**Review Article**
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# The Age-standardized Incidence Rate of Ovarian Cancer in Iranian Women: A Systematic Review and Meta-analysis

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## Abstract

**Background:** Cancer is the leading cause of morbidity and mortality worldwide. Among gynecological cancers, ovarian cancer is the first cause of cancer-related deaths. However, only a few studies have evaluated the age-standardized incidence rate of ovarian cancer in Iranian women. Therefore, the present study aims to systematically review the age-standardized incidence rate of ovarian cancer in Iran.

**Methods:** We systematically reviewed the literature that pertained to the incidence rate of ovarian cancer among Iranian women. In May 2016, we performed searches of national scientific databases that included SID, Magiran, IranMedex, and IranDoc. Searches of international databases included PubMed, Scopus, and ScienceDirect. The retrieved studies were then assessed according to the study's inclusion criteria.

**Results:** In this review, we included 14 from 115 articles obtained through searching national and international databases, grey literature, and hand searching. Based on the random effects model, the age-standardized incidence rate of ovarian cancer was 3.19 (95% CI: 2.78-3.59).

**Conclusion:** The study results indicated that the age-standardized incidence rate of ovarian cancer was considerably low in Iran. The registration methodology normally used by cancer registries has probably led to an underestimation of the incidence rate of ovarian cancer among Iranian women. Thus, we recommend the establishment of cancer registries that cover a broader population.

***Keywords:*** Ovarian neoplasm, Incidence, Iran, Systematic review, Meta-analysis

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## Introduction

Worldwide, cancer is the leading cause of morbidity and mortality whose global burden has increased considerably.[1,2] In 2008, most new cases of cancer and cancer deaths occurred in less developed countries.[3] In 2012, approximately 14.1 million new cancer cases occurred throughout the world; it has been estimated that approximately two-thirds of these patients died.[4]

Among gynecological cancers, ovarian cancer is one of the most prevalent malignancies.[5,6] Ovarian cancer refers to a group of malignancies that have tremendous histopathological diversity.[7] This type of cancer is the first cause of cancer deaths among gynecological cancers.[1,8] Based on age-standardized incidence rates, ovarian cancer is the ninth most common cancer among women. However, its mortality is higher compared to other cancers of female reproductive organs.[9] Nonetheless, there are large regional variations in the incidence of ovarian cancer in different parts of the world, with the highest incidence rates in Europe and North America.[10,11] In developed countries, ovarian cancer is the seventh most prevalent cancer and the sixth with respect to mortality.[10] In Iran, on the other hand, ovarian cancer has been ranked as the eighth cancer in terms of incidence, twelfth in mortality, and sixteenth for cancer burden.[7] Compared to the U.S. and other Western countries, Iran had less ovarian cancer cases. However, these cases occurred in younger age groups.[1] Additionally, the survival rate of ovarian cancer was 61% between 2000 and 2004. There were higher survival rates detected in younger women and some histological subtypes.[7]

In general, it is important to estimate the cancer incidence rate to obtain information about the disease risk. This information is of utmost importance for planning and evaluation of prevention as well as early detection of cancer.[5] However, only a few studies have evaluated the age-standardized incidence rate (ASR) of ovarian cancer. A number of these studies had small sample sizes. Thus, pooled estimates would be required to derive a good approximation of the incidence rate of ovarian cancer.

The present study aims to identify and summarize the studies that evaluate the ASR of ovarian cancer. The findings of this analysis may be useful for gynecologists and clinicians responsible for patients with ovarian cancer.

## Materials and Methods

This study was a systematic review of preliminary studies conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist.[12]

### *Search strategy of systematic reviews*

In order to systematically review the literature regarding the incidence rate of ovarian cancer among Iranian women, we searched national scientific databases (SID, Magiran, IranMedex, IranDoc) and international databases (PubMed, Scopus, ScienceDirect) during May 2016. In non-Iranian database searches, we used the word "Iran" in the title and abstract fields. We used the following keywords: "Ovary" OR "Ovarian Cancer" OR "Ovarian Neoplasm" OR "Ovarian Tumor" OR "Cancer of Ovary" OR "Cancer of the Ovary" AND "Incidence" OR "Occurrence" OR "Frequency" AND "Iran". The reference lists of the relevant full-text articles were then investigated to obtain all new and old studies that might have been overlooked in the initial search.

