

## RESEARCH ARTICLE

# Trends in Female Breast Cancer by Age Group in the Chiang Mai Population

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### Abstract

**Objectives:** This study was conducted to determine incidence trends of female breast cancer according to age groups and to predict future change in Chiang Mai women through 2028. **Method:** Data were collected from all hospitals in Chiang Mai in northern Thailand, from 1989 through 2013, and used to investigate effects of age, year of diagnosis (period) and year of birth (cohort) on female breast cancer incidences using an age-period-cohort model. This model features geometric cut trends to predict change by young (<40 years), middle-aged (40-59) and elderly (≥60) age groups. **Result:** Of 5,417 female breast cancer patients with a median age of 50 years (interquartile range: 43 to 59 years), 15%, 61% and 24% were young, middle-aged and elderly, respectively. Seventy nine percent of cancer cases in this study were detected at advanced stage. The trend in stage classification showed an increase in percentage of early stage and a decrease in metastatic cancers. Linear trends for cohort and period were not found in young females but were observed in middle-aged and elderly groups. Age-standardized rates (ASR) can be expected to remain stable around 6.8 per 100,000 women-years in young females. In the other age groups, the ASR trends were calculated to increase and reach peaks in 2024 of 120.2 and 138.2 per 100,000 women-years, respectively. **Conclusion:** Cohort effects or generation-specific effects, such as life style factors and the year of diagnosis (period) might have impacted on increased incidence in women aged over 40 years but not those under 40 years. A budget should be provided for treatment facilities and strategies to detect early stage cancers. The cost effectiveness of screening measures i.e. mammographic screening may need to be reconsidered for women age over 40 years.

**Keywords:** Female breast cancer- incidence trend- future trend- breast cancer stage- age groups- Chiang Mai population

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### Introduction

Breast cancer is the leading cancer among women worldwide. Breast cancer incidence has steadily increased in many countries over two decades (Stewart and Wild, 2014). According to the GLOBOCAN 2012 released by the International Agency of Research on Cancer (IARC), there were approximately 1.7 million newly breast cancer cases and 0.5 million deaths in women worldwide (Ferlay et al., 2013).

Nowadays, breast cancer is the most common cancer in Thai women and its incidence continuously increases. The age-standardized incidence rate (ASR) was 28.5 per 100,000 in Thai women based on data collected during 2010-2012. The next common cancers include cervical

cancer, liver and bile duct cancers, colorectal cancer and trachea, bronchus and lung cancers (Ferlay et al., 2013; Imsamran et al., 2015). The 3-year reports based on data collected from 16 center of cancer registry around Thailand by the National Cancer Institute (NCI) showed the increasing trend of breast cancer; ASR was 20.5 per 100,000 during 1998-2000; 25.6 per 100,000 during 2004-2006 and 28.5 per 100,000 during 2010-2012 (Khuhaprema et al., 2007; Khuhaprema et al., 2012; Imsamran et al., 2015).

It has been shown that the regions in Thailand vary in term of population characteristic, diet and breast cancer incidence rate (Khuhaprema et al., 2007). Breast cancer trends from the Songkhla Cancer Registry in the south and the Lampang Cancer Registry in the north showed

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that the trends in breast cancer in these two regions were expected to move to the same direction but the incidence rate were different (Virani et al., 2014; Lalitwongsa et al., 2015). Chiang Mai province neighbors by Lampang province. However, Chiang Mai has a larger diversity of population according to the variation in geography, ethnic, culture and life style (Chiang Mai province-Wikipedia, 2017; Lampang province-Wikipedia, 2017). Thus, it is probable that trend in breast cancer could be different between Chiang Mai province and other nearby provinces.

Furthermore, it is well known that cancer is an age-related disease in particular breast cancer. Aging plays an important role on incidence and also the efficacy of treatment because it is associated with various physical changes, including hormone change. Projecting trends in breast cancer incidence in difference significant age groups could help to identify age-specific targets for policy of incidence control and reduction of cancer stage at diagnosis.

This study aimed to describe the incidence trend of female breast cancer in difference age groups in Chiang Mai population by the year of diagnosis, year of birth and age at diagnosis and to predict future female breast cancer incidence in Chiang Mai through 2028.

