Review paper

Pancreatic cancer trends in Europe: epidemiology and risk factors

Tendencje dotyczące raka trzustki w Europie – epidemiologia i czynniki ryzyka

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Medical Studies/Studia Medyczne 2019; 35 (2): 164–171
DOI: https://doi.org/10.5114/ms.2019.86336

Key words: risk factors, epidemiology, pancreatic cancer, incidence, mortality.

Słowa kluczowe: czynniki ryzyka, epidemiologia, rak trzustki, zapadalność, śmiertelność.

Abstract

Pancreatic cancer is the 12th most common cancer worldwide and the seventh leading cause of cancer-related deaths worldwide. However, it is the seventh most common cancer in Europe. The estimated number of cases of pancreatic cancer worldwide in 2018 was 458,918 with a male to female ratio of 1:1.13. Among those 458,918 patients, 132,559 cases were found in Europe. Rates of pancreatic cancer are 3–4 times higher in the developed world. With incidence and mortality rates being very close, pancreatic cancer is considered one of the deadliest of all cancers. Lifestyle in developed nations, including the rise in physical inactivity and obesity, tobacco smoking, consumption of alcohol, dietary factors, and occupational exposures, may be responsible for the increased incidence of pancreatic cancer. Updated statistics on the epidemiology of pancreatic cancer along with a better understanding of the risk factors are essential for the primary prevention of this disease.

Streszczenie

Rak trzustki jest dwunastym najczęściej występującym nowotworem i siódmą główną przyczyną zgonów związanych z rakiem na świecie. Jest to także siódmy najczęściej występujący nowotwór w Europie. Liczba przypadków raka trzustki na świecie w 2018 roku wynosiła 458 918, przy stosunku mężczyzn do kobiet 1 : 1,13. W Europie stwierdzono 132 559 przypadków. Występowanie raka trzustki jest 3–4 razy częstsze w krajach rozwiniętych. Ponieważ częstość występowania i śmiertelność są bardzo zbliżone, rak trzustki jest uważany za jeden z najbardziej śmiertelnych nowotworów. Styl życia w krajach rozwiniętych, w tym brak aktywności fizycznej i otyłość, palenie tytoniu, spożywanie alkoholu, czynniki dietetyczne i narażenie zawodowe, może odpowiadać za zwiększoną częstość występowania raka trzustki. Zaktualizowanie statystyki dotyczącej raka trzustki oraz lepsze zrozumienie czynników ryzyka są niezbędne do zapobiegania tej chorobie.

Introduction

Based on the GLOBOCAN 2018 estimates by the International Agency for Research on Cancer (IARC), pancreatic cancer is the 12th most common cancer worldwide and the seventh most common cancer in Europe [1, 2]. With the incidence and mortality rates being very close, pancreatic cancer is considered one of the deadliest of all cancers. Rates of pancreatic cancer are 3–4 times higher in the developed world, particularly in Europe, North America, Australia, and New Zealand, despite the efforts and campaigns that aim at raising awareness in these countries to control the disease [3–5].

The most common type of pancreatic cancer is adenocarcinoma (tumour of the exocrine pancreas), which accounts for almost 85% of cases [6]. In most of the cases (around 75%) the cancer occurs at the head or neck of the pancreas, while 15–20% occur at the body, and only 5–10% at the tail of the pancreas.

The symptoms of pancreatic cancer are subtle, especially the body and tail tumours; therefore, the diagnosis of pancreatic cancer requires a physician with a high index of suspicion. Surgical resection is potentially curative in the very early stages of the disease [7]. However, most of the patients are diagnosed in the late stages of pancreatic cancer after metastasis has occurred [8]. Prognosis is generally very poor, with most patients dying 4–6 months after being diagnosed with the disease. Around 28% of the cases survive a year after being diagnosed, and the percentage declines to only 9% after 5 years.

