of *BRCA1* and *BRCA2* in Iranian patients with early onset PC [36] (Table 2). *KRAS, CDKN2A (p16), p53* and *SMAD4* are the main genetic mutations that play a specific role in increasing the risk of PC [35, 37]. Also, it is found that PC has been linked to several familial cancer syndromes such as Peutz-Jeghers syndrome, Lynch syndrome, familial atypical multiple mole melanoma (FAMMM) syndrome, familial adenomatous polyposis, hereditary breast-ovary cancer syndrome, hereditary non-polyposis colon cancer, Li-Fraumeni syndrome, and hereditary pancreatitis [40].

Prolonged inflammation of the pancreas causes chronic

pancreatitis, which is ultimately associated with increased PC risk. Zambirinis (2015) reported that the risk of PC in patients with chronic pancreatitis is 13-fold higher. Chronic pancreatitis is often observed in smokers and people who use heavy alcohol, and both of them are well-known risk factors for PC [41].

Other risk factors listed in global literature include high levels of HbA1c (hemoglobin A1c), hyperglycemia, hyperinsulinemia, the blood group, HCV and HBV infection and low physical activity. Moreover, trace elements can influence the incidence of PC [42-45]. However, there is no information on these risk factors in the Iranian population.

Immunity and inflammation in PC

The immune system including cell-mediated immunity, immunoglobulins, phagocytosis complement, interferon, lysosomes, hormones, metabolic function, respiratory and metabolic alkalosis defends against cancer naturally. Inflammation is closely related to immunity, and the same population of immune cells involved in inflammation is also partaking in the immune response [46]. Inflammatory cells, which control inflammation and increase the risk of cancer, also control the immune response against emerging cancer cells. In the case of PC, inflammation acts as both a risk factor and a cancer consequence [47]. A large amount of evidence suggests that inflammatory processes, cytokines and oxidative stress have a key role in PC progression [48]. Inflammatory conditions, such as chronic pancreatitis, diabetes, obesity and metabolic syndrome, also enhance the risk of PC[47]. As mentioned earlier, patients with acute or recurrent non-familial pancreatitis are at high risk of cancer. Physical and biochemical factors such as glucose and lipid intake, and macronutrients stimulate inflammation by increasing oxidative stress and activating transcription factors, which in turn induce inflammation [14]. C-reactive protein (CRP) is one of the mediators of inflammation and is mainly increased in PC patients. Patients with a high level of serum CRP have a higher distant metastasis that affects the treatment process [49]. Mohamadkhani et. al. (2017) observed a significantly increased level of CRP as an inflammatory marker in Iranian patients with PC [50]. Some evidence suggests that genetic alterations which result in increased inflammatory response and chronic inflammation can potentially elevate the risk of cancer [51, 52]. Cyclooxygenase-2 (COX-2) is a pro-inflammatory protein that often activates inflammation. Several studies report that an increased level of this enzyme is associated with the short survival of patients with PC [53]. Mohamadkhani et. al. (2015) reported a borderline significant difference of intronic deletion c.724- 10_724-7 (rs201231411) in COX-2 in Iranian PC cases compared with the control group, but their investigation did not show that this deletion causes any change in COX-2 protein expression [52]. COX-2 activates anti-apoptosis pathways and induces the expressions of several positive regulators of the cell cycle. It is reported that KRAS mutation is one of the earliest genetic changes in PC patients [40]. There appears to be a synergistic relationship between Kras activation and inflammation. For example, several studies indicate the positive correlation between the duration of pancreatitis and Kras mutations, which suggests a possible mutagenic role for repetitive bouts of inflammation [53]. In addition, Ling et. al. (2012) showed that mutant Kras increases IL-1α production from pancreatic tumor tissues, which in turn activates the NF-κB pathway and subsequently produces more IL-1α and p62 activation, and ultimately increases tumorigenesis and liver metastasis [54]. Altered levels or functions of cytokines such as IL-1, IL-6, IL-10 and several other cytokines contribute to PC progression by impairing immune function. For instance, Tjomsland et. al. (2011) found that PC subjects who express a higher level of IL-1α have a shorter survival than the patient group expressing the lowest levels [55]. Multiple in-vitro studies confirm the role of IL-1 in increasing tumor cell growth, invasion, migration, chemoresistance and the induction of angiogenesis [56, 57].

