



The Incidence of Hepatocellular Carcinoma in Iran from 1996 to 2016: a Systematic Review and Meta-analysis

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Abstract

Purpose Hepatocellular carcinoma or liver cancer (LC) is one of most important cancer around the world. There are several reports about LC incidence from various Iranian locations with conflicting results. The present study aimed to accomplish a systematic review to estimate the accurate incidence rate of LC among Iranian people.

Methods This systematic review was performed based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist in 2018. A literature search was conducted using international databases (Medline/PubMed, Scopus, ScienceDirect, and Google Scholar) for English papers and national databases (Scientific Information Database, MagIran, IranMedex, and IranDoc) for Persian papers which estimated incidence rate of LC in any geographical area of Iran. The incidence rate of LC was calculated using random effect model.

Results Of 171 papers in the primary searches, 15 studies were included by advanced screening and refinement. The age-standardized rate (ASR) of LC was 1.66 (95% CI 1.49–1.83) for males and 1.25 (95% CI 1.12–1.38) for females.

Conclusions The incidence rate of LC in Iran was lower in comparison to other countries. Afterwards, more studies are necessary to outline the accurate incidence rate and the trend of LC among Iranian population.

Keywords Incidence · Hepatocellular carcinoma · Iran · Systematic review · Meta-analysis

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Introduction

Liver cancer (LC) is the seventh most common cancer around the world in 2014, with 78,245 new cases [1]. More than 85% of the new cases of LC occur in developing countries [2]. The highest incidence rates of the cancer are observed in Asia and sub-Saharan Africa [3]. Evidence suggests that the incidence of LC is increasing globally [4, 5]. The increasing trend has been also observed in Europe, Oceania, and Asian countries [6, 7].

The incidence of this cancer has been most associated with the incidence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in different parts of the world [8, 9]. Several lines of evidence have shown that hepatitis is one of the most important risk factors for hepatocellular carcinoma (HCC) [10–12]. There are some non-infectious risk factors for LC including smoking, alcohol consumption, obesity, and immigration [13–15]. Some studies suggest that family history of LC does appear to influence the incidence of LC with a relative risk of 2.6 [16, 17]. Moreover, genetic factors influence men more significantly than women [18].

Cancer is the third cause of death in Iran [19]. The first study on cancer data in Iran was conducted by Habibi in 1962 [20]. The National Cancer Registry System (NCR) was founded in 1984 in Iran [21]. Since the establishment of the NCR, there have been various and inconsistent reports about the incidence of different types of cancer from pathology centers and cancer registries.

Although LC incidence rate in Iran is low compared to other parts of the world, a rising trend is continued in recent years [22, 23]. Moreover, there is no comprehensive information on the incidence rate, geographic distribution, and the changing trends of LC in Iran. Only some limited and scattered studies had been accomplished in different provinces of Iran [21]. Therefore, considering the importance of knowing the incidence rate and the trend of this disease for prevention and etiology programs, this study aimed to systematically review the age-standardized incidence rate (ASR) of LC in Iran.

Materials and Methods

The study was planned and conducted in July 2018. The review was performed based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist [24].

Search Strategy

A comprehensive literature search of published studies was carried out using Medline/PubMed, Scopus, Embase, ScienceDirect, and Google Scholar for international papers, and Scientific Information Database (SID) (www.sid.ir), MagIran (www.magiran.com), IranMedex (www.iranmedex.com), and IranDoc (www.irandoc.ac.ir) for national papers until 1 July 2018. The keywords included: “liver cancer,” “liver neoplasms,” “liver tumor,” “liver carcinoma,” “cancer of liver,” “neoplasms of liver,” “Hepatocellular carcinoma,” “HCC,” and “incidence,” and “Iran.” No time and language limitation was considered. EndNote X5 software (Thomson Reuters, Carlsbad, CA, USA) was used to check and manage the citation results.

Inclusion and Exclusion Criteria

In the present study, all papers contained a clear description of ASR of LC rate and obvious reports of Iranian populations were included. Additionally, the papers with the following criteria were excluded: duplicated studies, studies which reported prevalence rate, and the poster and conference papers.

Quality Assessment

In order to assess the quality of the articles, a checklist prepared by The Joanna Briggs Institute (JBI) was used [25]. 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.

