RESEARCH ARTICLE

Temporal Trends and Future Prediction of Breast Cancer Incidence Across Age Groups in Trivandrum, South India

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Abstract`

Background: Increasing breast cancer (BC) incidence rates have been reported from India; causal factors for this increased incidence are not understood and diagnosis is mostly in advanced stages. Trivandrum exhibits the highest BC incidence rates in India. This study aimed to estimate trends in incidence by age from 2005-2014, to predict rates through 2020 and to assess the stage at diagnosis of BC in Trivandrum. Materials and Methods: BC cases were obtained from the Population Based Cancer Registry, Trivandrum. Distribution of stage at diagnosis and incidence rates of BC [Age-specific (ASpR), crude (CR) and age-standardized (ASR)] are described and employed with a joinpoint regression model to estimate average annual percent changes (AAPC) and a Bayesian model to estimate predictive rates. Results: BC accounts for 31% (2681/8737) of all female cancers in Trivandrum. Thirty-five percent (944/2681) are <50 years of age and only 9% present with stage I disease. Average age increased from 53 to 56.4 years (p=0.0001), CR (per 10^5 women) increased from 39 (ASR: 35.2) to 55.4 (ASR: 43.4), AAPC for CR was 5.0 (p=0.001) and ASR was 3.1 (p=0.001). Rates increased from 50 years. Predicted ASpR is 174 in 50-59 years, 231 in > 60 years and overall CR is 80 (ASR: 57) for 2019-20. Conclusions: BC, mostly diagnosed in advanced stages, is rising rapidly in South India with large increases likely in the future; particularly among post-menopausal women. This increase might be due to aging and/or changes in lifestyle factors. Reasons for the increased incidence and late stage diagnosis need to be studied.

Keywords: Breast cancer - incidence rate - average annual percent change - bayesian model - projection

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Introduction

Breast cancer (BC) is the most common cancer among women in both more developed (MDC) (794,000 cases) and less developed countries (LDC) (883,000 cases, among these 16.4% are from India). Incidence rates (per 10^5) vary nearly four-fold across the world regions, with rates ranging from 27 in Middle Africa and Eastern Asia to 96 in Western Europe (Ferlay et al., 2013). The rate has decreased in the US and many other developed countries since early 2000s (Jemal et al., 2010), following the Women's Health Initiative report that led to a dramatic decline in use of hormone replacement therapy (Rossouw et al., 2002; Sprague et al., 2010). However, both incidence and mortality rates have increased in LDCs during the last two decades (Huang et al., 2010; Dhillon et al., 2011; Merlo et al., 2012; Jia et al., 2015; Li et al., 2015).

More than 60% of BCs are diagnosed at the localised stage in the US (SEER). Conversely, available evidence on stage at diagnosis, though scarce, indicates that a very high proportion of cases in the developing world are detected in late stages (Porter et al., 2008; Sloan et al., 2007). Existing data suggests that while more than 70% of breast cancer patients in high-income countries are diagnosed in stages I and II, only 20%-50% patients in low- and middle-income countries are diagnosed in these earlier stages (Unger et al., 2014).

Breast cancer crude incidence rates in India ranged from 7 in Tripura state to 44 in Bangalore per 10^5 women (NCRP 2016). Time trends in incidence in some areas in India have increased steadily for decades, although the reasons are not well understood (Yeole et al., 2003; Takiar et al., 2008; Murthy et al., 2009; Dhillon et al 2011; Dikshit et al., 2012). Given the large population of India, even subtle change in incidence can lead to a substantial burden of disease.

Pre-menopausal BC comprised substantially higher proportion of all incident breast cancers in LDCs (average 47.3%) compared to MDCs (average 18.5%). Specifically, 45.7%, and 48.4% of BC patients were diagnosed before age 50 years in China and India while corresponding proportions were 21.5%, 19.1% and 15.9% in Australia, UK and Denmark (Ghiasvand et al., 2014).

Several studies have documented etiologic differences

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in BC according to menopausal status (Anderson et al., 2004; Bertucci et al., 2008). Some reproductive factors such as early age at menarche, late age at menopause and decreased total duration of breast feeding, obesity and decreased physical activity have stronger association with the risk of developing post-menopausal BCs (Althuis et al., 2004; Rose et al., 2010; Hemminki et al., 2011; Amadou et al., 2013). Thus changes in reproductive and life-style factors mainly affect post-menopausal women whereas genetic factors probably play a more significant role in young women, though these factors alone cannot account for international variation in risk (Assi et al., 2013). Compared to post-menopausal women, BC in young women tend to display more aggressive features, and as a consequence a higher cause-specific mortality (Mathew et al., 2004; Anders et al., 2009).

