

RESEARCH ARTICLE

Editorial Process: Submission:06/12/2022 Acceptance:11/02/2022

Pancreatic Cancer in Iran - Result of the Iranian National Cancer Registry Program

Saba Alvand^{1*}, Gholamreza Roshandel², Peyman Nejat³, Hossein Poustchi¹

Abstract

Objective: In this article, we aimed to report the incidence rate of PC at the national and regional levels of Iran from 2014 to 2017 for the first time based on the IARC protocols. **Methods:** The data was recruited from the Iranian national program of cancer registry, a national cancer registry program reformed in 2014 after including cancer diagnosis based on clinical judgment and death certificates. This registry includes data from the pathology laboratories and clinical sectors included with death certificates from 60 medical universities in 31 provinces of Iran. Age-standardized incidence rates were calculated at the national and regional levels. **Results:** From 2014 to 2017, 8851 new cases (males=60.46%) were diagnosed, with a mean age of 66.2 ± 19.6 . Forty-one percent of the patients were diagnosed by microscopic verification, and 51% were diagnosed based on clinical judgment without microscopic verification and death certificates. The age-standardized incidence rate was measured as 3.45 per 100,000 in 2017, with the highest rates in individuals older than 85 (30.91 per 100,000), and the provinces of Qom, Tehran, and Isfahan recorded the highest incidence rates with 3.87, 3.85, and 3.66 per 100,000 respectively. **Conclusions:** PC incidence in Iran is still lower than in western countries. However, the incidence from 2014 to 2017 is higher than previous national and regional reports and should not be overlooked. Improvement in the national cancer registry program and documentation may be reasons for this difference.

Keywords: Incidence- Iran- pancreatic neoplasms- registries

Asian Pac J Cancer Prev, 23 (11), 3825-3831

Introduction

Pancreatic cancer's (PC) incidence rate has increased more than 1.5 times worldwide since 2000. The new cases of PC in US are expected to be near 60,000 in US, with 48,000 of death (Siegel et al., 2021). The Global burden of diseases (GBD) reported a global age-standardized incidence rate of 4.36 (4.19-4.48) and 6.85 (6.28-7.41) per 100,000 person-years in 2000, and 2019 respectively (Aslanian et al., 2020), with increase rate of 0.5% to 1% per year (Rahib et al., 2014). PC is the 7th leading cause of cancer-related death globally in both males and females with an age-standardized incidence rate (ASIR) of 5.3 and 3.8 per 100,000 person-years respectively. In 2020, 47.1% of the newly diagnosed cases and 48.1% of the total mortality of PC were reported in Asia (Arnold et al., 2020). Sedentary lifestyle, including tobacco use, alcohol consumption, and diets high in red and processed meat while low in fiber, along with the resulting disorders such as obesity and type 2 diabetes mellitus are suggested to be the main risk factors of PC (Arnold et al., 2020; Mizrahi et al., 2020; Klein, 2021).

Although PC may not pose a serious health burden for Asian countries at the moment, with improving the health system and promotion of sedentary lifestyle, a dramatic increase in incidence and mortality in the next decades would be quite plausible, as it is demonstrated in a study with quantile regression appliance (Momenyan et al., 2016). The International Agency for cancer research has predicted near twice the increase in both incidence rate and mortality of PC in Asia over the next two decades (Aslanian et al., 2020).

Since the majority of patients are diagnosed in the final stages of the disease because of unspecific symptoms (Arnold et al., 2019), Amiresmaili et al., (2013) reported PC as the most common unavoidable cause of death once established and diagnosed in an individual. The course of treatment and hospitalization is relatively shorter in these patients compared to those diagnosed with other malignancies thus this had led to a lower mean of the total cost for treatment in the US (O'Neill et al., 2012). Making diagnostic tools more accessible will also lead to higher survival rates and higher health system costs. This vicious cycle can effectively be interrupted by proper

¹Liver and Pancreatobiliary Diseases Research Center, Digestive Diseases Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. ²Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran. ³School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. *For Correspondence: sabalvand37@gmail.com

prediction of the disease in high-risk populations and deploying adequate financial and strategic planning, which then leads to a lower incidence rate in at-risk individuals and appropriate cost-beneficial treatment in the patients.

