A 30-YEAR TREND OF THE INCIDENCE AND DEATH OF TRACHEAL, BRONCHIAL, AND LUNG CANCERS IN IRAN AND FORECASTING UNTIL 2026 BASED ON TIME SERIES ANALYSIS

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Abstract – Objective: Lung cancer is the second most common cancer in the world, with an estimated 2.2 million new cases and 1.8 million deaths and is the fifth most common cancer in men and the sixth most common cancer in women in Iran. This study was conducted to investigate a 30-year trend of the incidence and death of tracheal, bronchial, and lung cancer in Iran and its forecasting until 2026.

Materials and Methods: The Iranian population's age-standardized (ASR) incidence and death rates of tracheal, bronchial, and lung (TBL) cancers were extracted from the Global Burden of Disease (GBD) Online Database from 1990 to 2019. Statistical analysis was performed using the time series method with Interactive Time Series Modeling (ITSM) software and Autoregressive Integrated Moving Average (ARIMA) model.

Results: The age-standardized incidence rate (ASIR) and the age-standardized death rate (ASDR) of lung cancer in Iranians (both gender) had an increasing trend from 2004 to 2019 among men and from 1990 to 2019 in women with a continued predicted increasing trend for 7 years. ASIR will increase to 13.53, 17.36, and 9.26 per 100,000 people in the total population, men and women, respectively. ASDR will increase to 14.13, 18.18, and 9.22 per 100,000 people in the total population, men and women, respectively.

Conclusions: In according to the predicted increasing trend of TBL cancers in Iran in the future, the reasons for the continuation of this increasing trend should be fully investigated, and then by using the experiences of successful countries in reducing lung cancer, effective measures should be considered to reduce the morbidity, mortality, and burden of these cancers in Iran.

KEYWORDS: Lung Cancer, Incidence, Death, Iran, Forecast.

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INTRODUCTION

Lung cancer is the second most common cancer in the world, with an estimated 2.2 million new cancers and 1.8 million deaths and is known as the leading cause of cancer deaths in 2020 and allocated for 18% of cancer-related deaths. It has the highest incidence and main cause of cancer mortality in men, while in women it ranks third in terms of incidence and second in terms of mortality[1].

In 2018, the incidence of lung cancer in West Asian countries was estimated at 38.8 for men and 7.8 for women per 100,000 populations[3]. The prevalence of lung cancer in Iranian men and women is also increasing[3,4]. According to the Cancer Registration Center of the Ministry of Health data in 2014, 6066 new cases of lung cancer were identified which accounts for 10.98% and 4.8% of all cancers in men and women, respectively, and is the fifth most common cancer in men and the sixth most common cancer in women[5]. However, the incidence and death rate of lung cancer in countries such as the United States, Canada, and many European countries is declining[6].

The survival rate of lung cancer is low; the average 3-year survival has been reported as 13.8% in Norway[7], 8.5 months after diagnosis[8], and the 5-year survival rate in Spain ranged from 3% in the advanced stages to 46% in the early stages[9].

Previous studies that have predicted lung cancer in Iran have used the time-linear age-period method[10,11]. Also, the prediction of other cancers is mostly done by Annual percentage change (APC)[12], data mining technique[13], and Joinpoint regression[11]. Golbabaei et al[14] used time series models to predict breast, bladder, and colorectal cancer.

Recently, time series models, including the Autoregressive Integrated Moving Average Model (ARIMA), have been increasingly applied in the field of healthcare. This model comprehensively considers trend changes, periodic changes, and random time series interference, and it also extracts the information contained in the data completely[15].

Therefore, a better understanding of the incidence and mortality of lung cancer in a population can help healthcare systems make the necessary decisions to implement prevention and control programs for risk factors and allocate resources for early diagnosis and treatment of patients in different stages of primary disease is helpful. Lung cancer modelling also helps researchers identify the disease in determining factors. Therefore, the present study was conducted to investigate the 30-year trend of incidence and death of tracheal, bronchial, and lung cancer in Iran based on GBD data from 1990 to 2019 and its forecasting until 2026 based on time series analysis.

MATERIALS AND METHODS

Data source

The age-standardized incidence and death rates (ASR) of tracheal, bronchus and lung (TBL) cancer for the Iranian population were extracted from the Global Burden of Disease (GBD) Online Database from 1990 to 2019, based on gender and year.

Statistical analysis

In the current study, statistical analysis was performed by the time series method and software Interactive Time Series Modeling (ITSM) 2000 and Autoregressive Integrated Moving Average (ARIMA) model. A time series is a set of consecutive observations that are regularly arranged at the same time intervals[16].

