

Epidemiology of pancreatic cancer

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Abstract

Cancer of the pancreas remains one of the deadliest cancer types. Based on the GLOBOCAN 2012 estimates, pancreatic cancer causes more than 331000 deaths per year, ranking as the seventh leading cause of cancer death in both sexes together. Globally, about

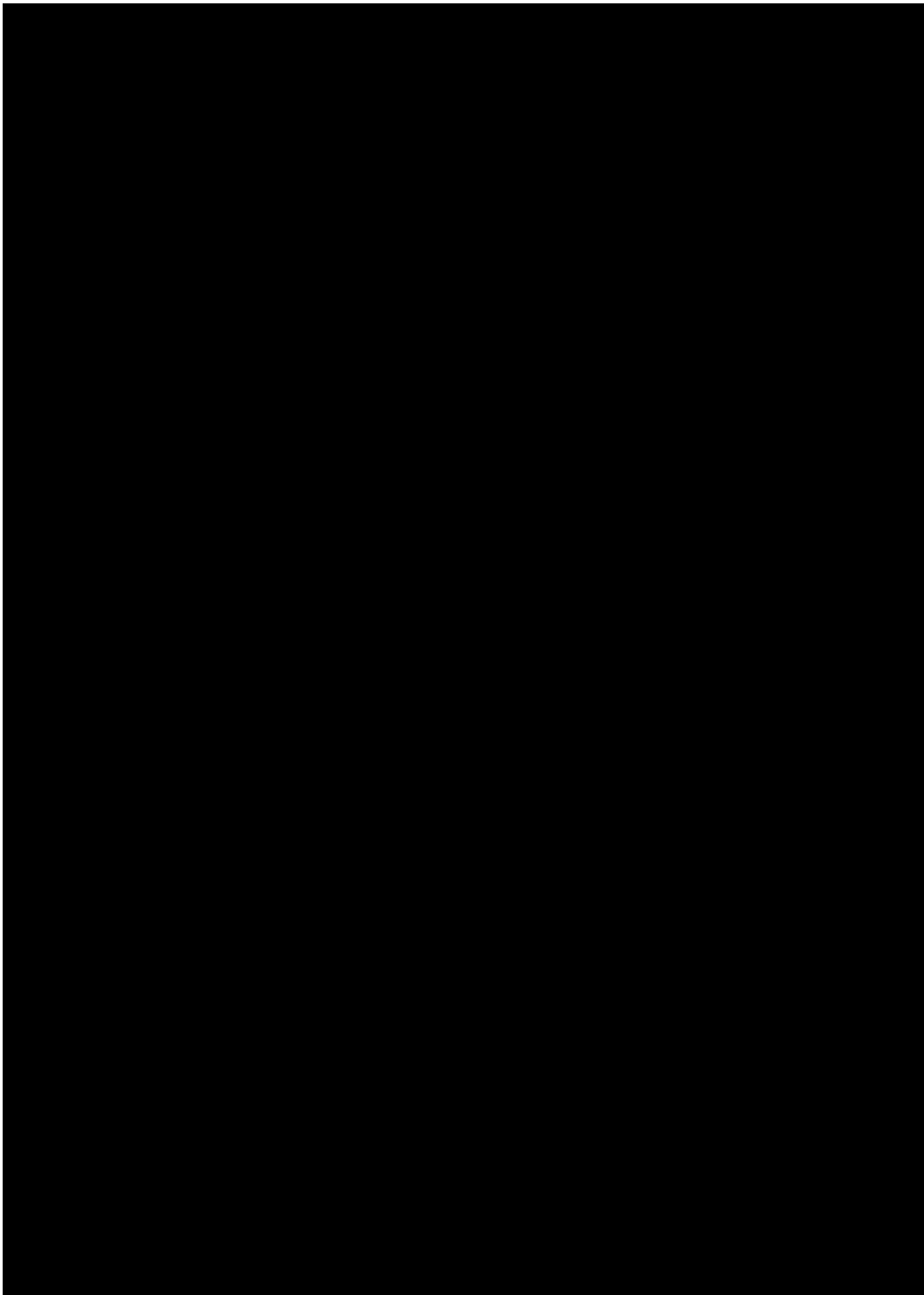
338000 people had pancreatic cancer in 2012, making it the 11th most common cancer. The highest incidence and mortality rates of pancreatic cancer are found in developed countries. Trends for pancreatic cancer incidence and mortality varied considerably in the world. A known cause of pancreatic cancer is tobacco smoking. This risk factor is likely to explain some of the international variations and gender differences. The overall five-year survival rate is about 6% (ranges from 2% to 9%), but this vary very small between developed and developing countries. To date, the causes of pancreatic cancer are still insufficiently known, although certain risk factors have been identified, such as smoking, obesity, genetics, diabetes, diet, inactivity. There are no current screening recommendations for pancreatic cancer, so primary prevention is of utmost importance. A better understanding of the etiology and identifying the risk factors is essential for the primary prevention of this disease.