Having a clear view of epidemiological features of the disease and demonstrating the differences at the regional level are the two main assets in achieving the milestones in controlling PC in the community. Iran is a multiethnic and multicultural country with a wide range of lifestyles seen among its population, which is probably the main reason for the heterogeneity seen in the distribution pattern of the non-communicable disease in this country. In a study on 5 provinces of Guilan, Golestan, Ardabil, Mazandaran, and Kerman, the ASIR of PC varied significantly among the regions from 0.35 to 1.07 per 100,000 person-years in females and 0.69 to 1.35 in males (Taefi et al., 2011). In another study conducted in Fars from 1998 to 2002, the ASIR was 1.3 in men and 0.8 in women (Masoompour et al., 2011). Subsequently, another study in Yazd reported the age-standardized incidence rate as 2.68 per 100,000 person-years in 2011 (Zahir et al., 2013). The previously reported differences among studied provinces implied a larger variety of PC incidence rates among different regions and ethnicities. This calls for the need of redistributing diagnostic and treatment facilities on a larger scale.

Iranian national program of cancer registry (INPCR) has been running since 1955 (Etemadi et al., 2008), and expanded to all provinces in 1999 by the Ministry of Health and Medical Education (Modirian et al., 2014). In 2014 the program was converted to an interdisciplinary program among health, treatment, and research section of ministry which aims to recruit all the related pathology reports, clinical data, and the data from death certificates from both public and private sectors. The registry platform has also been updated to an online web portal that is accessible from all provinces and can verify the quality of the entered data at the time of entry (Modirian et al., 2014; Mohammadi et al., 2016). In this article, we report the incidence of PC in Iran at a national and regional level from 2014 to 2017 based on the INPCR. This report will be useful for better visualization of PC distribution and incidence rate among the provinces of Iran.

Materials and Methods

Population

Iran is located in the middle east with an area of 1.648 million km² consisting of 31 provinces. Several ethnicities live in Iran and each one resides mainly in a subset of provinces. The majority are Fars, followed by Turks, Kurds, Gilaks, Lurs, Turkemans, Arabs, and other ethnicities. The diversity of cultures and lifestyles in this country makes health planning quite complicated. The national census is run every 5 years with the last one run in 2016, which the report was publicized by the statistics center of Iran ('Census IN. Statistical Center of Iran' n.d.). According to this report, the mean age of the population on the national level was 31.1 years and the median age was 30, further details on the regional level are summarized in Supplementary file Table 1. Overall,

in 2016 the population was 79,926,270 consisting of 40,498,442 males and 39,427,828 females.

Data collection

The national cancer registry started on 1999 based on the pathologic verification. Due to lack of information on death certificates and clinical judgement in the previous registry, a more comprehensive program took place on 2014 in the name of the Iranian national program of cancer registry (INPCR). Any patient received ICD-O code in microscopic verification, or coded cancer as the final diagnosis in medical documents and death certificates were included in INPCR since 2014 (Roshandel et al., 2019). A pilot province (Golestan) was selected for the INPCR in 2013 and succeeded to report the findings on the "IARC's Incidence of Cancer in the 5 Continents" editions X and XI (Bray et al., 2015; Bray et al., n.d.). The cancer registry data is recruited from 60 medical universities in 31 provinces. Each medical university contributes as administrative units of ministry of health and education and collects data from both public and private health facilities in its area under cover. Thus, the INPCR included a national-level secretariat and 60 regional-level secretariats. The data come from three sources of pathology reports, clinical histories, and death certificates collected from death registry units of the corresponding medical university. Provinces with one medical university submit the collected data directly to the INPCR secretariat. However, in provinces with more than one medical universities, regional-level data of each university merged into provincial-level and then submitted to INPCR secretariat. Eventually, INPCR secretariat merge all the provincial-level data into the national-level database.

