Another Evidence of an Increasing Trend in the Incidence of Breast Cancer in Developing Countries Over the Recent Years

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Abstract

Background: We examined and estimated the trend of breast cancer incidence in Kerman, the largest province in Iran.

Method: Having compiling the data of new cases from three sources (cancer registry, pathology, radiotherapy) in this longitudinal study, the number of untouched cases was estimated using log-linear model. We estimated the annual age-standardized rate (ASR) per 100,000 women in 2001-2015. We utilized joint point regression method to estimate the trend of breast cancer incidence during the examined years.

Results: The ASR of breast cancer increased from 25 in 2001-2005 to 37 in 2011-2015, showing that the annual average percentage increased by 5.9% (95% Confidence Interval: 3.5, 8.4, $P<0.001$). Moreover, during this period, the completeness of the cancer registry increased from 16% in the first five years to 70% in the last five years.

Conclusion: Our findings revealed that the coverage of the cancer registry increased significantly. It seems that part of the increasing trend of the reported cancer incidence was attributed to the enhancement of the cancer registry scheme, but our findings suggested that the real incidence of breast cancer had a growing trend.

Keywords: Breast neoplasms, Cancer registry, Incidence, Iran

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Introduction

Breast cancer is the most prevalent cancer in the world and among Iranian women.[1, 2] Investigations have shown an increasing trend of breast cancer in the most regions of

the world, particularly in developing countries.[1, 2] Some of the possible reasons behind this increase could be increased risk factors, running screening program, progress in diagnostic equipment, and improving the quality of cancer registration data.[3-5]

Cancer registry system is the best center to collect information about cancer and provides dataset about incidence, prevalence, and the burden of cancer for researchers and policy-makers. One of the main problems in developing countries is the lack of a cancer registry system or low-quality data of cancer registration.[6, 7] The first cancer registry center in Iran was launched in 1955 at Tehran University[8] and the first national cancer registration system was developed for all the universities in Iran in 1984.[9] The data collection method of cancer registry centers was initially pathology-based, yet it changed to a population-based method.[9] Kerman, the largest province of Iran, which is located in the southeast of Iran, launched a population-based cancer registry in 2007.

Recently, there has been evidence of an increase in the trend of breast cancer incidence in Iran and developing countries.[1, 3, 10-14] The present study hypothesized that this increasing trend may be due to the effect of cancer registry system transformation from pathology-based to population-based, changing health-seeking behaviors and development in diagnostic equipment. Therefore, in this study, we aimed to report valid incidence risks of breast cancer and its trends over the recent years taking into account the above-mentioned factors.