Even though the proportion of premenopausal BC is substantially higher in LDCs, the incidence rate of BC in these women is invariably lower in these countries due to higher proportion of premenopausal population than that in MDCs. Age-standardized rates (ASR) of premenopausal BC were 12.1, and 12.2 in China and India while corresponding ASRs in Australia, UK and Denmark were 30, 31.7 and 31.5 per 10^5 respectively (Ghiasvand et al., 2014).

In India, Trivandrum showed the highest incidence rate of BC and the proportion of premenopausal BC is substantial (NCRP 2013). Estimating temporal trend by menopausal status and the likely future burden of BC cases are valuable in setting priorities for evolving public health strategies to tackle this concern. This study aims to estimate trends in incidence by age from 2005 to 2014, to predict rates through 2020 and to assess the stage at diagnosis of BC in Trivandrum.

Materials and Methods

The Population Based Cancer Registry covering the population in Trivandrum Taluk (area: 300 sq.km, >80% urban) has been included under the network of National Cancer Registry Programme (NCRP) of Indian Council of Medical Research (ICMR) since 2006. Cancer incidence and mortality data have been collected since 1st January 2005. Regional Cancer Centre (RCC), Trivandrum is the physical location of the registry. Institute review board and ethics committee approval have been obtained for the registry.

The data collection is active and has been collected from more than 50 hospitals and 7 pathology laboratories. Address linkage of data, obtained from pathology laboratories were made. Data is provided voluntarily, however, an administrative letter was provided by the Government of Kerala to all health authorities in the district, and hence co-operation from all hospitals have been obtained since 2011. The permanent residents (duration > one year) of the registry area constitute the cancer cases. Duplicate registrations were eliminated and care was taken to see that multiple entries of the same patient were not made in the records after computerizing the data.

From the registry incidence database, female invasive BC cases (ICD-O-3: C50.0-C50.9) were identified from 2005 to 2014. The individual records were also grouped into five time periods (2005-06, 2007-08, 2009-10, 2011-12 and 2013-14) and five age groups (<40, 40-49, 50-59, 60-69 and 70+ years). UICC-TNM classification for stage at diagnosis was used.

Statistical methods

Based on the distribution difference method and using the census of India (2011) population and growth rate from 2001 to 2011, the Taluk female population for the years 2005 to 2014 were estimated (Takiar et al., 2009). Average age at diagnosis [standard deviation (SD)] and its statistical significance over the years was obtained using ANOVA. Crude incidence (CR) rates and age-specific incidence (ASpR) rates were calculated over the five time periods. ASR was obtained by direct standardization to the World Standard Population. We assessed average annual percent change (AAPC) using joinpoint regression program (Version 4.2.0.2), which enables the identification of points where the significant changes occur by fitting a series of joined straight lines on a logarithmic scale to the ASpR, CR & ASR. The test of significance was obtained by assuming the observed counts are Poisson distribution. Based on the Bayesian regression model and assuming that the current age specific rates will remain in future, the rates were predicted till 2020 (Kim et al., 2000).

Results

This is the first results of BC incidence, accounts for 31% (2681/8737) of all female cancers in the PBCR Trivandrum during 2005-2014. Microscopic verification of BC diagnosis ranged from 94% to 97% over the years. There was a 46% increase in the number of BC cases during the study period (n=448 in 2005-06 & n=656 in 2013-14). The peak age at incidence was 50-59 years

Table 1. Age-distribution: Female Breast Cancer (Trivandrum 2005-2014)

Age	2005-2006 (n=448)		2007-2008 (n=453)		2009-2010 (n=523)		2011-2012 (n=601)		2013-2014 (n=656)	
(years)	#	%	#	%	#	%	#	%	#	%
< 40	53	11.8	58	12.8	49	9.4	55	9.2	52	7.9
40-49	134	29.9	112	24.7	136	26	145	24.1	150	22.9
50-59	132	29.5	152	33.6	145	27.7	175	29.1	200	30.5
60-69	90	20.1	97	21.4	109	20.8	143	23.8	148	22.6
70 +	39	8.7	34	7.5	84	16.1	83	13.8	106	16.2
Mean	53		53.3		55.7		55.5		56.4	
SD*	11.8		11.3		12.8		12.4		12.6	

*Standard deviation

(30%) in all the years. Average age at diagnosis was slightly increased from 53 years (SD: 12 years) in 2005-06 to 56.4 years (SD: 12.6 years) in 2013-14 (p=0.0001) (Table 1).