The studies identified through database searches were entered into an EndNote X7 library (Thomson Reuters Reference Manager) and any duplicate studies were automatically removed. Then, we scanned the titles and abstracts of the studies and excluded all ineligible studies according to the eligibility criteria. Next, the full texts of the eligible studies were obtained and scanned.

There were two independent investigators (A.M. and S.H.) who evaluated the studies. Disagreements were resolved by discussion and a third reviewer (A.R) was consulted in case of ongoing disagreement.

### *Inclusion and exclusion criteria*

We included studies that reported a clear description of the ASR of ovarian cancer and reports from Iranian women in the analysis.

$$\frac{\sum_i d_i \; w_i}{y_i}$$

Excluded were subtype-specific studies and those that reported the prevalence rate as well as abstracts, letters, and posters whose full investigations were not published. We calculated the ASR according to the following formula:[13]

Where: Subscript i reflects the age groups, di represents the numbers of cases, yi represents the number of person-years at risk, and wi represents the number of persons (or weight) in the age group "i" in the world standard population.

### *Statistical analysis*

The heterogeneity of the studies was assessed according to Cochran's Q statistics (with a significance level of $P \leq 0.1$) combined with $I^2$ statistic (with a significance level of >50%). In case of significant heterogeneity ($P \leq 0.1$ and I2≥50%), we used the random effects model with the inverse variance method. Otherwise, the fixed effect model was employed. All the analyses were conducted by using Stata software, version 11.2 (Stata Corp L.P., College Station, TX, USA).

## Results

### *Description of the literature search*

We assess the studies according to a standard process. In the identification stage, out of the 115 articles obtained through searching the national and international databases, grey literature, and hand searching, we excluded 27 articles due to overlap in the databases. In the screening stage, the 87 remaining articles were evaluated in terms

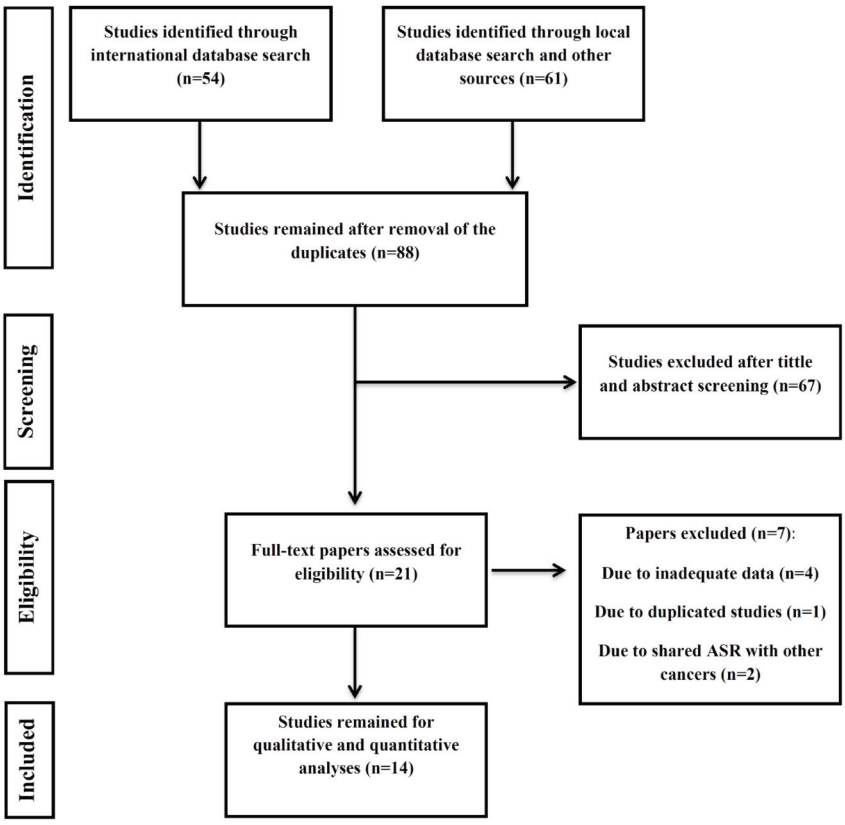


**Figure 1.** Flowchart of the included eligible studies for the age-standardized incidence rate (ASR) of ovarian cancer among Iranian women.

of title and abstract. We excluded 66 articles because they were not related to the research subject. In the eligibility stage, 21 full-text articles were reviewed according to the inclusion and exclusion criteria. In this stage, we excluded 7 articles because they either failed to provide relevant information or reported similar results. Finally, in the included stage, 14 studies[1,5,14-25] were considered for data extraction (Figure 1).

