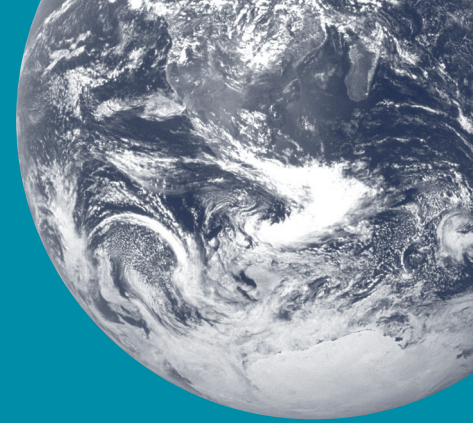




THE INCIDENCE OF BLADDER CANCER IN IRAN: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract – Objective: There are several reports related to the incidence of bladder cancer (BC) from various geographical locations of Iran. Nevertheless, no comprehensive systematic review has conducted in this regard. Therefore, the present systematic review and meta-analysis carried out to estimate the incidence rate of BC among Iranian people.

Patients and Methods: This systematic review was done based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) in October 2017. A search was performed in five international database (Medline/PubMed, Scopus, Embase, ISI Web of Science, and Google Scholar), and four national databases (Scientific Information Database, MagIran, Barakat Knowledge Network System, and IranDoc). The incidence rate of BC was calculated using random-effect model.

Results: An aggregate of 226 papers was obtained in the primary search of the databases. After further refinement of the retrieved studies, 29 studies were included. The age-standardized rate of BC was 10.92, 95% CI (9.88-11.96) and, 2.80, 95% CI (2.47-3.13) in males and females, respectively.

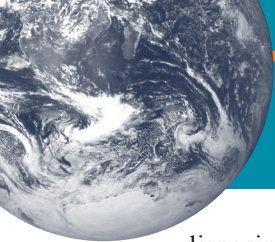
Conclusions: The incidence of BC was lower in Iran compared to other parts of the world. However, more investigations are needed to outline the exact incidence rate and the trend of BC among Iranian population.

KEYWORDS: Incidence, Bladder cancer, Iran, Meta-analysis.

INTRODUCTION

Bladder cancer (BC) is the 11th most common cancer and the 14th leading cause of cancer deaths worldwide¹. The mortality rate of BC is also high among patients diagnosed with the cancer. However, BC presents any symptoms in the early stages,

it appears with hematuria in approximately 75% of progressed cases². The incidence and mortality rate of BC varies around the world, because the distribution of BC risk factors is of different in different areas¹. The most important risk factors are smoking, Infection with *Schistosoma*, and occupational exposure to carcinogenic aromatic amines³. Other pre-



disposing factors include family history of BC and hemolymphopoietic cancers, nutritional patterns, environmental contamination, and genetic traits^{3,4}. While smoking is the main risk factor for the cancer in the United States, infection with *Schistosoma* is the most significant risk factor in most parts of Africa⁵. The treatment of BC is different based on tumor invasion into the layers of bladder wall. In the case of non-muscle invasive BC, transurethral resection and intravesicular immunotherapy are the best choices⁶. Radiation, chemotherapy, and also radical cystectomy are the current approach to treat muscle invasive BC. The most invaluable treatment for micrometastatic dissemination forms of BC is chemotherapy. Cisplatin-based chemotherapy, gemcitabine-paclitaxel doublet, and recently vinflunine are the standard of care in BC chemotherapy^{7,8}. The highest incidence rates of BC are observed in Europe, North America, West Asia, and North Africa. The lowest incidence rates are also occurred in Central, Eastern, and Western Africa. The highest mortality rate of BC among men is observed in Turkey, which is estimated 12.8 deaths per 100,000 in 2012 (50% higher than in Europe)⁹. Helminth infection with *Schistosoma haematobium* is cause of 50% of BC in some parts of Africa and about 3% of all cases worldwide¹⁰. Based on the studies which investigated the relationship between gender and BC, men are more susceptible to BC than women¹¹. In general, BC is more common in developed countries than developing countries. In western countries, BC is the fourth and the ninth most common cancer among men and women, respectively¹². Biostatistical investigations in Iran indicate the high importance of BC among health-care issues¹³. The incidence of the cancer has been also increasing steadily among Iranian men and women¹⁴. It is necessary to know current status and trend of the BC incidence rate for planning and evaluating cancer control programs. Several studies¹⁵⁻¹⁸ have been conducted in Iran to address the incidence rate of cancers. However, only few studies have evaluated the age-standardized incidence rate (ASR) of BC, most of them are not comprehensive. Actually, no systematic survey was carried out to explore the incidence of BC in Iran. This study aimed to systematically review the ASR of BC in Iran.

