Cross-Sectional Study

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Global, regional, and national burdens of early onset pancreatic cancer in adolescents and adults aged 15–49 years from 1990 to 2019 based on the Global Burden of Disease Study 2019: a cross-sectional study

Zheng Li, MD, Xiaojie Zhang, MD, Chongyuan Sun, MD, Zefeng Li, MD, He Fei, MD, Dongbing Zhao, MD

Background: Early-onset pancreatic cancer (EOPC) in younger populations (age ≤50 years) is likely to be a more aggressive phenotype characterized by poor differentiation. The emerging analysis of the global burden of EOPC is limited and outdated.
Aim: To systematically investigate the burden and trend of EOPC based on global populations.
Methods: In this systematic analysis based on the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, the authors present the number of cases, age-standardized rates (ASRs) per 100 000 population, and risk factors for 204 countries and territories. The average annual percentage changes (AAPCs) for the incidence, mortality, and disability-adjusted life-years (DALYs) of EOPC were calculated using joinpoint regression analysis.
Results: According to the GBD 2019 estimates, there were 36 852 new cases of EOPC and 32 004 related deaths. East Asia had the highest number of cases, with 11 401 incidences and 10 149 deaths. The ASRs were 0.94 per 100 000 individuals for incidence and 0.81 per 100 000 for mortality. From 1990 to 2019, the age-standardized incidence increased by 46.9%, mortality increased by 44.6%, and DALYs increased by 41.9% globally. In trend analysis, the global incidence (AAPC, 1.26), mortality (AAPC, 1.24), and DALYs (AAPC, 1.25) of EOPC showed an increasing pattern. The ASRs of incidence, mortality, and DALYs of EOPC in Africa, America, and Asia exhibited a continuous upward trend, while the trend in Europe was fluctuating. Asian males exhibited the fastest growth in incidence (AAPC, 2.15) and mortality (AAPC, 2.13), whereas males in the Americas experienced the slowest increase in new cases (AAPC, 0.72) and deaths (AAPC, 0.67). A certain proportion of EOPC DALYs were attributable to known risk factors: tobacco smoking (13.3%), high BMI, 5.6%, and high fasting plasma glucose 3.2%. Integrating the socio-demographic index (SDI), ASRs of incidence and mortality initially increased with rising SDI, reaching a peak in central Europe (1.5 per 100 000 <ASRs <2.0 per 100 000), and decreased with further increase in SDI in 2019.
Conclusions: The findings offer valuable insights into the global distribution and magnitude of the EOPC burden. The burden is increasing at a rapid pace worldwide, particularly in Asia, and is notably high in central and eastern Europe. This highlights the need for additional preventive control efforts targeting high-risk populations.

Keywords: early-onset pancreatic cancer, epidemiology, incidence, mortality, risk factor, trend in global burden

Background

Adolescents and young adults aged 15–49 years represent a diverse population experiencing various physical, emotional, and psychosocial changes as they navigate the transition into adulthood. These changes may be influenced by factors such as career development, higher education, relationships, and starting families[1–3]. Cancers in adolescents and young adults are often treated in pediatric settings, along with more common adult cancer types[4,5]. Individuals in this age group face

Department of Pancreatic and Gastric Surgical Oncology, National Cancer Center/National Clinical Research for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China

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**Corresponding author. Address: National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, People's Republic of China. Tel.:/fax: +86 8778 7120. E-mail: dbzhao@cicams.ac.cn (D. Zhao).*

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numerous healthcare obstacles, such as time constraints for physical examinations, work-related stress, unhealthy lifestyles, and social and financial challenges[3]. When patients aged 15–49 years are diagnosed with cancer, it is essential to ensure timely diagnosis, optimal care, and specific treatment strategies. Therefore, a comprehensive assessment of the disease burden and epidemiologic trends of malignancies in this age group is crucial.

Pancreatic cancer (PC) has a low 5-year survival rate of around 12% and is the fourth leading cause of cancer-related death in the United States. Epidemiologic models project that by 2030, PC is expected to become the second leading cause of cancer-related mortality[6]. Based on the cancer statistics in 2023, it is estimated that there will be 64 050 new cases of PC and 50 550 deaths[7]. Although PC mainly develops in individuals with a peak incidence between 60 and 80 years old, the incidence of early-onset pancreatic cancer (EOPC), which occurs in adults younger than 50 years, appears to be increasing[8]. Additionally, younger populations are more likely to be diagnosed with an advanced stage and a more aggressive phenotype, characterized by perineural invasion and poor differentiation, therefore, research on the burden of EOPC is necessary[9,10]. Emerging population-based analysis from the United States cancer registry revealed an increasing incidence of EOPC, with a steeper trend among younger age groups between 1995 and 2014[11]. A more in-depth analysis of recent epidemiological findings also reveals the similar worrisome trend of EOPC incidence[12]. While existing studies have shed light on the increasing incidence of EOPC, the data was limited to a single region and was outdated. Additionally, these studies did not systematically present a comprehensive assessment of the EOPC burden, integrating multiple metrics such as disability-adjusted life-years (DALYs) and socio-demographic index (SDI). These metrics are important for adjusting preventive strategies as they reveal the global differences in the heterogeneous burden.

The Global Burden of Diseases, Injuries, and Risk Factors Study is the sole global disease burden estimation framework, offering estimated metrics for age-standardized mortality, morbidity, and DALYs for cancer[13]. To the best of our knowledge, no comprehensive Global Burden of Diseases (GBD) analysis has been conducted for the global burden of EOPC in adolescents and adults aged 15–49 years. In this research, our aim was to systematically evaluate the trends in the burden of EOPC based on global populations, providing distinct insights into the distribution and magnitude of EOPC burden globally. The results informing regions with significant EOPC burden could also contribute to tailoring current preventive guidelines for disease control in different countries and territories.

HIGHLIGHTS

- Early-onset pancreatic cancer in younger populations is likely to be a more aggressive phenotype characterized by poor differentiation.
- East Asia had the largest number of new early-onset pancreatic cancer cases, deaths, and disability-adjusted life-years (DALYs) in 2019 around the world.
- Countries and territories with higher socio-demographic index tended to have lower age-standardized rates (ASRs) of incidence, mortality, and DALYs.
- Males had higher ASRs of incidence, mortality, and DALYs compared to the female. Concerning the state, aforementioned ASRs were distinctively high in Central and Eastern Europe.

