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Published in:
Gastroenterology

Published: 01/02/2021

Document Version:
Final Published version, also known as Publisher's PDF, Publisher's Final version or Version of Record

Published version (DOI):
10.1053/j.gastro.2020.10.007

Publication details:
Huang, J., Lok, V., Ngai, C. H., Zhang, L., Yuan, J., Lao, X. Q., Ng, K., Chong, C., Zheng, Z.-J., & Wong, M. C. S. (2021). Worldwide Burden of, Risk Factors for, and Trends in Pancreatic Cancer. *Gastroenterology*, *160*(3), 744-754. https://doi.org/10.1053/j.gastro.2020.10.007

Gastroenterology 2021;160:744–754

Worldwide Burden of, Risk Factors for, and Trends in Pancreatic Cancer

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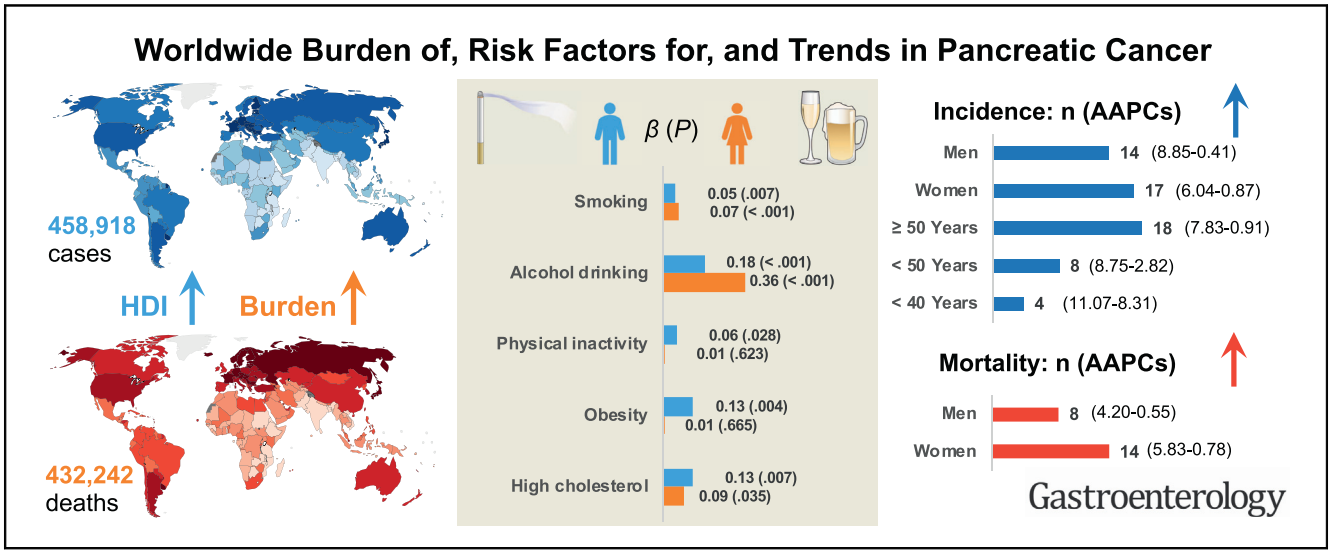
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e23. Learning Objective: Upon completion of this CME activity successful learners will be able to describe the (a) global and regional burden of pancreatic cancer and (b) recent epidemiological trends in pancreatic cancer.



BACKGROUND & AIMS: We evaluated global and regional burdens of, risk factors for, and epidemiologic trends in pancreatic cancer among groups of different sexes and ages. **METHODS:** We used data from the GLOBOCAN database to estimate pancreatic cancer incidence and mortality in 184 countries. We examined the association between lifestyle and metabolic risk factors, extracted from the World Health Organization Global Health Observatory database, and pancreatic cancer incidence and mortality by univariable and multivariable linear regression. We retrieved country-specific age-standardized rates (ASRs) of incidence and mortalities from cancer registries from 48 countries through 2017 for trend analysis by joinpoint regression analysis. **RESULTS:** The highest incidence and mortality of pancreatic cancer were in regions with very high (ASRs, 7.7 and 4.9) and high human development indexes (ASRs, 6.9 and 4.6) in 2018. Countries with higher incidence and mortality were more likely to have higher prevalence of smoking, alcohol drinking, physical inactivity, obesity, hypertension, and high cholesterol. From 2008 to 2017, 2007 to 2016, or 2003 to 2012, depending on the availability of the data, there were increases in incidence among men and women in 14 (average annual percent changes [AAPCs], 8.85 to 0.41) and 17 (AAPCs, 6.04 to 0.87) countries, respectively. For mortality, the increase was observed in 8 (AAPCs, 4.20 to 0.55) countries among men and 14 (AAPCs, 5.83 to 0.78) countries among women. Although the incidence increased in 18 countries (AAPCs, 7.83 to 0.91) among individuals 50 years or older, an increasing trend in pancreatic cancer was also identified among individuals younger than 50 years and 40 years in 8 (AAPCs, 8.75 to 2.82) and 4 (AAPCs, 11.07 to 8.31) countries, respectively. **CONCLUSIONS:** In an analysis of data from 48 countries, we found increasing incidence and mortality trends in pancreatic cancer, especially among women and populations 50 years or older, but also among younger individuals. More preventive efforts are recommended for these populations.

Keywords: ASR; Pancreas; Trend Analysis; Epidemiology.

Abbreviations: **AAPC, Average Annual Percent Change; ASR, age-standardized rates; BMI, body mass index; EOPC, early-onset pancreatic cancer; HDI, Human Development Index; PCN, pancreatic cystic neoplasm; WHO, World Health Organization.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2020.10.007

Globally, pancreatic cancer is the 12th most common malignancy and the 7th leading cause of cancer mortality.[1] It is also associated with a substantial number of years of life lost, with its disability-adjusted life years being approximately 9.1 million globally in 2017.[2] It remains a critical global burden of disease due to its extremely aggressive nature and poor survival rate.[3] The relatively low success rate of treatment is caused by the lack of appropriate screening and diagnostic approaches, the deep-seated position of the pancreas, difficulties in performing a tissue biopsy, its aggressive clinical course, and its low response rate to radiotherapy or chemotherapy.[3] Most pancreatic cancers are adenocarcinoma, whereas other slower-growing pancreatic cancers include neuroendocrine tumors and less commonly pancreatic exocrine cancers.[4] According to the American Cancer Society, the average lifetime cumulative risk of pancreatic cancer is approximately 1 in 64.[5] The modifiable risk factors for pancreatic cancer include cigarette smoking, obesity, diabetes, chronic pancreatitis, and occupational exposure to certain chemicals.[6] Other nonmodifiable risk factors include age, gender, race, family history, and inherited genetic syndromes.[6]

There is a crucial prospect to monitor the incidence and mortality of pancreatic cancer using cancer surveillance data of high quality. Evaluating the recent epidemiologic trends in pancreatic cancer is necessary, as it has implications for preventive measures and clinical care. Owing to its high variation in epidemiology between different populations, a comprehensive investigation of its global pattern and temporal trends among different population groups could inform resource planning and health care policy for health service providers. Recent studies also identified the trend in early-onset cancers in the younger population.[7] Investigating the trends in pancreatic cancer in a young population is important as it is more likely for them to have more advanced histologic features that are associated with poorer prognosis.[8]

However, there is a scarcity of studies that investigated the most updated incidence and mortality trend in pancreatic cancer on a global scale. The previous studies were limited for certain populations, such as the United States,[9] and used relatively old data (up to 2007).[10] The Global Burden of Disease Study in 2017[2] examined the trend in pancreatic disease based on estimation and modeling rather than cancer registries; hence, there remains a knowledge gap on the most recent temporal changes in the incidence and mortality based on real-world cancer registry data. Also, none of the previous studies have comprehensively examined the lifestyle and metabolic risk factors for pancreatic cancer at a county level, as well as the recent incidence trends in pancreatic cancer among the younger population. This study aimed to determine the (1) global and regional incidence and mortality of, (2) lifestyle and metabolic risk factors for, and (3) recent epidemiologic trend in pancreatic cancer among groups of different sexes and ages using cancer registries.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Little is known about the global and regional burdens of, risk factors for, and epidemiologic trends in pancreatic cancer among populations of different ages and sexes.

