

# Spatio-temporal mapping of breast and prostate cancers in South Iran from 2014-2017

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## Research article

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# Abstract

## Background:

The most common gender-specific malignancies are cancer of the breast and the prostate. In developing countries, cancer screening of all at risk is impractical because of healthcare resource limitations. Thus, determining high-risk areas might be an important first screening step. This study explores potential high-risk clusters in the incidence pattern of breast and prostate cancers in southern Iran.

## Methods:

This cross-sectional study was conducted in the province of Kerman, South Iran. Patient data were aggregated at the county and district levels and the incidence rate per 100,000 people both for cancer of the breast and the prostate were calculated. We used the natural-break classification with five classes to produce descriptive maps. A spatial clustering analysis (Anselin Local Moran's  $I$ ) was used to identify potential clusters and outliers in the pattern of these cancers from 2014 to 2017.

## Results:

The age-standardised incidence rate of breast cancer showed an increase from 29.93 to 32.27 cases per 100,000 people and that of prostate cancer from 13.93 to 15.47 cases per 100,000 during 2014-2017. Cluster analysis at the county level identified high-high clusters of breast cancer in the North-West of the province for all years, but the analysis at the district level showed high-high clusters for only two of the years. Furthermore, cluster analysis at the county and district levels of prostate cancer also identified high-high clusters in the North-West of the province for two of the years.

## Conclusions:

North-western Kerman had a significantly higher incidence rate of both breast and prostate cancer, which should help in designing tailored screening and surveillance systems. Furthermore, this study generates new hypotheses to test potential relationships between environmental risk factors and incidence of cancers in areas with higher cancer risk than the average.

## Background:

Cancers are the second leading cause of death worldwide (1). The world's ageing population leads to a significant increase in the incidence of chronic diseases such as cancers (2). Furthermore, human exposure to multiple risk factors has increased the cancer burden worldwide (3). Despite advances in timely diagnosis and medical treatment of neoplasms in recent years, malignancies in middle to low-income countries are expected to almost double by 2030 compared to high-income nations (4). If cancer is diagnosed promptly, cures can sometimes be found and life prolonged leading to considerably lower

disease burdens (5, 6). However, health systems, particularly in developing countries, cannot screen all people to identify patients in the early stages of the disease. Identifying high-risk geographical areas could help decreasing the cost of screening, finding the people at risk and implementing more efficient diagnostic strategies (7). Investigating high-risk areas should also provide valuable knowledge to scientists about the aetiology of some malignancies (3).

Cancer of the breast and the prostate are the two most common gender-specific malignancies worldwide (8). Furthermore, these malignant neoplasms cause high numbers of disability-adjusted life years (DALYs) (9). Risk factors for these two diseases are diverse and interrelated, as they include genetic (10), social-economic (11) as well as lifestyle and environmental factors (12). Further, there are interactions between these risk factors, particularly with those involving the environment (13, 14), whose spatial variation may lead to heterogeneity in the pattern of cancers in a given geographic catchment area. Studies by Wang et al. found a significant spatial variation of prostate cancer incidence and prostate cancer-specific mortality in Pennsylvania, USA. They evaluated potential effects of individual and county-level risk factors and found that spatial variations in prostate cancer-specific mortality rates existed in Pennsylvania with a particularly high risk in the Pen State catchment area (15, 16). County-level health and environmental factors might contribute to spatial heterogeneity in prostate cancer-specific mortality as shown by Olfatifar et al. (17), who examined spatial clustering of breast cancer at the provincial level in Iran between 2004 and 2010. Their results highlight that breast tumour incidence varied across the provinces (17). At the same time, Rohani-Rasaf et al. (18) detected some high-risk regions in Tehran, the capital of Iran, both for cancer of the breast and the prostate. Most studies in Iran have applied spatial analyses at a very coarse level (province scale) and the results are therefore not as useful as a finer geography scale would be.

Taken together, geographical information systems (GIS) constitute a useful tool for the identification of high-risk areas of cancer occurrence as well as investigation of the environmental effects on cancer incidence (19-21). GIS compounds spatial and non-spatial data together producing a geodatabase, making it possible to perform spatial analyses using this data structure. For example, spatial autocorrelation is a method of exploratory spatial data analysis which allows detecting spatial dependence in spatial data (22). There are two kinds of spatial autocorrelation methods: global and local statistics. Global methods are more sensitive to departures from the null hypothesis, which examine whether data, here patients, are randomly distributed or follow a spatial pattern. They can identify spatial structures in the pattern of cancer incidence but do not determine where the clusters are. Local cluster statistics, on the other hand, quantify spatial autocorrelation and clustering, but only in limited areas. These methods may find restricted areas characterized as high-high (HH), high-low (LH), low-low (LL) or low-high (LH) risk of incidence within a region. HH and LL are defined as target areas surrounded by areas with similar incidence rates, while for HL and LH, the target areas are surrounded by areas with dissimilar cancer incidence rates. In other words, HH and LL indicate clusters, while HL and LH indicate outliers (23). This study aims to identify the spatial patterns of cancer of the breast and the prostate and to investigate the potential clustering in gender-specific patterns of these cancers in south Iran between 2014-2017.

## Method

### ***Study Area and Time:***

This study was conducted in the province of Kerman, located in southern Iran (Figure 1). The first administrative level of Iran subdivisions is the province, each of which is further subdivided into counties that are in turn subdivided into districts. Our study area contains 22 counties and 58 districts. Kerman covers an area of 183,285 km<sup>2</sup> and has, according to the National Census of 2015, a population of 3,164,718 people (24). The study covered the time span of March 2014-March 2017

### ***Data Sources:***

Data were obtained from two different sources with three different spatial scales (individual, county and district). The individual patient data were obtained through the population-based cancer registry of Kerman. They were geocoded and aggregated to both county and district. The digital maps (county and district) were obtained through the mapping organisation of the country.

We used a crude incidence per 100,000 people and the age-standardised rate (ASR) per 100,000 people for the descriptive statistics.