Methods

GBD data retrieval

The retrospective study collected disease burden-related data using a method similar to the previous publication that systematically researched the burden of stomach cancer on a global, regional, and national scale[14]. In the Global Burden of Disease Study 2019 (GBD 2019) Data Resources, we obtained comprehensive GBD results data using a query tool. This included estimated incidence, prevalence, mortality, DALYs, and risk factors for 369 diseases and injuries, for both sexes, and across 204 countries and territories. The definitions of metrics are summarized in Table S1 (Supplemental Digital Content 1, http://links.lww.com/JS9/B658). In GBD 2019, cancers are classified into various groups according to the International Classification of Diseases 10th edition (ICD-10)[15]. PC includes all diagnoses coded C25.0 to C25.9 (malignant neoplasm of the pancreas). EOPC was generally defined as the occurrence of PC in individuals younger than 50 years[16]. Therefore, we sought data on EOPC in adolescents and adults aged 15–49 years from 1990 to 2019. To enable a meaningful comparison of rates between different populations worldwide, age standardization was utilized to adjust a country's prevalence rate of different risk factors using the same standard population in the GBD study. As a result, the age-standardized rates (ASRs) were obtained based on the Segi-Doll world reference population[17]. Furthermore, the SDI of 204 countries was integrated into the further analysis to identify the association between EOPC trends and the level of development, with the detailed SDI value of each country shown in Table S2 (Supplemental Digital Content 2, http://links.lww.com/JS9/B659). All countries were classified into five categories according to the SDI: Low SDI: SDI <0.46; Low-middle SDI: 0.46–0.64; Middle SDI: 0.65–0.74; High-middle SDI: 0.75–0.85; High SDI: SDI >0.85. Additionally, the World Bank income classification of these countries was based on Gross National Income (GNI) per capita: Low-income: GNI per capita <1006; Lower-middle-income: 1006–3955; Upper-middle-income: 3956–12 235; High-income: GNI per capita >12 235, which was demonstrated in Table S3 (Supplemental Digital Content 3, http://links.lww.com/JS9/B660).

Statistical analysis

After obtaining the ASRs of incidence, mortality, prevalence, and risk factors from the aforementioned global disease burden estimation framework, we investigated the epidemiologic trend in mortality, incidence, and prevalence by applying joinpoint regression analysis[18]. In the trend analysis, countries with 'missing' or 'zero' values in any year were excluded as these values could not be processed. The standard error (SE) was calculated using the formula: $SE = (upper - lower)/(1.96 \times 2)$, with the upper and lower representing the two boundaries of CIs acquired from GBD. The study calculated the average annual percentage change (AAPC) and the corresponding 95% CI

using geometric weighting in various regions to demonstrate the 30-year trend in mortality and incidence. The specified time interval was considered for assigning weights to the length of each segment. The formula of AAPC was as follows: $AAPC = \{\exp(\frac{\sum wibi}{\sum wi}) - 1\} \times 100$, in which wi indicates the length of each segment in the range of years, while the bi is the slope coefficient for each segment in the desired range of years. We compared the magnitude of AAPC with zero and considered the lack of significance as indicative of a stable trend, aiming to achieve statistical significance. The permutation test model and parametric method for CI were selected. If the AAPC was located in one segment, the *t*-distribution was performed; otherwise, the normal (z) distribution was applied. In addition, a hierarchy cluster analysis was conducted to classify 204 regions into four categories in terms of their temporal trends in etiologies related to EOPC ASRs. Statistical significance was considered if $P < 0.05$. All statistical analyses were conducted using Joinpoint 5.0.1 April 2023 and R software version 4.2.0 for Windows.

Ethics and STROCSS statement

The use of anonymized, publicly available epidemiologic data did not require ethical approval, and patient informed consent forms were not necessary when accessing and downloading the data from the database. The study adhered to the strengthening the reporting of cohort, cross-sectional and case–control studies in surgery (STROCSS) criteria[19] (Supplemental Digital Content 4, http://links.lww.com/JS9/B661).

Results

Incidence, mortality, and DALYs of EOPC

Based on the GBD 2019 estimates, a total of 36 852 new cases of EOPC were reported globally, with East Asia having the highest number of new cases. The global average incidence ASR was 0.94 per 100 000 individuals, with rates ranging from 0.14 (Ethiopia) to 4.32 (United Arab Emirates). The ASR of incidence increased by 46.9% between 1990 and 2019. From a continental perspective, Eastern Europe had the highest incidence (ASR, 2.27), while central and eastern Sub-Saharan Africa had the lowest incidence (ASR, 0.35). In terms of sex differences, men (ASR, 1.19) had ~1.8 times the global average incidence compared to women (ASR, 0.67), indicating sex-specific effects of EOPC. The detailed incidence ASRs of 204 countries and territories were visualized in Figure 1.

It was estimated that 32 004 individuals died due to EOPC globally, with East Asia reporting the largest number of fatalities. In terms of mortality, the worldwide average ASR was 0.81 per 100 000 individuals, ranging from 0.12 (Ethiopia) to 3.85 (United Arab Emirates), which increased by 44.6% from 1990 to 2019. At the regional level, Eastern Europe experienced the highest mortality (ASR, 2.00), while central Sub-Saharan Africa had the lowest (ASR, 0.31). In terms of sex, men (ASR, 1.05) had about twice the worldwide mortality as women (ASR, 0.57). Integrating the SDI, ASRs of incidence and mortality were relatively high in high-middle SDI and high SDI regions.

When considering DALYs due to EOPC, it was estimated that a total of 1 489 528 years were lost globally, with East Asia having the highest DALYs. The global average ASR was 37.85 per 100 000 population, ranging from 5.94 (Ethiopia) to 179.63 (United Arab Emirates), and increasing by 41.9% over the years. At the continental level, Eastern Europe experienced the highest rate of DALYs (ASR, 92.96), while the rate in central Sub-Saharan Africa was the lowest (ASR, 14.79). The DALYs ASRs of men (ASR, 48.77) were ~1.8 times those of women (ASR, 26.68). The comprehensive data on incidence, mortality, and DALYs is summarized in Table 1.

Trends in incidence, mortality, and DALYs

The study evaluated the change in cases of EOPC among 204 countries and territories from 1990 to 2019 using the changing rate. The change was classified into categories such as 30 to 60% decrease, less than 30% decrease, less than 50% increase, 50% to 100% increase, 100 to 200% increase, 200 to 300% increase, and over 300% increase, as shown in Figure 1A. Additionally, estimated annual percentage changes of incidence in each global region were calculated and visualized in Figure 1C. The analysis of AAPC revealed that seven regions had a significantly decreasing incidence, including Austria (AAPC, – 0.81), Burundi (AAPC, – 0.38), Czechia (AAPC, – 0.95), Finland (AAPC, – 1.11), Luxembourg (AAPC, – 0.64), Somalia (AAPC, – 0.74), and Sweden (AAPC, – 1.44). In contrast, the incidence of the remaining regions experienced an increase with varying degrees, reaching the peak in Cabo Verde (AAPC, 8.20), as shown in Table S4 (Supplemental Digital Content 5, http://links.lww.com/JS9/B662) and Figure 1D. Additionally, Kazakhstan (AAPC, 7.87), Belize (AAPC, 7.39), Saint Lucia (AAPC, 7.26), Suriname (AAPC, 7.08), and Grenada (AAPC, 7.04) demonstrated a high level of increasing trend in incidence. Furthermore, the trends of age-standardized incidence rate (ASIR) from 1990 to 2019 were demonstrated with subgroups of different sex. For both men and women, Africa, America, and Asia exhibited a generally consistent upward trend of ASIR, whereas Europe experienced an increasing but fluctuating trend, as shown in Figure 2. In terms of the continent, the global trends of EOPC incidence were increasing for both men (AAPC, 1.21) and women (AAPC, 1.38). The trend analysis revealed that Asian males exhibited the fastest growth of incidence (AAPC, 2.15), whereas males in the Americas experienced the slowest trend (AAPC, 0.72), as shown in Figure 3A.

