Exploring Risk Factors in PDAC Using System Dynamics

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***Abstract*—Pancreatic ductal adenocarcinoma (PDAC) is a lethal gastrointestinal cancer prevalent in developing countries with a low survival rate. Early detection remains challenging despite medical advancements. The exact causes of PDAC are unknown; however, genetic, environmental, and lifestyle factors are believed to contribute to this cancer. Modifiable and non-modifiable risk factors like smoking, obesity, gender, and age play a role in PDAC development. System dynamics is utilized to build causal loops, unraveling complex interactions between these factors. Further research is necessary to uncover additional modifiable causes of PDAC. Public health campaigns are essential to raising awareness, and educate about PDAC risks, and promoting preventive measures to reduce mortality and morbidity associated with the disease.**

***Index Terms*—pancreatic ductal adenocarcinoma, survival rates, risk factors, system dynamics, early detection.**

I. Introduction

Pancreatic cancer is the term used to describe pancreatic ductal adenocarcinoma and its related variations, which make up between 85 and 90% of all pancreatic neoplasms [1]. Pancreatic cancer (PC) is the fourteenth most prevalent cancer among people globally [2]. There were 495,773 new PC cases in 2020, and 466,003 cancer deaths worldwide, or 2.6% of new cancer cases [2]. By 2025, it is estimated that there will be 11.2 million cancer-related deaths annually, as well as 22 million new cases of cancer [3]. In the United States, there were reportedly 95,389 persons living with pancreatic cancer in 2020 [4]. Moreover, 64,050 or 3.3% are estimated to have new cases, and 50,550 or 8.3% were estimated to have deaths in 2023 [4]. PC is the third most common cause of cancer-related mortality, with a 5-year survival rate of only 10% [5].

There are modifiable and non-modifiable risk factors for pancreatic cancer; the specific cause of the disease is unknown. Non-modifiable risk factors are age, gender, ethnicity, ABO blood, age, family history, and genetic susceptibility. In contrast, smoking, alcohol consumption, dietary factors, chronic pancreatitis, obesity, chronic infection, diabetes, and socioeconomic status are all modifiable risk factors [6]. There are several individual and environmental factors associated with pancreatic carcinogenesis. The most significant recognized environmental risk factor for pancreatic cancer worldwide is cigarette smoking [7]. At least 20% of cases of pancreatic cancer are caused by smoking, making it one of the most significant environmental risk factors for the disease [8]. Given the low survival rate of PDAC, it is critical to determine its underlying causes or risk factors to create effective preventive measures as shown in in Fig. 1. Moreover, identifying high-risk people for pancreatic cancer screening could also be aided by knowing the risk factors, improving the likelihood of an early diagnosis. Furthermore, the five-year survival rate for pancreatic cancer can increase to more than 75% when the tumor is found and removed when it is less than 10 mm in size [9].

As the complexity that underlies environmental health issues and their management becomes more widely acknowledged, so does the requirement for competent ecological health policy and decision-making that considers this complexity [10]. In the late 1950s, Jay Forrester invented the problem-oriented modeling technique known as system dynamics modeling to aid business managers in understanding industrial issues [11]. System dynamics, which attempts to understand system behavior, includes causal mapping and the development of computer simulations [10]. Ever since, its application has grown to encompass fields including ecology and economics, healthcare systems [12]–[16], food industry [17], military [18], and climate dynamics [19]. Policy and scenario possibilities are assessed to answer the ”what-if” scenario [10]. In this decision-experimentation learning setting, policymakers better understand how the system will respond to their actions and the potential unintended consequences of policies. Before putting their decisions into action in the real world, policymakers can test them [10].

Traditional approaches to problem-solving usually include disassembling complex issues into their constituent elements and looking at each independently. System dynamics is based on the hypothesis that problems arise due to interactions, feedback loops, and delays in the flow of materials and information among the system's parts. To avoid focusing on individual pieces in isolation, system dynamics instead emphasizes the interactions between the parts [20]. System dynamics also heavily relies on the idea of endogeneity, which refers to the notion that system behavior should be explained

by understanding the internal structure of a system rather than by focusing on things outside of the system [21].