Numerous clinical studies prove the association of IL-10 with PC. The up-regulation of IL-10 level in the tissues and serum of PC patients is observed in several studies. A strong positive correlation is found between the up-regulation of IL-10 level and poor differentiation status and tumor stage [58-60]. Previous studies indicate the strongest association between high serum level of IL-6 and PC [58, 61]. Increased expression of IL-6 in the serum, pancreatic juice and tissues of pancreatic ductal adenocarcinoma (PDAC) patients represents a potential role of this cytokine as a predictor of malignancy in predicting tumor stage and survival [62]. In addition, Du et. al. (2015) reported the association of IL-6 gene polymorphisms with PC [63].

Apoptosis and metastasis in PC

Disruption of some cellular and molecular mechanisms, such as apoptotic deregulation, affects cancer cell survival, sensitivity to radiotherapy and chemotherapy and tumor development [64]. Apoptosis is a focal regulator of tissue homeostasis that plays a key role in both carcinogenesis and cancer treatment [64]. The main cause of high mortality rate in PC patients is delayed onset of symptoms, difficulty in diagnosis and consequently late diagnosis. Most patients with PC are diagnosed in the metastasis stage with a low chance of treatment options. Metastasis plays a crucial role in cancer progression that indicates a more advanced stage and a poorer prognosis. Apoptosis serves as an essential process for inhibiting metastasis, and thus, malignant tumor cells must disrupt the apoptosis to metastasize via generating genetic mutations or epigenetic modifications in key regulators of apoptosis. Notably, alterations in the expressions and mutations of apoptotic genes have been found in PC advancement [65].

TP53, as a major tumor suppressor gene, inhibits the regulation of cell cycle arrest and apoptosis and is mutated in most tumors. The mutation or deregulation of *p53* has

been shown in PC patients [66]. Mohammadkhani et. al. (2013) demonstrated the frequency of R249 mutation in *p53* gene in Iranian patients with PC. They also reported that cancer development in the exposure to carcinogens is faster in patients with a deficiency in one allele of *p53* gene [51, 67]. TGF-β is a multifunctional cytokine that is involved in growth inhibition and apoptosis induction. So far, several studies have demonstrated the strong association between *TGF-β1* variations and cancer susceptibility. Mutations and changes in the expression of *TGF-β* are observed in PC tissues [68]. Nonetheless, Farahbakhsh et. al. (2017) reported no association between two *TGF-β1* gene polymorphisms rs1800469 and rs1800471 and PC in the Iranian population [69]. Moreover, SMAD is a tumor suppressor in the TGF-β signaling pathway, and several mutations in this gene have been shown in PC patients [70]. Bak is a pro-apoptotic protein from the Bcl-2 family. Recent studies have demonstrated a higher expression of Bak in chronic inflammation regions surrounding cancer cells compared to tumor cells that can facilitate tumor growth and metastasis [71].

The pancreatic tumor usually is usually resistant to most oncology therapies because tumor cells evolve various strategies to escape apoptosis. Therefore, apoptosis is regarded as a novel treatment strategy for tumor cells. Recently, many studies have been performed on the treatment of PC using programmed cell death [64]. Piri et. al. (2012) showed that the injection of IL-25 gene in mesenchymal stem cells (MSCs) of a mouse model of PC can bind to IL-25 receptor and induce apoptosis via the activation of apoptotic mediators, including tumor necrosis factor receptor-associated factor (TRAF6), caspases 8 and 3. Due to IL-25 receptor expression in the surface of tumor cells, but not the normal cells, cytokine IL-25 only attacks the cancer cells and activates apoptotic pathways. They suggested that the use of IL-25 immunogenic therapy could lead to the novel PC treatment although it needs clinical trial and following human outcome [72]. Roshanravan et. al. (2018) introduced *Eryngium billardieri* as a promising approach for PC treatment. E. *billardieri* is an Iranian medicinal plant, and its anti-hyperglycemic and anti-inflammatory effects have been proved. The results of this study show that E. *billardieri* significantly induces apoptosis in cells treated with PANC-1 by increasing Bax expression and decreasing cyclin D1 expression [73].