Materials and Methods

The information to perform this longitudinal study was gathered in different levels; the first level was collection of the data about breast cancer incidence and the next level was obtaining other information which affects the cancer incidence rate. To examine the trend of breast cancer in
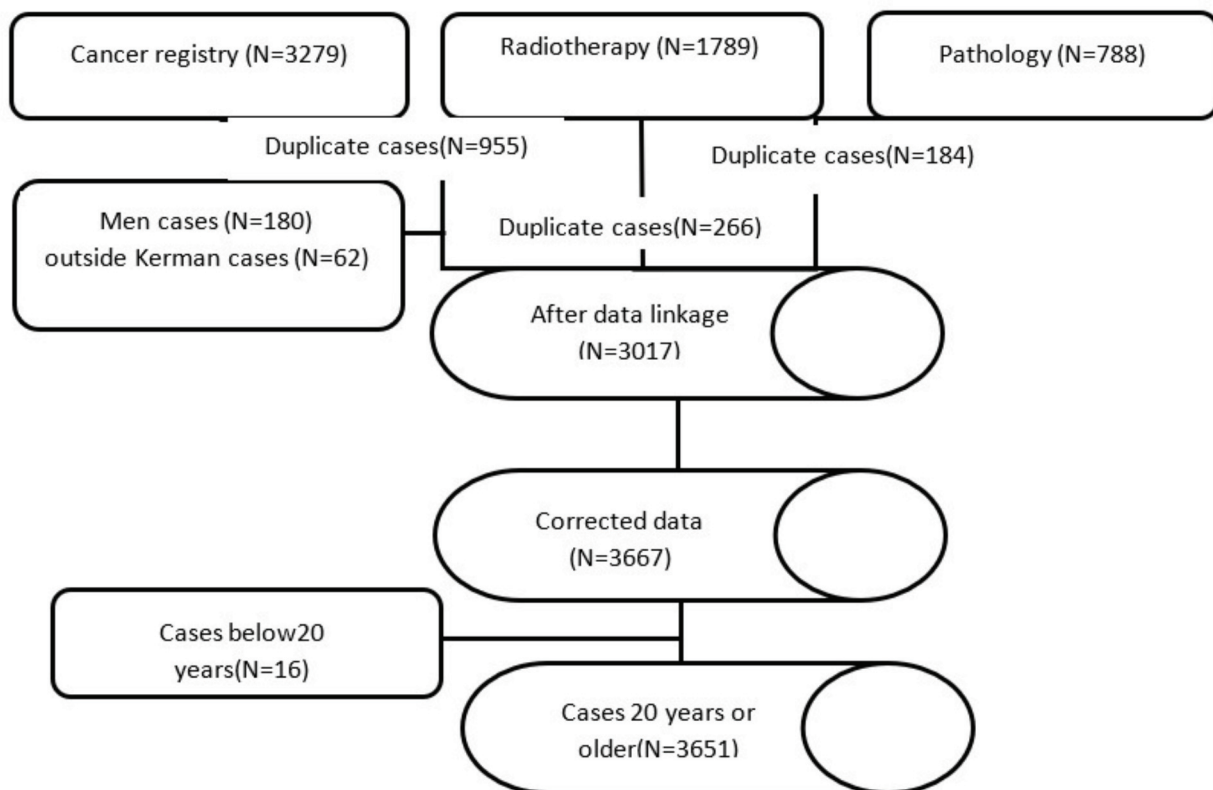

Figure 1. This figure shows the flowchart of the record linking from the three data sources (cancer registry, radiotherapy, and pathology) for using log-linear model and evaluate true incidence rate of breast cancer in female in Kerman province in the southeastern Iran in 2001-2015.

Table1. The number of cases and ASR* of breast cancer in females based on Cancer Registry and the corrected dataset in Kerman province, Iran, from 2001 to 2015

| Year	Observe		Estimate		Completeness%
	No. of cases	ASR* / 100000 (95%CI)	No. of cases	ASR* / 100000 (95%CI)	
2001-2005	123	4.52	643	25.3	15.9
		3.3, 5.8	516, 780	20.9, 29.7	
2006-2010	766	20.2	1236	32.4	57.9
		17.1, 23.3	1149, 1419	28.4, 36.4	
2011-2015	1247	33.6	1772	37.1	70.3
		30, 37.3	1705, 1873	33.2, 40.9	

*Age-standardized rate; No.= number; CI: Confidence interval

women, we selected the primary breast cancers cases aged 20 years and older from 2001 to 2015. We selected the cases above 20 years due to infrequency of breast cancer at ages below 20 years.

