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ORIGINAL RESEARCH ARTICLE

The study of trends in mortality of respiratory system cancers in Babol, North of Iran (2013-2021)

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ABSTRACT

Background: In Iran, cancers are known as the second leading cause of death, among which respiratory system cancers are particularly important because lung cancer is the second most common cause of death in this country. This study aimed to estimate the crude and age-standardized mortality and its trends during 9 years in the Northern city of Iran, Babol.

Methods: In this cross-sectional study, all the recorded deaths due to respiratory system cancers in Babol during the years 2013-2021 on the Classification of Causes of Deaths and Death Registration System of Babol University of Medical Sciences were taken into consideration, and the population estimate was based on the latest census. Finally, the crude and age-standardized rates of mortality and trends of cancer incidents were calculated.

Results: In general, 393 deaths with an overall mean age of 67.8±3.9 years have happened due to respiratory system cancers. The crude and standardized rates of respiratory system cancers increased from 6.5 and 5.5 per hundred thousand people in 2013 to 9.1 and 7.8 per hundred thousand people in 2021, respectively. With each decade in age, their trends increased significantly in men (p=0.024) and remained constant in women (p=0.262). In examining the trend of respiratory system cancers, we found an increasing trend for lung cancer and a constant trend for larynx and oropharynx cancers. There was also a decreasing trend for hypopharyngeal cancer.

Conclusions: The age-standardized rate and trend of respiratory system cancers are increasing. Therefore, it is important to prevent their prevalence by reducing the risk factors and increasing the general awareness of risks and timely diagnosis.

Key words: respiratory system, lung, trends, mortality, Iran.

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Ethics approval and consent to participate: This research has been approved by the Ethics Committee of Babol University of Medical Sciences with the reference number IR.MUBABOL.HRI.REC.1401.153.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Introduction

Cancer is a disease caused when cells divide uncontrollably and spread to surrounding tissues [1]. According to the latest reports (GLOBOCAN 2020), cancer is the first or second leading cause of death in many countries of the world, with the number of newly diagnosed cancer cases of 19.3 million, and almost 10.0 million deaths due to cancer [2]. In general, men die nearly one and a half times more than women due to cancer, while this ratio is reversed in cancer incidence [3]. Asia contains 60% of the global population and 50% of cancer cases. It accounts for 58% of cancer deaths in both genders [2]. Iran, located in West Asia, ranks 27th among countries for all ages and genders. It has more than 130 thousand incidences and nearly 80 thousand deaths among all cancers [3]. The increase in air pollution, smoking, and other risk factors, along with the low prognosis of patients' survival [4,5], has led to placing lung cancer in a special place among cancers in the world.

The respiratory system is divided into two main parts: the upper respiratory tract, from the nasal cavity to the upper part of the larynx; and the lower respiratory tract, which includes the lower part of the larynx to the alveoli. The lung is the most important part of the respiratory system in terms of oxygen exchange [6,7]. Lung cancer is the leading cause of death, responsible for more than 1.5 million deaths worldwide. With 9,000 deaths, lung cancer is the second most common cancer after stomach cancer in Iran [3]. Early symptoms of lung cancer are usually hidden. Lung cancer symptoms vary depending on the involvement of the upper or lower respiratory tract. However, it usually includes symptoms such as cough and shortness of breath at the beginning [8]. The first step is usually to perform a chest X-Ray to determine if the patient has any tumors, atelectasis, or other cases that require computed tomography (CT). Finally, the biopsy and pathology reports contribute to a final diagnosis [9,10]. The treatment of this cancer also includes radiotherapy, chemotherapy, surgery, and other options depending on the stage of the cancer and the type of lung cancer [11]. Although screening using some diagnostic parameters could be helpful [12], knowing the mortality trends will help us better plan and control this cancer in the future.

Increasing life expectancy and reducing mortality rates should be the goal of every country's socio-economic and health policies [13]. Furthermore, identifying mortality trends helps healthcare systems choose appropriate public health priorities and allocate resources accordingly. On the other hand, monitoring and evaluating the effectiveness of preventive and therapeutic measures can be increased by analyzing mortality data [14].

The city of Babol, with a population of nearly 550,000 people and an area of about 15,000 square kilometers, is the most populated city in Mazandaran province. Also, it has the highest Tabari population in the world [15]. Considering the importance of lung cancer in the world and in Iran, as well as the changes in its incidence and mortality trends within the past years and to update the mortality rate of this cancer, we decided to analyze the trend of lung cancer mortality in a 9-year period, so we can compare it with national and global statistics.