Oxidative DNA Damage in PC

Reactive oxygen species (ROS) are continuously made in mitochondria via the cell breathing process and play an important role in various cellular biological activities, including growth, proliferation, invasion and apoptosis [50, 74]. ROS acts in two ways in PC, which can both facilitate cell survival and cancer development and trigger programmed cell death via the release of cytochrome into the cytoplasm [74]. Oxidative stress damage DNA results in a variety of mutations and affects the DNA damage response (DDR) which promotes cancer. In addition, DNA damage induces systemic stress and triggers innate immune responses that promote inflammation [75]. Also, oncogenes increase ROS production and induce DNA damage and cancer progression. It is a well-known fact that accumulated DNA oxidative damage causes genomic instability [76] and eventually results in cancer. 8-Hydroxy-2′-deoxyguanosine (8-OHdG) is one of the well-known types of oxidative damage that is widely used as a biomarker of oxidative stress because of its reliable detectability [50]. The mismatch repair system is the principal mechanism that protects the reliability of human DNA in the subject of 8-OHdG through 8-oxoguanine DNA glycosylase (hOGG1) [48]. Mohamadkhani et. al. (2017) demonstrated the increased amount of leukocyte 8-OHdG adducts in Iranian PC subjects. They also observed higher CRP levels in PC patients than healthy individuals. Hence, they suggested that DNA oxidative stress and inflammation are increased in patients with PC [50]. Furthermore, several investigations identify several mutations in DNA repair system genes, including ATM, BRCA2, PALB2, FANCG and FANCC in chronic pancreatitis and PC. Moreover, BRCA2 is a tumor suppressor involved in DNA break repair during homologous recombination (HR) [77]. Poly adenosine diphosphate [ADP] ribose polymerase (PARP) enzymes play a key role in responding to DNA damage and maintaining genomic stability. Alimirzaie et. al. (2018) demonstrated that PARP4 could be a potential candidate susceptibility gene for PC in the Iranian population [36] (Table 2).

ATM is a serine/threonine kinase involved in the DNA repair system, and its impairment is pathogenic which results in DNA repair failure. Notably, germline mutations of ATM are found in families with hereditary PC since ATM mutations play a key role in the familial PC predisposition [78]. Exonuclease 1(EXO1) contributes to multiple DNA repair pathways, such as mismatch repair (MMR), and its impairment can lead to breast, ovary and gastrointestinal cancers, as well as PC [79]. Alimirzaie et. al. (2018) showed that EXO1 mutations can potentially contribute to tumorigenesis in the pancreas and exacerbate the overall survival of Iranian PC patients [36] (Table 2).

Taken together, the DNA repair system has a crucial role in the maintenance of genomic integrity and stability, so genetic variations in DNA repair genes are related to the risk of PC.

Non-coding RNAs in PC

Non-coding RNAs (ncRNAs) are RNA molecules that do not typically encode proteins and play an important role in several pathological and physiological situations, such as cancer [80]. It has recently been shown that ncRNAs, generally including long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), are down-regulated in many cancers. miRNAs are short, approximately 22 (18-25) nucleotides that can act as major regulators of the gene,

