Systematic review of pancreatic cancer epidemiology in Asia-Pacific Region: major patterns in GLOBACON 2012

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ABSTRACT

Pancreatic cancer is one of the deadliest cancers with short-term survival rates. Trends for pancreatic cancer incidence and mortality varied considerably in the world. To date, the causes of pancreatic cancer are not known sufficiently, although certain risk factors have been identified such as, smoking, obesity, life style, diabetes mellitus, alcohol, dietary factors and chronic pancreatitis. Since there are no current screening recommendations for pancreatic cancer, primary prevention is very important. Therefore, up-to-date statistics on pancreatic cancer occurrence and outcome are essential for the primary prevention of this disease. Due to the lack of information on epidemiology of pancreatic cancer in most Asian countries, and limited of statistics and registration system in this area, we conducted a systematic review study to evaluate the most recent data concerning epidemiology of pancreatic cancer in Asia-Pacific region. In this review we focused on collected recent data on incidence, mortality, survival and risk factors of pancreatic cancer in this region. In addition, we reviewed and used the data of GLOBOCAN 2012 in this paper to complete the information as a source of compiling pancreatic cancer incidence and mortality rate.

Keywords: Pancreatic cancer, Epidemiology, Risk factors, Asia, Pacific.

(Please cite as: Pourhoseingholi MA, Ashtari S, Hajizadeh N, Fazeli Z, Zali MR. Systematic review of pancreatic cancer epidemiology in Asia-Pacific Region: major patterns in GLOBACON 2012. Gastroenterol Hepatol Bed Bench 2017;10(4):245-257).

Introduction

Pancreatic cancer is a highly aggressive cancer and has ranked the 12th most common cancer in the world with 338,000 new cases and the 7th most frequent cause of cancer death worldwide with 331,000 deaths per year in both sexes in 2012 (1). The numbers of incidence cases and pancreatic cancer deaths are similar because prevention or early diagnosis at a curable stage is extremely difficult (2). Patients rarely exhibit symptoms in the early stages, so the disease is generally advanced when it is diagnosed (3).

Received: 15 June 2017 Accepted: 30 September 2017

Reprint or Correspondence: Sara Ashtari, MSc. Basic and Molecular Epidemiology of Gastrointestinal Disorders Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: sara_ashtari@yahoo.com GLOBOCAN estimated 5-year prevalence of people in the world living with pancreatic cancer is 4.1 per 100,000 in 2012 (1).

The survival rate of pancreatic cancer is exceedingly low and the case fatality rate for the disease is approximately 0.97 that has declined slightly (from 0.99 to 0.97) last 12 years (4). In different areas of the world, pancreatic cancer is quiet infrequent, based on the GLOBOCAN 2012, the age-standardized rate (ASR) incidence is highest in North America (7.4/100,000) and then followed by Europe (6-7.3/100,000), Oceania (>6/100,000) and lowest in South-Central Asia and most of Africa (1.0/100,000) (5) as represented in figure 1.

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Estimated age-standardised incidence rate per 100,000 Pancreas: both sexes, all ages



Figure 1. The age-standard incidence of pancreatic cancer in the world, based on GLOBOCAN 2012.

The burden of the pancreatic cancer is increasing due to aging, population growth and increasing risk factors such as smoking, obesity, lifestyle, diabetes mellitus, alcohol and chronic pancreatitis (6, 7). Based on estimation of International Agency for Research on Cancer (IARC) on 2015, global pancreatic cancer rates could increase by 24% to 418,000 by 2020 (8).

Since there are no current screening recommendations for pancreatic cancer, primary prevention is very important. Better understanding of the epidemiology and identifying the risk factors of pancreatic cancer are essential for the primary prevention of this disease. Therefore, we conducted a systematic review study to evaluate the most recent data concerning on epidemiology of pancreatic cancer in Asia-Pacific region. The purpose of this review is to examine and gather recent data on pancreatic cancer with focus on incidence, mortality, survival and risk factors related to this disease in this region. Moreover, we used the data

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of GLOBOCAN 2012 in order to complete information, compare and finalize conclusion as a source of compiling pancreatic cancer incidence and mortality rate.

Methods

We performed a comprehensive review according to the PRISMA guidelines. We chose articles published previously in Medline, PubMed, Scopus, Google Scholar, ISI Web of Knowledge (Science Citation Index Expanded) and Cochrane database. We searched previous studies on the epidemiology of pancreatic cancer, published up to 31 March 2017, with English language restriction.

Search with the following MeSH terms and keywords included: "epidemiology of pancreatic cancer", "incidence and mortality of pancreatic cancer" and "risk factors of pancreatic cancer" with specific risk factors such as: tobacco, alcohol, height, weight, diet, genetic, etc. Each study was cross-referenced with "Asia-Pacific region" and countries in this region such as Australia, New Zealand, India, Pakistan, Iran and others. We checked titles and abstracts and retrieved pertinent information from the full text of relevant studies. We also reviewed additional articles listed in the bibliography of retrieved publications.

We selected those papers that considered being most important and appropriate. All relevant articles were accessed in full text and all relevant materials were evaluated and reviewed. Moreover, we used the GLOBOCAN 2012 data that published about pancreatic cancer in order to complete information, compare and finalize conclusion. All findings were reviewed and analyzed, then reported as results in the tables and text.

