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Review

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Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors

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Abstract

Pancreatic cancer is the seventh leading cause of cancer-related deaths worldwide. However, its toll is higher in more developed countries. Reasons for vast differences in mortality rates of pancreatic cancer are not completely clear yet, but it may be due to lack of appropriate diagnosis, treatment and cataloging of cancer cases. Because patients seldom exhibit symptoms until an advanced stage of the disease, pancreatic cancer remains one of the most lethal malignant neoplasms that caused 432,242 new deaths in 2018 (GLOBOCAN 2018 estimates). Globally, 458,918 new cases of pancreatic cancer have been reported in 2018, and 355,317 new cases are estimated to occur until 2040. Despite advancements in the detection and management of pancreatic cancer, the 5-year survival rate still stands at 9% only. To date, the causes of pancreatic carcinoma are still insufficiently known, although certain risk factors have been identified, such as tobacco smoking, diabetes mellitus, obesity, dietary factors, alcohol abuse, age, ethnicity, family history and genetic factors, *Helicobacter pylori infection*, non-O blood group and chronic pancreatitis. In general population, screening of large groups is not considered useful to detect the disease at its early stage, although newer techniques and the screening of tightly targeted groups (especially of those with family history), are being evaluated. Primary prevention is considered of utmost importance. Up-to-date statistics on pancreatic cancer occurrence and outcome along with a better understanding of the etiology and identifying the causative risk factors are essential for the primary prevention of this disease.

Keywords: Pancreatic cancer; Epidemiology; Incidence; Mortality; Trends; Survival; Etiology; Risk factors; Prevention; Pancreatitis

Introduction

Pancreatic cancer is an intractable malignancy and is the seventh leading cause of global cancer deaths in industrialized countries [1] and the third most common in the USA [2]. Based on GLOBOCAN 2018 estimates, pancreatic cancer has ranked the 11th most common cancer in the world counting 458,918 new cases and causing 432,242 deaths (4.5% of all deaths caused by cancer) in 2018 [1]. Worldwide incidence and mortality of pancreatic cancer correlate with increasing age and is slightly more common in men than in women [1]. Despite advancement in the knowledge of potential risk factors that cause pancreatic cancer and newly available tools for early diagnosis, its incidence is estimated to increase and will include 355,317 new cases within 2040.

Although the cause of pancreatic cancer is complex and multifactorial, cigarette smoking [3] and family history are dominant [4]. Pancreatic cancer is mainly divided into two types of pancreatic cancer: pancreatic adenocarcinoma, which is the most common (85% of cases) arising in exocrine glands of the pancreas, and pancreatic neuroendocrine tumor (PanNET), which is less common (less than 5%) and occurs in the endocrine tissue of the pancreas [5]. Pancreatic adenocarcinoma has a very poor prognosis, typically after diagnosis, only 24% of people survive 1 year, and 9% live for 5 years [6].

Based on the clinical stage of the tumor, pancreatic cancer is classified into four types: I (no spread or resectable), the cancer is limited to the pancreas and has grown 2 cm (IA) or greater than 2 cm but less than 4 cm (IB); II (local spread or borderline resectable), the cancer is > 4 cm and is limited to the pancreas, or there is spread locally to the nearby lymph nodes; III (wider spread or unresectable), cancer may have expanded to the nearby blood vessels or nerves, but has not metastasized to distant sites; IV (metastatic), cancer has spread to distant organs. Because pancreatic adenocarcinoma and the other less common exocrine cancers are typically diagnosed at a late stage (III or IV), it has a very poor prognosis compared to PanNET. At its early stages, pancreatic cancer usually lacks symptoms [7]. Upon progression of the tumor, it manifests as a gradual onset of non-specific symptoms including jaundice, weight loss, light-colored stools, abdominal pain and fatigue [8].

The available diagnostic tests are non-specific and may miss patients with early-stage disease [7]. Surgery, chemotherapy and radiotherapy are traditionally used to extend survival and/or relieve the patients' symptoms. However, for advanced-stage cancer cases, there is still no definite cure [9]. There is a need for further research along with new local and systemic therapies, along with the need to assess the outcomes of these approaches. Therefore there is a necessity for ongoing evalu-

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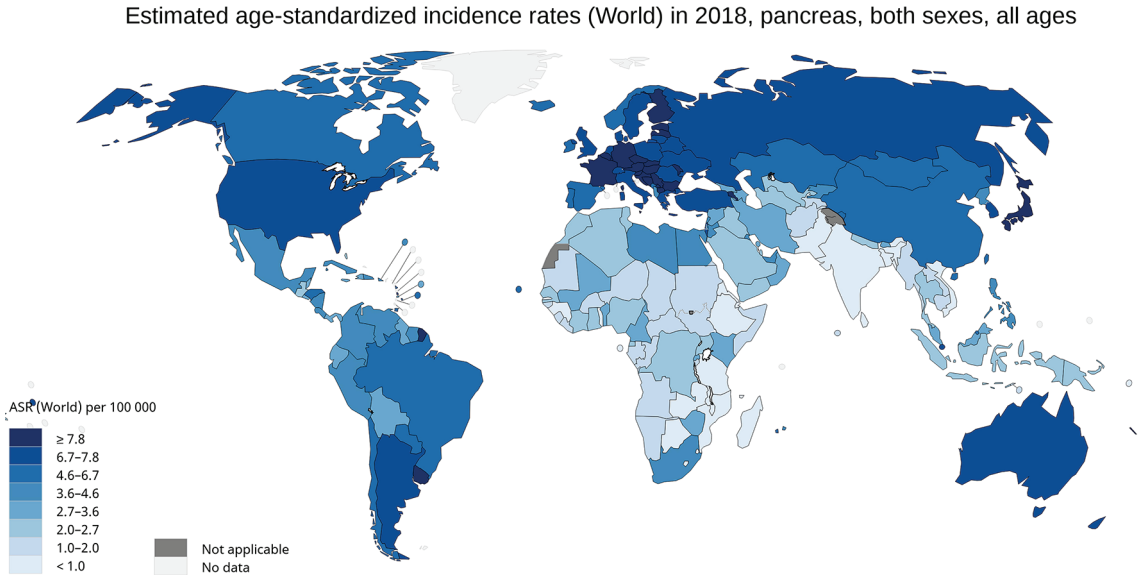

Figure 1. Map shows estimated age-standardized incidence rates (ASR) for pancreatic cancer worldwide in 2018, including both sexes and all ages (reproduced from http://globocan.iarc.fr/ [2]).

ation of the epidemiology and mortality trends of this malignancy.

Epidemiology

Analysis of pancreatic cancer epidemiology may be the key to interpreting the etiology of pancreatic cancer and thus, the cornerstone of developing an effective prevention strategy.

Incidence

The incidence of pancreatic cancer varies across regions and populations (Fig. 1). In 2018, 458,918 new cases of pancreatic cancer were registered worldwide, representing 2.5% of all cancers [1]. The age-standardized rate (ASR) incidence was highest in Europe (7.7 per 100,000 people) and North America (7.6 per 100,000 people), followed by Oceania (6.4 per 100,000 people). The lowest rate was observed in Africa with an estimated incidence of 2.2 per 100,000 people [1]. Differences in incidence rates were 30-fold between the populations at the highest rate (Hungary: 10.8), and the populations with the lowest rate (Guinea: 0.35) (Fig. 2a).

