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ORIGINAL PAPER

Evaluation of Nitrate Effects on the incidence of gastrointestinal cancers in Isfahan province, Iran

Saba Sepahvand[1] · Mojgan Entezari[1] · Reza Zakerinejad[1]

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Abstract

In Iran, cancer is the third leading cause of death, after cardiovascular diseases and accidents. In this study, the geographical distribution of gastrointestinal cancers (esophagus, gastric, colon) and the effect of nitrate in drinking water on its incidence have been investigated. This is a descriptive–analytic study that uses two data types to investigate the relationship between nitrate concentration in drinking water and the prevalence of gastrointestinal cancers in Isfahan province, in the center of Iran. Information on gastric, esophagus and colon cancers separately from 2005 to 2009 was obtained from the Isfahan Health Centre database, and the amount of nitrate in the drinking water from each of the cities in the province of Isfahan was collected. This is a descriptive–analytic study that uses two data types to investigate the relationship between nitrate concentration in drinking water and the prevalence of gastrointestinal cancers (gastric, esophagus and colon) in Isfahan province, Iran. Studies have shown that elevated levels of nitrate in drinking water may be one of the factors influencing the incidence of gastrointestinal cancer. The direct relation between nitrate in drinking water and increased incidence of gastric cancer was ($R = 0.42$, $P = 0.05$), esophageal cancer. The incidence of gastric and colon cancer in males over age of 70 and esophageal cancer in females aged 60 to 75 is highest. It is suggested that given the importance of nitrate pollution as one of the environmental and agricultural problems, as well as the value of groundwater resources, especially in arid and semi-arid regions.

Keywords Esophageal cancer · Gastric cancer · Colon cancer · GIS

Introduction

Cancer is a major public health problem in Iran and many other parts of the world. Gastrointestinal cancers are one of the most common cancers in the world and, with over 750,000 new cases each year, remain a significant public health burden around the world, especially in the developing countries (Türkdoğan et al.2003; Herszényi and Tulassay2010). In general, 66 percent of cancers occur in the developing countries, where only 5 percent of cancer control tools are available (Herszényi and Tulassay2010; Sung et al. 2005). Gastric cancer is the second most common cause of death after cardiovascular disease in the world (Babae et al. 2010; Mutafa et al. 2017).

Esophageal cancer is the ninth most common cancer in the world, and the disease is in fifth place in developing countries (Hebert et al. 2006). Higher genotypes are observed in the non-Semitic population living in the northern and southeastern parts of the Middle East (Hussein, 2010). The highest incidence was reported for South Africa, Iran, China and India, as well as Ceylon and Puerto Rico (Parkin et al. 2005). Approximately one million new cases of colon cancer are detected every year in the world, and about half a million people die from this disease (Stone et al.2004). Epidemiological characteristics of this cancer vary from one site to another (Ansari et al. 2006). While the annual prevalence of this cancer in North America and Europe is reported to be about 50 to 30 cases per 100,000 population, it is estimated to be in the range of 3 to 7 per 100,000 in the Middle East (Stewart and Klrihues, 2003). A number of underlying factors, including nutrition, genetics and environmental factors, are common in the etiology of this type of cancer. The overall reduction in the prevalence of these diseases in recent years has been a cause for hope that the effective environmental factors that influence their

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✉ Reza Zakerinejad
reza.zakerinezhad@geo.ui.ac.ir

[1] Department of Physical Geography, Faculty of Geographical and Planning, University of Isfahan, Isfahan, Iran

development may be corrected and the number of cases of infection (Türkdoğan et al.2003). Several risk factors are involved in the development of gastrointestinal cancers, consumption of tobacco, drinking alcohol, deficient of vitamins and trace elements, drinking hot drinks, especially the contamination of food products with carcinogens such as nitrosamines and fungal toxins in the development of esophageal cancers has been widely considered (Taneja et al., 2017; Zhang et al. 2018). In gastric and colon cancer, factors such as diet, exogenous chemicals, carcinogens produced in the gastrointestinal system, and genetic and infectious agents are known (Leung et al. 2003). One of the environmental factors involved in the development of superior and inferior gastrointestinal cancers is the quantity of nitrate and nitrite in food sources and drinking water (Ward et al. 2005). The increase in world population and the need for more food sources have led to the use of new methods of food production, particularly in the agriculture. One of these approaches is the use of chemical fertilizers in the agricultural sector, so today, chemical fertilizers have the largest share in the amount of human nitrogen produced around the world (Yang et al., 2007; Cantwell and Elliott 2017). Nitrates and nitrites are soluble in the aquatic environment and move around the environment.

During precipitation, wastewater can be discharged to wastewater via surface water and through leakage in underground water during the discharge (Guadagnin et al. 2005). Since Iran is in the arid and semi-arid region, its organic matter content is low and thus its nitrogen levels are low. Most plants in these areas suffer from nitrogen deficiency, which is the nitrogen supply needed by organic fertilizers (Malakoti and Homaie 2003;Tarighaleslami et al. 2012). Nitrogen is added to the soil through urban, industrial and agricultural waste water. In recent decades, the use of nitrogen fertilizer has been irrefutable regardless of its impact on soil and environmental properties (Jafari et al. 2003; Taneja et al. 2017).

Nitrite compounds by the bacteria in the gastrointestinal system to the second and third kinds of amines form nitrosamines which are more carcinogenic (Hamon, 2007).