Key words: Pancreatic cancer; Epidemiology; Incidence; Mortality; Trend; Risk factors

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Core tip: Pancreatic cancer is the one of leading causes of cancer mortality and one of the most lethal malignant neoplasms across the world. The highest incidence and mortality rates of pancreatic cancer are found in developed countries. The estimated 5-year survival rate for pancreatic cancer is about 5%. The causes of pancreatic cancer are still insufficiently known, although certain risk factors have been identified, such as cigarette smoking, positive family history and genetics, diabetes mellitus, obesity, dietary factors, alcohol use, physical inactivity. There are no current screening recommendations for pancreatic cancer, so primary prevention is of utmost importance.

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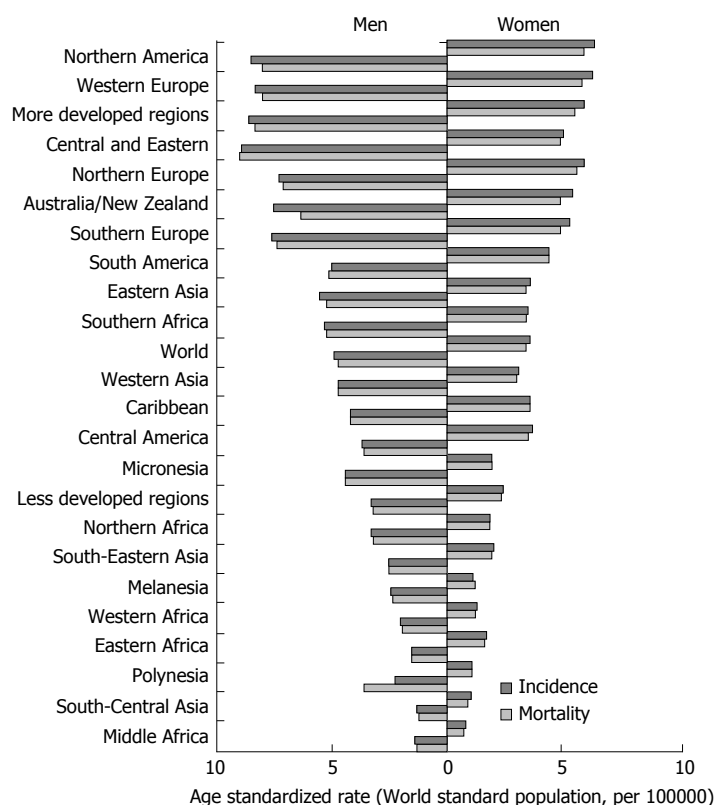


Figure 1 Pancreatic cancer incidence and mortality in men and women, by regions, GLOBOCAN 2012 estimates.