## Materials and Methods

### Data

Over two decades, data of women who had been diagnosed with breast cancer during 1989-2013 who live in Chiang Mai were collected from all hospitals in Chiang Mai by Chiang Mai cancer registry. Chiang Mai Cancer registry is a population based cancer registry, operating within Maharaj Nakorn Chiang Mai hospital, Faculty of medicine, Chiang Mai University. The data were collected from all hospital in Chiang Mai including Maharaj Nakorn Chiang Mai Hospital which is university hospital, government hospital, municipal hospital, private hospital and community hospital. Over two decades, data of patients were systematically collected and carefully verified. The data collected of each patient included patient's profiles for example date of birth, age at diagnosis, clinical diagnosis, pathological report, clinical extent of disease before treatment and initial treatment.

Non-invasive (In situ) breast cancer cases were excluded from the analysis. Stages of breast cancer were classified according to the extension of disease of cancer. Localized stage means tumors confined to the breast, regional stage means tumors involved axillary lymph nodes and distant stage means cancer spread to other parts of body.

Trend in breast cancer stage were determined by 5-years interval. The data of female breast cancer patients who were diagnosed during 1989-1993 were excluded from the staging trend analysis because there were too many missing data (52%) of staging in these early years of cancer registry.

### Population denominators

For the calculation of incidence rates, female population denominators were estimated from three

population censuses surveyed by the National Statistical Office (1992; 2002; 2011). Inter census populations were estimated using a log-linear function between two consecutive censuses. The populations beyond 2010 were estimated, and reported by the Office of the National Economic and Social Development Board (2013).

### Statistical analysis

Age-specific incidence rates (AIR) were calculated for 5-years intervals age groups ranging from 0-4 through to 80-84, and 85 years and older and 24 calendar periods from 1989 to 2013 (at 1-year intervals). ASRs standardized to the world population proposed by Segi (1960), and later modified by Doll (1976), were computed for each particular year using the Joinpoint-Regression Program version 4.3.1.0 (Surveillance Research Program National Cancer Institute, 2016) then plotted to visually illustrate the trends. Person-years used as the denominators in the computation were calculated from census data (National Statistical Office, 1992; National Statistical Office, 2002). We also used joinpoint regression model to identify statistically significant trend change points (Joinpoints) and the rate of change (annual percent change, APC) in each trend segment using a Monte Carlo permutation method (Kim et al., 2000). Analyses were conducted for all females, and then for young females (<40 years), middle-aged females (40-59 years) and elderly females ( $\geq 60$ ) to determine the incidence trends in difference age groups.

Age-period-cohort regression models (APC-model) were used to investigate the effects of age at diagnosis (age), the calendar year of diagnosis (period) and year of birth (cohort) on the incidence of breast cancer. We used the classical method which fits a log-linear model with a Poisson distribution to the observed data to estimate; age, period and cohort effects in a multiplicative APC-model as follows.

$$\log[R(a,p)] = f(a) + g(p) + h(c).$$

Where the expected log-incidence rates  $R(a,p)$  is assumed to be equal to a linear combination of effects that adjusts for age (a), period (p) and birth-cohort (c), where  $c=p-a$ . To address the well-known nonidentifiability problem of APC models, we fit two-effects models (age-period and age-cohort) and then fit the remaining effect (cohort or period) to the respective model's residuals using natural splines to reduce random variation (Carstensen et al., 2013). These are referred to as the AP-C and AC-P models. The analysis of APC models was performed using the Epi package (Carstensen et al., 2013) for R statistical software version 3.1.3 (R Core Team, 2015). The linear drift (D) of period and cohort parameter was identified. Since we considered no abrupt change in the population such as an organized screening program in the past, we decided to use the drift of all periods in the data set, rather than the recent drift, in projecting the future trend. With APC-model, the incidence rates were extrapolated out to 2028. We applied the cut trend concept to the projection with reduction of the trend in the first future 5 years by 0% and after that by geometric dampening with the factor of 0.92 (1-0.08) per year.