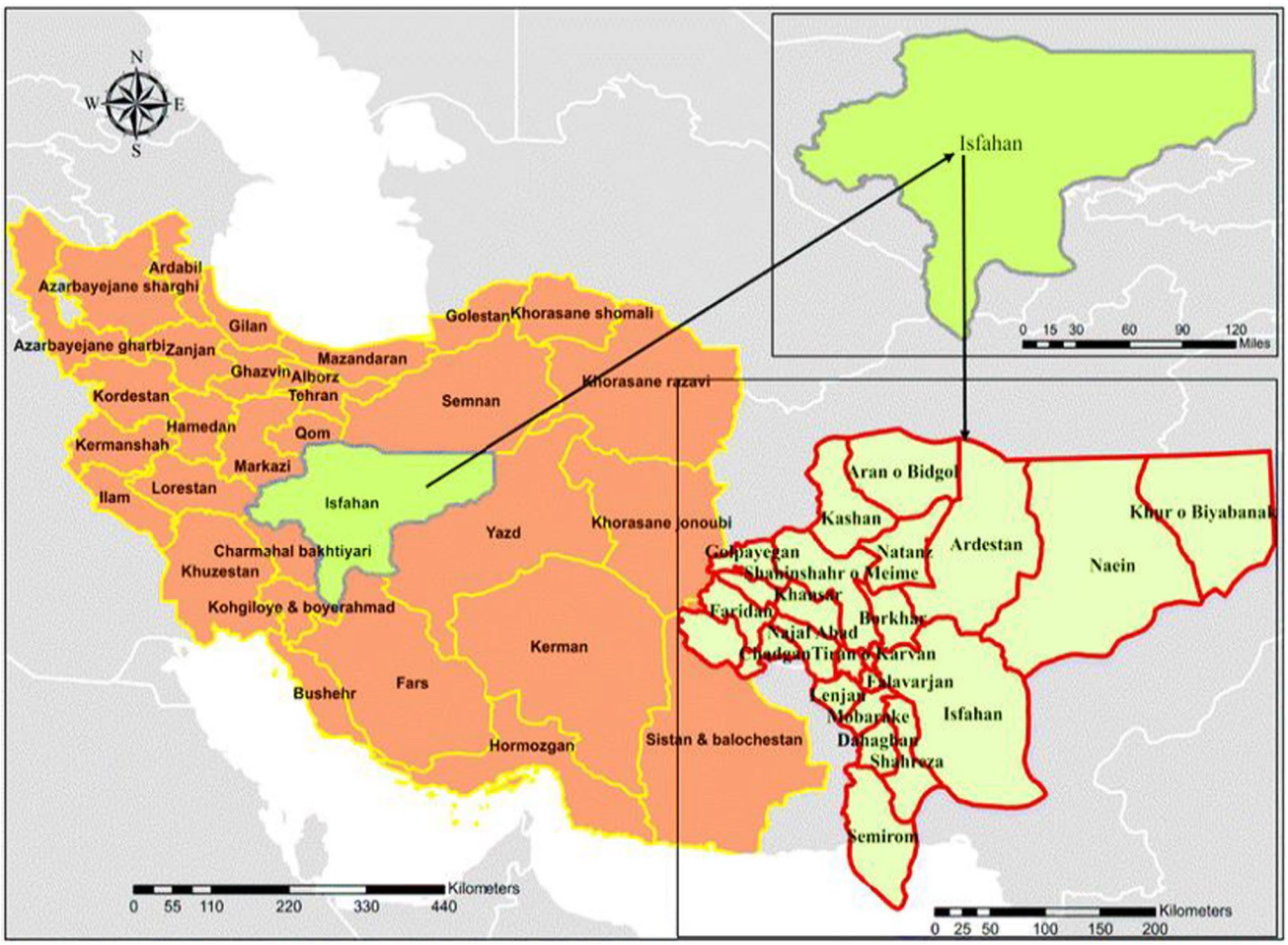

Fig. 1 Location of the study area

The results of numerous studies confirm that gastrointestinal cancer is positively related to nitrate (DellaValle et al., 2013; Taneja et al. 2017). A case–control study conducted in Iowa associated average nitrate concentrations above 5 mg/L (NO3-N) with a risk of colon and rectal cancer for a ten-year exposure (Taneja et al., 2017). An average nitrate concentration of 88 mg/L was reported to be positively associated with gastric cancer mortality in an ecological study to determine nitrate levels involved in the development of gastric cancers (Sandor et al., 2001; Mutafa et al. 2017).

Considering the increase in the incidence of gastrointestinal cancers in recent years and the variety of environmental factors that affect them, in this study, we intend to evaluate the relationship between nitrate levels in drinking water in the cities in Isfahan province and the incidence of esophagus, gastric and colon cancers in these regions.

Study area

The province of Isfahan has an area of 107,045 km2 or 6.3 percent of the total area of Iran. It is between 30 degrees and 43 min to 34 degrees and 27 min of northern latitude, 49 degrees, 38 min to 55 min and 32 min of the eastern part of the Greenwich Pass. And the provincial capital is 1550 m above sea level (Statistical Yearbook of Isfahan Province 2012) (Fig. 1).

Materials and Methods

This is a descriptive–analytic study that uses two data types to investigate the relationship between nitrate concentration in drinking water and the prevalence of gastrointestinal cancers (gastric, esophagus and colon) in Isfahan province, Iran. The first type of data is the information on patients with gastric and colon cancers separately (age, sex, year of diagnosis of disease and city of residence) between 2005 and 2009 which is obtained from the Isfahan Health Center database. The second type of data is information about the concentration of nitrate in drinking water in all cities in the province where sampling locations were selected randomly, and drinking water samples from residents of these areas were taken to determine nitrate concentration (Table 2) (Fig. 6 and 7).

Nitrate concentrations in the drinking water in the samples were divided into three groups: less than 20 mg/L, 20–45 mg/L and more than 45 mg/L. Finally, nitrate concentrations in drinking water maps were provided by ArcGIS10.5 software by using the IDW method.

In this research, Geography Information System (GIS) software is used. One of the most widely used applications of GIS software today is information and decision-making assistance for health management and prevention of the occurrence, prevalence and control of various diseases. In healthcare systems, many data are continuously collected and archived, without being converted into useful information. In addition, due to the vast expanses of the covered area and the high climatic variation, health managers in Iran are confronted with a great deal of data, which are very

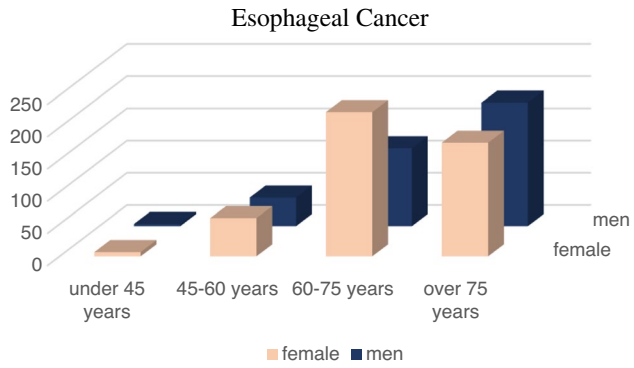

Fig. 3 Esophageal cancer incidence by age and sex according to ASR index

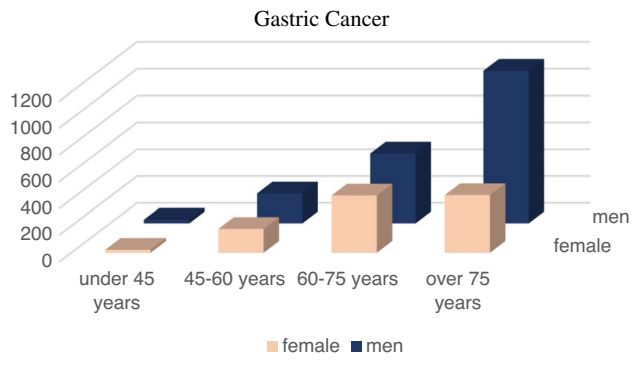

Fig. 2 Gastric cancer incidence by age and sex according to ASR index

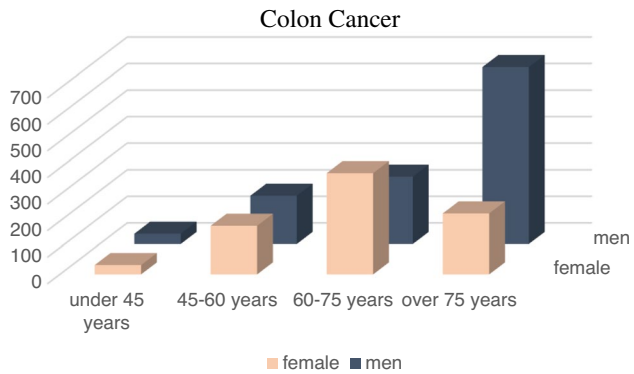

Fig4 Colon cancer incidence by age and sex according to ASR index

Table 1 Descriptive Table of Patients with Gastrointestinal Cancer Based on ASR Index

Descriptive table						
Maximum	Minimum	STD Deviation	Skewness	Median	Mean	Gastric Cancer
55.84	0	16.53	1.099	16.76	18.53	
17.92	0	1.10	%853	5.66	5.55	Esophageal Cancer
35.58	0	8.80	%665	12.86	12.57	Colon Cancer

difficult to interpret and manage with traditional methods. The importance of GIS is to prevent the epidemic and the prevalence of diseases through the use of the impacts of environmental factors and factors that affect the disease.