### ***Inclusion and Exclusion Criteria:***

We included all residents of Kerman diagnosed with either cancer of the breast or the prostate. Individuals who had come to the province for cancer treatment but lived outside of the province were excluded.

### ***Spatial Analyses:***

For the thematic maps, we used the natural-break classification with five classes. This approach is a [data-clustering](#) method designed to determine the best arrangement of values into different classes. This is done by seeking to minimise each class's average deviation from the class mean, while maximising each class's deviation from the means of the other groups. In other words, the method seeks to reduce the [variance](#) within classes and maximise the variance between them (25). For spatial visualisation, the crude incidence per 100,000 people and the ASR per 100,000 people were used.

### ***Spatial Cluster Analysis:***

Incidence rates of the two target cancers were calculated using total population and number of cases in each county and district of the province. There were 22 counties and 58 districts in the study area. The Local Moran's *I* statistic (26) was performed to quantify spatial autocorrelation of cancers frequency at

county and district level. This test calculates a z-score and *p*-value to determine whether the apparent similarity (a spatial clustering of either high or low values) or dissimilarity (a spatial outlier) is more pronounced than one would expect in a random distribution. The null hypothesis states that the cancers are randomly distributed across the study area. A high positive z-score for a feature indicates that the surrounding features have similar values (either high values or low values). However, a low negative z-score for a feature indicates a statistically significant spatial data outlier (26). We used a 95% Confidence Level (CL), and all clusters and outliers found in this study were significant at this CL.

We used ArcGIS, v. 10.5 (ESRI, Redlands, CA, USA) and GeoDa (<https://spatial.uchicago.edu/geoda>) for spatial analyses and Microsoft Excel 2016 for the descriptive analyses.

## Results:

There were 1,350 breast cancer patients (including, 42 male cases) and 478 prostate cancer patients in the province of Kerman, Iran during the period March 2014-March 2017. Table 1 shows the crude incidence per 100,000 people and ASR per 100,000 people of these cancers. The ASR of both breast and prostate cancers increased by 29.93 to 32.27 and 13.93 to 15.47 from 2014 to 2017, respectively.

**Table 1: Breast and prostate cancer incidence per 100,000 people during different time periods in the province of Kerman, Iran**

Period	2014-2015			2015- 2016			2016-2017		
	Number	Crude rate	ASR*	Number	Crude rate	ASR*	Number	Crude rate	ASR*
<b>Cancer:</b>									
Breast	438	26.64	29.93	445	28.71	32.49	467	29.73	32.27
Prostate	151	9.82	13.93	128	8.42	11.29	199	12.36	15.47

\*Age-standardised rate

As shown in Figure 2, the number of women (after 25 years of age) who developed breast cancer increased rapidly. Furthermore, the highest incidence occurred in the 50-54 age group in the 2014-2015 period, in the 65-69 age group in the 2015-2016 period and in the 75-79 age group between 2016 and 2017.

After 45 years of age, the number of men with diagnosed prostate cancer increased a way similar to that of breast cancer for women after 25 years of age. In contrast, however, the ascent of this cancer in relation to seniority was considerable in all years from 2014 to 2017 (Figure 3).

The descriptive maps of Figure 4 reveal that the breast cancer incidence was highest in the north-eastern part of the province from 2014 to 2017. However, as the cluster maps show, there were HH clusters of breast cancer in the north-western part of the province from 2014 to 2017; furthermore, there was a LL cluster in the South-East during the 2014-2015 period and the 2016-2017 but not in the time between. All clusters and outliers were statistically significant ( $p < 0.05$ ).

The descriptive maps of Figure 5 reveal that the breast cancer incidence was highest in the North stretching towards the centre of the province. However, as the cluster maps show, there were HH clusters of breast cancer in the north-western part of the province from 2014 to 2015 and 2016 to 2017; furthermore, there were LL clusters in the North-East of the province from 2014 to 2015 and from 2016 to 2017. All clusters and outliers in the figure were statistically significant ( $p < 0.05$ ).

The descriptive maps of Figure 6 reveal that the prostate cancer incidence was highest in the North-East. However, as the cluster maps show, there were HH clusters of prostate cancer in the north-western part of the province from 2014 to 2016; furthermore, there were LL clusters of prostate cancer in the South-East and East of the province from 2014 to 2017. All clusters and outliers in the figure were statistically significant ( $p < 0.05$ ).

The descriptive maps of Figure 7 reveal that the prostate cancer incidence was highest in the North-East of the province from 2015 to 2016. However, there was a HH cluster of prostate cancer in the North-West from 2014 to 2015 and some HH clusters in the North-West stretching towards the centre from 2016 to 2017. All clusters and outliers in the figure were statistically significant ( $p < 0.05$ ).

The four categories shown in Figures 4-7 correspond to the four quadrants in the Moran scatter plots as shown in Figure 8. If nearby or neighbouring areas are more alike, this is understood as positive spatial autocorrelation. Negative autocorrelation describes patterns in which neighbouring areas are unlike. For example, the first scatter plot (which shows the county level breast cancer for 2014-2015) has a Moran's value of 0.271 that should be interpreted as a spatial pattern with a tendency to be more clustered (HH and LL). Note that the incidence values have been standardized and are given in standard deviational units (the mean is zero and the standard deviation is 1). Similarly, the spatial lag is computed for those standardized values.

## **Discussion:**

The main aim of this study was to explore the spatio-temporal patterns of the incidence of breast and prostate cancer at a fine geography scale. To the best of our knowledge, this is the first study to assess spatial variations in the pattern of breast and prostate cancers in Iran. The study area in the South of Iran revealed a high incidence rate of both cancers in the Northwest of the Kerman Province, while it was low in the south-eastern part of the province. The number of people with breast or prostate cancer increased considerably after 25 and 45 years of age, respectively. Further investigations are needed to assess the drivers in the high-risk areas identified in north-western Kerman. They might be associated with environmental factors and lifestyles (12), poor access to cancer-specific services (27), hereditary reasons (10) and/or socio-economic inequalities (28, 29).

