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Longitudinal Pattern of Cancer Mortality Rates among Iranian Population from 1990 to 2015, Using a Growth Mixture Model

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Abstract

Background: Cancer is among the most important causes of death worldwide. This disease is the third main cause of death in Iran.

Method: In the present study, mortality rates of Iranian men and women due to various cancers were analyzed using a database from 1990 to 2015 (in 5-year intervals), available in the Global Burden of Disease (GBD) study. For statistical modeling, Latent Growth Mixture Models (LGMMs) were used to determine the subgroups of cancers, in which cancers within each group had similar trends of mortality rates over the period of study.

Result: The LGMM identified 3 classes for both female and male data. For females, most cancers were allocated to the class with a slow increase in cancers mortality over time. Cancers in Class 2, including breast, stomach, trachea, bronchus and lung, colon and rectum, liver, brain, and nervous system, ovarian, and pancreatic had an increasing trend until 2000; then, they reached a fixed trend during 2000-2005, followed by showing an increasing trend once again. In the last class, leukemia showed a decreasing trend of mortality rate over time. For male data, most cancers were allocated to the class with a very slowly increasing trend in mortality rate over time. In both Class 2 (including bladder, brain and nervous system, liver, non-Hodgkin lymphoma, and pancreatic cancers) and Class 3 (including breast, larynx, leukemia, prostate, stomach, trachea, bronchus, and lung cancers), there was an increasing trend of mortality rate over time until 1995 and then it reached an almost stable trend during 1995-2005 followed by an increasing trend once again.

Conclusion: Hence, the general status of cancer mortality rates shows an ascending trend. Therefore, it is necessary to provide programs for early detection, screening, preventing, public health program planning, and patient care improvement.

Keyword: Cancer, Mortality rate, GBD study, Growth mixture model, Iran

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Introduction

Human, as a multicellular organism, is at times exposed to a treacherous disease called cancer, which is the result of unbalanced and uncontrolled cell growth. More precisely, cancer develops from the uncontrolled proliferation of cells that do not follow the normal process of cell division.[1] This process ultimately leads to the production of malignant tumors in areas of the body that is able to spread to other areas.[2] Today, many families are suffering from cancer, which is the reason for almost one in six deaths across the world.[3]

The disease is the second leading cause of death in the world after cardiovascular disease.[4] According to estimates, by 2016, around 42 million people worldwide were affected by a variety of cancers, and about 8.9 million people had died from various cancers around the world.[5] For a variety of reasons, such as increasing population growth and improving public health as

