INTRODUCTION

Although the brain and other CNS cancers are rare, they cause morbidity and mortality that is disproportionate to their incidence\(^1\)\(^2\). In 2016, there were 330000 incident cases of brain and CNS cancers and 227000 deaths globally\(^3\), with ASIR 4.63 per 100 000. The ASIR was high in East Asia, central and western Europe, but low in Oceania and central and eastern sub-Saharan Africa\(^4\). The incidence was higher in men than in women\(^5\). Several environmental risk factors of the brain and other CNS cancers have been studied, but few are well established\(^6\). The following environmental risk factors have been investigated in epidemiological studies for association with the brain and other CNS cancers: Pesticides, Fertilizers, Formaldehyde, Synthetic rubber, Vinyl chloride, and Petrochemicals and petroleum\(^7\).

In Iraq (except Kurdish region), there were 1160 newly diagnosed brain and CNS cancers cases in 2015\(^5\), where the incidence had increased over the study period, from 2.882% in 2000 to 5.53% in 2015. The Iraqi Cancer Registry (ICR) was established in 1974 through close cooperation of Ministry of Health and the Iraqi Cancer Society. It is responsible for collecting and combining detailed information about cancer patients from all provinces of Iraq. The ICR publishes an annual report of Iraq cancer statistics including new cases, mortality for the provinces and district levels.

Iraq is a developing country located in western Asia, bordered by Iran in the East, Turkey in the North, Syria in the west and Jordan in the southwest, Saudi Arabia in the South, and Kuwait in the southeast. It has a total area of 437,072 km\(^2\). Administratively, the country is divided into 18 provinces, 117 districts. Iraq’s climate is subtropics with the mean temperature range from 5 °C to 10 °C in the coldest month of January and up to 30 °C in the hottest month of August. The estimated population of Iraq as on mid-year 2020, according to UN data, is 40,222,493. Figure 1 shows the location of Iraq. The spatial patterns at the province-level or district-level have not been explored in Iraq. Explaining how districts with high or low ASIRs of brain and CNS cancers cluster spatially may support government efforts to reduce the burden of brain and CNS cancers in specific areas of Iraq. This study is the first in Iraq to examine whether the ASIRs of brain and CNS cancers tend to clustering, to identify where hot/cold spots appear (groups of districts with extremely high or low of the ASIRs of brain and CNS cancers), and to identify spatial outliers (districts with high or low of the ASIRs of brain and CNS cancers
surrounded by districts with dissimilar values), during 2000 to 2015.

Figure 1: The location of Iraq

METHODS

Data
Brain and CNS cancers (ICD-10: C70-C72) records were obtained from the ICR in the Ministry of Health of Iraq. The ICR is responsible for aggregating data relating to every new cancer case in all provinces of Iraq. The ICR annually published annual reports of cancer include detailed statistical data of cancer from all government and private hospitals throughout the country. In total, this study covers all provinces with the exception of three provinces in the Kurdish region (Erbil, Duhok and Al-Sulaymaniyah, for which the data is incomplete) with 83 districts in the country during 2000-2015. District level population data were obtained from the Central Organization for Statistics in the Ministry of Planning. This study examined brain and CNS cancer incidence data for 2000-2015. To enhance statistical stability, the data were divided into three periods (2000-2004, 2005-2009, and 2010-2015).

Statistical methods
The (ASIRs) were calculated according to geographical region (provinces and districts) for each time period (2000-2004, 2005-2009, and 2010-2015) using the world standard population. The study employed the methods of spatial cluster, Global spatial autocorrelation, Local indicators of spatial association (Getis-Ord Gi* and Anselin Local Moran’s I). The Global indexes of spatial autocorrelation - Moran’s I were used to distinguish clusters of districts with high or low ASIRs and to distinguish spatial outliers. The descriptive analysis was performed using SAS (version 9.4) statistical software, and we used ArcMap 10.6 (Environmental Systems Research. Institute, Inc., Redlands, CA) for constructed maps of the brain and CNS cancers. Statistical significance was assumed at p<0.05.