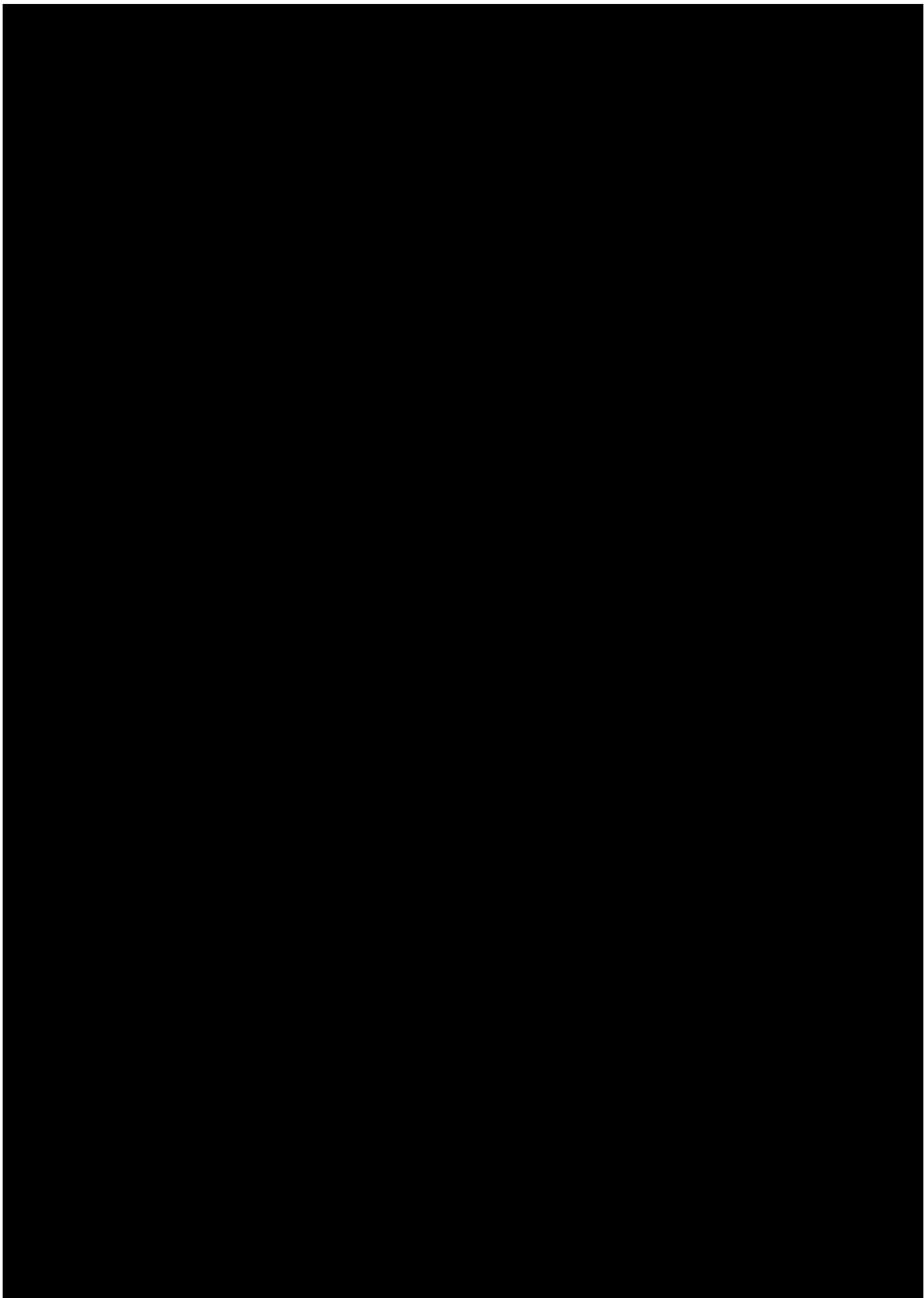
recorded in the countries in Middle Africa and South-Central Asia (less than 1.0 per 1000000 people). The differences in mortality rates were nearly fifty fold between the populations with the highest and lowest rate (Armenia vs Tanzania: 8.9 vs 0.2). More than one third (111029 deaths) of all deceased from pancreatic cancer are residents of Europe. Slightly less than half (41.5%; 137251 deaths) of all deaths from pancreatic cancer were recorded in 2012 in Asian countries^[1]. More than half (55.8%, 184429 deaths) of deceased of pancreatic cancer were registered in more developed regions. At least deaths were registered in Micronesia/Polynesia. The least number of deaths was registered in Micronesia/Polynesia.