The link between tobacco smoking and pancreatic cancer explains the variation in incidence between the different countries, as well as between sexes. Genetic predisposition, obesity, diabetes mellitus, and alcohol consumption are also important risk factors; however, the exact causes are not fully determined [6].

The number of deaths from pancreatic cancer is expected to be greater than the number due to breast cancer by 2025 [9]. Therefore, studying pancreatic cancer trends in Europe is important because it sheds light on the effectiveness of the measures previously taken by European countries to control pancreatic cancer. Also, the rising incidence and mortalities from pancreatic cancer should make us focus on formulating a plan to fight the disease in the future.

Epidemiology

Incidence

The estimated number of cases of pancreatic cancer worldwide in 2018 was 458,918, with a male to female ratio of 1 : 1.13. Among those 458,918 patients, 132,559 cases were found in Europe [1]. This indicates that around 29% of pancreatic cancer patients are found in such a small continent. Europe comes in second place regarding pancreatic cancer incidence (number of new patients), behind the Western Pacific region, and the estimated highest age-standardised incidence rates per 100,000 individuals exist in Europe (9.3 per 100,000 males and 6.3 per 100,000 females) [1]. Estimated incidence rates in each of the sexes separately, in the different world regions, showed that pancreatic cancer rates are highest among males in Central and Eastern Europe (9.9 per 100,000 men), namely Latvia and the Republic of Moldova, with a rate of 15.3 per 100,000 males in both countries [10]. The highest incidence rates among women were in Western Europe with a rate of 7.2 per 100,000 women. Hungary had the highest rate in Europe and was second highest globally regarding the incidence of pancreatic cancer among females (9.1 per 100,000), followed by Slovakia, Czech, and Serbia (all data extracted from GLOBOCAN 2018) [1].

Among European Union countries, Germany, France, and Italy, respectively, are the three counties with the highest numbers of pancreatic cancer patients (Figure 1). The incidence in Poland is 7.1 per 100,000 in 2018 [1]. The age of peak incidence is between 60 and 80 years of age.

Mortality

Pancreatic cancer resulted in 432,242 deaths worldwide in 2018, with 128,045 of them in Europe. This estimate shows that fatalities due to pancreatic cancer came in fourth place among fatalities from all cancers in Europe, following lung, colorectum, and breast [1, 6, 11, 12].

Mortality rates from pancreatic cancer in Europe in 2018 reached 8.8 per 100,000 males and 5.7 per 100,000 females. Corresponding with the incidence rates, mortality rates were most common among men in Central and Eastern Europe (7.9 per 100,000) and women in Western Europe (6.3 per 100,000). The Republic of Moldova had the most prominent mortality rates in Europe (Figure 2), while the Russian Federation had the highest total number of deaths from pancreatic cancer (226,910 men and 205,332 women) [1]. The mortality rate in Poland was 6.9 per 100,000 in 2018 [1].

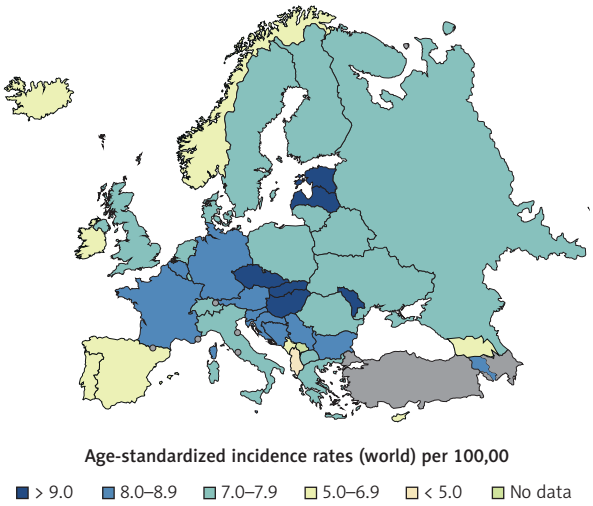

Figure 1. Map showing estimated age-standardised incidence rates in 2018, due to pancreatic cancer, both sexes, all ages, within Europe. Data obtained from Globocan 2018. Map created from https://mapchart.net/

