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PANCREATIC CANCER IN THE WORLD: AN EPIDEMIOLOGICAL REVIEW

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Abstract – *Objective:* *One of the most common malignant tumors around the world is pancreatic cancer. This cancer is the 12th most common malignancy and classified as the seventh cause of cancer deaths, depending on its high mortality rate. Considering the importance of the incidence, mortality rate, and risk factors in prevention programs, this study was conducted to investigate the incidence, mortality, and risk factors for pancreatic cancer in the world.*

Materials and Methods: *This review was conducted on published English publications by January 2017 by searching in the databases of PubMed, Scopus and Web of Acience. The search strategy included the following key words: "pancreatic cancer", "epidemiology", "incidence", "mortality", "risk factors" and "world". Articles related to the incidence, mortality, and causes of pancreatic cancer were studied and included into the study.*

Results: *The highest incidence of pancreatic cancer in North America in 2012 was 7.4 per 100,000 people and in Western Europe 7.3 per 100,000 people; in other regions of Europe, Australia and New Zealand, the highest rate was reported at about 6.5 per 100,000 people. Also, the maximum mortality rates from pancreatic cancer in North America and Western Europe countries were 6.9 and 6.8 per 100000 people, respectively, in other regions of Europe, Australia and New Zealand it was 6.0 per 100,000. Furthermore the lowest mortality rates were reported from countries of Central Africa and South-Central Asia, which were less than 1.0 in 1,000,000. The risk of the disease is affected by host and environmental factors such as aging, non-heritable blood type, heredity and its relation to other diseases, such as diabetes and chronic pancreatitis, smoking, obesity,* H. pylori *infection.*

Conclusions: *The incidence and mortality of pancreatic cancer in developed countries is higher than developing countries, and its incidence and death rates are rising gradually. In order to further acquaintance with the incidence and mortality rate and recognizing and controlling the risk factors for this cancer may provide opportunities to improve prognosis and reduce mortality.*

KEYWORDS: *Incidence, Mortality, Risk factor, Pancreatic cancer.*

INTRODUCTION

Pancreatic cancer is the 12th most common cancer in the world and with its high mortality rate, it is ranked as the seventh cause of cancer deaths[1]. According to GLOBOCAN 2012, it accounts for about 4.0% of all cancer deaths. It is estimated that 338,000 people with pancreatic cancer are diagnosed annually and about 331,000 of the cases die from this cancer. Also, it is worthwhile to note that pancreatic cancer is the fourth leading cause of death from cancer in the United States. At present, regar-

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ding the death rate due to this cancer, is on the rise. Pancreatic cancer is predicted to be the second leading cause of cancer deaths in the United States by 2030[2]. The increased mortality rate of this cancer in the European population has also been reported[3]. The incidence of pancreatic cancer varies in the two sexes, with an incidence of 50% higher in men than women. Cancer of the pancreas is an aging condition, with most cases occurring between the ages of 60 and 80[4]. The pancreatic cancer prognosis is very poor, and the survival rate is between 5% and 25%[5]. Most patients are diagnosed at an advanced stage of the disease. The disease is unexplained and has a modest survival (less than one year); therefore, the mortality rate for pancreatic cancer is about 99%[6]. The incidence and mortality of this cancer varies according to the geographical area. Moreover, there are various factors involved in the development of this cancer. Therefore, the knowledge of the geographical distribution of occurrence, death and its related factors can lead to appropriate planning and studies to reduce the incidence of this cancer. Due to the lack of a comprehensive overview in this regard, and since awareness of occurrence, death and risk factors can be used in planning, the aim of this study was to investigate the incidence, mortality, and risk factors for pancreatic cancer in the world.

MATERIALS AND METHODS

This review was conducted on published English publications by January 2017 by searching in the databases of PubMed, Scopus and Web of Science. The search strategy included the key words "pancreatic cancer", "epidemiology", "incidence", "mortality", "risk factors", and "the world". Articles related to the incidence, mortality, and causes of pancreatic cancer have been investigated and those with focus on treatment have been excluded.