The global trend of EOPC mortality was observed to be increasing (AAPC, 1.24). Further analysis of different sex revealed an increasing trend in deaths due to EOPC for women (AAPC, 1.34) and men (AAPC, 1.20). Decreasing trends of mortality were observed in six regions, including Finland (AAPC, – 1.36), Sweden (AAPC, – 1.34), Czechia (AAPC, – 1.07), Luxembourg (AAPC, – 0.84), Austria (AAPC, – 0.78), and Somalia (AAPC, – 0.65). The top five regions with the highest increasing trend of mortality included Cabo Verde (AAPC, 8.15), Kazakhstan (AAPC, 7.84), Belize (AAPC, 7.34), Saint Lucia (AAPC, 7.33), and Grenada (AAPC, 7.05). At the continent level, the Caribbean had the greatest rising trend (AAPC, 4.73), whereas western Europe had the lowest one (AAPC, 0.36). Integrating the SDI, regions with middle (AAPC, 2.34) and low-middle SDI (AAPC, 2.47) experienced a rapid growth of deaths, as summarized in Table S5 (Supplemental Digital Content 6, http://links.lww.com/JS9/B663). The age-standardized mortality rate (ASMR) increased steadily worldwide (Fig. 2). The ASMR in Africa, Asia, and America had a smooth upward trend, while the trend in Europe was fluctuating (Fig. 3B).

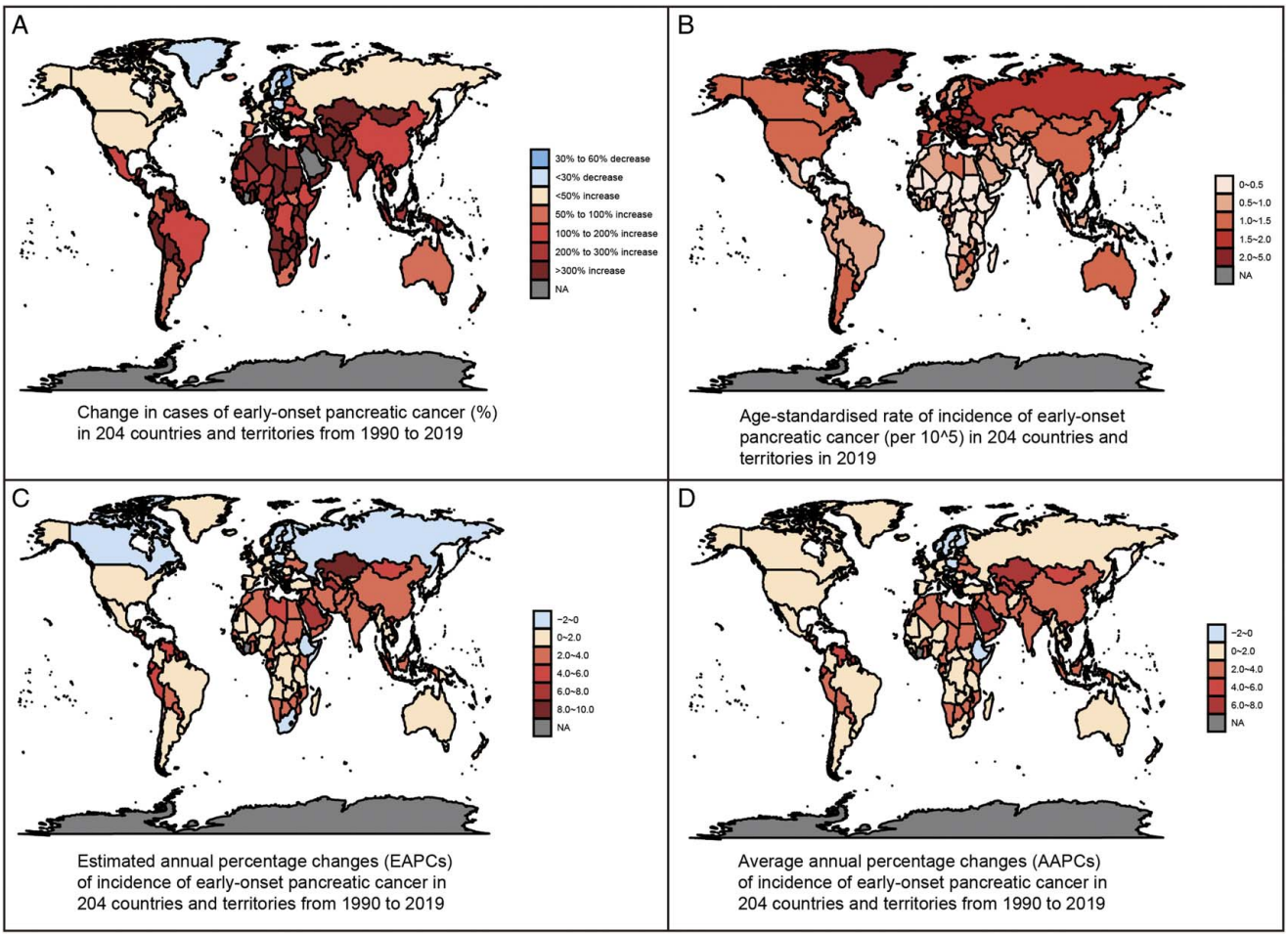

Figure 1. Incidence analysis of EOPC per 100 000 population in 204 countries and territories using multiple metrics. (A) Change in cases from 1990 to 2019; (B) Age-standardised rate in 2019; (C) Estimated annual percentage changes (EAPCs) from 1990 to 2019; (D) Average annual percentage changes (AAPCs) from 1990 to 2019.

The global trend of DALYs showed a pattern of increasing (AAPC, 1.25), with similar trends in women (AAPC, 1.25) and men (AAPC, 1.17). The top five countries with the highest trend of declining DALYs included Finland (AAPC, – 1.35), Sweden (AAPC, – 1.30), Czechia (AAPC, – 1.05), Austria (AAPC, – 0.82), and Luxembourg (AAPC, – 0.78), whereas the top five regions with the highest upward trend included Cabo Verde (AAPC, 8.03), Kazakhstan (AAPC, 7.75), Belize (AAPC, 7.27), Saint Lucia (AAPC, 7.15), and Suriname (AAPC, 7.03). At the regional level, the fastest-increasing trend of deaths due to EOPC was found in the Caribbean (AAPC, 4.64), whereas the slowest one was in Western Europe (AAPC, 0.30). Regarding the SDI, DALYs in regions with middle (AAPC, 2.26) and low-middle SDI (AAPC, 2.41) were increasing at a high level. Generally, the global burden of DALYs presented an increasing trend for both men and women (Table S6, Supplemental Digital Content 7, http://links.lww.com/JS9/B664). As shown in Figure 2, the level of DALYs showed a rising trend in America, Asia, and Africa. However, the tendency of DALYs in Europe was fluctuating.