All the universities follow the same protocol of data entry and deduplication which is extracted from multiple centers based on the IARC protocols (Jensen DMP et al., 1991; Working Group Report, 2005, 'Cancer incidence in five continents. Volume IX' 2008). The third edition of the ICD-O code is used for data entry, in which PC is coded as C25 ('International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3)' n.d.). The duplicates are identified preferably by national ID and less preferably by other identifying characteristics such as name, father name, and age. The data is entered into a web-based application and is accessible from all universities. All the universities cooperate with pathologists for clarification of undefined and vague cases. Overall, the data was collected from 1,540 centers including 324 hospitals and 1,216 laboratories from 2014 to 2017.

Quality control

Quality control was performed at the university level as well as by the INPCR secretariat via IARC-check tools for internal consistency of the data consisting of rechecking topography codes with morphology, age, and sex. After the two-step verification of the data, cancer registry records were gathered on the national level by the INPCR secretariat and rechecked for accuracy and completeness based on the with morphology, age, and sex.

Statistical analysis

We calculated age-specific incidence rates and age-standardized incidence rates (ASIR) of pancreatic cancers in total and in different subgroups. All rates were presented as per 100,000 person-years. We calculated ASIR by direct standardization method using the world standard population (Segi et al., 1950).

Ethical considerations

Ethical issues of this project were reviewed and approved by the ethics committee of the Golestan University of Medical Sciences and is in accordance with the ethical standards laid down in the declaration of Helsinki (Ethics code: IR.GOUMS.REC.1400.078).

Results

A total number of 8851 new cases with PC were diagnosed from 2014 to 2017. Male patients constituted 5352 of this figure and the mean age for all cases was 66.2 ± 19.6. The mean and standard deviation for the age were quite similar in both genders with men having slightly older ages than women in total (males: 66.4 ± 19.6, females: 66 ± 19.6). The distribution of the methods used for confirming the PC diagnosis in cases was 41% of cases in a 4-year spectrum being confirmed by microscopic verification (MV). However, the contribution of MV differed in different years, with the lowest contribution of 35.82% in 2014 to the highest contribution of 43.85% in 2016 (Table 1).

As it is expected, individuals with an older age had a higher ASIR of PC. Figure 1 depicts the ASIR in different age groups in total and for each gender separately. As can be seen, ASIR increased to more than 10 per 100,000 person-years after the age of 60. Men comprised a higher proportion of PCs and ASIR reached 40.86 per 100,000 person-years in the group of men older than 85 years. The ASIR in males increased to 4.10 per 100,000 person-years in 2017 which is 35% higher than 2014. Figure 2 demonstrates the ASIR in males and females in the studied period.

Due to the heterogeneity of socioeconomic status and health indices among the provinces, the regional ASIR in

the male and female groups for each province is reported as well (Table 2, Figs. 3 and 4). Qom, Tehran, and Isfahan had the highest record of overall PC incidence rate with 3.87, 3.85, and 3.66 per 100,000 person-years respectively. In contrast, Sistan Bloochestan with 0.82, Kohkilooye Boyerahmad with 1.47, and North Khorasan with 1.57 per 100,000 person-years ranked as provinces with the lowest rate. Tehran, West Azarbayjan, and Isfahan kept the highest record in males, while Qom, Yazd, and Tehran had the highest rate of females with PC. Sistan Baloochestan had the lowest ASIR in both genders (1.1 in males, and 0.54 in females).

Although the studied timeframe was not wide enough to perform a time trend analysis, we calculated the incidence rate of age groups amongst the years separately to assess the contribution of each age group in the overall rise of the age-standardized incidence rate (Supplementary file Table 2), however further comparisons between age groups is not possible due to descriptive essence of this study.

Table 3 demonstrates the age-standardized incidence ratio of PC during 2014 to 2017. Yazd, West Azarbayjan, Tehran, and Ilam had the highest age-standardized incidence ratio in 2014, 2015, 2016, and 2017 respectively. In contrast the lowest record in 2014 was for Ilam, 2017 in Bushehr, and 2015, and 2016 in Sistan Baloochestan.