Methods

In this cross-sectional study, we collected all deaths registered due to lung cancer from the Classification of Causes of Deaths and Death Registration System of Babol University of Medical Sciences, in Babol during a 9-year period from 2013 to 2021. This study was approved by the Code of Research Ethics (MUBABOL.HRI.REC.1401.153).

The Civil Registration and Vital Statistics (CRVS) system, which is responsible for registering and classifying deaths in almost all provinces of Iran, is an important source for studying cancer mortality data [16]. The Health Deputy of the University of Medical Sciences has a system for registering and classifying deaths including the sources for obtaining causes of death. It consists of official death certificates from funeral homes, hospitals, forensic medicine, and other sources. Experts examined the quality of information to qualitatively examine deaths caused by lung cancer. They remove duplicate cases and identify the improbable causes of death in terms of gender and age, the wrong definition of codes, and other cases; if necessary, they were reviewed by re-examining the relevant records. Finally, after rechecking and minimizing errors in data recording and after approval by the officials of the Ministry of Health in this program, the data has gained the validity to be reported in this study.

The causes of death were coded by the International Classification of Diseases 10th Revision (ICD-10) [17]. Therefore, the code of the respiratory system was according to its anatomy from top to bottom [7] and these codes were allocated by GLOBOCAN 2020 [3] as follows: oropharynx cancer C09-10, nasopharynx C11, hypopharynx C12-13, larynx C32, and lung C33-34. Since nasopharyngeal cancers have not been reported in Babol during 2013-2021, it was excluded from the study. It should also be noted that according to ICD-10, code C33 is related to malignant tracheal cancer. Since the code C33-34 was mentioned under the title of lung in the GLOBOCAN 2020 database, we also used the same method.

The sampling method in this study was census and all the currently registered cases of death due to lung cancer during these 9 years were examined. A population estimate was made for these 9 years to calculate and compare the death rates from respiratory cancers. For this purpose, the target population was calculated in general, separately by age groups, and by considering the population growth between census years.

The data were analyzed using STATA software version 14. Qualitative data were reported as frequency and percentage and mean and standard deviation were used to show quantitative data. The population of the city was analyzed by age groups, using the census data of the Iran Statistics Center to calculate the crude death rate. Also, the global standard population reported by International Agency for Research on Cancer (IARC) and the standard population presented in GLOBOCAN were used to calculate the age-standardized rate (ASR) using the direct method per 100,000 people. The crude rate and age-standardized rate were reported with a 95% confidence interval. According to the mentioned factors, the Cochran-Armitage Test was used to calculate the trend of mortality during the studied years. A $p<0.05$ was considered statistically significant.

Results

In this study, among 3,294 cancer patients in Babol who died during 2013-2021, 393 deaths (11.9%) were due to respiratory system cancers; 277 cases (70.5%) were male, and 189 patients (59.1%) were city residents. Among respiratory system cancers, lung cancer was the most common cancer with 314 (79.9%) deaths. Larynx cancer with 69 (17.6%) deaths, oropharyngeal cancer with 8 (2.0%) deaths, and hypopharyngeal cancer with 2 (0.5%) deaths are in the next ranks, respectively. The mean and

standard deviation of the overall age of the patients was 67.8±13.9 years (with an age range from 20 to 98 years). Although the mean age of men (68.3±13.6) was almost two years higher than women (66.5±14.7), this difference was not statistically significant (p=0.243). Hypopharyngeal cancer (76.5±4.9) and larynx cancer (70.0±14.5) had the highest mean age among other respiratory system cancers, respectively. The lowest age among respiratory system cancers includes oropharyngeal cancer (66.9±19.2) and lung cancer (67.3±13.7). The mean and standard deviation of the age of death cases by year are presented in Figure 1. In terms of the number of deaths by gender and age groups in respiratory system cancers, we have seen a continuous increase, which was significant in both genders (p<0.05) (Figure 2); respiratory system cancers based on age groups in Babol, Iran (2013-2021) (p<0.001 for men and p<0.001 for women). The crude death rate in all cases was higher than the age-standardized mortality rate (ASMR) for respiratory system cancers. The crude and ASMR of respiratory system cancer in 2013 were 6.5 and 5.5, respectively, which reached 9.1 and 7.8 per 100,000 people in 2021 with an increasing trend. This mortality rate was statistically significant (p=0.012) (Figure 3). In a more