PATIENTS AND METHODS

PATIENTS

The study was designed and conducted in 2017. The review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist¹⁹.

SEARCH STRATEGY OF SYSTEMATIC REVIEWS

In October 2017, a systematic search of literature was carried out using Medline/PubMed, Scopus, Embase, ISI/ Web of science, and Google Scholar as international databases, and Scientific Information Database (SID) (www.sid.ir), MagIran (www.magiran.com), Barakat Knowledge Network System (www.barakatkns.com), and IranDoc (www.irandoc.ac.ir) as national databases. The keywords included: "bladder cancer", "bladder neoplasm", "bladder tumor", "cancer of bladder", "neoplasms of bladder", "incidence", "epidemiology" and "Iran". The citation results were then imported into EndNote X5 software (Thomson Reuters, Carlsbad, CA, USA). Thereafter, the studies were checked out by two reviewers independently based on title, abstract and full-text. The reference list of included studies was reviewed to detect more eligible articles.

INCLUSION AND EXCLUSION CRITERIA

The papers contained clearly reports of the ASR of BC and obviously description of Iranian populations was included without language and time limitation. In addition, the papers with the following criteria were excluded: studies which reported prevalence rate based on pathological data, studies with insufficient sample size, case reports, reviews, letters, and posters or conference papers.

QUALITY ASSESSMENT

In order to assess the quality and relevance of the references, a checklist prepared by The Joanna Briggs Institute (JBI) was used²⁰. The purpose of this appraisal is to evaluate the methodological quality of a study and to determine the extent which a study has addressed the possibility of bias in its design, conduct and analysis.

RISK OF BIAS ACROSS STUDIES

Random-effect model was used for minimizing risk of bias across the studies^{21,22}.

STATISTICAL ANALYSIS

All the analysis was conducted using STATA software, version 12 (Stata Corp. LP, College Station, TX, USA). Statistical heterogeneity was assessed by Cochran's Q statistic (with a significance level of $p \leq 0.1$) and I^2 statistic (with a significance level of $I^2 \geq 50\%$). In the presence of significant heterogeneity, the meta-analysis was done by random-effect model (with inverse variance method). On the other hand, in the case with no evidence of heterogeneity ($p > 0.1$ and $I^2 < 50\%$), fixed-effect model was performed.

RESULTS

DESCRIPTION OF LITERATURE SEARCH

The literature searches yielded 226 potentially relevant studies from the primary searches. In total, 151 studies entered into the second stage of evaluation based on inclusion criteria. Some studies were excluded for the following reasons: irrelevant studies ($n=76$), incorrect populations ($n=16$), duplicate studies ($n=4$), and insufficient data ($n=19$). Finally, 29 unique studies were included in this systematic review and meta-analysis. The search process and study selection base on PRISMA flowchart in this systematic review has been outlined in Figure 1.

DESCRIPTION OF THE INCLUDED STUDIES

According to the geographical locations, four studies were conducted in Fars province²³⁻²⁶, two in Ardabil province^{27, 28}, two in Kerman province^{29, 30}, one in Mazandaran province³¹, one in Golestan province³², one in Semnan province³³, one in East Azerbaijan province³⁴, one in Yazd province³⁵, one in Sistan and Baluchestan province³⁶, one in Khuzestan province³⁷, one in Tehran metropolis³⁸, one in Shahroud city³⁹, one in Iranian immigrants to Sweden and Iranian residents in Sweden⁴⁰, one in three province at Caspian sea (Guilan, Mazandaran, and Golestan)⁴¹, and ten in all states of Iran⁴²⁻⁵¹. The basic characteristics of the included studies have been summarized in Table 1.