The ARIMA model is a popular time series forecasting method proposed by Box and Jenkins[14] in the early 1970s. This model is a combination of several models including the autoregressive (AR) model, moving average (MA) model, and autoregressive – moving-average model (ARMA). These models are based on the results of the autocorrelation function (ACF) and the partial autocorrelation function (PACF). The shape of the ARIMA model is represented by ARIMA (p, d, q), where p is the autoregressive order, d is the number of differentiation times used for data stationery, and q is the moving average order. Akaike information criterion (AIC) was used to measure the prediction error. The lower value of this indicator indicates the appropriateness of the selected model[17].

Given that the amount of data in this time series was 30 and according to scientific texts, predictions should be a maximum of one-fourth of the available data, the predictions were made for 7 years.

RESULTS

Time trend analysis of TBL cancer in Iranian from 1990 to 2019

The age-standardized incidence rate (ASIR) and the age-standardized death rate (ASDR) of TBL cancer in Iran as observed in Figure 1, has an increasing trend. The ASIR from TBL cancer has decreased from 11.07 (95% CI: 9.10-13.35) per 100,000 populations in 1990 to 10.32 (95% CI: 9.79-10.86) in 2003, then increased to 12.24 (95% CI: 11.26-13.16) in 2019. The ASDR from TBL cancer has decreased from 11.8 (95% CI: 9.73-14.37) per 100,000 populations in 1990
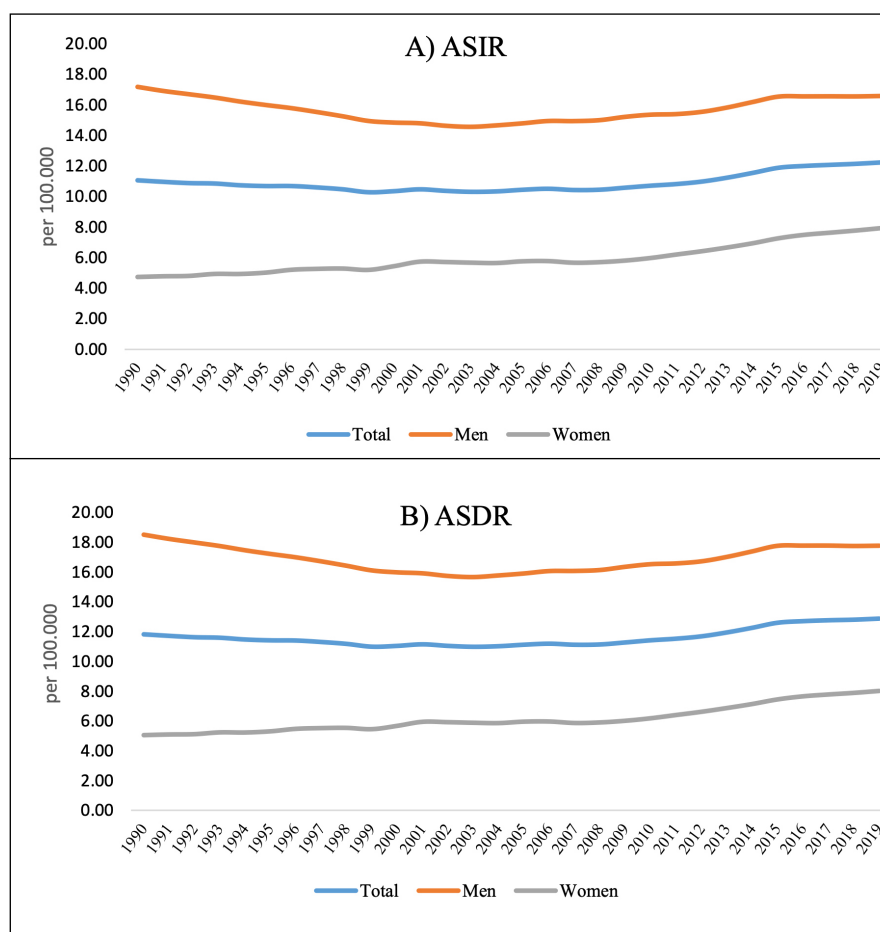
Fig. 1. The trend of age-standardized incidence rate (ASIR) (A) and age-standardized death rate (ASDR) (B) of Tracheal, bronchus, and lung cancer per 100.000 people in the Iranian population from 1990 to 2019.

to 10.99 (95% CI: 10.37-11.67) in 2003, then increased to 12.88 (95% CI: 11.86-13.89) in 2019.