NEW FINDINGS

In an analysis of data from 48 countries, the authors found increasing incidence and mortality trends in pancreatic cancer—especially among women and people 50 years or older, but also among younger individuals.

LIMITATIONS

Cancer registries differ among various regions, and cancer reporting can vary over time.

IMPACT

The incidence and mortality of pancreatic cancer are increasing worldwide, especially among women, people 50 years and older, but also among younger individuals. Strategies are needed for earlier detection, treatment, and prevention.

Methods

Source of Data

This analysis used a methodological approach similar to previously published reports on the global epidemiologic trend in colorectal cancer and prostate cancer by the same team.[11,12]

For the estimation on global and regional incidence and mortality of pancreatic cancer in 2018, we used the *GLOBOCAN* database, which consists of data available for 184 countries.[13]

The methods used to compile the 2018 estimates in GLOBOCAN were based on predictions, modeling of incidence-to-mortality ratios, and approximation from neighboring countries similar to the methods used in their last estimates in 2012.[14] We retrieved the human development index (HDI) in 2018 for each country, which is a composite measure derived from education, income, and life expectancy.[15] The cutoff points were less than 0.550 for low, 0.550 to 0.699 for medium, 0.700 to 0.799 for high, and 0.800 or greater for very high HDIs based on quartiles from their distributions.[16] For the analysis on risk factors associated with the cancer, we extracted the age-adjusted prevalence of risk factor mostly in 2010 for each country from the World Health Organization (WHO) Global Health Observatory database,[17] including smoking, alcohol drinking, physical inactivity, obesity, diabetes, hypertension, and high cholesterol (Supplementary Table 1). To allow meaningful comparison of rates between different populations in various countries, age-standardization was used to adjust a country's prevalence rate of different risk factors using the same standard population.[17] Smoking was defined as current use of any smoked tobacco product. Alcohol drinking was defined as the total amount of alcohol consumed per person over a calendar year. Physical inactivity was defined as less than 150 minutes of moderate-intensity physical activity per week, or less than 75 minutes of vigorous-intensity physical activity per week, or equivalent. Obesity was defined as body mass index (BMI) $\geq$30. Diabetes was defined as fasting blood glucose $\geq$7.0 mmol/L or use of antidiabetes medications. Hypertension was defined as systolic blood pressure $\geq$140 and/or diastolic blood pressure $\geq$90 mm Hg. High cholesterol was defined as total cholesterol $\geq$6.2 mmol/L. For the trend analysis, we extracted all incidence and mortality data available from global or national registries in all calendar years available

through 2017 for 48 countries (Supplementary Table 2). To extract the yearly data on incidence, we retrieved nation/region-specific cancer registries from the volumes I to XI of *Cancer Incidence in Five Continents* (*CI5*).[18] The WHO mortality database was used to retrieve yearly mortality data.[19] Only data with a quality at medium level or above were used to estimate mortality in the WHO mortality database.[20] More details on the quality classification of mortality data for different countries can be found on the Web site.[21] To acquire the more updated incidence and mortality data for Northern European countries and the United States, we used the Nordic Cancer Registries (NORDCAN)[22,23] and the Surveillance, Epidemiology, and End Results (SEER) Program, which are publicly available databases.[24] The International Classification of Diseases and Related Health Problems, 10th Revision codes (ICD-10) C25-C25.9 was adopted to identify "malignant neoplasm of pancreas" in the current study.[25] All figures were adjusted by age and presented as age-standardized rates (ASRs) according to the Segi-Doll world reference population.[26]

Primary Outcomes and Statistical Analysis

After obtaining the ASRs of incidence and mortality rates from the previously mentioned national and international registries, we evaluated the most recent 10-year epidemiologic trend in incidence and mortality of pancreatic cancer in different countries using Average Annual Percent Change (AAPC) and its 95% confidence interval by joinpoint regression analysis.[27] We conducted a logarithmic transformation of the incidence and mortality data and calculated standard errors by using a binomial approximation. We apportioned weights equivalent to each segment's length for the specified timeframe.[28] Countries with "missing" or "zero" values in any year of trend analysis were excluded for analysis, as the joinpoint regression could not be conducted in this circumstance. We calculated the AAPC as an average of annual percent changes using geometric weighting in populations of different age strata, genders, and countries. The association between prevalence of lifestyle and metabolic risk factors and incidence/mortality of pancreatic cancer for each country was examined using univariable and multivariable linear regression analysis. We presented beta coefficients (β) here, defined as the change in ASR of incidence or mortality associated with 1% increase of a certain risk factor. All P values less than .05 were considered statistically significant.

Results

Incidence and Mortality of Pancreatic Cancer in 2018 and Comparison by HDI

Globally, a total of 458,918 new cases of pancreatic cancer and 432,242 related deaths were reported in 2018.[13] The global ASR of incidence was 4.8 per 100,000, with a range between 10.8 (Hungary) and 0.35 (Guinea) for individual countries (Figure 1). The highest incidence rates were in Western Europe (ASR, 8.3), North America (ASR, 7.6), and Central and Eastern Europe (ASR, 7.5). The incidence of pancreatic cancer has a men to women ratio of 1.4:1.0. The incidence of pancreatic cancer was the highest in countries with very high HDI (ASR, 7.7) as compared with those with high (ASR, 4.9), low (ASR, 1.8), and medium HDI (ASR, 1.5). The global ASR of mortality was 4.4 per 100,000 persons in 2018, ranging from 9.9 in Uruguay to 0.32 in Guinea (Figure 2). The highest mortality rates were in Western Europe (ASR, 7.6), Central and Eastern Europe (ASR, 7.3), and North America (ASR, 6.5). The mortality of pancreatic cancer was the highest in countries with very high HDI (ASR, 6.9) as compared with those with high (ASR, 4.6), low (ASR, 1.7), and medium HDI (ASR, 1.4). We presented more detailed figures by region and sex in Supplementary Table 3.

Association With Lifestyle and Metabolic Risk Factors

Among men for different countries, higher ASR of incidence and mortality of pancreatic cancer were associated with a higher prevalence of smoking ($\beta = 0.05$, $P = .007$; $\beta = 0.04$, $P = .007$), alcohol drinking ($\beta = 0.18$, $P < .001$; $\beta = 0.15$, $P < .001$), physical inactivity ($\beta = 0.06$, $P = .028$; $\beta = 0.05$, $P = .017$), obesity ($\beta = 0.13$, $P = .004$; $\beta = 0.12$, $P = .002$), hypertension ($\beta = 0.13$, $P = .006$; $\beta = 0.11$, $P = .007$), and high cholesterol ($\beta = 0.13$, $P = .007$; $\beta = 0.13$, $P = .003$) and vice versa (Table 1, Supplementary Figure 1). The beta coefficient (β) refers to how much change in ASR of incidence or mortality per 1% increase of a certain risk factor. Among women, higher incidence and mortality of pancreatic cancer were associated with a higher prevalence of smoking ($\beta = 0.07$, $P < .001$; $\beta = 0.05$, $P = .005$), alcohol drinking ($\beta = 0.36$, $P < .001$; $\beta = 0.27$, $P = .002$), and high cholesterol ($\beta = 0.09$, $P = .035$; $\beta = 0.10$, $P = .008$) and vice versa. However, the analysis did not detect a significant association between the prevalence of diabetes and the ASR of incidence and mortality at a country level ($P > .05$).

