Systematic Review Article

Epidemiology, Genetic, and Risk Factors of Esophageal Malignancy in Asia-Pacific Region; A Review Study

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ABSTRACT

Background:
Esophageal cancer (EC) continues to be a largely deadly malignancy worldwide, with overall 5-year survival less than 20% due to poor prognosis. Current statistics on EC incidence and consequences are essential for the prevention and therapeutic strategies of the malignancy.

Materials and Methods:
This overview was compiled from up-to-date epidemiological and clinical information on EC to reflect the status of EC in the Asia-Pacific region. We performed this review using Medline, PubMed, Scopus, Google Scholar, ISI Web of Knowledge (Science Citation Index Expanded), and Cochrane databases. The following MeSH terms and keywords were used for searching: 'esophagus cancer', 'epidemiology', 'incidence', 'mortality', 'risk factors', and 'Asia-Pacific region'. In addition, we reviewed age-standardized rates (ASRs) of EC occurrence and mortality for Asia-Pacific countries from GLOBOCAN, national databases using frequency rates, and the WHO mortality database in 2020.

Results:
Based on these findings, EC incidence rates range from 0.33 to 18.5 per 100,000 in Asia-Pacific countries. Esophageal squamous cell carcinoma (ESCC) was the predominant subtype in East and South-East Asia and was followed by Central Asia, with rates of 8.9 and 4.7 per 100,000 in both sexes, respectively. The highest incidence rates of esophageal adenocarcinoma (ADC) in the Asian-Pacific region were found in Australia and New Zealand (1.8/100,000).

Conclusion:
In this region, an unhealthy lifestyle is considered the leading risk factor for EC. Thus, changing lifestyle and community awareness of EC risk factors and healthy lifestyle learning is promising.

Keywords: Esophageal cancer, Epidemiology, Incidence, Mortality, Risk factor, Asian-Pacific

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INTRODUCTION

Esophageal cancer (EC) is the seventh most common cancer, with 572,000 new cases (6.3%), and the sixth leading cause of cancer death with 509,000 deaths (5.5%), which accounted for an estimated 1 in every 20 cancer deaths worldwide in 2018 (1). Over 75% of ECs arise in Asian countries because of the Asian belt of ECs in this region. Asian belt of EC begins from East of Turkey and Northeastern of Iran, and continues to the southern part of the former Soviet Union (Kazakhstan, Turkmenistan, Uzbekistan, and Tajikistan), to Mongolia and Northern/ Central China, with an estimated EC rate of more than 100 cases/100,000 person-years (2). Esophageal adenocarcinoma (ADC) and esophageal squamous cell carcinoma (ESCC) are considered the two common subtypes of EC (3,4). ADC is the major type of esophageal cancer in North America and Europe, particularly amongst white men (5) while ESCC is the predominant subtype in Eastern and South-East Asia, Sub-Saharan Africa and Central Asia (6). The distribution of the two types of EC varies dramatically worldwide (7,8). The outstanding geographical difference suggests that environmental and genetic factors may be remarkably involved in EC tumorigenesis (9, 10). The contrast in age-standardized (ASR) incidence rate (3.4 per 100,000) of EC in Western countries compared with (8.3 per 100,000) in Asian countries highlights the need for further investigation to identify factors behind the higher occurrence rate in these countries.

It has been concluded that EC incidence and mortality rates differ worldwide. One of the greatest distinguishing features of EC is geographical variation. Improved knowledge of EC epidemiology and risk factors can support early cancer detection and improve clinical and therapeutic strategies. Therefore, we conducted a systematic review to update and address the most current data regarding epidemiological features of EC in the Asia-Pacific region. This study aimed to survey and collect current statistics on EC, with an emphasis on frequency, mortality, and genetic and risk factors related to the malignancy in the Asia-Pacific region.