THE RESULTS OF INDIVIDUAL STUDIES

The results showed the male to female sex ASR ratio is 3.9. The highest ASR was reported from Mazandaran province³¹ for males (18.5 per 100,000) and from Khuzestan province between 2002 and 2009³⁷ for females (2.9 per 100,000), while the lowest ASR was related to Sistan and Baluchestan province between 2004 and 2009³⁶ among males (2.1 per 100,000) and Fars province between 1990 and 2005²³ among females (0.4 per 100,000).

THE RESULTS OF META-ANALYSIS

The ASR of BC was 10.92, 95% CI (9.88-11.96) for males and 2.80, 95% CI (2.47-3.13) for females. The heterogeneity of the studies was demonstrated by Cochran's test ($Q=830.95$, $df=54$, $I^2=93.5\%$, $p<0.001$) for males and ($Q=132.54$, $df=36$, $I^2=72.8\%$, $p<0.001$) for females. The results of the random-effect meta-analyses for ASRs of BC for males and females have been represented in Figure 2 and 3, respectively.

PUBLICATION BIAS

Publication bias was assessed using Egger's tests⁵². Results of Egger's tests showed lack of publication bias ($p=0.137$ for males and $p=0.342$ for females).

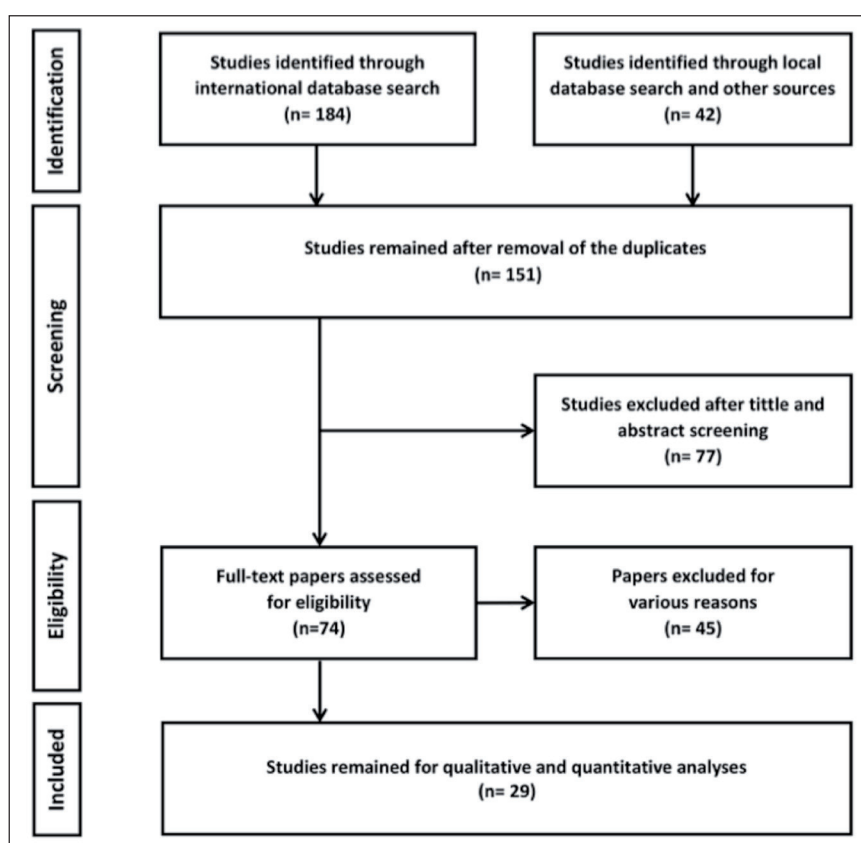


Fig. 1. Flowchart of the included eligible studies in the systematic review.

TABLE 1. Basic characteristics of the studies included in the review.

