

Incidence and mortality rate of cervix cancer in Iran from 1990 to 2016: A systematic review and meta-analysis

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Objective Cervix cancer (CC) is one of the major health problems among Iranian women and elsewhere around the world. Considering the importance of this cancer, this study was conducted to determine the age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) of CC in Iran.

Methods A search was conducted using international databases (Medline/PubMed, ProQuest, Scopus, Embase and ISI/web of knowledge), and national databases (Scientific Information Database, MagIran, IranMedex, and IranDoc). This systematic review was carried out according to the preferred reporting items for systematic reviews and meta-analyses check list in 2018. Thereafter, Persian and English language papers referring to the ASIR and ASMR of CC in Iran were included. Data were independently extracted by two reviewers. The Joanna Briggs checklist was carried out to evaluate the quality of studies.

Result A total of 522 papers were obtained in the initial search of the databases, and 25 articles were included to the review by further refinement and screening. Based on the random-effect model, the ASIR and ASMR of CC in Iran was 2.14 per 100,000, 95% CI (1.89–2.38) and 0.93 per 100,000, 95% CI (0.81–1.05), respectively.

Conclusion The incidence and mortality of CC in Iran was lower than other parts of the world. It should be noted that because of the high heterogeneity of the results of this study, we must judge with caution regarding the results.

Keywords incidence, mortality, cervical cancers, Iran, systematic review

Introduction

Today, cancer is one of the major health problems in Iran and in the rest of the world.¹ The findings revealed that female genital cancers are the fourth most common malignancy in women.^{2,3} The incidence rate and prevalence of female genital cancers in various parts of the world is different. According to GLOBOCAN 2012, the incidence of age-related cervical cancer is 13.1 per 100 000 and the standardized death rate is 6.9 per 100 000 population.¹ Cervix cancer (CC) is the seventh common among all other one, although in some parts of the world, such as Africa and South Asia, it is the first cause of cancer deaths.^{4,5} Among women in developing countries, this malignancy is one of the most important causes of female mortality and after breast cancer, it is the most frequent malignancy.^{6,7} CC is not only the most common and prevalent malignancy among women in many developing countries, but also the social significance of the disease becomes more pronounced because of their younger age at death.⁸ Certainly, for some reasons, such as having a long period before the invasion, the existence of a screening program and the availability of appropriate treatment for primary lesions, this cancer can be prevented.⁹ In epidemiology and demography, most rates, such as the incidence, prevalence, and morbidity are strongly related to age. This is also true for many types of cancers. For different purposes, age-specific comparisons may be helpful. However, the comparison of crude age-specific rates over time and between populations may be highly misleading if the age

composition of the compared population is different.¹⁰ For this reason, standardization is important when comparing disease rates between regions or countries and is widely used in cancer research. Age-standardized rate is a summary amount that will be observed for a population, provided that the age-specific rate of the population and the age composition of the population should be considered the same as the reference population (standard population).¹¹ Generally, genital cancers are one of the most common causes of female mortality. Detection and timely treatment of these cancers can increase women's longevity.¹² The first step is to control the burden of disease related to cancers in any community, recognizing their status in the population, as well as collecting information about the incidence, type, and location of cancers.¹³ Although organized review studies have been conducted on some of the risk factors for these cancers¹⁴ a comprehensive, structured review of ASIR and ASMR of CC, has not yet been conducted in Iran. Therefore, considering the above-mentioned points and the importance of this cancer, this study was conducted with the aim of estimating the standardized incidence and mortality rate of cervix cancer in Iran.

Materials and Methods

This study is a systematic and meta-analysis of the incidence and mortality of CC in Iran which was designed in 2018.

The methodology of this study is based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist.¹⁵

Search Strategy

In September 2018, the researchers examined six international databases Medline/PubMed, ProQuest, Scopus, Embase, ScienceDirect and Google Scholar, and four Iranian sites SID, MagIran, IranMedex and IranDoc. Selected keywords for international databases include “Gynecological cancer”, “Female genital cancer”, “Cervix”, “Cervix cancer”, Cervix neoplasms, “Cervix tumor”, “Cancer of cervix”, “Neoplasms of the cervix”, “Incidence”, “Epidemiology”, “Occurrence”, and “Iran”. The collected data entered the EndNote X7 software, and duplicate articles were automatically deleted. It is worth to mention here that two researchers explored articles individually.