MATERIALS AND METHODS

The databases including, Medline, PubMed, Scopus, Google Scholar, ISI Web of Knowledge (Science Citation Index Expanded) and Cochrane were subjected to search using the following MeSH terms and keywords included: 'esophagus cancer', 'epidemiology', 'incidence', 'mortality', 'risk factors' and 'Asia-Pacific region' for articles published in the English language up to 31 May 2019. We reviewed titles and abstracts, and extracted relevant information from the full text of appropriate studies. Moreover, we checked additional articles listed in the bibliographies of retrieved publications and selected the most relevant and appropriate articles. We reviewed all pertinent articles in full text and assessed all applicable materials. Notably, we excluded studies without full-text access and those with uncertain results. The incidence and mortality rates of EC (coding disease is ICD-10 C15) in Asia-Pacific countries were obtained from GLOBOCAN 2018 (11), published by the International Agency for Research on Cancer (IARC). These articles provide information on cancer occurrence and mortality burden in 185 countries worldwide, using a ranked set of methods based on data precision and availability. This publication presents age-standardized rates (ASRs) of occurrence and mortality per 100,000 people. IARC also provides key incidence and mortality data in its Cancer Incidence in Five Continents database (ci5.iarc.fr/) and the World Health Organization Cancer Mortality Database (http://www-dep.iarc.fr/WHOdb/WHOdb.htm).

Countries covered

All papers were cross-referenced with "Asia-Pacific region" and countries in this region such as Australia, New Zealand, India, Pakistan, Turkey, Iran, and others. Asia-Pacific is a region of the world in or near the Western Pacific Ocean. The region varies in area depending on the context, but it typically includes much of East Asia, South Asia, Southeast Asia, Central Asia, Oceania, and the Pacific. To cover all of Asia in this study, this paper also examined West Asia. Therefore, based on our purpose, Asia-Pacific region was divided into five sub-regions; East Asia (China, Mongolia, North Korea, South Korea, and Japan), South-Central Asia (Tajikistan, Uzbekistan, Kazakhstan, Turkmenistan, Kyrgyzstan, Sri Lanka, Bangladesh, India, Afghanistan, Pakistan, Islamic Republic of Iran, Bhutan, Nepal, and the Maldives), Southeast Asia (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam), West Asia (Georgia, Armenia, Azerbaijan, Turkey, Cyprus, Syria, Lebanon, Israel, Palestine, Jordan, Iraq, Kuwait, Bahrain, Qatar, Saudi Arabia, United Arab Emirates, Oman, and Yemen), Oceania (Australia and New Zealand) and the pacific sub-regions (Melanesia: Fiji, France, New Caledonia, Papua New Guinea and Solomon Islands, Micronesia: Guam and Polynesia: French Polynesia, Samoa).

RESULTS

Incidence and mortality of EC

EC is known as the sixth most commonly detected cancer and the fifth foremost cause of cancer-related death in the Asia-Pacific region, with an estimated 446,912 new cases and 399,705 deaths according to GLOBOCAN 2020. The highest ASR occurrence of EC in the Asia-Pacific

region was observed in Eastern Asia (12.2/100,000), South-Central Asia (5.3/100,000), Australia and New Zealand (3.5/100,000), South-Eastern Asia (1.9/100,000), and Western Asia (1.5/100,000) in 2018, respectively (1). Table 1 shows the overall ASR incidence and standardized mortality rates (SMR) of EC across different parts of the Asia-Pacific region in 2018 for both sexes. In Asia-Pacific countries, the five countries with the highest SMR for EC were Mongolia (16.3/100,000), Bangladesh (13.7/100,000), China (12.7/100,000), Tajikistan (10/100,000), and Turkmenistan (8.2/100,000). Five countries with the lowest SMR from the EC were Solomon Islands (0.3/100,000), Indonesia (0.4/100,000), Lebanon (0.7/100,000), Iraq (0.8/100,000), and Georgia (0.9/100,000). Tables 2 and 3 present the number, crude rate, ASR, and SMR of EC in Asia-Pacific countries by sex (male, female, and both sexes). Countries in the table are sorted from highest to lowest by SMR in both sexes. Worldwide ASR incidence of ESCC and ADC were 5.2 and 0.7 per 100,000 in 2012, respectively (14).

Table 1. The overall age-standardized incidence and mortality rates of esophageal cancer among different parts of the Asia-Pacific region in 2018.

