RESEARCH ARTICLE

Success of a Cervical Cancer Screening Program: Trends in Incidence in Songkhla, Southern Thailand, 1989-2010, and Prediction of Future Incidences to 2030

Hutcha Sriplung[1], Phathai Singkham[2], Sopon Iamsirithaworn[2], Chuleeporn Jiraphongsa[2], Surichai Bilheem[1]

Abstract

Background: Cervical cancer has been a leading female cancer in Thailand for decades, and has been second to breast cancer after 2007. The Ministry of Public Health (MoPH) has provided opportunistic screening with Pap smears for more than 30 years. In 2002, the MoPH and the National Health Security Office provided countrywide systematic screening of cervical cancer to all Thai women aged 35-60 years under universal health care coverage insurance scheme at 5-year intervals. Objectives: This study characterized the cervical cancer incidence trends in Songkhla in southern Thailand using joinpoint and age period cohort (APC) analysis to observe the effect of cervical cancer screening activities in the past decades, and to project cervical cancer rates in the province, to 2030. Materials and Methods: Invasive and *in situ* cervical cancer cases were extracted from the Songkhla Cancer Registry from 1990 through 2010. Age standardized incidence rates were estimated. Trends in incidences were evaluated by joinpoint and APC regression models. The Norpred package was modified for R and was used to project the future trends to 2030 using the power of 5 function and cut trend method. Results: Cervical cancer incidence in Songkhla peaked around 1998-2000 and then dropped by -4.7% per year. APC analysis demonstrated that in situ tumors caused an increase in incidence in early ages, younger cohorts, and in later years of diagnosis. Conclusions: Both joinpoint and APC analysis give the same conclusion in continuation of a declining trend of cervical cancer to 2030 but with different rates and the predicted goal of ASR below 10 or even 5 per 100,000 women by 2030 would be achieved. Thus, maintenance and improvement of the screening program should be continued. Other population based cancer registries in Thailand should analyze their data to confirm the success of cervical cancer screening policy of Thailand.

Keywords: Cervical cancer - screening program - efficacy - Songkla, Thailand

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Introduction

Cervical cancer has been a leading cause of cancer in females in Thailand for decades. The estimated age-standardized incidence rate (ASR) for females in Thailand reached the peak around 24.7 per 10^5 Thai female population in the period of 1998-2000, as presented in the book Cancer in Thailand vol. IV and (Khuhaprema et al., 2007). At that time, cervical cancer was the first leading cancer among Thai women. The estimated ASR of cervical cancer in Thailand continuously dropped and was down to 16.7 during the period of 2007 to 2009, in "Cancer in Thailand" vol. VII (Khuhaprema et al., 2013).

Screening has been long proven as the most effective preventive intervention for cervical cancer. The early detection methods for this type of cancer vary from low price tests such as the Pap smear, visual inspections with acetic acid (VIA) to high cost tests such as HPV DNA test. Opportunistic screening with a Pap smear was launched in Thailand more than 30 years ago and later VIA was introduced just before 2000. Organized countrywide cytologic cervical cancer screening has been demonstrated in many countries of the benefit in reduction of cervical cancer incidence and mortality (Laara and Hakama, 1987; Mahlck et al., 1994; Dickinson et al., 2012). A longitudinal Swedish study showed the success of the countrywide cytologic screening for cervical cancer in reduction of squamous cell carcinoma (SCC) incidence and mortality but an unapparent effecton adenocarcinoma (AC) (Gunnel et al., 2007). A review of literature on the effects of cytologic screening worldwide demonstrated the decline in SCC in other countries, and the effectiveness in reduction of AC incidences. In many countries when pre-invasive AC was noticed missed by routine cytologic smears, improvement in cytologic screening practices was implemented (Mathew et al., 2009). When cytologic

*[1]Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Thailand, [2]International Field Epidemiology Training Program, Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand *For correspondence: hutcha.s@psu.ac.th*

screening is not possible, VIA is a screening of choice that can reduce incidence and mortality of cervical cancer proven in India (Shaatri et al., 2014).

In Thailand, the Ministry of Public Health (MoPH) and the National Health Security Office (NHSO) decided to conduct a countrywide systematic screening coverage of cervical cancer. Therefore, systematic screening programs have been provided to all Thai women aged 35-60 years under universal health care coverage (UC) at a 5-year interval, since 2002 (Sriamporn et al., 2006). Available screening methods included Pap smear and, in some places, VIA. Responsible staff in each province could select one or both methods depending on their experience and resources. The goal of the program was to achieve a 50% cervical cancer incidence reduction (Srivatanakul, 2004; Khuhaprema et al., 2012).

