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# Clustering 46 Asian Countries According to the Trend of Breast Cancer Incidence Rate from 1990-2016: An Application of Growth Mixture Model

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## Abstract

**Background:** Breast cancer is the second cause of death in Asian countries, and 39% of all new breast cancer cases are diagnosed in Asia. The current study was designed to identify different patterns of breast cancer incidence rates among Asian countries.

**Methods:** In this secondary analysis study, information about the incidence rates of female breast cancer for 46 Asian countries was extracted from the Gapminder website from 1990 to 2016, and a growth mixture model was developed to describe the growth patterns and identify the main longitudinal trends in Mplus 7.4. Finally, the estimated trend in each cluster was characterized by intercept (the rate at 1990) and slope (the observed annual trend changes).

**Results:** Our findings suggested an overall increasing trend throughout the continent, but individual trajectories showed different behavior patterns amongst countries. Bayesian information creation showed that the 3-cluster model was the best choice. The annual growth of -0.13 (per 100,000 persons) suggests a slight negative trend for the incidence rate of breast cancer in cluster one countries, including Bangladesh, Israel, Kyrgyz Republic, Maldives, Nepal, North Korea, Tajikistan, and Timor-Leste. Seventeen countries, including Armenia, Bahrain, Brunei, Cyprus, Iraq, Japan, Jordan, Kazakhstan, Kuwait, Lebanon, Malaysia, Pakistan, Philippines, Qatar, Singapore, South Korea, and United Arab Emirates, which belonged to cluster 2 had not only a higher number of incidence rate in 1990, but also an annual growth of 0.96 (per 100,000 persons), indicating a sharp increase trajectory. Also, annual growth of 0.38 (per 100,000 persons) showed a slow increase in the incidence rate of breast cancer over time for the 21 remaining countries.

**Conclusion:** The observed sharp increase of breast cancer incidence in Armenia, Bahrain, Brunei, Cyprus, Iraq, Japan, Jordan, Kazakhstan, Kuwait, Lebanon, Malaysia, Pakistan, Philippines, Qatar, Singapore, South Korea, and United Arab Emirates is remarkable; therefore, effective strategies to prevent it are urgently required.

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**Keywords:** Asia, Breast cancer, Growth mixture model, Incidence, Trend

## Introduction

Breast cancer (BC) is the most common cancer amongst women in many countries worldwide.[1-3] Globally, it accounts for 23% of all cancer cases and 14% of cancer death cases amongst women.[4] According to the 2012 GLOBOCAN, the incidence of age-standardized BF is 73.4 per 100000 in developed countries and 31.3 per 100000 in developing countries.[5]

44% of deaths and 39% of all new breast cancer cases are diagnosed in Asia annually. Approximately 25% of women cancer cases in India are related to breast cancer.[6] This cancer among Asian countries is the second cause of death and remains a challenging issue in women's health.[7] Breast cancer is a critical issue in Arab countries, such as Qatar, Saudi Arabia, Iraq, and Bahrain.[8] In Saudi Arabia, the International Research Agency announced that the incidence rate of breast cancer in 2009 was 22.4 per 100000 in women, and the mortality rate was 10.4 per 100000.[9] BC is also the most common cancer in China and the fifth cause of women's death due to cancer.[10] As of 2015, 268,600 new cases and 69,500 breast cancer deaths were reported in China.[11]

Although the trend of breast cancer incidence across most Asian countries is increasing, heterogeneity among countries is particularly apparent due to different health policies, regional behaviors, and genetic and lifestyle variety.[7] While the incidence rate of breast cancer has doubled or more in Korea, Singapore, Hong Kong, and Japan, besides socioeconomic advancement[11] in the last decades,[7, 12] a substantial increase was found in China (2.96% per year),[13] Thailand[14] and Taiwan;[4] also, a gradual increase was reported in Sri Lanka,[15] Pakistan,[16] India,[17] and Iraq.[18]

As one of the well-known and practical statistical methods, growth mixture modeling is capable of dividing a heterogeneous population into multiple homogeneous clusters based on their temporal trends (detecting growth mixture). To the best of our knowledge, there are a few studies about the diversity of temporal trends of breast cancer in Asia, and previous studies are limited to a country or regional location. Therefore, the current study was devoted to clustering most of the Asian countries according to the trend of breast cancer incidence rate for the 27 years (1990–2016) via growth mixture models to show longitudinal heterogeneity among the countries. The current study implemented a powerful statistical technique to cluster breast cancer incidence rate patterns on a large temporal and spatial scale.