Incidence Trend

Among men, 14 countries had an increase in incidence (AAPCs, 8.85 to 0.41, Figure 3, Supplementary Table 4). Of all 14 countries with increasing trend, 9 were reported in Europe, with Iceland (AAPC, 8.85), Cyprus (AAPC, 5.51), and France (AAPC, 4.30) reporting the most drastic increase. Countries with the most significant increase in other regions included Thailand (AAPC, 4.48), Japan (AAPC, 1.47), and Australia (AAPC, 1.36). Only 1 country showed a decreasing trend (Costa Rica AAPC, −4.15). Among women, 17 countries showed an increasing trend (AAPCs, 6.04 to 0.87). The increase was reported in 12 European countries, whereas Malta (AAPC, 6.04), Slovakia (AAPC, 4.40), and France (AAPC, 4.22) were found to have the most drastic increase. Countries with the most significant incidence increase in other regions included New Zealand (AAPC, 2.57), Japan (AAPC, 2.48), and South Korea (AAPC, 1.71). Only Denmark (AAPC, −2.43) showed a decreasing trend.

Mortality Trend

Among men, 8 countries had an increase in mortality (AAPCs, 4.20 to 0.55, Figure 4, Supplementary Table 4). There were 3 countries with increasing trend in Europe, consisting of Russia (AAPC, 0.73), Spain (AAPC, 0.56), and Germany (AAPC, 0.55). Countries with the most significant increase from other regions included the Philippines (AAPC, 4.20), Thailand (AAPC, 4.13), and Chile (AAPC, 1.76). Only 2

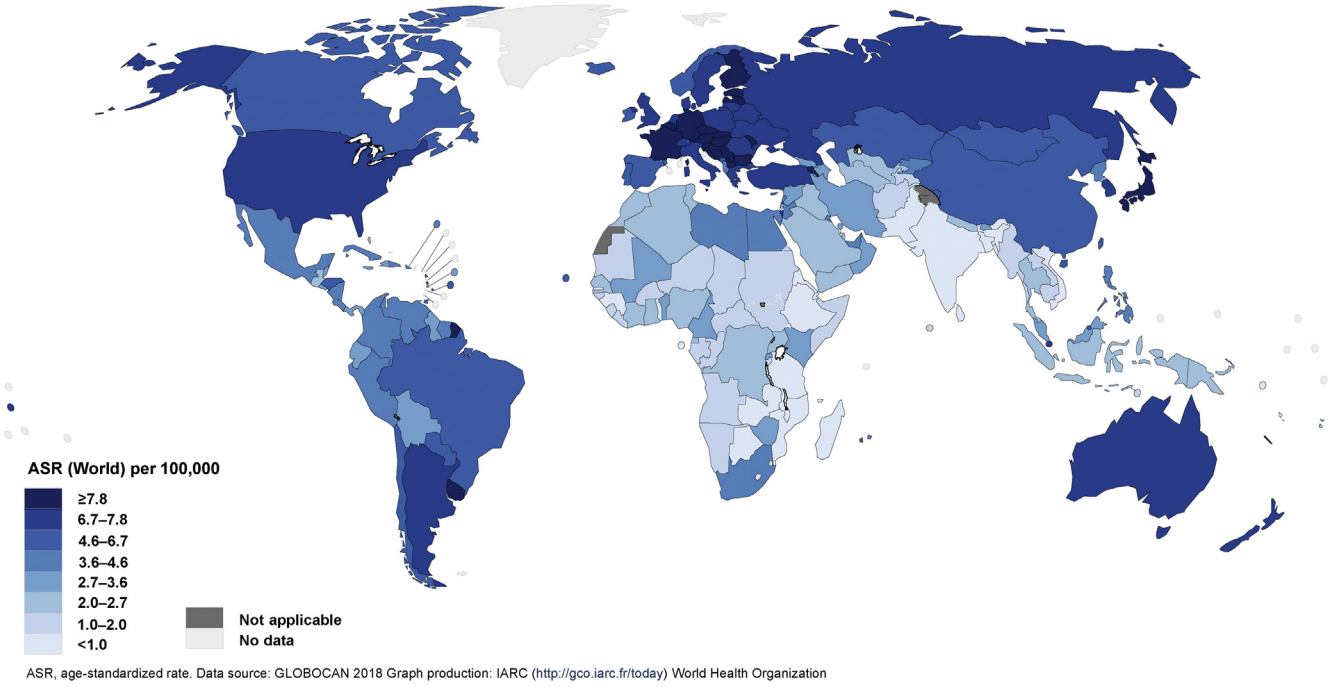


Figure 1. The global estimated incidence of pancreatic cancer in 2018, both sexes, all ages.

countries showed a decreasing trend (Kuwait AAPC, −9.67 and Lithuania AAPC, −1.02). Among women, 14 countries showed an increasing trend (AAPCs, 5.83 to 0.78). The increase occurred in 9 European countries, whereas Malta (AAPC, 3.06), Slovakia (AAPC, 2.97), and Lithuania (AAPC, 2.06) were found to have the most drastic increase. Countries with the most significant increase in other regions included the Philippines (AAPC, 5.83), Thailand (AAPC, 4.39), and Japan (AAPC, 1.41). No country showed a decreasing trend in mortality.

Incidence Trend Among Younger Vs. Older Individuals

The incidence of pancreatic cancer increased in 18 countries (AAPCs, 7.83 to 0.91) among individuals 50 years