In men, ASIR and ASDR of TBL cancer generally have a declining trend, as observed in Figure 1. The ASIR reached 17.18 (95% CI: 13.81-20.86) per 100,000 populations in 1990 to 16.58 (95% CI: 15.10-18.09) in 2019. However, it should be noted since 2004 (15.78 (95% CI: 14.85-16.73), there has been an increasing trend in TBL cancer ASIR in men. Also, the ASDR reached 18.52 (95% CI: 14.80-22.63) per 100,000 populations in 1990 to 17.78 (95% CI: 16.23-19.41) in 2019. However, it should be noted since 2003 (15.67 (95% CI: 14.68-16.77), there has been an increasing trend in TBL cancer mortality in men.

As observed in Figure 1, in women, the ASIR from TBL cancer has increased from 4.74 (95% CI: 3.98-6.57) per 100,000 populations in 1990 to 7.94 (95% CI: 7.13-8.68) in 2019. The ASDR from TBL cancer has decreased from 5.05 (95% CI: 4.20-7.05) per 100,000 populations in 1990 to 8.03 (95% CI: 7.19-8.80) in 2003, then increased to 12.88 (95% CI: 11.86-13.89) in 2019.

Modelling the ASIR and ASDR of TBL cancer in Iran from 1990 to 2019 and forecasting until 2026

According to the method, to model the trend of TBL cancer data, after plotting the time trend of the data (Figure 1), according to the observed trend in the data, the data stationary on mean was done by using the two-step first-order differentiation method for total and women data and two-step differentiation (once two- order and once first- order) for men data. Then, PAC and PACF diagrams in stationary data were used to determine the model parameters. Then the best model is selected. Evaluation of the model's fitness was examined by the indicator AICC, the residual correlation tests, the Q-Q Plot, and histogram diagrams of the residual distribution. Time trends of stationary data, PAC and PACF diagrams for all data, test results of model fitness, and graphs of residual normality are presented as supplementary material. The best-obtained model and forecasted data for each indicator by gender are described at continues. The predicted values are presented in Table 1 and Figure 2.
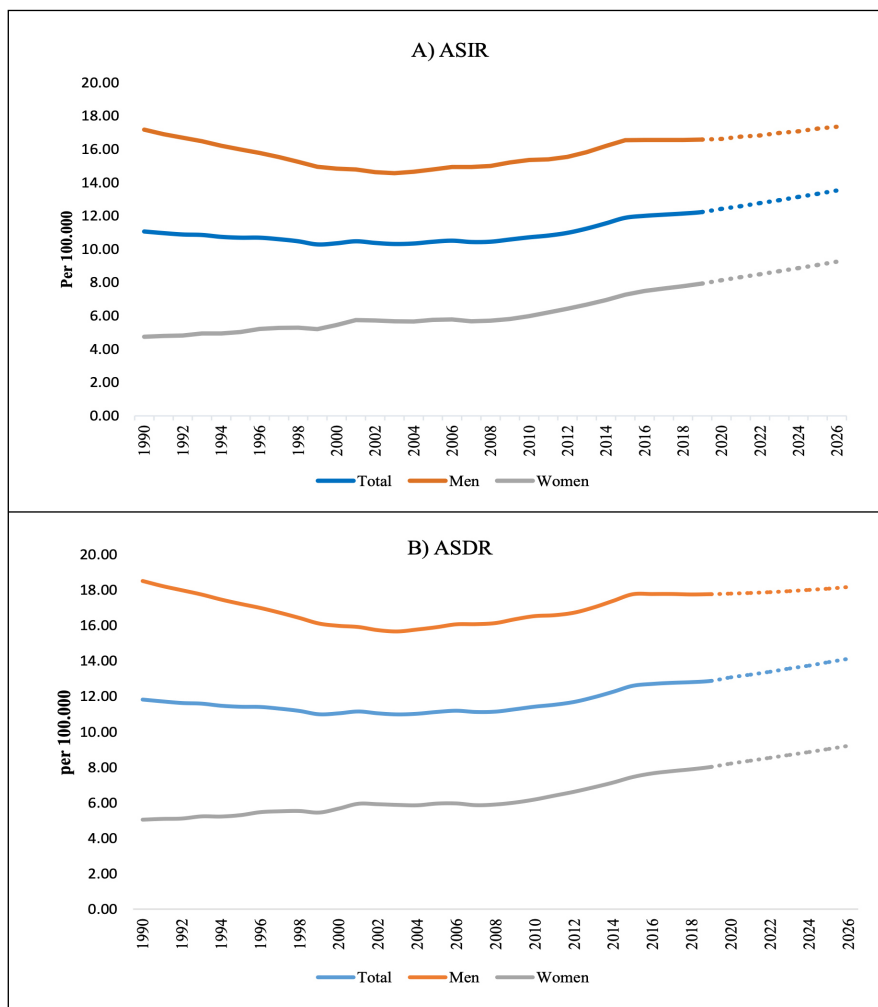
Fig. 2. forecasting of age-standardized incidence rate (ASIR) (A) and age-standardized death rate (ASDR) (B) of Tracheal, bronchus, and TBL cancer per 100.000 people in the Iranian population from 2019-2026.