Statistical Analysis

All the analyses were performed using STATA software, version 12 (StataCorp, College Station, TX, USA). Cochran's Q statistic (significance level of $p \leq 0.1$) and I^2 statistic (significance level of $\geq 50\%$) were used to assess statistical heterogeneity. A random effects model was conducted for meta-analysis of heterogeneous cases ($p < 0.1$ and $I^2 > 50\%$), and fixed-effect model was performed for meta-analysis of cases without evidence of heterogeneity ($p > 0.1$ and $I^2 < 50\%$).

Risk of Bias Across Studies

Random effect model was used for minimizing risk of bias across the studies [26, 27].

Results

Description of Literature Search

The primary searches of the literature identified yielded 171 potentially relevant studies. After title and abstract screening, 87 studies met inclusion criteria and entered into the second stage of evaluation. Some studies were excluded by full-text reviewing for the following reasons: duplicate studies ($n = 5$), being irrelevant to the aim of the study ($n = 45$), incorrect study population ($n = 16$), and inadequate data ($n = 6$). Subsequently, the review included 15 unique studies. The search process and study selection according to the PRISMA flowchart in the present systematic review have been summarized in Fig. 1.

Description of the Included Studies

Based on the geographical locations, three studies were conducted in Fars province [28–30], two in Ardabil province [31, 32], one in Kerman province [33], one in Semnan province [34], one in East Azerbaijan province [35], one in Tehran metropolis [36], one in Shahroud city [37], and five in all states of Iran [21, 38–41]. The basic characteristics of the included studies have been demonstrated in Table 2.

Table 1 JBI critical appraisal checklist applied for included studies

Author name/year	Sample was representative?	Participants appropriately recruited?	Sample size was adequate?	Study subjects and the setting described?	Data analysis conducted	Objective, standard criteria, reliably used?	Appropriate statistical analysis used	Confounding factors/subgroups/differences identified and accounted?	Subpopulations identified using objective criteria
Sadjadi (2003)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Babaei (2005)	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No
Sadjadi (2007)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Mehrabani (2008)	Yes	No	No	Unclear	Yes	Yes	No	Yes	Yes
Somi (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Babaei (2009)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Mohagheghi (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Mousavi (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Masoumpour (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Faeh (2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Roshandel (2014)	No	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Somi (2014)	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Unclear
Mirzaei (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mohammadian (2016)	Yes	No	Yes	No	Yes	Yes	Unclear	Yes	Yes
Almasi (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

The Results of Individual Studies

The current study showed that the male to female sex ASR ratio is 1.33. The highest ASR among males and females was reported from Semnan province between 1996 and 2000 (5.83 and 3.53 per 100,000 for males and females, respectively), while the lowest ASR among males and females was reported from Frasin province between 1990 and 2005 (0.29 and 0.42 per 100,000 for males and females, respectively).

The Results of Meta-analysis

The ASR of LC was 1.66 (95% CI 1.49–1.83) for males and 1.25 (95% CI 1.12–1.38) for females. The results of Cochran’s test were showed the heterogeneity of the studies ($Q = 2457.1$, $df = 22$, $I^2 = 99.1\%$, $p < 0.001$) for males and ($Q = 1892.7$, $df = 22$, $I^2 = 98.8\%$, $p < 0.001$) for females. The results of the random effect model for ASRs of LC have been represented in Figs. 2 and 3 for males and females, respectively.

Meta-regression

Results of meta-regression showed an association between publication year and ASR of LC. Thus, year of study is a cause of variability in results of LC incidence in males (Reg Coef = 0.070, $p = 0.031$). This relationship was not observed for females (Reg Coef = -0.0004, $p = 0.992$). According to the results, an increasing ASR across the study period was observed for males. Results of meta-regression are shown in Fig. 4.

Publication Bias

Publication bias was assessed using Egger’s tests [42]. Results of Egger’s tests showed a lack of publication bias ($p = 0.245$ for males and $p = 0.168$ for females).

Discussion

Cancer is the third cause of death in Iran [19]. Few studies have been conducted on the epidemiology of cancer up to now, in developing countries including Iran [43–50].