A slight difference in pancreatic cancer incidence among genders as well as a significant different geographic distribution was observed [1]. It is more common in men (5.5 per 100,000, 243,033 cases) than in women (4.0 per 100,000, 215,885 cases). In men, the risk of developing pancreatic cancer is high in Central and Eastern Europe, particularly Latvia and Republic of Moldova (15.3), Estonia (14.2) and Hungary (12.9), followed by Uruguay (12.0) and Japan (11.7), while the lowest rates are recorded in Guinea (0.23) and Malawi (0.30). The regions with the highest incidence of pancreatic cancer in women are Western Europe (7.2), North America (6.5), and Northern Europe and Australia/New Zealand (equally: 6.4) [1]. The regions with the lowest risk (less than 1.0 per 100,000) of contracting pancreatic cancer in women are Eastern Africa and South-Eastern Asia. There is no recorded case of pancreatic cancer for both sexes in the African regions of Comoros and Sao Tome and Principe [1].

The incidence rate for both sexes increases with age [1, 10, 11]. Pancreatic cancer is seldom diagnosed before 55 years of age, and it can be defined as a disease of elderly populations because the highest incidence is reported in people over 70 years [11, 12].

It is not entirely clear the reason for these differences among the countries. However, it may be possible that the environment and/or the exposure to certain risk factors account for the observed geographic variation in the incidence of pancreatic cancer. For example, some findings indicate that tobacco smoking [13] may have some effects on those differences, while others indicate dietary style and obesity [14-16]. Another thing to be considered is that diagnostic tools and the change in use of various diagnostic modalities vary between developed and undeveloped geographic areas [17]; furthermore, some differences in the estimated incidence may be attributed to the quality of registries, for which coverage, completeness and accuracy vary by country [18]. The reasons for the greater incidence of pancreatic cancer in men are still insufficiently known. Women are less exposed to risk factors from the environment responsible for their occurrence or are either less prone to these kinds of malignant tumors [19-21].

Mortality

International mortality rates for pancreatic cancer vary considerably in the world (Fig. 2b). In 2018, the highest mortality rates were recorded in Western Europe (7.6 per 100,000 peo-

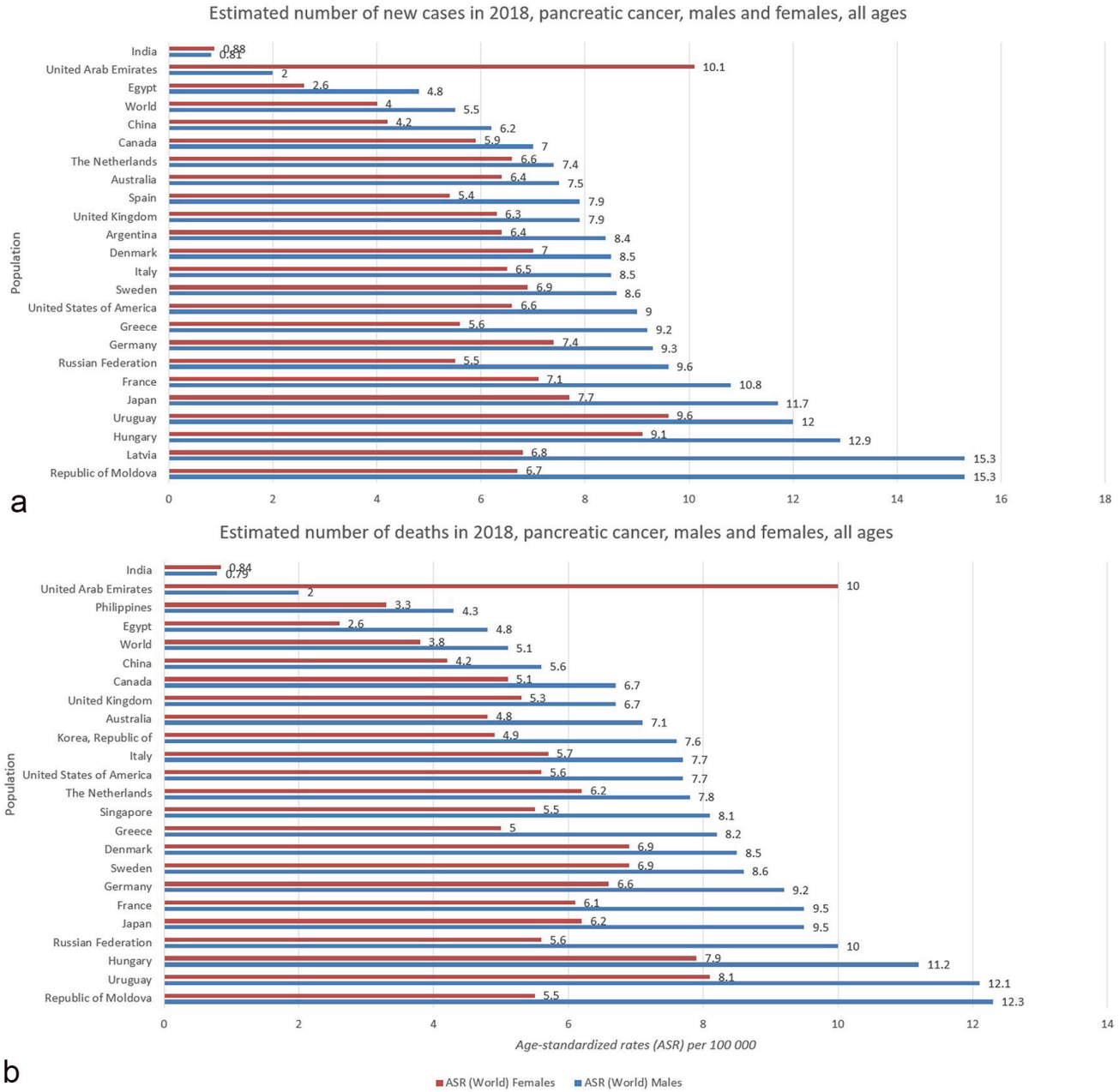

Figure 2. (a) Bar chart shows country-specific incidence age-standardized rates by sex for pancreatic cancer in 2018. Source: GLOBOCAN 2018 [2]. (b) Bar chart shows country-specific mortality age-standardized rates by sex for pancreatic cancer in 2018. Source: GLOBOCAN 2018 [2].

ple), Central and Eastern Europe (7.3), followed by Northern Europe and North America (equally: 6.5) (Fig. 3) [1]. The lowest rate was reported in the countries of Eastern Africa (1.4), South-Eastern Asia and Western Africa (equally: 2.1). The differences in mortality rates were 30-fold between the populations with the highest and lowest rate (Uruguay versus Guinea: 9.9 versus 0.32). Slightly less than half of the deaths for pancreatic cancer occurred in Asia in 2018 (46.4%, 200,681 of deaths), while slightly more than one-third were recorded in Europe (29.6%, 128,045 of deaths). More than half of deaths for pancreatic cancer were registered in the most developed countries (52.3%, 226,272 of deaths). The mortality rate of pancreatic cancer in both males and females increases with age, and almost 90% of all deaths occur after the age of 55 years [1].

