Bladder Cancer Incidence in Iran: Results of the Iranian National Population-Based Cancer Registry from 2014 to 2016

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Purpose: Bladder cancer is a common cancer in the world with the highest rates in Southern and Western Europe, North America, and Western Asia. It imposes a high economic burden to the health care system globally. The objective of this study is to provide the incidence of bladder cancer and its geographic distribution in Iran in 2014, 2015 and 2016.

Materials and Methods: Data was extracted from the Iranian National Population-Based Cancer Registry (INP-CR) covering 98% of the total Iranian population. We registered only those cases diagnosed with malignant primary tumors of the bladder in the National Cancer Information Management system (CIMA). The main sources of data were pathology laboratories, hospitals, and death registry units. After quality assessment, analysis of data was performed and Age Standardized Rates (ASR) of bladder cancer were reported at national and subnational levels.

Results: We registered 5817, 5662, and 6630 new bladder cancer cases in 2014, 2015, and 2016, respectively with men counting 82% of cases in every year. The ASR of bladder cancer in the total Iranian population was 8.50 (95% CI: 8.28-8.72), 8.05 (95% CI: 7.83-8.27) and 8.74 (95% CI: 8.52-8.96) per 100,000 in those years. The male to female ratio was 5 every year. Kerman has the highest ASR in each of the years, respectively 15.49, 13.07 and 12.46, and Ilam has the lowest ASR during 2014 to 2015, respectively 4.27 and 3.50, and Sistan and Baluchestan has the lowest rate in 2016 (ASR:3.56) in both sexes.

Conclusion: The highest incidence of bladder cancer was observed in the central, southern and northwestern parts of Iran. Through the analysis of the incidence patterns and the identification of risk factors associated with it, steps can be taken toward prevention and control measures.

Keywords: Bladder cancer; Incidence; Registry; Iran

INTRODUCTION

Bladder cancer with about 549,000 (ASR: 5.7 per 100,000) annual cases is the tenth most incident cancer in the world (1) and the highest incidence rates reported in most developed countries; Southern Europe (ASR: 15.2 per 100,000), Western Europe (ASR: 13.2 per 100,000), North America (ASR: 11.9 per 100,000) (2), and Western Asia (ASR: 9.2 per 100,000)[1,3]. According to Globocan 2018, in Asia, Lebanon is reported as the highest incidence of bladder cancer and Iran ranked sixth among other countries[1].

As an expensive cancer to treat[4], in the European Union, bladder cancer cost €4.9 billion, of which €2.9 billion was related to the health care system (59% of total economic burden)[5].

Based on the findings of recent studies in Iran the incidence of bladder cancer is rising[6,7]. An epidemiological and histological study of bladder cancer in Iran indicated that the ASR has increased from 8.35 to 14.42 (per 100,000) in men and from 2.12 to 3.78 in women between 2003 and 2008[7]. Another study in Isfahan, a central province, showed that the incidence of this cancer was increasing (ASR: 7.7 to 9.9 per 100,000) from 2011 to 2015[8].

Sex and age are also associated with the incidence of bladder cancer. Globocan 2018 estimated that the ASR of bladder cancer is approximately four times higher in men compared to women, worldwide[2]. In Europe in 2012, the incidence of bladder cancer in men and women were estimated to be 19.5 and 9.3 per 100,000,

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Table 1. The number, crude rate and ASR and 95% confidence interval (CI) of bladder cancer (per 100,000) in male and female in Iran, 2014, 2015 and 2016.

Bladder cancer	Sex	Number	Crude rate	ASR	95% CI of ASR
2014	Male	4776	12.37	14.30	13.88-14.72
	Female	1041	2.74	2.97	2.79-3.15
	Both	5817	7.59	8.50	8.28-8.72
2015	Male	4615	11.82	13.57	13.17-13.97
	Female	1047	2.72	2.86	2.68-3.04
	Both	5662	7.30	8.05	7.83-8.27
2016	Male	5393	13.32	14.41	14.01-14.81
	Female	1167	2.96	2.99	2.81-3.17
	Both	6560	8.21	8.64	8.42-8.86

respectively[9]. Based on some studies in Iran, bladder cancer incidence rate in men is 3 to 5 times those of women[4,7,8,10]. Bladder cancer incidence is associated with age and mostly has been seen in the elderly. The highest rate belongs to the individuals in their seventh and eighth decades of life[4,11].