Results

Asia-Pacific region

Asia is the most populous continent in the world and it covers approximately 4.3 billion people, about 60% of the world's current population (9). Two most populated countries in the world were located in this continent; China with 1.4 billion people and India with 1.2 billion people (10). Even with a relatively low population growth rate of 0.9%, the Asia-Pacific region added more than 40 million people to its population during 2013-2014 (10). Asia-Pacific region varies in size depending on context, but it typically includes East Asia, South Asia, Southeast Asia, and Oceania. To cover the entire Asia in this study, West Asia and Central Asia were also examined in this paper.

Incidence and Mortality of pancreatic cancer

The incidence and mortality of pancreatic cancer varies greatly across regions and populations. GLOBOCAN in 2012 for Asia and Oceania estimated the agestandardized rate (ASR) incidence 3.2 and 5.9/100,000 and ASR mortality was 3.0 and 5.2/100,000 respectively (table 1) (5). Based on table 1, in 2012 Eastern and Western Asia (4.5 and 3.9/100,000 ASR) have higher incidence of pancreatic cancers compared to southeast and center of Asia (2.2 and 1.2/100,000 ASR). And the highest rate (6.5/100,000) of ASR incidence is in Australia and New Zealand.

Japan in Eastern Asia (8.5), Kazakhstan in Central Asia (6.8), Singapore in Southeast Asia (5.1), Armenia in Western Asia (9.3) and Australia in Oceania (6.6) have a high ASR incidence of pancreatic cancer per 100,000 (Figure2-5). Figure 2 to 5 provide the incidence and mortality of pancreatic cancer in different regions of Asia for male and female. Armenia and Japan have the highest mortality rate due to pancreatic cancer in Asia-Pacific region (Table 2). In addition, the World Bank ranking was showing in table 2 for countries in Asia and the Pacific in terms of mortality among the

Table 1. The overall age-standardized incidence, mortality and 5-year prevalence rates from pancreatic cancer per 100,000 in different Asia regions and Oceania, based on GLOBACON 2012 (8).

Pancreatic Cancer		Incidence			Mortality			5-Yaer Prevalence		
Region		Number	(%)	ASR(W)*	Number	(%)	ASR(W)	Number	(%)	ASR(W)
Southeast	Male	6413	1.7	2.5	6207	2.1	2.5	4866	0.8	2.2
Asia	Female	5869	1.5	2.0	5651	2.4	1.9	4451	0.4	2.0
	Total	12282	1.6	2.2	11858	2.2	2.2	9317	0.6	2.1
	Male	9299	1.3	1.3	8560	1.6	1.2	5661	0.5	0.9
Central Asia	Female	7511	0.9	1.0	6999	1.4	1.0	4522	0.3	0.7
	Total	16810	1.1	1.2	15559	1.5	1.1	10183	0.4	0.8
Western Asia	Male	4013	2.4	4.7	3894	3.5	4.7	2849	0.9	3.3
	Female	2887	1.9	3.1	2823	3.6	3.0	1992	0.5	2.5
	Total	6900	2.2	3.9	6717	3.5	3.8	4841	0.7	2.9
Eastern	Male	60979	2.5	5.5	58037	3.3	5.2	42421	1.0	6.4
Asia	Female	46392	2.7	3.6	45080	4.5	3.4	30779	0.8	4.8
	Total	107371	2.6	4.5	103117	3.7	4.3	73200	0.9	5.6
Australia/	Male	1778	2.2	7.5	1520	5.2	6.3	950	0.4	8.7
New	Female	1572	2.5	5.4	1493	6.5	5.0	825	0.4	7.4
Zealand	Total	3350	2.3	6.5	3013	5.8	5.6	1775	0.4	8.0

*Age-standardized rate (W): A rate is the number of new cases or deaths per 100 000 persons per year. An age-standardized rate is the rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of cancer.

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countries	Regions	Mortality rate per 100,000	World Rank
Armenia	Western Asia	13.88	1
Japan	East Asia	9.35	13
Kazakhstan	Central Asia	7.50	38
South Korea	East Asia	7.39	39
Australia	Oceania	6.77	46
New Zealand	Oceania	6.17	49
Singapore	Southeast Asia	5.92	52
North Korea	East Asia	5.65	54
China	East Asia	4.13	70
Arab Emirates	Western Asia	4.12	71
Jordan	Western Asia	4.08	74
Kyrgyzstan	Central Asia	3.95	78
Syria	Western Asia	3.61	83
Malaysia	Southeast Asia	3.54	85
Indonesia	Southeast Asia	3.22	90
Bahrain	Western Asia	2.77	95
Iraq	Western Asia	2.75	96
Kuwait	Western Asia	2.62	100
Azerbaijan	Western Asia	2.46	105
Iran	Western Asia	1.95	119

Table 2.	Highest mortalit	v rate in twent	v countries	in Asia-	Pacific	region and	1 status of Iran.
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Data From: World Health Ranking 2014; http://www.worldlifeexpectancy.com/asia/pancreas-cancer-cause-of-death

Pancreas ASR (W) per 100,000, all ages Male 10.6 Japan 8.4 Korea, Republic of 5.7 5.6 Korea, Democratic Republic of Mongolia 3.6 Eastern Asia 2.8 China

10

15

GLOBOCAN 2012 (IARC) (13.5.2015)

Figure 2. The incidence and mortality of pancreatic cancer in Eastern Asia, according to GLOBOCAN estimation project 2012.