Results of the present study indicate that the incidence rate of LC among Iranian men (1.66 per 100,000) is lower compared to other parts of Asia. However, some Asian countries including Mongolia (97.8 per 100 thousand), Laos (78.7 per 100 thousand), and Vietnam (40.2 per 100 thousand) have high levels of ASR. Moreover, some other countries like Bangladesh (3.3 per 100,000), Lebanon (3.3 per 100,000), and Nepal (1.2 per 100,000) have the lowest ASR [51].

According to the results, the incidence of LC among Iranian women is lower compared to Iranian men (1.25

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

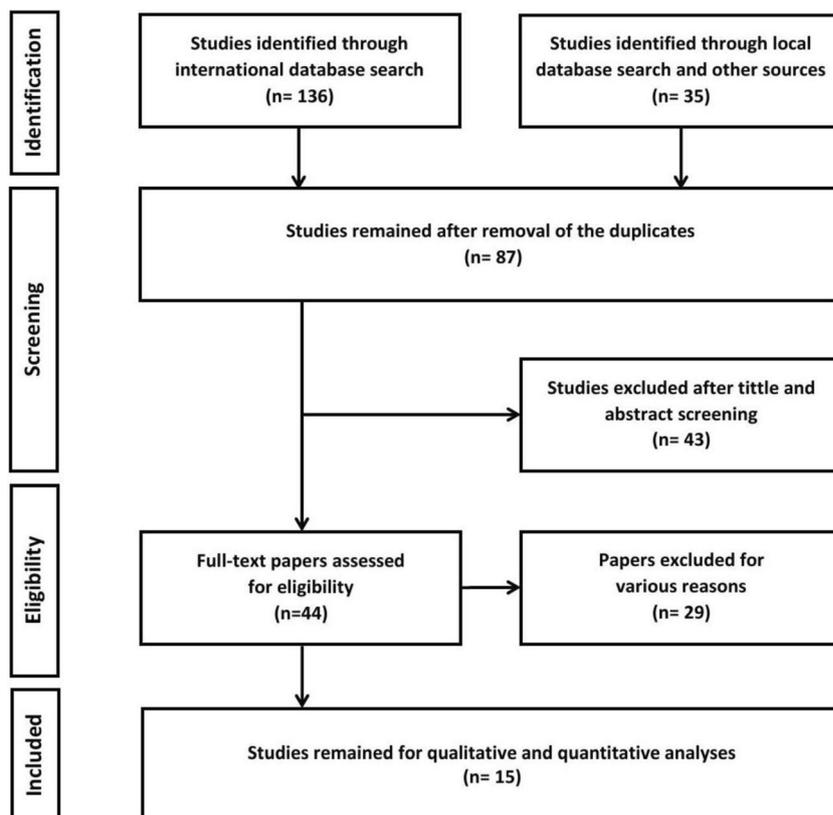


Table 2 Basic characteristics of the studies included in the review

Order	Author/year	Time period	Location	ASR (males)	ASR (females)
1	Sadjadi (2003)	1996–1999	Ardabil	1.6	2.3
2	Babaei (2005)	1998–2002	Semnan	5.83	3.53
3	Sadjadi (2007)	1996–2000	Kerman	1.5	0.8
4	Mehrabani (2008)	1990–2005	Fars	0.29	0.42
5	Somi (2008)	2006–2007	East Azerbaijan	2.23	2.03
6	Babaei (2009)	2004–2006	Ardabil	3.7	2.6
7	Mohagheghi (2009)	1998–2001	Tehran	3.8	3.2
8	Mousavi (2009)	2003–2004	Iran	0.55	0.43
		2004–2005		0.52	0.31
		2005–2006		0.68	0.37
9	Masoompour (2011)	1998–2002	Fars	2.3	1.6
10	Fateh (2013)	2000–2010	Shahroud	1.58	1.15
11	Roshandel (2014)	2012	Iran	2.8	2.1
12	Somi (2014)	2007–2011	East Azerbaijan	0.86	0.61
13	Mirzaei (2015)	2003	Iran	0.55	0.43
		2004		0.66	0.43
		2005		0.66	0.36
		2006		0.89	0.64
		2007		0.90	0.58
		2008		1.56	2.03
		2009		1.92	1.42
14	Mohammadian (2016)	2012	Iran	2.8	2.1
15	Almasi (2016)	2012	Iran	2.8	2.1