The incidence of bladder cancer varies based on socio-economic and life style risk factors. Smoking, occupational and industrial exposures are among the main risk factors[3,11-14]. Schistosomiasis[3,7], Human Papilloma Virus (HPV)[7], and arsenic-contaminated drinking or chlorinated water[13] are some other risk factors associated with bladder cancer.

Considering that population-based cancer registry has been carried out nationally since 2014 and cancer data are collected from at least three sources: pathology, clinical and death, and also since that year, the quality of cancer data has been accepted by the International Agency for Research on Cancer (IARC) standards, we needed to do a study to determine the incidence of bladder cancer in Iran and its geographical distribution in the country based on the latest and most accurate cancer data from 2014 to 2016.

MATERIALS AND METHODS

Study Population

This secondary data analysis was performed on newly diagnosed patients with primary bladder cancer registered in INPCR in three consecutive years (2014, 2015 and 2016).

Population statistics at provincial and national levels for those years were obtained from the statistics of the health Deputy of the Ministry of Health (MOH). Total population of Iran in 2014 and 2015 were estimated based on the 2011 national census to be 77,856,000 and 78,773,000, respectively[15]. The population of 2016 was calculated from the national census data including 40,498,442 men and 39,427,828 women which distributed in 31 provinces (**Figure 1** depicts the population pyramid of Iran in 2016)[16].

Study Design

Data on bladder cancer were derived from INPCR. A total of 64 Universities of Medical Sciences (UMS) are responsible for medical education as well as providing health services for the defined population in their catchment area. In brief, to cover all of the population, we considered all 64 UMS as administrative units of the MOH. Therefore, the INPCR included 64 University-level Secretariats, distributed in 31 provinces, and a National-level Secretariat which leads all those university secretariats. Each province has at least one university secretariat which is responsible for data gathering and processing. In the provinces with more than one university secretariats, data is merged by one of them as the provincial representative then submitted to the INPCR secretariat. Population-based cancer registry in Iran, follows the guidelines of IARC and North American Association of Central Cancer Registries (NAACCR)[17-19].

Accordingly, the INPCR registered cases with new primary bladder tumors of malignant behavior, among which only invasive bladder cancer cases (behavior code = 3) were considered in this study.

To determine the accurate geographical distribution of bladder cancer in different subdivisions, data of patients' residence was collected as a mandatory and an essential variable.

The main data sources were pathology reports form public and private pathology laboratories, clinical/paraclinical data from public and private hospitals, and cancer mortality data which collected from death registry units of the representative UMS.

Evaluations

The web-based system of the INPCR, named CIMA,

Table 2. Diagnosis methods for bladder cancer in INPCR, 2014, 2015 and 2016

Diagnosis method	Sex	MV Number	Percent	Clinical Number	Percent	DCO Number	Percent
2014							
	Male	4058	84.93	530	11.09	190	3.98
	Female	817	78.48	142	17	82	7.87
	Both	4875	83.78	672	11.55	272	4.67
2015	Male	4153	89.99	256	5.55	206	4.46
	Female	888	85	85	8.1	74	7.06
	Both	5041	89.03	341	6.02	280	4.95
2016	Male	4876	90.41	325	6.03	156	3.92
	Female	1001	85.77	102	8.74	64	5.48
	Both	5877	89.59	427	6.51	256	3.90