INCIDENCE IN THE WORLD

The highest incidence of pancreatic cancer in North America in 2012 was 7.4 per 100,000, in Western Europe 7.3 per 100,000, and in other regions of Europe and Australia, New Zealand 6.5 per 100,000. The lowest incidence of the cancer was observed in Middle Africa and Central and South Central Asia, about 1.0 per 100,000. In 2012, more than half of the new pancreatic cancer cases (55.5%) were reported in the developed countries and 45.0% of the new cases in Asian countries[7,8]. The reason for this difference in the incidence of pancreatic cancer in various parts of the world is due to exposure to known or suspected risk factors related to lifestyle and the environment[1,9-12]. Tobacco and sex are also the causes of the difference between different regions of the world[13]. The incidence of pancreatic cancer in men in 2012 was 4.9 per 100,000 and among women was 3.6 per 100,000[8]; the incidence of both gender increases with age, the highest rate is reported at the age of over 70 years[14-16]. The disease is primarily an aging condition and approximately 90% of cases are detected after 55 years of age[11,16]. The geographical differences in incidence probably indicate an increased capacity for diagnosis and development in the use of different diagnostic methods[17-20]. In 2012, one third of the overall incidence in Europe was reported; most likely due to accurate diagnosis of pancreatic cancer than etiology[21]. It should be noted that some dissimilarities in the likelihood of pancreatic cancer worldwide may be due to the difference in the quality of registrations, coverage and careful completion of it[22].

THE MORTALITY RATE IN THE WORLD

The international mortality rate for pancreatic cancer varies from region to region. The highest incidence of pancreatic cancer deaths in both sexes in North America in 2012 was 6.9 per 100,000 and in Western Europe, 6.8 per 100,000; in other European and Australian/New Zealand regions this incidence is reported as 6.0 per 100,000. The lowest deaths were observed in the countries of Middle Africa, and Central and South Asia, less than 1.0 per 1,000,000[36-38]. More than a half of deaths from pancreatic cancer deaths (55.8%) have been recorded from more developed areas[8,23]. The mortality rate of pancreatic cancer in both genders increases with age; approximately 90% of all deaths occur after the age of 55 years[14,23]. The mortality rate of pancreatic cancer is almost equal to its incidence, as it is one of the most fatal malignant tumors[24,25]. One of the most important reasons for the difference in the mortality rate of pancreatic cancer in various regions is that the quality of the published data on incidence and mortality is not the same by the WHO of all countries[22]. There are no screening tests for pancreatic cancer. Early diagnosis and effective treatment leads to a difference in mortality incidence reports between developed and developing countries[26]. The high prevalence of smoking is widely recognized as the major cause of high mortality of pancreatic cancer[13,27]. Besides, diet (fat and animal meat) plays an important role in raising the cause of mortality rate of pancreatic cancer[28,29]. In addition, high rates of pancreatic cancer deaths in Eastern Europe suggest that other factors, including the prevalence of diabetes, obesity, and alcohol consumption, can affect the death of pancreatic cancer[30]. In recent years, people

in developing countries have adopted lifestyles and behaviors such as smoking, high saturated fat and high calorie intake, and reduced physical activity, leading to pancreatic cancer, resulting in high death rates[28,30,31]. Economics and social differences (the difference between high and low-income regions for early detection) may also justify part of the high-level pancreatic cancer risk in some of the Southern, Central and Eastern European countries[22,30,32]. Figure 1 showed incidence and mortality of pancreatic cancer in the world.

RISK FACTORS FOR PANCREATIC CANCER

Host or non-modifiable factors

Age

The pancreatic cancer is mainly known as the disease of the elderly people. It is low in the first three decades. However, after the age of 30 years, its incidence in the seventh and eighth decades of life increases dramatically[1,6,33]. About 9 out of 10 patients