In 2018, the highest mortality rates in men were recorded in Republic of Moldova (12.3) and Uruguay (12.1), while in women the mortality rates were the highest in United Arab Emirates (10.0) and Uruguay (8.1). On the contrary, the least deaths in men were registered in Tanzania (0.3) and Malawi

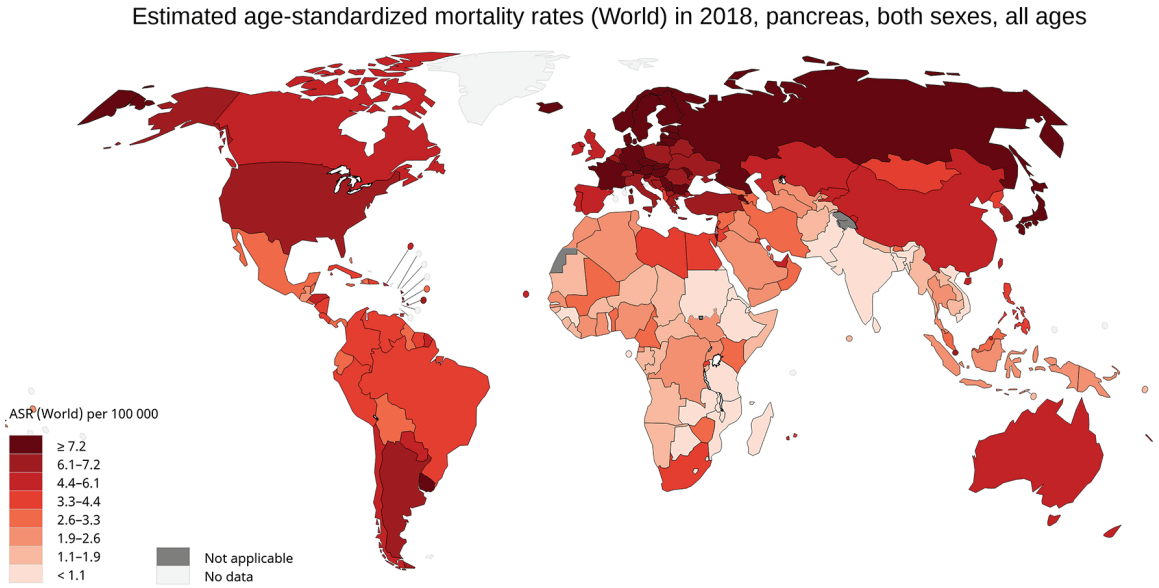

Figure 3. Map shows estimated age-standardized mortality rates (ASR) for pancreatic cancer worldwide in 2018, including both sexes and all ages (reproduced from http://globocan.iarc.fr/ [2]).

(0.32), while in women the lease death was seen in Guinea (0.2) and Pakistan (0.3). The close parallel between the incidence and mortality rates from pancreatic cancer reflects the fatal nature of this disease (Fig. 4) [22, 23]. Notably, because it is difficult to diagnose pancreatic cancer due to the lack of early symptoms, pancreatic cancer is the most common detected at the autopsy studies [17, 24]; 80-90% of patients have unresectable tumors due to the advanced stage at diagnosis. Additionally, the current chemotherapeutic regimen available is limited and often ineffective [12, 22, 25], especially for the adenocarcinoma that is mostly diagnosed at stage III or IV. Early detection may be the key to reduce mortality and may be supported by patients screening and prevention.

Trends

In the last decade, a trend towards an increase of pancreatic cancer incidence and mortality rates was observed regardless of the gender [1, 26]. Analysis of statistic data reported by SEER

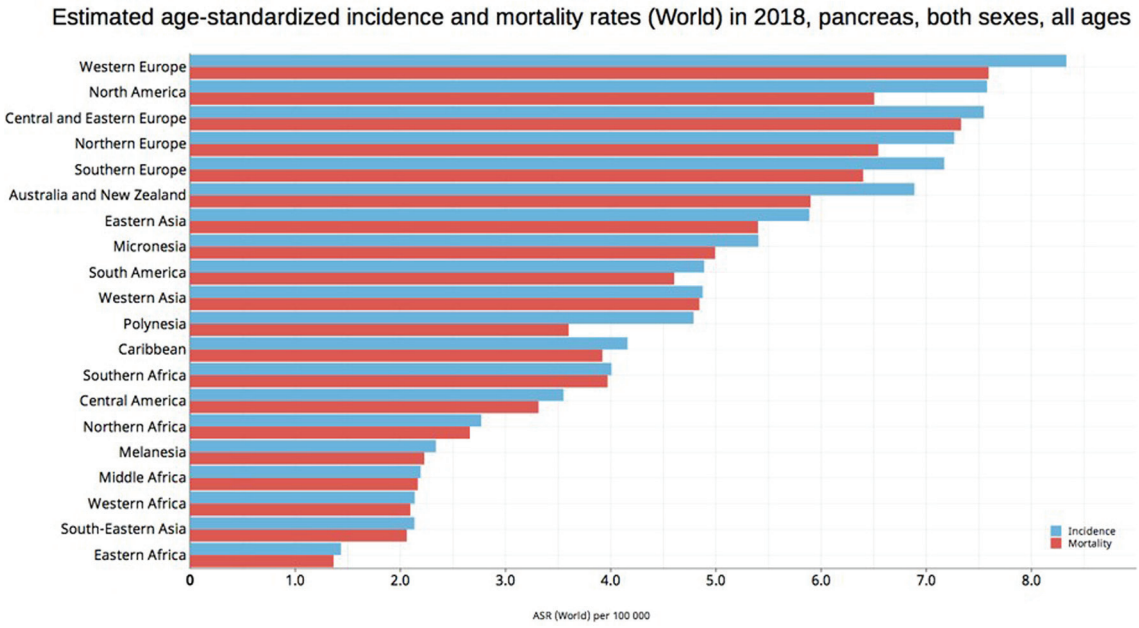

Figure 4. Bar chart shows estimated age-standardized incidence and mortality rates (ASR) for pancreatic cancer in world areas in 2018, including both sexes and all ages (reproduced from http://globocan.iarc.fr/ [2]).