This paper presents a systems dynamics model by introducing a causal model to discover the complex interactions between the risk factors in PDAC development.

II. Methodology

A system dynamics model is employed to analyze the root causes of pancreatic cancer by creating a causal loop that illustrates the complex interplay of the various risk factors for this disease. Since the 1970s, population health issues have been studied using system dynamics modeling. Various subject areas have been covered such as epidemiology of diseases, including research on heart disease [22] and diabetes [23]. Another subject area covered is epidemiology of substance abuse, including statistics on heroin addiction [24] and tobacco control measures [25]. System dynamics modeling has also been used in fields like dental care [26] and mental health [27], as well as in places devastated by natural disasters or terrorist acts [28].

Causal models are used in support of system dynamics in a complex system. Risk factors in the PDAC development create a complex environment with the various interrelations between these factors. Causal models are able to graphically illustrate factors and their relationships in a system as causal links. They have accompanying signs on these links that indicate an increasing (+) or decreasing (-) relationship. Advancing age is a significant risk factor for pancreatic cancer. The risk increases substantially after the of 50, and most cases are diagnosed in individuals over the age of 65 [29]. The causal model also shows a positive relationship from the age factor the pancreatic cancer factor on Fig. 1. Those with short-term diabetes were at a higher risk of developing pancreatic cancer than those with long-term diabetes, according to risk estimations. Two theories could account for the inverse relationship between the length of diabetes and the risk of pancreatic cancer. Firstly, reverse causality was predominantly responsible for the higher risk of pancreatic cancer in patients with short diabetes duration (2 years). A positive relationship can be seen from the diabetes factor to the pancreatic cancer on Fig. 1. Secondly, lifestyle modifications following a diabetes diagnosis or using specific anti-diabetic drugs may have played a role in reducing the risk of pancreatic cancer with prolonged diabetes. There is a positive relationship from poor diet factor to the pancreatic cancer factor according to Fig. 1. It is known that smoking and obesity increase the chance of developing type 2 diabetes mellitus and pancreatic cancer [30]. The relationship from the obesity factor to the pancreatic cancer factor and the smoking factor to the pancreatic cancer is a positive relationship as seen on Fig. 1.

PDAC risk factors can be categorized into modifiable and non-modifiable. Fig. 1 shows the causal loop of pancreatic cancer's modifiable and non-modifiable risk factors. The modifiable and non-modifiable risk factors of PDAC are explored in the following sections.

III. Modifiable Risk Factors of PDAC

A. Smoking

Smoking increases lung, stomach, colon, and pancreatic cancer risk. Smoking is anticipated to be a factor in 10-15% (25% in some sources) of sporadic PC cases [31], [32]. According to epidemiological research, smoking has the strongest positive correlation with the likelihood of developing the disease out of all the potential causes of pancreatic cancer [33]. Smoking for an extended period (over five years) is associated with an elevated risk of developing PC. In addition to being a known independent risk factor for developing chronic pancreatitis, smoking cigarettes is also suspected of hastening the progression of the disease by causing chronic inflammation. Because smoking causes an inflammatory reaction, it is likely to contribute to cancer development [34]. Smokers who experience the initial symptoms of PC are more commonly diagnosed within a year and at a younger age, indicating a potentially accelerated disease progression in this population. Moreover, a positive correlation exists between daily cigarette consumption(notably exceeding ten cigarettes per day) and the likelihood of developing PC [35]. Prior smoking increased the risk of death for pancreatic cancer patients by roughly 40% compared to nonsmokers [36]. Smoking increased the risk of pancreatic cancer by twofold, and it was estimated that smoking prevalence was above 30% in several parts of the world. However, since smoking contributes to about 25% of the risk of pancreatic cancer, quitting would reduce the disease's overall impact [37].