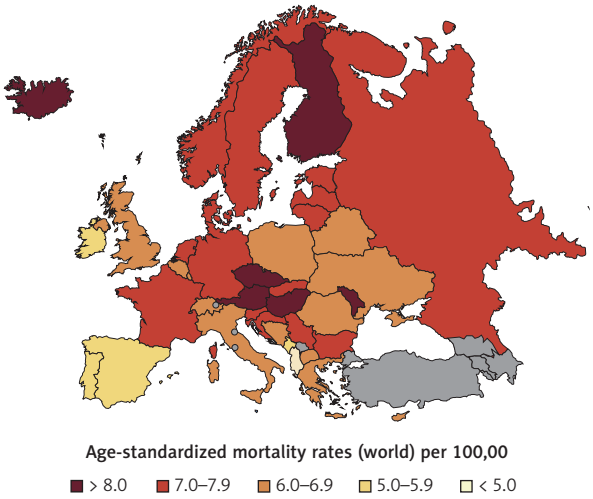

Figure 2. Map showing estimated age-standardised mortality rates in 2018, due to pancreatic cancer, both sexes, all ages, within Europe. Data obtained from Globocan 2018. Map created from https://mapchart.net/

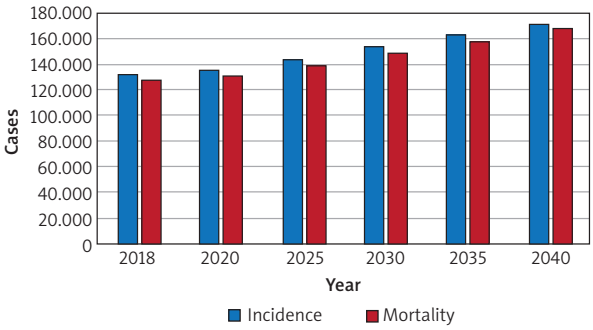

Figure 3. Estimated number of incident cases and deaths from 2018 to 2040, due to pancreatic cancer, both sexes, all ages, within Europe. Data obtained from Globocan 2018

Trends

In 2012, the number of patients diagnosed with pancreatic cancer worldwide, according to GLOBOCAN 2012, was 337,872, which means that the incidence increased by 121,046 patients in 6 years [13]. Recent advances in imaging and other diagnostic tools may have contributed to the apparent increase in pancreatic cancer incidence because more patients are diagnosed in the early stages of the disease [14]. This may have also affected the 5-year survival estimates.

Pancreatic cancer incidence and mortality in Europe were at their peak in the 1970s and 1980s in both men and women, and they markedly declined in the 1990s. Two studies showed this, one of which was conducted in England and Wales, and the other included 22 different European countries [15, 16]. Survival at 5 years has improved over time for patients with pancreatic cancer, worldwide. In 1975, the 5-year survival (regardless of the stage of the disease) was only 3%. While in 2006, the percentage increased to 7% [17]. Nowadays, 5-year survival has reached approximately 9%.

A retrospective observational study was published in 2013. It analysed data from different cancer registries across Europe and included more than 10 million patients with cancer from 1999 until 2007 [18]. The study stated that the average 5-year survival for pancreatic cancer was 6% in men and 8% in women in Europe. The relative 5-year survival was below average in the United Kingdom as compared to the rest of Europe. The percentage was 4% in men in England, Wales, and Scotland, and only 2% in Northern Ireland. In women, the average 5-year survival was 5% in England and 7% in Wales [18, 19].

The highest rate of 5-year survival in Europe was among men in Croatia (around 11%) and women in Belgium. (12%). Unlike many other cancers; such as prostate, breast, rectal cancer, and non-Hodgkin lymphoma, pancreatic cancer survival rates have not improved significantly over the past few decades in Europe [18]. By 2040 the estimated number of new pancreatic cancer cases in Europe is expected to reach 171,414 patients (Figure 3). Moreover, the number of deaths expected from pancreatic cancer is 168,489 [20]. The increasing numbers of pancreatic cancer cases are consistent with the demographic changes, while there is no anticipated change in the risk of developing the disease.