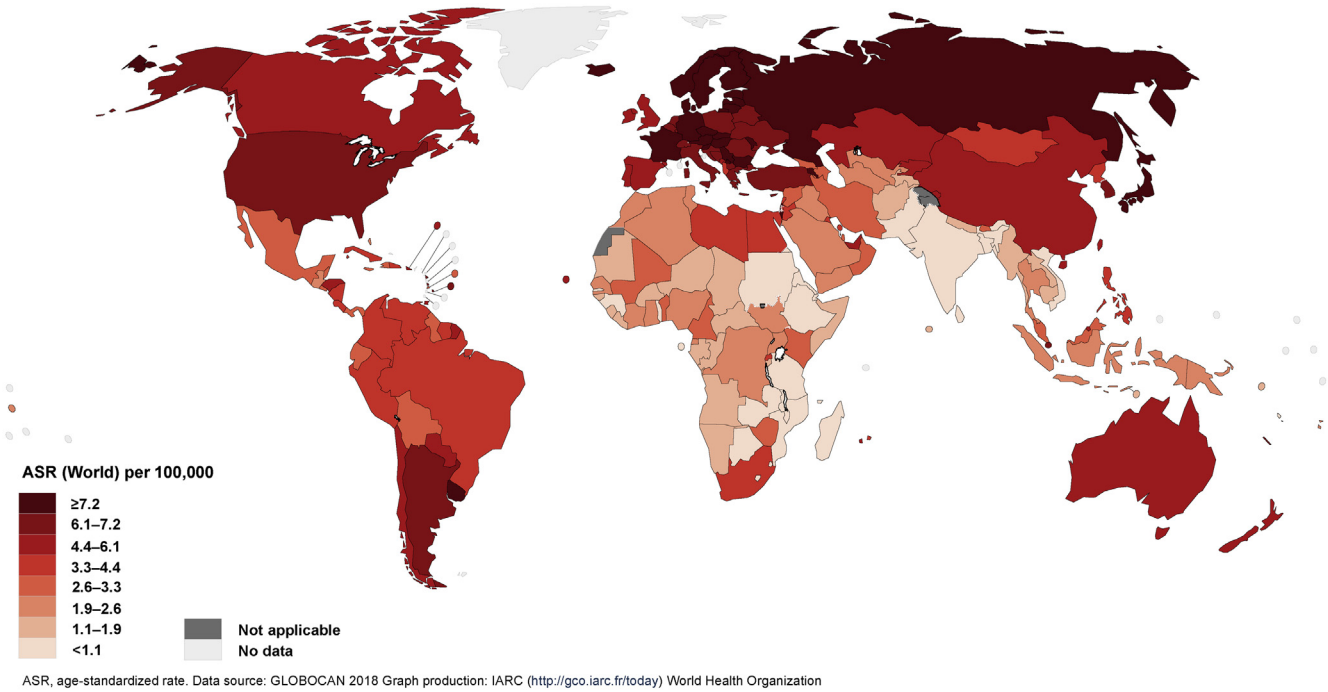


Figure 2. The global estimated mortality of pancreatic cancer in 2018, both sexes, all ages.

Table 1. The Association With Prevalence of Lifestyle and Metabolic Risk Factors

		Men				Women			
Outcome	Risk factor	β	95% CI		*P*	β	95% CI		*P*
Incidence (ASR)	Smoking	0.05	0.01	0.08	**.007**[a]	0.07	0.04	0.11	**< .001**[a]
	Alcohol drinking	0.18	0.08	0.27	**< .001**[a]	0.36	0.18	0.55	**< .001**[a]
	Physical inactivity	0.06	0.01	0.11	**.028**[a]	0.01	−0.02	0.03	.623
	Obesity	0.13	0.04	0.21	**.004**[a]	0.01	−0.04	0.06	.665
	Diabetes	−0.02	−0.26	0.23	.899	0.05	−0.09	0.19	.489
	Hypertension	0.13	0.04	0.23	**.006**[a]	−0.09	−0.16	−0.02	**.010**[a]
	High cholesterol	0.13	0.04	0.23	**.007**[a]	0.09	0.01	0.17	**.035**[a]
Mortality (ASR)	Smoking	0.04	0.01	0.07	**.007**[a]	0.05	0.01	0.08	**.005**[a]
	Alcohol drinking	0.15	0.07	0.23	**< .001**[a]	0.27	0.10	0.43	**.002**[a]
	Physical inactivity	0.05	0.01	0.10	**.028**[a]	0.01	−0.01	0.03	.281
	Obesity	0.12	0.04	0.19	**.004**[a]	0.02	−0.02	0.06	.307
	Diabetes	−0.05	−0.27	0.16	.899	−0.08	−0.20	0.05	.233
	Hypertension	0.11	0.03	0.20	**.006**[a]	−0.06	−0.12	0.00	.056
	High cholesterol	0.13	0.04	0.21	**.007**[a]	0.10	0.03	0.17	**.008**[a]

NOTE. The analysis was conducted using multivariable linear regression model at a country level.
β, beta coefficient, which can be interpreted as the change in ASR of incidence or mortality associated with 1% increase of a certain risk factor; CI, confidence interval.
[a]$P < .05$.

or older (Figure 5, Supplementary Table 4). The most marked increase was observed in Iceland (AAPC for men, 7.83), Malta (AAPC for men, 5.34 and AAPC for women, 6.57), and France (AAPC for men, 4.45 and AAPC for women, 4.76). As for individuals younger than 50 years, the incidence of pancreatic cancer also increased in 8 countries (AAPCs, 8.75 to 2.82, Figure 6, Supplementary Table 4). These included Germany (AAPC for women, 8.75), Sweden (AAPC for men, 5.98), the Netherlands (AAPC for women, 4.87), the United Kingdom (AAPC for men, 3.16 and AAPC for women, 4.72), Canada (AAPC for men, 4.68), Czech Republic (AAPC for women, 4.37), Turkey (AAPC for men, 4.26), and Australia (AAPC for men, 2.82). Similar patterns were observed in individuals younger than 40 years, where the incidence of pancreatic cancer increased in 4 countries (AAPCs, 11.07 to 8.31, Supplementary Figure 2, Supplementary Table 4). These included the Netherlands (AAPC for women, 11.07), Canada (AAPC for women, 9.57), France (AAPC for women, 8.70), and the United Kingdom (AAPC for women, 8.31).