TABLE 1. Forecasted annual volume of the age-standardized incidence rate (ASIR) and the age-standardized death rate (ASDR) of Tracheal, bronchus, and TBL cancer per 100.000 population in Iran from 2020 to 2026.

Year	ASIR			ASDR		
	Total (95% CI)	Men (95% CI)	Women (95% CI)	Total (95% CI)	Men (95% CI)	Women (95% CI)
2020	12.42 (12.28- 12.57)	16.63 (16.43- 16.83)	8.14 (7.97- 8.32)	13.08 (12.92- 13.23)	17.81 (17.59- 18.03)	8.22 (8.05- 8.40)
2021	12.59 (12.25- 12.93)	16.76 (16.32- 17.19)	8.32 (7.95- 8.69)	13.24 (12.88- 13.60)	17.85 (17.35- 18.34)	8.38 (8.01- 8.75)
2022	12.77 (12.30- 13.24)	16.84 (16.17- 17.50)	8.50 (8.01- 8.99)	13.40 (12.90- 13.91)	17.89 (17.07- 18.71)	8.54 (8.05- 9.04)
2023	12.95 (12.36- 13.54)	16.98 (16.09- 17.87)	8.68 (8.09- 9.27)	13.58 (12.94- 14.21)	17.95 (16.75- 19.15)	8.71 (8.11- 9.30)
2024	13.14 (12.44- 13.83)	17.08 (15.95- 18.22)	8.87 (8.20- 9.55)	13.75 (13.00- 14.51)	18.02 (16.39- 19.64)	8.87 (8.20- 9.55)
2025	13.33 (12.53- 14.13)	17.24 (15.85- 18.63)	9.06 (8.32- 9.81)	13.94 (13.06- 14.82)	18.09 (16.00- 20.19)	9.04 (9.04- 9.80)
2026	13.53 (12.62- 14.44)	17.36 (15.71- 19.02)	9.26 (8.44- 10.08)	14.13 (13.13- 15.13)	18.18 (15.58- 20.78)	9.22 (8.40- 10.04)

Modelling and forecasting the ASIR of TBL cancer

The PAC and PACF diagrams indicate q= 6 and p= 3 for the total population ASIR of TBL cancer. The best forecasting model was ARIMA (0, 2, 2) with AICC= -54.82:

$$X_{(t)} = Z_{(t)} + 0.08016\ Z_{(t-1)} - 0.9195\ Z_{(t-2)}$$

This obtained model predicts the increasing trend in the incidence of TBL cancer in Iran for the next 7 years, and the ASIR of TBL cancer will increase to 13.53 per 100,000 populations in 2026.

The PAC and PACF diagrams indicate q= 10 and p= 7 for men data and the best model for forecasting in this time series was ARIMA (0,2,3) with AICC= -34.98:

$$X_{(t)} = Z_{(t)} + 0.9803\ Z_{(t-1)} - 0.4122\ Z_{(t-2)} - 0.5359\ Z_{(t-3)}$$

Based on the obtained model, it is predicted that in the next 7 years, the ASIR of TBL cancer in men will increase to 17.36 per 100,000 populations in 2026.

The PAC and PACF diagrams indicate q= 7 and p= 6 for women data. The best model for forecasting in this time series was ARIMA (0,2,2) with AICC= -45.96:

$$X_{(t)} = Z_{(t)} - 0.1115\ Z_{(t-1)} - 0.8885\ Z_{(t-2)}$$

Based on the obtained model, it is predicted that in the next 7 years, the increasing trend of the ASIR of TBL cancer in women will be continued and will increase to 9.26 per 100,000 populations in 2026.