Mortality of pancreatic cancer in both genders increases with age, and almost 90% of all deaths are registered after the age of 55 years^[1,3]. The highest mortality rates in 2012 in males were recorded in Central and Eastern Europe (Latvia - 11.9, Hungary - 11.5) (Figure 3A)^[1]. The mortality from pancreatic cancer was lowest (less than 1.0 per 100000 people) in Belize and Bahrain. The highest mortality rates in 2012 in females were recorded in Hungary (7.5) and Malta (7.2) (Figure 3B)^[1]. The mortality from pancreatic cancer was lowest in women in Belize (0.8).

Mortality of pancreatic cancer is almost identical with its incidence, because it is one of the most fatal malignant tumors^[19,20]. Reasons for the substantial differences in mortality rates of pancreatic cancer were not completely elucidated. Differences in rates of incidence can be apparent and specious. Specious

differences may arise as a result of changes in the diagnosis of diseases and causes of death, as a result of a real shift in the incidence and/or fatality. Data on the incidence/mortality published by WHO are not of the same quality in all countries^[18]. Although the quality (accuracy and completeness of cause of death registration, primarily) and the coverage of information in most developing countries can be considered limited, the registry often remains the only available source. Symptoms, signs and insufficiently defined conditions as the underlying cause of death are significantly more often mentioned in Serbia, the Russian Federation and Greece than in more developed countries such as the United states of America, United Kingdom, and Finland, which points to the need for a cautious interpretation of the data statistics of mortality in international comparisons^[18]. Pancreatic cancer is difficult to diagnose. Malignant pancreatic neoplasm was among the most common cancers detected at autopsy studies^[16,21]. It is known that for pancreatic cancer there is no workable modality of screening, early detection and effective treatment, which has the consequence of survival rates varying very little between developed and developing countries^[22]. Current available treatment options for pancreatic cancer are limited. Due to the advanced stage at diagnosis, 80%-90% of patients have unresectable tumours and long-term survival after surgical resection is poor^[13,19,23].

High smoking prevalence has been widely recognized as the main contributor to the high mortality rates of