Esophagus Cancer		Incidence			Mortality		
Region		**Number**	**Crude Rate**	**ASR(W)***	**Number**	**Crude Rate**	**ASR(W)**
Asia-Pacific	Male	309,702	13.2	11.9	278,743	11.9	10.7
	Female	137,210	6.1	4.9	120,962	5.4	4.2
	Total	446,912	9.7	8.3	399,705	8.7	7.3
Eastern Asia	Male	237,160	28	17.9	212,430	25.1	15.8
	Female	97,920	12.1	6.8	88,448	11	5.9
	Total	335,080	20.3	12.2	300,878	18.2	10.7
South-Central Asia	Male	58,395	5.8	6.7	53,404	5.3	6.2
	Female	34,346	3.6	3.8	28,028	2.9	3.1
	Total	92,741	4.7	5.3	81,432	4.1	4.6
South-Eastern Asia	Male	10,418	3.2	3.3	9,614	2.9	3.1
	Female	2,446	0.74	0.68	2,243	0.68	0.62
	Total	12,864	2	1.9	11,857	1.8	1.8
Western Asia	Male	2,055	2.2	1.7	1,924	2.1	1.7
	Female	1,857	1.1	1.4	1,654	1.1	1.4
	Total	3,912	1.6	1.5	3,578	1.6	1.5
Australia/ New Zealand	Male	1,492	10.2	5.5	1,201	8.2	4.2
	Female	556	3.7	1.6	507	3.4	1.3
	Total	2,048	6.9	3.5	1,708	5.8	2.7
Melanesia	Male	155	2.9	4.9	147	2.7	4.8
	Female	83	1.6	2.2	80	1.5	2.1
	Total	238	2.3	3.4	227	2.2	3.3
Polynesia / Micronesia	Male	27	4.2	4.4	23	3.7	3.8
	Female	2	0.76	0.78	2	0.76	0.78
	Total	29	2.4	2.3	25	2.1	2.05

Crude rate per 100,000, *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 edifice (1).

Table 2. Number and age-standard incidence rate of EC in Asian-Pacific countries in 2018.

Countries	Region	All ages: both sexes		All ages: male		All ages: female	
		Numbers	ASR (W)	Numbers	ASR (W)	Numbers	ASR (W)
Mongolia	Eastern Asia	397	18.5	203	22	194	16
Bangladesh	South-Central Asia	20906	14.8	13483	18.7	7423	10.7
China	Eastern Asia	307359	13.9	214090	19.7	93269	8.2
Tajikistan	South-Central Asia	619	11.1	346	13.2	273	9.2
Turkmenistan	South-Central Asia	408	9.2	213	11.2	195	7.7
Afghanistan	South-Central Asia	1312	8.2	749	9.7	563	6.8
Kazakhstan	South-Central Asia	1615	8.1	895	11.4	720	5.9
Bhutan	South-Central Asia	44	6.8	26	7.4	18	6.1
Myanmar	South-Eastern Asia	3483	6.5	2703	10.8	780	2.8
Iran	South-Central Asia	4372	6	2482	6.6	1890	5.2
Yemen	Western Asia	785	5.9	304	5	481	6.8
Azerbaijan	Western Asia	594	5.6	317	6.9	277	4.5
Pakistan	South-Central Asia	7953	5.5	4713	6.5	3240	4.4
Japan	Eastern Asia	20019	5.4	16241	9.3	3778	1.9
Sri Lanka	South-Central Asia	1441	5	771	6	670	4.3
India	South-Central Asia	52396	4.2	33890	5.5	18506	2.9
North Korea	Eastern Asia	1440	4.1	1181	8	259	1.1
Papua New Guinea	Melanesia	206	4	130	5.8	76	2.7
Uzbekistan	South-Central Asia	939	3.8	502	4.6	437	3.2
New Zealand	Oceania	371	3.8	12	6.9	108	1.9
Kyrgyzstan	South-Central Asia	171	3.7	263	5.8	77	2.8
French Polynesia	Polynesia	12	3.5	94	5.1	-	-
Australia	Oceania	1667	3.4	1229	5.4	448	1.5
Thailand	South-Eastern Asia	3563	3.2	3021	5.9	542	0.87
France, New Caledonia	Melanesia	10	2.6	10	5.4	-	-
South Korea	Eastern Asia	2593	2.6	2352	5.2	241	0.4
Singapore	South-Eastern Asia	268	2.4	207	4	61	0.85
Fiji	Melanesia	21	2.4	14	3.2	7	1.6
Nepal	South-Central Asia	565	2.3	231	2	334	2.5
Guam	Micronesia	5	2.3	4	3.7	1	0.96
Viet Nam	South-Eastern Asia	2411	2.2	2074	4.2	337	0.5
Qatar	Western Asia	12	2	8	1.3	4	2.5
Kuwait	Western Asia	33	1.6	22	1.8	11	1.3
Brunei	South-Eastern Asia	5	1.6	5	3.2	-	-
Turkey	Western Asia	1470	1.5	784	1.9	686	1.3
Malaysia	South-Eastern Asia	422	1.4	294	1.9	124	0.8
United Arab Emirates	Western Asia	37	1.4	27	1.5	10	1.2
Philippines	South-Eastern Asia	1059	1.3	819	2.2	240	0.53
Oman	Western Asia	32	1.3	17	0.98	15	1.6
Saudi Arabia	Western Asia	262	1.2	164	1.3	98	1.1
Bahrain	Western Asia	9	1.2	5	1.3	4	1.2
Armenia	Western Asia	52	1.1	35	1.8	17	0.57