The national estimated annual percentage change of PC incidence was 9.64 % (-34.17 – 82.63) in the total population and 10.47 % (-30.78 – 76.31) in males and 8.54 % (-38.31 – 90.99) in females. Qom recorded the highest contribution in the estimated annual percentage change of pancreatic incidence rate with 56.24% (-10.64 – 173.17) change in 2017 compared to 2014, and Zanjan had the

Table 1. Method of Pancreatic Cancer Diagnosis in Years of 2014 to 2017

Year	Death Certificate Only (DCO)	Clinical/ Paraclinical	Microscopic Verification (MV)
2014	26.93%	37.25%	35.82%
2015	27.85%	30.28%	41.87%
2016	25.93%	30.24%	43.83%
2017	26.09%	32.09%	41.82%

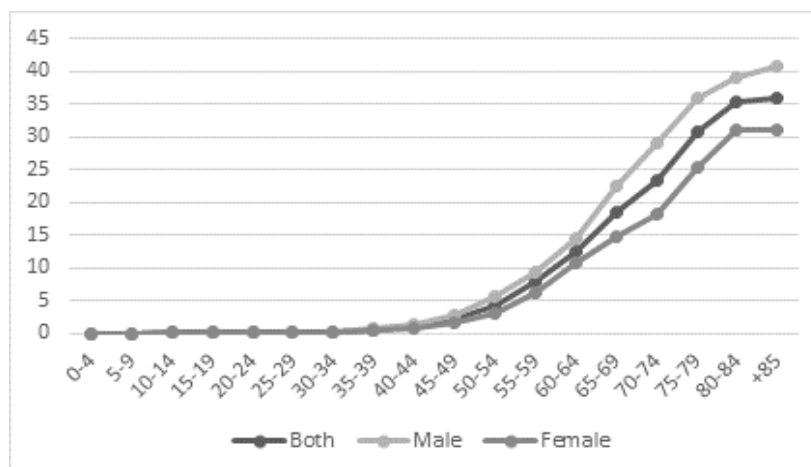


Figure 1. Line Graph of Age-Specific Rate per 100,000 Person-Years

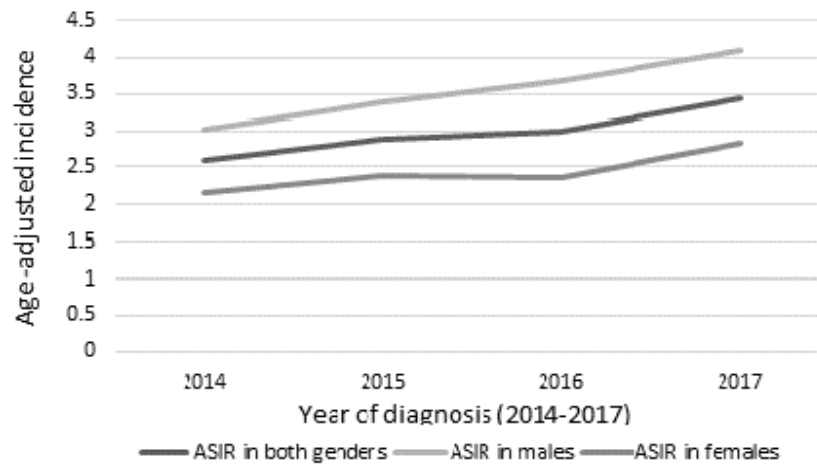


Figure 2. Trend Diagram of the Age-Standardized Incidence Rate of Pancreatic Cancer from 2014 to 2017

Table 2. PC Incidence Rate on a Regional Level from 2014-2017 in Ddiferent Provinces