5

countries of the world. Iran among Asian countries in rms of incidence and mortality of pancreatic cancer is ranked eleventh (5). Pancreatic cancer is the twelfth leading cancer to death in Iran (5). Trend of pancreatic cancer mortality in Iran slightly decreased in recent decade (11). Nonetheless, it is impossible to fully explain the differences in the incidence of pancreatic cancer in different parts of the world; most of the international variation in the incidence of pancreatic cancer has been attributed to exposure to known or

10

5

0

Female

15

Incidence

Mortality



International Agency for Research on Cancer Pancreas ASR (W) per 100,000, all ages

Figure 3. The incidence and mortality of pancreatic cancer in Central Asia, according to GLOBOCAN estimation project 2012.



Figure 4. The incidence and mortality of pancreatic cancer in Southeast Asia, according to GLOBOCAN estimation project 2012. suspected risk factors related to lifestyle or the

environment.

The incidence and mortality rate of pancreatic cancer in both gender has increased with age and almost 90% of all cases are diagnosed or all deaths are registered after age of 55 years (4). Pancreatic cancer still occurs in elderly people in Asia-Pacific region but compared to patients in western countries patients are relatively younger at the time of diagnosis. But similar to western countries, pancreatic cancer in this region occurs more in men than in women. This probably related to the higher prevalence of smoking and some other risk factors among males (12, 13). The results of study by Ansary Moghadam et al. in Asia-Pacific region showed that smoking, obesity and diabetes were important and they are potentially modifiable risk factors for pancreatic cancer in this region. The age-adjusted hazard ratios (HR) for mortality of pancreatic cancer; due to smoking and diabetes were (HR: 1.61; 95% CI, 1.12-2.32) and (HR: 1.76; 95% CI, 1.15-2.69) respectively (P<0.05); these results were similar for men and women. But in men, combination of smoking and diabetes was more effective on pancreatic cancer (HR: 2.47; 95% CI, 1.17-5.21) (14).

Survival of pancreatic cancer

The survival rate of pancreatic cancer is short; the relative one ear survival rate is only 24%, and the overall 5-year survival is about 6% (ranges from 2% to



Pancreas

Figure 5. The incidence and mortality of pancreatic cancer in Western Asia, according to GLOBOCAN estimation project 2012.

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9%) (15). Survival rates of pancreatic cancer in the community are affected by many factors, such as age, sex, type of cancer, staging at the time of diagnosis, serum albumin level, and tumor size. Age and tumor characteristics can have effect on survival of pancreatic cancer (16, 17); advancing of the age and advancing of the grade of abdominal lymph node and liver metastasis were all associated with poorer survival (18, 19). Moreover, the type of pancreatic cancer can also have effect on survival, according to the nine population-based cancer registries from 1973-2000; endocrine pancreatic cancer survival is longer than in patients with exocrine tumors with a 0.28-fold lower risk of mortality (95% CI, 0.26-0.30). These results were similar for both sexes (20).

Risk factors of pancreatic cancer

Several personal and environmental factors have been associated with pancreatic cancer. They are divided into two categories: modifiable and non-modifiable risk factors. Modifiable risk factors include smoking, obesity, alcohol and dietary factors. Risk factors that are not modifiable include gender, age, family history of pancreatic cancer, genetic factors, diabetes mellitus, chronic pancreatitis and chronic infections (21). Most host factors are non-modifiable whereas the environmental factors are modifiable risk factors. Recently systematic review on results of 117 metaanalytical or pooled data reported that smoking as strong evidence and helicobacter pylori infection as moderate evidence, with respective population attributable fractions of 11-32% and 4-25% were the major risk factors for pancreatic cancer worldwide, while the major protective factors were history of allergy and increasing fruits and vegetables intake with respective population preventable fraction of 3-7% and 0-12% (22).

Modifiable risk factors

- Smoking: Smoking is the most important environmental factor for pancreatic cancer in the world, approximately 25% to 35% of pancreatic cancers are associated with Cigarette smoking. The risk of pancreatic cancer is nearly two times higher in smokers than in non-smokers (23-25). Based on meta-analysis from the Asia-Pacific that included 30 cohort studies, current smokers had a 60% increased risk of pancreatic cancer compared to those who never had smoked (HR 1.61; 95% CI, 1.12–2.32) (14). According to previous studies, the summary relative risk (SRR) of pancreatic cancer was (1.6-2.2) for current smokers and (1.1-1.2) for former smokers (26-28). It should be noted that, the risk of pancreatic cancer will be increased in countries where smoking rates are high. Based on George Institute of Global Health in 2010; 30% of the world's smokers was located in Asia-Pacific region. The world's two most populous nations; India with 275 million and China with 300 million smoker users are home to more smokers than the entire population of the Europe (29). And also the rate of smoking in male of Asia and the Pacific are 8-fold higher than females (30).

- Obesity: Obesity has associated with increased risk for plenty of different types of cancer including pancreatic cancer (31). Obesity especially central type, has been associated with a higher incidence of pancreatic cancer (32, 33). It was found that being overweight (body mass index ≥ 25 kg/m2) or obese (BMI ≥30 kg/m2) during early adulthood may be associated with a greater risk of pancreatic cancer (34). In addition, a previous meta-analysis in Asia-Pacific region evaluated the positive association with central obesity (2-cm higher waist circumference) with an 8% (95% CI, 2-15%) greater risk of pancreatic cancer (14). Obese individuals have a 20% higher risk of developing pancreatic cancer than those who have normal range weight (35). Unfortunately, overweight and obesity are endemic in most of the Asia-Pacific region (36).