Table 2. Number and age-standard incidence rate of EC in Asian-Pacific countries in 2018.

Countries	Region	All ages: both sexes		All ages: male		All ages: female	
		Numbers	ASR (W)	Numbers	ASR (W)	Numbers	ASR (W)
Cyprus	Western Asia	22	1.1	15	1.7	7	0.63
Israel	Western Asia	144	1.1	89	1.5	55	0.74
Georgia	Western Asia	75	1	54	1.8	21	0.45
Jordan	Western Asia	61	0.97	37	1.3	23	0.70
Iraq	Western Asia	172	0.84	89	0.96	83	0.74

Table 3. Number and age-standard mortality rate of EC in Asian-Pacific countries in 2018.

Countries	Region	All ages: both sexes		All ages: male		All ages: female	
		Numbers	ASR (W)	Numbers	ASR (W)	Numbers	ASR (W)
Mongolia	Eastern Asia	345	16.3	184	20.4	161	13.4
Bangladesh	South-Central Asia	19357	13.7	12935	18	6422	9.3
China	Eastern Asia	283433	12.7	197823	18.2	85610	7.4
Tajikistan	South-Central Asia	565	10	333	12.5	232	7.8
Turkmenistan	South-Central Asia	366	8.2	187	9.8	179	7.1
Afghanistan	South-Central Asia	1267	8	731	9.5	536	6.6
Bhutan	South-Central Asia	42	6.6	25	7.3	17	5.8
Myanmar	South-Eastern Asia	3384	6.3	2657	10.7	727	2.6
Kazakhstan	South-Central Asia	1261	6.3	736	9.4	525	4.3
Yemen	Western Asia	752	5.8	289	4.8	463	6.6
Azerbaijan	Western Asia	562	5.3	302	6.6	260	4.2
Pakistan	South-Central Asia	7555	5.2	4608	6.3	2947	4
Papua New Guinea	Melanesia	198	3.9	125	5.7	73	2.6
Sri Lanka	South-Central Asia	1088	3.8	622	4.8	466	3
India	South-Central Asia	46504	3.7	31337	5.1	15167	2.4
North Korea	Eastern Asia	1196	3.3	961	6.7	235	0.91
Kyrgyzstan	South-Central Asia	153	3.3	90	4.8	63	2.3
Iran	South-Central Asia	2130	2.9	1244	3.3	886	2.5
Japan	Eastern Asia	12016	2.8	9842	5.1	2174	0.87
Thailand	South-Eastern Asia	3060	2.8	2595	5.1	465	0.73
New Zealand	Oceania	293	2.8	206	4.4	87	1.4
Australia	Oceania	1415	2.7	995	4.2	420	1.3
Uzbekistan	South-Central Asia	625	2.4	326	2.8	299	2.1
Nepal	South-Central Asia	519	2.4	230	2	289	2.2
French Polynesia	Polynesia	8	2.4	8	4.5	-	-
Fiji	Melanesia	20	2.3	13	3	7	1.6
Guam	Micronesia	5	2.3	4	3.7	1	0.96
France, New Caledonia	Melanesia	8	2.2	8	4.5	-	-
Singapore	South-Eastern Asia	237	2.1	187	3.6	50	0.68
Viet Nam	South-Eastern Asia	2222	2	1903	3.9	319	0.45
Qatar	Western Asia	12	2	8	1.3	4	2.5

Table 3. Number and age-standard mortality rate of EC in Asian-Pacific countries in 2018.