Provinces	The age-standardized incidence rate for both genders	Age-standardized Incidence rate	
		Male	Female
Ardabil	3.12	3.85	2.42
Alborz	3.26	3.9	2.6
Isfahan	3.66	4.3	3.01
Ilam	3.35	3.73	3
East Azarbayjan	2.84	3.61	2.08
West Azarbayjan	3.63	4.42	2.87
Busher	1.81	1.86	1.67
Tehran	3.85	4.62	3.08
Chaharmahal Bakhteiri	2.49	3.2	1.79
Razavi Khorasan	2.66	3.02	2.31
Khoozestan	3.35	3.7	3.02
Zanjan	1.87	2.61	1.17
Semnan	2.33	2.57	2.11
Sistan Baloochestan	0.82	1.10	0.54
Fars	2.92	3.49	2.36
Ghazvin	2.62	2.91	2.34
Qom	3.87	4.17	3.59
Kurdistan	2.21	2.51	1.88
Kerman	2.8	3.69	1.92
Kermanshah	3.13	3.98	2.33
Kohkilooye Boyer-ahmad	1.47	1.88	0.99
Golestan	3.22	3.9	2.58
Guilan	2.47	2.98	1.99
Lorestan	1.92	2.45	1.41
Mazandaran	2.39	2.72	2.09
Markazi	2.95	3.48	2.45
Hormozgan	1.67	1.88	1.5
Hamedan	2.61	3.33	1.93
Yazd	3.18	3.24	3.13
South Khorasan	2.08	2.18	1.97
North Khorasan	1.57	1.66	1.47

Table 3. PC Age-Standardized Incidence Ratio among Provinces in 2014 to 2017

Provinces	2014	2015	2016	2017
Zanjan	2.82	1.93	1.81	0.98
North Khorasan	1.99	0.8	2.24	1.21
Sistan Baloochestan	1.17	0.72	0.7	0.72
Kohkilooye Boyerahmad	1.69	1.75	1.41	1.08
Yazd	4.04	2.34	3.67	2.71
Semnan	3.22	1.96	1.91	2.29
Lorestan	2.38	2.1	1.5	1.71
West Azarbayjan	3.94	4.21	3.28	3.15
Markazi	2.95	2.98	3.1	2.72
Golestan	3.54	2.89	3.14	3.34
Chaharmahal Bakhteiri	1.82	2.59	3.81	1.74
Isfahan	3.72	4.12	3.17	3.62
Hamedan	3.04	2.07	2.13	3.23
East Azarbayjan	2.82	2.37	2.86	3.28
Busher	2.35	1.42	0.64	2.84
South Khorasan	1.26	2.82	2.54	1.71
Hormozgan	1.62	1.2	1.47	2.26
Kermanshah	2.53	3.12	3.23	3.55
Khoozestan	2.77	3.37	3.2	4
Ardabil	2.74	2.97	2.69	4.04
Mazandaran	1.93	2.26	2.48	2.85
Tehran	2.99	3.48	4.36	4.46
Kerman	1.89	3.37	2.9	2.98
Kurrdistan	1.76	1.9	2.29	2.86
Fars	2.56	2.42	2.24	4.39
Ghazvin	1.81	2.57	2.85	3.18
Razavi Khorasan	1.85	2.33	2.9	3.52
Alborz	2.18	3.31	3.08	4.31
Guilan	1.33	2.78	2.36	3.35
Ilam	1.11	3.35	3.46	5.26
Qom*	Unavailable	4	3.25	4.33

*Data on 2014 was not available in Qom province.

lowest change with -26.44% (-62.13 – 42.89). Although all of the record on the total level contains zero, males

in Ilam showed an absolute rise in the incidence of PC with annual percentage change of 75.22% (4.27-194.45).