Abbreviations: MV, Microscopically Verified. Clinical, Clinical investigation. DCO, Death Certificate Only
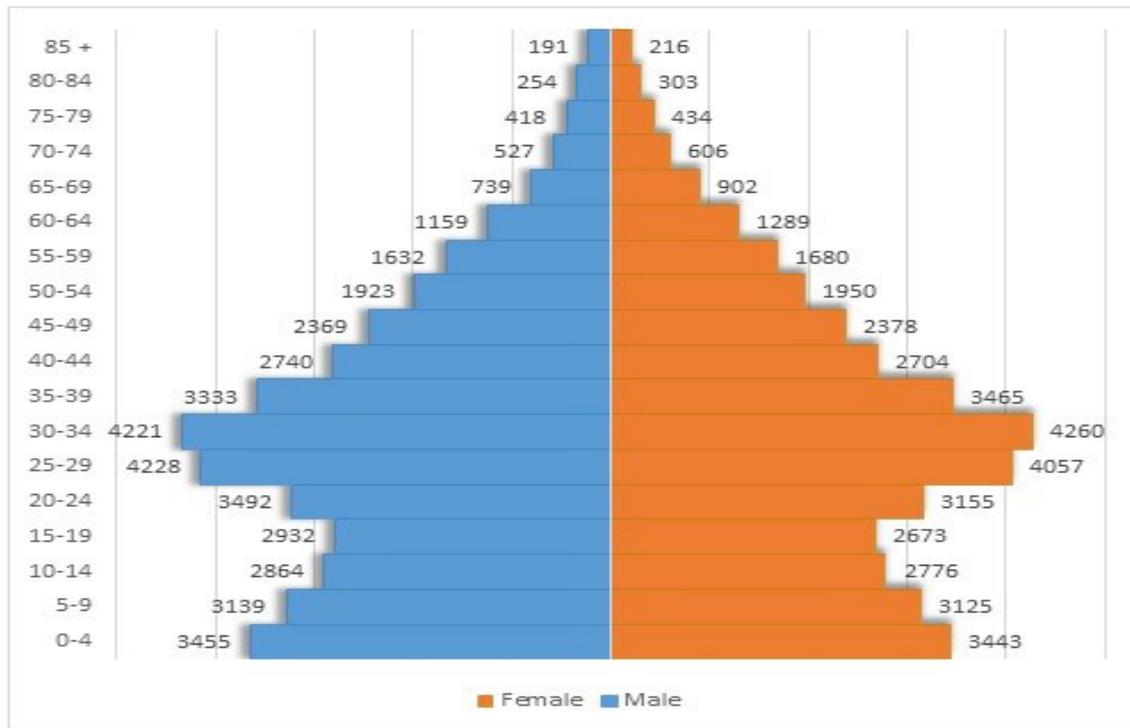
Figure 1. Population age pyramid of Iran, 2016.

used for data entry, cleaning, processing, and transferring from UMS secretariats to INPCR secretariat. Upon entering bladder cancer data to the CIMA, new cases of bladder cancer were identified and coded using the International Classification of Diseases for Oncology (ICD-O-3)[20], then multiple primary tumors were evaluated according to IARC rules[21]. Internal consistency was checked for age, sex, and primary cancer site with the type of cancer using the IARC check tools, which is included in CIMA software package (22). To check for bladder cancer data completeness, the percentages of diagnostic methods including Microscopically Verified
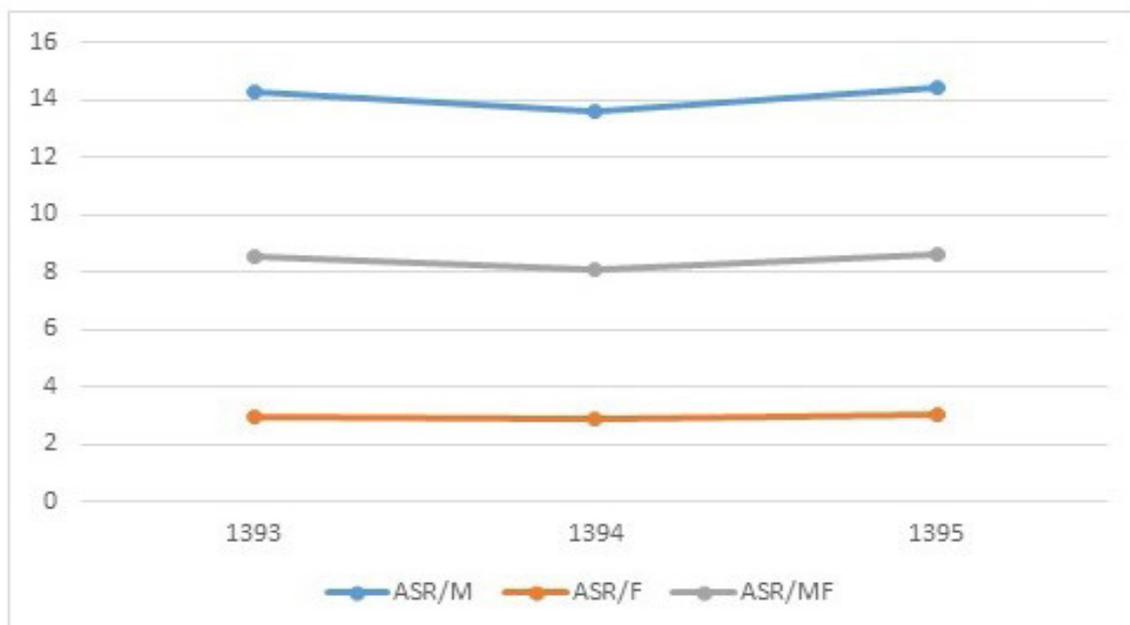