## Methods

In the current study, information about the incidence rates of female breast cancer (new cases per 100,000 women) within 1990-2016 years were extracted from the Gapminder website for 46 Asian countries. Gapminder is a non-profit venture registered in Stockholm, Sweden, and the current dataset was provided by the World Health Organization in Gapminder.

The growth mixture model (GMM) was developed to describe the growth patterns and identify the main longitudinal patterns. GMM tries to explore latent profiles of temporal trends by incorporating the mixed models to consider the intra-correlation of individuals in repeated measures. This method also identifies and discriminates heterogeneous unobservable clusters called latent groups using the latent models.[19] Recently, GMM has been used to model trend changes of lung cancer incidence in Europe,[20] to investigate the main patterns in the incidence of gynecological cancers among the provinces in Iran[21] and to model the 28-year trend changes of the mean annual exposure to particulate matter with an aerodynamic diameter of fewer than 2.5 μm ($PM_{2.5}$ particles) in the Middle East countries.[22]

In GMM, estimating the optimal number of latent classes is a critical issue. In the current manuscript, Bayesian information creation (BIC) was used to estimate the optimum number of latent clusters; all the statistical analyses were performed in Mplus software, version 7.4. Finally, the estimated trend in each cluster has been characterized by intercept (the rate at 1990) and slope (the observed annual trend changes).

## Results

The visualized trend of breast cancer incidence rate among 46 Asian countries is shown in Figure 1, and related descriptive statistics in 5-year intervals from 1990 to 2016 are reported in Table 1. The results suggest an overall increasing trend throughout the continent, but individual trajectories show different behaviors among countries. To consider heterogeneity in growth trajectories and model these complex patterns, we implemented the growth mixture model.

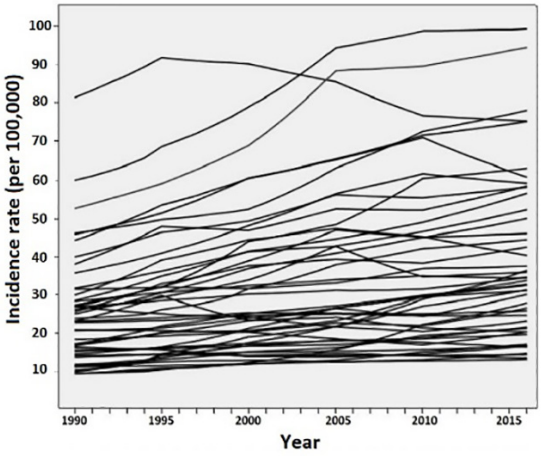


**Figure 1:** The trend of breast cancer incidence rate among 46 Asian countries (By authors)

**Table 1:** Descriptive statistics of breast cancer incidence rates (per 100000) among 46 Asian countries

| Year | Minimum | Maximum | Mean | Standard deviation | Median |
|---|---|---|---|---|---|
| 1990 | 9.6 | 81.4 | 25.5 | 14.7 | 23.2 |
| 1995 | 10.5 | 91.8 | 28.9 | 16.9 | 24.6 |
| 2000 | 11.9 | 90.2 | 31.8 | 18.5 | 25.0 |
| 2005 | 12.5 | 94.4 | 35.0 | 21.1 | 26.7 |
| 2010 | 12.7 | 98.8 | 36.6 | 21.7 | 29.6 |
| 2016 | 13.1 | 99.3 | 38.7 | 21.7 | 33.3 |

**Table 2:** Results of 3-cluster model to describe the growth patterns of breast cancer incidence rates among Asian countries

| Cluster | Number of countries | Intercept | | Slope | |
|---|---|---|---|---|---|
| | | Estimate | Standard error | Estimate | Standard error |
| 1 | 8 | 18.62 | 2.48 | -0.13 | 0.06 |
| 2 | 17 | 37.15 | 4.44 | 0.96 | 0.21 |
| 3 | 21 | 17.51 | 4.68 | 0.38 | 0.09 |

Bayesian information creation (BIC) showed that the 3-cluster model was the best model with minimum error (results not shown). Therefore, growth trajectories for the 3-cluster model were fitted, and for each cluster, intercept and slope of the incidence rate were obtained. As shown in Table 2, eight countries belonged to cluster 1, seventeen to cluster 2, and the other 21 countries belonged to cluster 3.