Pancreatic cancer survival is largely dependent on the patient's age. Between 15 and 49 years of age, five-year survival rates were around 17% in men and 26% in women in England between 2009 and 2013. Survival rates were much lower in the other age groups [21]. Western Europe is expected to replace Central and Eastern Europe as the region with the highest number of new cases, as well as mortalities, from pancreatic cancer by 2040 [20, 22].

Risk factors

Several risk factors have been identified relating to pancreatic cancer development. Here we discuss the important risk factors that play a role in the pathogenesis and development of pancreatic cancer. Risk factors of pancreatic cancer are mainly classified into two types: modifiable and non-modifiable. Modifiable risk factors include alcohol, smoking, diet, obesity, and exposure to toxic chemicals or substances. Non-modifiable risk factors include age, gender, ethnicity, family history and genetic factors, diabetes mellitus, chronic infections, chronic pancreatitis, and non-O blood group. Here we discuss mainly the modifiable risk factors for pancreatic cancer because these influence the epidemiology of pancreatic cancer worldwide.

Smoking

Smoking is a significant risk factor for pancreatic cancer development, and it can account for about 20–25% of the cases of pancreatic cancer [23, 24]. Pooled studies have attributed 22% of the pancreatic cancer cases in the United Kingdom (UK) to smoking [25]. Data from the International Pancreatic Cancer Case-Control Consortium (Panc4) study has shown that the risk of pancreatic cancer in current smokers is 2.2 times and that of former smokers is 1.2 times compared to those who have never smoked [26]. The risk increases with the number of cigarettes smoked and the duration of smoking [27]. The European Prospective Investigation into Cancer and Nutrition (EPIC) study has shown that the risk of former smokers never approaches that of smokers after 5 years or more of quitting smoking [28]. Those who smoke cigars are at 1.6 times increased risk of pancreatic cancer compared to non-smokers [29]. While there was no significant association seen with smokeless tobacco, studies have been inconclusive [29, 30]. Studies have shown that the use of snus (moist powdered tobacco) in the

Swedish population is not associated with pancreatic cancer risk [31].

Obesity and physical inactivity

Several studies have shown a link between pancreatic cancer risk and high body mass index (BMI) and physical inactivity [32–37]. Obesity and overweight are attributed to about 12% of pancreatic cancer cases in the UK [25]. Risk of pancreatic cancer increases by 10% for every 5-unit increase in BMI [33]. A 10-cm increase in waist circumference increases the risk for pancreatic cancer by 11%, and a 0.1 increase in waist-to-hip ratio increases the risk by 19% [33]. Studies have shown that regular leisure-time physical activity decreases the pancreatic cancer risk by 11% to 35% [38, 39]. Physical activity decreases the risk of pancreatic cancer especially in people who are overweight with a BMI of at least 25 kg/m^2 [40]. Being obese or overweight during early adulthood increases the risk of pancreatic cancer onset at a younger age [41]. Higher levels of prediagnostic BMI levels are associated with decreased survival in pancreatic cancer, according to two large prospective clinical trials [42].

Alcohol

Based on multiple studies, high alcohol consumption (more than three drinks per day) undoubtedly increases the risk of pancreatic cancer, whereas for low-to-moderate alcohol intake there was no association found [43–45]. Cigarette smoking confounded the relationships between alcohol use and pancreatic cancer risk. Alcohol intake was associated with a two-fold increased risk of pancreatic cancer in current smokers [46]. A meta-analysis has shown that the risk of pancreatic cancer is 20% higher in those who consume > 50 g of alcohol when compared to non-drinkers or occasional drinkers [47]. However, no increased risk of pancreatic cancer was seen in those who consume < 50 g of alcohol per day in the same meta-analysis [47].