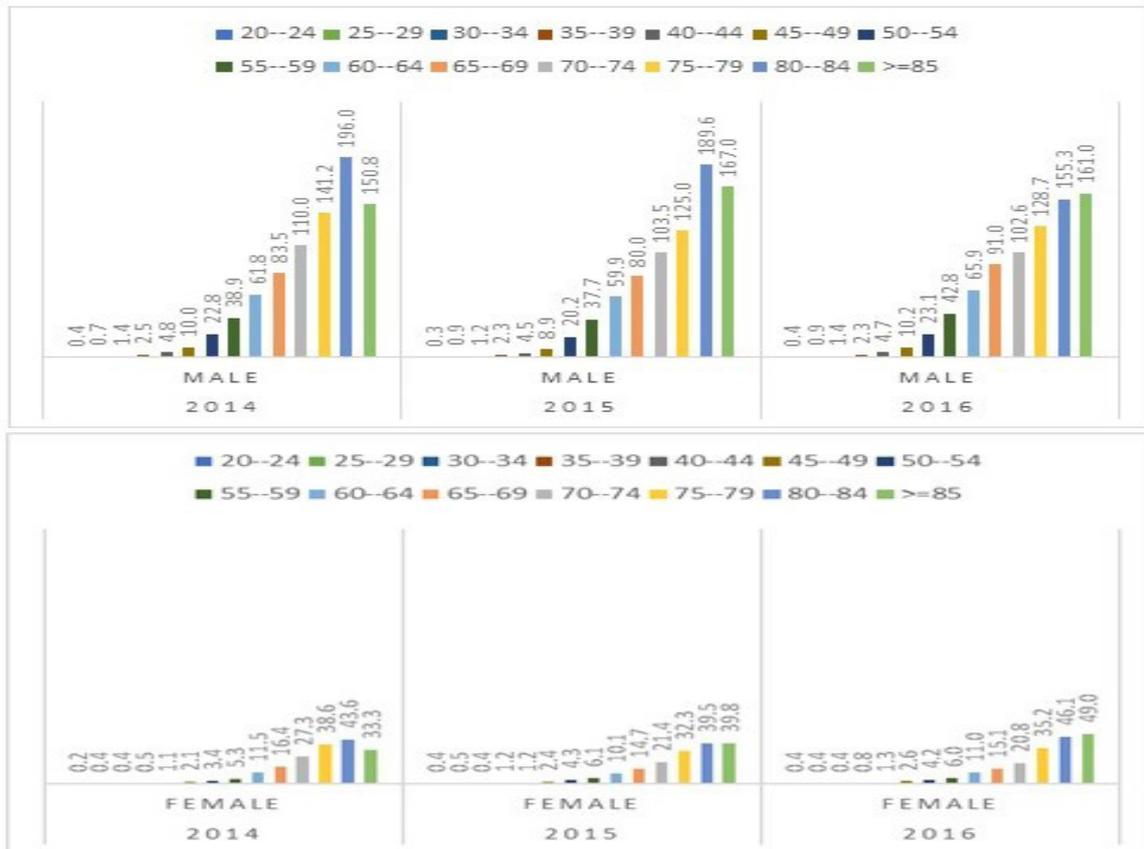**Figure 2.** Trend of bladder cancer incidence (ASR) in Iran, 2014 to 2016.