Source data

The data sources we used in this study were cancer registry, radiotherapy, and pathology dataset. Due to the inaccessibility of these data via the web, we accessed the data by referring in person and obtaining permission from the relevant gatekeeper. There was only one radiotherapy (2001-2015) and pathology (2001-2008) center in Kerman province, which was affiliated to the public sector to which most patients were referred. We received the crude data from the cancer registry in an excel file. We also reviewed the patients' records of radiotherapy and pathology to extract the data. The details we extracted from the original data were as follow: national security number, name, last name, fathers' name, date of birth, the first date of diagnosis (the earliest date of diagnosis was considered as a record), histological characteristics of the tumor (size of the tumor, the number of lymph node involved, stage of tumor), and address of residency. Inspection of the records of radiotherapy showed an average lag of about six months to one year from the time of diagnosis until the time of referring for radiotherapy; thus, we examined the patients' records from 2001 to 2016. Moreover, we reviewed the patients' pathology records from
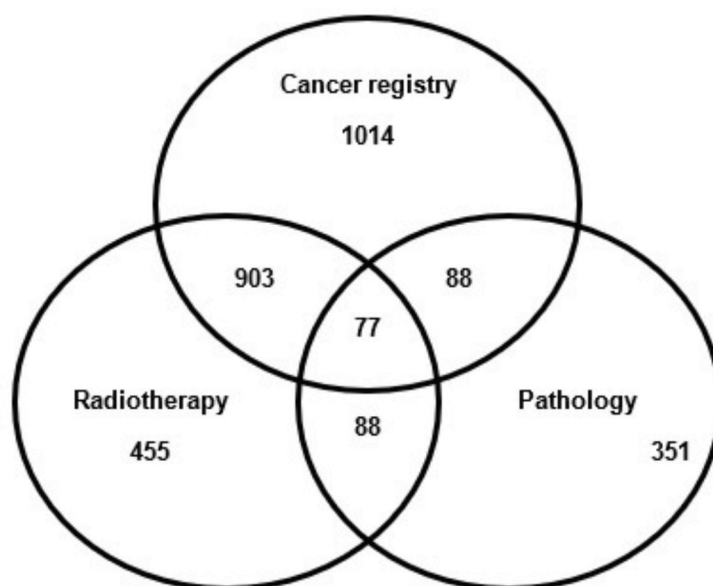
Figure2. This figure shows the venn diagram of the number of female breast cancer cases detected by each source and common cases between the resources, Kerman province in the southeastern Iran in 2001-2015.

2001 to 2008 because during these years, there was only one pathology center in Kerman province that performed estrogen receptor hormone test. According to an interview with oncologists in Kerman, all the patients diagnosed with breast cancer were referred to the pathology center for this test from 2001. Since 2009, in addition to the State Pathology Center, several other private centers have also been performing hormonal breast cancer tests. However, due to the lack of collaboration in providing the required information, we exclusively collected the data from 2001 to 2008 from the State Pathology Center.

Other data

We collected other data by examining the documents in the Iranian Health insurance organization about breast ultrasound, mammography, the number of radiology centers, and development in diagnostic equipment and personnel shifts from 2001 to 2015.

