# The Incidence of Esophageal Cancer in Iran: A Systematic Review and Meta-analysis

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# 1. Abstract

**Background:** Esophageal Cancer (EC) is the eighth most common cancer in terms of incidence. Despite various studies, there is no general estimate of EC incidence in Iran. Therefore, the present study is conducted to evaluate the incidence rates of EC in Iran. **Method:** A systematic search was conducted on all published studies of EC incidence using Medline/PubMed, Scopus, Web of sciences, Google scholar, and four Iranian databases (Scientific Information Database, MagIran, IranMedex, and IranDoc) until November 2017. This systematic review was done according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA). **Result:** The database, grey literature searches, and hand searching yielded 346 potentially relevant studies. A total of 22 studies were included. The results of the random effect model were demonstrated the age-standardized rate (ASR) of EC was 25.05, 95% CI (20.84 to 29.26) among males and 22.93 95 % CI (18.97-26.88) among females. **Conclusion:** In comparison to other geographical locations, the incidence of EC is higher in Iran. However, organized system for collecting data of cancer is required to specify the incidence and trend of EC in Iran.

## 2. Introduction

Esophageal cancer ranks as the eighth most frequent malignancy and the sixth most common cause of cancer-related deaths [1]. In 2013, there were 442,000 new cases of EC and 440,000 deaths due to this cancer worldwide [2]. Eighty-four percent (84%) of EC cases occur in developing nations [3]. Despite the recent advances in medical therapies, the 5-year survival rate for esophagus cancer remains less than 20% [4].

The highest incidence rate of EC in men was occurred in Eastern Asia (ASR=22.04 per 100,000) and in women was observed in the region of Eastern Sub-Sahra of Africa (ASR=12.74 per 100,000) [1]. Studies suggest that EC is more common in men than in women, in particular, the sex ratio varies from 2 to 4 among different regions [5]. The highest incidence of EC is observed in China, northern Iran, and southern Africa [6,7]. The ASR of cancer in these regions is reported to be higher than 100 per 100,000 [7–9].

The first study on cancer in Iran has been conducted by Habibi in 1962 [10]. The National Cancer Registry System (NCR) was established in 1984 in Iran. Since the establishment of the NCR, there have been various and inconsistent reports published on the incidence of different types of cancers by pathology centers and cancer registries. The published reports had many disparities [11,12].

EC is one of the most common cancers in Iran [13]. The northern part of the country shows the highest incidence rates for this malignancy [14]. According to studies, Golestan Province has one of the highest incidence and mortality rates of *EC* worldwide [15,16]. There are many assumptions about the high incidence of this cancer in Golestan region. Race, diet, drinking hot tea, and tobacco consumption are among the reasons associated with cancer incidence in this region [17–19].

According to studies conducted in Iran, the incidence of EC varies dramatically throughout different regions of the country. Although there is an obvious need to accurate statistical information for health planning and management in Iran, there is not any accurate information on EC incidence. In this regard, this study aims to investigate the incidence of EC in Iran through a systematic review.

## 3. Methods

The systematic review and meta-analysis were designed in 2017 and undertaken in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline [20].

## (a) Search strategy of systematic reviews

A literature search of published studies was conducted using international databases Medline/PubMed, Scopus, Web of sciences, and Google Scholar for English papers and Iranian databases Scientific Information Database (www.sid.ir), MagIran (www.magiran.com), IranMedex (www.iranmedex.com), and Irandoc (www.irandoc.ac.ir), for Persian papers.

The medical subject headings (MeSH) keywords included "esophageal cancer", "esophageal neoplasms", "esophageal tumor", "cancer of esophageal", "neoplasms of esophageal", "Oesophageal cancer", "Oesophageal neoplasms", "Oesophageal tumor", "cancer of Oesophageal", "neoplasms of Oesophageal", "epidemiology", "incidence", and "Iran". The obtained papers were imported into an EndNote X5 (Thomson Reuters, Carlsbad, CA, USA) library and the duplicates were removed. No language and time limitations were considered.