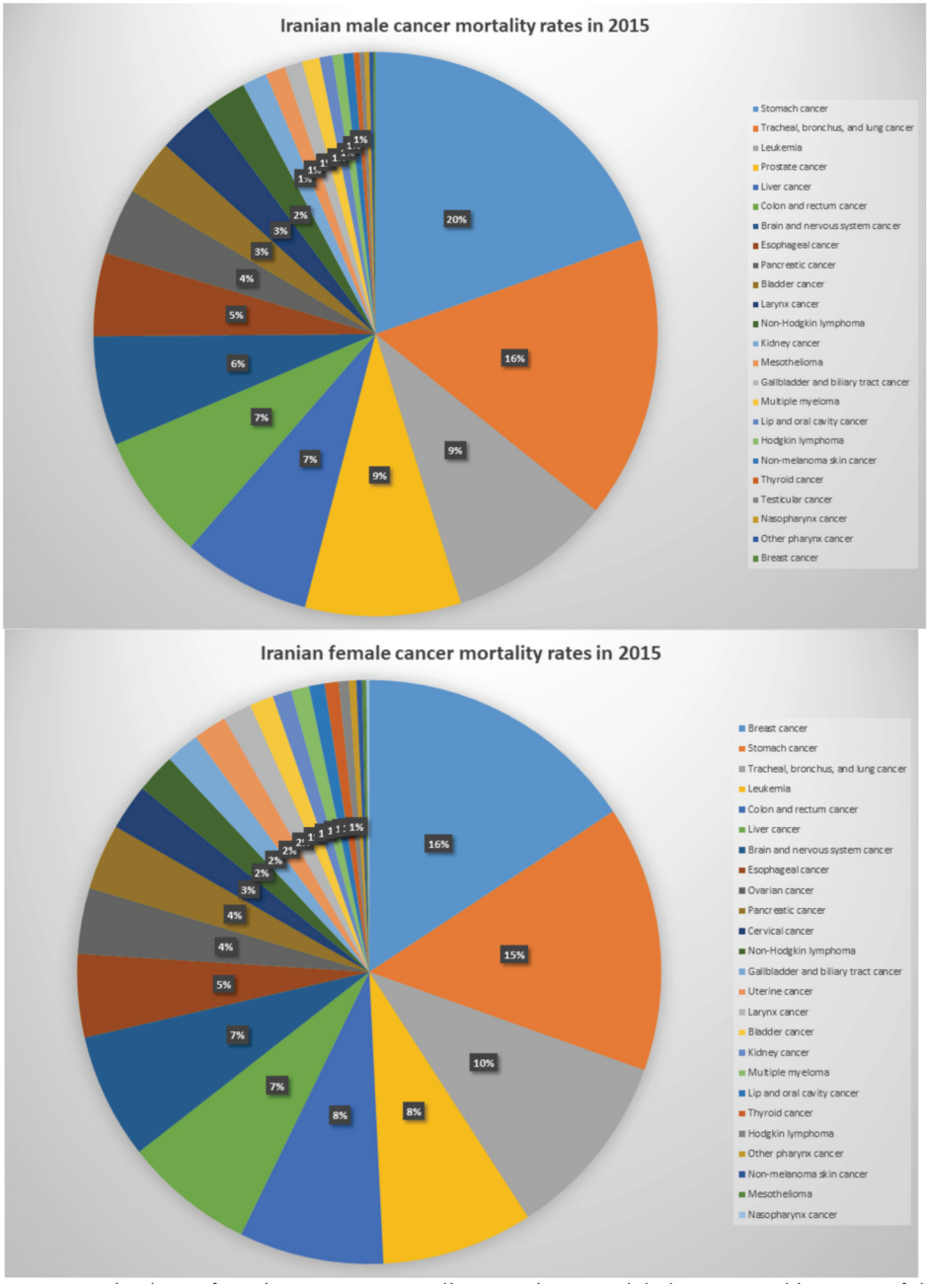

Figure 1. Pie chart of Iranian cancers mortality rates in 2015; labels are sorted in terms of the decrease in mortality rates.

a result of increasing life expectancy in different societies, cancer mortality rates, are still rising.[6] In general, statistics indicate that cancer is more prevalent in countries with higher income, due to unsatisfactory diets, inactivity, and alcohol and cigarette consumption.[7] The most common types of cancer in the world are breast cancer, followed by colon and rectum, lung, and prostate.[8] The stomach and liver cancers are in the lower ranks, with different prevalence rate in different countries. The highest burden of cancer is related to developed countries such as the United States, Denmark, Australia, and several other European countries.[9] Between 2006 and 2016, the number of new cases of cancer in the world rose by 33%, where the worst cancer death rate among women and men in 2016 was breast cancer with 523,000 victims and lung cancer with 1.2 million deaths, respectively.[10]

Iran as a developing country has witnessed an increase in the incidence of cancer in recent years due to more industrialization and changes in the lifestyle of the people. In Iran, following heart disease and natural disasters and events, cancer is the third cause of death. The incidence of various cancers among men is 110 and in women is 98 per 100,000 while the mortality rate is 61 and 41 per 100,000 people in men and in women, respectively.[11] The most common cancer among Iranian men and women is stomach and breast cancer, respectively.[11] In addition, the most common cancers in the Iranian men are currently stomach, prostate, bladder, colorectal and esophagus, and women are more commonly diagnosed with breast, stomach, liver, and thyroid cancer.[11] According to the results of a large study recently performed on 32 types of cancer in 195 countries of the world, Iran's cancer mortality rate has almost been doubled within 1990 and 2015.[10] According to the results of this study,