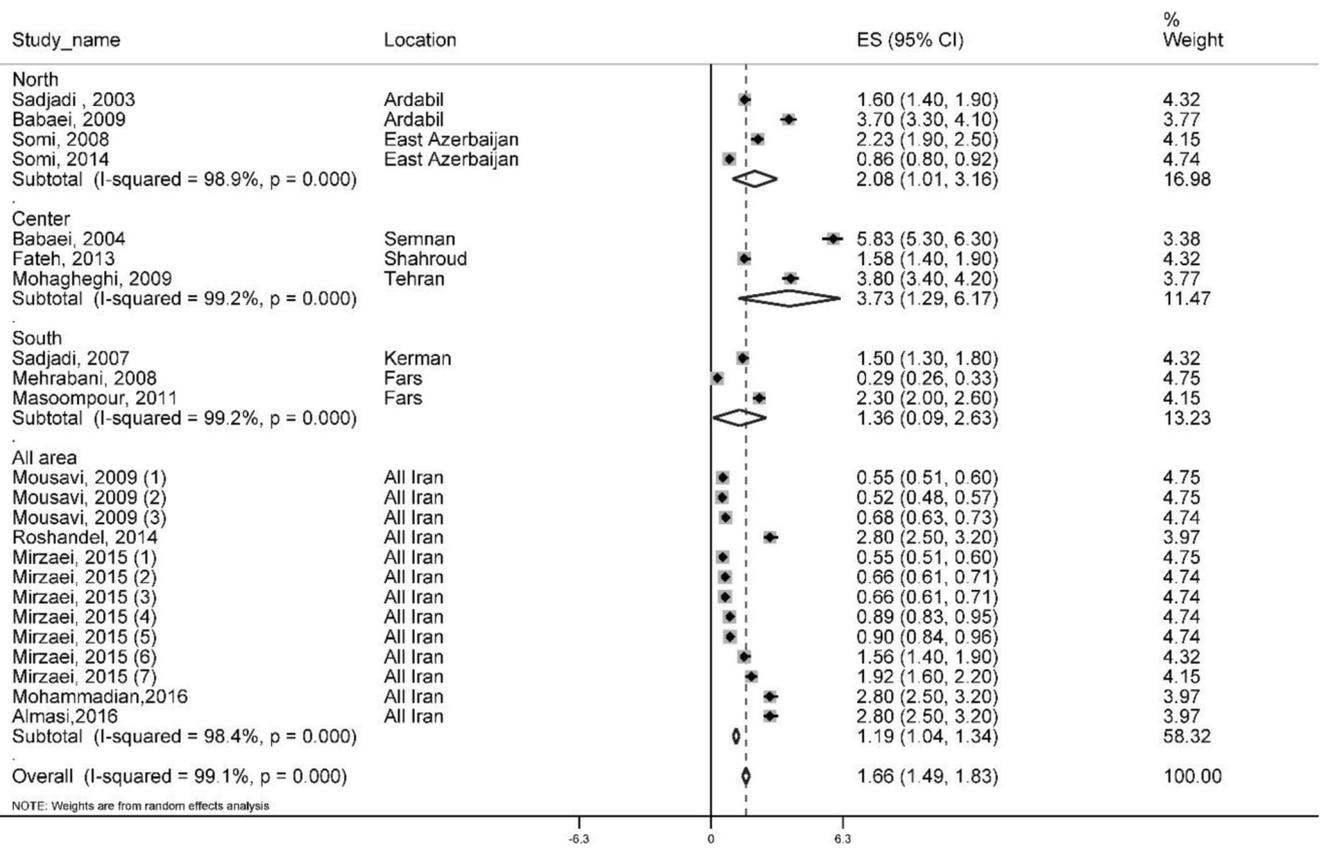


Fig. 2 Forest plot of the random-effect meta-analysis for ASRs of liver cancer among Iranian males