B. Obesity

The risk factor of pancreatic cancer from obesity is well established; however, it can be changed [38]. Obesity is connected to a higher incidence of pancreatic cancer, and likely worsens outcomes for this malignancy. Research has repeatedly discovered a link between obesity and a higher risk of pancreatic cancer. According to a pooled study of 2,170 cases of pancreatic cancer and 2,209 controls, an increased risk of pancreatic cancer was seen among people in the highest quartile of body mass index (BMI) compared to those in the lowest quartile, where the risk ratio (RR) was 1.33, with a 95% confidence interval (CI) of 1.12 to 1.58 [39]. Obesity (BMI $\geq$30) and a high BMI are risk factors for pancreatic cancer. In a recent meta-analysis, the risk ratios for both men and women who were obese and developed pancreatic cancer were higher than those for people who were of average weight. The RR for men was 1.36, with a 95% CI of 1.07 to 1.73; the RR for women was 1.34, with a CI of 1.22 to 1.46 [35]. Numerous hypothesized pathogenetic processes exist for an increased risk of pancreatic cancer with weight gain. Unknown genetic factors, a lack of exercise, a poor diet, and a poor lifestyle may increase the risk of obesity. Adipocytes may produce chronic inflammation at the cellular level or emit adipokines, insulin-like growth factor (IGF), and vascular endothelial growth factor (VEGF), which may be

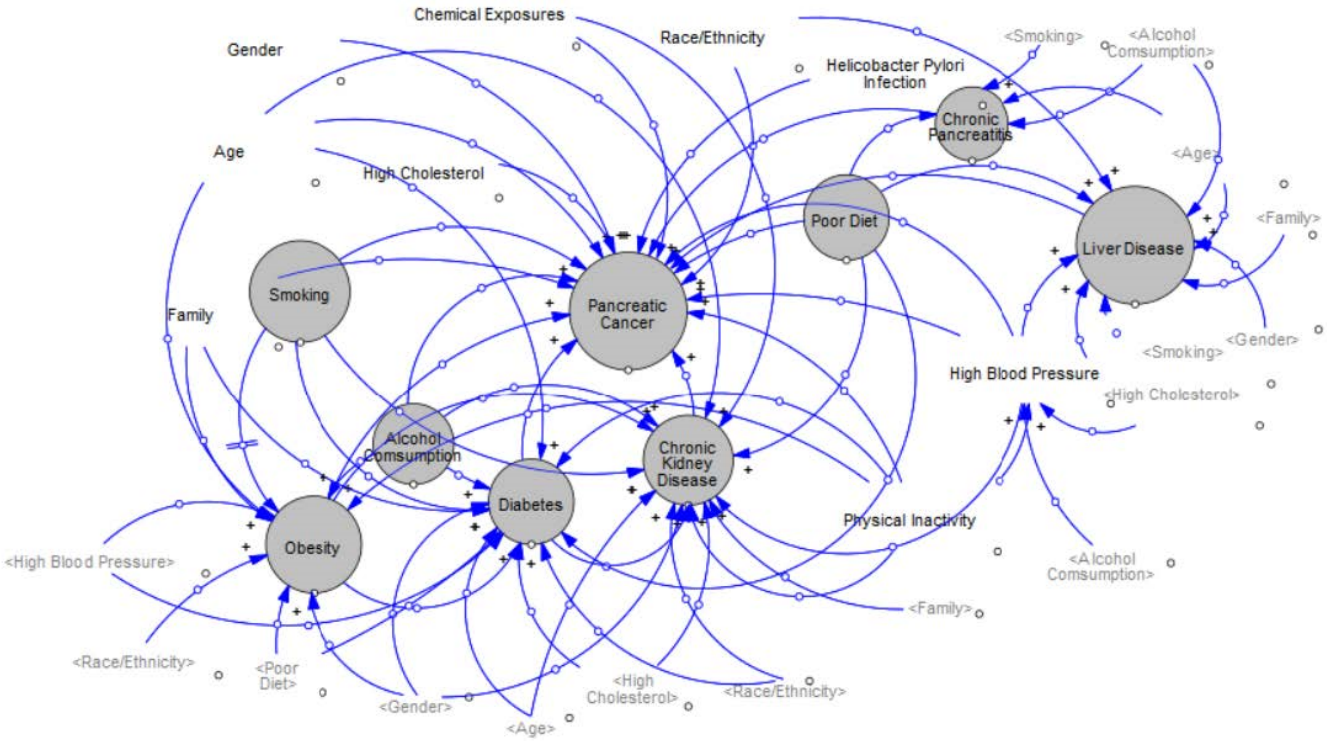

Fig. 1. The casual loop for the complex interactivity of pancreatic cancer risk factors.

potential pro-carcinogenic mediators and contribute to cancer development [40].