In this study, the ASR (Age Standardized Rate) index of gastric, esophagus and colon cancers was determined separately for each city based on the mean of the total number of cases recorded during the statistical period (2005–2009). The zoning map of the disease was drawn based on the classification of three areas including very high-risk, high-risk and low-risk areas in the prevalence of these cancers using the GIS software to match the zoning

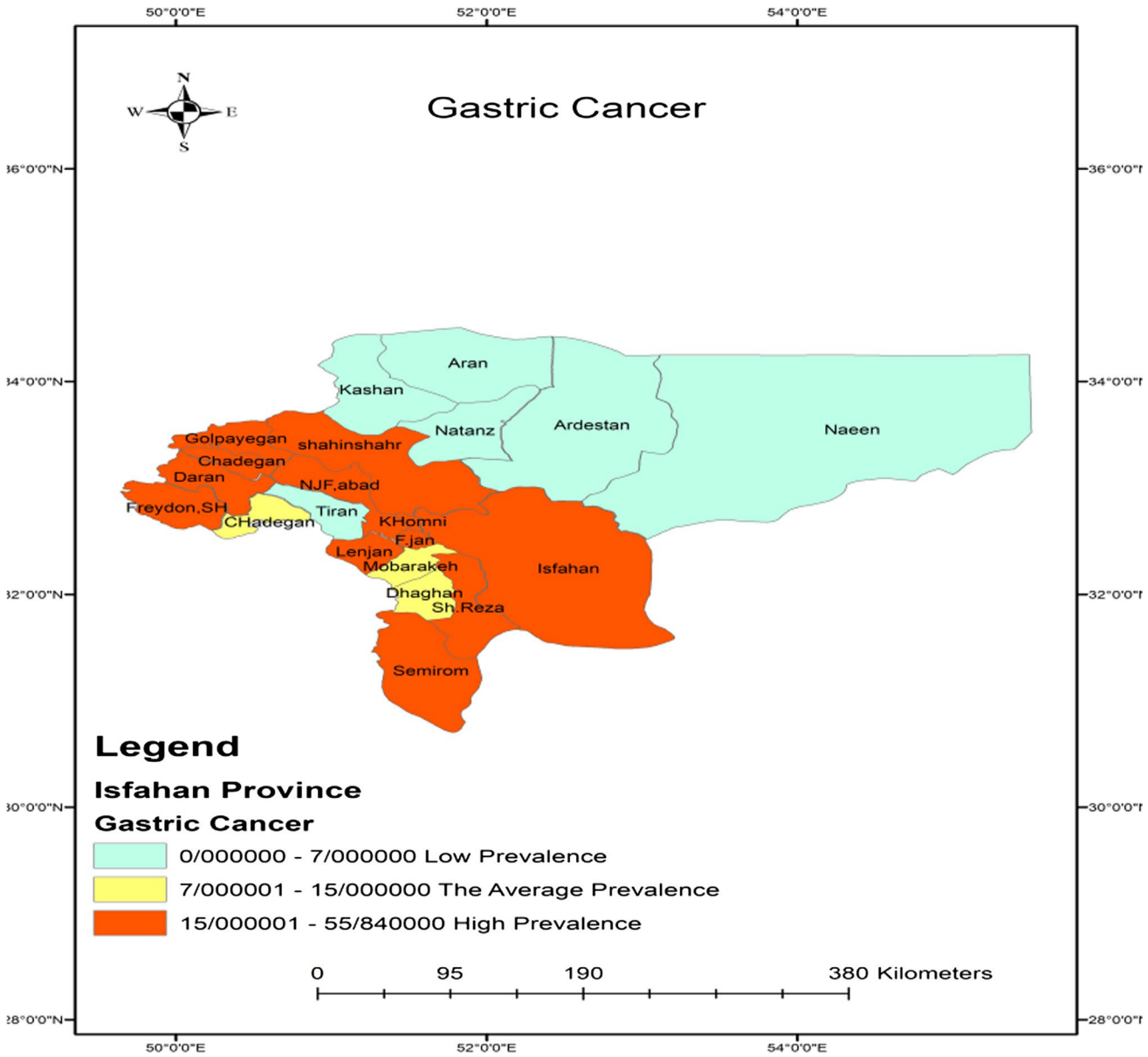

Fig. 5 Gastric Cancer Scale Map Based on ASR Index

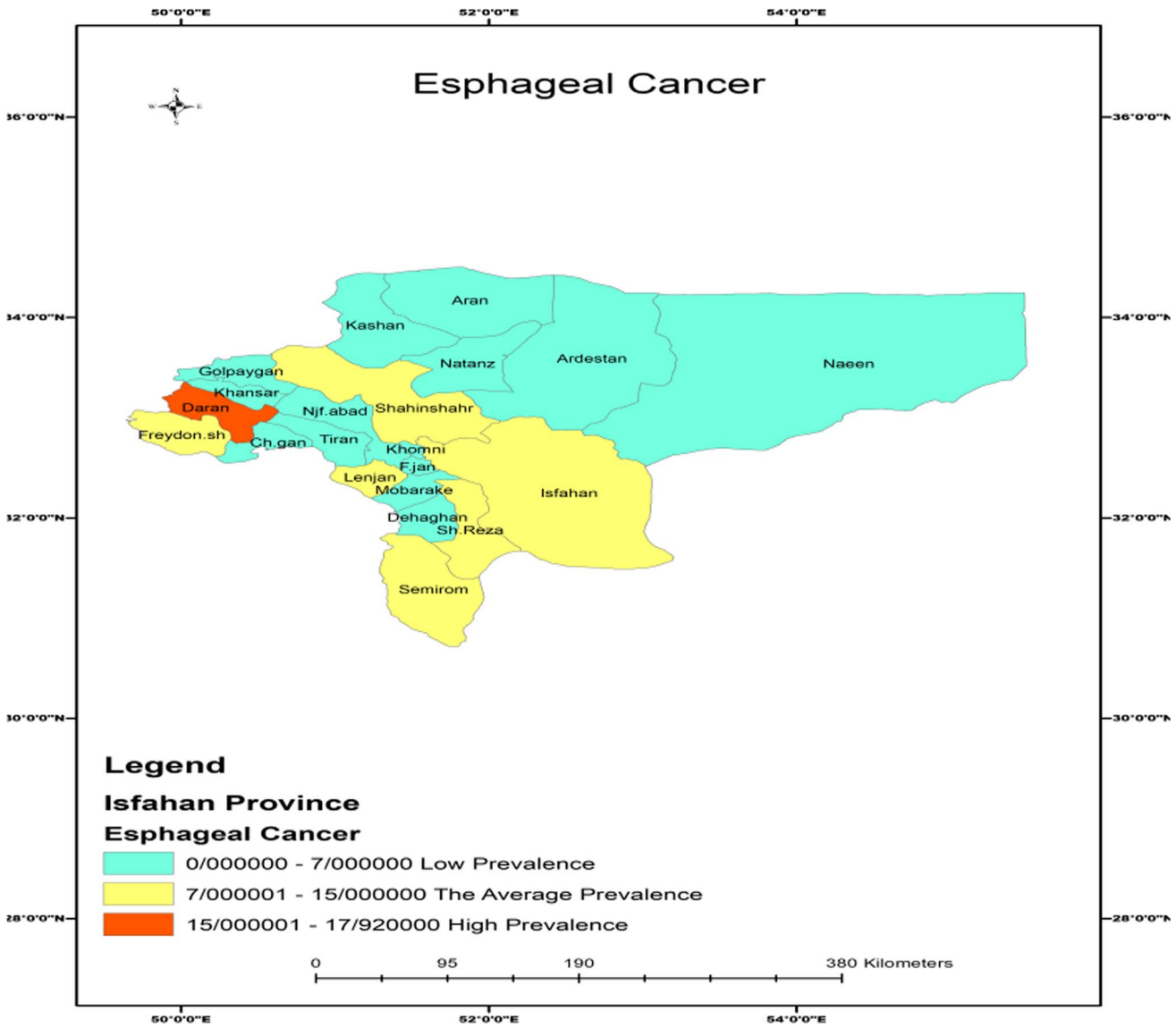

Fig. 6 Esophageal Cancer Scale Map Based on ASR Index

map of nitrate concentration in drinking water and the main sources of the prevalence of this disease in Isfahan province.

Using SPSS software, the mean of ASR indexes of gastric, esophagus and colon, cancers, standard deviation and skewness of data was calculated for the province and the significant trend of correlation between nitrate concentration in drinking water and spatial distribution of the esophagus, gastric and colon cancers was obtained from regression correlation.

The analysis of the incidence of these cancers in age subgroups based on the ASR index during the statistical period (2005–2009) after categorization of all patients with gastric, esophagus and colon cancers was divided into 4 age groups (under 45 years old, 45–60 years old, 75–60 years old and over 75 years old) using Excel software.