Inclusion and Exclusion Criteria

Studies that clearly reported the incidence and mortality rate of CC in Iran were analyzed. On the other hand, the studies that reported the incidence with insufficient sample sizes, as well as posters presented in the conferences were excluded.

Quality Assessment

To check and control the quality of the articles, the checklist used by the Joanna Briggs Institute was used. This tool consists of nine questions that are categorized as “Yes, No, Unclear, and Not Used.” The purpose of this tool is to assess the methodological quality of studies, and ways to achieve and identify the errors in studies, design, implementation, and analysis of data. The quality assessment results were presented in Table 1.

Screening Studies

Initial research was conducted by two people (first and second authors). Screening of studies, extraction of results, and also the quality control of articles was evaluated separately by two individuals (first and second authors). If there was no match between the two, the supervisor of the team (responsible author) would announce the final comment on that article.

Statistical Analysis

The heterogeneity of the studies was evaluated by Cochran test (with significance <0.1) and its composition using statistics I^2 . In the case of heterogeneity, the random effects model was used with the inverse-variance method and in the absence of

Table 1. JBI critical appraisal checklist applied for included studies in the systematic review

Author name (year)	Q. 1	Q. 2	Q. 3	Q. 4	Q. 5	Q. 6	Q. 7	Q. 8	Q. 9
Saalabian (1990)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Sadjadi (2003)	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No
Babai (2005)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Sadjadi (2005)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Fallah (2007)	Yes	No	No	Unclear	Yes	Yes	No	Yes	Yes
Sadjadi (2007)	Yes	Yes	Yes	Unclear	Yes	Yes	No	No	Yes
Mehrabani (2008)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Unclear
Somi (2008)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Unclear
Mohagheghi (2009)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Unclear
Mousavi (2009)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Babaei (2009)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Masoompour (2011)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Almasi (2012)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Fateh (2013)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Khorasanizadeh (2013)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Arab (2014)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Arab (2014)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Unclear
Taheri (2014)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Unclear
Sharifian (2014)	Yes	Yes	No	Yes	Yes	No	Yes	No	Unclear
Rahimi (2015)	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
Masoompour (2016)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Almasi (2016)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Singh (2012)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Unclear
Khorasanizadeh (2013)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Unclear

Q. 1: Samples were representative?

Q. 2: Participants were appropriately recruited?

Q. 3: Sample size was adequate?

Q. 4: Study subjects and the setting were described?

Q. 5: Data analysis was conducted?

Q. 6: Objective, standard criteria, and reliably were used?

Q. 7: Appropriate statistical analyses were used?

Q. 8: Confounding factors, subgroups, and differences were identified and accounted?

Q. 9: Subpopulations were identified using objective criteria?

heterogeneity, a fixed-effect model was used. All analyses were performed by the STATA version 12 software (Stata Corp LP, College Station, TX, USA).

Results

Description of Literature Search

After searching for all international and domestic databases, 564 articles were found that, after removing repetitive articles, 489 articles were entered into the review phase in terms of title and abstract. After reviewing the titles and abstracts of articles, 57 articles joined to the next stage. At this stage, the full text of the articles was examined and 27 articles considered for the final analysis. In the screening stages of studies, some articles were excluded for a variety of reasons, which included an unrelated topic (327 cases), an unrelated population (31 cases), and repeated results (four cases). The flowchart of the studies was presented in Fig. 1.

Description of Included Studies

The included studies¹⁶⁻⁴⁰ were published from 1990 to 2016. The main characteristics of the selected studies have been represented in Table 2.

ASIR of Cervix Cancer

The highest ASIR of CC (4.97 per 100,000) from Golestan province between 2004 and 2010 and the lowest ASIR (0.4 per 100,000) from Ardebil province between 1996 and 1999 was reported.

ASMR of Cervix Cancer

The highest ASMR of CC (0.9.9 per 100,000) from southern Khorasan province between 2003 and 2005 and the lowest ASMR (0.4 per 100,000) from Sistan and Baluchistan province between 2003 and 2005 was reported.