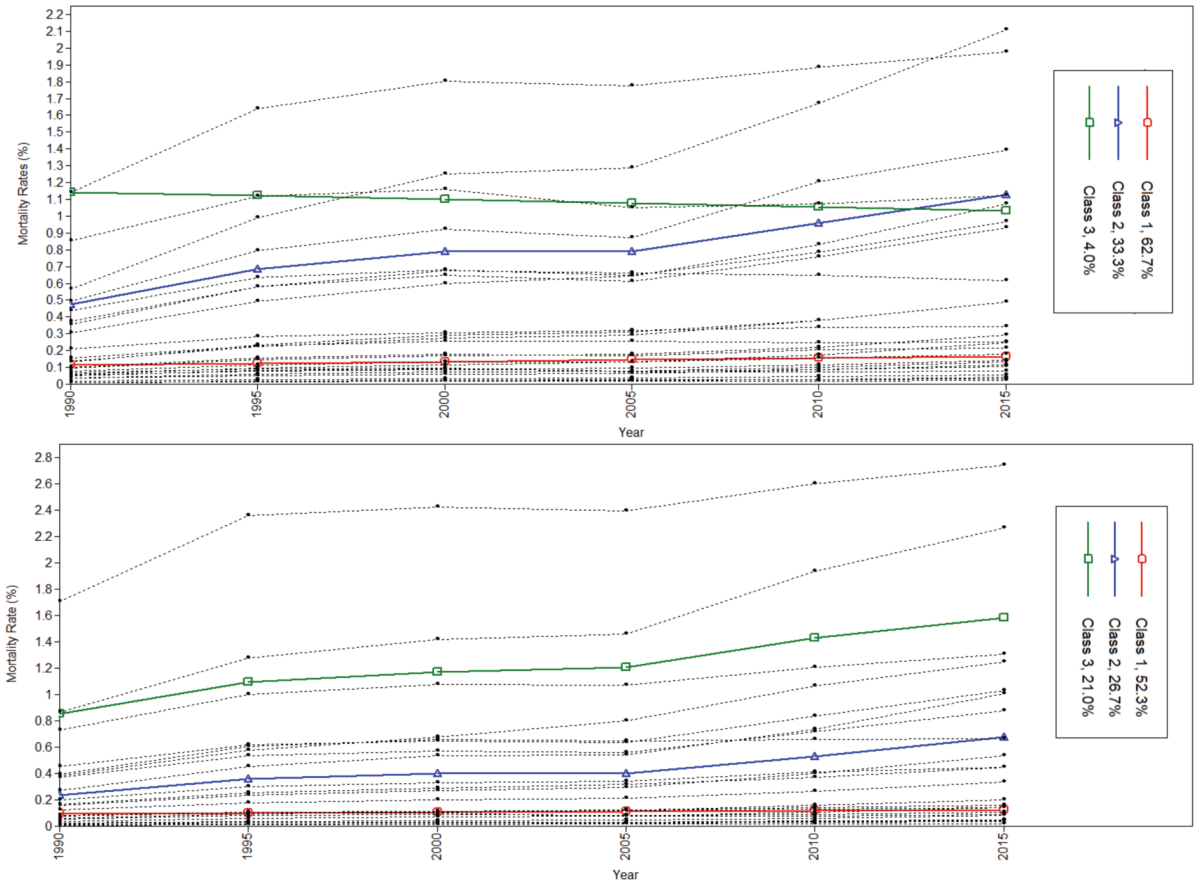

Figure 2. Cancer mortality and estimated trend in classes for females (above) and males (below).

Table 1. Mortality rates (per 100,000) for various cancer types for every block of 5 years.