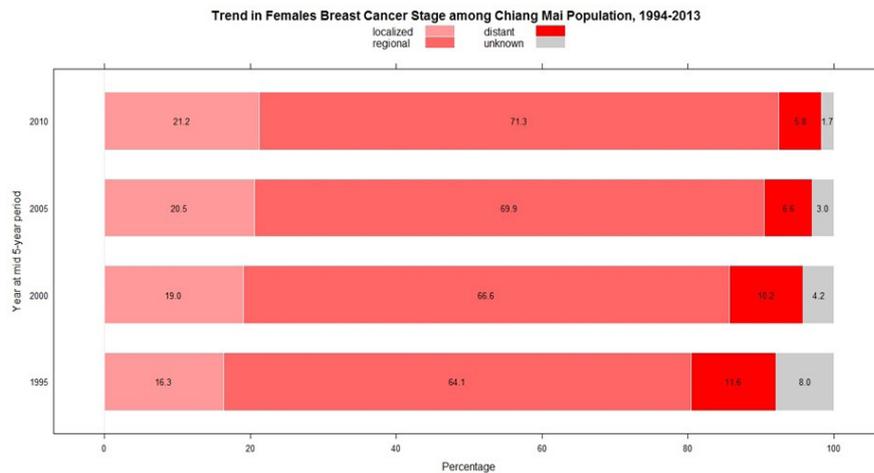


Figure 1. Trend in Stage Classification, 1994-2013

## Results

### Study population

Our study included 5,417 female breast cancer cases, diagnosed in Chiang Mai from 1989 through 2013, median age of 50 year (interquartile range: 43 to 59 years). Percentage of histology verification (%HV) was 96.1% and percentage of death certificate only case (%DCO) was 0.9%. Among these women, 789 (15%) were young females, 3,318 (61%) were middle-aged females and 1,310 (24%) were elderly females.

### Trend in stage classification

For overall, stage distribution was shown in Figure 1. From 1994-2014, the underlying trends in stage classification show an increase in the percentage of cases with localized cancers and a decrease in metastatic cancers.

### Age specific incidence rate

During 1989 – 2013, the age-specific incidence rate (AIR) increased from age 20-25 years (AIR =0.6 per 100,000 women-years) to the peak incidence at age 50-54 years (AIR=76 per 100,000 women-years). AIR declined to 61 per 100,000 women-years at age 55-60 years and then stable up to 75-79 years. The second drop in age-specific incidence rates was observed around the age groups of 80-84 (AIR=41 per 100,000 women-years).

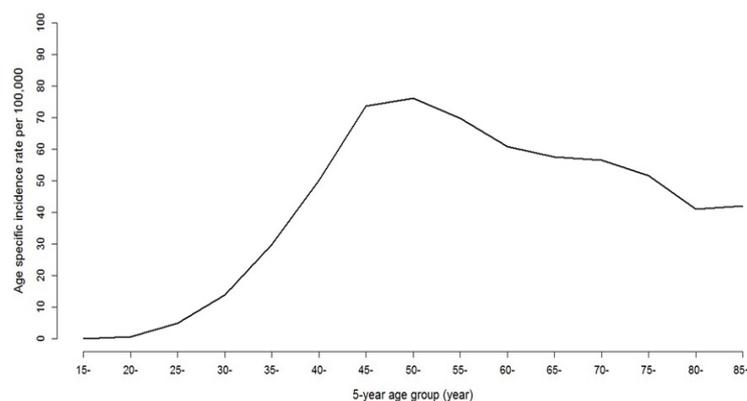


Figure 2. Age Specific Incidence Rate (AIR) Based on 5-Year Age Groups

### Age, period and cohort effects

The two-effect models: 1) AP-C (age-period) model which is the model that remaining period effect and 2) AC-P (age-cohort) model that remaining cohort effect of age-period-cohort trend analysis show rough linear trends in cohort and period across the calendar years (Figure 3a). Thus, the overall increase in incidence was explained by the age-drift model with the drift parameter (coefficient) of 0.031 (95%CI: 0.027, 0.035).

Separately by three age groups, linear trends in year of birth (cohort) and year of diagnosis (period) were not found in young females (Figure 3b), whereas, these effects were shown in middle-aged females (Figure 3c) and elderly females (Figure 3d).

### Trends in breast cancer incidence forward to 2028

Zero join point model was the best fit for all ages and the three different age groups; young females, middle-aged females and elderly females. Overall, breast cancer incidence rates increased from an ASR of 14.8 per 100,000 women-years in 1989 to 32.9 cases per 100,000 women-years in 2013. The incidence rate of female breast cancer increased at an APC of 3.1% (95%CI: 2.6%, 3.7%). By age groups, incidence rate of female breast cancer increased at an APC of 1.8% (95%CI: 0.7%, 3.0%), 2.9% (95%CI: 2.0%, 3.8%) and 4.3% (95%CI: 3.6%, 5.0%) in young, middle-aged and elderly females, respectively.

