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THE INCIDENCE OF NON-HODGKIN LYMPHOMA IN IRAN: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract – *Objective:* *Non-Hodgkin's lymphoma (NHL) is one of the common cancers of the blood. The present study is conducted to evaluate the incidence rates of NHL in Iran.*

Patients and Methods: *A systematic search was conducted on all published studies of NHL incidence using Medline/PubMed, Scopus, Embase, Web of sciences, and four Iranian databases (Scientific Information Database, MagIran, IranMedex, and IranDoc) until June 2018. This systematic review was done according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA).*

Results: *After first searching 262 potentially relevant studies was yielded. A total of 9 studies were included. The results of the random effect model were demonstrated the age-standardized rate (ASR) of NHL was 4.43, 95% CI (2.76 to 6.11) among males and 2.79, 95 % CI (1.71 to 3.88) among females.*

Conclusions: *In comparison with other geographical locations, the incidence of NHL is lower in Iran.*

KEYWORDS: *Incidence, Non-Hodgkin Lymphoma, Iran, Systematic review, Meta-analysis.*

INTRODUCTION

Cancer is currently the second leading cause of death worldwide, responsible for up to 9 million deaths in the world in 2018[1]. Non-Hodgkin's lymphoma (NHL) is a group of lymphoid-derived malignancies that are classified according to clinical and biological features[2,3]. Non-Hodgkin's cancer is one of the common cancers of the blood[4]. It is considered to be the eighth most common cancer in men and the eleventh most common cancer in women[5]. NHL includes 5.1 percent of all cancers and responsible for

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2.7 percent of cancer deaths[6]. The most commonly reported cases of the cancer include North America, Europe, and Oceania. ASR of this cancer is more common in men than men (6 per 100,000 for men and 4.1 per 100,000 for women)[7]. According to studies, the incidence of this cancer has increased in recent decades[8]. Known risk factors for this malignancy are limited. Possible risk factors for this cancer include family history, genetics, infectious agents, and exposure to chemicals and toxins[9,10]. According to studies in the United States and Canada, a genetic link has been identified between the incidence of this cancer and multiple gene polymorphisms[11]. Another risk factor for this cancer is the role of infectious agents such as HIV, Epstein-Barr virus, Helicobacter pylori, and Human T-cell leukemia virus in this cancer[12-15]. According to various studies, there is a strong association between the HIV virus and the incidence of NHL[16]. The HIV virus, by suppressing the immune system, provides very good conditions for the onset of this cancer (17). Since the introduction of new therapies for AIDS, such as HAART, the incidence of this cancer has been reduced in people with AIDS, which can justify the HIV-causing role of the disease[18,19]. The first study on epidemiology of cancers in Iran dates back to the 1970s. A study aimed at surveying the types of cancers in the Caspian littoral region[20]. Studies on the epidemiology of cancers in Iran are limited. Most studies have reported the total number of cancer cases in different regions of Iran or NHL risk factors in some occupations. In a study in Iran about the risk factors of this disease in people working in different industries, Welders, metal workers, founders, and aluminum workers had higher odds of NHL, On the other hand, administrative staff was at lower risk for the NHL[21]. There has not been a comprehensive study on the epidemiology of NHL in Iran. Therefore, the aim of this study was to evaluate the age-standardized incidence rate of NHL cancer in Iran by a systematic review.

MATERIALS AND METHODS

The systematic review and meta-analysis were designed in 2018 and undertaken in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline[22].

Search strategy of systematic reviews

A literature search of published studies was conducted using international databases Medline/PubMed, web of sciences, Scopus, and Embase 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 until June 2018. The medical subject headings (MeSH) keywords included "Non-Hodgkin Lymphoma", "NHL", "Non-Hodgkin cancer", "Non-Hodgkin neoplasm", "Non-Hodgkin tumor", "neoplasms of Non-Hodgkin", "epidemiology", "incidence", and "Iran". The obtained papers were imported into an EndNote X8 (Thomson Reuters, Carlsbad, CA, USA) library and the duplicates were removed. No language and time limitations were considered.

Inclusion and exclusion criteria

All studies with results of ASR of NHL 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, studies with inadequate sample size, and research articles (all type of conference abstracts, poster papers, letters, comments, and editorial).