	Female Data						Male Data					
						Year						
Cancer Name	**1990**	**1995**	**2000**	**2005**	**2010**	**2015**	**1990**	**1995**	**2000**	**2005**	**2010**	**2015**
Bladder cancer	0.06	0.10	0.12	0.13	0.16	0.18	0.16	0.25	0.29	0.31	0.37	0.44
Brain and nervous system cancer	0.37	0.58	0.65	0.61	0.76	0.93	0.37	0.53	0.57	0.56	0.71	0.88
Breast cancer	0.56	0.99	1.25	1.29	1.67	2.11	0.01	0.01	0.01	0.01	0.02	0.02
Cervical cancer	0.21	0.28	0.31	0.32	0.34	0.34	-	-	-	-	-	-
Colon and rectum cancer	0.31	0.49	0.60	0.64	0.83	1.07	0.27	0.45	0.54	0.54	0.74	1.01
Esophageal cancer	0.36	0.58	0.68	0.66	0.65	0.62	0.39	0.60	0.66	0.65	0.66	0.67
Gallbladder and biliary tract cancer	0.16	0.23	0.26	0.25	0.25	0.25	0.08	0.11	0.11	0.12	0.13	0.14
Hodgkin lymphoma	0.07	0.09	0.09	0.07	0.07	0.087	0.08	0.11	0.10	0.08	0.08	0.09
Kidney cancer	0.05	0.08	0.09	0.09	0.11	0.14	0.06	0.09	0.11	0.12	0.16	0.20
Larynx cancer	0.10	0.15	0.18	0.17	0.20	0.21	0.20	0.30	0.33	0.34	0.41	0.41
Leukemia	0.85	1.12	1.16	1.05	1.07	1.12	0.73	1.00	1.08	1.07	1.20	1.31
Lip and oral cavity cancer	0.05	0.08	0.09	0.08	0.08	0.12	0.05	0.08	0.09	0.08	0.09	0.10
Liver cancer	0.44	0.63	0.68	0.65	0.78	0.97	0.45	0.62	0.65	0.64	0.83	1.03
Mesothelioma	0.01	0.02	0.02	0.03	0.03	0.03	0.06	0.09	0.11	0.12	0.14	0.16
Multiple myeloma	0.04	0.06	0.07	0.08	0.10	0.13	0.03	0.06	0.07	0.08	0.10	0.14
Nasopharynx cancer	0.01	0.01	0.02	0.02	0.02	0.02	0.02	0.03	0.03	0.03	0.03	0.04
Non-Hodgkin lymphoma	0.10	0.15	0.17	0.187	0.227	0.29	0.12	0.18	0.20	0.21	0.26	0.34
Non-melanoma skin cancer	0.01	0.02	0.02	0.02	0.03	0.04	0.02	0.04	0.04	0.05	0.06	0.08
Other pharynx cancer	0.02	0.03	0.03	0.04	0.05	0.05	0.01	0.02	0.02	0.02	0.03	0.03
Ovarian cancer	0.14	0.22	0.27	0.29	0.38	0.49	-	-	-	-	-	-
Pancreatic cancer	0.13	0.23	0.29	0.31	0.38	0.49	0.16	0.24	0.27	0.30	0.40	0.53
Prostate cancer	-	-	-	-	-	-	0.38	0.58	0.68	0.80	1.06	1.25
Stomach cancer	1.14	1.64	1.80	1.77	1.88	1.97	1.71	2.36	2.42	2.39	2.60	2.74
Testicular cancer	-	-	-	-	-	-	0.01	0.02	0.02	0.03	0.03	0.04
Thyroid cancer	0.03	0.05	0.06	0.06	0.09	0.10	0.02	0.03	0.03	0.03	0.04	0.05
Tracheal, bronchus, and lung cancer	0.49	0.79	0.92	0.87	1.20	1.39	0.86	1.28	1.42	1.46	1.94	2.26
Uterine cancer	0.08	0.12	0.13	0.13	0.17	0.25	-	-	-	-	-	-

cancer incidence has been increased about 50% in underdeveloped and developing countries and 36% in developed countries, reflecting the increased control of the disease in developed countries.[10]

To our knowledge, there are numerous published papers about the mortality rates of cancers in Iran. However, no paper could be found on clustering the cancers based on their mortality trend from 1990 to 2015. Thus, we decided to conduct this study in order to identify the subgroup of cancers with increasing or decreasing trend during the last decades. To this end, the growth mixture models (GMMs) were used to classify similar cancers according to their mortality rate trend during the study period.