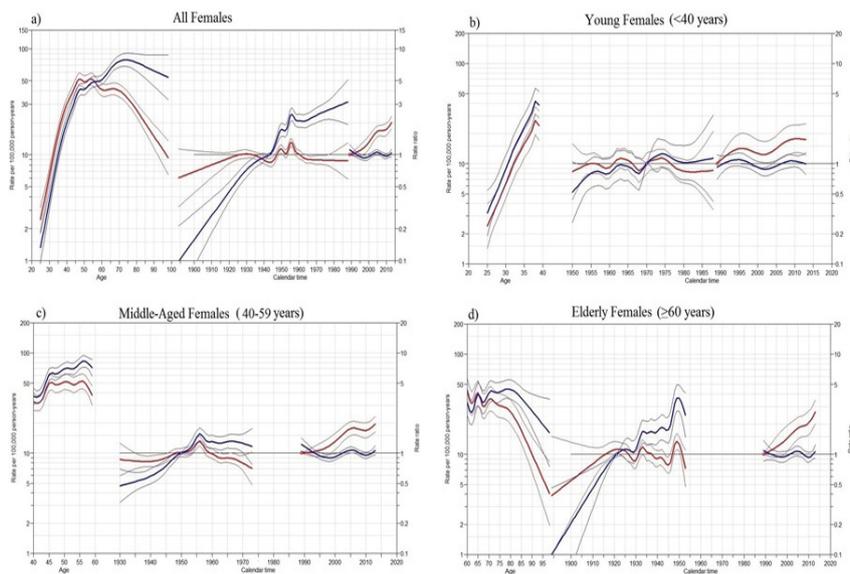


Figure 3. APC Trend Analyses

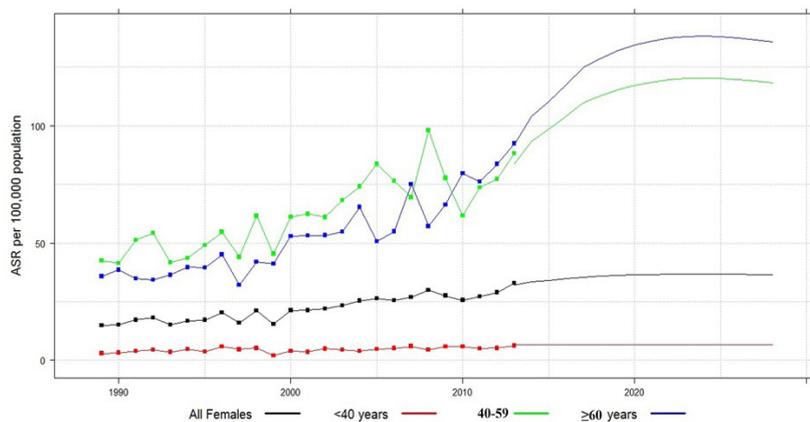


Figure 4. Trend in Female Breast Cancer, 1989-2013 and Future Trend Through 2028 According to Age Groups

From projections, we found that the highest incidence might reach an ASR of 36.7 per 100,000 women-years. Separately by age groups, ASR would be stable around 6.8 per 100,000 women-years in young females. In the other age groups, the ASR trend is expected to increase and reach the highest incidence in 2024 at 120.2 and 138.2 per 100,000 per women-years in middle-aged females and elderly females, respectively (Figure 4).

### Discussion

Overall, the female breast cancer incidence in Chiang Mai in Northern Thailand has continuously increased from 1989-2013. This was likely due to a combination of the rapid increase in proportion of elderly people because of longer life span of the population and more westernized lifestyle.

From our projections, the APC model predicted that the highest breast cancer incidence in all females could reach at 36.7 per 100,000 women-years in 2024. It was slightly lower than the highest predicted incidence rate in Songkhla population (Virani et al., 2014) but higher than the highest projected incidence rate in Lampang

population in 2020 (Lalitwongsa et al., 2015), 38.9 per 100,000 women-years and 30 per 100,000 women-years, respectively. The incidence was expected to rise faster and reach the highest at lower incidence in Lampang population compared to Chiang Mai population (Lalitwongsa et al., 2015). Over two decades, the large set of data were systematically collected and carefully verified. Using this high quality data allowed us to construct robust and informative models. This is one of the strength of this study. However, there was a limitation in staging record at the early years of data registry in our population. In addition, this population level registry data is limited due to lack of information on religion, genetic and other life style characteristics.

Understanding trends in breast cancer incidence in different age groups and identifying age-specific incidence trends can inform the types of treatments used for each age group, especially in resource limited countries. In our study, we determined the incidence in the three difference age groups including young females (<40 years), elderly female (>60) and an age group between these two groups. In Thailand, the elderly and the retired are defined at age 60. Moreover, Thai women have been reported

to have a median age at menopause, at age 49.5 years (Chompootweep et al., 1993). The impact of hormone replacement therapy (HRT) could be found in some years after initiation of menopause (Schmidt, 2012).