Global spatial autocorrelation - Moran’s I
Global Moran’s I was used to examine whether the pattern is clustered, dispersed, or random across districts with respect to ASIR. This statistic measures the spatial autocorrelation of districts in the provinces and the ASIRs simultaneously. The Global Moran’s I statistic is given as follows:

\[ I = \frac{n \sum_i \sum_j W_{ij} (X_i - \bar{X})(X_j - \bar{X})}{\sum_i \sum_j W_{ij} (X_i - \bar{X})^2} \]

Where:
- \(X_i\) = the ASIRs of brain and CNS cancers for the \(i\)th district;
- \(X_j\) = the ASIRs of brain and CNS cancers for the \(j\)th district;
- \(\bar{X}\) = the mean of ASIRs of brain and CNS cancers for all of the districts in the study area;
- \(W_{ij}\) = the spatial weight between pair of districts \(i\) and \(j\); and
- \(n\) = the total number of districts.

Moran’s I scores usually ranges between -1.0 (indicates a dispersed pattern) and 1.0 (indicates a clustered pattern).

Getis-Ord Gi* statistic
The hot and cold spot analysis calculate the Getis-Ord \(G^*_i\) tool for ASIRs in Iraq during 2000-2015. The Getis-Ord \(G^*_i\) statistic is given as follows:
The Anselin local Moran’s I identify spatial outliers of districts with high or low ASIRs as well as spatial clusters. Clusters of districts with high ASIRs (HH = “high-high”) are considered “hotspots”, whereas clusters of districts with low ASIRs (LL = “low-low”) are considered cold spots. Furthermore, Anselin local Moran’s I identify districts with high ASIRs that are surrounded primarily by districts with low ASIRs (HL = “high-low”) and districts with low ASIRs that are surrounded primarily by districts with high ASIRs (LH = “low-high”). The Anselin local Moran’s I statistic is given as follows:

\[ I_i = \frac{(X_i - \bar{X}) \sum W_{ij} (X_j - \bar{X})}{S^2} \]

Where:
- \( X_i \) = the ASIRs of brain and CNS cancers for the \( ith \) district;
- \( \bar{X} \) = the mean of ASIRs of brain and CNS cancers for all of the districts in the study area;
- \( W_{ij} \) = the spatial weight between pair of districts \( i \) and \( j \);
- \( n \) = the total number of districts; and
- \( S \) = the standard deviation of the ASIRs of brain and CNS cancers in the study area, where \( S = \sqrt{\frac{\sum_{j=1}^{n} W_{ij}^2 - \sum_{j=1}^{n} W_{ij}}{n-1}} \).

The \( G_i \) statistic is a z-score, so no further calculations are required. The \( G_i \) statistic returned for each feature in the dataset is a Z score. The larger the Z score, the more intense the clustering of high values. For statistically significant negative Z scores, the smaller the Z score is, the more intense the clustering of low values. The hotspot map can detect several hotspots and cold spots across Iraq.

The ASIRs of brain and CNS cancers over time (Figure 2).
Figures 3A, 3B and 3C displays the geographic distribution of the ASIRs of brain and CNS cancers during the periods 2000-2004, 2005-2009, and 2010-2015, respectively; the yellow scale represents the level of ASIRs and the browner the color, the higher the ASIRs.

Figure 3A shows that areas with the high ASIRs during the period 2000-2004 were concentrated in some districts in the northern, including AL Shikhan district in Nineveh province; some districts in the northeastern region, including AL-Hawija and Dakook districts in Kirkuk province; some districts in the north-central region, including Tikrit city in Salah al-Deen province; some districts in the central region, including Al-Rissafa district in Baghdad province. However, ASIRs in the southern and southwestern regions were relatively low.

Figure 3B displays the distribution of ASIRs of brain and CNS cancers during the period 2005-2009. The areas with high ASIRs were located in the northern, central and southwestern regions; the highest ASIRs was in Kirkuk city in Kirkuk province, Al-Sadir and Al-Karkh districts in Baghdad province, and Al-Najaf city in Al-Najaf province. In 2010-2015, the areas with high ASIRs were focused in some districts in the central region, including most of the districts in Baghdad province, AL Sadir, AL Karkh, Al-Rissafa, AL Kadhimiyah and AL Adhamia districts; Al-Hilla city in Babil province; Karballa city in Karballa province; some districts of the southern region, including AL Basrah city and AL Zubair district in Al-Basrah province, AL Nassiriyah city in Thi-Qar province; some districts of the southwestern region, including AL Najaf city in AL Najaf province; Kirkuk city in Kirkuk province in the northern region. However, ASIRs in the western regions were relatively low (Figure 3C).