Material and Methods

Dataset used in the study

Mortality rates for 24 and 25 cancers were compiled from the GBD database for both Iranian male and female, respectively, from 1990 to 2015 (in 5-year intervals). The mortality rates of 25 and 24 per 100,000 people respectively for female and male were considered as the main outcome of the study. These data are true for all age groups based on the GBD database. The GBD study presents different indices (e.g., death, DALY, the prevalence of causes) for the burden of diseases in each country within specified years. More details about the GBD study and the data can be found elsewhere.[12] The actual absolute numbers of mortality rates for various cancer types for every block of 5 years are presented in table 1. M-plus v.6.12 software (www.statmodel.com) was used for statistical analysis. The presented study was approved by Ethics Committee (ethics code: IR.SBMU.RETECH.REC.1397.365).

Statistical approaches

GMMs were used for exploring the various trend of cancers' mortality rates during the mentioned years. GMMs are specific extensions of LGMs. The LGM was used when all individuals in the sample had similar trends over time. Nonetheless, GMMs are applicable when there are different trends in the sample. Accordingly, it can be used to determine if subgroups exist within the population that follow similar trends over time. Therefore, GMMs considers population heterogeneity in outcome trend through classifying individuals into different trajectory classes.[13] The GMM utilizes the following equations for specifying each of the K latent classes as follows:

$$y_{it}^{k} = \eta_{i0}^{k} + \eta_{i1}^{k}\lambda_{t}^{k} + \varepsilon_{it}^{k}$$
$$\eta_{io}^{k} = \eta_{00}^{k} + \sum_{j}\beta_{01j}^{k}X_{j} + \varepsilon_{i0}^{k}$$
$$\eta_{i1}^{k} = \eta_{10}^{k} + \sum_{j}\beta_{11j}^{k}x_{j+} \varepsilon_{i1}^{k}$$

Where η_{00}^{k} represents the estimated overall mean level of the initial outcome in the k^{th} class and η_{10}^{k} is the average rate of outcome change over time for the kth class.[14] In the result section, GMM was used to determine the subgroups of cancers with similar trends of mortality rates with time, separately for males and females.

Results

The mortality rates of whole cancers explored for men and women in 2015 are reported in figure 1. In this figure, cancer labels were sorted in terms of the decrease in mortality rates in the left of plots. This descriptive pie chart reveals that breast cancer, stomach cancer, and trachea, bronchus, and lung cancers were the three most commonly reported mortality causes among Iranian women in recent years. Similarly, stomach cancer, tracheal, bronchus, and lung cancer and leukemia were reported as the three most common mortality cancers among Iranian men. As the rates in the table show, there are different trends in various types of cancers among the population. Accordingly, it is necessary to cluster these cancers according to their trends over time. Growth models were used to reach this aim.

In figure 2, each dashed line shows mortality rate trend over time for each cancer (25 trajectories for female and 24 trajectories for male). As can

Table 2. Results of a growth mixture model for clustering of various female' cancers mortality rate based on changing the trend with time.

Parameter	Class 1*	Class 2**	Class 3***
Intercept	0.113	0.473	1.14
Slop	0.010 (<0.001)	-0.016 (0.005)	-0.022 (0.001)
Time Scores	(0, 1, 2, 3, 4, and 5)	(0, -13.2, -19.7, -19.8, -30.4, and -41)	(0, 1, 2, 3, 4, and 5)

* Cancers in Class 1: Bladder, Cervical, Esophageal, Gallbladder, and Biliary Tract; Hodgkin lymphoma, Kidney, Larynx, Lip, and Oral Cavity; Mesothelioma, Multiple myelomas, Nasopharynx, Non-Hodgkin lymphoma, Non-melanoma skin, other Pharynges, Thyroid, and Uterine; ** Cancers in Class 2: Breast, Stomach, Tracheal, Bronchus, and Lung; Colon and Rectum, Liver, Brain and Nervous System; Ovarian and Pancreatic ; *** Cancers in Class 3: Leukemia.

be seen, these trajectories have different trends for various cancers. Therefore, the GMM was used to classify the cancers according to their mortality trend over time. These data were modeled for men and female separately.

GMM was explored through various numbers of classes and compared for their goodness-of-fit indices. The solutions showed that the 3-class model was the best choice. While analyzing female data, a model with 2 linear classes and 1 non-linear was selected as the most proper one.