Additionally, a subgroup analysis focusing on the burden of EOPC in adolescents was conducted by including individuals aged 15–19 years. From 1990 to 2019, a slight global upward trend in the number of EOPC deaths, DALYs, and incidence was identified, with Asia bearing the heaviest burden of EOPC. When considering percentages, increasing trends in deaths were observed in Asia, America, Africa, Europe, and globally. Subsequently, the trends in ASRs of death, DALYs, and incidence were demonstrated, indicating significant variations across different regions worldwide (Figure S1, Supplemental Digital Content 8, http://links.lww.com/JS9/B665).

A hierarchical cluster analysis was conducted to group 204 countries and territories based on the temporal trends in etiologies related to EOPC ASRs. These regions were clustered into four categories according to their similar trends. Each group was distinguished by different colors, indicating significant increase, minor increase, stable or minor decrease, and significant decrease, respectively (Figure S2, Supplemental Digital Content 9, http://links.lww.com/JS9/B666). In the analysis between ASRs and SDI, we compared the average ASRs of individuals in 204 countries and territories with varying SDIs. The observed regional and national ASRs in terms of SDI, versus the expected level for each region based on SDI, were demonstrated in Figure 4 and Figure S3 (Supplemental Digital Content 10, http://links.lww.com/JS9/B667). In 2019, nations with higher SDI seemed to have higher

Table 1

Incident cases of deaths and DALYs of EOPC in 2019, and the age-standardised rates by sex and GBD region.

	Incidence						Mortality						Disability-adjusted life years (DALYs)					
	Both sexes		Female		Male		Both sexes		Female		Male		Both sexes		Female		Male	
Regions	Cases	ASR per 100,000	Cases	ASR per 100,000	Cases	ASR per 100,000	Cases	ASR per 100,000	Cases	ASR per 100,000	Cases	ASR per 100,000	Number	ASR per 100,000	Number	ASR per 100,000	Number	ASR per 100,000
Global	36852	0.94	13086	0.67	23766	1.19	32004	0.81	11159	0.57	20845	1.05	1489528	37.85	519027	26.68	970501	48.77
Central Asia	460	0.94	166	0.68	294	1.2	409	0.84	148	0.61	261	1.07	19387	39.7	7000	28.77	12387	50.57
East Asia	11401	1.53	3027	0.83	8374	2.19	10149	1.36	2650	0.73	7499	1.96	473425	63.43	123099	33.87	350326	91.51
South Asia	4017	0.41	1817	0.38	2200	0.44	3578	0.37	1617	0.34	1961	0.39	168430	17.29	75981	15.91	92449	18.62
Southeast Asia	2976	0.82	1264	0.7	1712	0.94	2600	0.72	1101	0.61	1499	0.82	122329	33.79	51493	28.69	70836	38.8
Andean Latin America	247	0.75	114	0.69	133	0.8	215	0.65	99	0.6	116	0.7	10218	30.85	4669	28.16	5549	33.54
Central Latin America	1116	0.85	501	0.74	615	0.96	973	0.74	433	0.64	540	0.84	45688	34.69	20256	30.03	25432	39.58
Southern Latin America	468	1.37	199	1.16	269	1.59	400	1.18	167	0.98	233	1.38	18527	54.43	7761	45.24	10766	63.77
Tropical Latin America	1182	0.99	508	0.84	674	1.14	1039	0.87	444	0.74	595	1.01	48407	40.61	20643	34.23	27764	47.14
Caribbean	190	0.8	75	0.62	115	0.97	167	0.7	65	0.54	102	0.86	7717	32.27	3019	25.01	4698	39.67
Central Europe	1098	2.08	337	1.31	761	2.83	975	1.85	299	1.16	676	2.51	44314	84.06	13594	52.63	30720	114.26
Eastern Europe	2222	2.27	634	1.29	1588	3.26	1961	2	559	1.13	1402	2.88	91158	92.96	25985	52.71	65173	133.64
Western Europe	2901	1.52	1170	1.24	1731	1.79	2244	1.18	845	0.9	1399	1.45	101638	53.3	38370	40.77	63268	65.51
North Africa and the Middle East	2799	0.84	953	0.6	1846	1.06	2442	0.73	820	0.52	1622	0.93	114066	34.19	38374	24.17	75692	43.28
South Africa	242	0.8	85	0.56	157	1.03	218	0.71	76	0.5	142	0.92	10227	33.58	3550	23.45	6677	43.61
Central Sub-Saharan Africa	217	0.35	71	0.23	146	0.47	196	0.31	64	0.2	132	0.43	9195	14.79	3027	9.68	6168	19.95
Eastern Sub-Saharan Africa	701	0.35	276	0.27	425	0.44	633	0.32	250	0.25	383	0.39	30166	15.17	12096	11.91	18070	18.57
Southern Sub-Saharan Africa	363	0.86	144	0.68	219	1.04	324	0.77	127	0.6	197	0.94	15271	36.1	6009	28.26	9262	44.02
Western Sub-Saharan Africa	961	0.45	419	0.37	542	0.53	856	0.4	375	0.33	481	0.47	40797	18.98	17783	15.85	23014	22.38
Oceania	27	0.4	10	0.31	17	0.49	24	0.35	9	0.27	15	0.44	1131	16.62	426	12.76	705	20.35
Australasia	162	1.2	67	0.99	95	1.41	130	0.96	53	0.77	77	1.15	5941	43.93	2415	35.45	3526	52.54
High SDI	6702	1.43	2511	1.1	4191	1.73	5385	1.15	1927	0.85	3458	1.43	245633	52.27	88046	38.71	157587	65
High-middle SDI	11502	1.58	3526	0.99	7976	2.13	10072	1.38	3019	0.85	7053	1.89	467462	64.17	139909	39.47	327553	87.56
Middle SDI	11819	0.94	4156	0.67	7663	1.21	10455	0.83	3639	0.58	6816	1.07	488992	38.79	169592	27.14	319400	50.24
Low-middle SDI	5066	0.54	2176	0.47	2890	0.62	4515	0.48	1933	0.42	2582	0.55	212607	22.78	90929	19.54	121678	25.99
Low SDI	1745	0.32	709	0.26	1036	0.39	1561	0.29	635	0.23	926	0.35	74128	13.72	30277	11.12	43851	16.35