### *Description of the included studies*

After precise extraction of the required data, the results were summarized in an extraction table composed of authors, year, city, study period, and the ASR of ovarian cancer. Table 1 lists the characteristics of the included studies.

Among the studies entered into the analysis, two focused merely on ovarian cancer[1,5] whereas the others focused on all or several gynecological cancers, one of which was ovarian cancer.[14-25] Of note, all studies reported ASR for ovarian cancer. Based on the results, 3 studies[14,16,24] reported the ASR according to the population-based cancer registry (PBCR), while 11 studies reported this rate according to pathology-based or both population- and pathology-based cancer registries[1,5,15,17-23,25].

### *Individual study results*

The highest ASR of ovarian cancer was related to Tehran Province between 1998 and 2001 (6.5 per 100000), whereas the lowest rate was observed in Ardabil Province between 1996 and 1999 (0.8 per 100000).

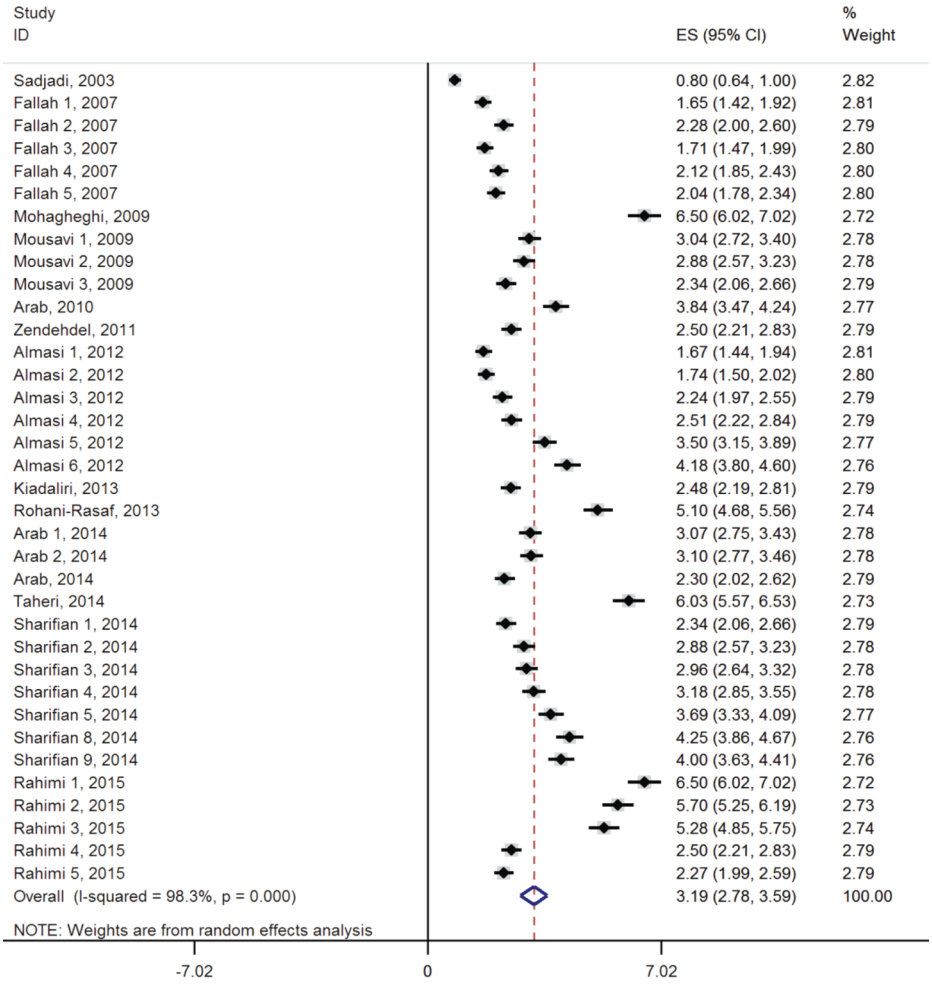


**Figure 2.** Forest plot of the random-effect meta-analysis for age-standardized incidence rates (ASR) of ovarian cancer in Iran.