- Alcohol: Based on many previous studies, the risk of pancreatic cancer is undoubtedly increased by high alcohol consumption (more than 3 drinks per day), whereas they did not find any association between the risk of pancreatic cancer and low-to-moderate alcohol intake (37-39). The status of alcohol consumption in Asia-pacific region is completely different; in developed countries of this region such as Australia, New Zealand, South Korea, Japan, and china the rate of alcohol consumption is equal to European countries over 7 liters of alcohol per capita in 2009 (40) while, the other part of this region especially in Middle-East and Western of Asia where the Moslem countries located because of cultural and religious traditions drinking of alcohol is forbidden, so the consumption in these areas is minimal. Therefore, we could not find

any association between alcohol and the risk of pancreatic cancer in these areas of Asia.

- Alcohol and Smoking: The association between alcohol and smoking is very close, so it is really difficult to implicate alcohol as an independent risk factor for pancreatic cancer. Based on recent study; heavy alcohol consumption was associated with a significantly increased pancreatic cancer risk (ageadjusted OR=4.04, 95% CI: 1.58, 10.37), whereas this significant association with heavy drinking was not observed among non-smokers (age-adjusted OR=2.01, 95% CI: 0.50, 8.18). Furthermore, low-to-moderate alcohol intake was associated with increased pancreas cancer risk among current smokers (41).

- Dietary factors: It seems reasonable that diet would affect the risk of different digestive diseases and cancers, including those of the pancreas that the dietary factors up to 30–50% impact on pancreatic cancer (21, 42). There are some evidence that the consumption of red meats (particularly when cooked at high temperatures), cholesterol, fried foods and other foods containing nitrosamines increase the risk of pancreatic cancer (43, 44).

A positive association between consumption of red meats and processed meats with risk of pancreatic cancer is biologically acceptable. Carcinogens in met and nitrite or N-nitroso compounds that used for preserved processed meats that can reach the pancreas via the bloodstream may be involved in pancreatic cancer (45). The results of meta-analysis that included 11 case-control studies showed the red meat consumption increased the pancreatic cancer risk by 48% (95% CI=1.25-1.76). On the other hand, high intake of vegetables and fruits especially those enrich in citrus and antioxidants are inversely associated with risk of pancreatic cancer, decreasing the risk by 38% (95% CI=0.54-0.73) and 29% (95% CI=0.59-0.84), respectively (46). In addition, another meta-analysis of 11 prospective studies, with 6643 pancreatic cancer cases, found a positive association between pancreatic cancer incidence and processed meat consumption. High consumption of red meat (120 g/day) was associated with increased risk of PC with the risk of PC (RR=1.13, 95% CI: 0.93-1.39) and also increased consumption of processed meat (50 g/day) was responsible for a 20% increased risk of PC (RR=1.19, 95% CI: 1.04-1.36) (47). But some studies have not supported these findings (48) or have provided support for the association among men only (49).

Non- Modifiable risk factors

- Gender: pancreas cancer is more common in males than in females (50). Globally, the age-standardized rate (ASR) incidence for pancreatic cancer is 4.9/100,000 for men and 3.6/100,000 for women (8). The incidence rates also differ among men and women in Asia; 3.8/100,000 in men and 2.6/100,000 in women are observed in Asia region (8). Pancreatic cancer occurs more in men possibly due to environmental or occupational risk factors as well as lifestyle such as heavy smoking habit and alcohol intake in men, although it is possible that there may yet be undiscovered genetic factors influencing cancer incidence and mortality in males and females.

- Age: The risk of developing pancreatic cancer is increased by age, more than 80% of cases are diagnosed at 60 and 80 years old (4). With only <10% of cases occurring in individuals under 50 years of age and is rare in people under 25 years old (16). The majority of pancreatic cancer patients in Asia and Oceania were 65 years or older, where 62% of Asia patients and 70% of Oceania patients were 65 years old or more (5). This was in accordance with the results reported in SEER Cancer Statistics Review that pancreatic cancer is predominately a disease of older individuals and almost all patients are older than fifty (51).

- Ethnicity: the incidence of pancreatic cancer is different in racial disparities. Many studies have been reported the significant differences in the incidence of pancreatic cancer between races (52-54). Pancreatic cancer incidence rates for African-Americans are higher than Caucasians, while the incidence is lowest in Asian-Americans and Pacific Islanders (55). Generally, the risk of pancreatic cancer rate is considerably higher in Blacks than in any other racial group (50). Differences in incidence of pancreatic cancer between races can be attributed to modifiable risk factors such as diet, alcohol, smoking, and vitamin D insufficiency. Nevertheless, some population based studies have reported that racial disparities in pancreatic cancer is not completely explained by the known and suspected risk factors. In addition other factors such as genetic factors, acquired mutations from known toxins e.g. the

ability to detoxify tobacco products, oncogene mutation and biomarker immune expression may contribute to the increased risk of pancreatic cancer (56, 57). In studies comparing the oncogene mutations and biomarker immune expression among Chines, Japanese and Western patients, results have shown that a gene component to pancreatic cancer might be different between Asian and Western pancreatic cancer; Asian patients with pancreatic cancer have different expressions of KRAS and p53 than Western patients (58, 59). These findings suggest that these differences in genetic and molecular related to race can affect the incidence of pancreatic cancer, and may also explain the difference in survival rates after treatment of pancreatic cancer in racial disparities. In general, it seems that Asian patients have a better survival rate than non-Asian patients (60).