The entropy was another goodness of fit index, which was at an acceptable level (entropy=0.96). Figure 2 shows both overall mean trends and estimated linear trajectories for different clusters.

Estimated slopes help us to find more information about the growth of breast cancer in the last decades among Asian countries. For cluster one countries (including Bangladesh, Israel, Kyrgyz Republic,

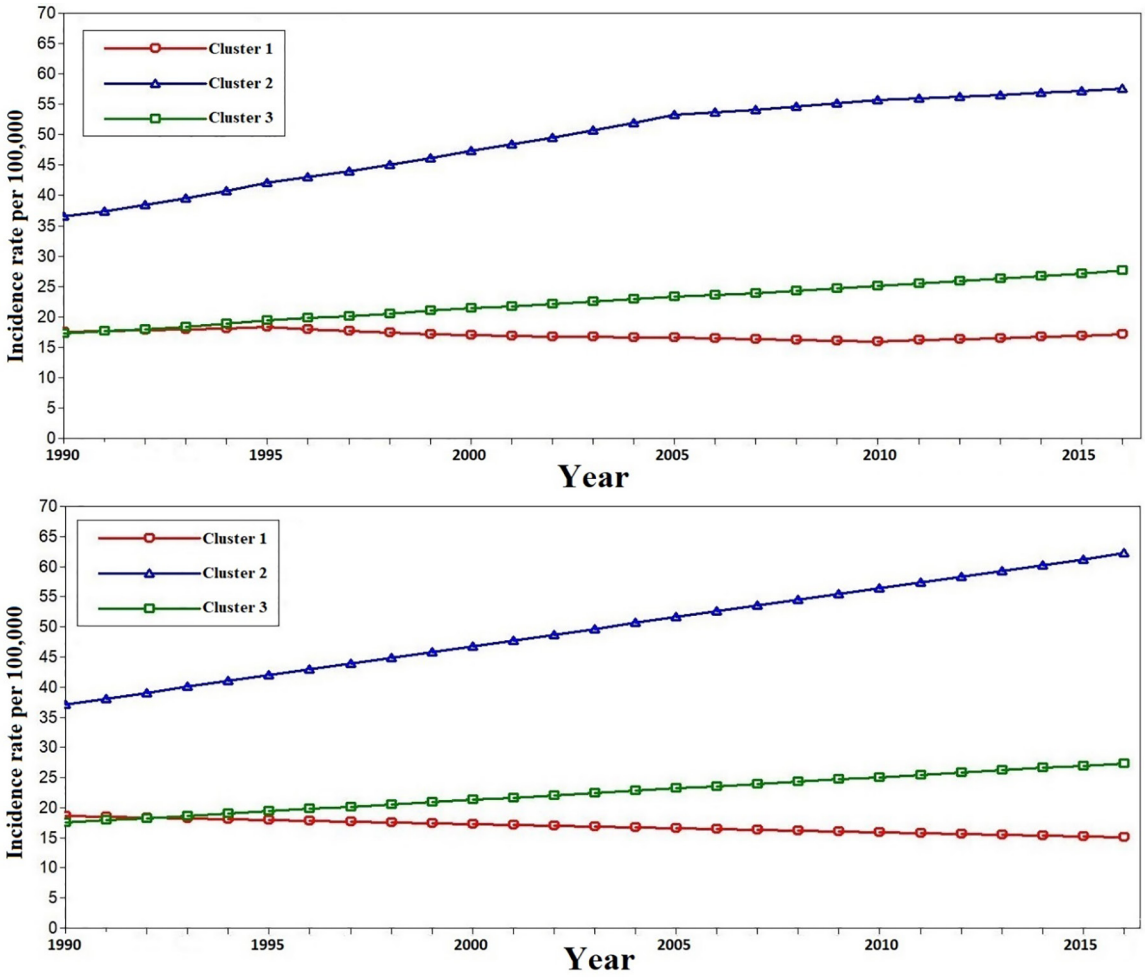


**Figure 2:** Trend of marginal mean and estimated linear trend in different clusters (By authors)

Maldives, Nepal, North Korea, Tajikistan, and Timor-Leste), the slope of -0.13 suggests a slight negative trend for the incidence rate of breast cancer; the incidence rate is almost constant over time. Twenty-one countries in cluster 3 (including Afghanistan, Azerbaijan, Bhutan, Cambodia, China, India, Indonesia, Iran, Lao, Mongolia, Myanmar, Oman, Palestine, Saudi Arabia, Sri Lanka, Syria, Thailand, Turkmenistan, Uzbekistan, Vietnam, and Yemen) showed a slow increase in the incidence rate over time. Seventeen countries (including Armenia, Bahrain, Brunei, Cyprus, Iraq, Japan, Jordan, Kazakhstan, Kuwait, Lebanon, Malaysia, Pakistan, Philippines, Qatar, Singapore, South Korea, United Arab Emirate) which belonged to cluster 2, had not only a high intercept that means higher amounts of incidence rate in 1990, but also a slope of 0.96, indicating a sharp increase trajectory (Table 2 and Figure 2).

## Discussion

In our study on 46 Asian countries, three types of behavior were noticed. The first cluster consists of the countries with a slight negative trend for the incidence rate of breast cancer. The second one is the cluster with a sharp increase trajectory, and the last pattern is the one with a slow increase in the incidence rate. Previous studies in eastern and southeastern Asia from 1993 to 2002 showed that all the countries experienced an increase in breast cancer rate from 1993 to 1998 compared to 1998 to 2003. Although the rates are different in various countries, Korea and Thailand had the highest (44.9% and 36.0%) and the Philippines had the lowest (5.2%) incidence rates. Korea had a significantly increased incidence rate during the ten years. This study asserts that early age at menarche and late in menopause, delay in marriage, fewer children, changes in infant feeding, and lifestyle are the risk factors of breast cancer.