## (b) Inclusion and exclusion criteria

All studies with results of ASR of EC and reports of Iranian populations were included in this review. Furthermore, studies with following criteria were not considered in this review; studies which reported prevalence rate based on pathological data, studies with inadequate sample size, and research articles (all type of conference abstracts, poster papers, letters, comments, and editorial).

## (c) Quality assessment

In order to assess the quality of the articles, a checklist prepared by The Joanna Briggs Institute (JBI) was used [21]. The purpose of this appraisal is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct, and analysis.

## (d) Risk of bias across studies

Random effect model was used for minimizing the risk of bias across the studies [22,23].

## (e) Statistical analysis

STATA version 12.0 software (Stata Corp LP, College Station, TX, USA) was used to perform all analysis. Statistical heterogeneity between the results of obtained studies was assessed using Cochran's Q statistic (with a significance level of $p \leq 0.1$) combined with $I^2$ statistic (with a significance level of $> 50\%$). The Meta-analysis was conducted with a random effect model (with inverse variance method) in the studies with significant heterogeneity ($p \leq 0.1$ and $I^2 \geq 50\%$). Additionally, in the absence of heterogeneity ($p > 0.1$ and $I^2 < 50\%$), the fixed effect model was used.

## 4. **Results**

### (a) Description of literature search

The database, grey literature searches, and hand searching yielded 346 potentially relevant studies. In total, 274 unique studies were reviewed, and 91 studies were entered into the second stage of evaluation. Overall, our review included 22 unique studies. Study retrieval and selection has been outlined in **Figure 1**. Some studies were excluded from the review due to not being relevant to the topic (n=190), incorrect study population (n=35), duplicate study (n=6), and inadequate data (n=21). The flowchart of the included studies in this review has been shown in **Figure 1**.
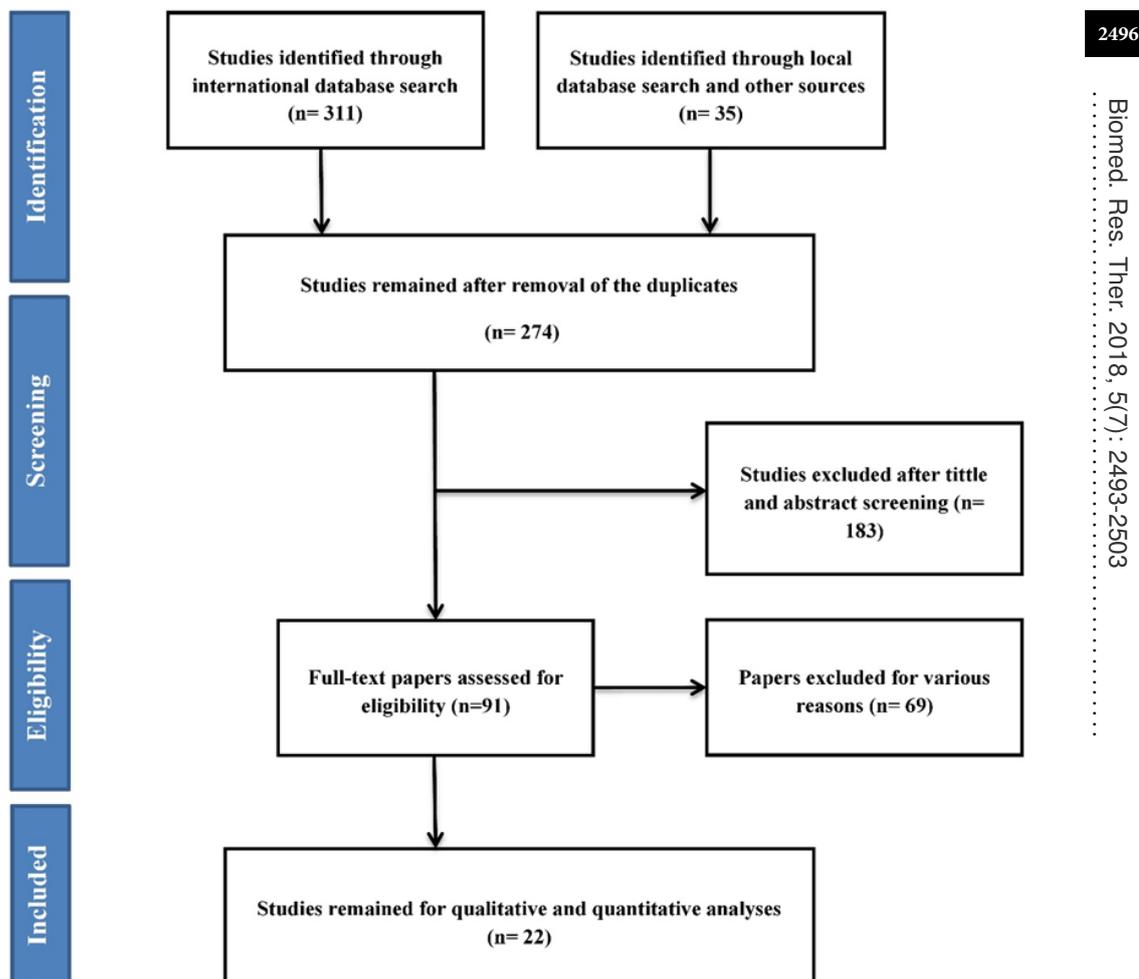
**Figure 1. Flowchart of the included eligible studies in the systematic review**