Diet

Studies evaluating the risk between diet and pancreatic cancer risk have been inconclusive; many studies have shown an increased risk, but not all studies. A meta-analysis of prospective studies has shown that red meat consumption of > 120 g/day was associated with an elevated risk of pancreatic cancer [48]. Other studies have shown that consumption of a high amount of red and processed meats and dietary fat of animal origin was associated with increased pancreatic cancer risk [48–50]. However, some other studies have not shown an association between diet and pancreatic cancer risk [51–53]. High intake of fruit and vegetables, especially those enriched in antioxidants and citrus, have a protective action [54]. Some studies have shown a decreased risk of pancreatic cancer with nut consumption [55]. A large cohort study in the UK has shown that pancreatic cancer mortality is lower with vegetarians, vegans, and low meat eaters when compared to regular meat eaters [56].

Occupational exposures

The fraction of pancreatic cancer within a population, which has been attributed to occupational exposure, is estimated at 12%. Studies have shown that exposure to nickel, cadmium, and arsenic was associated with increased pancreatic cancer risk [57–59]. Selenium, which is an essential micronutrient, has been shown in several studies to be inversely associated with several cancers, including pancreatic cancer [60, 61]. A study in Spain has shown an increased risk of pancreatic cancer with exposure to pesticides, aniline dyes, benzopyrene, diesel and gasoline exhaust, and hydrocarbon solvents [62].

Other risk factors

Approximately 5–10% of people with pancreatic cancer have a family history of pancreatic cancer [63]. Germline mutations of *BRCA*, *CDKN2A*, *MLH1*, *ATM*, and *PALB2* genes have been linked to pancreatic cancer [64]. *KRAS*, *p53*, and *SMAD4* are seen in inherited genetic mutations and are linked to increased pancreatic cancer risk [65, 66]. Studies have also shown that individuals with non-O blood group (type A, AB, or B) were significantly more likely to develop pancreatic cancer when compared to blood group O individuals, and the genome-wide association study confirmed this [67, 68]. Patients with cystic fibrosis are also at increased risk for pancreatic cancer [69]. Studies have shown that 1.8% of patients with chronic pancreatitis will develop pancreatic cancer within 10 years from the diagnosis, and 4% after 20 years [70].

The association between diabetes mellitus type I and II with pancreatic cancer has been reported in multiple studies [71–74], although some studies have shown that diabetes is a consequence of the tumour rather than it causing cancer [75, 76]. Studies have shown that existing chronic pancreatitis is a strong risk factor for pancreatic cancer [77, 78]. The risk reaches 1.8% at 10 years and 4% at 20 years after diagnosis of chronic pancreatitis [77, 79, 80]. The relationship with coffee consumption and pancreatic cancer risk has been controversial; some studies have shown an increased risk at higher levels of coffee consumption while some have not shown any relationship [81].

Some studies have shown an association between *Helicobacter pylori* infection and increased pancreatic cancer risk, although this has been controversial [82]. Some studies have also shown an association between hepatitis B and hepatitis C infection and increased pancreatic cancer [83–85].

Conclusions

The incidence of pancreatic cancer in Europe is considerably higher when compared to other continents. In Europe, pancreatic cancer is the ninth most common cancer and the fourth most deadly cancer. With incidence and mortality rates being very close together, pancreatic cancer is considered one of the deadliest of all cancers. Lifestyle in developed nations, including the rise in physical inactivity and obesity, tobacco smoking, consumption of alcohol, dietary factors, and occupational exposures, may be responsible for the increased incidence of pancreatic cancer. Survival for pancreatic cancer remains low, and prevention by behavioural modification and controlling risk factors could save thousands of lives each year. Updated statistics on the epidemiology of pancreatic cancer along with studies allowing a better understanding of the risk factors are needed in the near future and are essential for the primary prevention of this disease.

Conflict of interest

The authors declare no conflict of interest.

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