Environmental risk factors such as air pollution (30-32) and presence of heavy metals (33, 34) could be linked to the geographic outcome disparities for both cancer forms. We found high-risk areas for the

whole study period of breast and prostate cancers in the Northwest of Kerman, which is located in the Southeast of the Iranian volcano-plutonic copper belt (35), and arsenic contamination is one of the most significant environmental concerns in the Northwest of this province (36). The Sarcheshmeh copper industrial plant, the biggest copper mine of Iran, is located in the Kerman's Northwest and this area could be contaminated by heavy metals such as arsenic. Field studies report widely distributed travertine rocks north of the Sarcheshmeh copper mine indicating that a highly concentrated range of arsenic exists in the travertine rocks (36). This arsenic could seep into the water system and contaminate the drinking water in nearby urban and rural communities (36, 37). In these areas, the arsenic concentration is higher than the values recommended by the World Health Organisation (WHO) for drinking water (36, 38, 39). Indeed, arsenic-enriched water is one of the critical challenges in Kerman (36). Arsenic has been categorised as a Group 1 carcinogen factor by the International Agency for Research on Cancer (IARC) (40) and some studies associate arsenic and breast cancer (41-44); its presence in the study area is thus a potential explanation for the increased incidence of breast cancer found. However, it should also be mentioned that other studies do not show any significant such association with arsenic (45, 46). The power of this association can change due to local and individual diversities (43).

Previous studies also indicate a significant association between arsenic-enriched water and prostate cancer incidence (44, 47, 48), while increased levels of copper has been linked with the initiation of prostate cancer (33). Copper smelting and toxic discharges have led to soil pollution, especially in the region of the smelting plant in Sarcheshmeh Copper Complex. Studies indicated that most contaminated areas are located in the most common wind directions (49), which is particularly disturbing is that the polluted areas are also used as grazing land so the toxic elements of this soil may this way enter the food chain. These elements include various heavy metals in addition to copper and arsenic, e.g., lead, molybdenum and cadmium (49). Therefore, soil, water and nutrition of Rafsanjan and the adjacent townships, located in the North-West of the province are subject to these potential negative effects. Indeed, previous studies have found associations between heavy metals and both breast and prostate cancers (50-52). The current study strongly recommends examining the hypothesis which exposure to heavy metals, especially arsenic and copper, may associate with high incidence of gender-specific cancers. In fact, the high incidence of both breast and prostate cancers in north-western Kerman may be associated with these contaminants and this need to be investigated in future studies

Air pollution, such as that due to particulate matter, has been shown to be associated with breast cancer (31, 32). Further studies to confirm the effects of airborne pollution, especially particulate matter, on the risk of breast cancer is suggested. Fazzo et al. (2016) used a spatial approach to estimate the industrial air pollution impact on 17 selected neoplasms in the territory around the industrial Sicilian area of Priolo, Italy. This area has been defined as a contaminated site of national priority for remediation because of diffuse environmental contamination caused by large industrial settlements, and their study found a higher incidence of breast cancer in the contaminated area compared to the rest of the province (53).

Previous studies highlight that poor access to health care services lead to poor health outcomes (54, 55), such as increased incidence of cancer (27, 56). The high incidence of gender-specific cancers in some

regions of the study area may be due to their considerable distance from the provincial capital with limited cancer screening programmes. On the other hand, parts of the study area in the South had the lowest incidence of both cancers investigated here although they were located even further away from the provincial capital. However, proximity to health care services does not directly translate into access because of potential factors such as poor socio-economic status and low level of education that also is associated with poor access (54). GIS enable researchers to assess the revealed access to cancer services through combining spatial and non-spatial factors (55, 57, 58) and the results suggest measuring access to cancer prevention programmes should be the first step of examining this hypothesis. Previous studies have highlighted the impact of the socio-economic status on the differences in the incidence of cancers of the breast and prostate (59-61). Assessing the impact of socio-economic status on the geographic disparities of the gender-specific cancers incidence in the study area can be done by analysing the overall spatial structure or identifying high-risk areas. This also warrants further studies.

Hereditary cancer syndromes, a type of inherited disorder in which there is a higher-than-normal risk of certain types of cancer, are caused by mutations in certain genes passed from parents to children (62-66). Certain such family-related cancers are well-known, e.g., hereditary breast (65) and Lynch syndrome, which is a hereditary non-polyposis colorectal cancer (63). Hereditary cancer screening programmes (67-69) have made it possible to detect many of the approximately 5–10% of breast cancers caused by a genetic predisposition (70, 71) and thus making it possible to prevent them before they occur. There are also studies assessing the risk of prostate cancer associated with hereditary cancer syndromes. This highlights the risk of prostate cancer in people in families associated with early-onset diseases of various kinds (66). We strongly recommend researchers and policymakers to perform hereditary cancer screening and genetic testing in high-risk areas of the province with a high incidence rate of cancer of either the breast or the prostate.

Spatio-temporal cluster analysis plays a significant role in visualising and quantifying geographical variation in patterns of disease incidence. Local Moran's  $I$  to identify the HH and LL clusters as well as spatial outliers of breast and prostate cancer. Global Moran's  $I$  and Getis-Ord General G statistic are both global cluster methods which can be used to investigate the level of spatial autocorrelation of disease patterns, while Local Moran's  $I$  and Getis-Ord  $G_i^*$  are indicate the location of the clusters. Although Getis-Ord  $G_i^*$  statistic is used for identifying hotspots and the opposite, Local Moran's  $I$  method is also effective for assessing statistically significant spatial outliers (72). Thus, it was applied over other local methods (26, 73) and successfully assessed the hotspots (74, 75). Those using these methods for analysis of the spatial pattern of incident data should consider [aggregating the incident data](#) into polygons. The main question here is the geographical scale that should be used for aggregation because it could affect the results. In this study, we conducted the analyses both at the county and the district level, which are geographical scales providing practically useful information.