Quality assessment

In order to assess the quality of the articles, a checklist prepared by The Joanna Briggs Institute (JBI) was used[23]. 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. All papers were evaluated on the basis of data relevance and methodological rigor. The results of Quality assessment presented in Table 1.

Risk of bias across studies

Random effect model was used for minimizing risk of bias across the studies[24,25].

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 $I^2 < 50\%$), fixed effect model was used.

Heterogeneity in meta-analysis refers to the variation in study outcomes between studies. The I^2 statistic describes the percentage of variation across studies that are due to heterogeneity rather than chance. When there is heterogeneity that cannot readily be explained, one analytical approach is to incorporate it into a random effects model. A random effects meta-analysis model involves an assumption that the effects being estimated in the different studies are not identical, but follow

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
Sadjadi et al[30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Babai et al[31]	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No
Sadjadi et al[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Mehrabani et al[28]	Yes	No	No	Unclear	Yes	Yes	No	Yes	Yes
Babaei et al[33]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Mohagheghi et al[34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Masoompour et al[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Roshandel et al[26]	No	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Almasi et al[27]	Yes	Yes	Yes	Unclear	Yes	Yes	No	No	Yes

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?

some distribution. The model represents the lack of knowledge about why real, or apparent, treatment effects differ by treating the differences as if they were random. The center of this symmetric distribution describes the average of the effects, while its width describes the degree of heterogeneity.

RESULTS

Description of literature search

The database, grey literature searches, and hand searching yielded 262 potentially relevant studies. In total, 205 unique studies were reviewed and 63 studies were entered into the second stage of evaluation. Overall, our review included 9 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=148), incorrect study population (n=28), duplicate study (n=4), and inadequate data (n=16). The flowchart of the included studies in this review has been shown in Figure 1.

Description of the included studies

The included studies were published from 2003 to 2016. Based on geographical locations, Two studies were conducted in all states of Iran[26,27], two in Fars Province[28,29], two in Ardabil Province[30,31], one in Kerman Province[32], one in Semnan Province[33], and one in Tehran metropolis[34]. All the studies have reported ASRs. The main characteristics of the selected studies have been presented in Table 2.

The results of individual studies

The highest ASR was reported from Tehran between 1998 and 2001 (7.1 per 100,000 for males and 4.8 per 100,000) for females (34). The lowest ASR was reported from Fars province between 1990 to 2005 (0.97 for males and 0.54 for females per 100,000)[28].

The results of meta-analysis

The results of the random effect model were demonstrated the age-standardized rate (ASR) of NHL was 4.43, 95% CI (2.76 to 6.11) among males and 2.79, 95 % CI (1.71 to 3.88) among females. Additionally, the results of Cochran's test showed the heterogeneity of the studies (Q 2320.0, df =8, I^2=98.7%, p<0.001) for males and (Q= 1422.7, df =7, I^2=99.5%, p<0.001) for females. The forest plots of the random-effect meta-analysis for ASR of NHL in Iran have been presented in Figure 2 and 3 for males and females, respectively.

Publication Bias

Publication bias was assessed using Egger's tests[45]. Results of Egger's tests showed lack of publication bias (p=0.345 for males and p= 0.412 for females).

DISCUSSION

Cancer is the third cause of death in Iran (36). Little studies have been done on the epidemiology of cancer in developing countries such as Iran (37-42). The result of the present study showed that ASR of NHL was low in Iranian men and women than the global average (4.43 per 100,000 for men and 2.79 for 100,000 for women). Compared to other Asian regions, Western Asia has a high ASR (7.8 in males and 5.6 in women), while in the South-Central Asia region (3.3 in males and 1.8 in males) has a lower incidence[43]. Worldwide in the countries of North America and Australia / New Zealand, the highest incidence was observed in men and women (14.6 and 14.3 per 100,000 in men, and 10.2 and 10.1 in 100,000 for women), and South-Central Asia and West Africa had the lowest ASR (3 and 3.7 per 100,000 in men, and 1.8 and 2.5 per 100,000 in women)[44]. This difference can be due to environmental contexts, diagnostic methods, risk