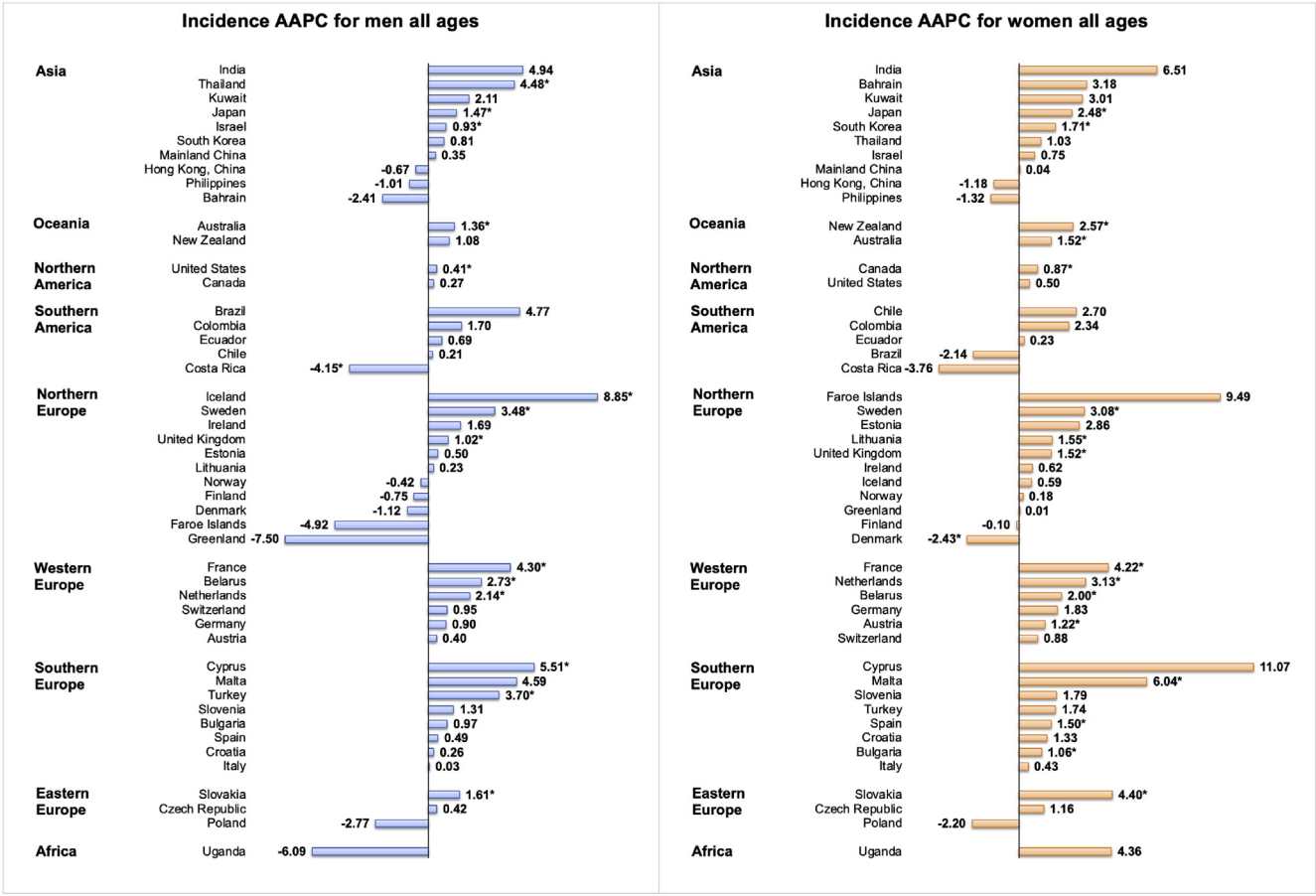
Discussion

Summary of Major Findings

This analysis provides up-to-date data on worldwide incidence and mortality of, risk factors for, and trends in pancreatic cancer. It was found that (1) the highest incidence and mortality of pancreatic cancer was in regions with very high and high HDIs, whereas the lowest was in regions with medium and low HDIs; (2) the higher incidence and mortality observed were associated with a higher prevalence of lifestyle and metabolic risk factors among the population; (3) many countries reported an increasing trend in both incidence and mortality for pancreatic cancer in the recent past decade, especially among women and those 50 years or older; and (4) an increasing trend in pancreatic cancer was also identified among individuals younger than 50 years and 40 years in some countries.

Disparities in Disease Burden Across Different Regions

There were substantial disparities in the burden of pancreatic cancer across different regions in 2018. We found that the highest incidence and mortality tended to predominate in regions with very high and high HDIs, whereas the lowest was observed in regions with medium and low HDIs, which is consistent with findings from previous literature.[2,10] This could be explained by the higher proportions of aging population, unhealthy lifestyle habits, and metabolic disorders in these countries with higher HDI. The higher incidence observed in regions with higher HDI also may be related to the higher availability of imaging and increased health awareness. In regions with relatively higher HDI, people are more health-conscious and have



AAPC, annual percentage change; *P values less than .05; The 95% confidence intervals and P values for the tests of AAPC were presented in **eTable 4**.

Figure 3. The AAPC of the incidence of pancreatic cancer in individuals all ages.

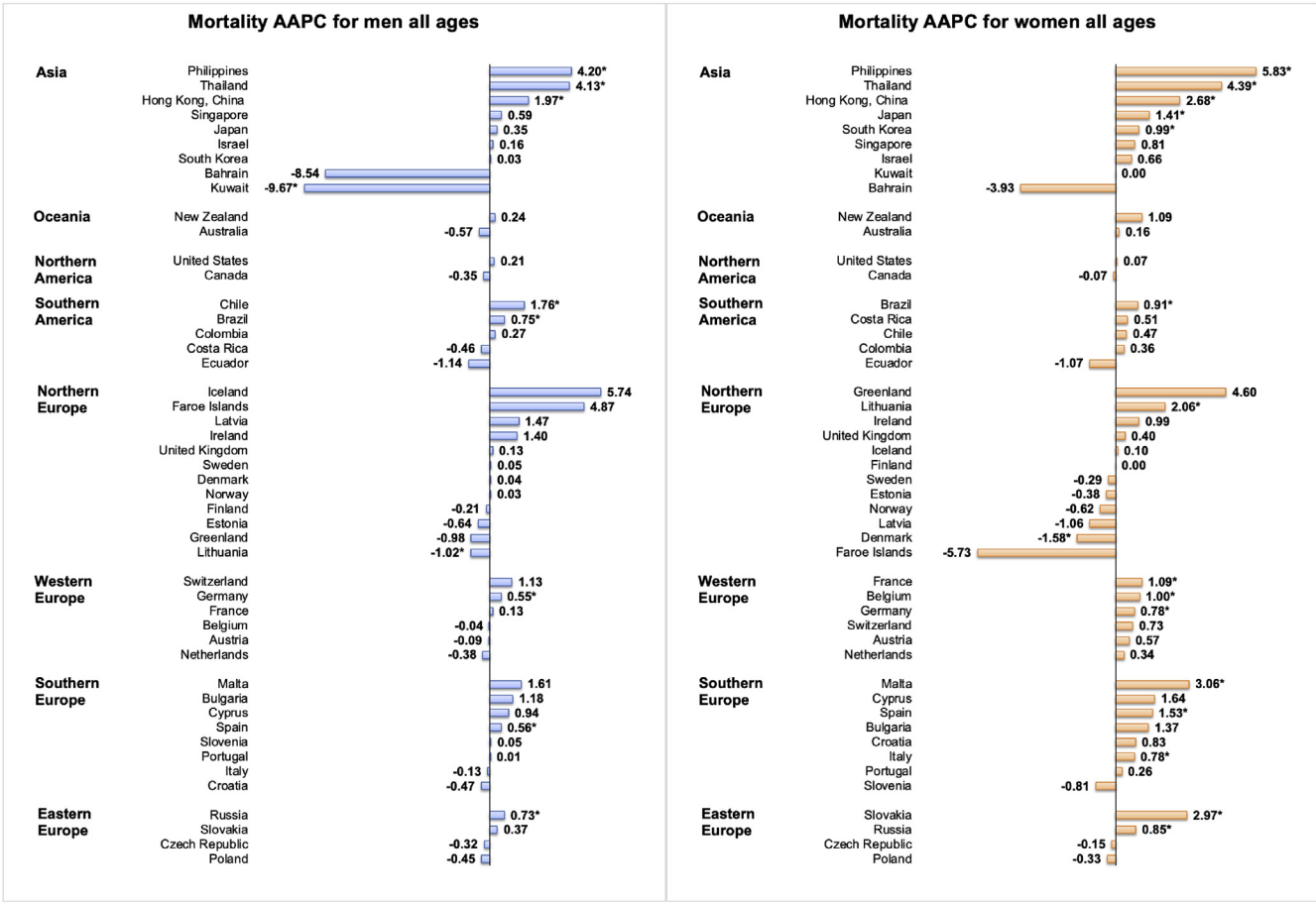
easier to access to radiology.[29] More incidental cancers may be picked up, even before they have symptoms. Nevertheless, it is also possible that the incidence of pancreatic cancer and related risk factors was underestimated in regions with lower HDI due to the possibility of underreporting.

Associated Lifestyle and Metabolic Risk Factors

The current study identified some risk factors associated with the incidence and mortality of pancreatic cancer at a country level, including smoking, alcohol drinking, physical inactivity, obesity, hypertension, and high cholesterol. The findings are generally consistent with previous risk factor analysis at an individual level. A study found that the estimated attributable fractions of pancreatic cancer caused by smoking was 11% to 32%.[30] A history of binge drinking increased the risk of pancreatic cancer by 2.5 times.[31] A meta-analysis indicated that individuals with BMI of 30 to 35 and 25 to 30 kg/m^2 had 19% and 13% increased risk of pancreatic cancer, respectively, when compared with people with normal BMI.[32] Such associations were also observed for high cholesterol,[33] diabetes,[34] and hypertension.[35] However, we did not observe a positive association between the prevalence of diabetes and burden of pancreatic cancer. This might be attributable to the study design in which analysis was performed at country level. Some individual-level confounders, such as antidiabetes medications, could not be accounted for. Evidence shows that metformin use can reduce the risk of pancreatic cancer incidence and mortality among patients with diabetes,[36,37] which may partially explain the results observed. Also, ecological fallacy caused by the difference between ecological correlation and individual correlations might be contributory.[38] Similar reasons also can explain the negative association with prevalence of hypertension for incidence detected among women.