and involved in a variety of cellular pathways in normal cells and the expansion of cancer [81]. Also, miRNAs can be both oncogenic and tumor-suppressing molecules [82, 83]. In addition to miRNAs, lncRNAs are the largest portion of the mammalian non-coding transcriptome which are longer than 200 nucleotides. Many studies confirm the critical roles of lncRNAs in epigenetic and transcriptional regulation, the small RNAs processing and other regulatory functions. Recent studies suggest that ncRNAs play a key role in PC expansion via the regulation of gene expression at the chromatin, transcriptional or post-transcriptional level. Altered expressions of particular microRNAs in PC have diagnostic and prognostic consequences [83, 84]. Emerging data demonstrate the important roles of miR-486-5p and miR-938 in distinguishing PC patients from healthy and chronic pancreatitis individuals [85]. Previous reports show that miR-96 overexpression prevents cell proliferation, migration and invasion via NUAK1 and KRAS down-regulation [86, 87]. Moreover, Cioffi M, et. al. (2015) observed that the enforced expression of miR-17-92 increases chemoresistance and inhibits tumorigenicity in PDAC stem cells through the TGF-β1 pathway [88]. Microarray analysis of miRNA expression profiles in tissue samples from healthy individuals and patients with PDAC and chronic pancreatitis reveals that miR-96 and miR-29c have different expressions in both PDAC and chronic pancreatitis samples while miR-196s, miR-203 and miR-210 expressions are changed just in PDAC tissues [89]. Moreover, Calatayud D, et. al. found that the expressions of miR-21-5p, miR-31-5p, miR-622, miR-203, miR-23a-3p, miR-222-3p, miR-135b-3p, miR-miR-492, miR-186-5p, miR-196b-5p, miR-34c-5p, miR-205-5p, miR-210, miR-93-3p, miR-451, miR-614 and 155-5p are significantly increased in PC tissues compared to normal tissues or tissues from patients with chronic pancreatitis. They also found the down-regulation of miR-375, miR-130b-3p, miR-217, miR-216b and miR-122-5p in those samples [90]. Moreover, they reported miR-196b and miR-217 as new diagnostic markers to distinguish PC patients from healthy subjects and also patients with chronic pancreatitis [90, 91]. In addition, other studies show that miR-18a and miR-21 are up-regulated while miR-146a is down-regulated in the plasma of PC patients compared with healthy subjects [91].

Furthermore, Sun et. al. (2015) found that down-regulation of miR-615-5p can prevent proliferation, migration and invasion of PC cell lines by targeting AKT2. They also observed that miR-615-5p expression in PDAC is much less than that in adjacent normal tissues [92]. In another study, Azizi et. al. (2014) showed that miR-148b and miR-152 can target DNA methyltransferase1 (DNMT1) and decrease the methylation of DNA upstream of tumor suppressor genes(TSGs) in PC cell lines [93]. They also found that the expression of DNMT1 is repressed after the restoration of miR-377 expression in the PC cells. They demonstrated that overexpression of miR-377 inhibits the expression of DNMT1 at the transcriptional level in PC cell lines. Also, they observed a negative correlation between miR-377 and DNMT1 expressions in PC tissues and cells, which means that the down-regulation of miR-377 expression results in an up-regulation of DNMT1 expression. Moreover, miR-377 leads to the reactivation of some TSGs such as BNIP3 and SPARC via promoter DNA hypomethylation through DNMT1 down-regulation. Finally, they suggested that miR-377 may act as a tumor suppressor gene [94]. All of these results indicate the important roles of miRNAs in PC progression. In addition, the impaired regulation of various lncRNAs has been found to contribute to PC initiation and progression. For example, lncRNA XIST can increase PC cell growth by interacting with miR-133a [95]. In addition, Shi et. al. (2019) showed that LINC00346 is overexpressed in PC [96]. In another study, loci harboring intronic lncRNAs (PPP3CB, MAP3K1 and DAP K1 loci) are identified. These loci are differentially expressed in PDAC metastasis and are enriched in genes related to the MAPK pathway [97]. Yang et. al. (2017) found that HOTAIR in PC tissues has a higher expression level than that in adjacent non-cancerous pancreatic tissues. In addition, they observed that the decreased expression of the lncRNA HOTAIR can alter cell cycle progression and apoptosis induction. Moreover, they found that HOTAIR is a negative prognostic factor for PC patients [98]. Li et. al. (2015) showed the significant up-regulation of HOTTIP expression in PC tissues and cell lines compared with non-cancerous and non-tumor pancreatic cell lines [99]. In several studies, the up-regulation of MALAT-1 expression is observed in PC tissues and cell lines [100, 101]. Besides, according to JIAO et. al. (2014) investigation, overexpression of MALAT-1 is associated with clinically advanced tumor stage, poor survival, positive lymph node and distant metastasis[102]. In another study, the expression of PVT1 is much higher in PC tissues than in normal tissues, and PVT1 expression level is positively correlated with the poor survival of patients [103]. Sun et. al. (2014) showed that the expression level of ENST00000480739 is significantly lower in PC tissues than adjacent normal tissues and is inversely correlated with the stage of tumor node metastasis and lymph node metastasis. Also, ENST0000048073 is associated with patients' poor survival following surgery [104].