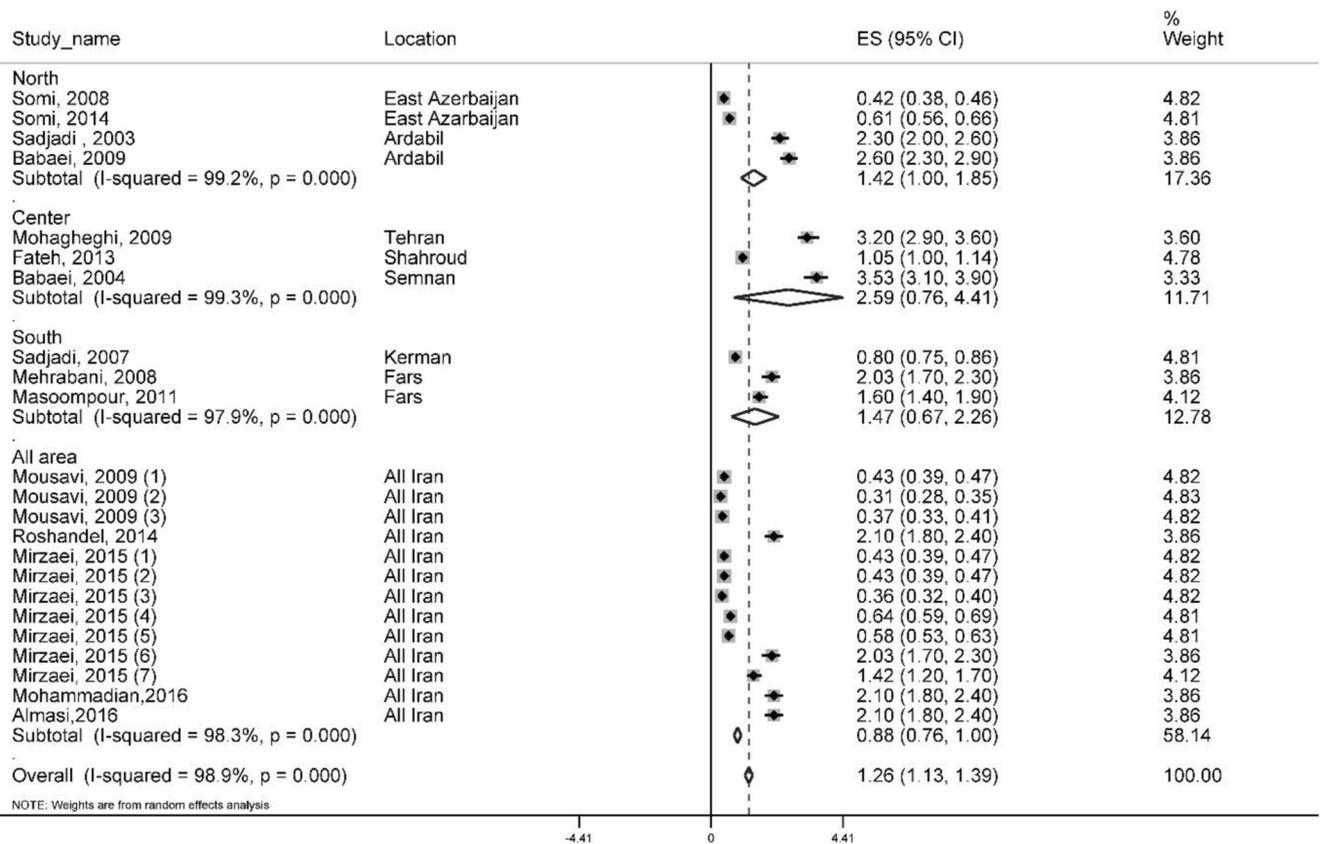


Fig. 3 Forest plot of the random-effect meta-analysis for ASRs of liver cancer among Iranian females