Increasing Trend in Incidence and Mortality

We observed an overall increasing trend in its incidence and mortality in the past decade, especially among women and the older population. The substantial increase in the incidence and mortality of pancreatic cancer may indicate a growing prevalence of its risk factors associated with globalization, urbanization, and economic development. Another possible reason for its incidence increase is a rising incidence of pancreatic cystic neoplasm (PCN). PCN is a new disease entity with increasing awareness in the past 2 decades.[39] Some of them have malignant potential and will be



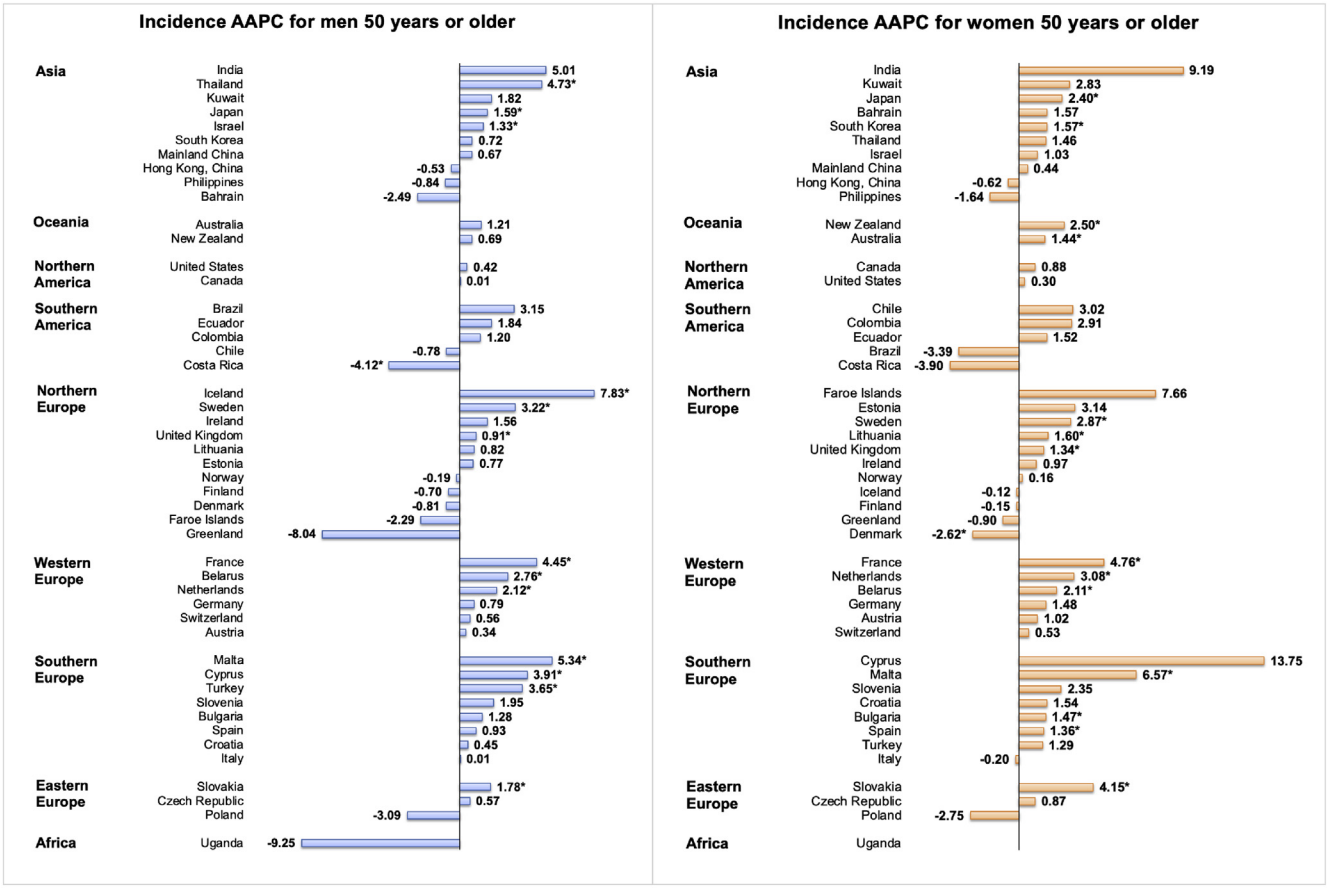
AAPC, annual percentage change; **P* values less than .05; The 95% confidence intervals and *P* values for the tests of AAPC were presented in **eTable 4**.

Figure 4. The AAPC of the mortality of pancreatic cancer in individuals all ages.

under active follow-up once identified. There is limited information on incidence of PCN in the general population. A study showed the ASR of incidence of PCN was 4.35 per 100,000 persons in 2005 compared with 0.31 per 100,000 in 1985.[40] However, the increasing incidence was thought to be secondary to diagnostic scrutiny rather than a true rise over time.[41] We also found the increase was more evident among women, which might be attributed to its higher prevalence of obesity and a more marked increase in the metabolic syndrome with the population aging related to menopause and sex hormones.[42] According to WHO, although the prevalence of obesity is lower in girls (6%, 5–19 years) compared with that in boys (8%), its prevalence is higher in women (15%, 20 years or older) than men (11%) in 2016.[43] Similar patterns were also observed for the prevalence of metabolic syndrome between men and women. In China, the prevalence of metabolic syndrome has increased more rapidly among women (from 7.9% to 30.7%) than in men (9.4% to 27.2%) in the past 2 decades.[44]

Increasing Trend Among the Younger Population

A notable finding of the results includes an increasing trend in incidence of pancreatic cancer observed among younger individuals in 8 countries (AAPCs, 8.75 to 2.82). The reasons behind the increasing trend in incidence and mortality of early-onset pancreatic cancer (EOPC) remain unknown.[45,46] A study found that genetic mutations and smoking were the major risk factors for EOPC.[47] Although genetic factors may play an important role in EOPC, they do not explain most EOPC. This is supported by the findings of another study that EOPC seems to be associated with smoking but not with familial syndromes.[48] However, as smoking prevalence was deceasing among younger people, the increasing trend observed may be caused by other risk factors.[49] A more recent study with a large sample size found obesity and metabolic disease were also the risk factors for EOPC.[50] According to the recent report by WHO, childhood obesity has increased from 4% to 18% during the period of 1975 to 2016.[51] This could partially result in the increase in incidence and mortality of pancreatic cancer among the younger individuals. From another study, the recent 3 decades witnessed a more evident increase in the prevalence of central obesity among the younger population between 15 and 40 years (16.3% to 33.9%) than those 40 years or older (43.6% to 57.9%) from 1985 to 2014.[52] As for metabolic syndrome, a meta-analysis of 14.6 million individuals also identified a more drastic increase in



AAPC, annual percentage change; *P values less than .05; The 95% confidence intervals and P values for the tests of AAPC were presented in **eTable 4**.

Figure 5. The AAPC of the incidence of pancreatic cancer in individuals 50 years or older.

prevalence and incidence of metabolic syndrome in the younger population between 15 and 40 years (7.6% to 16.5%) than those 40 years or older (33.0% to 35.2%) in the past 3 decades.[53] All of these factors may have accounted for a higher incidence in the younger populations. This trend is expected to continue further considering the aging population and the lifelong exposure to these obesity-related risk factors.