Songkhla is a province in the Southern region of Thailand occupying an area of 7392 km2 on the eastern side of the Malay Peninsula (Figure 1). While it borders Malaysia to the south, Muslims constitute approximately 25% of its population (National Statistical Office, 2013). The incidence of cervical cancer of women in Songkhla increased from 16.1 to 20.6 and was the leading cancer from 1996 to 1999. Although the ASR was decreased to 16.2 in 2002, cervical cancer was still the second most common cancer type in women of Songkhla. Pap smear test was the only method used in cervical cancer screening in the province. The organized cervical screening program according to the UC scheme was implemented in 2004.To illustrate the change in incidence rates of cervical cancer in Songkhla, we investigated cervical cancer data from the population-based registry of the province from 1990 to 2010 using joinpoint regression and age period cohort models. The aim of these analyses was to characterize the cervical cancer incidence trends in the province by calendar year, birth-cohort and age of diagnosis, to observe the effect of cervical cancer screening activities in the past decades in the province,and with the background incidence rates and the screening intervention program, to project cervical cancer rates in the province which also represent the southern Thailand to 2030.

Figure 1. Map of Thailand. Songkhla is on the Thailand/Malaysia Border

Materials and Methods

Cancer registry and cancer case recruitment

The population-based cancer registry of Songkhla covers sixteen districts in southern Thailand. The population of southern Thailand at the 2010 census was 8.9 million people of which 4.4 million were females (National Statistical Office, 2012). This registry actively compiles cancer cases from 23 sources including community hospitals, private hospitals, and the population registration office. The number of undetected cases is difficult to estimate due to a number of remote villages with limited access to health facilities and the use of traditional Thai medicine instead of using existing governmental health care services. Cervical cancer cases were extracted from the Songkhla Cancer Registry from 1990 through 2010 using ICD-10 codes C53.X for invasive cancer and D06.9 for carcinoma *in situ* of the cervix uteri. Information collected from the cancer registry included age and date of diagnosis.

Population denominators

Population denominators to calculate incidence rates were estimated from the three population censuses surveyed by the National Statistical Office in 1990, 2000, and 2010 (National Statistical Office, 1992; 2002; 2012). The population denominators by both sexes for all districts were readily present in the censuses. Intercensus 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 were calculated for eighteen different age groups (0-4, 5-9, …, 80-84, and 85+) and twenty-one calendar periods from 1989 to 2010 (1-year intervals). This stratification resulted in data for 90 single-year birth cohorts from 1902 through 1992. ASRs standardized to the world population proposed by Segi (1960) and later modified by Doll (1966) were estimated for each particular year and were plotted to visually illustrate the trends.

We then evaluated trends in incidence using the Joinpoint Regression Program version 4.0.4 (2013). Joinpoint regression identifies statistically significant trend change points (joinpoints) and the rate of change (annual percent change) in each trend segment using a Monte Carlo permutation method (Kim, et al., 2000).

Age-period-cohort (APC) regression models were used to investigate the effect of age, calendar year and birth-cohort on the incidence of cervical 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 adjust for age a, period p and birth-cohort c, where *c=p-a*. To address the non-identifiability problem of the APC models, two-effects models (age-period and age-cohort) were first chosen and the remaining effect (cohort or period) was then identified to the respective model's residuals using natural splines to reduce random variation (Carstensen, 2012). These are referred to as the AP-C and AC-P models. The analysis of APC models was performed with the Epi package (Carstensen et al., 2013) for R statistical software version 3.0.2 (R Core Team, 2013).

The Norpred package (2013) was modified for the R statistical software and was used to generate the projection and graph plot. Nordpred fit an APC model to the data and then calculated world-standardized incidence rates for eighteen age groups (from 0-4 to 85+, 5-year intervals) and 5-year interval periods (1990-1994, …, 2004-2009). Trends based upon all of the observed data were then extrapolated out to four 5-year periods, ending in 2030. To avoid overestimation of cases from the multiplicative model, as recommended by Olsen et al. (2008) and Mistry et al. (2011), a power of 5 function was used. The prediction model is written as:

$R(a,p)=[f(a) + D^{*}p + g(p) + h(c)]^{5}$,

where $R(a,p)$ is the incidence rate for age group a and period p, $f(a)$ is the age effect of age group a, D is the common linear drift of period and cohort, $g(p)$ is the non-linear period effect and $h(c)$ is the nonlinear cohort effect, where $c=p-a$.We also follow the cut trend system mentioned by Olsen et al. (2008) in projection by attenuation of the linear drift by 0/4 D, 1/4 D, 2/4 D, and 3/4 D respectively, for the four future 5-year projection periods.We also applied the cut trend concept to the projection with joinpoint method with reduction of the trend in the first future 5 years by 0% and after that by 5% per year so that we could get 1/4 D by the year 2020 up to 3/4 D by the year 2030 at the end of the forth 5-year period. With this method, the result was comparable to the cut trend used in Nordpred.