DNA methylation in PC

Increased information on the disease's molecular pathogenesis has shown that genetic changes, such as *Kras* and *BRAF* mutations and suppressor gene mutations, include *p16, p53, SMAD4, BRCA2, STK11, hMLH1, hCDC4, MKK4* and *FancC*, and especially the epigenetic dysregulation of tumor-associated genes play a key role in PC progression [105-107].

Aberrant patterns of DNA methylation affect the regulation of genome stability and gene transcription. DNA methylation regulates numerous genes and signaling targets in PC. DNA methylation at cytosine-phosphate-

guanine (CpG) island sites can be used to assess PC risk, progression and therapeutic responses that are more sensitive and informative than individual DNA mutations[106]. DNA methylation in CpG islands suppresses the expressions of various genes especially TSGs including SPARC, BNIP3, TFPI2 and PENK in Iranian PC patients [94]. The expressions of several genes are down-regulated by this mechanism in PC. For example, *CDKN2A/p16, TP53* and *SMAD4/DPC4* are inactivated in PC. *CDKN2A/p16* and *TP53* play key roles in controlling and arresting the cell cycle while *SMAD4/DPC4* is involved in the signal transduction of the TGF-β pathway and cellular proliferation [108]. In addition, several studies report that a group of genes are seldom methylated in the non-neoplastic pancreas and are aberrantly methylated and silenced in human PC tissues, including *ppENK, SPARC, TFPI2, FOXE1, NPTX2, p14, p57* and *Cyclin D2* [107, 108]. Also, several miRNAs are inactivated by aberrant CpG methylation in PDAC. For instance, Zhang et. al. (2011) showed that the methylation of the miR-132 promoter reduces the expression of miR-132 in PC tissues by impairing the binding of essential transcription factors (TFs) [109]. Wang et. al. (2014) found that the promoters of the miR-124 family members are highly methylated in PC tissues compared to normal tissues [110]. Also, it is found that miR-107 and miR-148a expressions are down-regulated in PC due to hypermethylation in the promoter region [111, 112]. Moreover, the miR-34 family is inactivated by aberrant CpG methylation in PDAC [113].

Azizi, et. al. (2017) showed that miR-377 reduces the DNA methylation of some tumor suppressor genes by targeting DNMT1, resulting in the restoration of TSG expression in PC cells and the reduction of *DNMT1* expression as well. Previous reports demonstrate reduced miR-377 expression and enhanced *DNMT1* expression in PC tissues and cell lines compared to non-cancerous tissues [94].

Furthermore, hypomethylation can dysregulate cell proliferation, cycle progression and adhesion. Several studies show that hypomethylation and high ectopic expression of a gene indicate an epigenetic trait in PC [108, 114]. Sato et. al. (2003) showed hypomethylation and consequent overexpression of seven genes, including *CLDN4, LCN2, MSLN, PSCA, S100A4, SFN* and *TFF2*, in PC compared to the normal pancreatic tissues[115]. However, the literature review shows that there are currently no studies on the role of DNA methylation in PC among Iranian patients.