Result

In this study, 2,692 people with a diagnosis of gastrointestinal cancer (esophagus, gastric and colon) who were enrolled at the provincial Health Center were studied. Of these, 355 people suffered from esophageal cancer, 1110 from gastric cancer and 1227 from colon cancer. The proportion of males and females in gastric cancer was 1.65, esophageal cancer was 1.20, and colon cancer was 1.29. The trend in all three cancer types increased during the study period.

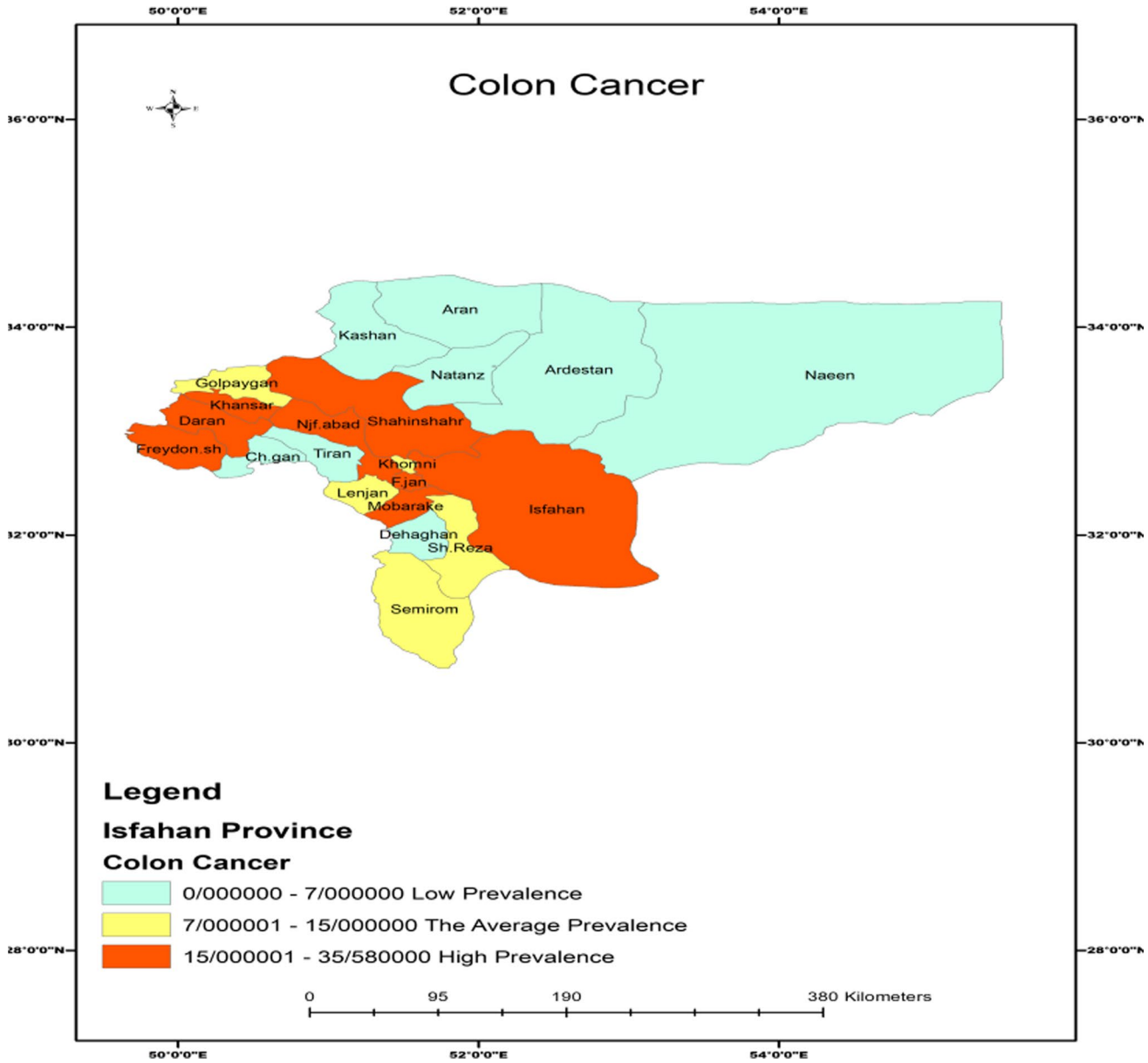

Fig. 7 Colon Cancer Scale Map Based on ASR Index

According to ASR, the incidence of gastric and colon cancer in male over the age of 70 and esophageal cancer in female aged 60 to 75 is the highest (Fig. 2). (Fig 3), (Fig 4)

The mean number of patients, according to the ASR index for gastric cancer, was 18.53 percent, for esophagus cancer was 5.55 percent and for colon cancer was 12.57 percent. The skewness coefficient of the gastric cancer data shows the skewness to the right which indicates that the ASR index is lower than the average in most cities of the province and a small number of counties have an ASR index of high gastric cancer in the province, which require special attention. The skewness of the esophagus and colon cancer data in the province also shows that the data are almost normal (Table 1).