The global Moran’s I test and the associated z-score for each of the three time periods 2000-2004, 2005-2009, and 2010-2015 demonstrated that there was significant spatial autocorrelation of district-level ASIRs of brain and CNS cancers. In other words, across Iraq, districts with similar ASIRs of the brain and CNS cancers exhibits spatial clustering for each of the three time periods 2000-2004, 2005-2009, and 2010-2015.

Significant spatial clusters of districts with hotspots and cold spots ASIRs of brain and CNS cancers, as assessed by the hotspot analysis (Getis-Ord Gi* tool) for each of the three time periods 2000-2004, 2005-2009, and 2010-2015 can be seen in Figures 4A, 4B and 4C. In 2000-2004 (Figures 4A), 10 districts were identified as a hotspot, and 4 districts were identified as a cold spot. In 2005-2009 (Figures 4B), the number of districts designated as a hotspot declined to 9
and the number of districts that designated as a cold spot decreased to 2. In 2010-2015 (Figures 4C), the number of districts that appeared as a hotspot and cold spot remained the same as the period 2005-2009.

Conversely, nine districts located in the provinces of Al-Diwaniya (Al-Diwaniya and Affak districts), Al-Muthanna (Al-Rumaitha and Al-Salman districts), Thi-Qar (Sook Al-Shiookh and Al-Jabaish districts), Maysan (Al-Majar Al-Kabere district), and Al-Hasra (Al-Zubair and Al-Mdainah districts) showed low-low cluster patterns. Generally, these patterns changed in 2005-2009 (Figure 5B), the notable changes were in Kirkuk, Tikrit, Door, Al-Shirkatt, Al-Sadir, and Al-Madain, which no longer a hotspot.

In 2005-2009 (Figure 5B), The high-high appeared in the provinces of Baghdad (Al-Rissafa, Al-Adhamia, and Al-Karkh districts), Babil (Al-Mahaweeel and Al-Hilla districts), Karbala (Al-Hindia district), and Al-Najaf (Al-Najaf and Al-Kuffa). The cold spots districts were located in the provinces of Diyala (Al-Khalis district), Salah al-Deen (Dooz district), Al-Anbar (Rawa and Al-Kaaim districts). In 2010-2015 (Figure 5C), there were seven districts showed high-high cluster patterns, included Baghdad (Al-Sadir, Al-Kadhimiyyah, Adhamia, Al-Karkh, Al-Rissafa, and Al-Madain districts), and southern region (Abu-Al-Khaseeb district in Al-Hasra province).

The cold spots districts were located in the provinces of Al-Anbar (Heet district), Salah al-Deen (Balad district), and Diyala (Al-Khalis district). Additionally, several districts were labelled as spatial outliers. In 2000-2004 (Figure 5A), there were three districts identified as the high-low type, where the ASIRs of brain and CNS cancers were high, but the district was surrounded by a cold spot, these districts were located in the provinces of Al-Najaf (Al-Najaf district), Al-Muthanna (Al-Samawa district), and Thi-Qar (Al-Nassiriyah district). Conversely, there were 3 districts identified as the low-high category, where the ASIRs of brain and CNS cancers were low, but the district was surrounded by a hotspot, these districts were located in the provinces Nineveh (Al-Hamdaniya district), Kirkuk (Dibis district), and Salah al-Deen (Biegy district). In 2005-2009 (Figure 5B), we identified three districts spatial outliers, included one neighborhood with high ASIRs of brain and CNS cancers surrounded by a cluster of low ASIRs of brain and CNS cancers (high-low) (Heet district in Al-Anbar province); and two neighborhood with low ASIRs of brain and CNS cancers surrounded by a cluster of high ASIRs of brain and CNS cancers (low-high) (Dibis district in Kirkuk province and Al-Hamza district in Al-Diwaniya province).

A spatial cluster analysis (Anselin Local Moran’s I) was used to examine clusters of districts with high or low ASIRs of brain and CNS cancers. In 2000-2004 (Figure 5A), the high-high districts were located in the provinces of Kirkuk (Kirkuk district), Salah al-Deen (Tikrit, Door, and Al-Shirkatt districts), and Baghdad (Al-Sadir, Al-Rissafa, Al-Adhamia, and Al-Madain districts).
During the period from 2010 to 2015 (Figure 5C), we identified five districts spatial outliers, included three neighborhood with high brain and CNS cancers ASIR surrounded by a cluster of low ASIRs of brain and CNS cancers (high-low) (Aana and Al-Ramadi districts in Al-Anbar province and Dakook district in Kirkuk province); and two neighborhood with low ASIRs of brain and CNS cancers surrounded by a cluster of high ASIRs of brain and CNS cancers (low-high) (Abu-Graib in Baghdad province and Al-Hindia district in Karballa province).