<i>Order</i>	<i>Author, Year</i>	<i>Time period</i>	<i>Location</i>	<i>Sample size</i>	<i>ASR (Males)</i>	<i>ASR (Females)</i>	<i>Quality Level</i>
1	Sadjadi et al ²⁷	1996-1999	Ardabil	-	7.6	1.8	Medium
2	Babaei et al ³³	1996-2001	Semnan	-	7.2	3.0	Low
3	Sadjadi et al ⁴²	2002	Iran	1677	8.0	-	Medium
4	Sadjadi et al ²⁹	1996-2000	Kerman	290	6.7	1.6	Medium
5	Mehrabani et al ²³	1990-2005	Fars	-	2.6	0.4	Low
6	Mousavi et al ⁵¹	2005-2006	Iran	3936	11.5	2.9	Medium
7	Somi et al ³⁴	2006-2007	East Azerbaijan	295	15.7	3.7	Medium
8	Mohagheghi et al ³⁸	1998-2001	Tehran	1802	13.3	3.8	High
9	Babaei et al ²⁸	2004-2006	Ardabil	219	13.1	2.5	Medium
10	Mousavi et al ⁴³	2003-2004	Iran	2745	8.3	2.1	High
		2004-2005	Iran	3301	9.9	2.5	
11	Mousavi et al ⁴⁰	1996-2006	IIS	56	17.7	4.1	Medium
		1996-2006	IRS	4052	11.7	3.0	
12	Masoompour et al ²⁴	1998-2002	Fars	540	6.8	1.9	Medium
13	Roshandel et al ³²	2004-2008	Golestan	222	8.7	-	Medium
14	Akbarzadeh et al ³¹	For three years	Mazandaran	310	18.5	3.6	Low
15	Fateh et al ³⁹	2000-2010	Shahrud	-	9.4	3.2	Medium
16	Talaiezhadeh et al ³⁷	2002-2009	Khuzestan	1255	10.7	4.1	Medium
17	Farahmand et al ²⁶	2003-2008	Fars	1828	12.7	2.7	Medium
18	Roshandel et al ⁴⁴	For five years	Iran	-	13.2	3.4	Medium
19	Basiri et al ⁴⁵	2003-2009	Iran 2003	2745	8.3	2.1	High
			Iran 2009	4601	12.6	3.3	
20	Vakili et al ³⁵	2005-2009	Yazd 2005	344	10.0	-	Medium
			Yazd 2006		10.2	-	
			Yazd 2007		12.6	-	
			Yazd 2008		9.8	-	
			Yazd 2009		15.9	-	

Continued

TABLE 1 (CONTINUED). Basic characteristics of the studies included in the review.

<i>Order</i>	<i>Author, Year</i>	<i>Time period</i>	<i>Location</i>	<i>Sample size</i>	<i>ASR (Males)</i>	<i>ASR (Females)</i>	<i>Quality Level</i>
21	Koohi et al ⁴⁶	2003-2009	Iran 2003	2745	8.3	2.1	Medium
			Iran 2004	3301	9.9	2.5	
			Iran 2005	3936	11.3	2.9	
			Iran 2006	4077	11.7	3.0	
			Iran 2007	4398	13.0	3.3	
			Iran 2008	4840	14.5	3.8	
			Iran 2009	4601	12.6	3.3	
22	Keyghobadi et al ³⁰	2004-2009	Kerman 2004	826	7.7	-	Medium
			Kerman 2005		9.7	-	
			Kerman 2006		9.4	-	
			Kerman 2007		11.2	-	
			Kerman 2008		13.2	-	
			Kerman 2009		14.7	-	
23	Rafiemanesh et al ³⁶	2004-2009	SB	119	2.1	-	Medium
24	Pakzad et al ⁴⁷	2012	Iran	5343	13.2	3.4	Medium
25	Masoompour et al ²⁵	1985-1989	Fars	-	7.5	2.0	High
		1998-2002			6.8	1.9	
		2007-2010			15.6	3.93	
26	Enayatrad et al ⁴⁸	2004-2008	Iran 2004	41169	11.3	2.9	Medium
			Iran 2005		11.7	2.9	
			Iran 2006		13.0	3.3	
			Iran 2007		14.4	3.8	
			Iran 2008		12.6	3.3	
27	Amori et al ⁴⁹	2004-2008	Iran	-	11.2	2.5	Medium
28	Salehiniya et al ⁴¹	2004-2009	Mazandaran	-	9.8	-	
			Guilan	-	15.4	-	
			Golestan	-	6.8	-	
29	Almasi et al ⁵⁰	2012	Iran	5343	13.2	3.4	Medium

IIS; Iranian immigrants to Sweden, IRS; Iranian residents in Sweden, SB; Sistan and Baluchestan.