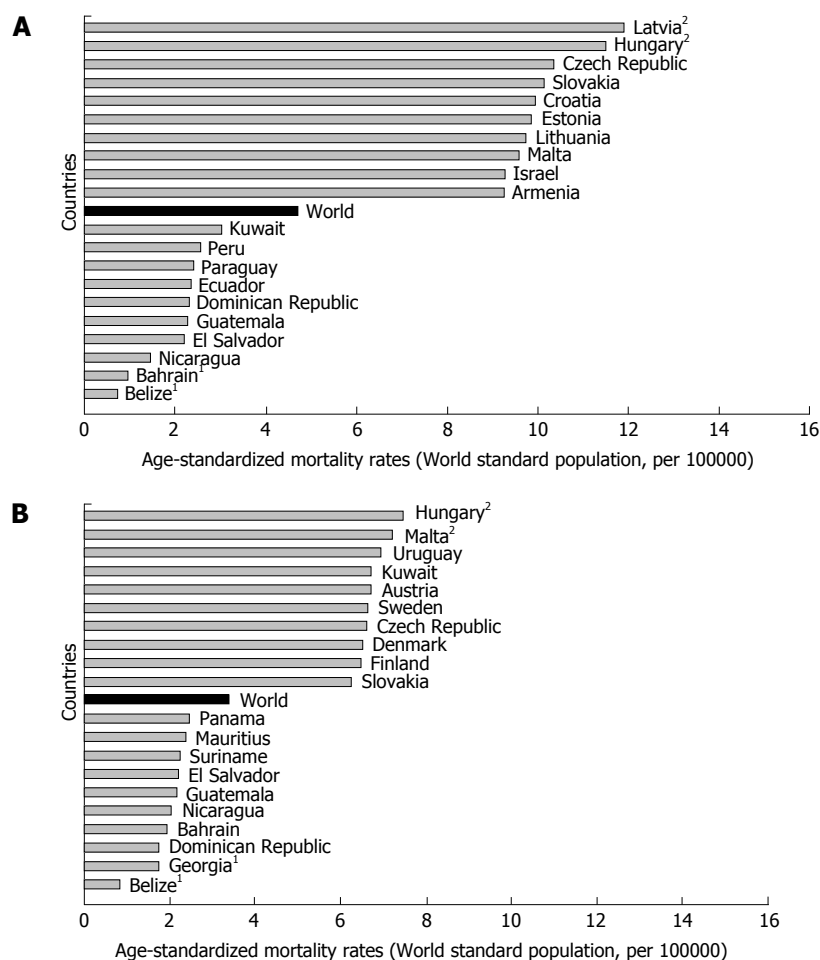


Figure 3 Pancreatic cancer mortality in men (A) and women (B), GLOBOCAN 2012 estimates. ¹Country with the lowest mortality rates; ²Country with the highest mortality rates. GLOBOCAN 2012 estimates^[1].

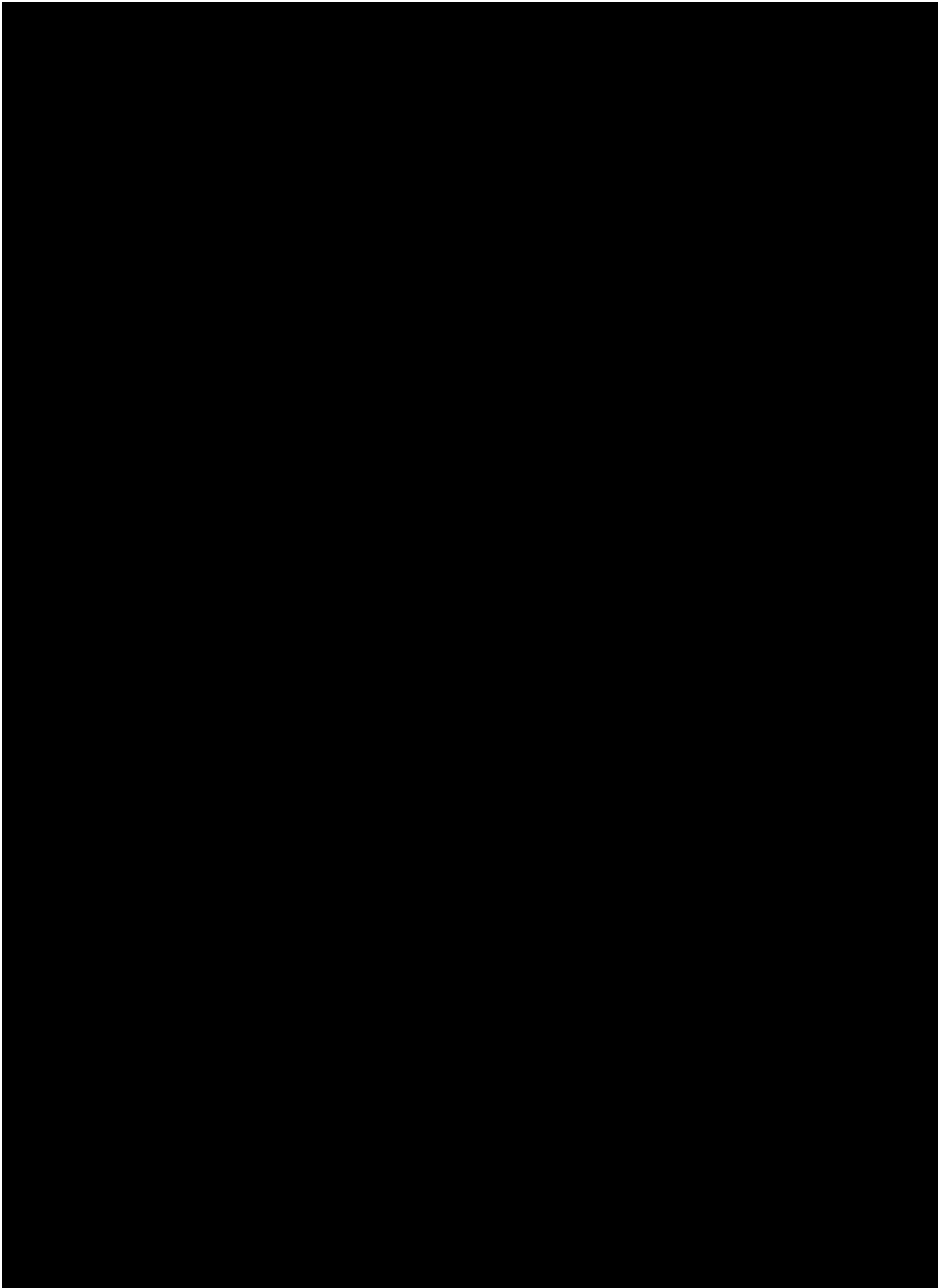
cancer incidence and mortality have not been well understood. In both sexes, temporal trends in cigarette smoking prevalence were related to temporal trends in pancreatic cancer mortality with a roughly lag of several decades^[9,11,24]. Decreased smoking, particularly in men, has been widely recognized as the main contributor to the decreases in mortality trends from pancreatic cancer in developed countries^[24,32]. The mortality rate of pancreatic cancer began to decline earlier in the countries where the tobacco control started to be implemented earlier (such as United States, the United Kingdom, Australia). However, the recent increasing trends in some countries in the European Union suggest that other factors (including mainly obesity, physical inactivity, diabetes, and dietary factors), besides smoking, may have influenced the pancreatic cancer mortality^[20,22,31,33]. In recent years, people in developing countries adopt lifestyles and behaviors that are typical for developed countries, such as cigarette smoking, higher consumption of saturated fat and calorie-rich foods, and reduced physical activity^[25,27,34]. Besides, the trends might be due to disparities in socioeconomic circumstances between high- and low-income areas. Improved diagnostic and death certification of the