Results of Meta-analysis

Due to the high heterogeneity of the studies, the random effects model was used. Thus, the ASIR and ASMR of CC in Iran was

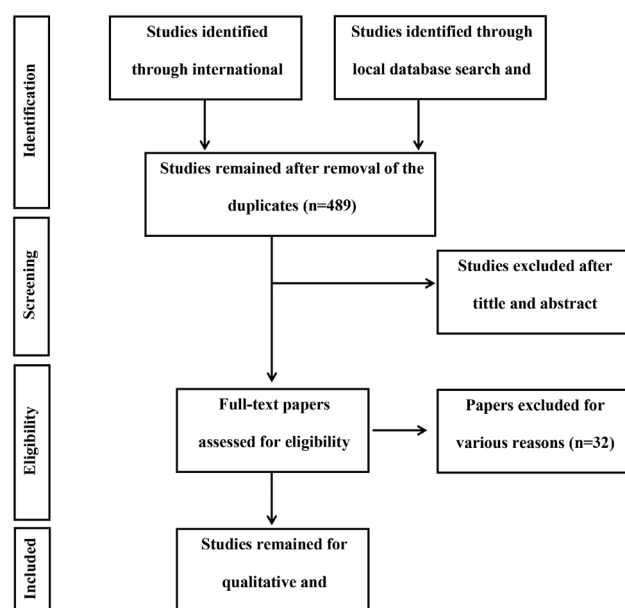


Fig. 1 Flowchart of the included eligible studies in systematic review.

Table 2. Characteristics of the included articles in the study

Author name (year)	Study region	Time period	ASIR	ASMR
Saalabian (1990)	Fars	1985–1989	2.30	-
Sadjadi (2003)	Ardabil	1996–1999	0.4	-
Babai (2005)	Semnan	1998–2002	1.08	-
Sadjadi (2005)	Iran (All area)	2002	4.5	-
Fallah (2007)	Ardabil	1996–2000	0.93	-
	Gilan		1.84	
	Mazandaran		2.33	
	Golestan		2.76	
	Kerman		3.02	
Sadjadi (2007)	Kerman	1996–2000	1.4	-
Mehrabani (2008)	Fars	1990–2005	1.13	-
Somi (2008)	East Azerbaijan	2006–2007	1.87	-
Mohagheghi (2009)	Tehran	1998–2001	4.8	-
Mousavi (2009)	Ardabil	2003–2004	1.64	-
	Esfahan	2004–2005	1.90	
	Kerman	2005–2006	1.90	
	Golestan			
	Lorestan			
Mousavi (2009)	Iran (All area)	2003–2006	-	1.0
Babaei (2009)	Ardabil	2004–2006	1.4	-
Masoompour (2011)	Fars	1998–2002	1.5	-
Almasi (2012)	Fars	2003–2009	0.87	-
			1.07	
			1.2	
			1.1	
			3.55	
			3.66	
Fateh (2013)	Shahroud	2002–2010	1.80	-
Khorasanizadeh (2013)	Iran (All area)	2007	2.47	-
Arab (2014)	Iran (All area)	2004 and 2008	1.71 and 2.2	-
Arab (2014)	Iran (All area)	2005	1.4	-
Taheri (2014)	Golestan	2004–2010	4.97	-
Sharifian (2014)	Iran (All area)	2003–2009	-	-
Rahimi (2015)	Tehran	1998–2001	1.87	-
	Golestan	2004–2008	2.56	-
	East Azerbaijan	2006–2007	1.8	-
	Khuzestan	2002–2009	1.08	-
	Shahroud	2001–2010		
	Semnan	1998–2002		
Masoompour (2016)	Fars	2007–2010	2.55	-
Almasi (2016)	Iran (All area)	2012	2.8	1.2
Singh (2012)	Iran (All area)	2012	-	1.0
Khorasanizadeh (2013)	Iran (All area)	2003–2005	-	1.4
	East Azarbaijan		-	1.8
	West Azarbaijan		-	1.6
	Ardabile		-	0.5
	Isfahan		-	0.9
	Ilam		-	0.9

(Continued)

Table 2. Characteristics of the included articles in the study—
(Continued)