Figure 3. Age specific incidence rates of bladder cancer (per 100,000) by sex, Iran, 2014 to 2016.

(MV%), Clinical Investigation (Clinical %) and Death Certificate Only (DCO%) were compared to NAACCR standards[19] (MV% > =80 and Clinical% <15, DCO% < 5). All the mentioned steps were taken by UMS secretariats. In INPCR, the dataset submitted by UMS secretariats were rechecked based on IARC standardized quality control indicators.

Statistical Analysis

Quality controlled data was analyzed, after removing in situ cases (behavior code=2), using CanReg5 software[23] and incidences reported as the numbers, percentage, crude rates, age specific incidence rates and ASR, for the country and by province. To calculate the ASRs, the age-specific incidence rate of 18 age groups was calculated by dividing the number of cases by the population of each age group per 100,000 population, and then the values obtained for standardization were multiplied by the world standard population defined for each age group. Finally, the sum of the values obtained from the 18 groups is divided by the sum of the world standard population.The reference population used to calculate ASRs was the world standard population in 18 age groups of 5 years (0–4, 5–9 ... 85+) considered per 100,000 population[24,25]. Using a method described by Bray and Ferlay, we calculated the 95% confidence intervals for ASRs[26]. Ethical issues of this study were reviewed and approved by ethical committee of Golestan Universuity of Medical Sciences (ethics code: IR.GOUMS.REC.1397.335).

RESULTS

Overall, 5817, 5662 and 6630 new bladder cancer cases were registered in INPCR in 2014, 2015 and 2016 of which 4776, 4615 and 5433 were male, respectively (82% of cases, annually). The median of age in bladder cancer cases were calculated to be 64 years in men and 56 years in women in every year.

The ASR of bladder cancer was 8.50 (95% CI: 8.28-8.72), 8.05 (95% CI: 7.83-8.27) and 8.74 (95% CI: 8.52-8.96) per 100,000 in total Iranian population from 2014 to 2016, respectively.

The number, crude rates, ASRs and 95% CI of bladder cancer by gender and year are presented in Table 1. Overall male to female ratio was 4.8, 4.7 and 4.7 in 2014, 2015 and 2016, respectively.

The bladder cancer ranked as the seventh most incident cancer among diagnosed cancers after breast, prostate, skin (Non-melanoma), stomach, colorectal and lung cancers during 2014 to 2015 and the sixth most common cancer among diagnosed cancers after breast, prostate, colorectal, skin (Non-melanoma), and stomach in 2016. Specifically, it ranked with fifth in males and thirteenth in females for all the three years.

The trend of bladder cancer over three years is shown in **Figure 2**.

The highest incidence rates of bladder cancer become clear in sixth and seventh decades of life, **Figure 3** shows age specific incidence rates of bladder cancer in male and female in those three years.