## Limitations and future course of the study:

We included all patients with breast and prostate cancer in the province of Kerman during 2014-2017. However, we did not have the migration data and used the current address of patients at the time of cancer diagnosis as the patients' residence. However, some patients might have lived in other regions in the years that might have affected their health differently.

We recommend other researchers performing cohort studies examining the hypotheses proposed here.

## **Conclusions:**

We identified a great deal of spatial variations with significant clusters in the patterns of cancer of the breast and the prostate. This suggests that policymakers need to develop prevention strategies tailored to areas where the risk of these conditions are greater than elsewhere. Further, there is a need to conduct further research to test the causal relationship between environmental risk factors and cancer incidence.

## **Abbreviations**

GIS: Geographical information system; HH: High-High; LL: Low-Low; HL: High-Low; LH: Low-High; WHO: World Health Organization; IARC: International Agency for Research on Cancer;

## **Declarations**

### **Ethics approval and consent to participate:**

This study has been approved by Ethical Committee of Kerman University of Medical Sciences (number= IR.KMU.REC.1397.290).

### **Consent for publication:**

Not applicable:

### **Availability of data and materials:**

The cancers data have been uploaded as supplementary files. However, due to protect the patients' data, the latitude/longitude of patients' location has been removed.

### **Competing interests:**

The authors declare that they have no competing interests.

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## Authors' contributions:

M.M and L.A provided the data and funding. N.F conducted spatial analyses and manuscript writing. H.R-M and A.B and F.K geocoded the data. A.D contributed to manuscript writing. V.Z performed the descriptive analyses. R.B and N.B contributed to manuscript writing and revising the text. B.H and B.K drafted the manuscript, designed the study and reviewed the literature. B.K was the research leader. The author(s) read and approved the final manuscript.

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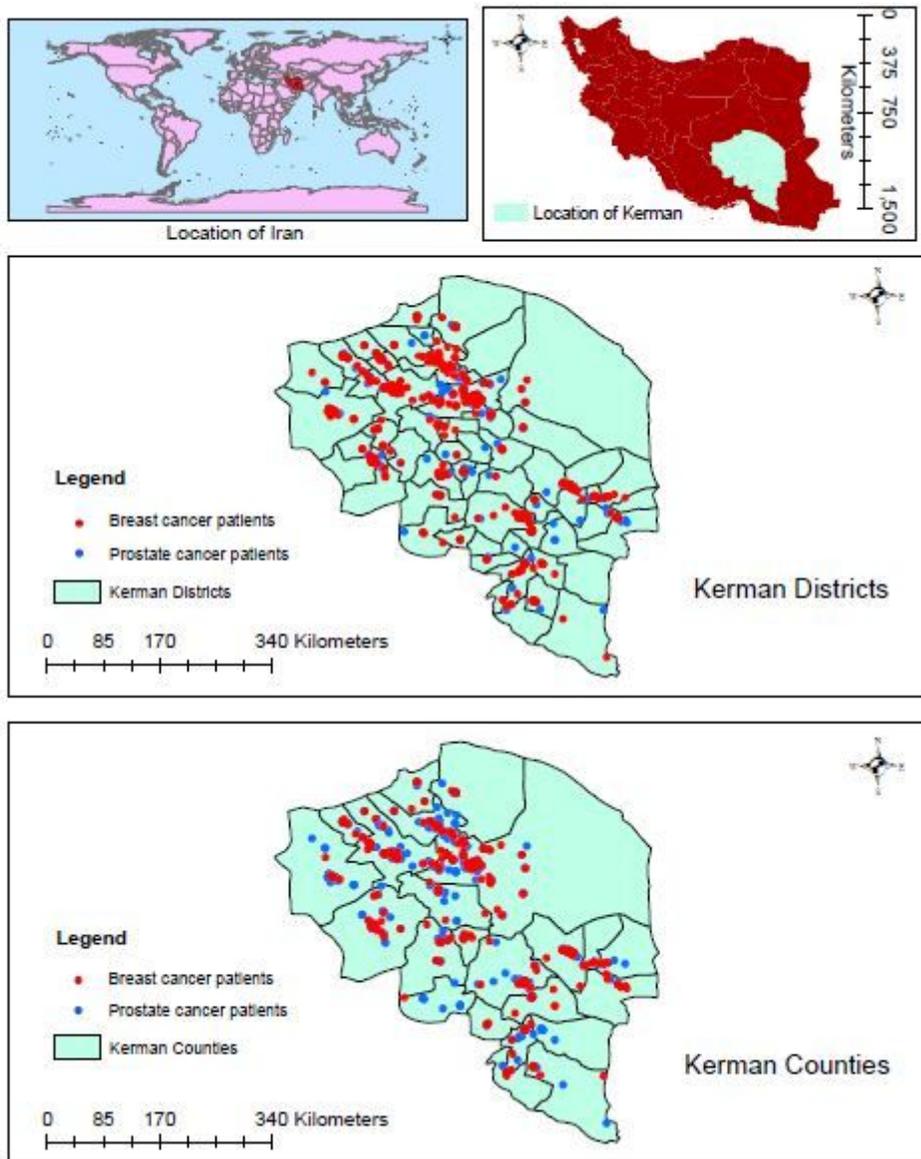
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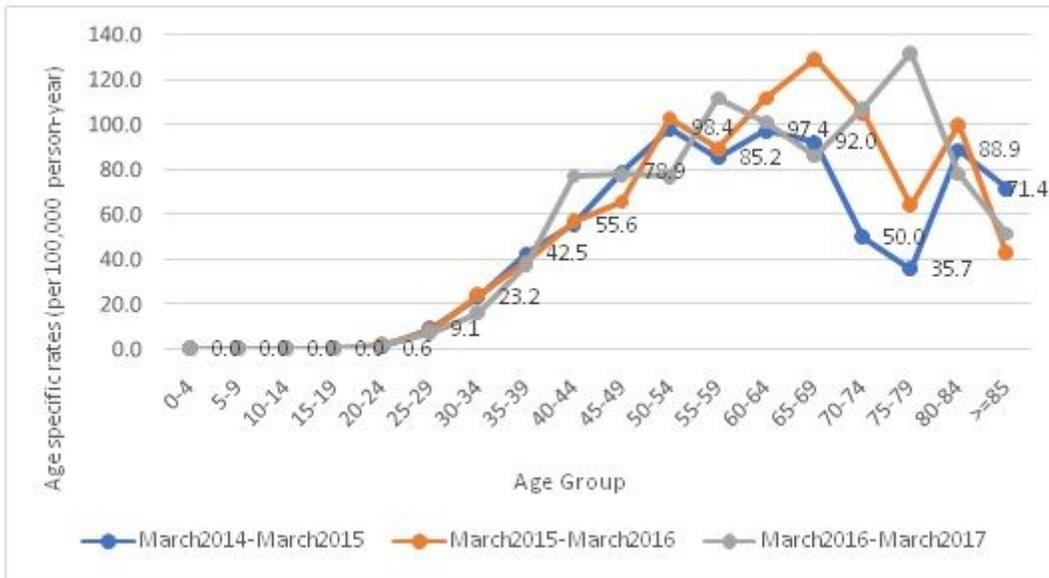
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## Figures