Using a gastric cancer incidence index of 100,000 people during the period (2005–2009), esophagus, gastric and colon cancer zonation maps for province are drawn to identify the high-risk cells of these three cancers. Based on this index, cities in the province were classified into three prevalence groups.

The gastric cancer zonation map shows that the cities of Nayin, Ardestan, Natanz, Aran and Bidgol, Kashan, Semirom sofla (Dehaghan), Mobarakeh, Chadegan and Tiran and Keron with the standardized age average of incidence of less than 7 are the low prevalence regions in the province. The cities of Chadegan, Dehaghan, Mobarakeh Golpayegan, Khansar, Shahin Shahr, Najaf Abad, Khomeyni Shahr, Falavarjan and Lenjan with the standardized age average of incidence

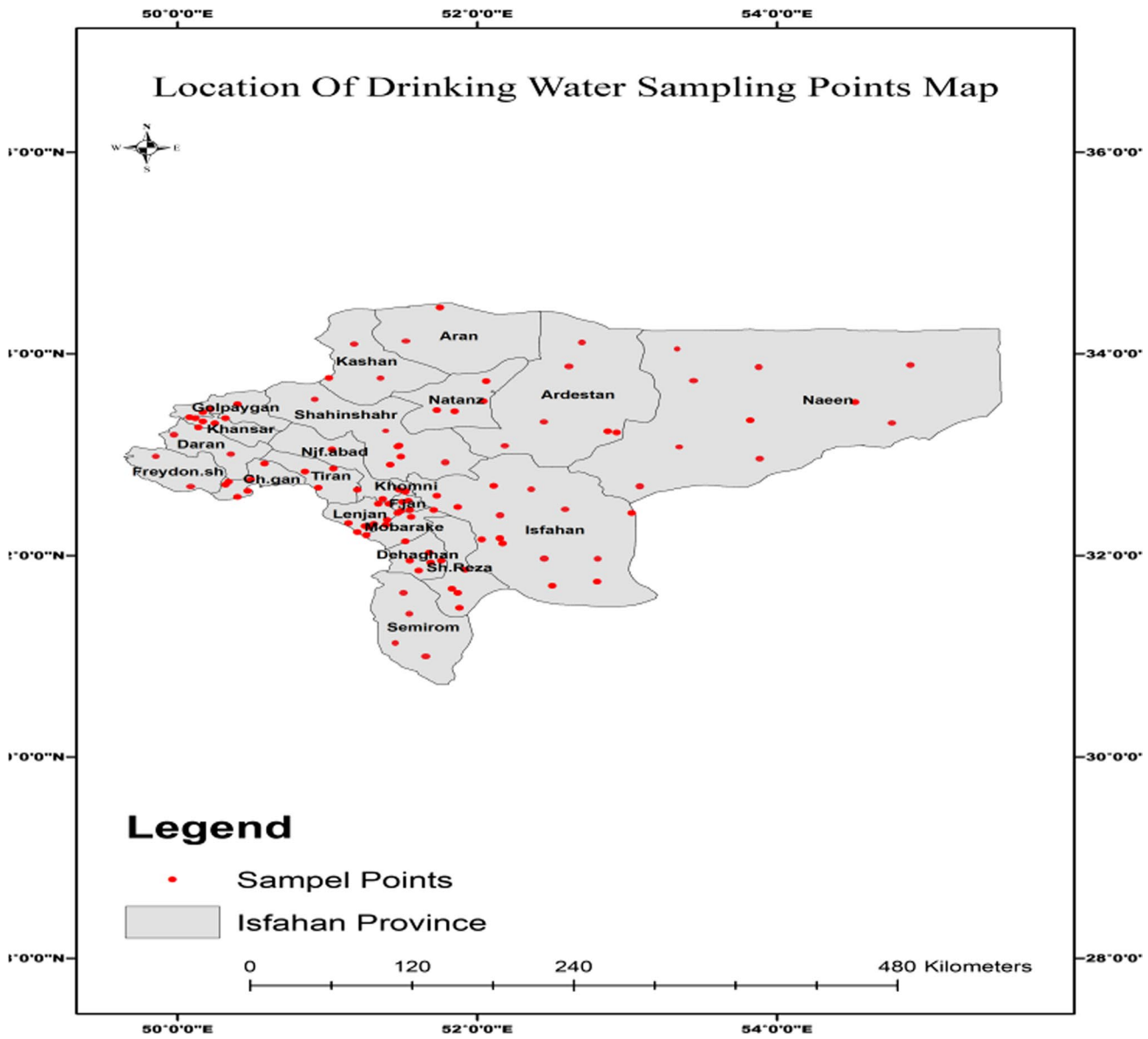

Fig. 8 Location of drinking water sampling points by Isfahan Health Center based on Table 2

of between 7 and 15 are the mean prevalence regions in the province. The cities of Fereydoun Shahr, Semirom, Daran (Fereydan), Isfahan, Shahreza, Khomeyni Shahr, Chadegan, Golpaygan, Shahin Shahr, Najaf abad, Falavarjan and Lenjan with the standard Bino 15–58.84 index are of high prevalence and major focal regions of gastric cancer in Isfahan province (Fig. 5).

In the esophageal cancer zonation map in the cities of Natanz, Aran and Bidgol, Kashan, Semirom sofla (Dehaghan), Mobarakeh, Golpayegan, Najaf Abad, Khansar and Chadegan with the standardized age average of incidence of less than 7 are the low prevalence regions in the province. The cities of Isfahan, Semirom, Shahreza, Shahin Shahr and Fereydan Shahr Lenjan with the standardized age average of incidence between 7 and 15 are the mean prevalence regions in the province, and Fryedan city with a standard index of 17.92 is the main focal area of esophageal cancer in Isfahan province (Fig. 6).