**Table 1.** Characteristics of the investigated articles.

| | Author, year | Study region | Time period | Sample size | ASR |
|---|---|---|---|---|---|
| 1 | Sadjadi et al,[14] 2003 | Ardabil | 1996-1999 | 1309 | 0.8 |
| 2 | Fallah,[15] 2007 | Ardabil | 1996-2000 | 1405 | 1.65 |
| | | Guilan | | 3116 | 2.28 |
| | | Mazandaran | | 3399 | 1.71 |
| | | Golestan | | 1391 | 2.12 |
| | | Kerman | | 2391 | 2.04 |
| 3 | Mohagheghi et al,[16] 2009 | Tehran | 1998-2001 | 15773 | 6.5 |
| 4 | Mousavi et al,[17] 2009 | Ardabil | | | |
| | | Esfahan | 2003-2004 | 24495 | 3.04 |
| | | Kerman | 2004-2005 | 20473 | 2.88 |
| | | Golestan | 2005-2006 | 16849 | 2.34 |
| | | Lorestan | | | |
| 5 | Arab et al,[5] 2010 | Iran | 2004-2005 | 782 | 3.84 |
| 6 | Zendehdel et al,[18] 2011 | Iran | 2004-2006 | - | 2.5 |
| 7 | Almasi & Farahmand,[19] 2012 | Fars | 2003-2004 | 64 | 1.67 |
| | | | 2004-2005 | 67 | 1.74 |
| | | | 2005-2006 | 96 | 2.24 |
| | | | 2006-2007 | 120 | 2.51 |
| | | | 2007-2008 | 172 | 3.5 |
| | | | 2008-2009 | 221 | 4.18 |
| 8 | Kiadaliri,[20] 2013 | Iran | 2003-2009 | - | 2.48 |
| 9 | Rohani-Rasaf et al,[21] 2013 | Tehran | 2008 | - | 5.1 |
| 10 | Arab & Noghabaei,[22] 2014 | Iran | 2004 and 2008 | 24498 | 3.07 |
| | | | | - | 3.1 |
| 11 | Arab, Noghabaei & Kazemi,[23] 2014 | Iran | 2005 | 24498 | 2.3 |
| 12 | Taheri et al,[24] 2014 | Golestan | 2004-2010 | 6064 | 6.03 |
| 13 | Sharifian et al,[1] 2014 | Iran | 2003 | | 2.34 |
| | | | 2004 | | 2.88 |
| | | | 2005 | | 2.96 |
| | | | 2006 | - | 3.18 |
| | | | 2007 | | 3.69 |
| | | | 2008 | | 4.25 |
| | | | 2009 | | 4 |
| 14 | Rahimi et al,[25] 2015 | Tehran | 1998-2001 | | 6.5 |
| | | Golestan | 2004-2008 | | 5.7 |
| | | East Azerbaijan | 2006-2007 | - | 5.28 |
| | | Khuzestan | 2002-2009 | | 2.5 |
| | | Shahroud | 2001-2010 | | 2.27 |

### *The results of meta-analysis*

Based on the random effects model, the ASR of ovarian cancer was 3.19 (95% CI: 2.78-3.59). The results of the Cochran's Q test indicated the heterogeneity of the studies (Q=2043.55, df=35, $I^2$=98.3, $P$<0.001; Figure 2). Figure 2 shows the forest plot of the random-effect meta-analysis for ASR of ovarian cancer in Iran.

## Discussion

Based on World Health Organization (WHO) estimates in 2011, cancer deaths were more than coronary heart diseases and stroke. In 2012, ovarian cancer (239,000 cases and 152,000 deaths) was the seventh most prevalent cancer and the eighth cause of cancer death among women with 3.6% of the cases and 4.3% of deaths.[26] Because of changes in global demographic and epidemiological features, a consistent increase in the

burden of ovarian cancer is expected over the next decades, especially in low- and middle-income countries.[26,27] Thus far, in developing countries like Iran, few studies have been conducted on the incidence of cancer.[2,28]