DISCUSSION

Cancer is the third most common cause of death in Iran⁵³. So far, few studies have been conducted on the epidemiology of cancer in developing countries like Iran¹⁷. Results of the present study indicated the ASR of BC among Iranian men (10.91 per 100,000) is lower than other parts of Asia. However, some Asian countries such as Lebanon (29.1 per 100,000), Turkey (28.7 per 100,000), and Armenia (27.3 per 100,000) have high ASRs. Moreover, some other countries like Bhutan (1.1 per 100,000), Vietnam (1.8 per 100,000), and Mongolia (2.2 per 100,000) have the lowest ASRs⁴⁷. Based on the results of the present study, the ASR of BC among Iranian women was lower than that of Iranian men (2.79 per 100,000). In spite of that, some Asian countries such as Lebanon (6.1 per 100,000), Iraq (5.2 per 100,000), and Israel (4.3 per 100,000) have high ASRs. These findings indicate BC in Asia is more common among men compared to women. Also, some countries such as Maldives and Brunei

(almost 0 in 100,000), and Yemen (0.3 per 100,000) have the lowest ASRs⁴⁷. Internationally, the first three countries with the highest ASR of BC are Belgium (17.5 per 100,000), Lebanon (16.6 per 100,000), and Malta (15.8 per 100,000)⁵⁴. Studies have confirmed incidence rate of BC in the European and North American countries has decreased, while it has been rising in some Asian countries⁵⁵. This may be due to the differences in the distribution of risk factors of BC in different parts of the world³. For instance, the rate of tobacco and harmful chemicals consumption is declined in developed countries, while this trend has been growing in developing countries^{56, 57}. This can lead to an increased risk of developing certain cancers including BC⁵⁸. Moreover, the significant relation between cigarette smoking and BC incidence has been also confirmed in developing countries¹⁴. There is a strong association between current smokers and BC incidence compared to never-smokers. A high proportion of male BC cases has been attributed to smoking⁵⁹. Additionally, a significant relationship