## (b) Description of the included studies

The included studies were published from 1968 to 2017. Based on geographical locations, four studies were conducted in all states of Iran [24–27], three in Fars province [28–30], three in East Azerbaijan [15,31,32], two in Ardabil province [33,34], two in Guilan province [35,36], two in Golestan province [37,38], one in Kerman province [39], one in Semnan province [40], one in Tehran metropolis [41], one in Mazandaran province [42], one in Caspian littoral [43] and one in Shahroud city [44]. All the studies have reported ASRs. The main characteristics of the selected studies have been presented in **Table 1**.

## (c) The results of individual studies

The results of the study showed the sex ASR ratio of male to female is 1.09. The highest ASR was reported from Golestan province between 1995 and 1997 (144.09 per 100,000) for men [38], and 1968 (174.1 per 100000) for women [43]. The lowest ASR was reported from Fars province between 1990 to 2005 (1.05 for males and 0.87 for females per 100,000) [28].

**Table 1. Basic characteristics of the studies included in the review**

| Order | Author/Year | Time period | Location | ASR (Males) | ASR (Females) | Quality level |
|---|---|---|---|---|---|---|
| 1 | Kmet, 1972 | 1968 | Caspian littoral | 108.8 | 174.1 | Medium |
| 2 | Saidi, 2000 | 1995-1997 | Golestan | 144.09 | 48.82 | Medium |
| 3 | Sadjadi, 2003 | 1999-1996 | Ardabil | 15.42 | 14.36 | Medium |
| 4 | Babai, 2005 | 1997-2001 | Semnan | 11.7 | 8.8 | Low |
| 5 | Sadjadi, 2007 | 1996-2000 | Kerman | 3 | 1.8 | Medium |
| 6 | Mehrabani, 2008 | 1990- 2005 | Fars | 1.05 | 0.87 | Low |
| 7 | Mousavi, 2008 | 2003-2006 | Iran | 2003=4.64 2005=5.5 2006=5.83 | 2003=4.93 2005=5.41 2006=6.25 | HIgh |
| 8 | Somi, 2008 | 2006-2007 | East Azerbaijan | 12.43 | 11.64 | Medium |
| 9 | Mohagheghi, 2009 | 1998-2001 | Tehran | 6.8 | 5.3 | High |
| 10 | Babaei, 2009 | 2004-2006 | Ardabil | 19.5 | 19.7 | Medium |
| 11 | Norouzi Nejad, 2009 | 2006 | Mazandaran | 10.6 | 8.68 | Medium |
| 12 | Somi, 2009 | 2006-2007 | East Azerbaijan | 136 | 92 | Medium |
| 13 | Masoompour,2011 | 1998-2002 | Fars | 2 | 1.4 | Medium |
| 14 | Ghanae, 2012 | 1996-2005 | Guilan | (1996-7)=7.2 (2005-6)= 6.9 | (1996-7)= 5.2 (2005-6)= 4.1 | High |
| 15 | Roshandel, 2012 | 2004-2008 | Golestan | 24.3 | 19.1 | Medium |
| 16 | Fateh, 2013 | 2000-2010 | Shahroud | 9.96 | 9.78 | High |
| 17 | Atrkar-Roushan, 2013 | 1997-2011 | Guilan | 1997 =6.26 2011= 4.36 | - | Medium |
| 18 | Somi,2014 | 2007-2011 | East Azerbaijan | 9.69 | 7.35 | Medium |
| 19 | Amori, 2015 | 2004-2008 | Iran | 5.05 | - | Medium |
| 20 | Masoompour, 2016 | 2007-2010 | Fars | (2007)= 2 (2010)=3.25 | (2007)= 1.4 (2010)= 3.04 | High |
| 21 | Darab, 2016 | 2001- 2010 | Iran | 2001=3.25 2010=5.25 | 2001=2.10 2010=5.62 | Medium |
| 22 | Kulhánová, 2017 | 2012 | Iran | 130 | 115 | Medium |