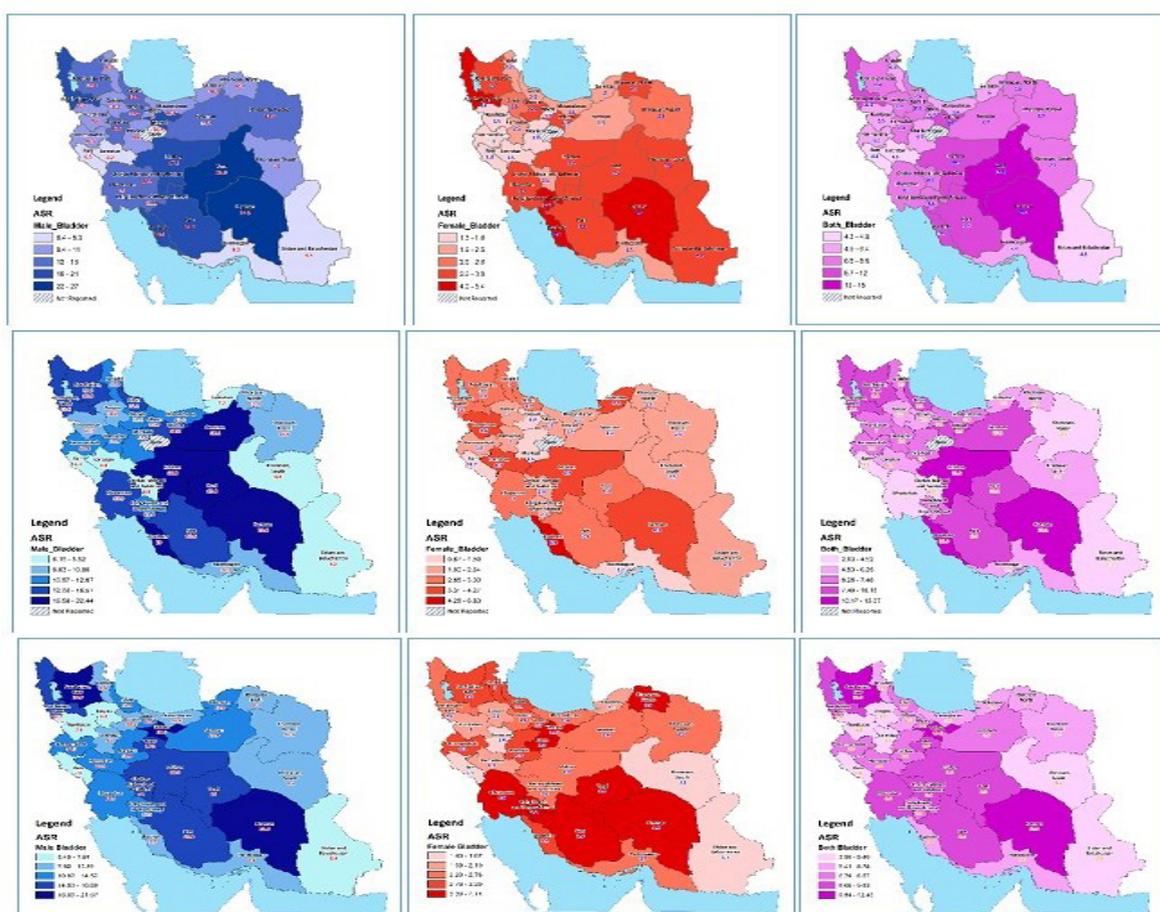The distribution of incidence of bladder cancer (ASR)

Figure 4. The distribution of Age Standardized Incidence Rates (ASR) of bladder cancer in different regions and provinces of Iran in 2014 (In the first row), 2015 (In the second row) and 2016 (In the third row), Male, Female and Both sexes, respectively.

is mapped in different regions and provinces of Iran by sex in 2014, 2015 and 2016 in Figure 4. The highest incidence rate of bladder cancer was reported from Kerman province.

Of the total cases registered for bladder cancer, 4875, 5041 and 5877 cases were diagnosed by microscopic verification (MV=83.78%, 89.03% and 89.59%), 272, 280 and 256 cases were found from death certificate only (DCO=4.67%, 4.95 % and 3.90%) and the remaining 672, 341 and 427 cases were diagnosed via clinical only or other clinical investigation methods (Clinical: 11.55%, 6.02 % and 6.51%) in 2014, 2015 and 2016, respectively (**Table 2**).

Transitional Cell Carcinomas (TCC) with 4661, 4610 and 5408 cases were 80 to 81% of bladder cancers in those years, respectively.

DISCUSSION

The ASR of bladder cancer based on three recent cancer registry reports in 2014, 2015, and 2016 were about 8 per 100,000 ranked sixth and seventh among all cancers in Iran. The bladder cancer was more prevalent in male (ASR: 14 in male and ASR: 3 in female) and older age groups. Central, southern and northwestern parts of the country had a higher rates of bladder cancer.