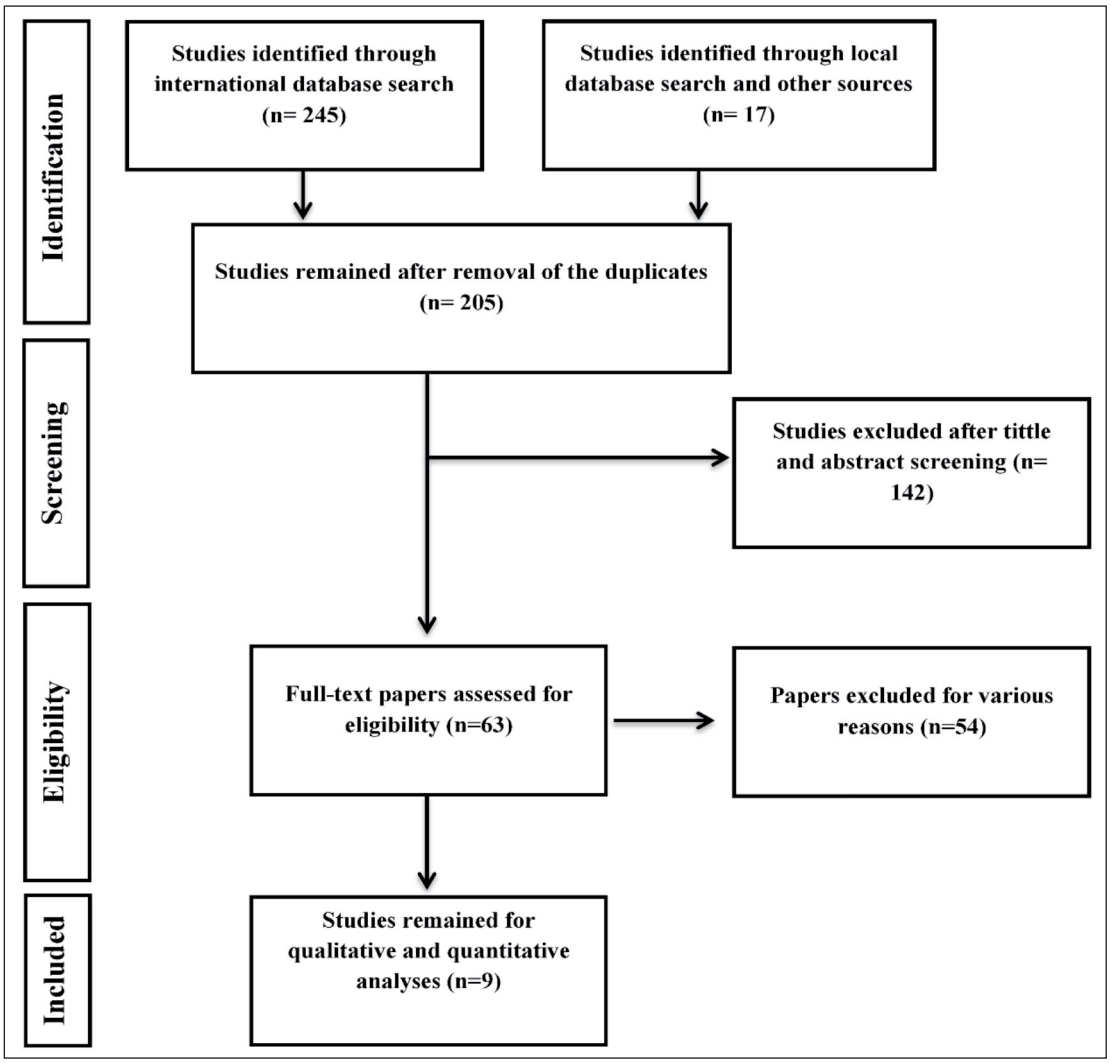

Fig. 1. Flowchart of the included eligible studies in systematic review.

factors and lifestyle[7]. One of the most important factors in the incidence of NHL is the role of infectious agents such as HIV, Epstein-Barr virus, Human T-cell leukemia virus and Helicobacter pylori[9,13,45]. Another important factor in the incidence of this cancer is ethnicity, which is more common in the United States in white than in other races[46]. Based on the results of our study, the highest ASR of NHL in Iranian men and women was in Tehran (7.1 per 100,000 for men and 4.8 per 100,000 for women). The high probability of NHL cancer in this area can be due to factors such as the high

TABLE 2. Basic characteristics of the studies included in the review.