For male data, a model with 2 non-linear and 1 linear class was selected. Linear classes had time scores of 0, 1, 2, 3, 4, and 5 while free time scores were specified for non-linear classes. The entropy statistics that show quality for latent class membership classification were 0.95 and 0.92 for female and male, respectively, representing a good quality of clustering. The results of these models are reported in tables 2 and 3. The colored line in figure 1 reveals the estimated trend for the clusters obtained from GMM.

For female data, Class 1 can be determined as having a slow increase in cancer mortality over time, respectively. Cancers in Class 2 had an increasing trend until 2000; they then reached a fixed trend during 2000–2005, and after that, they had an increasing trend again. In Class 3, leukemia had a decreasing trend of mortality rate over time. For male data, cancers in Class 1 had a very slow increasing trend in mortality rate over time. In both Classes 2 and 3, cancers had an increasing trend of mortality rate over time until 1995, then reached an almost stable trend during 1995–2005, and after that, they had an increasing trend all over again.

The results for non-linear classes in tables 2 and 3 can be interpreted regarding the specified free time scores. For example, in Class 2 of female data modeling, the difference in time scores between 1990 and 1995 is -13.2, so the change in mortality rates of cancers in this class would be slope*(-13.2)=(-0.016)*(-13.2) = 0.2112, which represents an increasing trend during this period of time. The rest of the results for nonlinear classes are interpreted in the same way. As shown in tables 2 and 3, a gender-based clustering is seen in the mortality rate of cancers over time.

Discussion

In the present study, various cancers were clustered based on their mortality trend over the past 25 years for female and male, separately. The results showed that cancers including brain and nervous system cancer, liver cancer, pancreatic cancer, breast cancer, stomach cancer, and tracheal, bronchus, and lung cancer have an increasing trend in both male and female. As a result, the mortality rate of leukemia in female had a decreasing trend; nonetheless, it had a steady increasing trend among males. Females had an increasing trend of mortality rate in colon and rectum cancer, while males had an almost steady trend during the time. In men, there was an increasing trend in mortality associated rate with bladder, non-Hodgkin lymphoma, larynx, leukemia, and prostate cancers. The results of the present study also show that bladder, cervical, esophageal, gallbladder and biliary tract, Hodgkin lymphoma, kidney, larynx, lip, and oral cavity, mesothelioma, and multiple cancers had very little steady increase over the years in the female population. Besides, the mortality rates of cancers including colon and rectum, esophageal, gallbladder and biliary tract, Hodgkin lymphoma, kidney, lip, and oral cavity, mesothelioma, multiple

Table 3. Results of a growth mixture model for clustering of various male' cancers mortality rate based on changing the trend with time.

Parameter	Class 1*	Class 2**	Class 3***
Intercept	0.093	0.23	0.852
Slop	0.006 (0.032)	-0.027 (0.399)	0.016 (0.089)
Time Scores	(0,1,2,3,4,5)	(0,-4.5,-5.9,-6,-10.7,-16.2)	(0,15.3,20,22.3,36.4,46.1)

*Cancers in Class 1: Colon and Rectum, Esophageal, Gallbladder and Biliary Tract, Hodgkin lymphoma, Kidney, Lip, and Oral Cavity, Mesothelioma, Multiple Myelomas, Nasopharynx, Non-melanoma Skin Cancer, Pharynges, Testicular, and Thyroid; ** Cancers in Class 2: Bladder, Brain and Nervous System, Liver, Non-Hodgkin lymphoma, and Pancreatic; *** Cancers in Class 3: Breast, Larynx, Leukemia, Prostate, Stomach, and 'Tracheal, bronchus, and lung'

myeloma, nasopharynx, non-melanoma skin, other pharynges, testicular, and thyroid cancers had very little steady increase over the years in the male population.