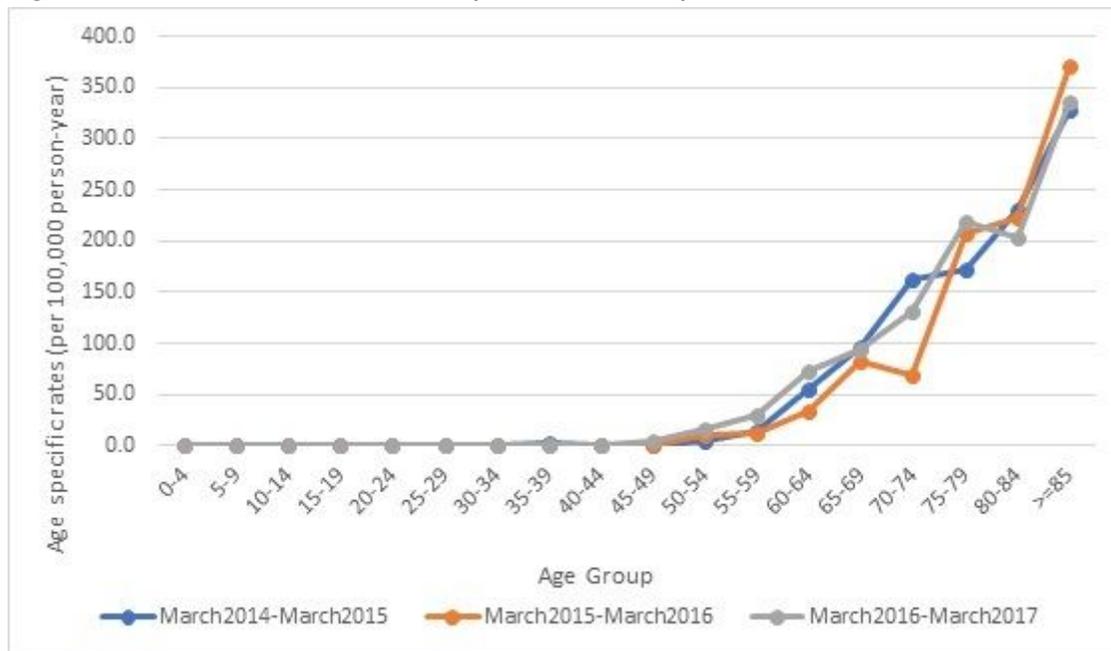
**Figure 1**

Map of Kerman counties and districts including the distribution of cancer (prostate and breast) patients during 2014-2017