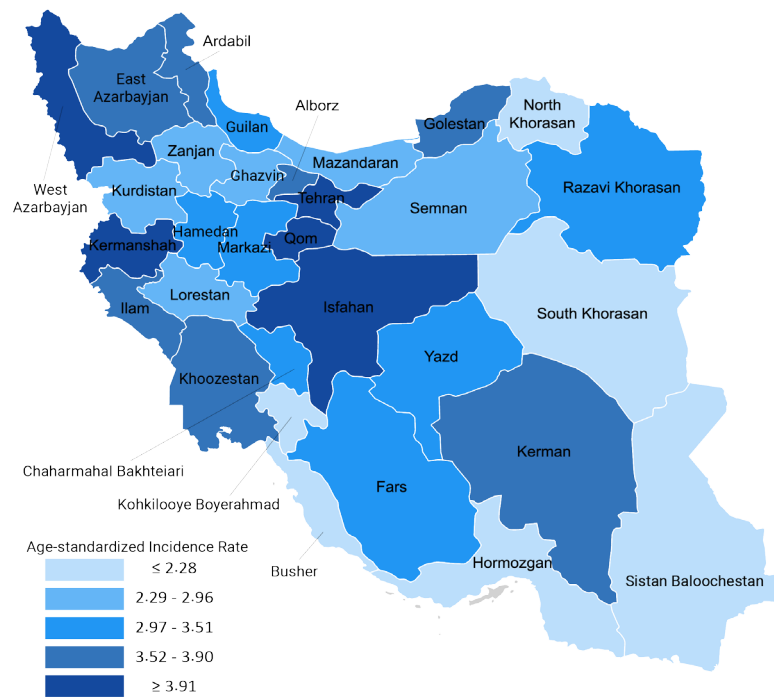


Figure 3. Heat Map of the Age-Standardized Incidence Rate of Pancreatic Cancer in Males (2014-2017)

Supplementary file Table 3 provides further information on the provincial level of estimated annual percentage change.

Discussion

This is a descriptive study, reporting the national and regional number of cases and age-standardized incidence of PC for the first time after reforming the registry method based on the IARC protocols (Jensen DMP et al., 1991;

Working Group Report, 2005, ‘Cancer incidence in five continents. Volume IX’ 2008). Our study found an ASIR of 3.45 per 100,000 in 2017. The incidence rate varied from 0.82 in Sistan Baloochestan to 3.87 in Qom, which is lower than the 4.8 global age-standardized incidence rate reported in 2018. The highest global rate with an ASIR equal to 7.7 in was Europe and the lowest in south-central Asia with less than 2 per 100,000 person-years (Ilic and Ilic, 2016; Khalaf et al., 2021). PC is reported to be the 12th most common cancer of men and the 11th most

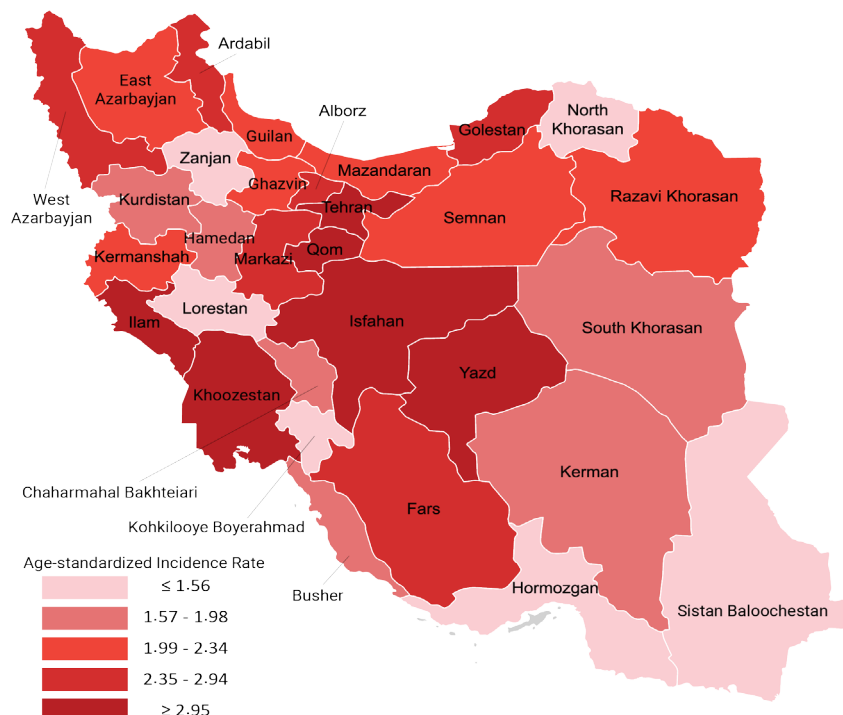


Figure 4. Heat Map of the Age-Standardized Incidence Rate of Pancreatic Cancer in Females (2014-2017)

common cancer of women worldwide (Bray et al., 2018). The ASIR of pancreatic cancer in Iran was reported to be 0.49 in females and 0.60 in males in 2005-2006 (Mousavi et al., 2009).