Order	Author/Year	Time period	Location	ASR (Males)	ASR (Females)
1	Sadjadi et al[30]	1996-1999	Ardabil	2.60	1.00
2	Babaei et al[31]	1998-2002	Semnan	5.39	4.47
3	Sadjadi et al[32]	1996-2000	Kerman	5.80	2.80
4	Mehrabani et al[28]	1990-2005	Fars	0.97	0.54
5	Babaei et al[33]	2004-2006	Ardabil	4.00	-
6	Mohagheghi et al[34]	1998-2001	Tehran	7.10	4.80
7	Masoompour et al[29]	1998-2002	Fars	2.70	1.20
8	Roshandel et al[26]	2012	Iran	5.70	3.80
9	Almasi et al[27]	2012	Iran	5.70	3.80

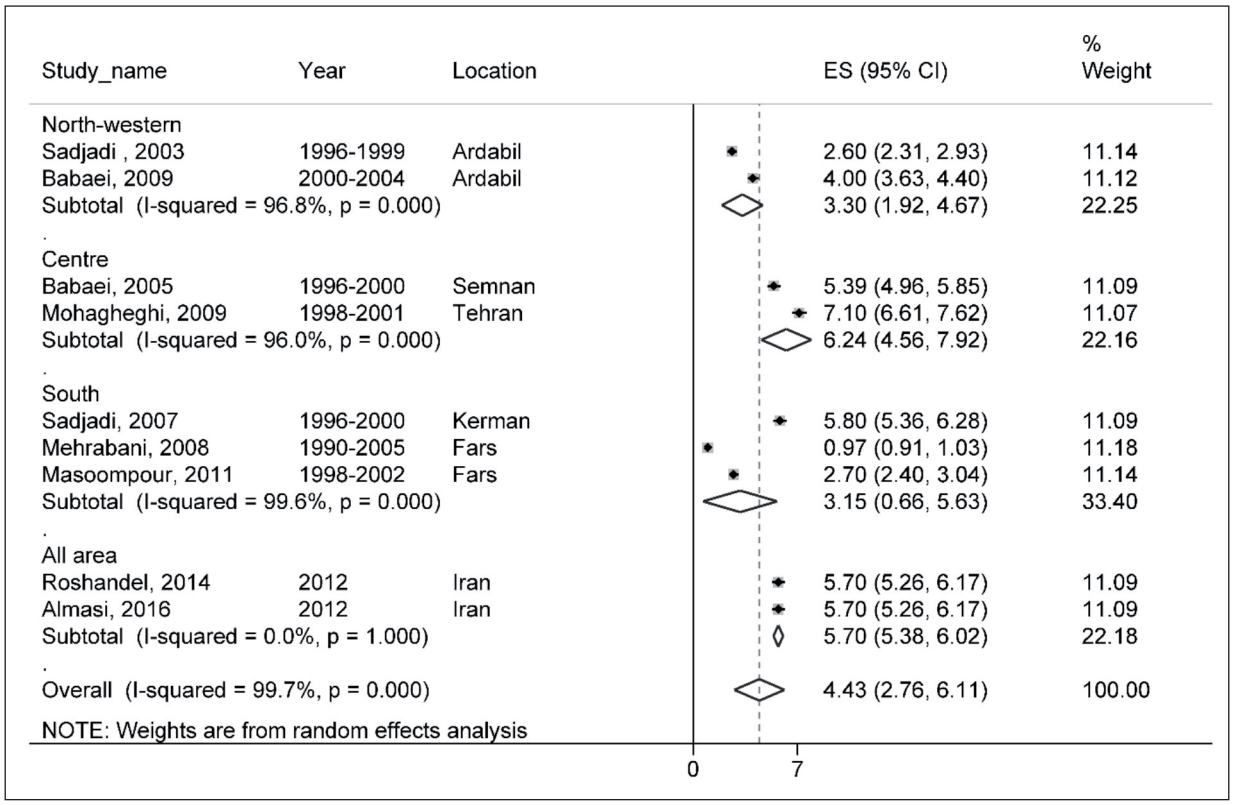

Fig. 2. Forest plot of the random-effect meta-analysis for ASRs of NHL in males in the Iran.