## (d) The results of the meta-analysis

The results of the random effect model were demonstrated the ASR of EC was 25.05, 95% CI (20.84 to 29.26) among males and 22.93 95 % CI (18.97-26.88) among females. Additionally, the results of Cochran's test showed the heterogeneity of the studies (Q= 61805.49, df =27, $I^2$=100%, *p*<0.001) for males and (Q= 52477.52, df =24, $I^2$=100%, *p*<0.001) for females. The forest plots of the random-effect meta-analysis for ASR of EC in Iran have been presented in **Figure 2** and **Figure 3** for males and females, respectively. All measurements in the forest plot were multiplied by $10^5$ because of the small values of ASRs.
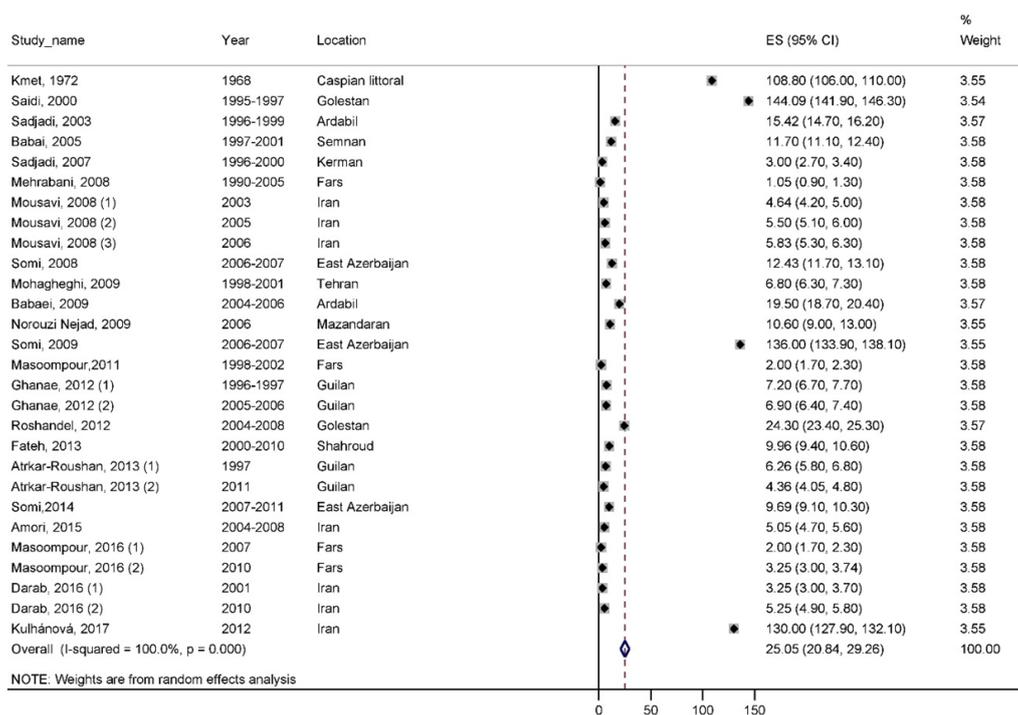
| Study_name | Year | Location | | ES (95% CI) | % Weight |
|---|---|---|---|---|---|
| Kmet, 1972 | 1968 | Caspian littoral | | 108.80 (106.00, 110.00) | 3.55 |
| Saidi, 2000 | 1995-1997 | Golestan | | 144.09 (141.90, 146.30) | 3.54 |
| Sadjadi, 2003 | 1996-1999 | Ardabil | | 15.42 (14.70, 16.20) | 3.57 |
| Babai, 2005 | 1997-2001 | Semnan | | 11.70 (11.10, 12.40) | 3.58 |
| Sadjadi, 2007 | 1996-2000 | Kerman | | 3.00 (2.70, 3.40) | 3.58 |
| Mehrabani, 2008 | 1990-2005 | Fars | | 1.05 (0.90, 1.30) | 3.58 |
| Mousavi, 2008 (1) | 2003 | Iran | | 4.64 (4.20, 5.00) | 3.58 |
| Mousavi, 2008 (2) | 2005 | Iran | | 5.50 (5.10, 6.00) | 3.58 |
| Mousavi, 2008 (3) | 2006 | Iran | | 5.83 (5.30, 6.30) | 3.58 |