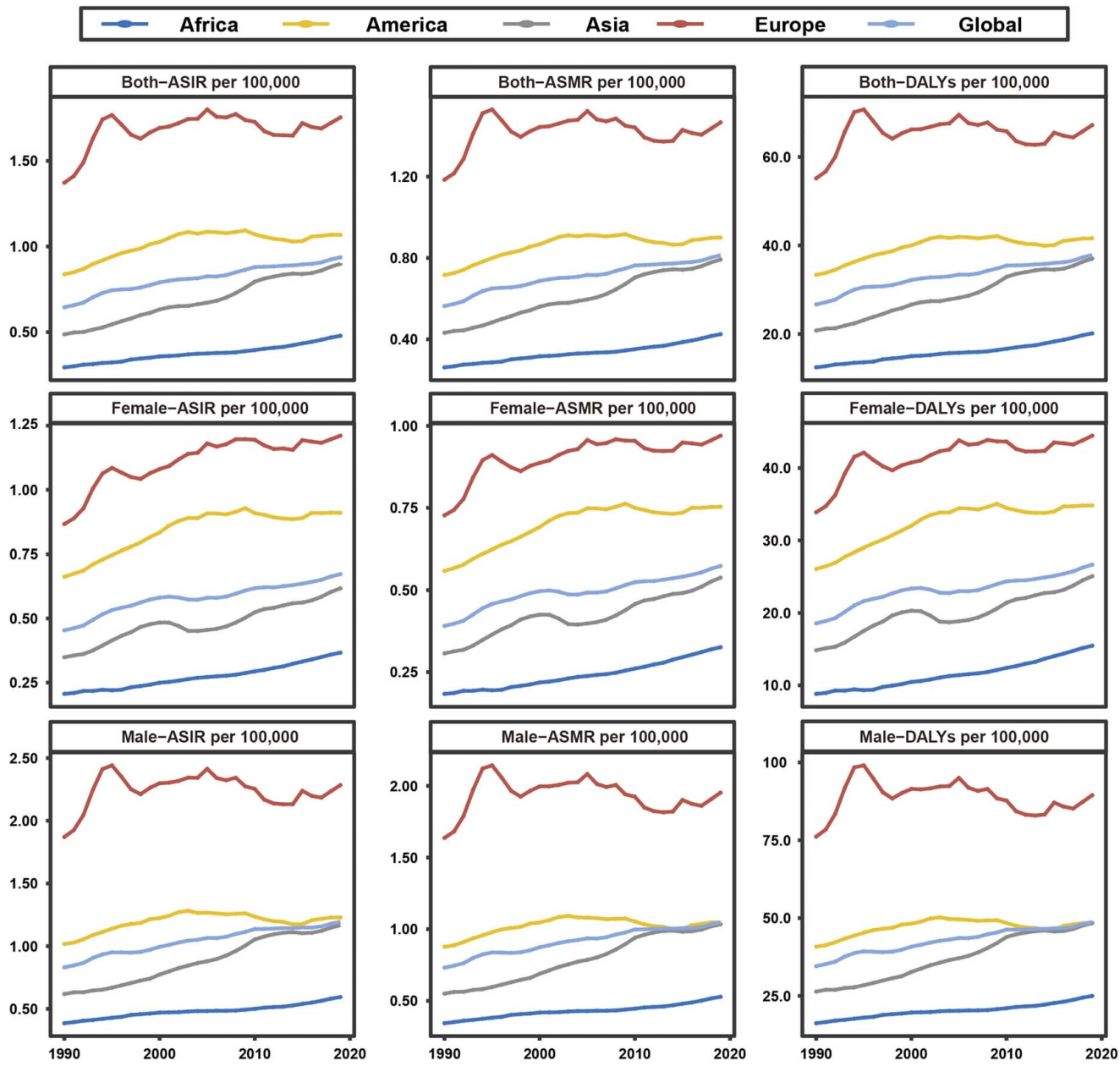

Figure 2. Trend analysis of age-standardised rates of EOPC (per 100 000 population) across continents from 1990 to 2019. ASIR, age-standardised incidence rate; ASMR, age-standardised mortality rate; DALYs, disability-adjusted life-years.

rates of EOPC incidence. Interestingly, it was revealed that the ASIR and ASMR initially increased with rising SDI, reaching the highest point in central Europe (ASMR 1.5 per 100 000, ASIR between 1.5 and 2.0 per 100 000). Subsequently, the rates tended to decrease with a further increase in SDI (Fig. 4A). The low-income to middle-income regions, Oceania, Southeast Asia, and Central Latin America closely followed expected trends over the study period. However, in high-income countries, the observed trends changed widely, with several territories staying below or above expected levels throughout the study period with fluctuating or increasing ASRs (Fig. 4B). Similar patterns were found for mortality in relation to SDI, as shown in Figure S3 (Supplemental Digital Content 10, http://links.lww.com/JS9/B667).

Proportion of deaths and DALYs attributable to risk factors

The global substantial proportion of mortality and DALYs attributable to three risk factors for which the Global Burden of Disease (GBD) framework estimates were accessed. For mortality, it was indicated that 13.3% [95% uncertainty interval (UI), 9.2–17.0] of deaths were attributable to tobacco smoking, 5.7% (95% UI: 1.8–11.3) to high BMI, and 3.3% (95% UI: 0.7–7.7) to high fasting plasma glucose (FPG). For DALYs, 12.8% (95% UI: 8.8–16.3) of DALYs were attributable to tobacco smoking, 5.6% (95% UI: 1.8–11.2) to high BMI, and 3.2% (95% UI: 0.7–7.4) to high FPG. The influence of the aforementioned risk factors in various regions varies. Tobacco smoking accounted for the highest proportion of deaths (20.4%; 95% UI: 15.5–24.8) and

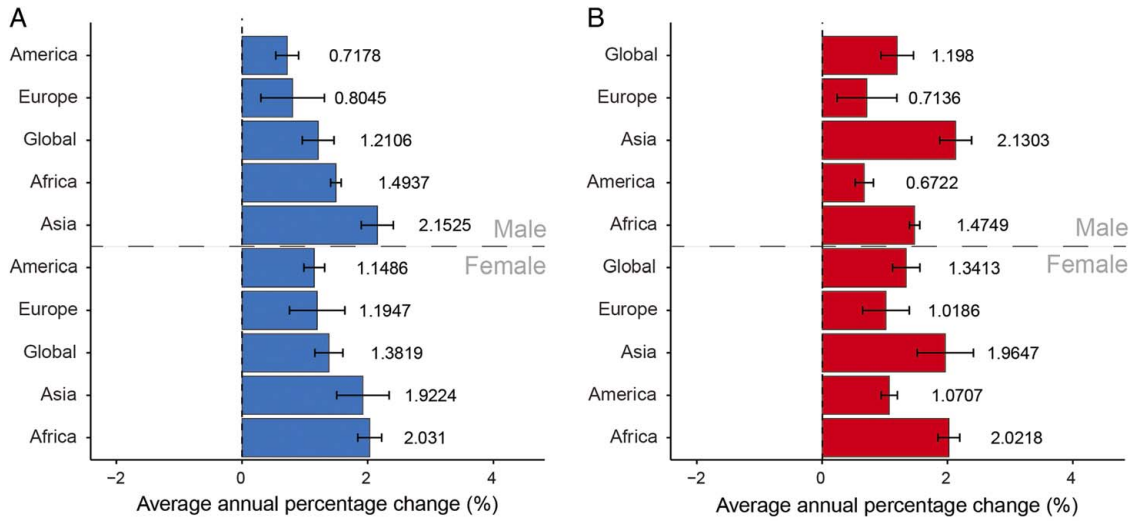

Figure 3. Average annual percentage change (AAPC) analysis of sex subgroups across continents from 1990 to 2019. (A) AAPC analysis of incidence; (B) AAPC analysis of mortality.