- Family history: Family history is one of the pancreatic cancer risk factor (61). About 5% to 10% of individuals with pancreatic cancer report a history of pancreatic cancer in first-degree relatives (62). In meta-analysis of seven case-control and two cohort studies showed a significant increase in pancreatic cancer risk associated with having an affected relative with summery relative risk (RR= 1.80, 95% CI, 1.48-2.12) (61). Also in nested case-control study of pooled data from 10 cohort studies reported that a family history of pancreatic cancer in a close family member was associated with increased risk of pancreatic cancer (OR=1.76, 95% CI, 1.19-2.61) (63).

- Genetic factors: Genetic variation or mutation (Germ-line mutation) plays an important role in of pancreatic risk increased cancer (64). Approximately, 10% of patients with pancreatic cancer have some genetic predisposition such as gene variations or alterations to developing the disease (65). Several germ-line mutations have been identified to be involved in hereditary forms of PC, including both familial PC (FPC) and PC as one of the manifestations of a hereditary cancer syndrome or other hereditary conditions (BRCA1, BRCA2, PALB2, ATM, CDKN2A, APC, MLH1, MSH2, MSH6, PMS2, PRSS1 and STK11) (66). Pancreatic cancer is also found to be associated with a number of familial cancer syndromes such as Lynch syndrome, Peutz-Jeghers syndrome, the Familial atypical multiple mole melanoma syndrome, Hereditary breast and ovarian cancer syndrome, LiFraumeni syndrome, Familial adenomatous polyposis (67). Furthermore, four main genes in inherited genetic mutations that have special role in increased risk of pancreatic cancer include; KRAS, CDKN2A (p16), p53, and SMAD4 (68).

- Diabetic mellitus: The positive association between both type I and II diabetes and the risk of pancreatic cancer has been reported in numerous studies (69, 70). Diabetes mellitus may be associated with a 1.8-fold increase in the risk of developing pancreatic cancer, particularly in Hispanic men and Asians in comparison with Whites and Blacks (71, 72). Unfortunately, almost one fifth of people with diabetes globally live in just seven countries in South-East Asia and the Western Pacific; in those countries, 132 million adults have diabetes, the largest number in any region of the world (73).

- Chronic pancreatitis: The relationship between chronic pancreatitis (CP) and pancreatic cancer have been reported in previous studies (74, 75). CP is uncommon, only about 4% of these patients will develop pancreatic cancers within 20 years of diagnosis (76, 77). The prevalence of CP is very high in India (114-200/100000 population) in contrast to the Japan (4.2/100000 population) (78, 79). Chronic pancreatitis has several causes such as, hereditary and idiopathic but alcohol abuse is the commonest cause of it (80). Alcohol consumption has been increasing in the developing countries and is the most common etiological factor of CP in Australia, Japan, China and India (78, 81).

- Infection: Few studies have been reported the association between pancreatic cancer with some chronic infections such as hepatitis B virus (HBV), hepatitis C virus (HCV) and Helicobacter pylori (82, 83). The global prevalence of HBV infection also varies widely, in Asian countries divided in three groups; low, intermediate and high endemic areas of HBV. China is now the only country in Asia that classified as high endemic of HBV. Intermediate endemic areas in Asia include; India, Taiwan, Thailand, Philippines, Korea, Iraq and United Arab Emirates, and countries with low endemicity include Japan, Pakistan, Singapore, Sri Lanka, Bangladesh, Malaysia, Iran, Kuwait and Bahrain (84). The highest prevalence rate of HCV occurs in African and Asian countries (5.3% in Africa and 2.15%-3.9% in Asia) (85). The prevalence

of HCV infection in Asia-Pacific region is varies but in Japan, Saudi Arabia, Egypt and Pakistan HCV is high (84). The incidence rate of H. pylori varies by region however; it is highly prevalent in Asia and developing countries (86). A meta-analysis of 7 studies reported an increased risk of pancreatic cancer in people infected with H. pylori (87). Nevertheless, these data are not sufficient to confirm, so further studies evaluating this association are needed.

- Blood group: Numerous epidemiological studies have found an association between ABO blood groups and the risk of developing pancreatic cancer (88, 89). Based on two meta-analyses; the risk of PC about 30 to 40% will be increased among people with non-O blood group (90, 91). People with blood groups A, AB, or B have a higher risk of developing pancreatic cancer than people with blood O group; (the OR for pancreatic cancer in subjects with types A, AB, and B were (OR=1.38, 95% CI, 1.18–1.62), (OR=1.47, 95% CI, 1.07– 2.02, and OR=1.53, 95% CI, 1.21–1.92), respectively (91).

Conclusion

In summary, pancreatic cancer is less common than the lung, breast, stomach, liver, bowel and prostate cancer. Nonetheless, because of high mortality rate and 7th rank in the world, it remains as a challenging disease to diagnose and treat. In some countries in Asia-Pacific region, such as Armenia, Japan, Kazakhstan, New Zealand, Australia and Korea, the mortality rate of pancreatic cancer are high but, in other countries such as China the death rate due to pancreatic cancer was rising and the peak mortality might arrive in future. For the prevention of pancreatic cancer first, it is necessary to understand the epidemiology, etiology and identifying its risk factors and second, it is needed to screen and identify high-risk individuals for pancreatic cancer.

Acknowledgment

This project was completely supported and funded by Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences.

Conflict of interests

The authors declare that they have no conflict of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.

2. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, et al. Pancreatic cancer. Nat Rev Dis Primers 2016;2:16022.

3. Xiao AY, Tan ML, Wu LM, Asrani VM, Windsor JA, Yadav D, et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and metaregression of population-based cohort studies. Lancet Gastroenterol Hepatol 2016;1:45-55.

4. Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol 2016;22:9694-705.

5. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC Cancer Base No. 11 [Internet]. International Agency for Research on Cancer, Lyon 2014.

6. Pourhoseingholi MA, Vahedi M, Baghestani AR. Burden of gastrointestinal cancer in Asia; an overview. Gastroenterol Hepatol Bed Bench 2015;8:19-27.

7. Parr CL, Batty GD, Lam TH, Barzi F, Fang X, Ho SC, et al. Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424,519 participants. Lancet Oncol 2010;11:741-52.

8. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. Lyon 2015.

9. United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2012 Revision, Highlights and Advance Tables. 2013;Working Paper No ESA/P/WP.228

10. Statistical Yearbook for Asia and the Pacific 2014. United Nations PublicationCopyright. United Nations 2014 All rights reserved ST/ESCAP/2704.

11. Taghavi A, Fazeli Z, Vahedi M, Baghestani AR, Zali MR, Pourhoseingholi MA. Pancreatic Cancer Mortality and Misclassification - Bayesian Analysis. Asian Pac J Cancer Prev 2011;12:2271-4.

12. Hadizadeh M, Padashi M, Mohammad Alizadeh AH, Zali MR. Clinical, laboratory biomarkers and imaging findings of pancreatic adenocarcinoma in Iran. Asian Pac J Cancer Prev 2014;15:4349-52.

13. Hassanzade J, Molavi EVH, Farahmand M, Rajaiifard AR. Incidence and Mortality Rate of Common

Gastrointestinal Cancers in South of Iran, a Population Based Study. Iran J Cancer Prev 2011;4:163-9.

14. Ansary-Moghaddam A, Huxley R, Barzi F, Lawes C, Ohkubo T, Fang X, et al. The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. Cancer Epidemiol Biomarkers Prev 2006;15:2435-40.

15. Cancer Facts and Figures; 2009. American cancer Society. Available at http://www.cancer.org/downloads/STT/500809web.pdf>.

16. Al-Majed HT, El-Basmi AA, Al-Mohannadi SH, Govindan R, Rajakumari GB. Pancreatic cancer: Incidence, clinical profile, and frequency of associated factors in Kuwait. AJM 2012;49:75-80.

17. Weber A, Kehl V, Mittermeyer T, Herberich E, Rothling N, Schmid RM, et al. Prognostic factors for survival in patients with unresectable pancreatic cancer. Pancreas 2010;39:1247-53.

18. AlGhamdi HJ, Alfaifi SA, Alolayan AA, Musaad SMA, Jazieh AM. Pancreatic cancer in Saudi patients treated at tertiary institution Ten years retrospective study. Saudi Med J 2013;34:604-8.

19. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29.

20. Fesinmeyer MD, Austin MA, Li CI, De Roos AJ, Bowen DJ. Differences in survival by histologic type of pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1766-73.

21. Midha S, Chawla S, Garg PK. Modifiable and nonmodifiable risk factors for pancreatic cancer: A review. Cancer Lett 2016;381:269-77.

22. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol 2015;44:186-98.

23. Kuzmickiene I, Everatt R, Virviciute D, Tamosiunas A, Radisauskas R, Reklaitiene R, et al. Smoking and other risk factors for pancreatic cancer: A cohort study in men in Lithuania. Cancer Epidemiol 2013;37:133-9.

24. Mizuno S, Nakai Y, Isayama H, Kawahata S, Saito T, Takagi K, et al. Smoking, Family History of Cancer, and Diabetes Mellitus Are Associated With the Age of Onset of Pancreatic Cancer in Japanese Patients. Pancreas 2014;43:1014-7.

25. Pelucchi C, Galeone C, Polesel J, Manzari M, Zucchetto A, Talamini R, et al. Smoking and Body Mass Index and Survival in Pancreatic Cancer Patients. Pancreas 2014;43:47-52.

26. Matsuo K, Ito H, Wakai K, Nagata C, Mizoue T, Tanaka K, et al. Cigarette smoking and pancreas cancer risk: an evaluation based on a systematic review of epidemiologic evidence in the Japanese population. Jpn J Clin Oncol 2011;41:1292-302.

27. Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, et al. Cigarette smoking and pancreatic cancer:

a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol 2009;170:403-13.

28. Katanoda K, Marugame T, Saika K, Satoh H, Tajima K, Suzuki T, et al. Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. J Epidemiol 2008;18:251-64.

29. Tan D. Smoking In Asia: A Looming Health Epidemic, Read more from Asian Scientist Magazine at: http://www.asianscientist.com/2012/08/features/smoking-inasia-looming-health-epidemic-2012/George Asian Scientist Magazine 2012.

30. World Health Organization. Global Status Report on Noncommunicable Diseases 2010 (Geneva, WHO, 2010).

31. Davoodi SH, Malek-Shahabi T, Malekshahi-Moghadam A, Shahbazi R, Esmaeili S. Obesity as an important risk factor for certain types of cancer. Iran J Cancer Prev 2013;6:186-94.

32. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-38.

33. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. Br J Cancer 2003;89:519-23.