Modelling and forecasting the ASDR of TBL cancer

The PAC and PACF diagrams indicate q= 6 and p= 3 for the total population ASDR of TBL cancer. ARIMA (0,2,2) with AICC= -51.91 was selected as the best model for forecasting in this time series:

$$X_{(t)} = Z_{(t)} + 0.09600\ Z_{(t-1)} - 0.9040\ Z_{(t-2)}$$

ìBased on this model, it is predicted that in the next 7 years, the ASDR of TBL cancer will increase to 14.13 per 100,000 populations in 2026.

The PAC and PACF diagrams indicate q= 8 and p= 7 for men data and the best model for forecasting in this time series was ARIMA (0,2,1) with AICC= -33.73:

$$X_{(t)} = Z_{(t)} + 0.9998\ Z_{(t-1)}$$

Based on this model, it is predicted that in the next 7 years, the ASDR of TBL cancer in men will increase to 18.18 per 100,000 populations in 2026.

The PAC and PACF diagrams indicate q= 7 and p= 6 for women data. While the best model for forecasting in this time series was ARIMA (0,2,2) with AICC = -46.18:

$$X_{(t)} = Z_{(t)} - 0.08280\ Z_{(t-1)} - 0.9172\ Z_{(t-2)}$$

Based on the obtained model, it is predicted an increasing trend in the death rate of TBL cancer in women in the next 7 years and the ASDR of TBL cancer will increase to 9.22 per 100,000 population in 2026.

DISCUSSION

This study aimed to investigate the incidence and mortality of TBL cancer in Iran based on GBD data and predict these rates in the next 7 years using the ARIMA time series model.

Monitoring the development and prognosis of a disease is essential for healthcare providers and health policymakers to strengthen their awareness and have the necessary planning to allocate the necessary resources to deal appropriately with the probable issues[18]. ARIMA is one of the most widely used statistical methods for predicting time series that studies a set of time structures in time series data. The ARIMA time series model is an accepted method of forecasting due to its simplicity and systematic structure. The proposed model consists of 4 stages of modelling, which include "evaluation, parameter prediction, feature review, and prediction"[19].

The results of the study show that according to GBD data, the trend of standardized age rates of incidence and death due to TBL cancer in Iran from 1990 to 2019 and in women is increasing generally. Although it shows a decreasing trend compared to 1990 in men, it has had an increasing trend since 2004 and it is predicted that this increasing trend will continue in the coming years.

The results of this study are consistent with the findings by Khanali et al[20] based on the data from the National Cancer Registration Program. The study also showed that the incidence of TBL cancer in Iran in 2016 compared to 2000 had increased by an average of 6.8 (6.7, 6.9) per year in men and 7.7 (7.5, 7.9) in women. In addition, our findings agree with the results of a study by Roshandel et al[21] which predicted that the standardized age incidence of lung cancer in Iran in 2025 will increase by 49.1% compared to 9.5% in 2008.

Meanwhile, the incidence and mortality rate of lung cancer in Iran is on the rise[4], and also predicted that lung cancer with the highest global incidence, motility, and an upward trend by 2040, has considerable global importance[22]; some countries have shown a declining trend. According to GBD data,

the highest decrease in the incidence and standardized age of mortality was observed in Kyrgyzstan (incidence: -54.5% [95% UI: 60.9 to 47.8]), mortality: -53.5% [95% UI: 59.8 to 46.8]), Bahrain (Incidence 52.1% [95% UI: 64.7 to 34.8], mortality 52.1% [95% UI: 64.5 to 34.7] and Kazakhstan (incidence 49.7% [95% UI: 57.1 to 42), mortality 49.5% [95% UI: 56.8to 41.7])[23]. In Europe, the overall incidence of lung cancer in men and women is increasing and decreasing, respectively[24].

The reason for the difference in the incidence and death of lung cancer in Iran with the regions that are witnessing a decreasing trend in these rates needs to be investigated. Smoking is the leading cause of most lung cancers[25] and one of the major health concerns in developing countries including Iran[26]. The risk of lung cancer in a country is determined by the number of cigarettes smoked in that country[27]. In addition, the number of years of smoking, the type of cigarette, and the time of onset of smoking is important concerning the carcinogenicity of smoking[28]. Several studies showed that smoking has been identified as a major risk factor for lung cancer in Iran[4,29,30]. The chance of developing lung cancer in smokers compared to non-smokers is 5.4 (95% CI: 3.2 -8.9)[30], and its detection rate in long-term smokers is reported to be 3.73%[31]. Results of various studies demonstrate that the decrease, increase, or stable trend in lung cancer incidence and mortality rates occurs based on smoking trends and after a delay time[27,32-34]. The implementation of the National Tobacco Prevention Program in Iran has been able to reduce the consumption of cigarettes and other tobacco types. If smoking decreases in the country, is it time to see its effect on reducing lung cancer rates? Or the implementation of the tobacco prevention program in the country needs to be reviewed.