According to the National Center for Mortality Statistics, the Ministry of Health and Medical Education in Iran (MOH & ME), from 1995 to 2004, the mortality rate for leukemia has been increasing significantly such that the annual mortality rate per 100,000 people has increased from 0.79 to 6.45, but in the following years, the rate of this type of cancer in men has been higher than that of women.[15] The reasons for the increase in this type of cancer among adult males can be attributed to obesity and smoking, which are also risk factors for lung cancer that are more prevalent among males.[15] Breast cancer in women is also rising among Asian countries, including Iran. The risk factors of this cancer include high-fat diets, abortions, menopause, increased stress, and the use of contraceptive pills.[9] Ovarian cancer is also one of the deadly cancers among women and is the fifth cause of death among women around the world compared with various other cancers.[9] Iran has the 8th rank among countries with the highest incidence of female cancers. In a study conducted on women in Iran from 2003 to 2009, cancer had a growing trend, especially in women over 50 years of age.[19] According to the World Health Organization (WHO), gastric cancer is the third most common cancer in the world, with 723,000 deaths in 2012.[20] In Iran, this type of cancer has increased significantly among both men and women by 2012.[21] The causes of this type of cancer include nutrition and inappropriate diets, including the use of salty foods, red meat, and processed meat, foods containing fats and nitrates, ready-made foods, smoked and roasted foods, hot foods, or oils used several times, as well as bottled drinking water.[20] Moreover, according to the International Agency for Research on Cancer (IARC), the annual incidence of lung cancer is more than one million people in the world.[22] Among women, this cancer is the fourth most common cancer and the second leading cause of cancer deaths.[23] The highest incidence is seen in developing countries.[24,25] A study on this cancer among Iranian men and women from 2008 to 2003 has shown that the rate of this cancer is increasing in both sexes, but this increase is higher in men than in women.[26] The most important risk factor for this cancer is smoking, which increases the risk to 20 times.[23] Other influential factors include air pollution, previous pulmonary diseases, viral infection, sex, race, and age.[27] Liver cancer is one of the five most deadly cancer in the world, with a rising prevalence in developing countries such as Iran.[28] According to the results of a study on Iranian men and women from 2003 to 2009, the prevalence of this cancer during these years was higher among men than women and increased with age.[28] Risk factors include chronic hepatitis B and C infections, fatty liver disease, alcohol consumption, diabetes, smoking, and obesity.[28] The cancer of the brain and the nervous system make up about 2% of all cancers. According to a study conducted on Iranian men and women in the time range of 2000 to 2005 in several regions of Iran, the incidence of this cancer in men is higher than women.[29] Scientific knowledge about the causes of this type of cancer is not sufficient, but the risk of possible factors is the contact with diagnostic ionization rays, artificial rubber production, filtered cigarettes, cell phone use, and active and passive smoking.[29] Cancer of the pancreas is the 13th most common cancer in the

world and the 8th cause of cancer-related deaths.[24] Its prevalence in Iran is relatively low but rising to the west. According to the Iranian Cancer Registry, from 2003 to 2005, this cancer has been more common in males and females with an average age of over 60 years, which is younger than that in Western countries.[30] Genetic defects, hereditary factors, genetic syndromes such as Peutz-Jeghers syndrome, familial marriage and at an early age, which is still common in some parts of Iran, can be attributed to this issue.[30]

It is of note that improving cancer registry system for the purpose of comparing with the past may lead to increasing the trend of cancers mortality rate in Iran. Besides, the other causes are an inactive lifestyle, changes in dietary habits, awareness about signs and symptoms of cancer, developments in diagnosis technic and equipment, and an increase in the number of elderly people.[1]

It is necessary to note that the cancer registry system in Iran is not complete in all cancers, leading to a slight underestimating or misestimating in some cases. Consequently, this study revealed some very important limitations such as lack of accurate and reliable data for mortality rate in some cancers. Finally, based on existing data, the general trend in the mortality rates of cancers shows an upward trend. Therefore, it is necessary to provide programs for early detection, screening, preventing, public health program planning, and patient care improvement. In future studies, it may be possible to integrate the cancer death rate from other databases using advanced statistical methods and re-evaluate the epidemiology of cancers. Also, the effect of important risk factors on cancers – which have been presented in the GBD valuable database such as environmental, occupational, behavioral, and metabolic risk factors – can be considered using appropriate statistical methods.

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Conflict of Interest

None declared.

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