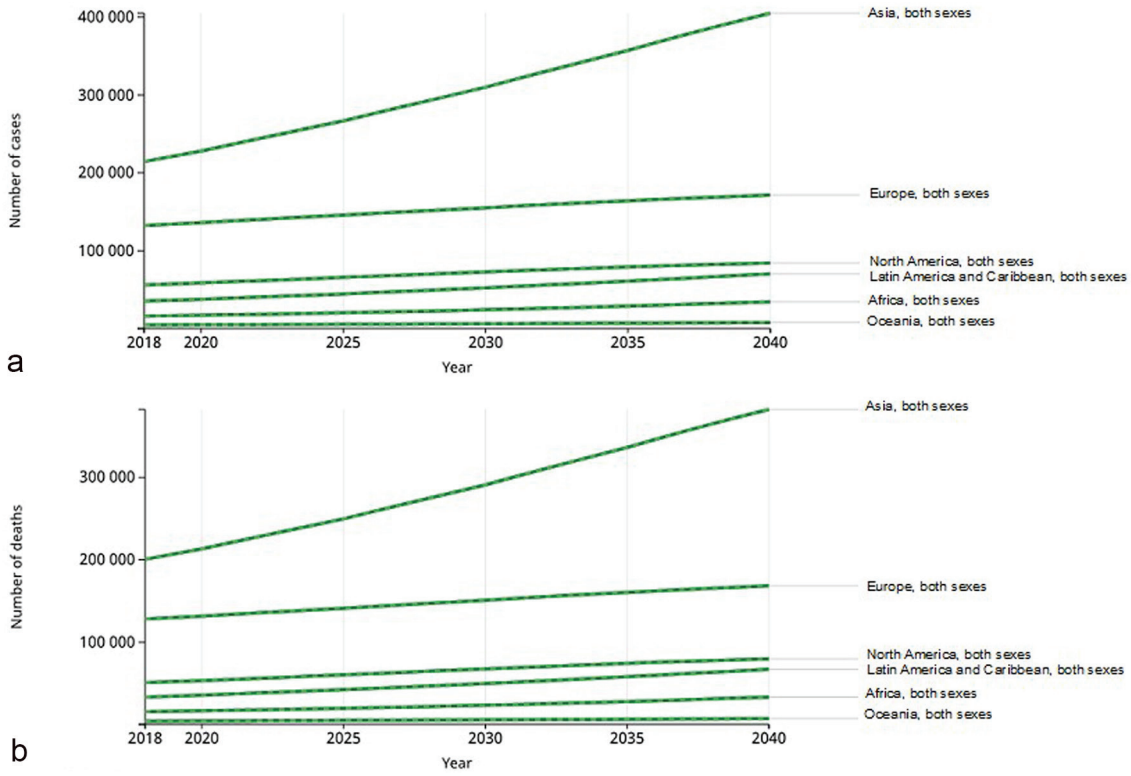

Figure 5. Trends in pancreatic cancer incidence and mortality predicted for the years 2018 to 2040 (reproduced from http://globocan.iarc.fr/ [28]). (a) Estimated incidence from 2018 to 2040, in both sexes and all ages (0 - 70+ years). Asia: 214,499 in 2018 and +190,532 in 2040, (+88.8% of increase); Europe: 132,559 in 2018 and +38,855 in 2040 (+29.3%); North America: 56,002 in 2018 and +28,325 in 2040 (+50.6%); Africa: 16,059 in 2018 and +18,327 in 2040 (+114.1%); Latin America and the Caribbean: 35,270 in 2018 and +35,007 in 2040 (+99.3%); Oceania: 4,529 in 2018 and +3,268 in 2040 (+72.2%). (b) Estimated mortality from 2018 to 2040, in both sexes and all ages (0 to 70+ years). Asia: 200,681 in 2018 and +182,127 in 2040 (+90.8%); Europe: 128,045 in 2018 and +40,444 in 2040 (+31.6%); North America: 50,745 in 2018 and +29,011 in 2040 (57.2%); Africa: 15,458 in 2018 and +17,744 in 2040 (+114.8%); Latin America and the Caribbean: 33,311 in 2018 and +33,637 in 2040 (+101.0%); Oceania: 4,002 in 2018 and +2,985 in 2040 (74.6%)

13 demonstrated that between years 2000 and 2014, there is an age-specific trend towards an increase in pancreatic cancer incidence in two particularly group of ages, 20 - 29 years old and > 80 years in the USA [27]. When ethnicity-specific trends were analyzed, the incidence and mortality rates were higher in whites than in blacks patients [27], which is a reverted trend if we consider that between 1975 and the late 1990s the number of deceased for pancreatic cancer was increased among the black population and then significantly decreased [26].

Temporal trends about the pancreatic cancer incidence and mortality over the period 2018 - 2040 were abstracted from GLOBOCAN 2018. It was observed that there is a trend towards an increase of pancreatic cancer incidence (+77.7% with 356,358 new cases) and mortality (+79.9%, 345,181 deaths) from 2018 to 2040 (Fig. 5a) [1, 28]. These trends vary significantly internationally. The highest incidence of pancreatic cancer will be registered in Africa (+114.1%), followed by Latin America and the Caribbean (+99.3%). On the contrary, the lowest incidence will be registered in Europe (+29.3%). Some regional differences will be observed between men and women. In men, the highest incidence rates will be registered in North America (+52.3% men versus +48.7% women) and Europe (+30.7% men versus +27.8% women). On the other hand, in Asia, Latin America and the Caribbean and Oceania, the highest incidence of pancreatic cancer will be registered among women (women versus men: 97.4% versus 81.9%, 74.3% versus 70.0% and 101.7% versus 96.6%, respectively), while in Africa, the estimated incidence will be the same in both sexes [28].

From 2018 to 2040, the same trend is also observed for the estimated mortality rate for pancreatic cancer among continents in both sexes (Fig. 5b) and for the regional differences between men and women. Indeed, the highest mortality rate is estimated to be in Africa (+114.8%), followed by Latin America and the Caribbean (+101%), while the lowest incidence will be registered in Europe (+31.6%). Additionally, in North America, Europe and Africa, the highest mortality rates will be registered in men (men versus women: +58.7% versus 55.2%, +33.0% versus +30.1% and 115.0% versus 114.5%, respectively), while in Asia, Latin America and the Caribbean and Oceania, the highest mortality rates of pancreatic cancer will be registered in women (women versus men: 98.3% versus 84.4%, 103.4% versus 98.4% and 77.9% versus 74.6%, respectively).

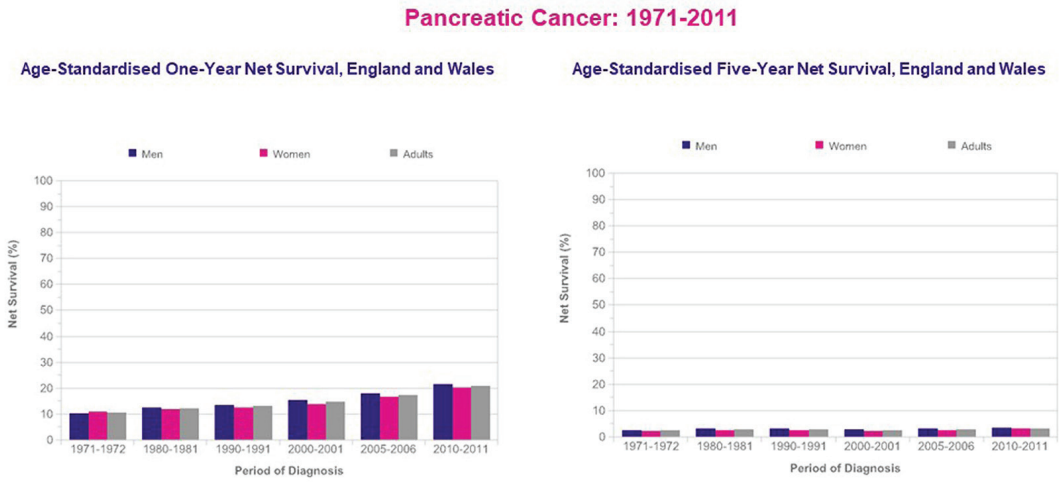

Figure 6. Pancreatic cancer, age-standardized 1-year and 5-year net survival, adults (age: 15 - 99 years), England and Wales 1971 - 2011 (reproduced from reference [34]).