Data preparation

The data collected from the cancer registry, radiology, and pathology were entered in an excel file and were then integrated to decrease under-registry bias of cases. However, there was a lack of ID numbers for most of the records in these three sources; therefore, we had to obtain individual data (name, last name, father's name, date of birth, and address of residency) to link the datasets. We obtained this information after the approval of the Kerman University of Medical Sciences Ethics Committee, under the ethical code of IR.KMU.REC.1396.1617. Before linking the three sources of data, data cleaning was done in each dataset separately, based on four conditions: cases of breast cancer in men, cases outside Kerman province based on address, duplicate cases, and cases younger than 20 years. We linked the three datasets based on national code, if available, otherwise, based on other extracted information. The final step was to
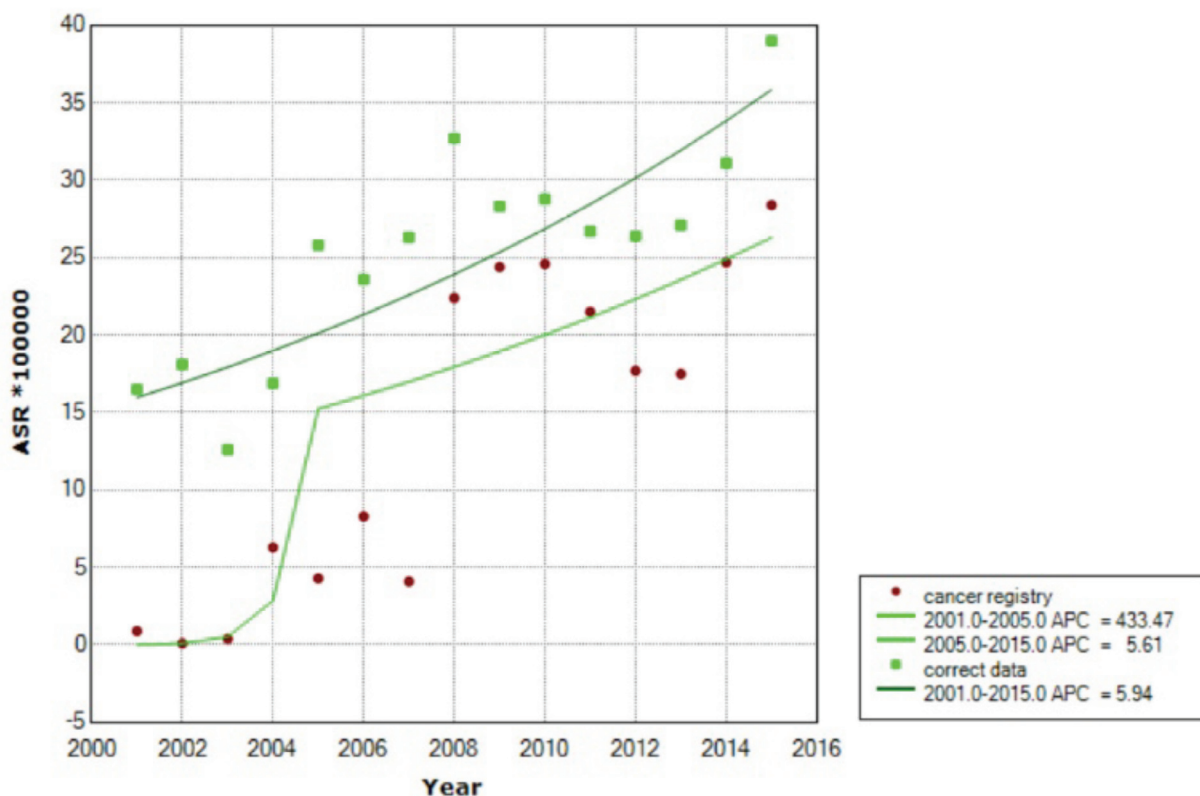

Figure3. The ASR trend of female breast cancer based on Cancer Registry and the corrected estimated dataset in Kerman province, Iran, from 2001-2015.

ASR: Age-standardized rate; APC: Annual percent change

remove duplicate cases in the integrated files, based on available information to be considered as a record. However, we just collected the data of three sources and there was a possibility of incomplete data. Therefore, we used the log-linear model to estimate the number of the cases not identified by any of the sources.

In addition, to estimate the number of undocumented cases in these three databases and decrease the under-registry bias, a log-linear model was used. This model was applied on the data of each year separately to allow the model to set different interaction terms between the data of these sources. The best model was selected according to the smallest value of Akaike's Information Criterion (AIC) index.[15] More details of this method have been reported in another manuscript, which is under review.

To calculate the age-standardized rate (ASR) of breast cancer per 100,000 women, we considered the numerator to be the number of new cases of breast cancer per year from 2001 to 2015. Furthermore, we considered the annual female population of Kerman province, based on census data 1996, 2006, 2011, and 2016, to be the denominator. Moreover, the annual population between the censuses over the years was calculated based on population growth (Available through www.amar.org.ir). The direct age-adjusted rate of breast cancer based on 11 age groups with a 5-year interval (20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, and 70+) was standardized according to the World Health Organization's population from 2000 to 2020.

To investigate the trend of stage and tumor size of breast cancer, we recoded the stage classification according to TNM system to numeric value from 1 to 9[16] and used the tumor size, which was recorded in the patients' records in millimeter unit. We calculated the mean of the stage and tumor size of breast cancer at the diagnosis time for every year to examine the trend change of these variables from 2001 to 2016.