disease might also partially explain the observed figures, at least part of the recent trends in some countries of Southern, Central and Eastern Europe^[18,27,31]. It is unlikely, however, that progress in the treatment of pancreatic cancer could have a significant impact on mortality trends, also given the negligible changes in survival over the last decades^[19,22,23,35]. Also, it is known that the changes in coding of pancreatic cancer had minimal influence on mortality trends of pancreatic cancer in the second half of the XX century^[18,36].

SURVIVAL

Cancer of the pancreas remains one of the most deadly common cancer types: the Mortality/Incidence ratio is 98%^[1]. The overall five-year survival rate is about 6% (ranges from 2% to 9%), but this partly reflects varying data quality worldwide^[37,38]. For pancreatic cancer, survival rates vary very small between developed and developing countries^[37].

Based on the United States National Cancer Institute' data for pancreatic cancer in both sexes and all races, 9.4% are diagnosed at the local stage while the 5-year survival for localized disease was 29.3%



for pancreatic cancer compared with regular meat eaters^[61]. The EPIC study found no association between intakes of red and processed meat and pancreatic cancer risk, while poultry consumption was associated with an increased risk^[62]. A recent meta-analysis of 11 prospective studies found a positive association between pancreatic cancer incidence and processed meat consumption^[63]. But, some studies have not supported these findings^[64], or have provided support for the association among men only^[65]. On the other hand, frequent nut consumption is inversely associated with risk of pancreatic cancer in women^[66,67]. A recent large nested case-control study in 2010 showed increased risk even at consumption of 60 g/d or more of liquor (spirits), and found no association with beer or wine^[68]. Findings from the latest meta-analysis support that fruit and vegetable intake is associated inversely with the risk of pancreatic cancer^[69]. Additionally, a summary review of meta-analytical studies showed that the major protective factor is increasing fruit or folate intake, with respective population preventable fractions of 0-12%^[70]. In the Italian population, 11.9% of pancreatic cancers were attributable to a low adherence to Mediterranean diet^[71].