[23] A study conducted in the Turkish Republic of North Cyprus from 2007 till 2012 found similar results and reported that the trend of breast cancer incidence rate in Asia was rising. Hormonal therapy, fewer children, late menopause, early menarche, late reproductivity, and obesity are considered the risk factors in breast cancer.[24]

The study of Poudel et al. in Nepal showed breast cancer as the second most common cancer of women over the period of 2003 to 2012. In contrast to our findings, the incidence rate rose from 2.35 in 2003 to 4.59 in 2012. This rise may be due to a lack of information on breast cancer risk factors and a lack of breast screening programs.[25] The difference between the obtained results may be due to different time periods. Also, previous studies about breast cancer incidence from 1993 to 2012 years showed that North Korea had a slight decrease and South Korea had a sharp increase, which was consistent with the obtained results in the current study 23. A study in Pakistan claimed that the total projected breast cancer incidence would increase by approximately 23.1% in 2020; it was predicted that it would rise to 60.7% by 2025. Also, cases of breast cancer diagnosed in younger women aged 30 to 34 years will increase from 70.7 to 130.4% in 2020 and 2025 as compared to 2015. Lifestyle factors like smoking, physical activity, westernized diet, illiteracy, and cultural and economic status are the influencing factors.[26]

In line with our study, previous studies in Lebanon confirmed a high increase in breast cancer incidence. Lakkis et al. showed that the age-standardized rate of BC in Lebanon was 46.7 per 100000 in 1998 which increased to 52.5 in 2002. This increase is higher than several Asian countries like Iran, Malaysia, and Japan. The reasons for this increase may be related to improvement of NCR data collection and the rise in the use of mammography. Reproductive factors, such as the mean age of marriage had increased from 23.2 in 1970 to 27.5 in 1996; also, the fertility rate had decreased from 4.4 to 2.5 during the same period. The age of menarche and menopause became younger and later, respectively. Hormone replacement therapy and obesity, smoking and Hookah use among Lebanese women were the other possible risk factors.[27]