Previous studies have shown that in both sexes, temporal trends in cigarette smoking prevalence were related to temporal trends in pancreatic cancer mortality [13, 20, 29]. In developed countries, decreased smoking, particularly in men, has been widely recognized as the main contributor to the decrease in mortality trends from pancreatic cancer [29], particularly in the USA, UK and Australia where the tobacco control started to be implemented earlier. Besides cigarette smoking, alcohol abuse, high consumption of saturated fat and reduced physical activity may also influence pancreatic cancer mortality. Interestingly, the fact that in underdeveloped countries like Africa there will be a dramatic increase of pancreatic cancer incidence and mortality suggesting that socioeconomic disparities have a significant impact on the trends, as improved diagnostic tools and access to therapies may be very limited.

Possible ways to reverse these trends and improve pancreatic cancer patient outcomes are through the prevention (lifestyle change) and more research and increased awareness of the disease and its symptoms. Early stage and small tumor size (< 2 cm) are two important prognostic factors for pancreatic cancer [30]. Scientists and clinicians around the world are working tirelessly to solve some of pancreatic cancer's biggest questions. Indeed, it would be important to understand the mechanism that turns a healthy pancreatic cell into a cancerous one and to identify clues, or biomarkers that are present in the early and more treatable stage of the disease. These findings will consequently lead to new treatments that can selectively and effectively kill the cancer cells and lower the mortality rate with a higher expectation of survival.

Survival

Although every pancreatic cancer patient's case is unique, and it is not possible to predict each person outcome, population-wide studies reported that a person diagnosed with any cancer, including pancreatic cancer, will survive 5 years. From 2014 to 2018, the 5-years survival rate for pancreatic cancer increased from 6% to 9%, which shows that progress is being made and there is an urgent need to improve the survival even more. Indeed, to date, pancreatic cancer remains one of the most lethal malignancies, with a dismal prognosis and mortality/incidence ratio of 94% [1].

Despite significant differences in incidence and mortality rate between very high/high-human development index (HDI) regions and low-HDI regions, survival rates vary very little between them [1].

Over the period 2014 - 2018, the United States National Cancer Institute data for pancreatic cancer in both sexes and all races showed that 10% of people diagnosed at the local stage had a 5-year survival rate of 32%. If the cancer is at stage III, the 5-year survival rate is 12%. More than half (52%) of people were diagnosed at stage IV and had a 5-year survival rate of 3% [31]. EUROCARE-5 Working Group analyzed the cancer-registries data of patients diagnosed with pancreatic cancer from 2000 to 2007 in 29 European countries and showed that 5-year survival rates were the highest in Croatia (10.9%) and Belgium (10.5%) in both sexes, while the lowest survival rates were reported in Malta (0%) and Northern Ireland (3.02%) [32, 33].

In the UK, the 1-year survival rate for pancreatic cancer in men has increased from 10% during the 1971 - 1972 period to 22% during the 2010 - 2011 period. In women, 1-year survival has increased from 11% to 20% over the same period. However, the 5- and 10-year survival rates for pancreatic cancer have not shown much improvement since the early 1970s (Fig. 6) [34].

Survival rates of pancreatic cancer are affected by several factors, such as age, sex, type of cancer, staging at the time of diagnosis, tumor size, serum albumin level, treatment modalities, differences and availability of healthcare systems, and other factors including overall health and lifestyle [25, 32,

Table 1. Survival Rates According to the Clinical Stage of Pancreatic Cancer

Clinical stage	Five-year survival (%)	
	Exocrine pancreatic cancer	PanNET treated with surgery
IA	14	61
IB	12	61
II	7	52
III	3	41
IV	1	16

35-38]. Because pancreatic adenocarcinoma and the other less common exocrine cancers are usually diagnosed at stage III or IV, it has a very poor prognosis compared to PanNET, and even for those cases not treatable with surgery, the 5-year survival rate is 16% [39] (Table 1). Besides, pancreatic cancer survival rates may be influenced by factors such as the validity of the cancer registry, accuracy and quality of registration data and completeness of follow-up [40, 41].

Etiology and Risk Factors

The etiology of pancreatic cancer has been extensively studied and is the subject of numerous meta-analyses and pooled analyses. Thus far, several risk factors have been identified and can be divided into two categories: modifiable and non-modifiable risk factors [42].

Modifiable risk factors

Modifiable risk factors include smoking, alcohol, obesity, dietary factors and exposure to toxic substances.

Smoking

Over one thousand million people practice smoking of tobacco worldwide, and it represents the most important environmental factor for pancreatic cancer in the world. The International Agency for Research on Cancer has confirmed that smoking is causally associated with pancreatic cancer [13, 43]. The risk of pancreatic cancer increases with the duration of smoking and number of cigarettes smoked daily. The risk is nearly two times higher in smokers than in non-smokers [44-46]; additionally, a recent meta-analysis of 82 studies found that the relative risk (RR) of pancreatic cancer was RR = 1.74 for current and RR = 1.2 for former smokers and the risk persists for at least 10 years after smoking cessation [47-49].

In 2012, the European Prospective Investigation into Cancer (EPIC) study showed that the risk of pancreatic cancer increases for every five cigarettes smoked per day and also, the passive smoking can increase the risk of pancreatic cancer by 50% [49, 50]. While smoking prevalence has declined in many developed countries, it remains high in others and is increasing among women and in developing countries. For example, in 2011, a study estimated that around 26.2% of pancreatic cancers in men and 31.0% in women were linked to tobacco smoking in the UK [20], while in the world's two most populous nations, India and China, smoker users are home to more smokers than the entire population of Europe [51].

The risk of pancreatic cancer associated with smoking remains elevated after allowing for potential confounding factors such as alcohol consumption.

Alcohol

Based on many studies, the risk of pancreatic cancer is undoubtedly increased by high alcohol consumption (more than three drinks per day), whereas there was no association found with low-to-moderate alcohol intake [52-54]. A large case-control study in 2010 showed increased risk even at the consumption of 60 g/day or more of liquor (spirits) but found no association with beer or wine [55].

A recent study found that heavy alcohol consumption was associated with a significant increase of pancreatic cancer risk among current smokers (age-adjusted odds ratio (OR) = 4.04, 95% CI: 1.58 - 10.37), whereas it was not observed among non-smokers (age-adjusted OR = 2.01, 95% CI: 0.50 - 8.18). Furthermore, low-to-moderate alcohol intake was associated with increased pancreas cancer risk among current smokers [56], suggesting that smoking can modify the alcohol-cancer relationship. However, the association between alcohol and smoking is very close. Therefore, it may be challenging to implicate alcohol as an independent risk factor for pancreatic cancer.

Obesity

Obesity is associated with increased risk for several types of cancer including pancreatic cancer [57]. Some studies found that obesity increases the incidence and mortality of pancreatic cancer [58, 59]. A study by Li et al [60] found that being overweight (body mass index (BMI): 25.0 - 29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2) during early adulthood is associated with a higher risk of pancreatic cancer. Furthermore, obesity at an older age (30 - 79 years) was associated with lower overall survival.

According to an American Cancer Society (ACR) study, in both sexes, risk of pancreatic cancer among obese was higher

(RR = 2.08) compared to people of healthy BMI (18.5 - 24.9 kg/m^2) [59]. A recent meta-analysis has confirmed the hypothesis that both general and abdominal fatness is associated with increased pancreatic cancer risk [61]. Besides, physical inactivity (which can contribute to fat accumulation and overweight) has been linked to increased risk of pancreatic cancer.

Dietary factors

It seems reasonable that diet would affect the risk of different digestive diseases and cancers, including those of the pancreas. Dietary factors impact up to 30-50% on pancreatic cancer, and there is evidence that certain foods are associated at higher risk, while others are even protective [42, 62, 63].