C. Diabetes Management

Diabetes may be a risk factor for pancreatic cancer and one of its symptoms. It has been established that having diabetes for a long time increases the risk of developing pancreatic cancer. According to research, those with type 2 diabetes who have had their condition for more than or equal to ten years are at an increased risk of acquiring pancreatic cancer [41]. Research shows a long-standing association between diabetes and pancreatic cancer. Almost 175 years ago, a patient with diabetes mellitus (DM) who died of pancreatic cancer six months later was documented [42]. Chronic hyperinsulinemia increases the risk of endometrial and colon cancers, as well as probably other tumors, according to a growing body of epidemiological and experimental findings (such as pancreas and kidney) [43]. Patients with prediabetes or early type 2 DM who are obese and insulin resistant may experience hyperinsulinemia, contributing to the observed increased risk of PDAC [44]. Patients with diabetes have a strong positive for having PDAC because it is associated with other variables as illustrated in the Fig. 1.

D. Dietary Habits

Food can predispose to various diseases, as is well recognized; however, it is challenging to demonstrate a link between specific dietary elements and the chance of developing cancer [45]. It makes sense that dietary choices could have a 30-50% influence on the likelihood of developing pancreatic cancer and other digestive disorders and cancers [46], [47] The frequency of pancreatic cancer was investigated in various studies concerning eating habits, dietary patterns, and nutritional consumption. Average oil and fat consumption have been associated with increased animals [48], and humans pancreatic cancer [49]–[51]. Several researchers say eating more meat and dairy product [52] increases the risk of pancreatic cancer [49], [53], [54]. Obesity, diabetes, chronic kidney disease, liver disease, and other dietary-related diseases, such as pancreatic cancer, can all be avoided by adopting healthy eating habits. It includes eating nutrient-dense meals, avoiding processed foods, red meats, and sugary foods, managing quantities, lowering salt and sugar intake, remaining hydrated, engaging in physical activity, practicing mindful eating, getting professional advice, and implementing long-term dietary adjustments. People can lower their risk of diet-related diseases by prioritizing healthy eating and improving their general well-being, as depicted in Fig. 1.

E. Alcohol Consumption

PDAC and alcohol usage may be related; however, the evidence for this is still inconclusive [42], [55]–[57]. High alcohol consumption (more than three drinks per day), shown to increase the risk of pancreatic cancer in numerous prior

studies, is unquestionably associated with this disease. In contrast, low-to-moderate alcohol consumption has not been associated with an increased risk of pancreatic cancer [57], [58]. The risk of pancreatic cancer, liver disease, chronic pancreatitis, diabetes, obesity, and chronic kidney disease is increased by excessive alcohol use as demonstrated in Fig. 1. The pancreas and digestive system are negatively impacted. People should consume alcohol in moderation, maintain a healthy lifestyle, be aware of their boundaries, and support others to reduce these hazards. By taking these precautions, one can lessen the possible harm that alcohol might cause to the pancreas and digestive system, which lowers the likelihood of associated illnesses.

F. Chronic Pancreatitis

In recent years, increasing evidence has been shown that long-term, pre-existing chronic pancreatitis is a significant risk factor for developing pancreatic cancer [59]. The most frequent cause of chronic pancreatitis is alcohol, but other factors also raise the risk. Hereditary pancreatitis is a rare genetic condition that mimics other forms of chronic pancreatitis regarding its sign and symptoms. It begins in childhood or early adulthood and is inherited as an autosomal dominant condition. The overall lifetime risk of pancreatic cancer is roughly 40% for these people [60], [61]. A high-risk group with latent PDAC is defined by a low BMI and pancreatic exocrine insufficiency in patients with chronic pancreatitis [62]. Compared to the general population, patients with chronic pancreatitis had a significantly increased risk of acquiring pancreatic cancer, especially if they were older at the time of onset and had smoked for more than 60 years [63]. Research into how pancreatitis promotes pancreatic cancer will aid in early discovery and direct prevention. However, more research is required to understand how pancreatitis leads to pancreatic cancer development. Further research will help us comprehend how pancreatitis affects pancreatic cancer development and enable us to create more focused preventive measures.