Author name (year)	Study region	Time period	ASIR	ASMR
	Bushehr		-	0.7
	Charmahal-bakhtiari		-	0.7
	North Khorasan		-	1.0
	Khorasan Razavi		-	0.5
	South Khorasan		-	1.9
	Khuzestan		-	1.1
	Zanjan		-	0.8
	Semnan		-	0.6
	Sistanbaluch-estan		-	0.3
	Fars		-	1.1
	Ghazvin		-	1.1
	Ghom		-	1.2
	Kohgiluyeh-boirahmad		-	0.5
	Kordestan		-	1.1
	Kermanshah		-	1.6
	Kerman		-	0.5
	Golestan		-	0.6
	Gilan		-	1.2
	Lorestan		-	0.5
	Mazandaran		-	0.8
	Markazi		-	0.8
	Hormozgan		-	1.2
	Hamedan		-	0.6
	Yazd		-	0.8

2.14 per 100,000, 95% CI (1.89–2.38) and 0.93 per 100,000, 95% CI (0.81–1.05), respectively. The results of the forest plot for incidence and mortality rate are shown in Figs. 2 and 3.

Subgroup Analysis

Due to the heterogeneity of the results, subgroups were analyzed based on the geographical region. According to the results of the analysis of subgroups, the highest ASIR of CC in the northern region was 2.97 (95% CI; 2.28–4.14) and the lowest in the northwestern region of the country was 1.28 (95% CI; 0.83–1.73).

The highest ASMR in Northwest provinces was 1.39 (95% CI; 0.74–2.04) and the lowest in the Southwest was 0.64 (95% CI; 0.46–0.81).

Meta-regression

Results of meta-regression manifested a significant association between publication year and ASIR of CC. Thus, year of study is a cause of variability in results (Regression coefficient = 0.038, $p = 0.011$). According to the results, an increasing survival rate across the study period was observed.

Due to the limitation of the number of reported years for ASMR, no meta-regression analysis was possible. Results of meta-regression has been shown in Fig. 4.

Publication Bias

The publication bias among the studies was evaluated using the Egger test. Based on the results, there was no publication

bias among the studies (Bias: 6.62, 95% CI = -1.79 to 15.06; $p = 0.107$ for ASMR, Bias: 3.65, 95% CI = -5.09 to 13.91; $p = 0.443$ for ASIR).

Discussion

Cancer is the third leading cause of death in Iran (41). There are few studies on the epidemiology of cancer among population of developing countries including Iran.^{6,10,42–47}

Based on the findings of this study, the ASIR of CC in Iran was 2.14 and ASMR was 0.93 per 100 000. In a study in Korea, the incidence of CC in the years 1993–2002 has declined from 19.0 to 15.1 per 100,000.⁴⁸ A research conducted in India represented that the ASIR of CC was 22.9 per 100,000.⁴⁹

Therefore, as it is observable, the incidence of CC in Iran differs from that of the world as well as in other countries and is at a lower level. One of the possible reasons for this is that the incidence of CC is related to sexual factors, fertility, as well as human papillomavirus, which has a lower prevalence in Islamic countries.²⁰ As an example, the overall incidence of female genital cancers in Qatar was 0.9 per 100,000.⁵⁰ In a study on female genital cancers in one of the major provinces of Iran, it was found that the relative frequency of CC in the period of 1391–1394 was declining, and one of the reasons is to perform a screening for early diagnosis of cervical cancer by testing Pap smears in the country.^{6,51}

In this study, the highest incidence of CC in the provinces of Golestan and Tehran and its lowest incidence was reported in Ardebil province between 1996 and 1999. According to the studies, changes in the age of marriage, sexual activity at an early age, the number of pregnancies and individual health associated with reproductive organs can be a factor in the incidence of CC.^{3,51} In our country, women are more likely to be married at an early age and have used contraceptive pill for a longer time. On the other hand, the prevalence of hepatitis B infection, which has regional varieties, may affect the incidence of CC. Therefore, the differences between regions can be due to the above-mentioned issues.⁵²

The probability of higher diagnostic errors in smaller cities due to less facilities and the possibility of referring patients with ovarian cancer from other provinces to Tehran (for more advanced diagnostic and therapeutic measures) can be effective in increasing the incidence rate in Tehran province.