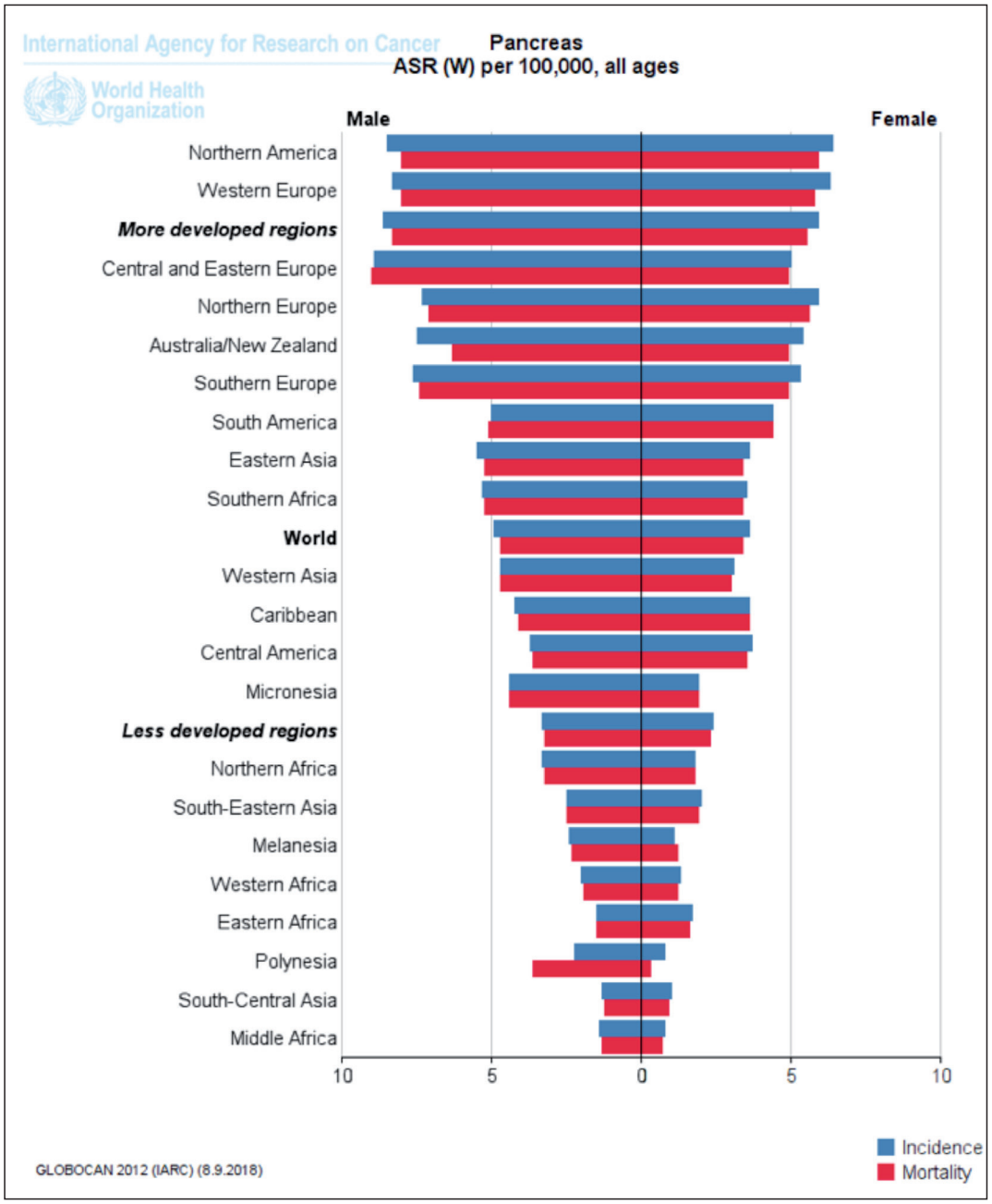

Fig. 1. Incidence and mortality of pancreatic cancer. (extracted from http://globocan.iarc.fr/Pages/references.aspx / Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 1/8/2018.)

TABLE 1. Related factor to pancreatic cancer.

Variable		Risk factor	Protective	Controversial
Host or non-modifiable factors				
Age		*		
Sex Gender (Male)		*		
Race (African Americans)		*		
Blood Groups	A	*		
	B	*		
	AB	*		
	O			*
Genetics		*		
Chronic Pancreatitis		*		
Diabetes Mellitus		*		
Anti-diabetic drugs	Insulin	*		
	Metformin		*	
Autoimmune Diseases (celiac disease)		*		
Environmental or modifiable factors				
Obesity		*		
Dietary factors	Meat	*		
	Sweet drink sugars	*		
	Citrus fruits		*	
	Folate and methionine		*	
	Vitamin D		*	
Alcohol		*		
Smoking		*		
Infection		*		
Drugs	Aspirin			*
	Non-steroidal anti-inflammatory			*

with pancreatic cancer are at least 55 years old. Nearly half of all patients develop their disease after age 71 years and rarely before age 45 years[34]. In the United States, most patients with pancreatic cancer are diagnosed between the ages of 40 and 80[35]. Furthermore, the incidence of pancreatic cancer also rises in the fifth and sixth decades of life in India[36].