34. Li D, Morris JS, Liu J, Hassan MM, Day RS, Bondy ML, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. JAMA 2009;301:2553-62.

35. Arslan AA, Helzlsouer KJ, Kooperberg C, Shu XO, Steplowski E, Bueno-de-Mesquita HB, 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.

36. Asia Pacific Cohort Studies Collaboration. The burden of overweight and obesity in the Asia-Pacific region. Obes Rev 2007;8:191-6.

37. Wang YT, Gou YW, Jin WW, Xiao M, Fang HY. Association between alcohol intake and the risk of pancreatic cancer: a dose-response meta-analysis of cohort studies. BMC Cancer 2016;16:212.

38. Lucenteforte E, La Vecchia C, Silverman D, Petersen GM, Bracci PM, Ji BT, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol 2012;23:374-82.

39. Tramacere I, Scotti L, Jenab M, Bagnardi V, Bellocco R, Rota M, et al. Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation. Int J Cancer 2010;126:1474-86.

40. OECD (2014), "Alcohol", in OECD/WHO, Health at a Glance: Asia/Pacific 2014: Measuring Progress towards Universal Health Coverage, OECD Publishing, Paris.

41. Rahman F, Cotterchio M, Cleary SP, Gallinger S. Association between Alcohol Consumption and Pancreatic

Cancer Risk: A Case-Control Study. Plos One 2015;10: e0124489.

42. Michaud DS, Skinner HG, Wu K, Hu F, Giovannucci E, Willett WC, et al. Dietary patterns and pancreatic cancer risk in men and women. J Natl Cancer Inst 2005;97:518-24.

43. Lightsey D; National Council Against Health Fraud and Quackwatch. Comment on "Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies." Br J Cancer 2012;107:754-5.

44. Stolzenberg-Solomon RZ, Cross AJ, Silverman DT, Schairer C, Thompson FE, Kipnis V, et al. Meat and meatmutagen intake and pancreatic cancer risk in the NIH-AARP cohort. Cancer Epidemiol Biomarkers Prev 2007;16:2664-75.

45. Beaney AJ, Banim PJR, Luben R, Lentjes MAH, Khaw KT, Hart AR. Higher Meat Intake Is Positively Associated With Higher Risk of Developing Pancreatic Cancer in an Age-Dependent Manner and Are Modified by Plasma Antioxidants: A Prospective Cohort Study (EPIC-Norfolk) Using Data From Food Diaries. Pancreas 2017;46:672-8.

46. Paluszkiewicz P, Smolinska K, Debinska I, Turski WA. Main dietary compounds and pancreatic cancer risk. The quantitative analysis of case-control and cohort studies. Cancer Epidemiol 2012;36:60-7.

47. Larsson SC, Wolk A. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. Br J Cancer 2012;106:603-7.

48. Miller PE, Alexander D. A Review and Meta-Analysis of Prospective Studies of Red and Processed Meat and Pancreatic Cancer. FASEB J 2016;30:902-9.

49. Aschebrook-Kilfoy B, Cross AJ, Stolzenberg-Solomon RZ, Schatzkin A, Hollenbeck AR, Sinha R, et al. Pancreatic cancer and exposure to dietary nitrate and nitrite in the NIH-AARP Diet and Health Study. Am J Epidemiol 2011;174:305-15.

50. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013;144:1252-61.

51. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2012. Natl Cancer Inst 2015.

52. Brotherton L, Welton M, Robb SW. Racial disparities of pancreatic cancer in Georgia: a county-wide comparison of incidence and mortality across the state, 2000-2011. Cancer Med 2016;5:100-10.

53. Shavers VL, Harlan LC, Jackson M, Robinson J. Racial/ethnic patterns of care for pancreatic cancer. J Palliat Med 2009;12:623-30.

54. Ma J, Siegel R, Jemal A. Pancreatic cancer death rates by race among US men and women, 1970-2009. J Natl Cancer Inst 2013;105:1694-700.

55. American Cancer Society, Cancer Facts and figures 2014, ACS, Atlanta. 2014.

56. Arnold LD, Patel AV, Yan Y, Jacobs EJ, Thun MJ, Calle EE, et al. Are racial disparities in pancreatic cancer explained

Gastroenterol Hepatol Bed Bench 2017;10(4):245-257

by smoking and overweight/obesity? Cancer epidemiol biomarkers prev 2009;18:2397-405.

57. Pernick NL, Sarkar FH, Philip PA, Arlauskas P, Shields AF, Vaitkevicius VK, et al. Clinicopathologic analysis of pancreatic adenocarcinoma in African Americans and Caucasians. Pancreas 2003;26:28-32.

58. Dong M, Nio Y, Tamura K, Song MM, Guo KJ, Guo RX, et al. Ki-ras point mutation and p53 expression in human pancreatic cancer: a comparative study among Chinese, Japanese, and Western patients. Cancer epidemiol biomarkers prev 2000;9:279-84.

59. Song MM, Nio Y, Dong M, Tamura K, Furuse K, Tian YL, et al. Comparison of K-ras point mutations at codon 12 and p21 expression in pancreatic cancer between Japanese and Chinese patients. J surg oncol 2000;75:176-85.

60. Longnecker DS, Karagas MR, Tosteson TD, Mott LA. Racial differences in pancreatic cancer: comparison of survival and histologic types of pancreatic carcinoma in Asians, blacks, and whites in the United States. Pancreas 2000;21:338-43.