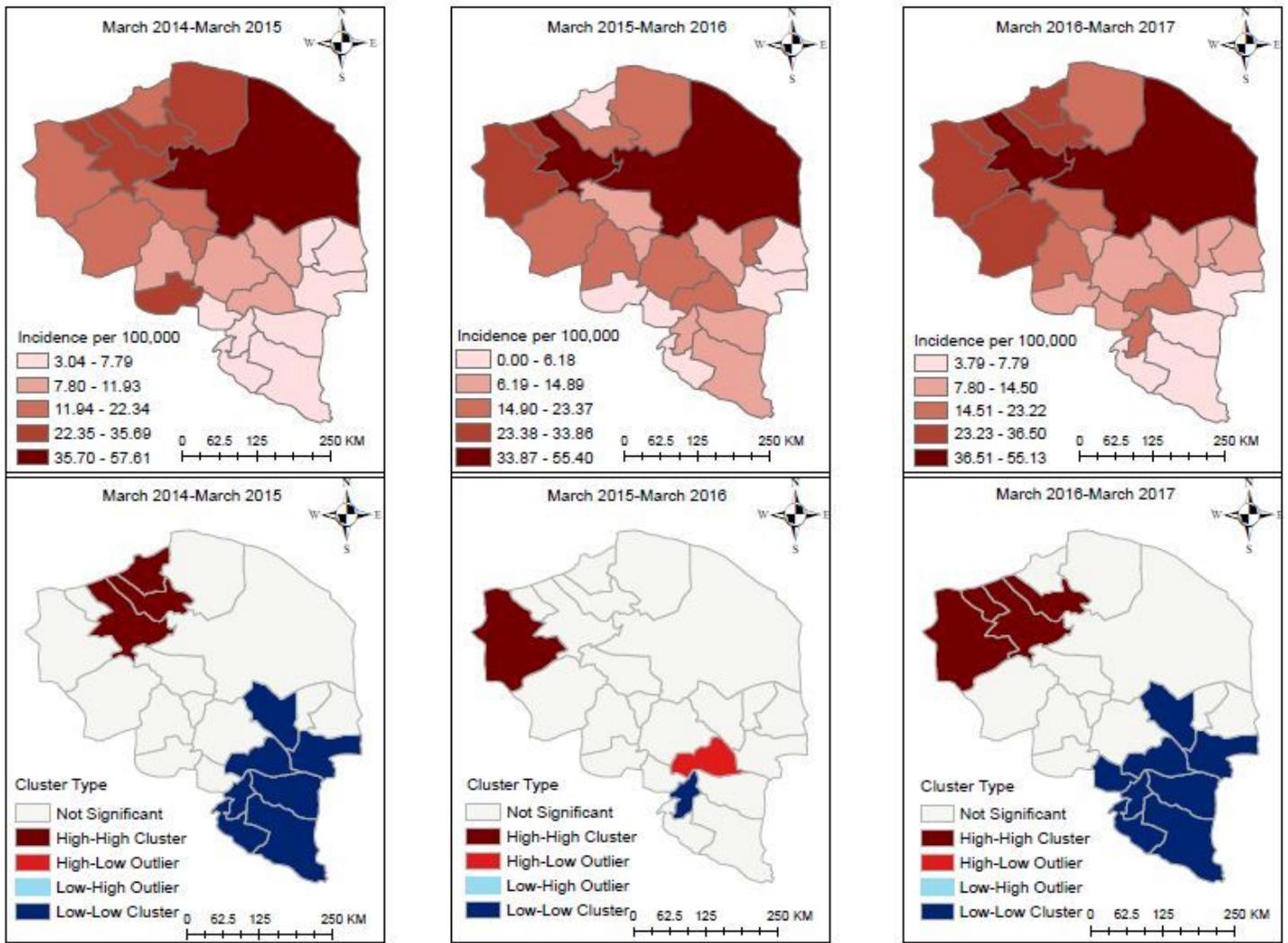
**Figure 2**

Age distribution of breast cancer patients in the province of Kerman, Iran



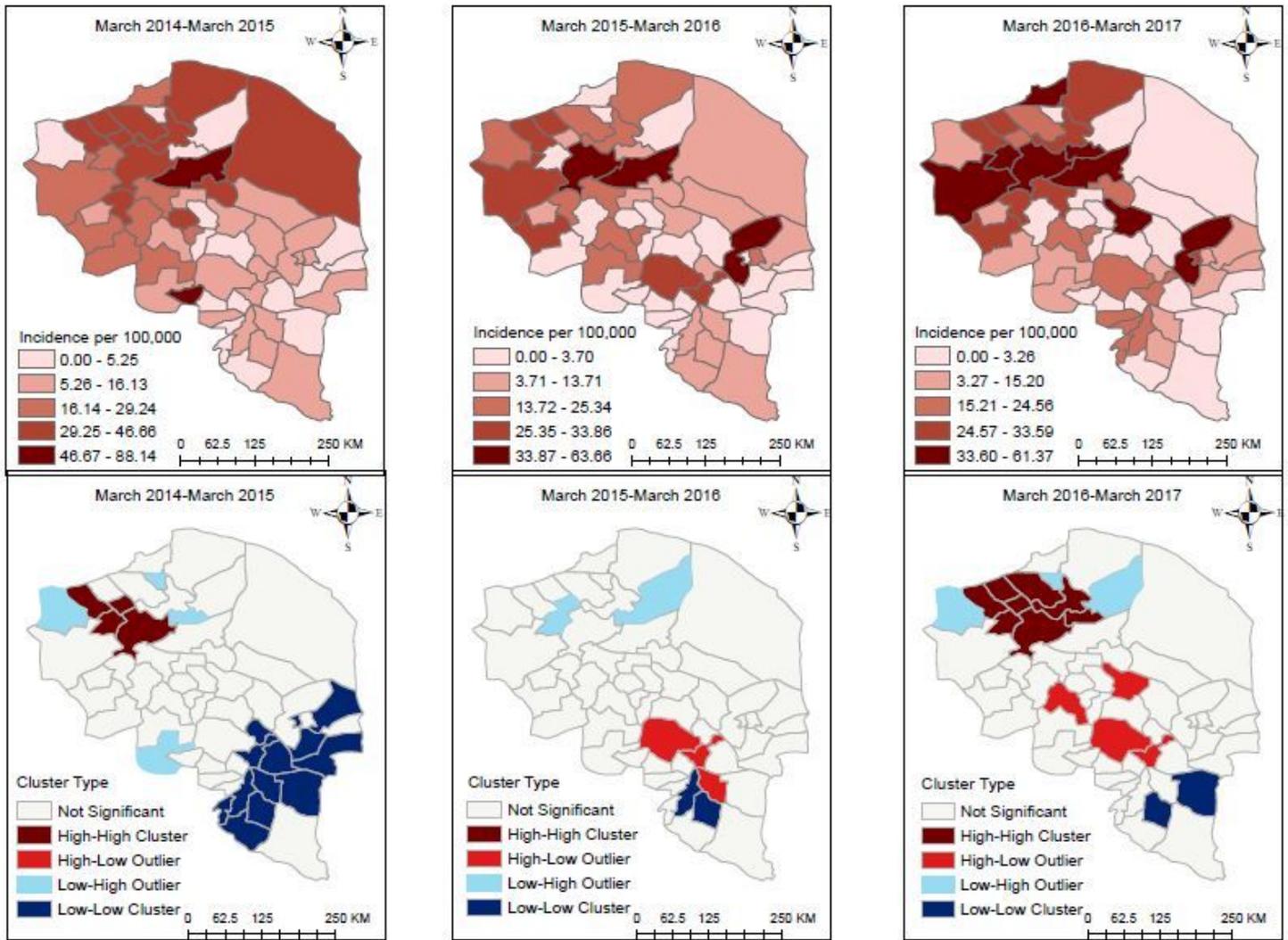
**Figure 3**

Age distribution of prostate cancer patients in the province of Kerman, Iran



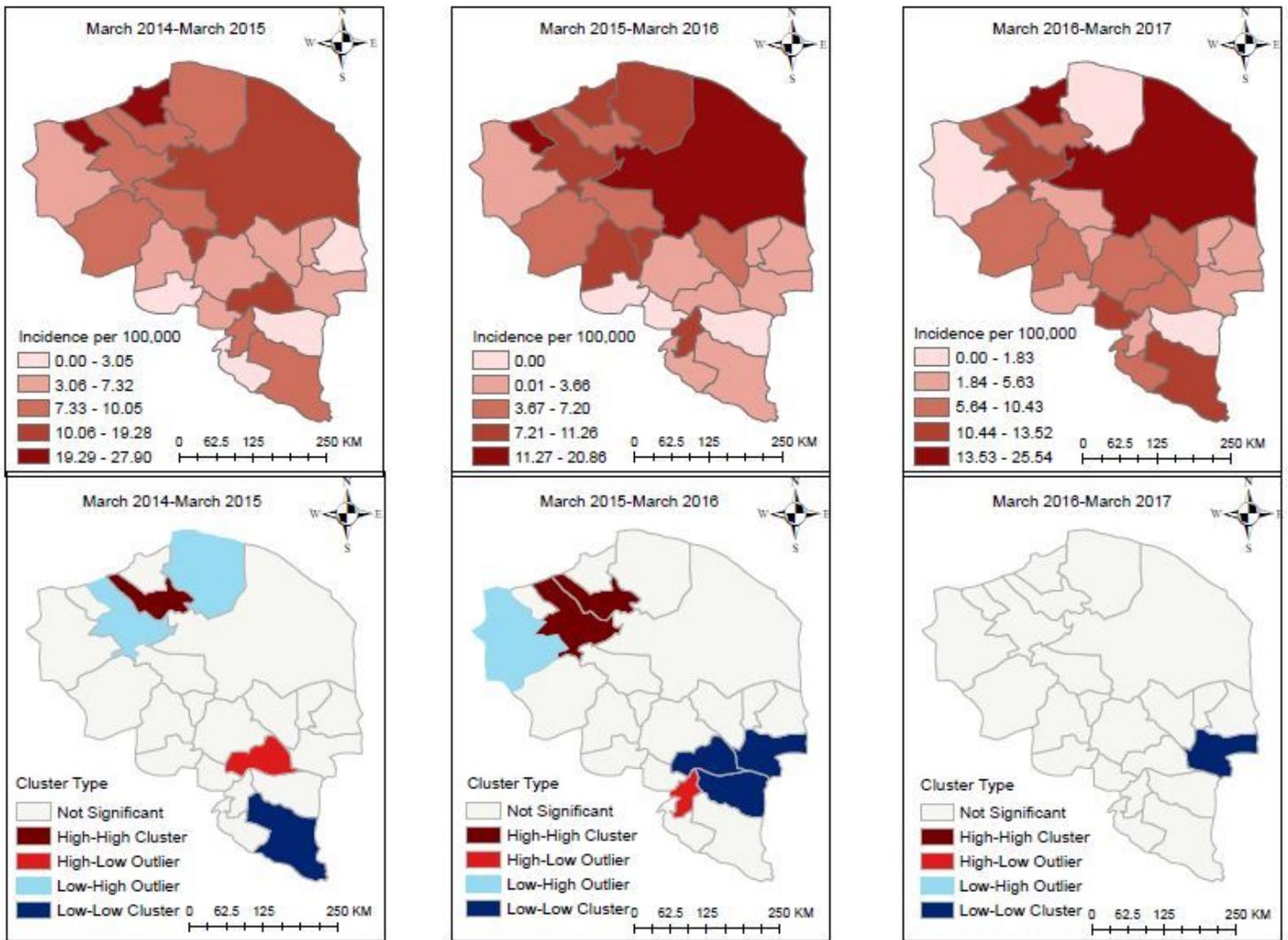