Based on the results of this study, the mortality rate of this cancer at the age of 45–75 has a steady increase and after age 60 there is a sharp increase, suggesting that people with a higher average age may have a higher incidence of CC.⁵³

Accordingly, one of the reasons for the higher mortality of CC in Tehran than other provinces can be attributed to the difference in the mean age of women in these districts.⁵⁴ Another possible contributing factor is the contamination of air. There is a close relationship between air pollution and some of the cancers of women, including breast and cervical cancer.⁵⁵ The results of the study manifest that jobs with low sitting time or low energy consumption are associated with an increase in the incidence of breast, uterine, and ovarian cancer.⁵⁶

Strengths and Limitation of Study

The strengths of this study is that it is the first study with a wide range on the incidence and mortality of CC in Iran. Its limitations include lack of examination of dissertations, non-electronic, and non-printed sources, as well as the type of studies available in Iran. It should be mentioned that in the previous studies,

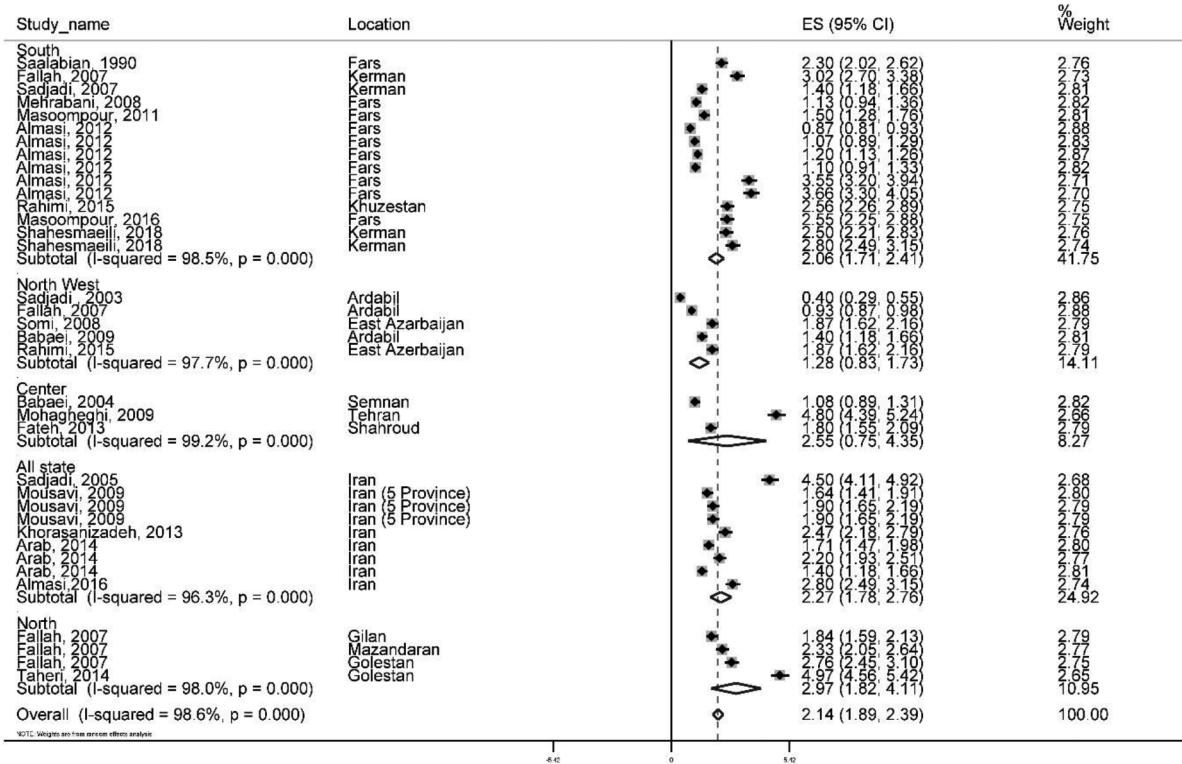


Fig. 2 Forest plot of the random-effect meta-analysis for age standardized incidence rates of cervix cancer in Iran.