In the zonation map of colon cancer in the cities of Aran and Bidgol, Kashan, Ardestan, Nayin, Natanz, Tiran and Krone, Chadegan and Dehaghan with the standardized age average of incidence of less than 7 are the low prevalence regions in the province. The cities of Semirom, Shahreza, Lenjan and Golpayegan with the standardized age average of incidence between 7 and 15 are the mean prevalence regions in the province. And Isfahan, Mobarakeh, Falavarjan, Khomeini City, Najaf Abad, Shahin Shahr, Khansar, Dardan (Frieden) and Fereydoun with a standard index of between 15 and 35.58

Table 2 Geographical position of the sampled points in Isfahan province

Sample points	Longitude	Latitude	Nitrate of drinking water (mg / l)	Sample points	Longitude	Latitude	Nitrate of drinking water (mg / l)
1	25.50	31.33	5.41	28	73.51	44.33	9
2	12.50	36.33	7.16	29	04.52	53.33	4.10
3	12.50	36.33	8.33	30	71.51	45.32	8
4	08.50	37.33	27	31	34.51	51.32	6.9
5	14.50	27.33	1.14	32	49.51	98.32	6.22
6	17.50	33.33	5.41	33	42.51	9.32	6.14
7	22.50	45.33	6	34	48.51	09.33	8.14
8	17.50	42.33	7.3	35	47.51	08.33	6.30
9	32.50	36.33	2.7	35	94.50	67.32	3.47
10	4.50	5.33	7.12	37	04.51	86.32	3.30
11	55.51	95.31	6.40	38	85.50	83.32	6
12	69.51	93.31	1.31	39	49.50	75.32	55
13	61.51	85.31	4.33	40	2.51	65.32	7.7
14	76.51	95.31	4.33	41	73.51	56.32	3.4
15	68.51	03.32	4.24	42	41.51	51.32	3.6
16	83.51	67.31	7.10	43	03.51	05.33	4.44
17	87.51	63.31	26	44	52.51	14.32	2.6
18	92.51	86.31	36	45	26.52	2.32	5.5
19	88.51	48.31	8.40	46	56.51	38.32	5.5
20	52.51	64.32	40	47	39.51	3.32	5.5
21	52.51	63.32	3.30	48	47.51	42.32	4.25
22	48.51	65.32	7.7	49	55.51	45.32	6
23	52.54	52.33	9.19	50	5.51	53.32	9.5
24	82.53	34.33	3.13	51	54.51	54.32	6.6
25	06.52	73.33	6.8	52	31.51	31.32	1.6
26	85.51	43.33	6/8	53	28.51	28.32	6
27	87.52	23.33	5.5	60	11.52	69.32	3.40
55	93.52	22.33	6.13	61	4.51	35.32	5.15
56	87.51	48.32	3.6	62	49.51	44.32	8.6
57	5.52	7.31	4.11	63	25.50	31.33	5.41
58	8.52	74.31	2.10	59	73.51	59.32	5.25

are the main focal areas of colon cancer in Isfahan province (Fig. 7).

In this study, in order to investigate the relationship between drinking water nitrate and the incidence of gastrointestinal cancers (gastric, esophagus and colon) in Isfahan province using the data of drinking water sampling points, the zoning map of the concentration of nitrate in drinking water in the following three groups was prepared (Fig. 8, 9), and Table 2 shows this category.

If the concentration of nitrate of water exceeds 45 mg / l, it will be in the group of highly contaminated water group. If the concentration of water nitrate is between 20 and 45 mg / l, it will be in the mean contaminated water group. If the concentration of nitrate in water is less than 20 mg / l, it will be in the least contaminated water group (Mehdinia and Shamsollah 2003).

Based on the above categorization, the mean nitrate content of Fereydoon Shahr, Khansar, Chadegan, Tiran and Freydan cities is between 20 and 45 mg/L, and drinking water in these areas was high polluted with nitrate. In other areas, the average of nitrate in drinking water was less than 20 and it was low (Fig. 9).

Correlation between Nitrate and Cancer

Distribution of nitrate pollution has a close relationship with the extent and intensity of agricultural activities. As shown in the following map (Fig. 10) and Table 3, the dispersion of a large area of agricultural land and water crops in Isfahan province overlaps with areas where their drinking water has higher nitrate than other