The incidence of lung cancer is not common among young people as the average age of lung cancer in Iran is old age and mainly in the age group of 80 to 84 years[4], therefore the aging rate in each population is another risk factor in the incidence of cancer[35]. Regarding increased aging in the country, is it possible to expect a decrease in the incidence and mortality rate of TBL cancer? In general, informing and educating teenagers and young people about the harmful effects of smoking, providing smoking cessation programs, reducing access to tobacco products by adopting appropriate laws and encouraging tobacco companies to publish information on cigarette ingredients can reduce the prevalence of smoking[26].

Another substantial factor in the incidence of lung cancer in Iran is occupational exposure[4]; Whether the Occupational Medicine and Periodic Examination Act and early detection of patients have been successful in reducing occupational exposure is also one of the issues that should be considered in reducing lung cancer statistics.

Human Development Index (HDI) can be an important factor in reducing the incidence and mortality of patients[22,36]. So that the correlation between HDI and the standardized incidence rate of lung cancer in Asia has been reported as 0.345 (p=0.019)[37]. In the United States, the reason for the increase in the survival rate of lung cancer has been attributed to the implementation of new methods of prevention, screening, and treatment[38]. According to the United States Preventive Services Task Force (USPSTF) in 2021, lung cancer screening for all individuals over the age of 50 with a history of smoking at least 20 packs per year by low-dose computed tomography CT) is essential[39]. It is also recommended to redefine lung cancer screening in women[31]. However, there is currently no codified program for lung cancer screening in Iran[40].

Air pollution is probably a risk factor for lung cancer, therefore, the results of a study in Tehran showed that areas with higher concentrations of NOx (IRR = 1.05, for every 10 units increase in air pollution), benzene (IRR = 3.86), toluene (IRR = 1.50), ethylbenzene (IRR = 5.1-9.6), p), o-xylene (IRR = 7.93), m-xylene (IRR = 2.63) and TBTEX (IRR = 1.21) were significantly high in lung cancers incidence[41]. Therefore, controlling air pollution, especially in metropolitan areas, and providing effective solutions to reduce its impact on individuals, can be effective in reducing the incidence of lung cancer in Iran.

Another important point to consider in reducing mortality and increasing the survival of TBL cancer patients is to take advanced treatment. Although lung cancer survival has only slightly improved in recent decades, available screening, and early diagnosis as well as advanced targeted therapies and immunotherapy are likely to reduce mortality and improve patient survival outcomes[42].

In general, it can be said that expecting a reduction in lung cancer incidence and mortality in Iran soon is a far-fetched issue, but this issue should not affect the country's health decision-makers at the macro level for accreditation and planning to control its risk factors such as prevention and control of smoking, reducing occupational exposure and reducing air pollution, as well as setting up a TBL cancer screening system in the country.

CONCLUSIONS

The current trend in the incidence and mortality of TBL cancer in Iran is an increasing trend and it seems it will continue in the coming years. Therefore, the reasons for the increase in this trend in

Iran along with the reasons for the decrease in other countries should be fully investigated and – using the experiences of successful countries in reducing TBL cancer statistics – effective measures should be considered to reduce the incidence and mortality and consequently the burden of the disease in the country.

Authors' Contributions:
A. M and A. M. M are the guarantors of the manuscript. A. M., G.H and A. M. M participated in the conception of the research ideas, study design, interpretation of the findings, and writing of the first draft of the manuscript. A. M. M, H. S and Z. Gh retrieved information from the relevant databases and performed the statistical analysis. All authors read and approved the final manuscript.

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Informed consent:
In this study, informed consent was not required due to the use of an online database.

Availability of data and material:
The data and material used in the current study are available from the corresponding author upon reasonable request.

Conflict of interest:
All authors declare that they have no conflict of interest.

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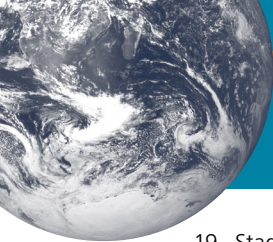
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