Data analysis

We examined the ASR trend of breast cancer based on the Cancer Registry and corrected the estimated dataset using joint point regression method from 2001 to 2015. In addition, we applied this method to examine the trend changes of certain effective variables on breast cancer incidence, such as stage and size of the tumor at diagnosis and rate of breast sonography and mammography per 100,000 women during these years. We also employed the joint point regression on a logarithmic scale to determine the significant changes in the studies' variables over the study period. We estimated joint point regression of the average annual percent change (AAPC). We used the AAPC index to evaluate the ASR trend of breast cancer from 2001 to 2015 and after cancer registry change (pathology based to population-based) from 2008 to 2015. If the incidence of the disease was significant according to the AAPC index, the term "increase" or "decrease" was used and if not, the term "constant", "insignificant increase", or "insignificant decrease" was used ($P \geq 0.05$).

We linked the data sources with excel software, calculated ASR in STATA14, (StataCorp, Tex., USA), and performed trend analysis using joint point regression 4.5.0.1. The significance level was set at a maximum 5% type I error and *P*-value was 2-tailed.

Results

Descriptive results

In this study, based on cancer registry dataset, 3279 cases of breast cancer were registered in Kerman province. After data cleansing, the number of cases decreased to 2082 (36%) from 2001 to 2015. The corrected dataset was estimated to be approximately 3651 cases aged 20 years or more from 2001 to 2015 (Figure 1). The mean and standard deviation of women's age at the time of breast cancer diagnosis was 49.8 ± 12.8, ranging from 10 years to 94 years.

The number of cases detected by each source and the common cases between the resources, which was used to run the log-linear model, is displayed in the proportional Venn diagram (Figure 2). According to the Venn diagram, the most common cases were found in the Cancer Registry and radiotherapy dataset (Figure 2).

Table 1 depicts the details of the number of

breast cancer cases and ASRs based on the Cancer Registry and corrected estimated dataset. The average ASR of breast cancer according to the corrected estimated dataset increased from 25 during 2001-2005 to 37 per 100'000 people in 2011-2015. During this period, the completeness of the Cancer Registry increased from 16% in 2001-2005 to 70% in 2011-2015 (Table 1).