Consumption of red meats (especially when cooked at high temperature), processed meats, cholesterol, fried foods and other foods containing nitrosamines may increase the risk of pancreatic cancer [64, 65]. It is possible that carcinogens in meat and nitrite or N-nitroso compounds that are used for preserving processed meats are involved in pancreatic cancer [66]. The results of a meta-analysis that included 11 case-control studies showed that red meat intake increased the pancreatic cancer risk by about 48% (95% CI: 1.25 - 1.76). On the other hand, high intake of vegetables and fruits, especially those enriched in citrus and antioxidants, has a protective action, decreasing the risk by 38% (95% CI: 0.54 - 0.73) and 29% (95% CI: 0.59 - 0.84), respectively [67].

Also, another meta-analysis of 11 prospective studies found a positive association between pancreatic cancer incidence and high consumption of red (120 g/day) or processed meat (50 g/day) (RR = 1.13 and RR = 1.19 respectively) [68]. However, some studies have not supported these findings [69], or have provided support for the association among men only [70]. For example, the EPIC study found no association between pancreatic cancer risk and intake of red and processed meat, while poultry consumption was associated with an increased risk [71]. Interestingly, two studies reported that frequent nut consumption significantly lowers the risk of pancreatic cancer in women [72, 73]. Additionally, in a large UK cohort study in 2016, mortality for pancreatic cancer was lower for low meat eaters (about 30-45% lower mortality), as well as vegetarians and vegans (about 50% lower mortality) compared with regular meat eaters [74].

Occupational exposures

The etiological fraction of pancreatic cancer due to occupational exposures (involving exposure to metalworking and pesticides) within a population was estimated at 12%.

A meta-analysis of occupational exposures and pancreatic cancer reported an increased risk with nickel exposure [75]. However, in occupational settings, nickel may be associated with high concentrations of polychlorinated biphenyls, and the latter compounds could account for the observed increased risk [76, 77]. Carcinogenic mechanisms of nickel may include increasing DNA methylation, inhibiting DNA repair and inducing apoptosis through the generation of reactive oxygen species [78-82].

Additionally, few studies have found a link between exposure to cadmium and arsenic and pancreatic cancer risk. Cadmium is a non-essential metal that is known to accumulate in the human pancreas increasing the risk and mortality of pancreatic cancer [83, 84]. Cadmium is a well-established carcinogen that acts on different steps of carcinogenesis, inhibiting DNA repair and causing genomic instability [85-87]. Furthermore, it causes transdifferentiation of pancreatic cells, inhibits DNA repair and induces or regulates the activity of several oncogenes or tumor-suppressor proteins that are expressed in human pancreatic cancer [83, 88, 89]. Arsenic exposure has been associated with increased cancer risk [90], but regarding its association with pancreatic cancer, little has been published. A potential link between childhood exposure to milk powder contaminated with arsenic and an almost two-fold excess mortality due to pancreatic cancer was recently reported [91, 92]. Inorganic arsenic is a highly toxic and carcinogenic metalloid, which can induce oxidative stress leading to inhibition of DNA repair [90, 93, 94] and DNA strand breaks as well as DNA adducts [95]. Moreover, alterations in the methylation status of oncogenes and tumor-suppressor genes, mediated by arsenic, may also play a role in carcinogenesis [96].

As opposite, selenium, which is an essential micronutrient [97, 98], has been inversely associated with several cancers including pancreatic [99-103], while only a small study published in 1989 showed an increased risk of pancreatic cancer due to high selenium levels [104]; however, no replication studies have been published. Aberrant expression patterns of some selenoproteins suggest that they are relevant in scavenging reactive oxygen species and diminishing oxidative damage [105, 106]. Also, selenium may boost p53 activity, leading to either DNA repair or apoptosis [107]. Selenium also seems to play a role as the antagonist of arsenic, cadmium and lead, decreasing the oxidative stress caused by exposure to these elements [108, 109].

Finally, high-quality studies are called for on interactions between occupational, environmental and lifestyle factors as well as interactions between genes and the environment.

Non-modifiable risk factors

Risk factors that are not modifiable include gender, age, ethnicity, diabetes mellitus, family history of pancreatic cancer, genetic factors, chronic infections, non-O blood group and chronic pancreatitis.

Gender

Pancreatic cancer is more common in men than in women. Globally, the incidence of pancreatic cancer is 5.5 per 100,000 for men and 4.0 per 100,000 for women [1]. Pancreatic cancer occurs more in men possibly due to environmental or occupational risk factors as well as lifestyles such as heavy smoking habit and high alcohol intake in men; however, it is also possible that there may yet be undiscovered genetic factors influencing cancer incidence and mortality in males and females.

Age

SEER Cancer Statistics review states that pancreatic cancer is predominantly a disease of an older population and most of the patients are older than 50 years [10]. Indeed, the risk of developing pancreatic cancer increases with age, with the highest peak occurring between 60 and 80 years of age [1, 8, 12]. It rarely occurs before the age of 40 years, and the average age for more than half of the cases of pancreatic adenocarcinoma is 71 years. The reason for this late age onset is not apparent yet. It may be possible that from the moment a pancreatic lesion or inflammatory condition occurs, it takes several years before it will eventually switch into a malignant neoplasm. However, further studies are needed in this subject.

Ethnicity

Many studies have shown significant differences in the incidence of pancreatic cancer between races [110-112]. Pancreatic cancer incidence rates for African-Americans are higher than Caucasians, while the incidence is the lowest in Asian-Americans and Pacific Islanders [113]. Generally, the risk of pancreatic cancer rate is considerably higher in black people than in any other racial group [114]. Differences in the incidence of pancreatic cancer between races can be attributed to modifiable risk factors such as diet, alcohol, smoking and vitamin D insufficiency.

Nevertheless, some population-based studies have reported that racial disparities in pancreatic cancer are not entirely explained by the known and suspected risk factors. Also, other factors such as genetic factors acquired mutations from known toxins, e.g. the ability to detoxify tobacco products, oncogene mutation and biomarker immune expression, may contribute to the increased risk of pancreatic cancer [115, 116]. Studies comparing the oncogene mutations and biomarker immune expression among Chinese, Japanese and Western patients, showed that Asian patients with pancreatic cancer have different expressions of KRAS and p53 than Western patients [117, 118], suggesting that each race has genetic and molecular diversity that can affect the incidence of pancreatic cancer, and may also explain the difference in survival rates after treatment of pancreatic cancer in racial disparities. In general, it seems that Asian patients have a better survival rate than non-Asian patients [119].

Diabetes mellitus

The positive association between both types I and II diabetes and the risk of pancreatic cancer has been reported in numerous studies [63, 120-124]. Pancreatic cancer burden study in Italian population estimated that diabetes is attributable to 9.7% of pancreatic cancers [125]. Diabetes mellitus may be associated with a 1.8-fold increase in the risk of developing pancreatic cancer, particularly in Asians and Hispanic men in comparison with Whites and Blacks [126, 127]. Pancreatic cancer risk decreases with the duration of diabetes, but a 30% excess risk persists for more than two decades after diagnosis of diabetes [128]. Oral anti-diabetic medications or insulin use were associated with a reduced risk of pancreatic cancer [126, 128]. Among some patients with pancreatic cancer and peripheral insulin resistance, removal of the tumor improved glucose metabolism [129], providing evidence that altered glucose metabolism may be a result of the tumor.