We found that ASR would be stably low, around 6.8 per 100,000 women-years in young females (<40 years). This finding was similar to the trend in young women in United States, but the incidence rate in our population was lower than their population (Brinton et al., 2008). While magnitude in incidence rate may be small, the impact on young female diagnosed with breast cancer is large. Breast cancer that occur in young females are of concern because these cancer are often hormone receptor negative (estrogen receptor negative, ER- and progesterone negative, PR-, HER2-) (Anders et al., 2008). The impact of genetic factors, particularly on breast cancer incidence rates at young females, may also contribute to the poorer prognosis (John et al., 2007; Anders et al., 2008). Further understanding of factors influencing breast cancer trends among young females may benefit from a focus on breast cancer subtypes that usually occur among young females including triple negative (Millikan et al., 2008). We found that the effect of cohort and period were not shown in the age groups. This reflects that the change in life style and the nation policy in breast cancer reduction may not impact to the incidence of breast cancer in this age group. The mammography is neither recommended for nor is sensitive in young females because of high breast tissue density (Houssami et al., 2003). Therefore, additional efforts are needed to identify preventive approaches for young women.

In our study, linear trends in year of birth and year of diagnosis were found in middle-aged females and elderly females. The increase in ASR in the middle-aged female could be partly affected by screening measures such as the use of self-examination and mammography but these could increase the detection rates of early disease (Buranaruangrote et al., 2014).

We found an increase in the percentage of localized cancers and a decrease in metastatic cancers in our population. It was likely because of higher education level in the population which increases awareness of breast cancer and practice of screening measures (Kanaya et al., 2003; Azami-Aghdash et al., 2015). Increased awareness of breast cancer in the population could be playing a role and the decrease in stage of the disease would be the effect of both awareness and screening measures.

The coverage of mammography examination in Thailand has been low especially in northern and north-east regions (Mukem et al., 2014). This may result to the slow improvement of localized or early stage detection in our population. In Thailand, an organized mammography screening has not been established due to lack of human resource and infrastructure. Moreover, according to the incidence rate based on data collected during 2001-2003 (ASR=20.9), the mammography screening of once-in-a- lifetime was not effective in the cost in the context of Thailand (Anothaisintawee et al., 2013). However, in more recent years, the higher breast cancer incidence in Thailand was reported at 28.5 of ASR based on data collected during 2010-2012 (Imsamran et al.,

2015). It may be worth to re-analyse the cost effectiveness of mammography screening in Thai population.

It is anticipated that, by the years 2028, approximately 231,400 of Chiang Mai female population were expected to be aged over 60. This population expansion is expected to be accompanied by a marked increase in patient requiring care for disorders included breast cancer. Interestingly, our study found that the incidence in elderly females trend to be higher than the middle-aged females, likely to be impacted by the change in demography and the use of HRT. During 1990 to 2000, a progressive a steady trend in HRT use was shown by sale statistics (Dusitsin, 1997). However, the updated trend in HRT use in Thai women has not been found, in particular in Chiang Mai population. There was only a hospital-based study conducted in six hospitals included Maharaj Nakorn Chiang Mai Hospital reported that only 25% of menopause clinic visitors were hormone users (Chaikittisilpa et al., 2007).

Although, it has been reported that HRT benefits on reduction in cardiovascular disease and increase of bone mineral density in post menopause women according to age of females and time since menopause (Cauley et al., 2003; Rossouw et al., 2007), HRT has been found to increase the risk of developing breast cancer (Nelson et al., 2002; Rossouw et al., 2002). The use of HRT probably has decreased thereafter. However, our model did not take into account this change for the projection.

In conclusion, cohort effects or generation-specific effects, such as life style factors, might have caused an increase incidence rate in women aged over 40 years rather than those under 40 years. The change in demographic and screening measures may impact to breast cancer incidence regarding to the increasing of ASR over the year of diagnosis (period) in the older age groups. Since the increasing trend of breast cancer incidences were expected in coming decade, a budget should be provided for treatment facilities and strategies to detect early stage of cancer. The cost effectiveness of screening measures i.e. mammography screening may need to be reconsidered for women age above 40 years especially in the era of aging society.

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#### *Statement conflict of Interest*

No potential conflicts of interest were disclosed.

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