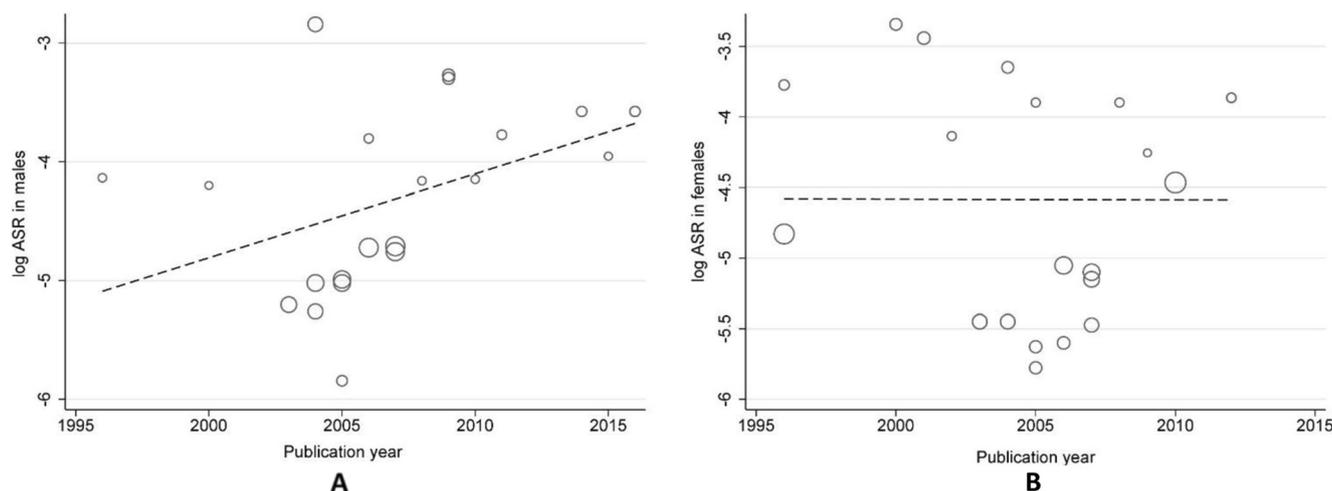


Fig. 4 Meta-regression plots of change in ASR of liver cancer in males (a) and females (b) according to changes in continuous study moderator's year

compared to 1.66 per 100,000). In spite of that, some Asian countries including Mongolia (61.1 per 100,000), Laos (29.7 per 100,000), and Cambodia (14.2 per 100,000) have high ASR. These findings indicate that LC in Asia is more common among men than women. Also, countries like Maldives (almost zero in 100,000), Nepal (0.7 per 100,000), and Israel (1.3 per 100,000) have the lowest ASR [51].

Based on the six world health organization (WHO) regions, the highest ASR of LC is observed in WPRO region, and the lowest occurred in EUROP [52]. It should be noted that Eastern Asia has the highest age-standardized incidence and mortality rates of LC worldwide [53]. The age-standardized incidence and mortality rates of LC in this region are 31.9 and 29.9 per 100,000, respectively among men. These parameters are 10.2 and 9.6 per 100,000, respectively among women. Moreover, the lowest age-standardized incidence and mortality rates are observed in Northern Europe [52].

The correlation between the human development index (HDI) and the ASR of LC has been examined, and a significant reverse relationship was identified. Thus, countries with higher levels of HDI have shown lower incidence rates of LC [52].

The results of the study indicated that the highest ASR of LC in Iran is observed in Semnan province (5.83 and 3.53 per 100,000 among men and women, respectively). The high incidence of cancers in various locations is associated with the difference in the risk factor distribution and exposures [54, 55]. The high incidence of LC in Semnan province can be due to the high spread of HBV and HCV infection and the high prevalence of other risk factors like liver cirrhosis in this province [56]. Moreover, the difference in the accuracy of diagnosis and registration of cancer in different regions is another cause of the different incidence rates in various regions.

The results from the study showed that the lowest ASR of LC in Iran is observed in Fars province between 1990 and 2005 (0.29 and 0.42 per 100,000 among men and women,

respectively). The low ASR of LC in this province can be attributed to the demographic characteristics, differences in lifestyle, and the presence of other types of diseases and cancers among people who are living in the region. Gastric, colorectal, and bladder cancers among men and breast, colorectal, and stomach cancers among women have higher incidence rates in Fars province [29]. However, based on a recent study conducted by Massoorpour, the ASR of LC was estimated to be 2.3 per 100,000 among men and 1.6 per 100,000 among women, which has a significant ascending trend [30]. This increase can be related to a more accurate registration system and a better identification of patients during recent years.

Although the incidence of LC in Iran is lower compared to other parts of the world, it is expected to see more new cancer cases in the future, due to the epidemiological transition, increasing life expectancy, population aging, and more exposure to risk factors.

Conclusion

The incidence rate of LC in Iran was lower in comparison to other countries. Afterwards, more studies are necessary to outline the accurate incidence rate and the trend of LC among Iranian population.

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Compliance with Ethical Standards

This study was conducted in compliance with the provisions of the Helsinki Declaration. The protocol was approved by the ethics committee of Guilan University of Medical Sciences.

Conflict of Interest The authors declare that they have no conflict of interest.

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