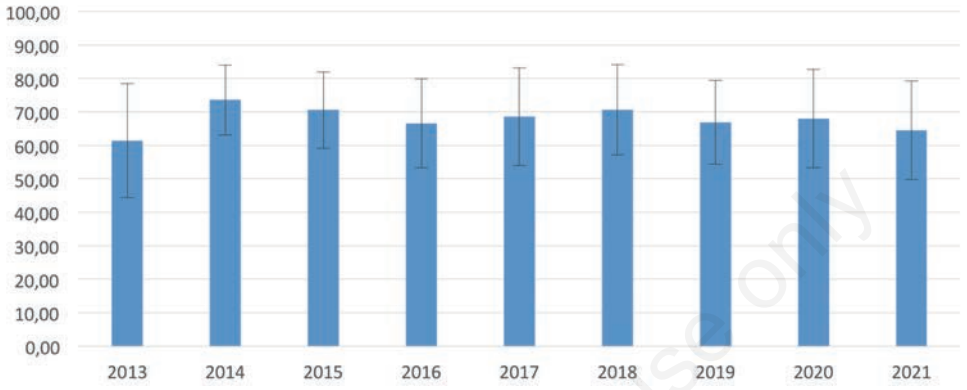

Figure 1. Mean (standard deviation) age of respiratory system cancers in the studied years.

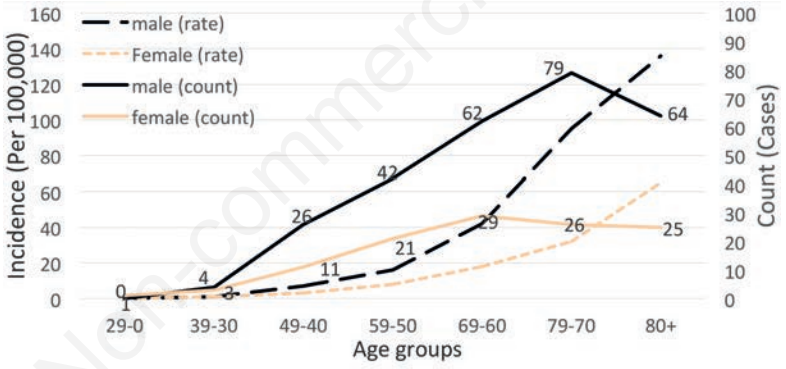

Figure 2. Trend of the number and incidence of death per 100.000 population.

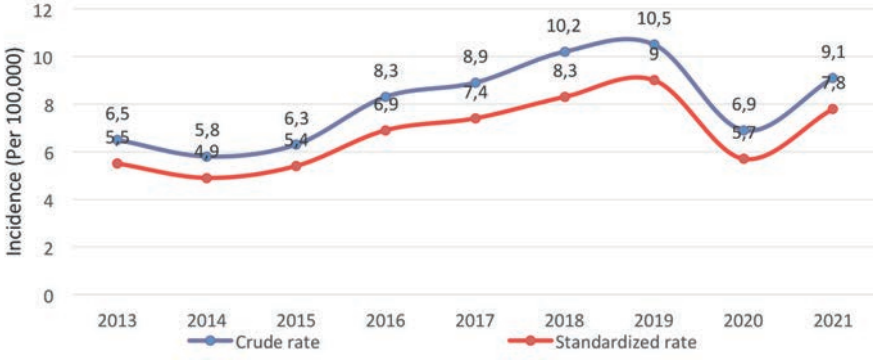

Figure 3. Crude mortality and ASMR of respiratory system cancers per 100,000 population in Babol, Iran (2013-2021).

detailed examination of the mortality rate of respiratory system cancers based on gender and year, we observed the highest crude death rate in 2018 among men and in 2019 among women, and the highest age-standardized rate in 2019 among both genders. The lowest mortality rate for men was in 2014 and for women was in 2015 which were actually the initial years of the study (Table 1). In examining the mortality trends of respiratory system cancers, the trend of ASMR for lung cancer had a significant increasing trend. Hypopharyngeal cancer, with only two deaths reported in 2013, had a decreasing trend. The oropharynx and larynx cancers have not changed during these years and had a constant trend (Table 2).

Discussion

This study was conducted in the 9-year period of 2013-2021 in Northern Iran. The results showed a significant upward trend in respiratory system cancer mortality rates. Lung cancer was the most common cancer, followed by larynx and oropharynx cancers. The average age of respiratory system cancers has been almost constant within 9 years of our study. However, the trends in death rates increased as the study years progressed from 2013 to 2021. In terms of gender, men died more than women due to respiratory system cancers in most of the years under study (the ratio of men to women was 2/4).

The ASMR for respiratory system cancers in Northern Iran has increased 1.4 times between 2013 (5.5 per hundred thousand peo-

Table 1. Crude mortality and ASMR of respiratory system cancers divided by each studied year and gender per 100.000 population in Babol, Iran (2013-2021).