DALYs (19.9%; 95% UI: 15.1–24.1) in Western Europe. High BMI could explain the most deaths (9.8%; 95% UI: 3.6–17.7) and DALYs (9.8%; 95% UI: 3.6–17.6) in high-income North America. In terms of FPG, 7.6% of mortality (95% UI: 1.7–16.7) and 7.3% of DALYs (95% UI: 1.6–16.1) were attributable to high FPG in Oceania, as shown in Figure 5.

Discussions

The findings of GBD 2019 demonstrate that the great variations in ASRs of incidence, mortality, and DALY across 204 countries and territories remain an epidemiological distinction of EOPC, implying the importance of finer delineation of hotspots for identifying at-risk populations. Compensated for the limited and outdated results of the emerging study based on populations of the United States[11,20,21], we provided up-to-date statistics on a comprehensive range of EOPC health metrics, including ASRs of incidence, mortality, DALYs, and deaths and DALYs attributable to known major risk factors of EOPC, unfolding the view of trends of these measures from 1990 to 2019. We revealed that (1) East Asia had the largest number of new EOPC cases, deaths, and DALYs in 2019 around the world; (2) countries and territories with higher SDI tended to have lower ASRs of incidence, mortality, and DALYs; (3) males had higher ASRs of incidence, mortality, and DALYs compared to the female. Concerning the state, aforementioned ASRs were distinctively high in Central and Eastern Europe; (4) trend analysis revealed the increasing global trends of EOPC burden. In terms of state and sex variations, Asian males exhibited the fastest growth of incidence and mortality, whereas males in the Americas experienced the slowest ones. Apart from some twists and turns in the burden trend in Europe, the trend was on the rise in Africa, America, and Asia; (5) a proportion of DALYs were attributable to known risk factors, including tobacco smoking (13.3%), high BMI (5.6%), and high FPG (3.2%).

In the study based on GBD 2019, there were 11 401 new EOPC cases, 10 149 deaths, and 473 425 DALYs estimated in East Asia, accounting for approximately one-third of global data. This result may be due to the large population base and widespread implementation of disease screening in East Asia. Recently, Huang *et al.*[22] conducted a study targeting the updated epidemiology of gastrointestinal cancers in East Asia, indicating that there is a substantial burden of gastrointestinal cancers in East Asia. Compared with Western regions, East Asia has a higher burden of stomach, liver, esophageal, and gallbladder cancer, but the burden of colorectal and PC is increasing[23,24]. Furthermore, they calculated the mortality-to-incidence ratio (MIR), a population-based measure, which assesses cancer diagnosis, treatment, and survival disparities[25–27]. It is calculated by dividing the ASR of mortality by the ASR of incidence (MIR = ASR*mortality*/ASR*incidence*). The overall MIR for gastrointestinal cancers was greater in East Asia (0.689) compared to Oceania (0.487), Northern America (0.491), and Europe, with values ranging from 0.516 in northern Europe to 0.663 in central and eastern Europe. This pattern was consistent across all subtypes of gastrointestinal cancer, with MIR being higher in East Asia than in Western regions for each subtype. In East Asia, the highest MIR was observed for PC (0.949), followed by liver (0.904), esophageal (0.87), gallbladder (0.714), stomach (0.652), and colorectal cancer (0.456). From both the perspective of comparing East Asia with the Western regions and comparing PC with other gastrointestinal malignancies, such a high MIR value of PC provided evidence to support that the disease burden was heavy in East Asia. Additionally, previous studies demonstrated an increasing trend in the incidence of early-onset colorectal, pancreatic, and gallbladder cancer in East Asia[28–30], and a similar trend was also observed in Western regions[31–35], which were consistent with the findings of this study.

In general, there was an inverse association between the incidence, mortality, and DALYs of EOPC and the SDI at the country level, with some exceptions. Previous literature has elucidated that the mortality and morbidity rates of most cancers exhibited an upward trend in regions with higher development or SDIs based on the World Bank's Human Development Index (HDI), while the specific characteristics of cancer varied across countries on a global scale[36,37]. In this study, a majority of new cases,