Diabetes mellitus is linked with increased risk of pancreatic tumors^[70,72]. Both type I and type II diabetes have doubled the risk of pancreatic cancer^[72-74]. The pancreatic cancer burden study in the Italian population estimated that 9.7% of pancreatic cancers were attributable to diabetes^[71]. The United States National Cancer Institute estimates that diabetes is associated with a 1.8-fold increased risk of pancreatic cancer, particularly in Hispanic men and Asians in comparison with whites and blacks^[75]. Pancreatic cancer risk decreased with duration of diabetes, but a 30% excess risk persists for more than two decades after diabetes diagnosis^[76]. Oral antidiabetics or insulin use were associated with a reduced risk of pancreatic cancer^[75,76].

Some studies showed that *Helicobacter pylori* (*H. pylori*) infection is the major risk factors associated with pancreatic cancer, with estimated population attributable fraction of 4%-25%^[70]. But, other studies did not observe an association of *H. pylori* infection with pancreatic cancer^[77].

Patients with pancreatitis, especially the chronic or recurrent forms, had a moderate excess of pancreatic cancer risk^[78]. About 4% of chronic pancreatitis patients developed pancreatic cancer^[79]. It is estimated that 1.34% of pancreatic cancers are attributable to chronic pancreatitis, but for those who were under the age of 65 that risk was two times higher^[80]. Patients with hereditary pancreatitis (rare, autosomal-dominant disease, usually occurs at a young age) have a risk that is 50-60 times greater than expected^[81].

It is estimated that 5%-10% of pancreatic cancers are hereditary^[9,52]. A family history of pancreatic cancer in a parent, sibling or child was associated with increased

risk of pancreatic cancer^[82]. People with at least two first-degree relatives (mother, father, brother, sister) with pancreatic cancer have almost double the risk of people without pancreatic cancer in their family^[83].

There are many of inherited genetic disorders which are known to increase the risk for pancreatic cancer, including Lynch syndrome, Peutz-Jeghers syndrome, the Familial atypical multiple mole melanoma syndrome, Hereditary breast and ovarian cancer syndrome, Li-Fraumeni syndrome, Familial adenomatous polyposis, etc^[83]. Individuals with mutations or deletion in such genes as PRSS1, K-ras, p16, p53, and BRCA2 have an increased risk of developing pancreatic cancer^[84].

Some findings show a link between pancreatic cancer and previous cancers (cancer of the gallbladder, lung, stomach, uterus, breast, colon, etc.) and other conditions (Crohn's disease, gastric ulcer)^[84-86].

Other potential risk factors include aspirin use, occupational exposure to certain pesticides, and dietary factors such as carbohydrate or sugar intake^[70,86]. Most of pancreatic cancer risk factors are only weakly associated with the disease. Additionally, many people with pancreatic cancer do not have any one specific risk factor for it.