| Somi, 2008 | 2006-2007 | East Azerbaijan | | 12.43 (11.70, 13.10) | 3.58 |
| Mohagheghi, 2009 | 1998-2001 | Tehran | | 6.80 (6.30, 7.30) | 3.58 |
| Babaei, 2009 | 2004-2006 | Ardabil | | 19.50 (18.70, 20.40) | 3.57 |
| Norouzi Nejad, 2009 | 2006 | Mazandaran | | 10.60 (9.00, 13.00) | 3.55 |
| Somi, 2009 | 2006-2007 | East Azerbaijan | | 136.00 (133.90, 138.10) | 3.55 |
| Masoompour,2011 | 1998-2002 | Fars | | 2.00 (1.70, 2.30) | 3.58 |
| Ghanae, 2012 (1) | 1996-1997 | Guilan | | 7.20 (6.70, 7.70) | 3.58 |
| Ghanae, 2012 (2) | 2005-2006 | Guilan | | 6.90 (6.40, 7.40) | 3.58 |
| Roshandel, 2012 | 2004-2008 | Golestan | | 24.30 (23.40, 25.30) | 3.57 |
| Fateh, 2013 | 2000-2010 | Shahroud | | 9.96 (9.40, 10.60) | 3.58 |
| Atrkar-Roushan, 2013 (1) | 1997 | Guilan | | 6.26 (5.80, 6.80) | 3.58 |
| Atrkar-Roushan, 2013 (2) | 2011 | Guilan | | 4.36 (4.05, 4.80) | 3.58 |
| Somi,2014 | 2007-2011 | East Azerbaijan | | 9.69 (9.10, 10.30) | 3.58 |
| Amori, 2015 | 2004-2008 | Iran | | 5.05 (4.70, 5.60) | 3.58 |
| Masoompour, 2016 (1) | 2007 | Fars | | 2.00 (1.70, 2.30) | 3.58 |
| Masoompour, 2016 (2) | 2010 | Fars | | 3.25 (3.00, 3.74) | 3.58 |
| Darab, 2016 (1) | 2001 | Iran | | 3.25 (3.00, 3.70) | 3.58 |
| Darab, 2016 (2) | 2010 | Iran | | 5.25 (4.90, 5.80) | 3.58 |
| Kulhánová, 2017 | 2012 | Iran | | 130.00 (127.90, 132.10) | 3.55 |
| Overall (I-squared = 100.0%, p = 0.000) | | | | 25.05 (20.84, 29.26) | 100.00 |