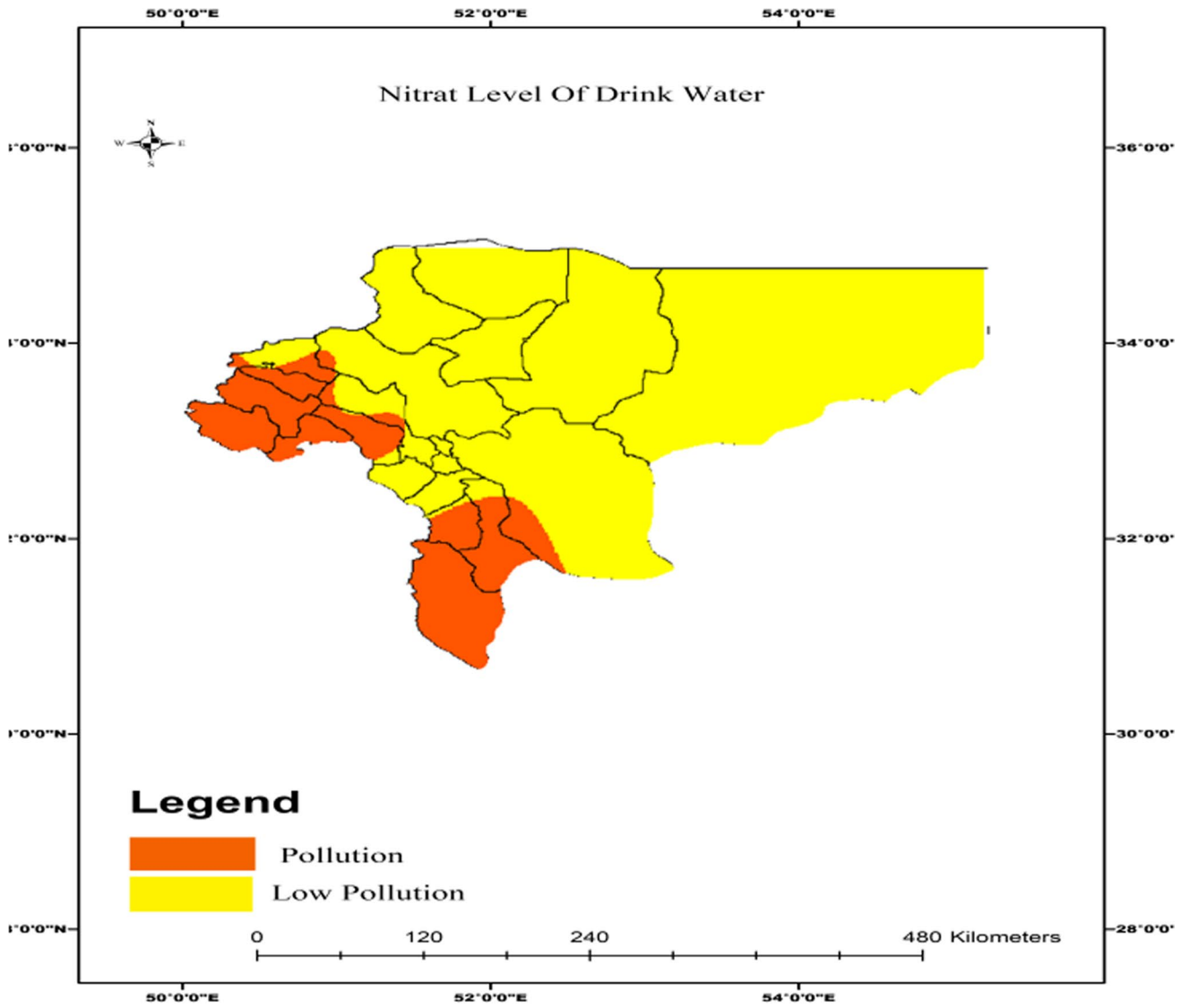

Fig. 9 Nitrate Level of Drinking Water

cities in the province. This is one of the reasons chemical fertilizers could be used to improve the productivity of farmland. The regression correlation between nitrate in drinking water and the risk of gastric cancer in Isfahan province with R = 0.42 and P = 0.05 showed moderate correlation. This means that despite the fact that nitrate in drinking water in any of the province's cities does not exceed about 50 mg/L, but with increasing nitrate levels, the number of patients with gastric cancer is going up, and the nitrate concentration in drinking water zoning map also confirms the main focal points for gastric cancer prevalence are those infected with nitrate (Fig. 11).

The regression correlation between nitrate in drinking water and the risk of esophageal cancer in Isfahan province with R = 0.23 and P = 0.05 showed a weak correlation (Fig. 12).

Nitrate in drinking water (mg/L).

Regarding the regression correlation between drinking water nitrate and the risk of colon cancer in Isfahan province, there was no statistically significant relationship with R = 0.053 and P = 0.05 (Fig. 13).

Discussion

According to the WHO (2015), the third most common cause of cancer death is gastric cancers. In this study, the amount of nitrate in drinking water in all cities in the province of Isfahan met the national standard (45 mg / l).

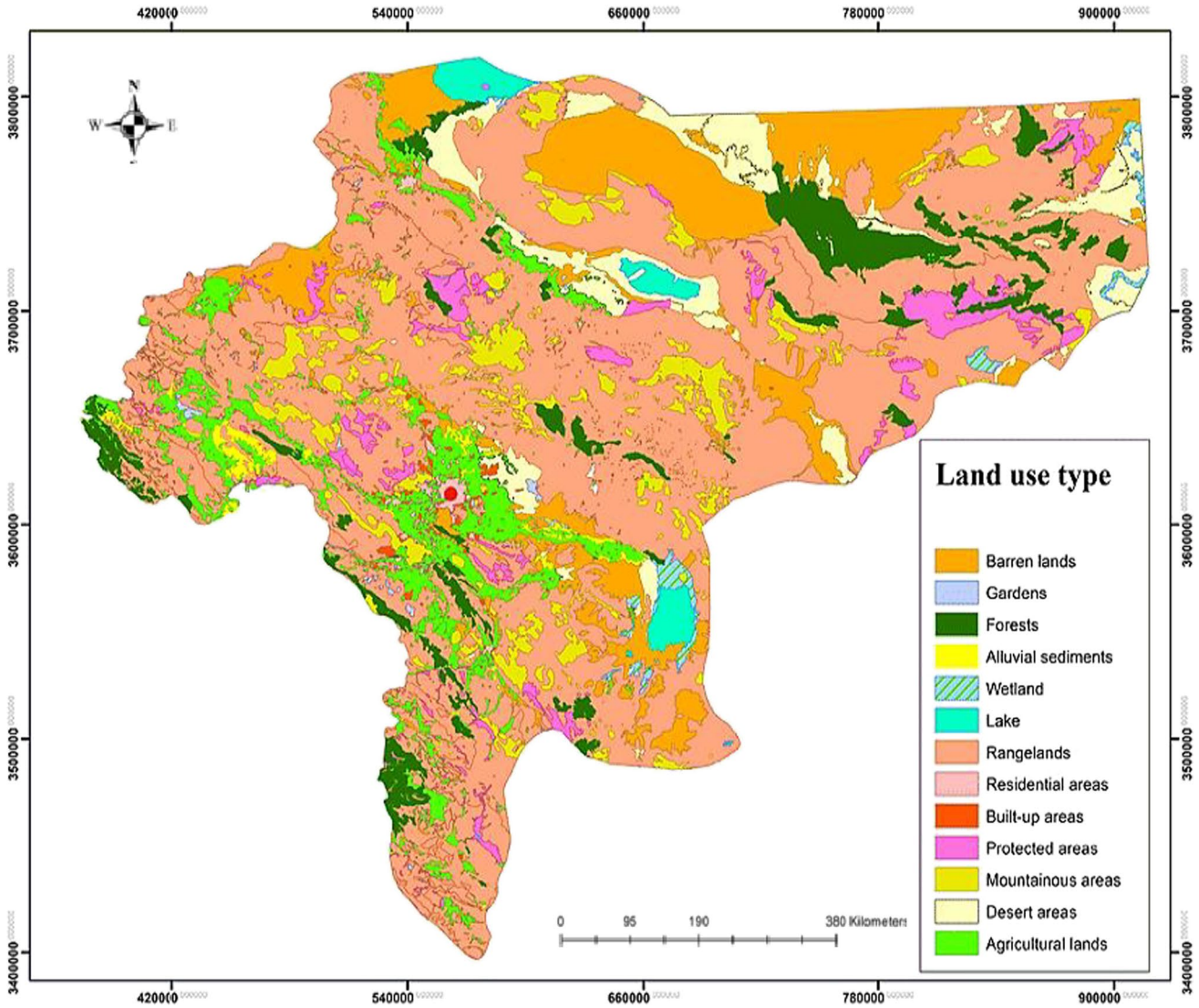

Fig10 Land use map of Isfahan province

Table 3 Distribution of nitrogen fertilizer and cultivation area of the city in 2009 years by percent

City	Percentage of Nitrogen fertilizer distribution	Cultivated area	City	Percentage of Nitrogen fertilizer distribution	Cultivated area
Aran and Bidgol	3.32	21,000	Kashan	3.02	16,127
Ardestan	5.23	15,000	Khansar	1.25	114.6
Borkhar	0	7500	Lanjan	1.84	14,000
Chadegan	4	11,000	Mobarakeh	4.52	14,000
Semirom	2.28	20,000	Naieen	0.71	4000
Isfahan	24.87	150,000	Najaf Abad	3.17	20,000
Falavarjan	5.48	15,000	Natanz	2.56	12,000
Fereydan	8.36	28,841	Shahreza	4.65	19,355
Fereydon shahr	3.27	18,500	Tiranokaron	2.12	9700
Golpaygan	4.5	30,000	Khomeyni Shahr	1.52	2825