**Figure 4**

Breast cancer incidence map at the county level in the province of Kerman, Iran



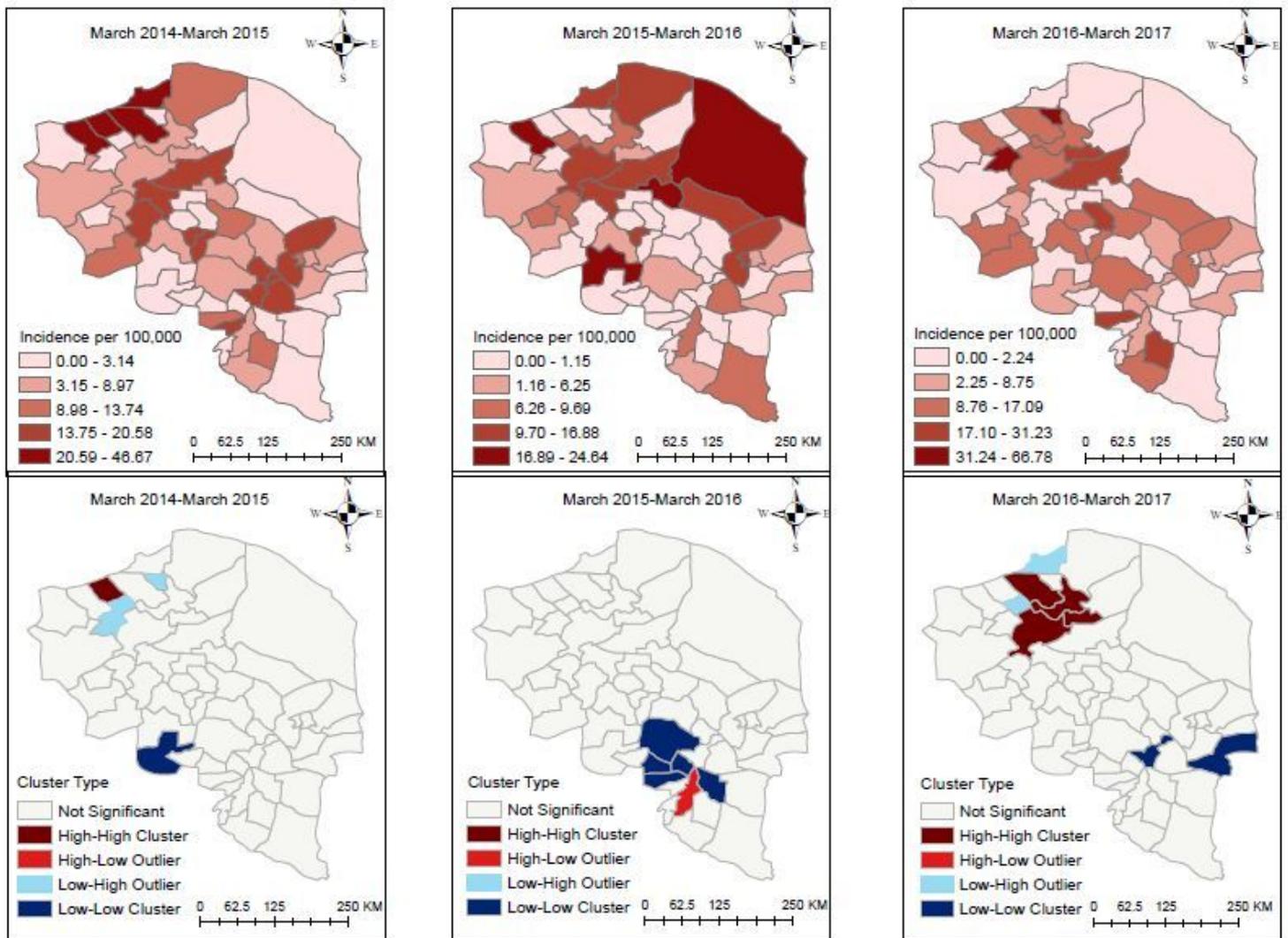
**Figure 5**

Breast cancer incidence map at the district level in the province of Kerman, Iran



**Figure 6**

Prostate cancer incidence map at the county level in the province of Kerman, Iran