Countries	Region	All ages: both sexes		All ages: male		All ages: female	
		Numbers	ASR (W)	Numbers	ASR (W)	Numbers	ASR (W)
South Korea	Eastern Asia	1717	1.6	1557	3.3	160	0.23
Kuwait	Western Asia	31	1.6	21	1.8	10	1.3
United Arab Emirates	Western Asia	37	1.4	27	1.5	10	1.2
Turkey	Western Asia	1255	1.3	720	1.7	533	0.99
Malaysia	South-Eastern Asia	396	1.3	278	1.8	118	0.78
Oman	Western Asia	31	1.3	17	0.99	14	1.6
Brunei	South-Eastern Asia	4	1.3	4	2.6	-	-
Philippines	South-Eastern Asia	1011	1.3	782	2.2	229	0.51
Bahrain	Western Asia	9	1.2	5	1.3	4	1.2
Saudi Arabia	Western Asia	227	1.1	147	1.2	80	0.88
Cyprus	Western Asia	22	1.1	17	1.9	5	0.42
Israel	Western Asia	148	1	82	1.3	66	0.72
Armenia	Western Asia	49	1	33	1.7	16	0.62
Georgia	Western Asia	72	0.96	53	1.8	19	0.4
Jordan	Western Asia	60	0.96	38	1.3	22	0.69

Sex

Globally, around 70% of all EC cases occurred in men, and the incidence and mortality rates are 2-4 times higher than those for women (12). Overall, 309,702 cases (69.3%) were males and 137,210 cases (30.7%) were females in Asia-Pacific countries. The sex ratio in this region was 2.25. The five highest ASR of incidence in Asia-Pacific countries in the year 2018 among males were observed in Mongolia (22/100,000), China (19.7/100,000), Bangladesh (18.7/100,000), Tajikistan (13.2/100,000) and Kazakhstan (11.4/ 100,000), whereas the lowest rates were found in Solomon Islands (0.66/100,000), Indonesia (0.76/ 100,000), Lebanon (ASR: 0.86/100,000), Iraq (0.96/100,000), and Oman (0.98/100,000) and Saudi Arabia. In women, the incidence rates in 2018 among Asia-Pacific countries were generally lower than in men, with the highest rates in Mongolia (16/100,000), Bangladesh (10.7/100,000), Tajikistan (9.2/100,000), China (8.2/100,000), and Turkmenistan (7.7/100,000), and the lowest rates were observed in Indonesia (0.22/100,000), North Korea (0.4/100,000), Vietnam (0.5/100,000), Philippines (0.53/100,000) and Lebanon (0.56/100,000).

Risk factors

EC tumorigenesis is concluded to be a multifaceted process involving various etiological features, including environmental, geographical, and genetic factors (13, 14)]. In addition, risk factors of EC are somewhat diverse between the two main subtypes (15). Tobacco smoking, alcohol consumption, hot beverage drinking, high-fat diet, low-vitamin diet, achalasia, celiac disease, human papillomavirus (HPV), and Helicobacter pylori (H. pylori) infections are the major risk factors for ESCC (16, 17). In contrast, the ADC is more associated with obesity, gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), age, and male sex (16, 18). Moreover, a genetic abnormality is also suspected to play a role in both subtypes of EC.