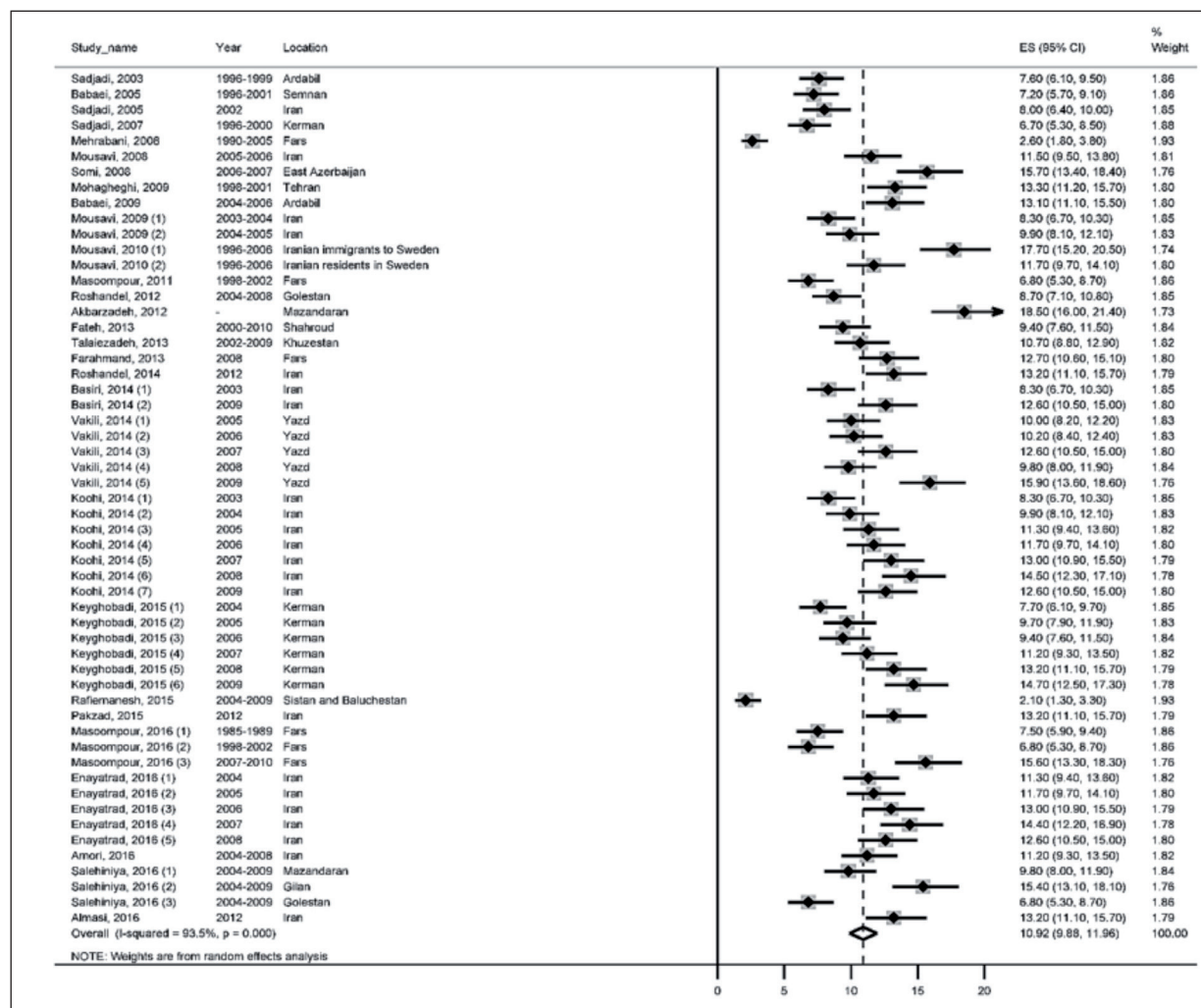


Fig. 2. Forest plot of the random-effect meta-analysis for ASR of BC among men in Iran.