Sex Gender

Cancer of pancreas in men is 30% higher than women[1,34,37]. The standardized incidence rate in men and women is 13.9 and 10.9 per 100,000, respectively. The incidence rate among men and women varies greatly between developed and less developed countries. The incidence rate in advanced countries for men is 8.5 per 1,000,000 and for women 5.6 per 100,000, respectively. in less developed or developing countries, the incidence rate in men and women are 3.3 and 2.4 per 100,000 respectively[37]. Several studies have been conducted to determine the role of recently mentioned factors. A systematic study concluded that fertility factors and sex hormones are not associated with an increase in the incidence of pancreatic cancer in women[38,39]. This suggests that differences in pancreatic cancer risk between men and women may be due to environmental factors such as smoking. Genetic factors have not been found to have an effect on the incidence of cancer and mortality in men and women[38]. Life expectancy increases the risk of pancreatic cancer by about 1.5% for men and women[34].

Race

Race is a known risk factor for pancreatic cancer. There are significant differences in the incidence of inter-racial pancreatic cancer. The incidence of this disease in the United States is higher among African Americans than in the Americas of the Caucasians, with the lowest rates reported for Asian Americans and Pacific Islanders[1,40]. An increase in African Americans is due to risks such as diet, alcohol, smoking, and vitamin D deficiency in this breed[41,42].

Blood Groups

Major epidemiological studies have identified the association between ABO blood groups and the risk of pancreatic cancer[1,43]. People with blood groups A, AB, or B have a higher risk of pancreatic cancer than

those with blood type O[44]. In a common smoking model, smokers with blood groups A, AB, or B have a 2.68-fold increase in the odds of pancreatic cancer compared with non-smokers with an O group[43-45].

Genetics

Cancer of the pancreas, like all other cancers, is essentially genetic. This means that the disease is inherited by genetic mutations. The genetic variation of mutation in Inherited Genetic Mutations (Germline Mutations) and non-familial Acquired Genetic Mutations (Somatic Mutations) play an important role in pancreatic cancer. More than 80% of this cancer is due to non-familial genetic mutations. A small fraction of pancreatic cancer cases is due to inherited genetic mutations. Although there are no mutations in all tumors, key mutations are different from one tumor to another. In recent decades, the progression of molecular biology has improved our diagnosis of the pathogenesis of pancreatic cancer. By identifying a number of genes that have mutated in pancreatic cancer, development of biomarkers and effective treatment will be increased[46-53].

Chronic Pancreatitis

Chronic pancreatitis (CP) is a progressive pancreatic inflammatory disease characterized by degeneration of acinar cells and pathological fibrosis. Its main causes are alcohol abuse, heredity and idiopathic. Chronic pancreatitis is known to be a risk factor for pancreatic cancer[36,54-56]. Recent investigations demonstrate that the association between pancreatitis and pancreatic cancer in patients with rare autosomal is very strong. The risk is approximately 70 times higher than expected in the normal population, and the life-threatening risk of these patients to pancreatic cancer is approximately 40-55%[1,57]. The incidence and severity of chronic pancreatitis is relatively low, and the 20-year cumulative incidence of pancreatic cancer in these patients is only about 5%. The risk of pancreatic cancer due to chronic pancreatitis is low compared with other common causes[58].

Diabetes Mellitus

The relationship between diabetes and pancreatic cancer is known since almost 175 years ago. A diabetic patient died six months later with pancreatic cancer[1,56,59]. A large case-control study found that the risk of developing pancreatic cancer is high among people who are 20 years old or more with diabetes[60]. The results of a prospective study suggested that the risk of pancreatic cancer in people who are newly diagnosed with diabetes is low without other risk factors for this cancer, but the risk for those with long-standing diabetes with two or three other common risk factors increases to 0.72%[61]. Recent studies[62,63] have shown that hyperglycemia, exposure to high levels of insulin, and insulin resistance, are associated with an increased risk of pancreatic cancer.

Anti-diabetic drugs and the risk of pancreatic cancer

According to basic and epidemiological studies, insulin may increase the risk of pancreatic cancer in diabetic patients[64,65]. The relative risk of pancreatic cancer in patients treated with insulin was 3.54 times higher than those treated only with oral hypoglycemic drugs. In contrast, metformin users may have a protective effect with a lower incidence of pancreatic cancer compared to non-consumer of metformin[66-68].

Autoimmune Diseases

Celiac disease increases the risk of pancreatic cancer by approximately 3 times (hazard ratio 2.85)[69]. Risk of pancreatic cancer is also elevated in patients with inflammatory bowel disease, systemic lupus erythematosus and other disorders. Only 10 to 25% of autoimmune pancreatitis suffer from pancreatic cancer at the time of diagnosis[70].