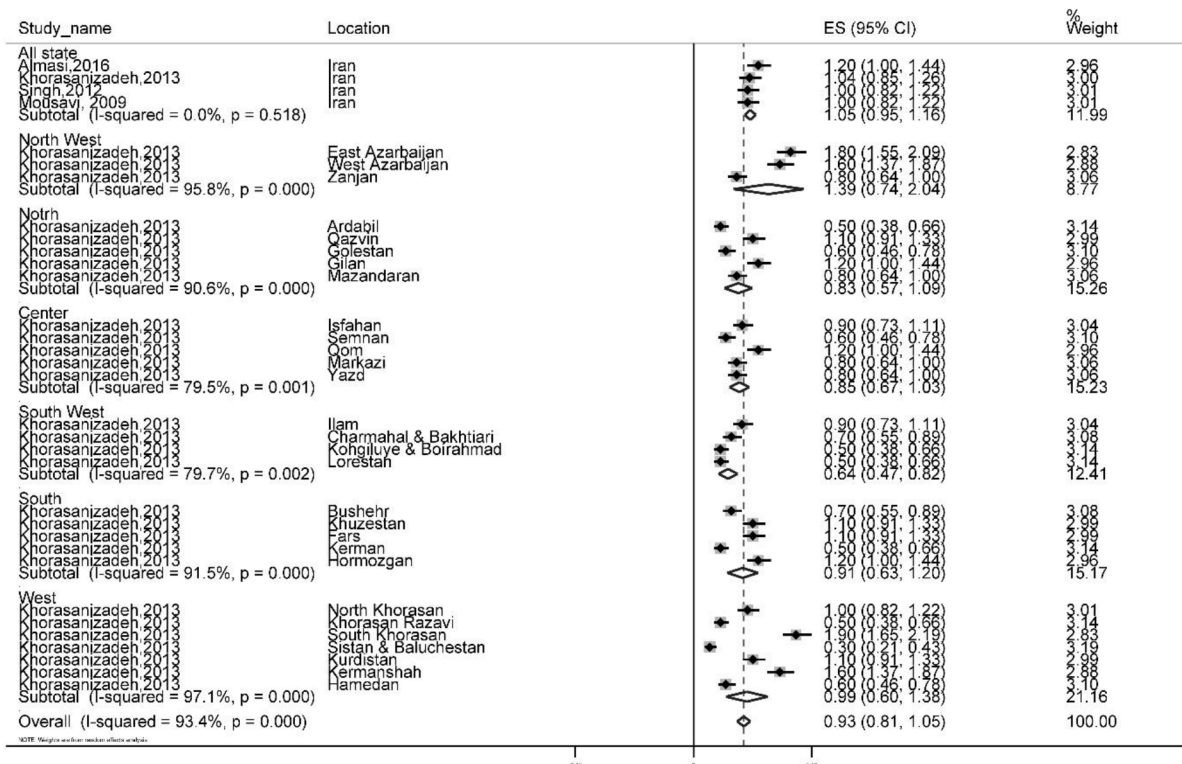


Fig. 3 Forest plot of the random-effect meta-analysis for age standardized mortality rates of cervix cancer in Iran.

CC were diverse, in other words, different studies classified this malignancy in a special way and eventually reported the standardized incidence of age. To give an instance, in some studies, CC has been reported in general, some have been divided into two or three distinct categories, and in some, only the uterine body cancer has been examined. Therefore, it was not possible to

compare the standardized incidence rates reported in all existing studies and it was decided to investigate studies that reported only cancer of the uterus. Another major limitation of our study was the lack of sufficient information on age composition and other information such as sample size and confidence interval that could be used to analyze.

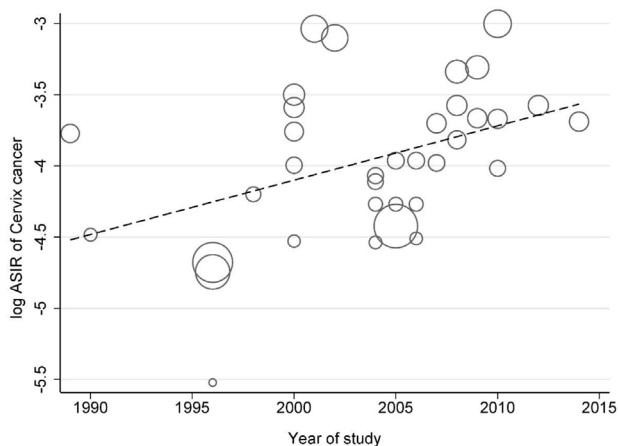


Fig. 4 Meta-regression plots of change in ASIR of cervix cancer according to changes in continuous study moderator's year.

Conclusion

Overall, according to the findings of this study, the ASIR and ASMR of CC in Iran is lower than in other countries of the world. On the other hand, given the heterogeneity observed in studies in different regions, the interpretation of the results should be more cautious.

Acknowledgments

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Conflicts of Interest

None. ■

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