NOTE: Weights are from random effects analysis

0    50    100    150

**Figure 2. Forest plot of the random-effect meta-analysis for ASRs of Esophageal cancer in males in the Iran**

## (e) Publication Bias

Publication bias was assessed using Egger's tests [45]. Results of Egger's tests showed a lack of publication bias (*p*=0.197 for males and *P*= 0.442 for females).

## 5. **Discussion**

EC is the eighth most common cancer worldwide (3.8% of all cancers) and is the sixth most common cause of cancer-related deaths (5.4% of all cancer-related deaths). More than 80 percent of all EC deaths occur in developing countries [1,2].

Cancer is the third most common cause of death in Iran [46]. So far, few studies have been conducted on the epidemiology of cancer in developing countries such as Iran [47–50]. The first study on cancer incidence in Iran dates back to the 1970s. That study investigated cancer incidence in the Caspian littoral region between 1968 and 1972 [43].
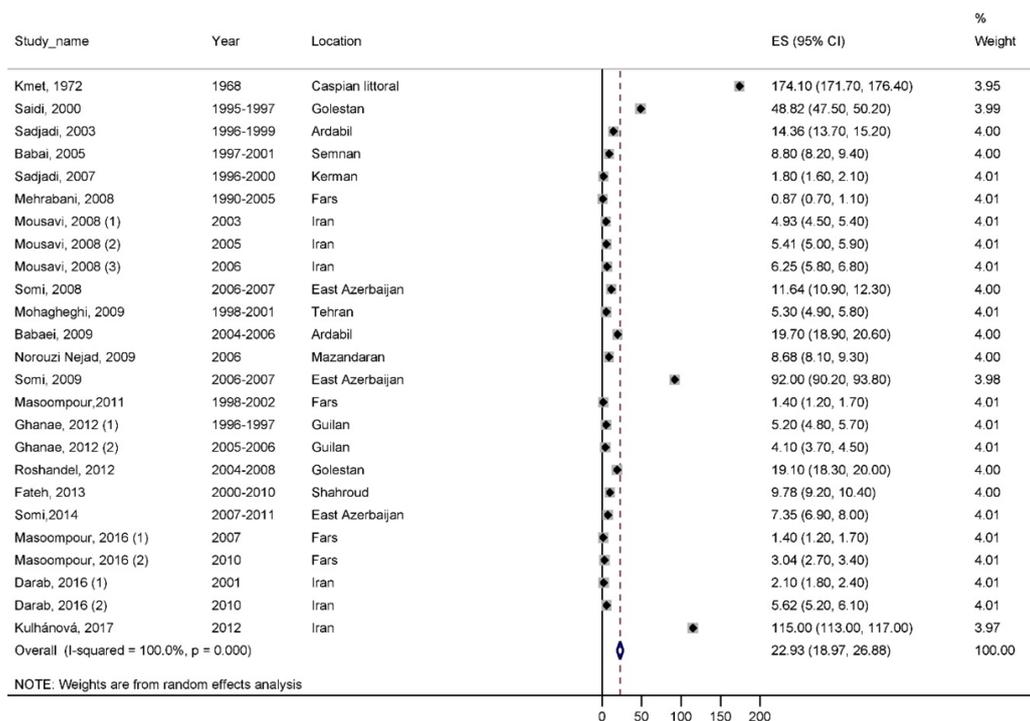
| Study_name | Year | Location | | ES (95% CI) | % Weight |
|---|---|---|---|---|---|
| Kmet, 1972 | 1968 | Caspian littoral | | 174.10 (171.70, 176.40) | 3.95 |
| Saidi, 2000 | 1995-1997 | Golestan | | 48.82 (47.50, 50.20) | 3.99 |
| Sadjadi, 2003 | 1996-1999 | Ardabil | | 14.36 (13.70, 15.20) | 4.00 |
| Babai, 2005 | 1997-2001 | Semnan | | 8.80 (8.20, 9.40) | 4.00 |
| Sadjadi, 2007 | 1996-2000 | Kerman | | 1.80 (1.60, 2.10) | 4.01 |
| Mehrabani, 2008 | 1990-2005 | Fars | | 0.87 (0.70, 1.10) | 4.01 |
| Mousavi, 2008 (1) | 2003 | Iran | | 4.93 (4.50, 5.40) | 4.01 |
| Mousavi, 2008 (2) | 2005 | Iran | | 5.41 (5.00, 5.90) | 4.01 |
| Mousavi, 2008 (3) | 2006 | Iran | | 6.25 (5.80, 6.80) | 4.01 |