61. Permuth-Wey J, Egan KM. Family history is a significant risk factor for pancreatic cancer: results from a systematic review and meta-analysis. Fam Cancer 2009;8:109-17.

62. Shi C, Hruban RH, Klein AP. Familial pancreatic cancer. Arch Pathol Lab Med 2009;133:365-74.

63. Jacobs EJ, Chanock SJ, Fuchs CS, Lacroix A, McWilliams RR, Steplowski E, et al. Family history of cancer and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Intl J Cancer 2010;127:1421-8.

64. Ghiorzo P. Genetic predisposition to pancreatic cancer. World J Gastroenterol 2014;20:10778-89.

65. Shi C, Daniels JA, Hruban RH. Molecular characterization of pancreatic neoplasms. Adv Anat Pathol 2008;15:185-95.

66. Solomon S, Das S, Brand R, Whitcomb DC. Inherited pancreatic cancer syndromes. Cancer J 2012;18:485-91.

67. Greer JB, Whitcomb DC, Brand RE. Genetic predisposition to pancreatic cancer: a brief review. Am J Gastroenterol 2007;102:2564-9.

68. Klein AP. Genetic susceptibility to pancreatic cancer. Mol Carcinog 2012;51:14-24.

69. Toki M, Yamaguchi Y, Kurata I, Tabei K, Hata H, Hasue T, et al. Diabetes Mellitus As a Risk Factor for Pancreatic Cancer-for Realization of Efficient Screening of Pancreatic Cancer in Patients With Diabetes Mellitus. Gastroenterology 2013;144:S659-S.

70. McAuliffe JC, Christein JD. Type 2 Diabetes Mellitus and Pancreatic Cancer. Surg Clin N Am 2013;93:619-27.

71. Li D, Tang H, Hassan MM, Holly EA, Bracci PM, Silverman DT. Diabetes and risk of pancreatic cancer: a pooled analysis of three large case-control studies. Cancer Causes Control 2011;22:189-97.

72. Liao KF, Lai SW, Li CI, Chen WC. Diabetes mellitus correlates with increased risk of pancreatic cancer: A population-based cohort study in Taiwan. J Gastroenterol Hepatol 2012;27:709-13.

73. International Diabetes Federation. IDF Diabetes Atlas,6 th edn. Brussles, Belgium: IDF 2013.

74. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol 2010;24:349-58.

75. Duell EJ, Lucenteforte E, Olson SH, Bracci PM, Li D, Risch HA, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol 2012;23:2964-70.

76. Yadav D, Whitcomb DC. The role of alcohol and smoking in pancreatitis. Nat Rev Gastroenterol Hepatol 2010;7:131-45.

77. Hirota M, Shimosegawa T, Masamune A, Kikuta K, Kume K, Hamada S, et al. The sixth nationwide epidemiological survey of chronic pancreatitis in Japan. Pancreatology 2012;12:79-84.

78. Garg PK, Tandon RK. Survey on chronic pancreatitis in the Asia-Pacific region. J Gastroenterol Hepatol 2004;19:998-1004.

79. Mohan V, Farooq S, Deepa M. Prevalence of fibrocalculous pancreatic diabetes in Chennai in South India. JOP 2008;9:489-92.

80. Midha S, Sreenivas V, Kabra M, Chattopadhyay TK, Joshi YK, Garg PK. Genetically Determined Chronic Pancreatitis but not Alcoholic Pancreatitis Is a Strong Risk Factor for Pancreatic Cancer. Pancreas 2016;45:1478-84.

81. Global Status Report on Alcohol and Health. WHO 2011.

82. Trikudanathan G, Philip A, Dasanu CA, Baker WL. Association between Helicobacter pylori infection and

pancreatic cancer. A cumulative meta-analysis. JOP 2011;12:26-31.

83. Ben Q, Li Z, Liu C, Cai Q, Yuan Y, Wang K, et al. Hepatitis B virus status and risk of pancreatic ductal adenocarcinoma: a case-control study from China. Pancreas 2012;41:435-40.

84. Ashtari S, Pourhoseingholi MA, Sharifian A, Zali MR. Hepatocellular carcinoma in Asia: Prevention strategy and planning. World J Hepatol 2015;7:1708-17.

85. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol 2007;13:2436-41.

86. Ashtari S, Pourhoseingholi MA, Molaei M, Taslimi H, Zali MR. The prevalence of Helicobacter pylori is decreasing in Iranian patients. Gastroenterol Hepatology Bed Bench 2015;8:S23-9.

87. Risch HA, Yu H, Lu L, Kidd MS. ABO blood group, Helicobacter pylori seropositivity, and risk of pancreatic cancer: a case-control study. J Natl Cancer Inst 2010;102:502-5.

88. Franchini M, Liumbruno GM, Lippi G. The prognostic value of ABO blood group in cancer patients. Blood Transfus 2016;14:434-40.

89. Zhang BL, He N, Huang YB, Song FJ, Chen KX. ABO blood groups and risk of cancer: a systematic review and meta-analysis. Asian Pacific J Cancer Prev 2014;15:4643-50.

90. Risch HA, Lu L, Wang J, Zhang W, Ni Q, Gao YT, et al. ABO blood group and risk of pancreatic cancer: a study in Shanghai and meta-analysis. Am J Epidemiol 2013;177:1326-37.

91. Wolpin BM, Kraft P, Gross M, Helzlsouer K, Bueno-de-Mesquita HB, Steplowski E, et al. Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium. Cancer Res 2010;70:1015-23.