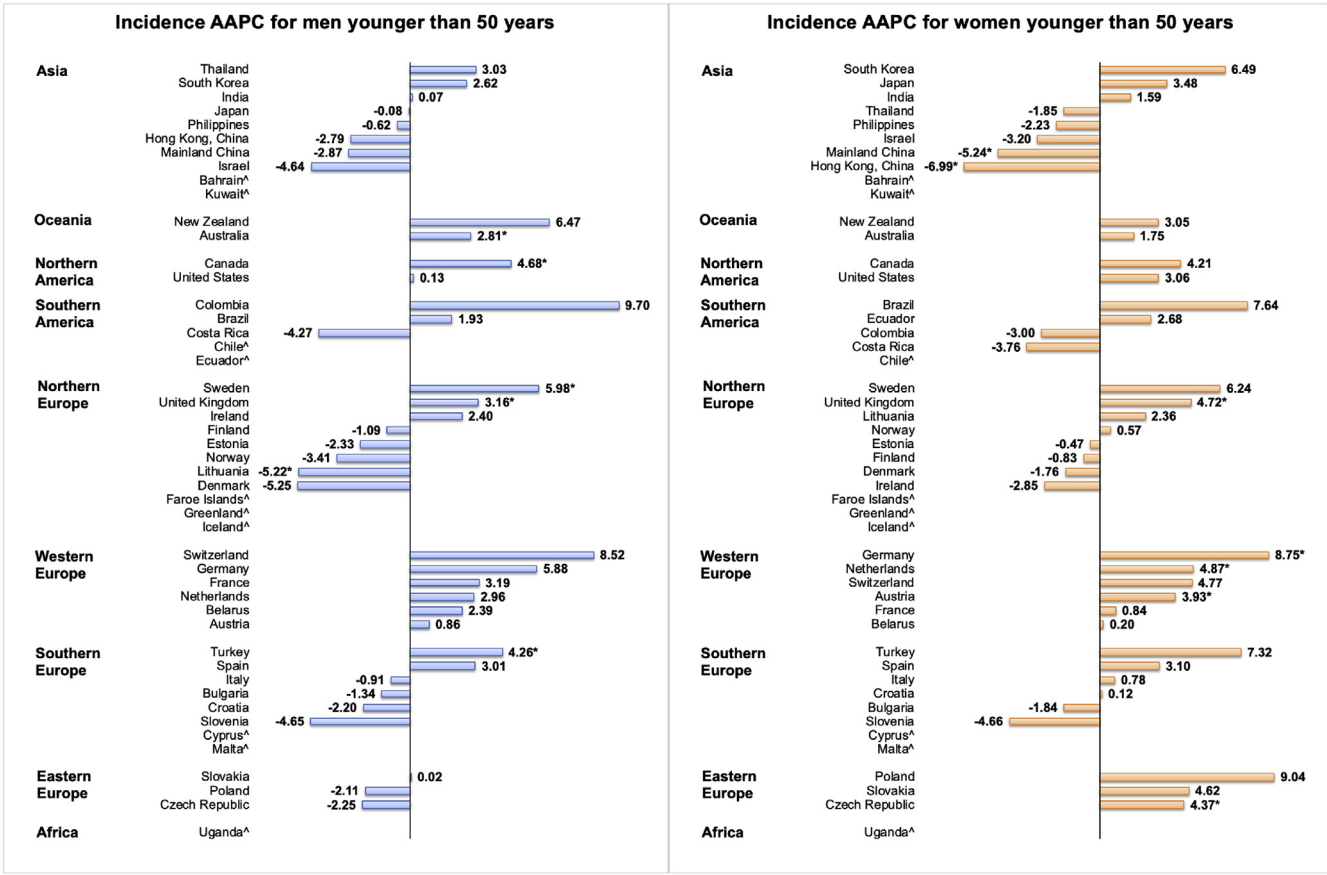
Strengths and Limitations

This analysis is the most recent report on worldwide burden and risk factors of pancreatic cancer, as well as its epidemiologic transitions by age, gender, and countries. The results were retrieved from cancer registries of a high standard with more than 1 million cases. However, there are several limitations. First, there might be underreporting of the cancer in regions with low income because of the suboptimal reporting infrastructure and mechanism, whereas the figures might have been overestimated for countries with higher HDI.

Second, an ecological fallacy may exist in the analysis between prevalence of risk factors and burden of pancreatic cancer. Although data a decade ago were used for most risk factors, as we expected a lead time between these factors and the development of pancreatic cancer, the prevalence of risk factors may have changed over time and been underestimated because some of these disease risk factors might exist previously and have no symptoms. Third, the cancer registries used in this study may be different by various regions and over time, making direct comparison among countries difficult. However, the robustness of the conclusions drawn from the comparison between different gender groups and age groups within a country might not be affected.

Implications

The incidence and mortality of pancreatic cancer increased in many countries for the past decade. With population aging and growth, policymakers and health care service providers might expect a further substantial increase in its disease burden, especially for regions with high socioeconomic development. For the general public, preventive measures, such as promotion of smoking cessation, overcoming alcohol addiction, increased physical activity, and management of chronic metabolic diseases, are required. These findings also call for targeted strategies for identifying and treating high-risk populations earlier to reduce its burden on the well-being of the individuals, families, and societal productivity.



AAPC, annual percentage change; *P values less than .05; ^AAPC for these countries could not be generated as zero or missing values were identified in any year of trend analysis; The 95% confidence intervals and P values for the tests of AAPC were presented in **eTable 4**.

Figure 6. The AAPC of the incidence of pancreatic cancer in individuals younger than 50 years.

Given the rise in incidence and mortality trends, treatment of pancreatic cancer based on pharmacotherapy and surgery should be assigned a top priority in policy agendas and clinical guidelines so as to reduce its associated mortality, especially for developed countries. In parallel, more medical resources are required to cope with the treatment and surveillance of patients diagnosed with pancreatic cancer. This is particularly true for the more developed regions that are yet to formulate preventive strategies. Future research should investigate the reasons behind these epidemiologic transitions, which could provide further insights into the specific etiology of pancreatic cancer.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.10.007.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. Collaborators GBDPC. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2019;4:934–947.
3. Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer:an update. Dig Dis 2010;28:645–656.
4. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013;144:1252–1261.
5. American Cancer Society. Key Statistics for Pancreatic Cancer. Available at: https://www.cancer.org/cancer/pancreatic-cancer/about/key-statistics.html. Accessed May 10, 2020.
6. Midha S, Chawla S, Garg PK. Modifiable and non-modifiable risk factors for pancreatic cancer:A review. Cancer Lett 2016;381:269–277.
7. Sung H, Siegel RL, Rosenberg PS, et al. Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry. Lancet Public Health 2019;4:e137–e147.
8. Ntala C, Debernardi S, Feakins RM, et al. Demographic, clinical, and pathological features of early onset pancreatic cancer patients. BMC Gastroenterol 2018;18:139.
9. **Wu W, He X**, Yang L, et al. Rising trends in pancreatic cancer incidence and mortality in 2000–2014. Clin Epidemiol 2018;10:789–797.