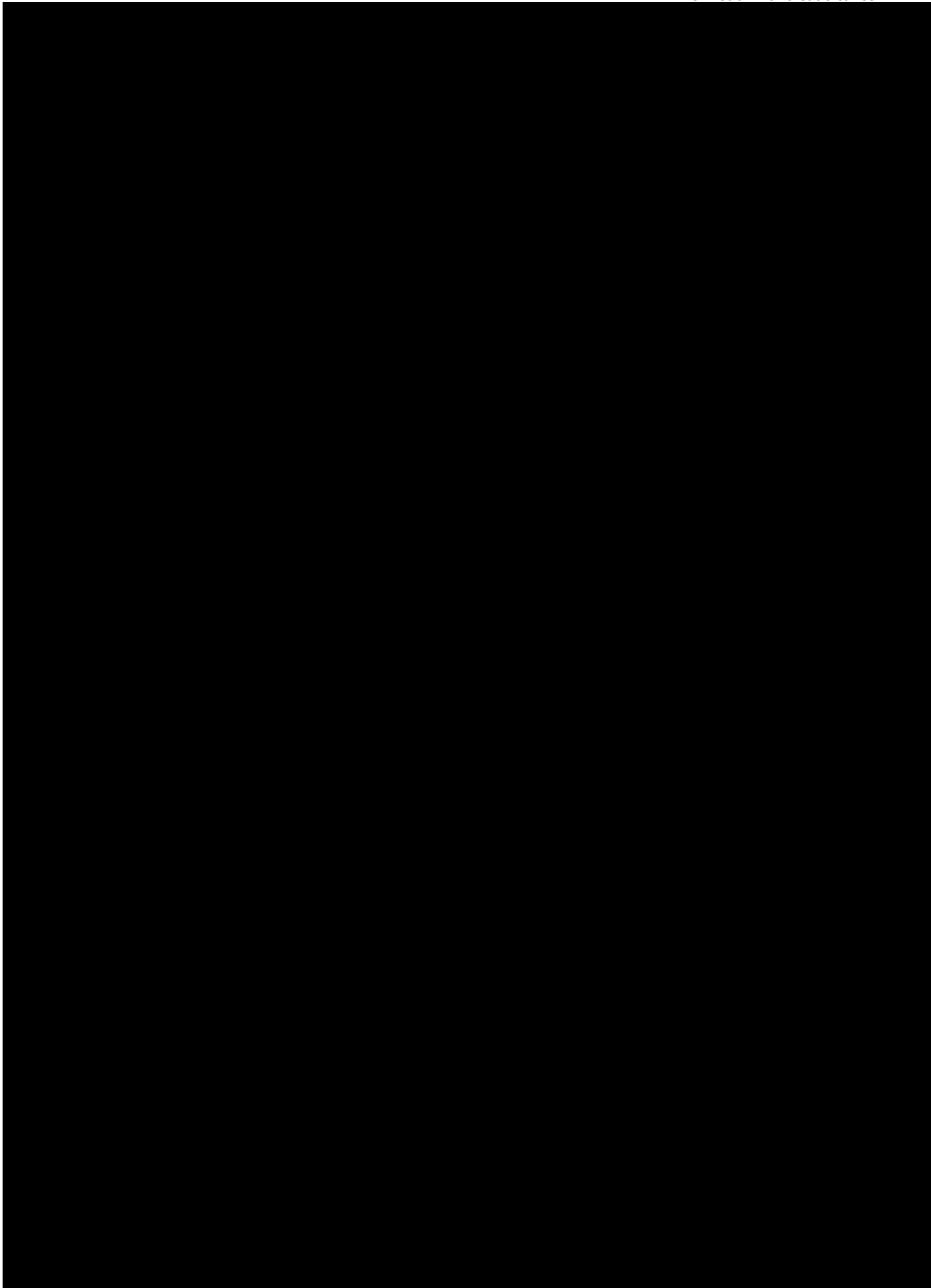
PREVENTION

There are no current screening recommendations for pancreatic cancer, so primary prevention is of utmost importance. A better understanding of the etiology and identifying the risk factors is essential for the primary prevention of this disease. Potentially modifiable risk factors include tobacco smoking, obesity, and diabetes mellitus, diet, alcohol consumption. So far, the best preventive strategy against pancreatic cancer is risk reduction, including lifestyle modification (smoking cessation, healthy weight, diet high in fruits and vegetables, regular exercises), and regular control of health issues^[9,13,52,53].

Lifestyle modifications

Control of smoking offers the best available strategy for reducing the incidence of pancreatic cancer. It has been estimated that about 30% of pancreatic cancers could be prevented by prevention of smoking^[9]. A European-wide prospective study in 2009 showed that risk is reduced to the levels of a non-smoker after just five years of cessation^[54].

Epidemiological data show that dietary factors which are associated with increased risk of pancreatic cancer are meat, red meat in particular, and energy: preventive measures include recommendations for reducing the intake. Protection is mainly provided by means of a "prudent", well balanced diet, diet containing ample fruits and vegetables, nut consumption, vitamins (β -carotene, vitamin D and E), and more dietary compounds^[26,87,88]. Also, it is necessary to limit the alcohol use, which is known to increase the



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