Year	Male			Female		
	Crude death rate	Age - Standardized mortality rate		Crude death rate	Age - Standardized mortality rate	
		Rate	95% Confidence interval		Rate	95% Confidence interval
2013	9.0	7.5	4.4-10.6	3.9	3.3	1.2-5.4
2014	7.3	6.1	3.2-8.9	4.3	3.7	1.5-5.9
2015	9.8	8.4	5.1-11.7	2.7	2.3	0.6-4.0
2016	12.7	10.8	7.1-14.6	3.8	3.0	1.1-4.9
2017	11.0	8.8	5.5-12.0	6.7	5.9	3.2-8.7
2018	14.2	11.2	7.5-14.9	6.3	5.3	2.7-7.8
2019	13.6	11.8	7.9-15.7	7.3	6.1	3.4-8.9
2020	10.2	9.0	5.6-12.4	3.6	2.6	0.9-4.2
2021	13.6	11.5	7.8-15.2	4.6	4.0	1.8-6.2

p trend for male = 0.024 and female = 0.262.

Table 2. The trend of crude mortality and ASMR of the respiratory system cancers divided by each studied year per 100.000 population in Babol, Iran (2013-2021).

Year	Rate	Oropharynx	Hypopharynx	Larynx	Lung
2013	Crude	0.2	0.4	0.2	5.7
	Standardized	0.2	0.3	0.1	4.8
2014	Crude	0.2	0	1.7	3.9
	Standardized	0.2	0	1.5	3.2
2015	Crude	0.4	0	1.5	4.4
	Standardized	0.3	0	1.3	3.8
2016	Crude	0.2	0	0.8	7.3
	Standardized	0.2	0	0.6	6.1
2017	Crude	0.4	0	2.0	6.5
	Standardized	0.3	0	1.7	5.5
2018	Crude	0	0	1.8	8.4
	Standardized	0	0	1.4	6.9
2019	Crude	0	0	1.8	8.7
	Standardized	0	0	1.6	7.4
2020	Crude	0	0	1.4	5.5
	Standardized	0	0	1.1	4.7
2021	Crude	0.2	0	1.4	7.5
	Standardized	0.1	0	1.1	6.5
p		0.231	0.025	0.183	0.010

ple) and 2021 (7.8 per hundred thousand people) and this increasing trend was significant. In terms of gender, we observed an increasing trend in respiratory system cancers in men, unlike women, which had a constant trend. In this study, the mortality rate has also indicated an increasing trend by age. Since various studies have examined respiratory system cancers separately, here two important and common cancers of the respiratory system (lung and larynx cancers) have been compared with other studies.

In this study, lung cancer was the most common cancer with a standardized rate of 6.5 per hundred thousand people. It was the cause of death for nearly four-fifths of patients with respiratory system cancers. Also, lung cancer had an increasing trend in Northern Iran for 8 years. In a systematic review and meta-analysis study conducted using Iranian death registration data from 1990-2016, in both sexes, the ASMR reached from 8.0 per hundred thousand people in 1990 to 15.1% per thousand people in 2001. After that, this rate decreased from 2001 and reached 7.7 per hundred thousand people in 2015. In general, they reported a decreasing trend in lung cancer and noted that this rate has changed by nearly 3% every year [18]. Lung cancer with ASMR of 6.5 per hundred thousand people compared to worldwide cases (0.18 per hundred thousand people) [3], Asia (19.3 per hundred thousand people) [3] and Iran (10.9 per hundred thousand people) [3] has caused less deaths in Babol. The cultural status of smoking cigarettes and tobacco as the most important risk factor for lung cancer in men and women may explain the difference in the lung cancer death rate in this city compared to other major cities in the world and Asia. In Iran, the provinces located in the West and Center of the country have higher ASMR than the Northern provinces. This is due to more air pollution and high concentration of dust in their air. Although the standardized rate of lung cancer in this city was lower than in Iran, Asia, and worldwide, it has an increasing trend, the cause of which can be other risk factors of this cancer, such as chronic obstructive pulmonary disease (COPD). The prevalence of lung cancer in COPD patients is reported to be more than 5%; it is reported to be 1.5 times higher in people who smoke or have smoked before. Also, this rate is higher in men than in women [19]. Three of the important risk factors for this disease are smoking, household air pollution exposure, and ambient particles. Although the trend of disability-adjusted life years (DALYs) was stable for smoking factor and decreasing for household air pollution exposure due to COPD in low-middle-SDI regions (including Iran), this trend was increasing for ambient particles [20]. In this city, the ambient particles have also increased probably due to the increase in urbanization, the increase in the habit of using cars, more construction sites, etc. Also, in the study of Hashemi *et al.*, they found an upward trend of COPD during 1995-2015 in terms of DALYs in Iran [21]. This can justify the increasing trend of lung cancer in this city due to the increase of ambient particles.