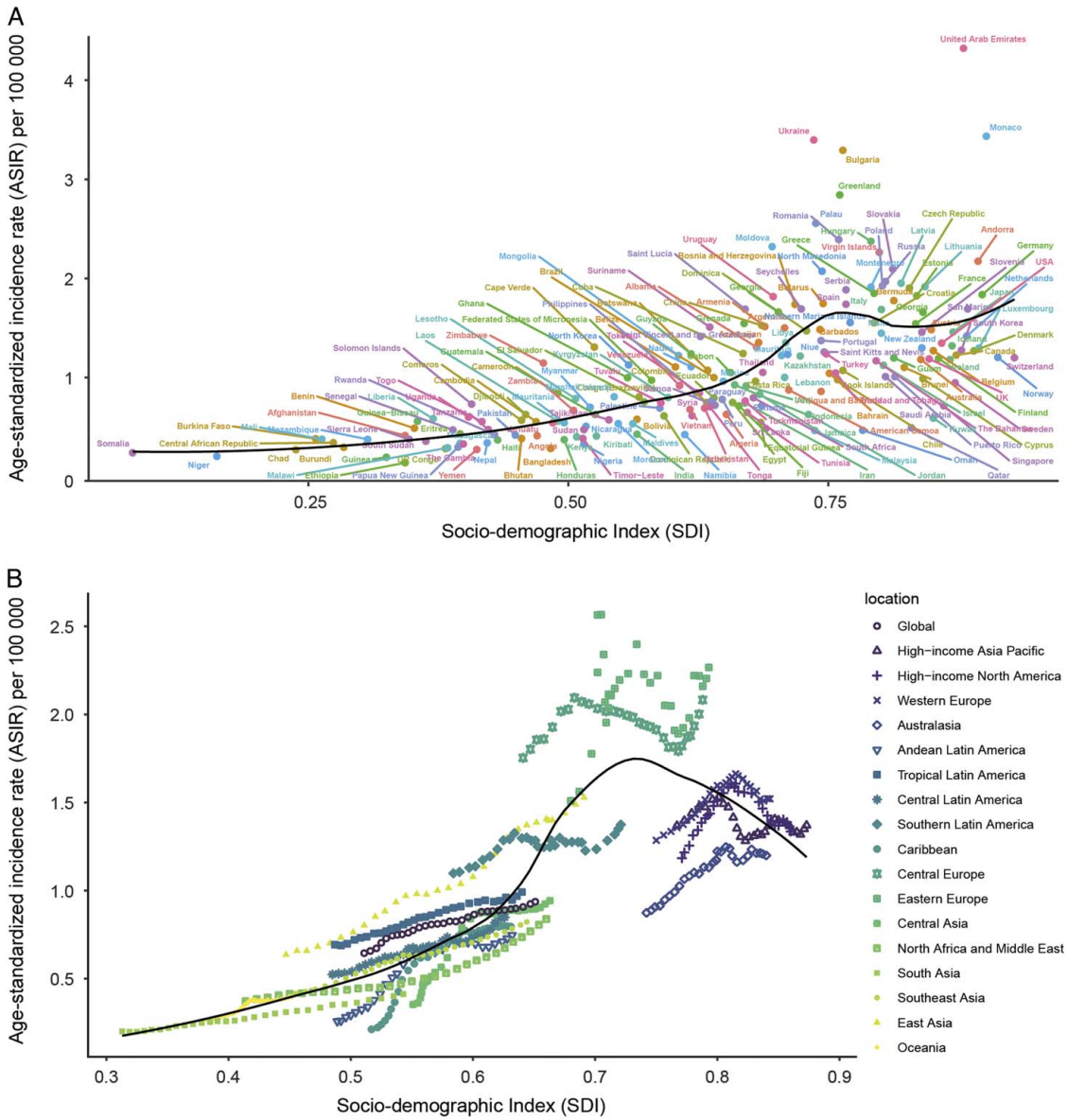

Figure 4. Age-standardised incidence rates for EOPC for 17 GBD regions (A) and 204 countries and territories (B) by Socio-demographic Index, 1990–2019.

deaths, and DALYs due to EOPC were observed developing in regions with high-middle and middle SDIs. In terms of ASRs, the rates of incidence, mortality, and DALYs reached a high level in regions with high-middle and high SDIs, whereas the gradually decreasing ASRs appeared in middle SDI regions, low-middle SDI regions, and low SDI regions in turn. Low SDI is a proxy for diverse correlated and interconnected variables such as unimproved water sources and high indoor air pollution. Multiple variations of environmental factors, lifestyle, and disease control strategy may lead to the ASR disparity between regions with different SDI levels. PC, a highly malignant digestive system tumor, is often diagnosed at an advanced stage or even metastasis due to its highly aggressive characteristics and lack of typical symptoms at an early stage. In recent years, the goal of early detection of PDAC is laudable and likely to result in significant improvement in overall survival[38,39]. In nations with relatively high SDI levels, people are more health-conscious and can undergo physical examination more easily such as computed tomography and tumor biomarker testing, leading to lower ASRs of incidence and mortality. Potential at-risk individuals could be identified at an early stage in regions with high SDI, then properly examined for detection and treated promptly, significantly decreasing the disease burden of EOPC. Accordingly, to practically control the disease burden of EOPC in the future, greater attention should be directed toward at-risk individuals residing in countries with lower SDI, in addition to those in countries with high HDI.

Despite global efforts in healthcare and cancer prevention, the burden of EOPC remained high in several regions worldwide. Among these regions, the typical ones included Kazakhstan (Central Asia), Belize (Central America), Saint Lucia (Caribbean), Suriname (Southern America), Grenada (Caribbean), and Cabo Verde (Africa). A majority of these nations had a low SDI level, causing a heavy EOPC burden due to the inability to receive

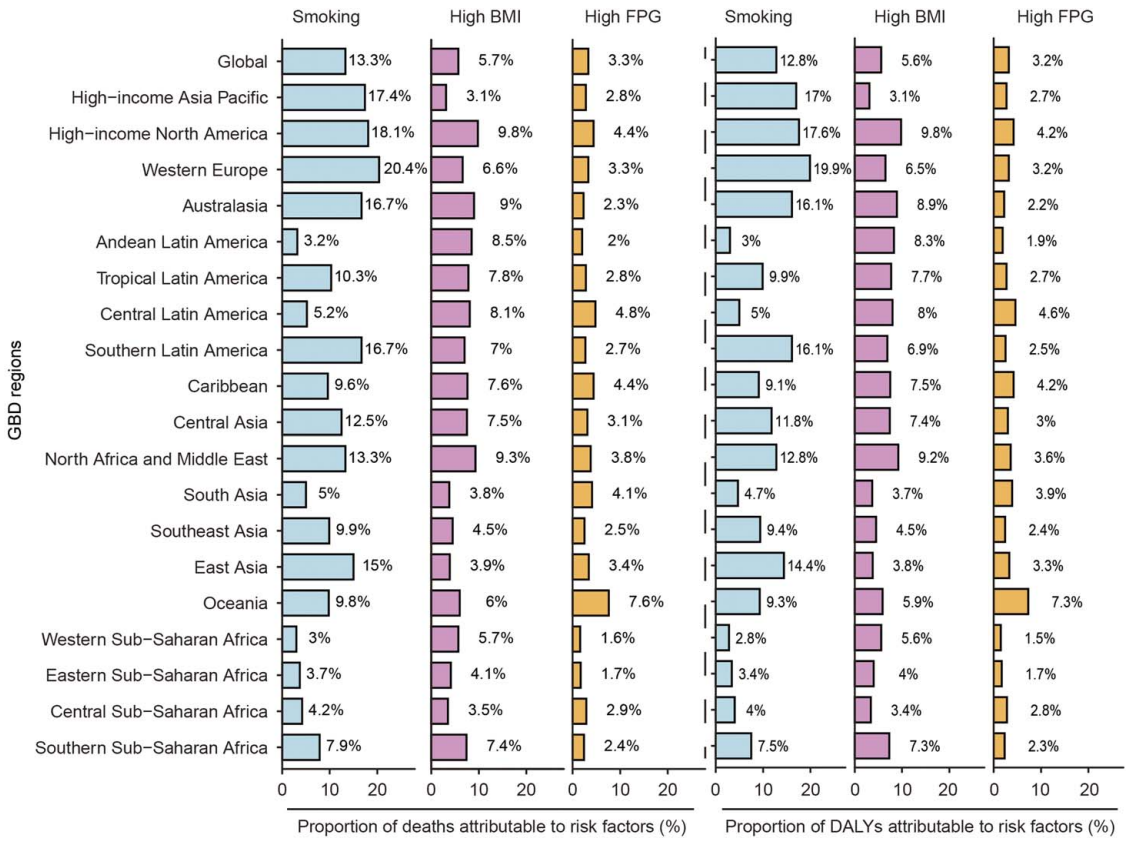

Figure 5. Proportion of EOPC deaths and DALYs attributable to tobacco smoking, high BMI, and high FPG, for 19 GBD regions, 2019. DALY, disability-adjusted life-year; GBD, Global Burden of Diseases, Injuries, and Risk Factors Study.