| Somi, 2008 | 2006-2007 | East Azerbaijan | | 11.64 (10.90, 12.30) | 4.00 |
| Mohagheghi, 2009 | 1998-2001 | Tehran | | 5.30 (4.90, 5.80) | 4.01 |
| Babaei, 2009 | 2004-2006 | Ardabil | | 19.70 (18.90, 20.60) | 4.00 |
| Norouzi Nejad, 2009 | 2006 | Mazandaran | | 8.68 (8.10, 9.30) | 4.00 |
| Somi, 2009 | 2006-2007 | East Azerbaijan | | 92.00 (90.20, 93.80) | 3.98 |
| Masoompour,2011 | 1998-2002 | Fars | | 1.40 (1.20, 1.70) | 4.01 |
| Ghanae, 2012 (1) | 1996-1997 | Guilan | | 5.20 (4.80, 5.70) | 4.01 |
| Ghanae, 2012 (2) | 2005-2006 | Guilan | | 4.10 (3.70, 4.50) | 4.01 |
| Roshandel, 2012 | 2004-2008 | Golestan | | 19.10 (18.30, 20.00) | 4.00 |
| Fateh, 2013 | 2000-2010 | Shahroud | | 9.78 (9.20, 10.40) | 4.00 |
| Somi,2014 | 2007-2011 | East Azerbaijan | | 7.35 (6.90, 8.00) | 4.01 |
| Masoompour, 2016 (1) | 2007 | Fars | | 1.40 (1.20, 1.70) | 4.01 |
| Masoompour, 2016 (2) | 2010 | Fars | | 3.04 (2.70, 3.40) | 4.01 |
| Darab, 2016 (1) | 2001 | Iran | | 2.10 (1.80, 2.40) | 4.01 |
| Darab, 2016 (2) | 2010 | Iran | | 5.62 (5.20, 6.10) | 4.01 |
| Kulhánová, 2017 | 2012 | Iran | | 115.00 (113.00, 117.00) | 3.97 |
| Overall (I-squared = 100.0%, p = 0.000) | | | | 22.93 (18.97, 26.88) | 100.00 |
| NOTE: Weights are from random effects analysis | | | | | |

**Figure 3. Forest plot of the random-effect meta-analysis for ASRs of Esophageal cancer in females in the Iran**

Iran is one of the countries with very high incidence of EC [8,26]. Some parts of Iran, which have common borders with Turkmenistan and Afghanistan countries, experience much higher incidence rates of this cancer. These regions include Mazandaran, Golestan, and Khorasan provinces [14,35].