A study done in Singapore showed that the overall incidence rate of breast cancer had significantly increased from 1968 to 2002. The increase mentioned above was 3.1% per year for the Chinese, 2.8% per year for the Malaysians, and 1.7% per year for Indians who were living in Singapore. Transition of Singapore from an industrialized country to a developed country has brought about changes in lifestyle amongst the population: late marriage, delay in childbearing, smaller family sizes, and genetic interaction are the reasons for the change in the breast cancer incidence in Singapore. Other risk factors like reproductive issues, height, dietary habits, obesity, duration of breastfeeding, childhood growth, age at menarche, and menopause make variations in different ethnic groups and could also influence breast cancer risks.[28] A cross-sectional study in Kazakhstan reported that 45891 breast cancer cases were registered from 1999 to 2013, and 20112 women died of this cancer. These figures showed an increase in the incidence and a decrease in mortality. Astana and Almaty showed a high incidence rate in Kazakhstan. Ethnicity and compliance with screening recommendations affect breast cancer.[29]

Zahmatkesh et al. showed that the trend of breast cancer incidence in 2000-2002 in Iran had a sharp increasing slope due to the evolution of the Iranian cancer registration system;[30] in contrast to our study, from 2005-2009, the trend had a mild slope. However, another study on Iranian women showed a considerable increase from 15.96 per 100000 in 2003 to 33.21 per 100000 in 2008, which is not consistent

with our study. This may be due to differences in lifestyle changes and exposure to risk factors in various provinces, such as lack of physical activity, reproduction patterns, and obesity.[31] A study in India showed that the age-standardized incidence rates of breast cancer increased from 24.8 in 1988 to 41.0 in 2012 in Delhi. Also, they claimed that a statistically significant increase in breast cancer was also seen in Delhi over 25 years. The same pattern was also reported among Indian urban registries. This trend had occurred due to adherence to more westernized lifestyles like changes in diet, physical activity, and fertility and reproductive pattern.[17]

Our findings showed a slow increase in the incidence rate of breast cancer in China, which confirms the findings of previous studies. For example, the study of Yang et al. showed that the incidence rate of female breast cancer in urban areas of Beijing was 55.43 in 2004 and rose to 70.7 per 100000 women in 2008. In addition, in rural areas, it was 30.6, which increased to 44.78 per 100000 women in 2008.[32] The reasons for the trends above in these countries are socio-cultural background, poverty, increasing population, and limited access to advanced screening diagnosis and treatment.[33] In another study in the Arab world, a gradual increasing incidence was seen from 1990 to 2016, similar to the global trend, and this trend will increase over the next ten years. The incidence of breast cancer was 28 per 100000 women in 2016, and Lebanon, Bahrain, and Morocco had the highest incidence rate among the Arab nations, respectively.[9]

Taiwan had an increasing trend from 1970 to 2000 (6.23 to 23.76 per 100000). In 1996, there were 3801 cases in South Korea (16.7 per 100000), and it increased to 9668 in 2004 (40.5 per 100000).[34] Sri Lanka showed an increasing age-standardized incidence of breast cancer from 9.2 in 2001 to 12.9 per 100000 in 2010; however, a slight drop in the incidence was observed in 2007. These trends are related to the westernization of lifestyle, such as the use of junk food, sedentary life that causes obesity, delay in childbearing, and duration of breastfeeding.[15] Changes in demographics and the risk profile of the population are related to the increasing trend of BC in Thailand. In two surveys in 2004 and 2009, the percentage of overweight, diabetes, or hypertension increased. The parity and total fertility rate were 6 in 1970, 3 in 1985, 2 in 1998, and 1.6 in 2020.[14]

One of the strengths of our study is the use of a powerful statistical technique to identify the main patterns of breast cancer incidence rate on a large temporal and spatial scale. Due to the small number of published studies on breast cancer trends in Asia, their assessment to adequate information was limited for most countries.

## Conclusion

The observed sharp increase of breast cancer incidence in Armenia, Bahrain, Brunei, Cyprus, Iraq, Japan, Jordan, Kazakhstan, Kuwait, Lebanon, Malaysia, Pakistan, Philippines, Qatar, Singapore, South Korea, and United Arab Emirates is remarkable; therefore, effective strategies to prevent it are urgently required. For future studies in this field, assessing the trend of changes of breast cancer incidence in different races and age calories is highly suggested.

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**Conflict of Interest:** None declared.

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