Crude incidence rate per 10^5 women increased from 39 (ASR: 35.2) in 2005-06 to 55.4 (ASR: 43.4) in 2013-14. During the 10-year period, the AAPC for CR was 5.0 (p=0.001) and ASR was 3.1 (p=0.001). Statistically significant monotonic increases in incidence rates were observed from 50 years with highest increase in 70+ age group (64 in 2005-06 to 145 in 2013-14 per 10^5 women; AAPC: 13.0; p=0.001). The ASpR in <40 years was approximately 8 (per 10^5 women) in all the years. The results showed a stable AAPC for BC incidence among women <40 years and in 40-49 years. Among women in 50-59 years, ASpR (per 10^5 women) increased from 114 to 134 (AAPC: 4.4, p=0.001) and in 60-69 years, it increased from 108 to 153 (AAPC: 5.1, p=0.001). It was predicted that the results would increase to 174 in 50-59 years and 231 in both 60-69 and 70+ years and the overall CR would increase to 80 (ASR: 57) in 2019-20 (Table 2 & Figures 1 & 2).

A total of 65% of cases were diagnosed in <60 years (10% in <40 years, 25% in 40-49 years, and 30% in 50-59 years). More than 70% of the cases presented with stage II (41%) and stage III (30%) cancers. Overall, only 9% of cases were diagnosed with stage I disease. Only 5% in 40-49 years and 8% in 50-59 years reported in stage I. Nearly 46% of cases in 50-59 years and 40% of cases in 40-49 years were diagnosed in stage III or IV (Table 3).

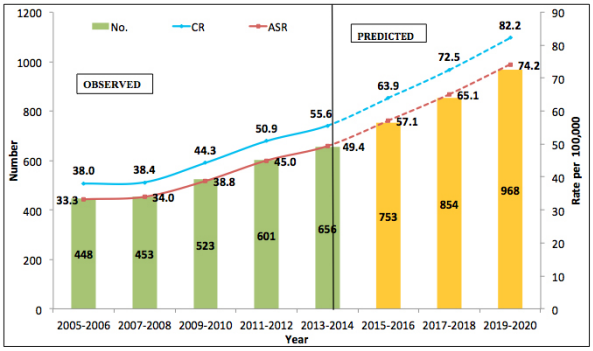

Figure 1. Average Annual New Cases, Crude (CR) and Age-Standardised (Observed and Predicted Incidence Rates (ASRs) for Female Breast Cancer, 2005-2020, Trivandrum

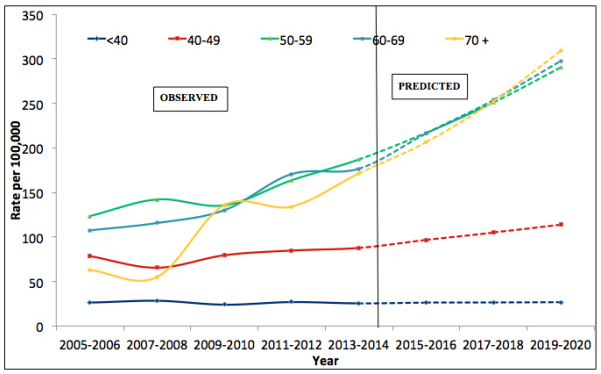

Figure 2. Observed and Predicted Age-Specific Incidence Rates (ASpRs) for Female Breast Cancer by Age Group, 2005-2020, Trivandrum

Discussion

This is the first results of BC in Trivandrum which described stage at diagnosis, incidence rates and trends stratified by age as well as predicted rates through 2020. The data collection system in Trivandrum is active. Co-operation from all the data sources was very good because of an administrative letter, from the Government of Kerala in 2011 and hence the coverage has improved in the latter years. The under-reporting in early years is also not surprising during this initial "learning" year of operations. Duplicate registrations and a series of consistency checks on the incidence database locally as well as at the NCRP were done. The best possible effort was made to clean the data. This was reflected in the quality indicators such as the microscopic verification which ranged from 94% to

Table 2. Breast Cancer Incidence Rates (2005-2014) and Average Annual Percent Change (AAPC) and Bayesian Projection (2015-2020) by Age (Trivandrum 2005-2014)

Age	Year					AAPC	P-value	Year		
	2005-2006	2007-2008	2009-2010	2011-2012	2013-2014			2015-2016	2017-2018	2019-2020
< 40	7.3	8.1	7	8	7.7	0.5	0.7	8.1	8.3	8.6
40-49	82.4	66.4	77.9	80.3	80.3	0.7	0.7	85.7	89.9	94.3
50-59	113.8	122.3	109.3	124.1	133.8	4.4	0.001	146.5	159.7	174
60-69	108.4	112.3	121.4	153.4	153.1	5.1	0.001	180.5	204.1	230.9
70 +	64	53.2	125.6	118.7	145.3	13	0.001	167.9	196.8	230.7
CR[1]	38.8	39	44.8	51.1	55.4	5	0.001	63.2	71.1	80.1
ASR[2]	35.2	34.5	37.4	41.7	43.4	3.1	0.001	47.9	52.1	56.7

[1]CR: Crude; [2]ASR: Age-standardized rate per 100,000 women

Table 3. Breast Cancer Incidence : Age vs. Stage (%) (Trivandrum 2005-2014)

Stage	<40 (n=267)	40-49 (n=677)	50-59 (n=804)	60-69 (n=587)	70+ (346)	Total (n=2681)
Stage 1	12	7.7	5.2	11.7	12.5	8.8
Stage 2	34.1	43.9	43	46.1	29.4	40.9
Stage 3	29	28.5	31.3	22.8	30.9	29.6
Stage 4	12	11.2	14.3	7.8	16.2	11.1
Unknown	12.9	8.7	6.2	11.6	11	9.6

97% over the years.