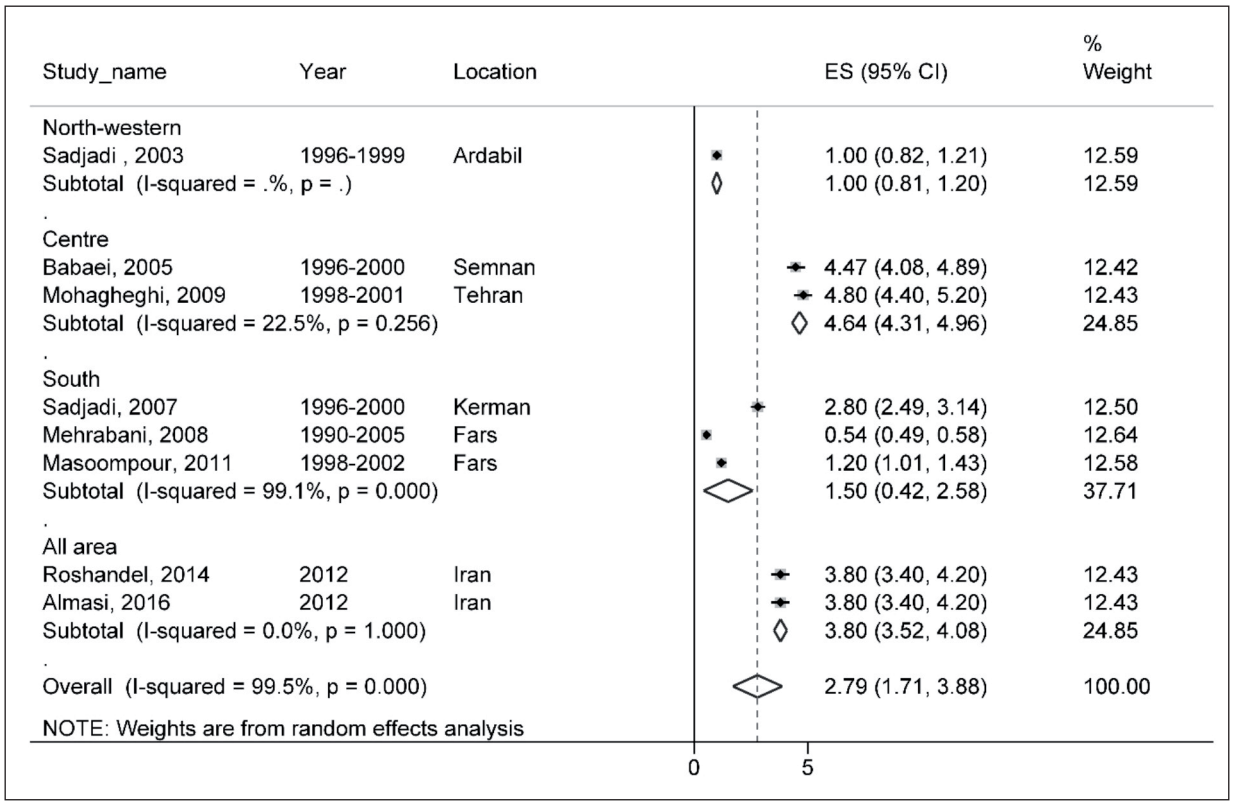

Fig. 3. Forest plot of the random-effect meta-analysis for ASRs of NHL in females in the Iran.

prevalence of HIV infection in other provinces, the high prevalence of exposure to environmental factors in various occupations and air pollution in the area. According to studies in Tehran, this province is one of the areas with the highest HIV prevalence in Iran[47-49]. Another potential risk factor that is seen in Tehran more than other areas is exposure to benzene. According to a study by Aminian et al[21], People working in some industries, such as metals (such as jewelry and aluminum), had higher odds of NHL in Tehran[21]. Other reasons that can be noted are better diagnostic methods in Tehran than in other parts of the country[50]. The results of our study showed that the lowest ASR of NHL in Iranian men and women was in Fars province (97.9 per 100 000 for men and 0.54 per 100 000 for women). Low incidence in this province can be attributed to the demographic characteristics of people living in this area, less exposure to possible risk factors, lifestyle, and other diseases and cancers[51-53]. Another possible reason for low NHL cancer in Fars is low levels of exposure to environmental contaminations, toxins and some infections associated with this cancer[54,55].

CONCLUSIONS

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

Conflict of Interest:

The Authors declare that they have no conflict of interests.

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