**DISCUSSION**

Spatial variation of brain and CNS cancers in Iraq at the district level has not been explored. This study is the first to explore the geographic distribution of the brain and CNS cancers in Iraq using spatial autocorrelation analyses.

In this study, we found that brain and CNS cancers was the fifth most common type of cancer in Iraq, contributing 5.53% of the total number of new cases diagnosed in 2000 to 2015, with an ASIR of 5.051 per 100,000, which is lower than the ASIR in Albania, Sweden, Armenia, Serbia, Macedonia, Nordic countries, and Iran and higher than global ASIR. We found that ASIR of brain and CNS cancers higher in males than females, which is in line with most studies.

Our results suggested that ASIRs of brain and other CNS cancers increased significantly during the period 2000 to 2015.

Worldwide, brain and other CNS cancers are rare, representing 1.6% of all cancers in both sexes. The incidence of brain and other CNS cancers differs worldwide, East Asia was the region with the most incident cases of CNS cancer for both sexes in 2016, followed by western Europe, and south Asia. It is not known what causes brain and other CNS cancers however, A variety of factors have been identified that may increase a person's chances of developing brain and other CNS cancers. Recent studies indicate that exposure to radiation, hormonal factors, nutrition, alcohol, smoking, Fertilizers, Air pollution, Electromagnetic fields, and family history may increase person's risk of developing brain and another CNS cancers.

This study demonstrates geographic variation and risk clusters in ASIRs of brain and CNS cancers at the district level in Iraq. Results of global indicators of spatial autocorrelation confirm that ASIRs of brain and CNS cancers exhibit spatial autocorrelation. In other words, districts with high ASIRs of brain and CNS cancers tend to cluster together geographically. Conversely, districts with low ASIRs of brain and CNS cancers also tend to locate closer together. Using of Getis-Ord Gi* tool of the spatial distribution, we were able to detect several hotspots and cold spots in Iraq that represent clusters of districts with significantly high or low ASIRs of brain and CNS cancers.
In the present study, relatively high ASIRs of brain and CNS cancers were mainly focused in some districts in the northern and central regions (specifically most districts of Baghdad province were higher than those in other provinces of Iraq) in Iraq, while relatively low rates were concentrated in the southeastern and northwestern regions during the three study periods 2000-2004, 2005-2009, and 2010-2015.

The causes of global variation in incidence of brain and CNS cancers are unclear, but they may be partly explained by differences in risk factors such as a genetic susceptibility, environmental, lifestyle exposures. However, it is beyond the aim of this paper to know the reasons of geographical variation of brain and other CNS cancers incidence in Iraq. The causes of this spatial pattern of brain and other CNS cancers in Iraq are unknown, but they may be due to exposure to lifelong, variations in socioeconomic status and health behaviors. However, the reasons for the higher incidence rates in some districts merits further investigation.

CONCLUSIONS

In summary, there is substantial geographic variation in ASIRs of brain and CNS cancers among Iraq, districts with high and low ASIRs of brain and CNS cancers tend to cluster together. Explaining how districts with high or low ASIRs of brain and CNS cancers cluster spatially may support government efforts to reduce the burden of brain and CNS cancers in specific areas of Iraq. Results of this study may be considered by public health practitioners as the cornerstone for setting brain and CNS cancers control plan and programs. Additionally, results may be used as a reference for the officials in the estimation of the need of labor force, medical and technical equipment and cancer medications toward high-need areas. Our finding determined clusters of areas with high brain and CNS cancers incidence in Iraq, specifically in the central (including Al-Sadir, Al-Kadhimiyyah, Adhamia, Al-Karkh, Al-Rissafa, and Al-Madain districts in Baghdad province) and southern region (Abu-Al-Khaseeb district in Al-Basrah provinces). The government efforts should focus on those regions, and the factors related to spatial pattern of brain and CNS cancers incidence in Iraq should be investigated.

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Conflict of interest

We declare that we have no conflicts of interest to disclose regarding this manuscript.

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REFERENCES