IV. Non-Modifiable Risk Factors of PDAC

A. Age

Age increases the risk of developing pancreatic cancer; more than 80% of cases are identified between the age of 60 and 80 [64]. The SEER Cancer Statistical Review's findings indicate that pancreatic cancer is more common in older people aged 65-74 [29]. The average age at which cancer was detected in the United States was 65-67 years, according to data from 13,131 PC patients (30-95 years old). The disease affected men (65.2 years) earlier than women (66.8 years). In addition, pancreatic cancer struck African Americans earlier than Caucasians (62-63 vs. 66 years) [65].

B. Gender

In 2022, there were 25,970 male fatalities and 23,860 female deaths from pancreatic cancer in the United States, with 32,970 male cases and 29,240 female cases of the disease newly diagnosed [66]. Men are more likely than women to get pancreatic cancer and die from it globally, with men having a cumulative risk of 0.65% and 0.59% from birth to 74 years and females with 0.45% and 0.41% [67]. The higher incidence of pancreatic cancer in men can be attributed to environmental or occupational risk factors and lifestyle choices such as heavy smoking and alcohol consumption. However, it is essential to acknowledge that undiscovered genetic factors could influence cancer incidence and mortality in both males and females. Further research is needed to fully understand the complex interplay of these factors in pancreatic cancer development among different populations [68]. Both men and women can reduce their risk by leading a healthy lifestyle, which includes quitting smoking, consuming less alcohol, eating a balanced diet, and exercising regularly. Reduced exposure to some chemicals and poisons at work and other environmental risk factors may benefit males. Routine medical examinations and screenings can also aid the early detection and prevention of PC in both sexes.

C. Ethnicity/Race

There are racial inequalities in pancreatic cancer incidence. Significant racial disparities in pancreatic cancer incidence have been observed in numerous studies [69], [70]. Behavioral variables strongly influence the higher prevalence of PC among African Americans. Black Americans have many risk factors, including smoking, alcoholism, obesity, eating more high-calorie foods, type 2 diabetes, and a low socioeconomic level [71]. Recent population-based studies, however, have demonstrated that the known and suspected risk factors listed above may not fully account for the higher incidence of pancreatic cancer, pointing to additional factors that may also be involved in the increased risk [47].

D. Family History

Approximately 5% to 10% of individuals with PC mention first-degree relatives with a history of the disease [72]. According to a meta-analysis of seven case-control and two cohort studies, having an affected relative significantly increased the likelihood of developing pancreatic cancer (RR = 1.80, 95% CI, 1.48–2.12) [73]. Moreover, a family history of pancreatic cancer in a close relative was associated with an elevated risk of pancreatic cancer (RR = 1.76; 95% CI, 1.19–2.61) in a nested case-control study using pooled data from 10 cohort studies [68].

V. Conclusion

In conclusion, PDAC is a formidable and deadly cancer with a high mortality rate. Although the precise origins of PDAC are still unknown, genetic, environmental, and lifestyle factors are thought to impact the disease. The incidence and mortality of pancreatic cancer are expected to rise, posing a significant public health challenge globally. Several modifiable risk factors have been identified, including smoking, diabetes,

obesity, chronic kidney disease, liver disease, dietary habits, and alcohol consumption. Non-modifiable risk factors such as age, gender, ethnicity/race, and family history also play a role in the development of PDAC. System dynamics modeling can aid in understanding the intricate interactions among these risk factors and help develop effective preventive strategies. Public health campaigns and awareness programs are crucial for educating the public about the risks associated with PDAC and promoting healthier lifestyle choices to reduce the risk of developing the disease. Further research is necessary to uncover additional causes and risk factors for PDAC and to improve early detection methods. Understanding modifiable and non-modifiable risk factors makes it possible to lower the morbidity and mortality rates associated with pancreatic cancer.

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