In the present analysis, distinct patterns were observed in BC trends by age. The most striking finding in the current study is that the rate of increase in BC is almost exclusively seen in post-menopausal women. However, many LDCs have reported an increase in BC incidence and mortality in young women (Lima et al., 2012; Ilic et al., 2013). We observed that the proportion of young BC women in Trivandrum is substantially higher (35% in <50 years) compared to developed countries, even though, the incidence rate is indeed invariably lower than that in the developed countries (Ghiasvand et al., 2014).

Some established risk factors including early age at menarche, late age at menopause, decreased duration of breast feeding, increased duration of sedentary activity and obesity, include hormonal mechanisms, which are involved in the development of BC (Keramatinia et al., 2014; Brenton et al., 2005; Gajalakshmi et al., 2009; Mathew et al., 2008, Mathew et al., 2009). Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2, are the tumor markers that have been widely studied in relation to the etiology, prognosis and treatment of breast cancer subtypes (Althuis et al., 2004; Brenton et al., 2005; Dolle et al., 2009). Some epidemiological studies have reported heterogeneity of BC risk factors with hormone receptors (Dey et al., 2009). Certain reproductive factors and obesity were shown to be associated with ER + and PR + BC, compared with ER- and PR- tumors (Althuis et al., 2004; Bauer et al., 2007). The prevalence of hormone receptor negative cancer is higher among premenopausal women than among postmenopausal women, while ER + and PR + BC in more prevalent after menopause and its incidence increases with age (Leung et al., 2002; Anderson et al., 2004).

Evidence exists that in the high-income countries, more than 70% of breast cancer patients are diagnosed in stages I and II, where as in the low- and middle-income countries only 20%-50% patients are diagnosed in these earlier stages (Porter et al., 2008; Sloan et al., 2007; Unger-Saldaña et al., 2014). In the present study, it was observed that only <10% of the cases were diagnosed in stage I disease. No organized screening programme has been ongoing in the Trivandrum registry area and hence this results in most people presenting only when symptomatic, and on an average, most 'symtomatic' cancers are stage IIB and beyond irrespective of the age.

Incidence rates in Trivandrum were much higher (CR: 55.4; ASR: 43.4 per 10^5 women in 2013-14) than the national average of 25.8 (Ferlay et al., 2013) and the rate observed is the highest in the country (NCRP 2016). One reason could be due to higher older age population in Kerala than other states in the country (14.2% in Kerala vs. 8.4% in India in > 60 years, Census of India, 2011), as the increase is only in post-menopausal women. Another possibility is that the completeness in coverage of the active method of data collection may be higher in Trivandrum than in other places in the country.

Major limitation of this trend analysis was the unavailability of accurate breast cancer mortality data. In the state of Kerala, almost all deaths are registered in the vital statistics department, but cause of death is not accurate. Even though the incidence rates are observed to be the highest in the country, mortality rate was <10 per 10^5 women (personal communication) and this is low compared to the estimated national figure of 13 (Ferlay et al., 2013).

Our data do not allow us to understand the reasons for the increased BC incidence. However, it is possible that it relates to two factors: 1) cancer is predominantly a disease of older persons and therefore with increased life expectancy in South India there is a larger population of people at risk of developing cancer; and 2) changes in lifestyle among women of South India may take many years to lead to the development of cancer and therefore the rise in BC incidence is not observed in younger women. Future epidemiologic research is required to what extent each of these potential mechanisms is responsible for the substantial rise in BC incidence. Finally, it is worth noting that although incidence rates are not rising among younger women in South India, due to population demographics, younger women represent a substantial proportion of BC compared to western countries. Moreover, the fact that the disease is most often diagnosed in advanced stages highlights the importance of public health efforts to improve disease awareness and access to health services.

In conclusion, Breast cancer incidence is rising rapidly in South India; particularly among post-menopausal women. These data forecast further large increases in the future burden of BC. The increase in the incidence rate might be due to the aging of the population and/or changes in lifestyle factors or introduction of new risk factors. Most BCs are diagnosed in advanced stages. Public health efforts are required understand the reasons for this striking increase and to promote education and awareness of BC to facilitate diagnosis at earlier stage.

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