Tobacco smoking and alcohol consumption are foremost risk factors for ESCC in the Asia-Pacific region. The risk of EC in smokers is 4 to 6 times more probable than in non-smokers, and the relative risk (RR) of EC increases with alcohol intake, varying from 1.7 to 7.7 based on the volume of alcohol intake per week (19). A study from Taiwan showed that the odds ratio (OR) of EC was 4.1 and 3.3 in smokers and former smokers in comparison with individuals who never smoked (20). However, there are parts of the Asia-Pacific where smoking and alcohol consumption are not major risk factors for ESCC, and other factors including; betel-nut chewing or tobacco chewing in India and Pakistan, drinking hot tea and opium consumption in Iran and Afghanistan and poor nutrition such as lack of fruit and vegetables in the food in low-income countries are the other factors for ESCC. Based on a review of the evidence, eating hot traditional teas and foods and meat were significant risk factors for EC in Mongolia (21). Furthermore, smoking, low fruit

and vegetable intake, and high alcohol consumption are also risk factors for EC in this country (9, 22, 23). In Bangladesh, nearly 50% of men smoke tobacco or chew tobacco, which is one of the most important risk factors for EC (24). Due to drinking contaminated groundwater, millions of people in Bangladesh have been exposed to arsenic (25). In addition, HPV and H. pylori infections are known as other EC risk factors in Bangladesh (26, 27). China showed a high occurrence of EC, particularly in rural areas, and ESCC was the predominant histological type of the disease in China; the most important risk factors are cigarette smoking, alcohol consumption, positive family history of EC, consumption of preserved vegetables, salty meat intake, late-night eating, and drinking contaminated water with nitrosamine (28). The high incidence of EC in Bhutan could be attributed to the high prevalence of *H. pylori* infection (29).

The incidence of ADC in high-income countries such as Australia, New Zealand, European countries, and the United States of America is rising rapidly with increasing body mass index (BMI), increasing GERD, BE, and possibly decreasing H. pylori infection (30-32). Excess body weight accounted for approximately 30 percent of esophageal ADC worldwide in 2012 (33). Each 5-unit increase in BMI has been estimated to be related to a 42% increased risk of ADC in smokers (34). Relative risk (RR) of EC related to an increase of 5 kg/m2 in excess BMI is 1.48 (95% CI: 1.35-1.62) based on the IARC Report in 2016 (35). Overweight and obesity are prevalent in the Asia-Pacific region, especially in Polynesian countries (41-60% in men and 52-65% in women), Australia, New Zealand, and several Middle Eastern countries such as Kuwait, Qatar, Iran, and Saudi Arabia (36). Based on previous evidence, a positive relationship between obesity and increased risk of GERD symptoms has been revealed(37). GERD is a common disease in the USA and Western countries, which now appears to be also increasing in prevalence in the Asia-Pacific region (38). GERD is known as a risk factor for esophageal ADC, and weekly and daily symptoms of it increased the risk of ADC by 5- and 7-fold, respectively (39). This change in GERD prevalence in Asia-Pacific countries is related to significant economic development and consequent lifestyle changes, increased obesity, and more accurate diagnosis. While the prevalence of BE in most parts of the Asia-Pacific region is low, the range of BE prevalence was reported from 0.06% to 6% in this region (40-47).

Genetic factors associated with EC

Studies in the Asia-Pacific region, from China through Central Asian republics toward the northeastern part of Iran, found a positive relationship between genetic factors and the prevalence of EC, and especially high incidence rates were reported among populations with “Mongolian phenotype” (48). Previous reports in Iran and China have revealed that the risk of EC in people with first-degree relatives with EC is more than (2-fold) that of those without a family history of EC (49, 50). Genetic differences or alterations may be involved in the increased risk of EC (9, 51).

Many molecular events are involved in EC tumorigenesis and progression, such as chromosome alterations and epigenetic changes in DNA repair genes, cancer-related genes, and genetic instability (51, 52). Although ESCC and ADC are distinct entities, genetic alteration studies have often grouped them; therefore, discussing specific alterations will help distinguish between them whenever possible. The discovery of molecular biomarkers for EC can be pertinent for screening, early detection, and prognosis of high-risk individuals. This approach may also help predict drug response and support personalized medicine for the malignancy.