**Figure 7**

Prostate cancer incidence map at the district level in the province of Kerman, Iran

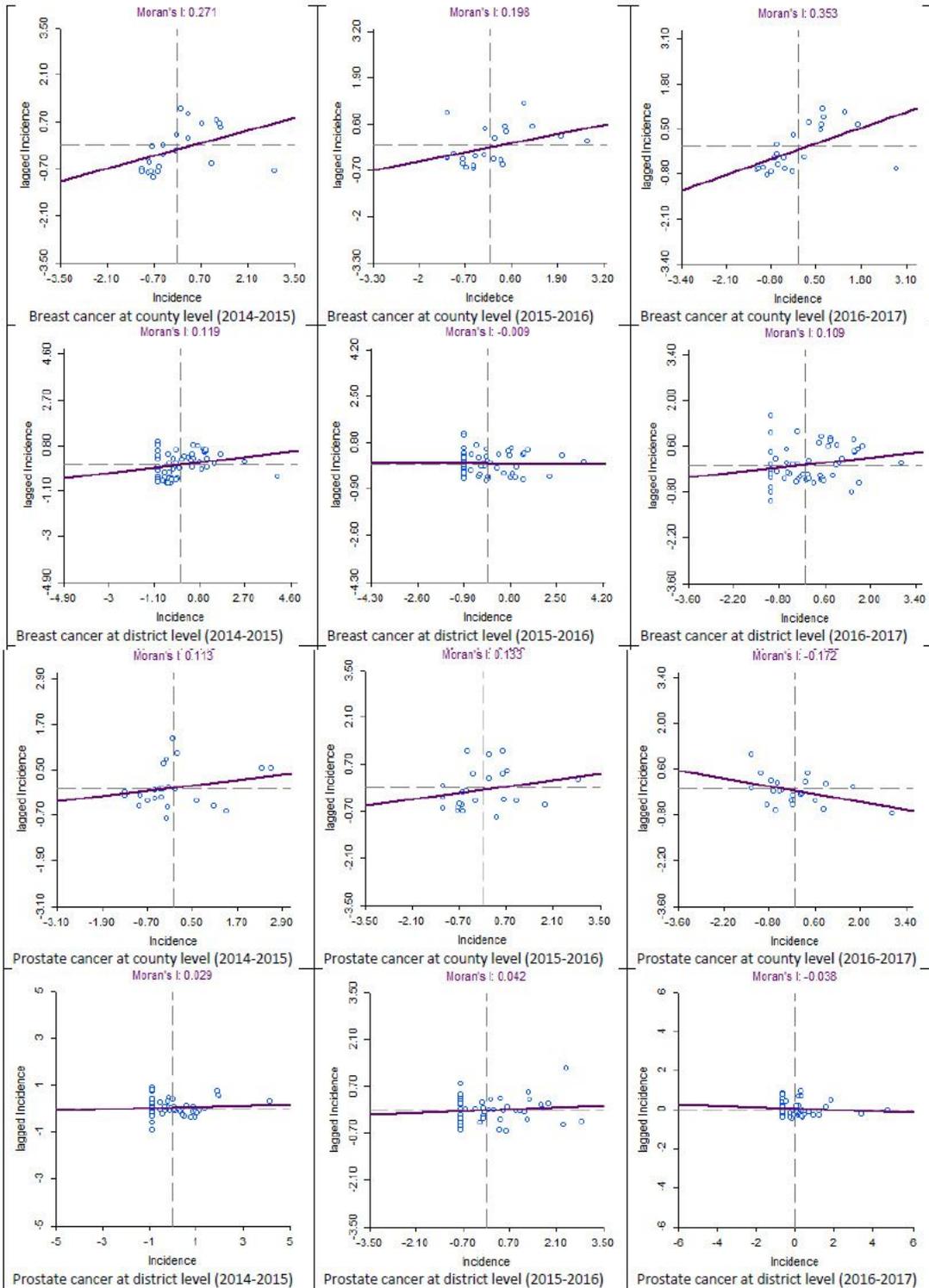


Figure 8

Moran's scatter plots for breast and prostate cancers cluster maps

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [ProstateData.xlsx](#)
- [BreastData.xlsx](#)