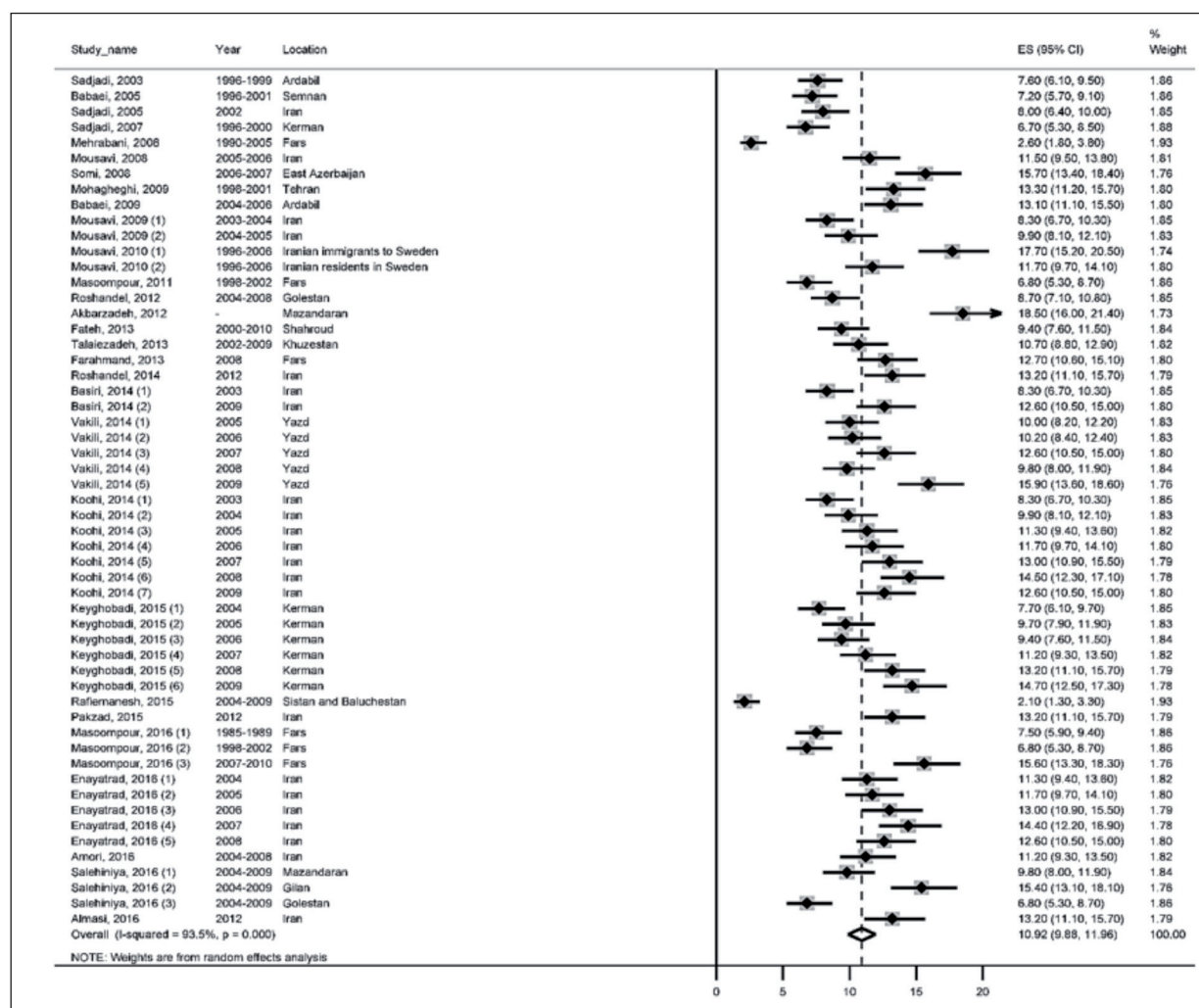


Fig. 3. Forest plot of the random-effect meta-analysis for ASR of BC among women in Iran.

was identified between human development index (HDI) and ASR of BC⁵⁴. The ecological analyses also showed that fruit consumption has a protective role in developing BC⁶⁰. In a meta-analysis, BC relative risk was estimated to be 0.8 (95% CI: 0.7 - 1.0) for population with high levels of fruit consumption⁶¹. On the other hand, no significant association between BMI and physical activity levels, and BC risk was observed⁶². Results of the study showed the highest ASR of BC among Iranian men is observed in Mazandaran province (18.5 per 100,000). The high prevalence of the risk factors and exposures in one region compared to another is one of the most important reasons of different BC incidence. Cigarette smoking, exposure to toxins and pesticides, and some occupations such as driving and hairdressing are identified to be associated with the high incidence of BC⁶³⁻⁶⁶. Mazandaran province, which has the highest ASR of BC among Iranian men, is one of the richest agricultural areas with high use of toxins and pesticides^{67,68}. There is also strong association between

smoking and risk of BC in north states of Iran⁶⁰. Moreover, it has been shown race, environmental exposures, family history, chronic urinary tract infection, and artificial sweeteners have no meaningful effect on BC incidence⁶⁹⁻⁷¹. The results of present study also indicated the highest ASR of BC among Iranian women is observed in Khuzestan province (2.79 per 100,000). This can be attributed to the environmental exposures to BC risk factors, the presence of diseases including high prevalence of schistosomiasis, cigarette, and hookah smoking among People living in this area⁷²⁻⁷⁴. This study showed that the lowest ASR of BC among Iranian men is observed in Sistan and Baluchestan province (2.1 per 100,000). The low incidence rate of BC in this province can be related to the demographic characteristics of people living in this area, differences in lifestyle, and the presence of other types of diseases and cancers^{75,76}. The incidence rates of gastric, skin, and blood cancers are high among men in Sistan and Baluchestan province³⁶. It has been shown that fruit consumption is associated with low



BC incidence in Sistan and Baluchestan province⁶⁰. The lowest ASR of BC among Iranian women is observed in Fars province (0.4 per 100,000). The low ASR in this province can be attributed to lower exposure of women to BC risk factors including cigarette smoking, environmental and occupational exposure to pesticides and toxins, and existence of other diseases associated with BC^{25, 77}.

CONCLUSIONS

The ASR of BC in Iran was lower compared to other parts of the world. However, further studies are necessary to outline the exact incidence rate and the trend of BC in Iran.

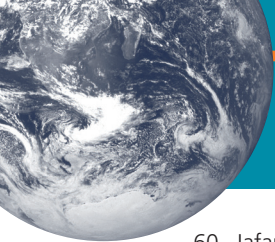
CONFLICT OF INTEREST

None declared.

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