In regional studies, Zahir et al., (2013) found an increased rate in the pancreatic incidence in Yazd in 2011, with the ASIR of 2.68 per 100,000. In the four years of 1998-2002, Masoompour noted the ASIR of 1.3 in men and 0.8 in women in Fars (Masoompour et al., 2011), another study on the five selected provinces in Iran from 1996 to 2000, also reported a much less incidence rate (Taefi et al., 2011). In the northeast of Iran, A study on Ardabil in 1996-1999, reported ASIR of 0.7 and 0.2 in males and females respectively (Sadjadi et al., 2003), which both have increased in our study to 3.85 and 2.42 per 100,000. The reason lied on the use of a more comprehensive method in registering the PC patients.

The mean age of diagnosis was 66.2 years in our study, which is lower than the US report that was 71 years (Rawla et al., 2019). About 3% of patients were younger than 50 years old, which is less than half of the cases with the same age reported from cancer registries of the USA from 1975 to 2016 (Khalaf et al., 2021). The rise of incidence in youngsters may be due to the increase of diabetes mellitus and obesity in the younger age groups. The growth of PC numbers was especially noticeable in a study conducted in a reference gastrointestinal hospital in Iran, reporting a doubling admission rate of patients with PC over the last decade (Abedian et al., 2012).

The importance of close monitoring for PC incidence rate is due to the short survival period that makes the incidence rate of PC an indicator of its mortality. The 5-year survival rate of PC in the US is reported as 9.2% of patients with a confirmed diagnosis between 2007 and 2011 (Khalaf et al., 2021), and 10% in 2020 (Siegel et al., 2021). However, in Iran, the 5-year survival rate is significantly lower and measured to be 1.5% for the patients diagnosed in 2011-2018 (Sheikh et al., 2020). With the incidence rate rising, the death toll will consequently proceed in numbers. It is predicted that in the decades to come, the mortality of PC will surpass breast and colorectal cancer worldwide (Khalaf et al., 2021). In the US alone, PC is predicted to be the first cause of mortality due to gastrointestinal malignancies in 2040, (Rahib et al., 2021) and in Germany, the estimated time is more imminent, which is predicted to be 2030 (Quante et al., 2016). In European Union, PC-related mortality is forecast to rise to 25% in 2025 (Ferlay et al., 2016). The models predicting the future incidence rates and mortalities suggest a near future surge in Iran based on the current situation, calling for immediate action.

The proposed solutions include risk factor identification in accordance with ethnic variations, primary prevention by lifestyle modification, screening in high-risk groups, and early diagnosis followed by effective management through proper imaging and medical care. However, a study suggests artificial intelligence is able to substitute imaging and biopsies in diagnosis. A machine learning model was proposed by Alizadeh Savareh and colleagues for patients in late stages which used miRNA expression level as a diagnostic feature and showed 93% sensitivity,

92% specificity, and 93% accuracy in diagnosis (Alizadeh Savareh et al., 2020).

In conclusion, pancreatic cancer incidence in Iran is lower than in western countries but has grown dramatically in recent years and should not be overlooked. The possible explanations for this change are the true rising of the incidence because of the aging of the population, rise in risk factors, improvement in cancer registry documentation, and improvement in pancreatic cancer diagnosis. Identifying various risk factors in provinces and taking tailored actions in each of them would help overcome the uprising trend of PC in the following years. Implementing screening guidelines for high-risk groups tailored based on the economic status and health system abilities and further research on the novel tools of diagnosis are highly recommended.

Author Contribution Statement

Authors contribution HP assembled the co-authorship team, edited the manuscript. SA interpreted the analysis, conducted literature review and drafted the manuscript. GR analyzed data and provided intellectual input and edited the manuscript. PN contributed in drafting, visualization, and edited the manuscript. SA, GR, PN, and HP have reviewed and approved final version for submission.

Acknowledgements

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Golestan University of Medical Sciences. (Ethics code: IR.GOUMS.REC.1400.078) and written informed consent was obtained from all participants.

Funding statement

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

The project was scientifically approved by the research council of the Golestan University of Medical Sciences.

Conflict of interest

The authors declare no potential conflicts of interest.

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