The incidence of bladder cancer in Iran is considerably high compared to the rest of Asia and many parts of the world. According to regional divisions listed by Globocan 2018, Iran ranked the first in the South-Central Asia and the third in neighboring countries after Syria and Turkey[1]. This rank may be partly due to under-reporting of bladder cancer in other countries, however, numerous known behavioral and environmental risk factors should be taken into account in interpreting these findings, especially smoking, occupational and industrial exposures[3,11-13].

Smoking is known to be the main risk factor for bladder cancer with a strong association[9,14,27,28]. Some studies have demonstrated that the risk of bladder cancer occurrence is about four times higher in smokers than in non-smokers[29,30]. Therefore, it can be assumed that because smoking is more common in men than women, bladder cancer is more common in men and Studies have mentioned that 50% of men and 25% of women with bladder cancer are smokers[27,28].

In the latest survey of risk factors of Non-Communicable Diseases Risk Factors in Iran (STEPS) in 2016, the spatial distribution of tobaccos use is higher in Bushehr, Fars, Azerbaijan-West, Yazd, Isfahan, and Kerman which shows similarity to the geographic pattern of higher bladder cancer incidence[31].

Besides, the effect of opium in increasing the risk of bladder cancer incidence has been proven in different studies[32-35]. Latest estimations show that Kerman ranks fifth in the country for opium and third for shire (combi-

nation of Opium residue and pure opium) consumption, which may be one of the major reasons for the increased incidence of bladder cancer in Kerman[36]. There is also a strong relationship between the use of opium and bladder cancer in Shiraz city (located in the south of Iran), which proposes opium as a major potential risk factor for bladder cancer in Iran[37].

Apart from smoking and opium consumption, occupational risk factors, especially industrial exposures, are viewed as an important risk factor attributable to bladder cancers[3,11-14], accounting for 20-27%[12,38]. Similarly, a case control study about occupations and the risk of bladder cancer in Yazd province located in the center of Iran shows an increased risk of this cancer among a group working with metal compared to the control group[39]. Other risk factor proposed for bladder cancer is infectious diseases such as schistosomiasis[3,11], and HPV[7,40], the correlation between HPV infection and bladder transitional cell carcinoma in Iran has reveals the presence of the HPV in 36.5% of tissue samples [40]. In this study, the incidence of bladder cancer in men is 5 times that of women, many studies have shown this ratio 3 to 5 times[2,7,8,10]. The highest incidence of bladder cancer is observed in people over 60 to 80 years of age. The results of this study indicated the highest incidence in the 60 and 70 decades[4,8,10,11,41].

At the national level, the incidence of bladder cancer has not changed significantly over the years (**Figure 2**). It should be noted that the completeness of bladder cancer cases collected from pathology laboratories in those years was 80% to 90% and is based on IARC standards (**Table 2**).

At the provincial level, however, Kerman ranked first every three years while the rankings of the provinces have not been the same each year (**Figure 4**). This can be a result of the under-reporting or over-reporting of bladder cancer in those provinces. In this regard, quality control procedures such as case-findings for under-reporting, eliminating duplicates for over-reporting and the subsequent accurate recoding of bladder cancer cases are necessary.

By providing data for the upcoming years which is currently being collected and processed, the correct trend of bladder cancer incidence and its geographical distribution will be achieved. Access to accurate bladder cancer data in provinces and their association with possible risk factors can be a starting point to control and prevention of bladder cancer in Iran.

One of the limitations of bladder cancer incidence studies is the incompatibility between studies which include in situ bladder cancers (behavior code = 2) in addition to the invasive cancers and the studies which are based only on invasive bladder cancers.

CONCLUSIONS

In this study, the highest incidence of bladder cancer was observed in central, southern and northwestern parts of Iran. Continuous and annual studies of the incidence of bladder cancer incidence reveal a pattern of incidence among different geographical regions. Through the analysis of these patterns and the identification of risk factors associated with bladder cancer (smoking, opium, occupational exposures and etc.), further steps can be taken toward prevention and control of this cancer.

CONFLICT OF INTEREST

The authors had no conflict of interest to declare.

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