10. Wong MCS, Jiang JY, Liang M, et al. Global temporal patterns of pancreatic cancer and association with socioeconomic development. Sci Rep 2017;7:3165.
11. Wong MC, Goggins WB, Wang HH, et al. Global incidence and mortality for prostate cancer: analysis of temporal patterns and trends in 36 countries. Eur Urol 2016;70(5):862–874.
12. **Wong MC, Huang J**, Lok V, et al. Differences in incidence and mortality trends of colorectal cancer, worldwide, based on sex, age, and anatomic location [published online ahead of print February 21, 2020]. Clin Gastroenterol Hepatol https://doi.org/10.1016/j.cgh.2020.02.026.
13. International Agency for Research on Cancer, WHO. Data visualization tools for exploring the global cancer burden in 2018. Available at: https://gco.iarc.fr/today/home. Accessed May 10, 2020.
14. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941–1953.
15. United Nations. 2018 Statistical Update: Human Development Indices and Indicators. Available at: http://hdr.undp.org/en/2018-update. Accessed May 10, 2020.
16. United Nations. Human development classification, 2018 Statistical Update. Available at: http://hdr.undp.org/sites/default/files/2018_human_development_statistical_update.pdf. Accessed July 30, 2020.
17. World Health Organization. Global Health Observatory data repository. 2016. Available at: https://apps.who.int/gho/data/node.main. Accessed May 10, 2020.
18. Bray FCM, Mery L, Piñeros M, et al, eds. Cancer incidence in five continents, vol. XI (electronic version). Lyon: International Agency for Research on Cancer, 2017. Available at: https://ci5.iarc.fr. Accessed May 10, 2020.
19. World Health Organization. WHO mortality database. 2020. Available at: https://www.who.int/healthinfo/mortality_data/en/. Accessed May 10, 2020.
20. Mathers CD, Fat DM, Inoue M, et al. Counting the dead and what they died from: an assessment of the global status of cause of death data. Bull World Health Organ 2005;83:171–177.
21. World Health Organization. An assessment of the global status of cause of death data. 2020. Available at: https://apps.who.int/iris/handle/10665/72966. Accessed July 31, 2020.
22. Danckert B, Ferlay J, Engholm G, et al. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 8.2 (26.03.2019). 2019. Available at: https://www-dep.iarc.fr/NORDCAN/english/frame.asp. Accessed May 10, 2020.
23. Engholm G, Ferlay J, Christensen N, et al. NORDCAN—a Nordic tool for cancer information, planning, quality control and research. Acta Oncol 2010;49:725–736.
24. U.S. Department of Health and Human Services NIoH. Surveillance, Epidemiology, and End Results (SEER) Program. 2020. Available at: https://seer.cancer.gov/about/. Accessed May 10, 2020.
25. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision. 2016. Available at: https://icd.who.int/browse10/2016/en. Accessed May 10, 2020.
26. Segi M, Fujisaku S, Kurihara M. Geographical observation on cancer mortality by selected sites on the basis of standardised death rate. Gan 1957;48:219–225.
27. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335–351.
28. Clegg LX, Hankey BF, Tiwari R, et al. Estimating average annual per cent change in trend analysis. Stat Med 2009;28:3670–3682.
29. Poruk KE, Firpo MA, Adler DG, et al. Screening for pancreatic cancer: why, how, and who? Ann Surg 2013;257:17–26.
30. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol 2015;44:186–198.
31. Gupta S, Wang F, Holly EA, et al. Risk of pancreatic cancer by alcohol dose, duration, and pattern of consumption, including binge drinking:a population-based study. Cancer Causes Control 2010;21:1047–1059.
32. Arslan AA, Helzlsouer KJ, Kooperberg C, et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Arch Intern Med 2010;170:791–802.
33. Chen WC, Boursi B, Mamtani R, et al. Total serum cholesterol and pancreatic cancer: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2019;28:363–369.
34. Wolpin BM, Bao Y, Qian ZR, et al. Hyperglycemia, insulin resistance, impaired pancreatic β-cell function, and risk of pancreatic cancer. J Natl Cancer Inst 2013;105:1027–1035.
35. Wang Z, White DL, Hoogeveen R, et al. Anti-hypertensive medication use, soluble receptor for glycation end products and risk of pancreatic cancer in the Women's Health Initiative Study. J Clin Med 2018;7:197.
36. Li D, Yeung SC, Hassan MM, et al. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology 2009;137. 482–438.
37. Li X, Li T, Liu Z, et al. The effect of metformin on survival of patients with pancreatic cancer:a meta-analysis. Sci Rep 2017;7:5825.
38. Loney T, Nagelkerke NJ. The individualistic fallacy, ecological studies and instrumental variables:a causal interpretation. Emerg Themes Epidemiol 2014;11:18.
39. European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut 2018;67:789–804.
40. Klibansky DA, Reid-Lombardo KM, Gordon SR, et al. The clinical relevance of the increasing incidence of intraductal papillary mucinous neoplasm. Clin Gastroenterol Hepatol 2012;10:555–558.
41. Mukewar S, Chari ST. Epidemiology of cystic neoplasms of the pancreas. Pancreas 2018:565–572.
42. Lovejoy JC. The influence of sex hormones on obesity across the female life span. J Womens Health 1998;7:1247–1256.

43. World Health Organization. Obesity and overweight. 2020. Available at: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight. Accessed August 1, 2020.
44. Junjie Huang JLH, Withers M, Chien KL, et al. Prevalence of metabolic syndrome in Chinese women and men: a systematic review and meta-analysis of data from 734 511 individuals. Lancet 2019;392:S14.
45. **Beeghly-Fadiel A, Luu HN**, Du L, et al. Early onset pancreatic malignancies: clinical characteristics and survival associations. Int J Cancer 2016;139:2169–2177.
46. Tingstedt B, Weitkämper C, Andersson R. Early onset pancreatic cancer: a controlled trial. Ann Gastroenterol 2011;24:206–212.
47. Raimondi S, Maisonneuve P, Löhr JM, et al. Early onset pancreatic cancer:evidence of a major role for smoking and genetic factors. Cancer Epidemiol Biomarkers Prev 2007;16:1894–1897.
48. Piciucchi M, Capurso G, Valente R, et al. Early onset pancreatic cancer: risk factors, presentation and outcome. Pancreatology 2015;15:151–155.
49. World Health Organization. Global report on trends in prevalence of tobacco smoking. 2019. Available at: https://apps.who.int/iris/bitstream/handle/10665/156262/9789241564922_eng.pdf;jsessionid=1801CE2061DF2AC673A6B974FF8E3366?sequence=1. Accessed May 10, 2020.
50. **McWilliams RR, Maisonneuve P**, Bamlet WR, et al. Risk factors for early-onset and very-early-onset pancreatic adenocarcinoma: a pancreatic cancer case-control consortium (PanC4) analysis. Pancreas 2016;45:311–316.
51. World Health Organization. Obesity and overweight. 2019. Available at: https://wwwwhoint/news-room/fact-sheets/detail/obesity-and-overweight. Accessed May 10, 2020.
52. **Wong MCS, Huang J, Wang J**, et al. Global, regional and time-trend prevalence of central obesity: a systematic review and meta-analysis of 13.2 million subjects. Eur J Epidemiol 2020;35:673–683.
53. Wong MCS, Huang J, Pang TWY, et al. Worldwide incidence and prevalence of metabolic syndrome:a systematic review and meta-analysis of 14.6 million individuals. Gastroenterology 2020;158:S-1003.

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Received June 20, 2020. Accepted October 3, 2020.

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Acknowledgments
We express our gratitude to Dr Jeremy Teoh and Dr Erica Chan for technical assistance in the research process. Edited by Dr Kristine Novak.

The abstract of this study was awarded as poster of distinction by the International Digestive Disease Forum (IDDF) 2019, June 8, 2019, Hong Kong.

Author contributions
MCSW and JH participated in the conception of the research ideas, study design, interpretation of the findings, writing of the first draft of the manuscript, and provided intellectual input to the translational aspects of the study. JH, VL, and CHN retrieved information from the relevant databases and performed statistical analysis; LZ, JY, XQL, KN, CC, and ZJZ made critical revisions on the manuscripts and provided expert opinions on implications of the study findings.

Conflict of interest
The authors disclose no conflicts.