An in-depth study of the association between diabetes and risk of pancreatic cancer may become of fundamental importance for two main reasons: the possible use of recent onset diabetes as a marker of the disease and, in particular, as a specific marker of pancreatic cancer, and the selection of a population at risk for pancreatic cancer. For example, Gullo et al [130] suggested that insulin resistance and diabetes may be induced by precancerous conditions or undiagnosed cancer of the pancreas, although it was shown that the risk of pancreatic cancer is 1.5- to 2-fold higher in type II diabetes even when impaired glucose tolerance is detected more than 5 years [131] or 10 years before the onset of cancer [132]. Therefore, further studies are needed to understand whether diabetes can predict the onset of pancreatic cancer or be a marker.

Family history

It is estimated that about 5-10% of individuals with pancreatic cancers report a family history of pancreatic cancer [20, 133-136]. Familial pancreatic cancer is defined in most studies as families in which a pair of first-degree relatives (parent, sibling or child) have been diagnosed with pancreatic cancer. Prospective analysis of families with this malignant disease shows that first-degree relatives of individuals with familial pancreatic cancer have a nine-fold increased risk of pancreatic cancer over the general population [4]. This risk doubles when at least two first-degree relatives in the family have pancreatic cancer [137] and rise to 32-fold higher in kindreds with three or more first-degree relatives with pancreatic cancer [138]. Furthermore, evidence indicates that the risk is the highest in kindreds with familial pancreatic cancer with a case of young-onset pancreatic cancer (age < 50 years) in the family compared with those without a young-onset case [139]. Patients with familial pancreatic cancer also have more precancerous lesions than those with sporadic pancreatic cancers [136] and have an augmented risk of developing extra-pancreatic cancers [140].

Genetic factors

Genetic variation or mutation (Germ-line mutation) plays an important role in increased risk of pancreatic cancer [141]. Approximately 10% of patients with pancreatic cancer have some genetic predisposition such as gene variations or alterations to developing the disease [142]. Several germ-line mutations have been identified to be involved in hereditary forms of pancreatic cancer, such as *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CDKN2A*, *APC*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *PRSS1* and *STK11* [138, 143]. Pancreatic cancer is also found to be associated with some familial cancer syndromes such as hereditary non-polyposis colon cancer (Lynch syndrome), the familial

atypical multiple mole melanoma syndrome, Peutz-Jeghers syndrome, hereditary breast and ovarian cancer syndrome, familial adenomatous polyposis and Li-Fraumeni syndrome.

Germ-line *BRCA2* gene mutations account for the highest proportion of known causes of inherited pancreatic cancer and have been identified in 5-17% of families with familial pancreatic cancer [144-146]. *PALB2* (partner and localizer of *BRCA2*) has been identified as a pancreatic cancer susceptibility gene [147], and germ-line mutations are recorded in up to 3% of patients with familial pancreatic cancer [148, 149]. Furthermore, germ-line *CDKN2A* gene mutations are noted generally in families with familial atypical multiple-mole melanoma, while germ-line *STK11* mutations in patients with Peutz-Jeghers syndrome and germ-line *PRSS1* mutations in people with hereditary pancreatitis [138]. Additionally, four main genes in inherited genetic mutations that have a special role in increased risk of pancreatic cancer include *KRAS*, *p53* and *SMAD4* [150].

Infection

Gastric colonization with *Helicobacter pylori* (*H. pylori*) is also associated with greater risk of pancreatic cancer, with an estimated population attributable fraction of 4-25% [63]. A meta-analysis of seven studies reported an increased risk of pancreatic cancer in people infected with *H. pylori* [151] and that this effect is strain-specific (CagA-positive strain) [151, 152]. One hypothesized mechanism behind that is that *H. pylori* colonization enhances the pancreatic carcinogenic effect of *N*-nitrosamines conveyed by smoking or dietary sources [153]. This effect is modulated by host inflammatory responses to the organism, by various virulence and other properties of the *H. pylori* itself, and by the host-organism interactions. However, on the other hand, many studies did not observe any correlation between *H. pylori* infection and the risk of pancreatic cancer [154]. However, all together these data are not sufficient to drive conclusions, so further studies evaluating this association are needed.

Some studies have reported the association between pancreatic cancer with some chronic infections such as hepatitis B and C virus (HBV and HCV) [155].

ABO blood group

The antigens of the ABO system are expressed on red blood cell membranes as well as on the surface of several other normal and pathological cells and tissues. Following the first clinical observations more than 60 years ago, the role of ABO blood group in cancer biology has been intensely studied by several investigators, and it is now widely recognized that ABO antigens are associated with the risk of developing several types of cancers, including pancreatic [156-160].

A study in the UK [161] and a six-country study [162] observed an increased risk of pancreatic cancer for blood group A individuals. A study in Italy [163] found an increased risk of pancreatic cancer among blood group B individuals, and also a cohort study in the USA [164] found increased risk for individuals who self-reported blood types A, B and AB compared with O. Finally, findings of genome-wide association study "Panscan I" showed an association between non-O blood group and pancreatic cancer [165], and their results were then replicated by Rizzato et al [166]. Studies about the association with ABO group and the overall survival are controversial. The study of Dandona et al [167] conducted on 417 patients also confirmed that non-O blood group is associated with an increased risk of developing pancreatic cancer. However, the overall survival was not affected by the blood type. By contrast, the study of Ben et al [155] on 1,431 Chinese patients found that the median overall survival of patients with blood type O was longer compared to non-O blood group. Multivariate analysis revealed that blood group O was an independent predictor of long-term survival in a study based on 627 patients undergoing resection for pancreatic ductal adenocarcinoma [168]. Finally, a study by Wang et al [169] failed to find evidence of an impact of ABO blood type on the prognosis of pancreatic cancer patients. Proposed mechanisms in support of this link include inflammation, immune-surveillance for malignant cells, intercellular adhesion and membrane signaling.

However, it now seems consolidated that altered ABO glycosyltransferase activity plays a crucial role in carcinogenesis, mainly by affecting cell proliferation, tumor invasion and metastatic spread [34, 170]. Interestingly, an association among non-O blood group, *H. pylori* colonization and risk of pancreatic cancer was described in a meta-analysis study [151]. The hypothesis is that the presence of the terminal A or B blood group antigens in gastrointestinal mucins influences the properties of *H. pylori* binding and thus, the risk of pancreatic cancer is more significant for non-O individuals with seropositivity for *H. pylori*.

Pancreatitis and Pancreatic Cancer

Pancreatitis is an inflammation of the pancreas that can be acute or chronic and induces pancreatic damage because the activation of digestive enzymes occurs before they are released in the small intestine and consequently, they attack the pancreas.

Recurrent bouts of acute pancreatitis can cause glandular damage and lead to chronic pancreatitis by inducing a progressive, destructive inflammatory process that ends in the total destruction of the pancreas and results in malabsorption of dietary nutrients, diabetes mellitus and severe, unrelenting pain [171].

In recent decades, accumulating evidence has defined that longstanding pre-existing chronic pancreatitis as a strong risk factor for pancreatic cancer [172-174]. However, only 1.8% of these patients will develop pancreatic cancer within 10 years from the diagnosis and 4% after 20 years [175-177]. A considerable proportion of cases of pancreatitis is thought to be a consequence of pancreatic tumor-related ductal obstruction [173, 177-179], indicating that this condition can be either a risk factor or a sign of early disease.