Other documents results

Another document reviewed revealed that before 2008, only two oncologists worked in Kerman; afterwards, their number increased to five by 2018. Additionally, one female radiologist specialized in breast cancer detection started working in Kerman after 2008. Sonography and mammography devices were upgraded and in addition to conventional ultrasound, 3D ultrasound and digital mammography were added in these years. Magnetic resonance imaging (MRI) is another device that has been used to detect breast cancer in the last five years. The most common diagnostic method was surgery and biopsy in the preceding years, but core needle method has been utilized more frequently over the recent years.
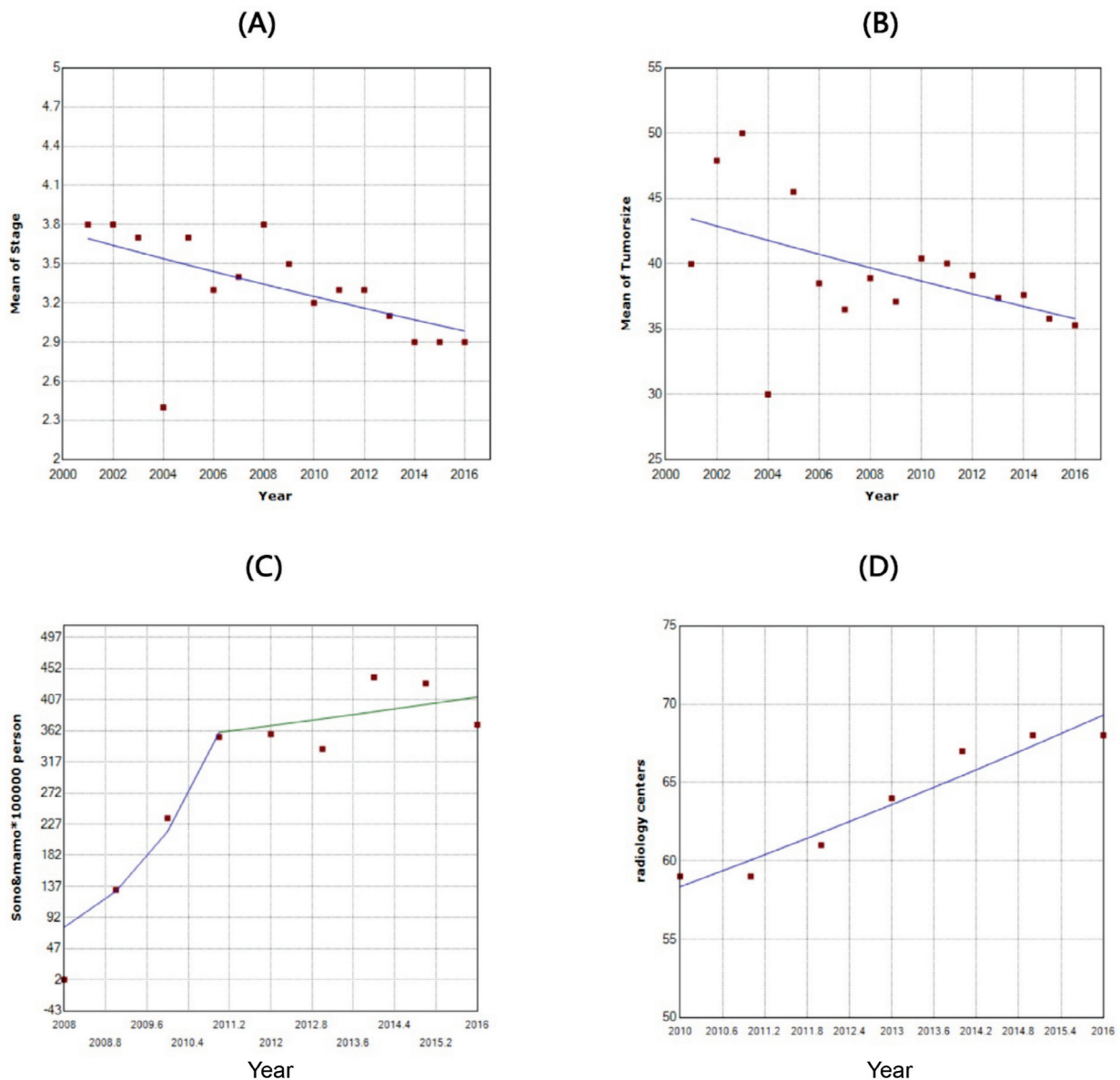

Figure 4. This figure shows the trend of some effective variables on breast cancer incidence in Kerman province, Iran, from 2001-2015; A) the mean stage, B) tumor size at diagnosis time, C) rate of sonography or mammography used among the females, D) number of radiology centers.

Officials acknowledged that we have not had a nationwide breast cancer screening program during these years.

The trend of breast cancer incidence, stage at diagnosis, and mammography rate from 2001 to 2015

The average annual percentage change for the ASR of breast cancer based on the corrected estimated dataset over the study period (2001 to 2015) and after cancer registry change (2008-2015) increased by 5.9% (95% CI:3.5, 8.4, *P*<0.001) per year during these two periods (Figure 3). The AAPC for the stage of breast cancer at the diagnosed time decreased by an average of -1.4% (95% confidence interval (CI): -2.7, -0.1, *P*<0.001) per year. However, tumor size was stable (-1.3%, 95% CI: -2.6, 0.1, *P*=0.1) during 2001 to 2016. The rate of use of breast sonography and mammography insignificantly increased by 23% (95% CI: -5.8, 60.0, *P*=0.1) per year from 2008 to 2016. The number of radiology centers increased by 3% (95% CI: 2, 3.8, *P* < 0.001) from 2010 to 2016 (Figure 4).

Discussion

This study revealed that the coverage of cancer registry in Kerman University of Medical Sciences increased and was about 70% over the recent years. The ASR of breast cancer increased from 25.3 during 2001 to 2005 to 37 from 2011 to 2015. Thus, the study results indicated that the stage of breast cancer at the time of diagnosis decreased and the rate of sonography and mammography increased from 2008 to 2016.