Environmental or modifiable factors

Obesity

Obesity (BMI> 30) and BMI increase are both risk factors for pancreatic cancer. A recent meta-analysis of the association between obesity and pancreatic cancer in men and women was evaluated reporting that the risk ratio of pancreatic cancer in obese men and women is higher than those of normal weight[1,71-74]. There are several pathogenic mechanisms to increase the risk of pancreatic cancer with weight gain. Obesity may be accompanied by physical inactivity, unhealthy diet and lifestyle, while identifying genetic factors may play a role[75].

Dietary factors

Since pancreas is intermittently involved in food metabolism, type of food is likely to be an effective factor in pancreatic cancer and it is responsible for 30-50% of pancreatic cancers[1,36,76]. An increased risk of pancreatic cancer is associated with high consumption of meat (especially kebab), cholesterol, fried foods and other nicotine-rich foods[77]. Similarly, an elevated risk of pancreatic cancer has been reported with the high consumption of sweet drink sugars[78-80]. On the other hand, high intake of citrus fruits and some flavonoids that naturally contain antioxidants are associated with a certain decrease in the risk of pancreatic cancer[81,82]. Folate and methionine have a fairly good protective effect on

the progression of pancreatic cancer[83-85]. Also, the potential role of vitamin D in reducing the risk of pancreatic cancer has been analyzed[86]. A score above 25-hydroxyvitamin D is associated with a 35% of reduction in pancreatic cancer[87].

Alcohol

Alcohol has long been recognized as a risk factor for pancreatic cancer due to its role as a chronic pancreatitis. There are a variety of effects of alcohol on the functioning of pancreatic tumors[1,88,89]. Generally, the metabolism of ethanol can change the internal state of the cancer cells. Recently, the main role of alcohol in the development of chronic pancreatitis and pancreatic cancer has been reported[90-92]. A meta-analysis study examined the relationship between alcohol consumption and pancreatic cancer. According to the results of this study, there is an increased risk of pancreatic cancer in people who consume more alcohol[93].

Smoking

Smoking is a major environmental factor that has the greatest impact on pancreatic cancer; researches showed that the population risk is from 25% to 35%[1,89,94,95]. The results of a meta-analysis demonstrated that the risk of pancreatic cancer in smokers, in comparison with those who never smoked, was higher than 60%[96]. In a cohort study, exposure to cigarette smoke in childhood has doubled the risk of pancreatic cancer[97].

Infection

In two studies, the association between hepatitis B and C virus with pancreatic cancer has been reported; hepatitis B virus infection is more potent[1,98,99]. There is also a correlation between *Helicobacter pylori* infection and pancreatic cancer. A meta-analysis of seven studies reported a growth risk of pancreatic cancer in people with H. pylori up to 65%[100,101]. Viral diseases such as mumps and bacterial infections like *Salmonella typhi* and *Salmonella typhoid* may be associated with a high risk for pancreatic cancer[36].

Drugs

Several types of drugs can increase or decrease the risk of pancreatic cancer[102]. Regular use of aspirin and non-steroidal anti-inflammatory drugs can reduce the risk of pancreatic cancer. More and better studies should consider the protective effect of this drug[103,104]. Larsson et al[104] did not find the role of these agents as protective against pancreatic cancer.

To sum up, the incidence and mortality of pancreatic cancer in developing countries is higher than in developed countries. This difference may be due to precursors and early detection of the disease in developed countries compared with developed countries. The mortality rate has not diminished due to the delayed diagnosis and ineffective treatment. Epidemiological research suggests that the risk of the disease is also affected by host and environmental factors. Aging, non-O blood type, association with specific cancer syndromes, heredity and its relation to other diseases, such as diabetes and chronic pancreatitis, cannot be changed, but could be a warning to the physician to identify people at risk. Other risk factors, such as exposure to tobacco, obesity, *H. pylori* infection, red meat and nitrosathene, can be changed, and a control of these factors may reduce the incidence of pancreatic cancer, especially in patients at high risk for the disease due to the genetic and host factors, thereby reducing the mortality due to this cancer. Further acquaintance with the incidence and mortality rate, and recognizing and controlling these risk factors may improve the prognosis of the disease.

CONCLUSIONS

The incidence and mortality of pancreatic cancer in developed countries is higher than developing countries, and its incidence and death rates keep rising. Knowing the incidence and mortality rate and recognizing and controlling the risk factors for this cancer may prognosis and reduce mortality.

Conflict of Interest:

The Authors declare that they have no conflict of interests.

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