Results of the present study indicate that the incidence rate of EC among Iranian men and women (ASR=25.05 and 22.93 per 100,000 in men and women, respectively) is higher compared to other countries in the region. However, some Asian countries such as Turkmenistan (ASR=24 for men and 16.4 for women per 100,000), Mongolia (21.2 for men and 14.9 for women per 100,000), and Tajikistan (19.8 for men and 10.7 for women per 100,000) have ASR. Also, countries such as United Arab Emirates (1.8 per 100 thousand), Qatar (.1.8 per 100 thousand) and Nepal (3.6 per 100 thousand) in men and South Korea (0.4 per 100 thousand), Vietnam (0.7 per 100 Thousand) and Thailand (0.8 per 100,000) in women have the lowest ASR [51].

Globally, the highest age standardized incidence rate of EC is observed in Eastern Asia (ASR=11 per 100,000), and Western Pacific (ASR=10.2 per 100,000). Also, Central America (ASR=1.1 per 100,000), and Western Africa (ASR=0.6 per 100,000) has the lowest incidence rates of EC [1].

According to the study that examined the correlation between the human development index (HDI) and the ASR of EC, a significant reverse relationship between HDI and the standardized incidence rate of EC was identified. Thus, countries with higher levels of HDI reported lower incidencerates of EC [1].The difference in incidence rates of EC among different countries can be due to the development, distribution, and prevalence of risk factors, as well as better application of cancer registration techniques and more accurate diagnosis of the disease [4,52–54].

According to the results of this study, the highest ASR of EC in Iranian men and women is observed in Golestan province (ASR=144 per 100 thousand in men during 1995-7 and 174.1

per 100,000 in women in 1968). The high incidence of cancer in different regions is due to the difference in the distribution of the risk factors and its associated exposures in one region compared to another. Based on studies, risk factors such as drinking hot tea, burned opium consumption, gastric *Helicobacter pylori* infection, family history of esophageal cancer, drinking contaminated water, inappropriate diet, low physical activity, and smoking are associated with EC incidence [19,55]. The genetic role is also a major contributor to the high incidence of EC in Golestan province, having one of the highest worldwide rates of this type of cancer incidence [56–58].

The results of this study indicated that the lowest ASR of EC in Iran, in both sexes, is observed in Fars province (1.05 for men and 0.87 for women). The low incidence rate of EC in this province can be attributed to the demographic characteristics of people living in this area, differences in lifestyle, and the presence of other types of risk factors and diseases. In Fars province, other types of cancer such as breast, colorectal, and gastric cancers in women and bladder, prostate and gastric cancers in men have higher incidence rates [30,59,60].

Finally, it should be noted that the prevalence of cancer-related risk factors in Iran is high and is rising with an upward trend. The number of new cancer cases in Iran is expected to rise in future due to the epidemiological transition, increasing life expectancy, and aging the population.

## 6. **Conclusion**

In comparison to other geographical locations, the incidence of EC is higher in Iran. However, organized system for collecting data of cancer is required to specify the incidence and trend of EC in Iran.

## 7. Open Access

## 8. List of abbreviations

**ASR**: age-standardised rate; **EC**: Esophageal Cancer; **NCR**: National Cancer Registry System; **PRISMA**: Preferred reporting items for systematic reviews and meta-analyses

## 9. Ethics approval and consent to participate

Not to be applied

## 10. Competing interests

The authors declare that they have no conflicts of interest.

## 11. Funding

## 12. Authors' contributions

All authors contributed to the design of the research, HS, FMG, SM, FJ, EA, MF extracted the data and summarized it. HS, SH AND MAZ analyzed the data. All authors drafted the first version.

FMG, and HS edited the first draft. All authors reviewed, commented and approved the final version.

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