This study also showed that the quality of cancer registry was upgraded over the recent years. However, there is still significant under registration for cancer registry dataset. The coverage was approximately 70% during the last five years of the study. Molavi reported the completness of cancer registry to be about 67% in Kerman University using network scale-up method from 2007 to 2011, which was very close to the results of this study, yet we should consider this coverage estimated for all types of cancer.[17]

The ASR of breast cancer based on the corrected estimated dataset was 37 in 2011-2015

per 100 000 person-year and GLOBOCAN 2012 was estimated to be 28 for Iran.[2] The corresponding figure was 34.5 in 2014 according to Iranian Health Ministry and 36 based on the Global Burden of Disease reported in 2015 for Iran, which were more consistent with our results.[1, 18] According to the latest report by the Iranian Ministry of Health in 2014, the ASRs of breast cancer in Kerman and neighboring provinces, such as Isfahan, Fars, and Yazd, were 29.9, 42.7, 35.8, and 47.5, respectively based on the cancer registry dataset.[18] The difference between the results of the Health Ministry and our findings in the corresponding figures of breast cancer in Kerman might be due to the lack of elimination of the cases aged below 20 years and duplicate data. This was checked by reanalyzing cancer registry data with all age groups and no duplicate removal, which resulted in an ASR of 30, which is very close to the figure reported by the Health Ministry. In addition, lower figures of Kerman than the neighboring provinces might be in view of the lower accuracy of the data registry in Kerman than that in other provinces or lack of elimination of duplicates in other provinces. Furthermore, provinces such as Isfahan, Fars, and Yazd have premier medical centers.[11] Numerous patients from other regions of Iran refer to medical centers located in these provinces. Therefore, these factors might have contributed to a lower incidence in Kerman province than its neighboring provinces.

The results of this study indicated an increasing trend in the ASR of breast cancer according to the corrected estimated dataset during 2001 to 2015 and after Cancer Registry modification (2008-2015). Most studies in Iran and other countries of the Eastern Mediterranean Region or developing countries aligned with this study reported an increasing trend in the incidence of breast cancer.[1, 11, 19-23]

The obtained results herein revealed that despite the absence of a national breast cancer screening program for women, the average annual change rate of breast sonography and mammography increased by 66% and 3% during 2008 to 2011 and 2011 to 2016, respectively, which was not

significant. In addition, the study results indicated that the stage of breast cancer at the time of diagnosis decreased. The insignificant increase in the rate of use of mammography might be due to the few data points in each segment. On top of that, we used the mammography only from health insurance organization, the coverage of health insurance organization is about 60% in Kerman province, while there are other insurance agencies and a number of people are not under insurance.[24] Accordingly, the increasing trend of breast cancer since 2008 might be explained partially through the progress in diagnostic equipment and promotion-seeking health care behavior of women.[25-27]

The most important strength of this study was the use of different datasets and improving cancer registry data, whereas other studies were conducted only based on Cancer Registry data. Moreover, in this study, we examined the histological characteristics of tumor and mammography use and how these factors varied depending on breast cancer incidence.

Although the use of corrected dataset was the advantage of the current study, we encountered certain limitations to estimate the corrected dataset. We did not have access to pathological data for all the study years (2001-2008). Furthermore, there were no unique codes for all the patients. The other limitation was that the data on ultrasound and mammography were not available for all the study years (2008-2016) and it was not possible to estimate the size effect of these factors on the increasing trend of breast cancer. We could suggest further investigation of the effect of progress in diagnostic equipment and promotion-seeking health care behavior of women on the increasing trend of the ASR of breast cancer.

Conclusion

In spite of the improvement in the quality of data registration during the study years, due to under registration of data, we still need to correct the estimations to reach a valid report of the disease. It seems that a part of the increasing trend of the reported cancer incidence is attributed to the enhancement of the Cancer Registry system. However, our findings confirmed that the actual incidence of breast cancer had a growing trend. Moreover, advances in diagnostic equipment and promotion of women's behavior in receiving health care also justify the increase in the incidence of disease.

Conflict of Interest

None declared.

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