Clinical features of EC

The middle third of the esophagus is the more frequent location for ESCC, and the lower third is the more common location for ADC (53). The symptoms of EC typically appear 3 to 4 months prior to diagnosis, and such symptoms diverge depending on the section of the esophagus primarily affected (54). Dysphagia and weight loss are the most common and the first symptoms of EC (55). Dysphagia, correlated with a poorer prognosis, occurs in over 90% of cases, and weight loss above 5% to 10% of body weight happens in nearly all patients (56). Different clinical features and prognoses are also associated with the two histological types of EC. Patients with ADC may have more advanced tumors than patients with ESCC, and a higher proportion of invasive lymph nodes, shorter hospital stay, higher rate of relapse, and lesser occurrence of tobacco-associated second primary tumors (57). Furthermore, various investigations have documented that ESCC represents a slight diffusion of early local lymph node and distant metastasis compared to ADC (58). The principal precursor lesion of ESCC is squamous dysplasia. Previous studies have confirmed that ESCC initiates through a sequence of molecular changes that result in dysplasia, followed by carcinoma and eventually invasive carcinoma (7). While ADC is associated with obesity and GERD, the precursor lesion of ADC is BE (56).

DISCUSSION

The present study focused on the incidence, mortality, clinicopathological features, and risk factors of EC based on an overview of studies conducted in the Asia-Pacific

region and GLOBOCAN 2018. According to the data presented in this review, the ASR incidence of EC in the Asia-Pacific region shows great heterogeneity. Mongolia has the highest ASRs of incidence and mortality (18.5 and 16.3/100,000) in this region, followed by Bangladesh (14.8 and 13.7/100,000). The national average ASR incidence of EC in Mongolia is 21.7/100,000 and 15.6/100,000 for males and females, respectively (59). A comparison of EC incidence and mortality rates in Asian-Pacific countries based on GLOBOCAN 2012 and 2018 shows that incidence and mortality have decreased in Turkmenistan, Tajikistan, Kazakhstan, Afghanistan, Iran, and Japan. In contrast, rates appear to be increasing in Mongolia, Bangladesh, China, Bhutan, Azerbaijan, Yemen, Pakistan, India and Thailand. However, incidence and mortality were stable in Australia and New Zealand (1). Variations in EC occurrence across Asia-Pacific countries may reflect differences in risk-factor distribution, ethnicity, dietary habits, and cancer registration approaches. In addition, our findings revealed that the burden of esophageal cancer was higher in males than in females for all age groups; sex hormones have been suggested to protect women against this tumor. For example, breastfeeding reduces the risk of EC in women (60). Moreover, dysregulated levels of adipokines such as leptin, which are more commonly seen in men, have been indicated to be involved in the occurrence of EC in men and women (33, 61).

As mentioned earlier, the risk factors for EC differ slightly between ESCC and ADC. Despite rising obesity and GERD in Asia-Pacific countries, ESCC is still the predominant subtype of EC in the Asia-Pacific region due to tobacco smoking and alcohol consumption. ESCC is the predominant subtype in East and South-East Asia, followed by Central Asia, with rates of 8.9 and 4.7 per 100,000 in both sexes, respectively. China accounted for more than half of the ESCC global incidence (>53%), so the occurrence of the malignancy in the country is meaningfully higher than in other countries [10]. On the other hand, the highest incidence rates of ADC in the Asia-Pacific region were found in Oceania (1.8/100,000) compared with that of ADC in East and South-East Asia or Central Asia (0.4/100,000) in both sexes (62).

CONCLUSION

ASRs of EC incidence and mortality show great heterogeneity in the Asia-Pacific region. In addition to different risk factors, this heterogeneity can be a result of improved approaches in cancer registration and diagnostic accuracy. Despite rising obesity and GERD in Asia-Pacific countries, esophageal SCC is still the predominant subtype of EC in the Asia-Pacific region, with the exception of Australia and New Zealand. The most important risk factors for EC in Asia-Pacific countries are tobacco smoking, alcohol consumption, hot beverage drinking, an inappropriate diet, and low physical activity. Based on recent findings, the foremost cause of EC in this region is an unhealthy lifestyle. Hence, awareness of EC risk factors and a healthy lifestyle may prevent cancer and improve life expectancy.

DECLARATIONS

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

AUTHORS' CONTRIBUTIONS

All authors contributed to this study; Akbari A and Faghihi Kashani AH designed the study, Tabaeian SAP, Namazi A, Ahmadi A, and Nazar Beigi S contributed to the concept of the review, Ashtari S and Babaali Sh performed the database and paper selection for the review and wrote the draft of the review; all authors edited and revised the manuscript and approved the final version of the manuscript.

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AVAILABILITY OF DATA AND MATERIALS

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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