In this meta-analysis, we reviewed 14 studies published between 2003 and 2015 to calculate the ASR of ovarian cancer. The findings revealed that the ASR of ovarian cancer was 3.19 per 100000 persons among Iranian women. Previous studies demonstrated an ASR of 6.1 among females worldwide in 2012, which was higher than reported in Iran. Based on Global Burden of Cancer Study (GLOBOCAN) in 2012, the highest incidence rates of ovarian cancer were related to more developed countries, which exceeded 7.5 per 100000, whereas the lowest rates were related to Sub-Saharan Africa at less than 5 per 100000.[26]

Generally, accurate estimation of cancer occurrence and outcomes is essential for planning and assessment of cancer control programs.[3,29,30] Accurate data should be available for calculating the sex- and age-specific incidence rates of cancer in each country. Yet, the accuracy of these rates differs in various countries according to the quality of the available data. For instance, high-quality data (including incidence and mortality) are available in Northern Europe and American countries. No data is available in most African countries and some populous Asian countries. Therefore, these countries use data from adjacent countries for estimation.[3] In country-specific estimates, the incidence rate of cancer is gathered from local sources (cancer registries) and, consequently, the results vary in different countries depending on the extent and accuracy of the available data. Nevertheless, changes in the incidence rates may be partially due to increase in the quality and availability of the data from cancer registries.

The results of the current study has indicated that the ASR of ovarian cancer was lower in Iran (3.19) compared to Asian countries (5.0) and Western Asian regions (5.3). This might be attributed to the fact that Iran is among the middle-income countries with a low incidence rate of ovarian cancer. Indeed, the data might have been recorded differently with respect to quality and availability. According to GLOBOCAN 2012, high-quality data were available with regards to the incidence rate of cancer in Iran (coverage <10%). Thus, any problems in the data might result from the quality of registration.

Based on the present study results, all the included studies have obtained their data from cancer registries (pathology-based, population-based, or both) or population census data. A PBCR more often covers small, subnational areas and only particular cities in developing countries.[26] Population-based cancer registry coverage comprised approximately 21% of the world's population in 2006, with sparse registration in Asia (8% of the total population) and Africa (11%).[3,30]

In the current study, the highest ASR of ovarian cancer (6.5 per 100000) was reported in Tehran Province between 1998 and 2001 based on population-based cancer registry,[16] while the lowest rate (0.8 per 100000) was reported from Ardabil Province between 1996 and 1999 based on PBCR14.

According to the previous studies, the risk of ovarian cancer decreased with increased numbers of pregnancies. Infertility was considered to be a risk factor for ovarian cancer.[31] Thus, different reproductive patterns in Ardabil (i.e., greater number of pregnancies, earlier age at first pregnancy, environmental conditions, older age at menarche) might justify the lower risk of ovarian cancer among women in this province.[32,33] Another reason for the lower incidence rate reported in Ardabil Province could be the difference in the time of the study. Generally, estimates reported in earlier periods should not be compared to current estimates[34-40] due to improvements in estimation methodology and change in data availability in terms of time and geographic coverage.[3] In a previous study, potential years of life lost (PYLL) up to the age of 64 years was expressed as the ASR per 100,000 persons. The results of that study demonstrated that ovarian cancer followed an ascending trend from

the mid-1960s to 1970s, but stabilized and showed a descending trend since the 1970s.[41]

The current meta-analysis has estimated the ASR of ovarian cancer in Iran. Our estimates will serve as a guide to clinicians to determine the most appropriate methods for management of their patients. These estimates will also be of tremendous value in counseling women and enabling them to make informed decisions about their health.

The main strength of this study was our use of the national data regarding the incidence rate of ovarian cancer in Iran. Additionally, we have assessed heterogeneity among the studies with Cochran's Q and $I^2$ statistics. $I^2$ statistics allows inclusion of different types of outcome data from a complex set of studies. Hence, by calculating $I^2$ in addition to Q-value, absence of heterogeneity could be demonstrated more reliably.

The weak point of this study was that we derived data on the incidence rate of ovarian cancer from PBCR. Although PBCR might cover the entire national population, more often it covers smaller, subnational areas, and some particular cities in developing countries.

The available evidence showed that the ASR of ovarian cancer was considerably lower in Iran compared to other parts of the world. This could be due to the fact that the registration methodology normally used by cancer registries might underestimate the incidence rates of ovarian cancer among Iranian women. Thus, we have recommended the establishment of cancer registries that cover more expansive populations. Further studies should be conducted on the ASR of ovarian cancer in Iranian women.

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## Conflict of Interest

No conflict of interest is declared.

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