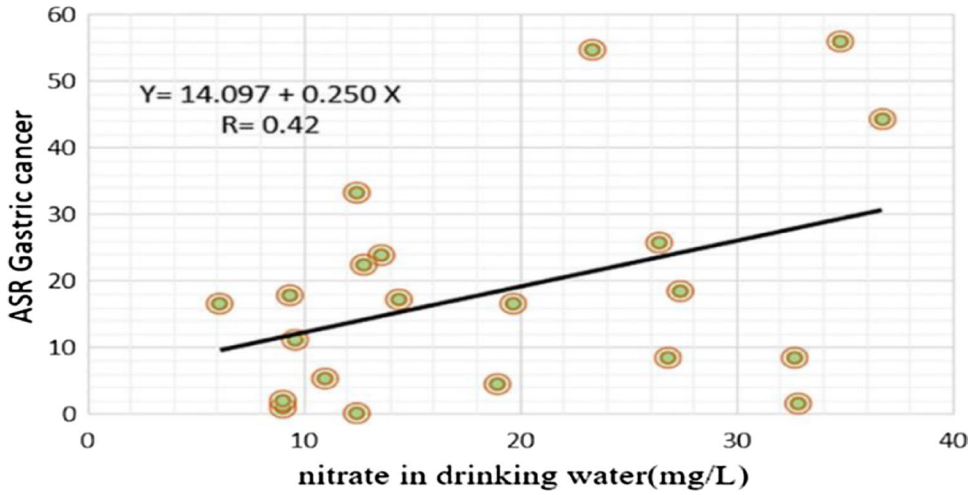

Fig. 11 Correlation of gastric cancer and nitrate in drinking water

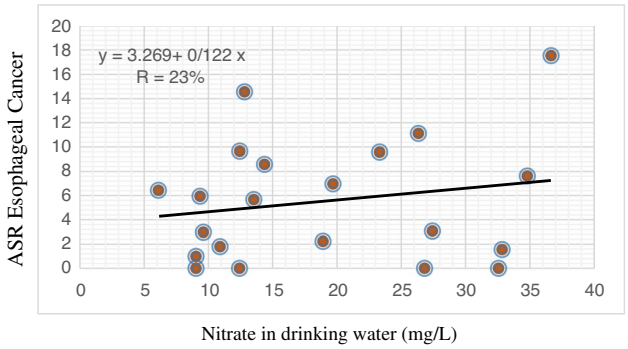

Fig. 12 Correlation of esophageal cancer and nitrate in drinking water

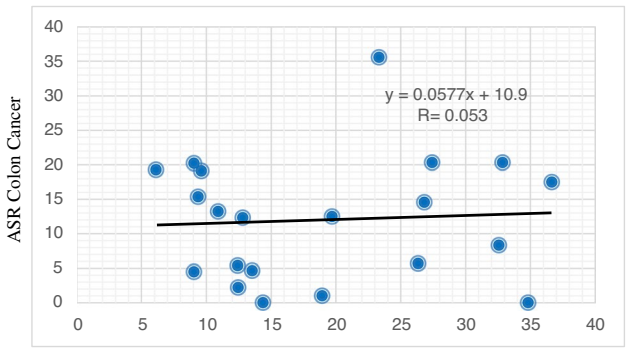

Fig. 13 Correlation of colon and nitrate drinking water Nitrate in drinking water (mg/L)

Due to the fact that the increase in the amount of nitrate in drinking water was associated with increased incidence of gastrointestinal cancers (gastric, esophagus and colon), knowing that nitrate may be a precursor to carcinogens N Nitro's. Therefore, high levels of nitrate in drinking water may be considered as one of the factors influencing the incidence of gastrointestinal cancers in the province of Isfahan.

Many studies have been conducted on the effect of drinking water nitrate on the incidence of gastrointestinal cancers (gastric, esophagus, colon), which confirmed the effect of this factor on the incidence of these diseases. Due to the importance of the association of these materials with the incidence of cancers in the province of Isfahan, it can be argued that these results are more controversial in medical terms. In some studies, there was a relatively strong correlation between increased nitrate levels in drinking water and the incidence of gastric cancer and its mortality (Sandor et al. 2001; Stepanov, et al., 2014). Some research has also shown a significant correlation between increased nitrate levels in drinking water and the incidence of esophageal and gastric cancer (Türkdoğan et al. 2003). A survey by the United States Geological Survey in the eastern Iowa showed that nitrate levels are more than MCL[1] in almost 50 percent of the samples in agricultural areas. This indicates the entry of high nitrogen into surface water sources, which increases this in relation to nitrate in public water supplies and the risk of colon cancer (Kalkhoff et al. 2000). Nitrates can be ingested through food as well as from drinking water. Seventy to eighty percent of the consumption of nitrates is estimated to be from plant sources (Hord et al. 2009). Changes in nitrate concentration with variations of static depth have a negative relationship that increasing in depth the nitrate concentration decreases, which indicate impact of depth lower than the location of agricultural land (Fazeli et al., 2010). The epidemiological study showed a strong and positive association between drinking water nitrate and colon cancer (Zaki et al. 2004; Taneja et al, 2017).

[1] Maximum Contaminant Levels (MCLs) are standards that are set by the United States Environmental Protection Agency (EPA) for drinking water quality.

In the present study, nitrate in drinking water had a direct linear relationship with gastric cancer ($P < 0.05$, $R = 42\%$). It was weakly correlated with esophageal cancer with ($P < 0.05$, $R = 23\%$) and colon cancer with ($P < 0.05$, $R = 0.053$). Despite the positive correlation between drinking water nitrate and this type of cancer in other parts of the world, in our study area, there is not a statistically significant relationship. It has already been proven that processed meat can cause colon cancer because of the higher N-nitroso compounds in comparison.

with fresh meat (Ward et al., 2005). Researchers from other countries have generally concluded that existing epidemiological and ecological studies are inadequate to investigate the association between exposure to these harmful substances and their adverse effects (Manassaram et al. 2007). In most studies, such as the present study, researchers measured the amount of this substance when it comes to exposure to illness in the past and it might be doubtful whether the level of nitrate of water remains constant over the time. In a study in the USA (2008), this question was answered positively and stated that these studies have a good reputation (Ruckart et al., 2008).

Conclusion

In general, by comparing the results of this study with other similar studies, it can be concluded, in Isfahan province, the prevalence of gastrointestinal cancers in areas where nitrate is higher in drinking water. But despite this issue, according to statistical studies of nitrate in drinking water that has a relatively high relation with gastric cancer, it has a weak relationship with esophageal cancers and poor relationship colon cancer. The incidence of gastric and colon cancer in male over the age of 70 and esophageal cancer among female aged 60 to 75 75–60 is highest. Considering that the present study was carried out at the ecological level, other studies, both at the ecological level and at the individual level, are suggested. It is also suggested that given the importance of nitrate pollution as one of the environmental and agricultural problems, as well as the value of groundwater resources, especially in arid and semi-arid regions. It is also suggested that the concentration of this ion in the groundwater of the region is studied continuously and in throughout the year, and more research is done on the amount of nitrate in food and the effect of these parameters on other gastrointestinal cancers.

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Declarations

Conflict of interest The author declares no competing interests.

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