sufficient social support and appropriate environmental governance. In terms of nations with decreasing ASRs of incidence, mortality, or DALYs, most of them were high-income countries in Europe with high SDI levels, including Finland (Northern Europe), Sweden (Northern Europe), Czechia (Central Europe), Austria (Central Europe), and Luxembourg (Northwest Europe). The decrease in EOPC burden may be attributed to the adoption of strong, resilient, and accessible health systems, such as Europe's Beating Cancer Plan, a cornerstone of this new initiative, to assist member states in their efforts to prevent cancer and enhance the quality of life for cancer patients, survivors, as well as their families and caregivers[40]. Interestingly, the decreasing trends of incidence observed in Burundi (Central Africa) and Somalia (Eastern Africa) with low SDI levels appear to be inconsistent with the aforementioned findings. However, potential reasonable interpretations underlying this phenomenon can be gleaned from the relative literature. Burundi, a landlocked country in East Central Africa, has endured years of civil war strife. The importance of cancer care has been largely overlooked, leading to inadequate infrastructure and insufficient human resources. This is evident from the estimated global incidence and mortality rates. Critical cancer care was needed in Burundi, seeking to garner global oncology support for the country[41]. Meanwhile, Somalia's unique background in medical care presents additional complexities that can influence disease management and healthcare outcomes. In 2013, the terrorists, community leaders, and armed groups were complicit in targeting Médecins Sans Frontières (Doctors Without Borders) agency's medical facilities and ambulances, making the close of all its programs in the country inevitable. In such a poor medical environment, enhanced collaboration between the government and external stakeholders has the potential to significantly improve the health outcomes of the population[42,43]. It is important to note that while the decrease in incidence rate in these regions could be attributed to factors such as the lack of medical resources leading to a failure in timely disease management, it is also possible that the decline could be influenced by a variety of other factors. It is essential to consider the multifaceted nature of healthcare systems and the complex interplay of socio-economic, environmental, and public health factors when interpreting changes in disease incidence rates.

This study identified tobacco smoking, high BMI, and high FPG as important risk factors of EOPC, contributing to a proportion of the burden, which is consistent with the previous studies that have highlighted smoking, alcohol use, and high BMI as the most significant factors for both sexes[44]. Obesity cancer linkage to young adults was also recognized as a variable of EOPC among 12 other factors based on an epidemiologic review reported by the International Agency for Research on Cancer[45,46]. A case–control study conducted in the United States involving 841 patients with pancreatic adenocarcinoma and 754 healthy individuals from 2004 to 2008 revealed that individuals with a BMI of 25 to 29.9 between the ages of 14 and 39, or a BMI of 30 or higher between the ages of 20 and 49, had an elevated risk of PC, regardless of their diabetes status. Notably, this association was particularly robust among male participants and

smokers. Among the overweight and diabetes population, PC had an earlier onset by 2–6 years. Switching to other known risk factors such as cigarette smoking, exposure to chemicals and heavy metals, pancreatitis, heavy alcohol consumption, periodontal disease, and impaired fasting glucose, only alcohol consumption seems to be associated with EOPC, while heavy drinkers who consume greater than or equal to 3 drinks daily are at higher risk of pancreatic cancer[47–49]. However, the hereditary pancreatitis along with cigarette smoking was identified as an important component of PC risk[50,51]. According to previous studies, the Western diet may contribute to the rising risks of EOPC. Moderate dose of vitamin D, green tea, curcumin, melatonin, nuts, and anti-inflammatory diets may provide a protection against EOPC[52,53]. For populations of adolescents, the etiology of PC may be different from that of adults. Genetic factors dominate in the development of pancreatic cancer. Emerging studies revealed that *KRAS* mutations were less frequent in the early-onset cohort than those in average-onset one, while mutations in the *SMAD4* gene were significantly more prevalent in early-onset cohort. Meanwhile, EOPC had more RAS wild-type compared with the classical rate in pancreatic cancer[12]. More studies focusing on the genetic factors are warranted to develop the potential targeted therapy for EOPC. Integrating the previous findings that inherited germline mutations in cancer predisposition genes and positive family history were associated with risk of pancreatic cancer, the EOPC of adolescents was probably a hereditary disease[54–56]. Therefore, in addition to paying attention to the aforementioned dietary habits and lifestyle, for individuals with a documented family history of pancreatic cancer, early screening using computed tomography, EUS, MRI, biomarkers, and even genetic sequencing may aid in the early detection of EOPC, leading to early treatment and improved prognosis.

Presenting data from 204 countries and territories over three decades, this analysis is, to our knowledge, the most all-around and up-to-date study of the global burden, trends, and risk factors of EOPC. Perspectives were figuratively uncovered that the burden of EOPC was significantly increasing globally and was heavier in lower-SDI regions than those with higher-SDI, with East Asia having the most EOPC cases, deaths, and DALYs. The data and findings; however, have some limitations. Firstly, for certain reasons, ASRs of PCcan change dramatically over relatively short distances due to multiple factors such as living habits and environmental conditions. A country with no epidemiologic report or low incidence rates probably is considered a high-incidence country if it gets a neighboring country with high-incidence rates. Hence, there is a necessity to collect more detailed geographical data in the future. Secondly, the GBD framework did not include the histological data so we are unable to stratify EOPC patients properly. Therefore, although it was a very small proportion, the occurrence of multiple endocrine neoplasia may lead to an overestimation of the incidence of EOPC in results. In addition, the data on incidence and mortality was lacking in certain regions, which could lead to a bias in the analysis. Thirdly, the epidemiological statistics for a country are often derived from one or multiple registries located in certain regions. In some underdeveloped countries, with a limited number of registries, data may be collected from a single regional registry. To enhance data representativeness, it is advisable to add more cancer registries. Fourthly, bias and confounders emerged when concluding an interpretation of the findings due to the nature of cross section study. It should be taken into consideration that the study offered a hypothesis but not robust evidence. Meanwhile, more accurate up-to-date statistics are warranted to relieve the temporality lost, a character of this study.

Conclusions

With increasing global trends in ASRs of incidence, mortality, and DALYs demonstrated in 204 countries and territories, EOPC has become an important cause of cancer-related mortality and burden across the world. Trends of ASRs in Europe were fluctuating, while the rates were on the rise in Africa, America, and Asia. The majority of the burden of EOPC derives from East Asia, particularly in China. Although there are several exceptions, regions with lower SDI tend to suffer a heavier EOPC burden, which may be due to the shortage of improved environmental conditions, lifestyle, health consciousness, and practical disease control strategy. Although the exact reasons underlying the increasing rates are still unclear, several known risk factors are identified including tobacco smoking, high BMI, and high FPG. Targeted primary prevention is necessary for and a cornerstone of the burden reduction. Meanwhile, more studies are warranted to investigate the potential molecular genetics and interaction mechanisms of EOPC development. The findings in this analysis and discoveries shortly could be attributable to the implementation of advanced preventive guidelines for disease control of EOPC.

Ethical approval and consent to participate

This was a retrospective, observational cohort study; therefore, the requirement for informed consent was waived by the National Cancer Center in China.

Consent for publication

This was a retrospective, observational cohort study based on open-access GBD database. Therefore, the consent was not applicable.

Sources of funding

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Author contribution

D.Z.: guarantor of study integrity; Z.L., X.Z., and D.Z.: study concept and design; Z.L., X.Z., C.S., H.F., Z.L., and D.Z.: provision of study materials or patients; Z.L., X.Z., C.S., H.F., and Z.L.: data collection and assembly; Z.L.: statistical analysis. All authors contributed in manuscript preparation and manuscript editing.

Conflicts of interest disclosure

The authors have declared that no competing interest exists.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
2. Unique identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

Guarantor

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Availability of data and materials

The datasets used during the current study are available from the corresponding author upon reasonable request.

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