Chronic pancreatitis has several causes such as hereditary and idiopathic, but alcohol abuse is the most frequent cause of it [180, 181]. Although ~70% of chronic pancreatitis cases were attributed to alcohol abuse, ~95% of alcoholics never de-

velop it [181]. Patients with hereditary pancreatitis (mutations associated cationic trypsinogen gene (*PRSS1*) and the serine protease inhibitor, Kazal type 1 gene (*SPINK1*)) have a risk to develop pancreatic cancer that is 50 - 60 times greater than expected [182]. The EUROPAC study, the largest study of hereditary pancreatitis to date reporting the incidence of pancreatic cancer in 112 families from 14 countries, confirms a high risk of pancreatic cancer in subjects with hereditary pancreatitis, regardless of underlying mutation [183]. Additionally, these mutations may increase the risk of pancreatitis diagnosis at younger ages, and in some of these patients, younger ages at diagnosis of pancreatic cancer [173, 181, 184]. Also, patients with hereditary pancreatitis may be at higher risk of pancreatic cancer than patients with other forms of pancreatitis [173, 181, 183, 185, 186].

The association between long-standing chronic pancreatitis and cancer has now been established. Pancreatic cancer develops in the setting of chronic pancreatitis from all known etiologies but appears to require 30 - 40 years of inflammation before an appreciable percentage of patients develop pancreatic cancer.

Screening and Prevention

Early detection may be the key to reduce mortality and may be supported by patients' screening and prevention.

Screening of large groups in the general population is not currently considered effective to detect the disease at its early stage, although newer techniques, and the screening of tightly targeted groups (especially of those with family history), are being evaluated [187, 188], including blood markers for pancreatic cancer CA19-9, CA-50, SPAN-1, DUPAN-2, cell surface-associated mucins (MUC), carcinoembryonic antigen and heat shock proteins [189, 190]. However, these tests have not been well studied yet. Furthermore, the focus of screening efforts up to now has been to detect preinvasive lesions, rather than early pancreatic cancer, since resection of preinvasive lesions can prevent development of an invasive pancreatic cancer, whereas once an invasive pancreatic cancer develops, its spread beyond the pancreas is probably rapid, restricting use of markers of invasive pancreatic cancer. Therefore, primary prevention is of utmost importance.

Understanding the etiology and illuminating the risk factors identifying high-risk individuals are essential to the primary prevention of this often rapidly fatal disease. The best preventive strategy against pancreatic cancer is risk reduction, acting on the modifiable risk factors (tobacco smoking, overweight and alcohol use, reducing red meat consumption and increasing fruit and vegetable intake, having regular exercise) and through regular control of health issues [12, 20, 48, 133].

Tobacco smoking is highly associated with pancreatic cancer risk, and it has been estimated that by prevention of smoking, about 30% of pancreatic cancers could be prevented [20]. Interestingly, after 10 years of smoking cessation, the risk is reduced to the levels of a non-smoker [49].

Dietary modification is important in preventing pancreatic cancer for several reasons. First, high consumption of red and processed meat is associated with greater risk of pancreatic cancer [64, 65], while high fruit and vegetable intake [67], as well as nut consumption, is found protective [72, 73]. Therefore, a well-balanced diet enriched in fruits, vegetables and vitamins is highly recommended. Also, lower intake of saturated fat, together with increased physical activity, is highly suggested to help to reduce the risk of overweight or obesity, which are also associated with risk of pancreatic cancer.

Patients who have cystic neoplasms of the pancreas develop pancreatic cancer in about approximately 60-70% of cases [191]. The complete extirpation of cystic neoplasms is now performed as a cancer preventive strategy [192]. Furthermore, limitation of alcohol use is necessary to reduce the risk of pancreatic cancer through the development of pancreatitis [181].

Non-modifiable risk factors cannot be controlled. However, patients with family history and genetic susceptibility may undergo screening tests for early detection of pancreatic cancer. Unfortunately, there are no screening tests yet available that may be widely applied, and researchers are working on developing effective screening tests. For people with high risk of pancreatic cancer (including patients with hereditary pancreatitis or with a family history of pancreatic cancer), some screening techniques, such as endoscopic ultrasound and spiral computerized tomography, are promising but have not been thoroughly evaluated [193]. There is no consensus about when to initiate the screening; however, in patients with hereditary pancreatitis (PRSS1 germ-line mutation) who have a higher risk of early onset of pancreatic cancer, screening can begin at the age of 40 years [194].

Diagnosis

Pancreatic cancer is mostly diagnosed in an advanced stage, and 80-90% of patients have unresectable tumors at the moment of diagnosis. There are several reasons because this occurs.

First, early-stage pancreatic cancer is usually clinically silent, and most people who present with symptoms attributable to pancreatic cancer have advanced disease. Symptoms are non-specific and include abdominal pain, jaundice, pruritus, dark urine and acholic stools, which may be presenting symptoms as a result of an obstruction within the biliary tree [195]. Furthermore, anorexia, weight loss (which can arise from anorexia), early satiety, dyspepsia and nausea occur too [196], while less common manifestations include panniculitis and depression. Given the wide range of non-specific symptoms, there are a broad number of diseases that need to be differentiated [7], which include but are not limited to: cholangitis, cholecystitis, cholelithiasis, choledocholithiasis, choledochal cysts, duodenal or gastric ulcers, gastritis, pancreatitis, abdominal aortic aneurysm, lymphomas, and primary or secondary cancers of the biliary tree, liver, pancreas, stomach or intestine. Therefore, diagnosis can be delayed or missed, which makes pancreatic cancer the most common tumor detected at the autopsy studies [17, 24]. To date, there are several diagnostic tools available, such as abdominal ultrasonography, tri-phasic pancreatic-protocol CT (which is the standard for diagnosis and staging [197, 198]), magnetic resonance imaging (MRI) [7, 138] and endoscopic ultrasound-guided fine-needle aspira-

tion for cytological diagnosis [7] (which sensitivity is reported to be about 80% [199]). Additionally, in symptomatic patients, measurement of blood levels of cancer antigen 19-9 can help to confirm the diagnosis and predict prognosis and recurrence after resection [200]; however, it cannot stand as an individual screening tool for asymptomatic patients because it is not tumor-specific [201].

Of note, diagnostic tools and the change in use of various diagnostic modalities vary between developed and undeveloped countries, which may explain the observed vast differences in incidence and mortality rates. For example, in 2012, Europe carried one-third of the overall incidence, which likely reflected the more accurate diagnosis of pancreatic cancer rather than etiology [19].

Conclusions

Pancreatic cancer is a global problem that requires a global solution. Although its etiology remains still mostly unknown, many risk factors have been identified, and among them, smoking has been widely recognized as the main contributor to the high mortality rates of pancreatic cancer [13, 29]. Healthcare professionals and policy makers could make more efforts to control the associated risk factors that may range from advocating for lifestyle changes, awareness campaigns and to imposing more strict smoking-related laws. Analysis of pancreatic cancer epidemiology may be the key to elucidating the etiology of pancreatic cancer and thus, the cornerstone of developing future cancer control strategies.

Conflict of Interest

None of the authors have conflict of interest.

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