In the study by Yang *et al*. [22], the almost 40-year trend of lung cancer was compared between China and the United States from 1980-2018. According to their study, lung cancer has been increasing in men and -with a slower trend- in women, while ASMR in the United States has been decreasing from 1990-2000. At the beginning of the study, this death trend was higher in men and women in the United States than in both genders in China; at the end of the study period, this rate decreased for both genders [22]. Compared to Iran and even in this study, both countries have higher ASMR. The reason for this difference is that the death rates are positively related to the human development index (HDI) in different countries [2]. Therefore, countries like the United States, many European countries, and even China have higher death rates due to a much higher HDI than Iran.

Although in this study, the gender status of the patients was examined in general, since lung cancer covers nearly 80% of all cancers of the respiratory system, the results can be generalized to this cancer as well. In a study on the ASMR from 2002-2012 in many countries of the world from Korea to England and from the United States to Australia, they pointed out that the Average Annual Percent Change (AAPC) and the trend of the ASMR have been decreasing for men in many countries of the world, while this trend has increased for women in many countries [4]. During the last decade, tobacco consumption decreased in men in many countries. However, this consumption had an upward trend in women, which can explain the increase in lung cancer death rates in women. In our study, we found an increasing trend for men along with a constant trend for women in recent years. The reason could be the lack of proper policies for smoking cigarettes and tobacco (especially hookah smoking), along with the lack of proper screening of patients [low dose computed tomography (CT)] for this cancer. In this study, laryngeal cancer was the second most common cancer of the respiratory system. It had an ASMR of 1.1 per hundred thousand people and was the cause of death for nearly one-fifth of patients. Also, the trend of this cancer during 2013-2021 in Northern Iran had a constant trend (a non-significant increase). The importance of timely and accurate diagnosis and the conditions affecting laryngeal cancer make it an uncommon case in oncology. The ASMR in this study was lower than the whole country of Iran (2.0 per hundred thousand people) [3], but it was higher compared to the world (1.0 per hundred thousand people) [3] and even Asia (1.0 per hundred thousand people) [3]. The trend of this cancer decreased in the world from 1990-2019, and in countries with higher socio-demographic indices (SDIs), this decrease was steeper. But low or low-medium SDI countries (like East and Southeast Asia, South Africa, and the Middle East countries) have an increasing trend [23]. Examining the trend for almost two decades in Central and South American countries, we generally see a decrease in the ASMR, especially in men compared to women [24]. It should be noted that it is common for respiratory system cancers, including the larynx, to occur a few years after exposure to a risk factor. This creates a delay in diagnosis, which hinders their timely diagnosis. Also, because of the lack of proper screening methods, reducing risk factors has become the only effective method. Smoking cigarettes and tobacco are the most important risk factors for this cancer. Occupational exposure to asbestos and sulfuric acid is another risk factor [23]. Because of applying the appropriate policies to reduce smoking cigarettes and tobacco in the world, we have seen a decrease in the ASMR and in the trend of this cancer over the recent years; while in Iran and in Babol, we have a high ASMR due to the lack of proper policy for these risk factors and the increase in their use, especially in women. This rate will increase in the coming years if it is not controlled.

Study limitations and strengths

This study has limitations due to the lack of examination of other variables such as occupational and educational status because of the high missing and also due to the low estimation of respiratory system cancer mortality resulting from improper diagnosis or insufficient records. The study strength includes reporting the ASMR for each respiratory cancer along with their trends within a 9-year period.

Conclusions

This study showed respiratory system cancers in Babol, Northern Iran had an increasing trend during 2013 to 2021. This trend is not limited to a specific age and gender. In Babol, the occurrence of oropharynx and hypopharynx cancers was stable and decreasing. However, this control should be also implemented for lung cancer (with an increasing trend) and larynx cancer (with a

stable trend), which are the most prevalent cancers of this system. The respiratory system cancers take several years to appear after exposure to its risk factors and have the problem of late referral of patients, which hinder their timely diagnosis. Besides, diagnostic methods are only performed for lung cancer which is only possible in developed countries, and they are not performed supervised and precisely in other countries. Therefore, reducing exposure to risk factors, especially smoking cigarettes and tobacco, and increasing public awareness of the dangers of these risk factors should be on politicians' agendas. It is necessary to determine the contribution of each of these factors in future studies for better investigation.

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