Chemical elements in PC

Trace elements (TEs) have a crucial function in human safety and diseases[46]. Many studies confirm the link between TEs and cancer. Some of them are known as possible risk factors for cancer, and others appear to protect against cancer. Several TEs, such as zinc (Zn), selenium (Se), copper (Cu) and cadmium (Cd), have an important role in many biochemical processes including DNA and RNA production, cellular respiration, cellular oxygen utilization, maintenance of cell membrane integrity and free radical scavenging [46]. Cd is known as a carcinogen that contributes to carcinogenicity by increasing oxidative stress. Many studies show the high level of Cd associated with various physiological impairments in humans [46]. For example, Cd can cause the transdifferentiation of PC, increase the synthesis of pancreatic DNA and regulate the expressions of oncogenes that are implicated in pancreatic carcinogenesis [116]. Farzin et. al. (2013) observed a significant increase in blood Cd in Iranian cases with PC compared to controls. They reported that a higher level of the Cd could increase the risk of PC. They also observed that Cd level in the blood of the PC and control groups is much higher in smokers than in non-smokers [46]. A significant relationship between Cd exposure and PC has also been reported [46]. Se is one of the most extensively studied TEs involved in many biological processes. Se supplementation can decrease the morbidity and mortality of various cancers[117]. The results of a study in Iran show a non-significant difference in serum Se level among 80 PC patients and 100 healthy participants. High Cu/Se ratios may increase the risk of PC development and/or progression [46]. According to Amaral et al. (2012), those with diets rich in mineral Se have a lower incidence of PC [117].

Lener et. al. (2016) observed that the Se level is higher in healthy subjects than in patients with PC and those with chronic pancreatitis in the Polish population. Also, patients with chronic pancreatitis have higher serum Se levels than patients with PC [118]. Se has an effect on p53 activation, apoptosis and DNA repair. Se also appears to be an antagonist of arsenic, cadmium and lead, reducing the oxidative stress generated by their exposure [119]. Abnormal expression patterns of some selenoproteins indicate that they act to reduce the effects of excessive ROS and decrease oxidative damage involved in PC pathogenesis [117]. Zn is an essential micronutrient that regulates cell division and proliferation in several ways. High amounts of Zn are toxic to cells; therefore, a complex system has been developed to maintain the balance of Zn uptake, intracellular storage and flow in cells [46]. They observed that the Zn level is lower in Iranian patients with PC compared to controls, and notably, they observed a significant decrease in female patients compared to males. They also noted the association between zinc metabolism and PC [46]. Cu is another important micronutrient that is associated with ROS production. In cancer and inflammation, plasma Cu and ceruloplasmin concentrations increase, so the liver increases the synthesis and secretion of ceruloplasmin, which provides extra Cu uptake by normal tissues cells as well as cancer cells. Also, transcuprein (Cu-binding protein) increases in malignancy. Therefore, high level of Cu in tumor cells has been observed and suggests that serum Cu level is required for pancreatic disease

progression. Several studies observe that patients with PC have the highest serum Cu level [118]. However, in the Iranian population, a non-significant difference in serum Cu level between healthy individuals and PC patients is observed [46]. Similarly, Amaral et. al. (2012) reported the relation of higher levels of lead and arsenic with an increased risk of PC, as well as the inverse correlation with higher levels of nickel and selenium[117].

Conclusion and perspective

In this study, we have reviewed published articles with information on PC in the Iranian population. We have provided an overview of epidemiology and also have studied the role of genetic and epigenetic factors in the development of PC. Literature review in the Iranian population illustrates that the incidence of PC increases with age, and it is higher in males than in females. Smoking, alcohol consumption, obesity, diabetes mellitus and genetic factor are the most relevant risk factors of PC in the Iranian population. Genetics plays a key role in the progression of PC although the genetic basis of this cancer is still widely unknown in the Iranian population.

PC is rarely diagnosed in the early stages when it is more treatable. This is because it often does not cause symptoms until it spreads to other organs, though there are several studies of predictive and prognostic molecular biomarkers including SMAD4, MUC1, SPARC, HuR and BRCA2 family [122-125]. In Iran, due to the lack of early signs or specific predictive biomarkers for the early diagnosis of PC, this cancer is detected late, and therefore the survival rate is low among patients with this cancer. In addition, little is known about the current status of various treatments for PC in Iran. However, epigenetic and genetic factors including DNA polymorphisms, mRNAs, miRNAs, lncRNAs and DNA methylation patterns can introduce a set of biomarkers that can act as potential diagnostic, prognostic and/or therapeutic biomarkers to manage patients with PC.

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Author contributions

Z.A.K. wrote the manuscript and revised it. Z.S.F. designed the study and supervised it. Z.R. and M.S. collected the data and designed the figures and the tables. All authors read and approved the manuscript.

Disclosure

The authors have no relevant financial or non-financial interests to disclose.

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