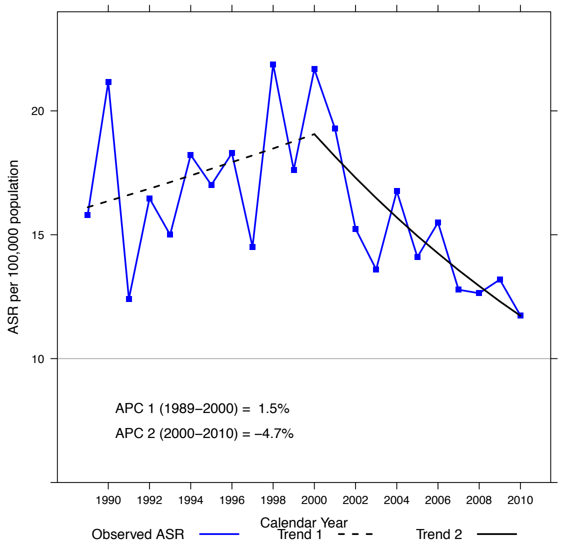

Figure 2. Trends in Incidence of Cervical Cancer in Songkhla from 1989 to 2010. Joinpoint Analysis Identifies Two Trends at 1989-2000 and 2000-2010 with Annual Percent Change of 1.5% and -4.7% Respectively

Results

Between 1989 and 2010, a total of 2,227 cases were diagnosed with ICD10 code C53 (invasive cervical cancer) and 554 cases with code D06.9 (carcinoma *in situ* of cervical cancer). The incidence of cervical cancer in Songkhla peaked around 1998-2000 and continuously dropped after that (Figure 2). Before the year 2000, annual ASR varied widely throughout the years according to opportunistic screening campaign, obviously seen in 1990, 1998 and 2000. However, the APC computed by the Joinpoint software was increasing at 1.5% per year on average. The drop in ASR after the year 2000 was obvious and continuous with APC of -4.7% per year. The percentage of *in situ* tumor gradually increased until 2003 which was the year the ASR dropped and started to increase again (Figure 3). The percentage of a localized (stage I) tumor increased after 2004 but the proportion of metastatic tumors was not decreasing in the same period. Unexpectedly, the unknown stage increased in later years while it had been declining since 1995.

Figure 4, the classic age period cohort plot, shows a

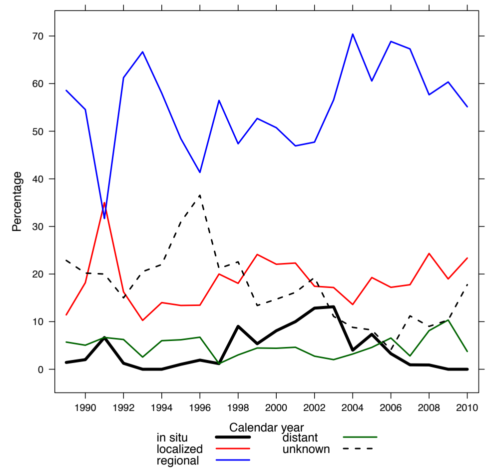

Figure 3. Stage Distribution in Percentage, Including *in situ* Tumors

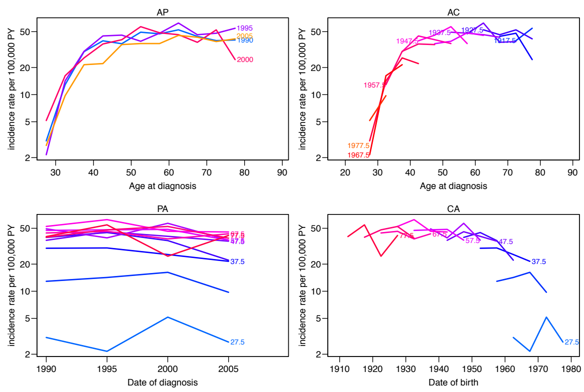

Figure 4. Incidence rates of cervical cancer in women per 10^5person-years by age, period and birth cohort. Graphs are arranged as incidence rates of age by period (AP), age by birth cohort (AC), age by period by age (PA), and age by birth cohort (CA). In AP plot, 1990, …, 2005 lines represent the periods 1990-1994, …, 2005-2009 respectively. Age groups are labeled at the middle point of the period like 27.5=25-29, and so on. Birth cohorts are the results of period - age. (*In situ* tumors not included.)

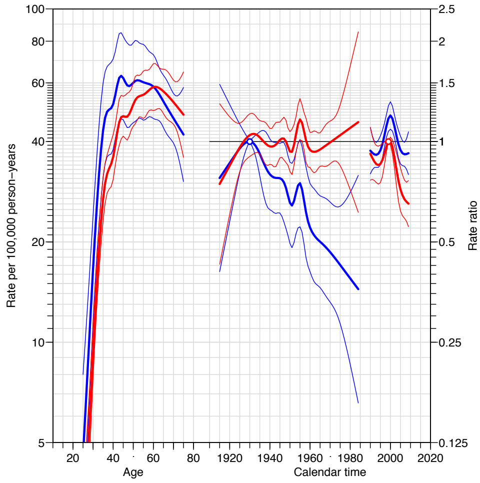

Figure 5. APC Trend Analysis. AC-P (Blue) and AP-C (Red) Models

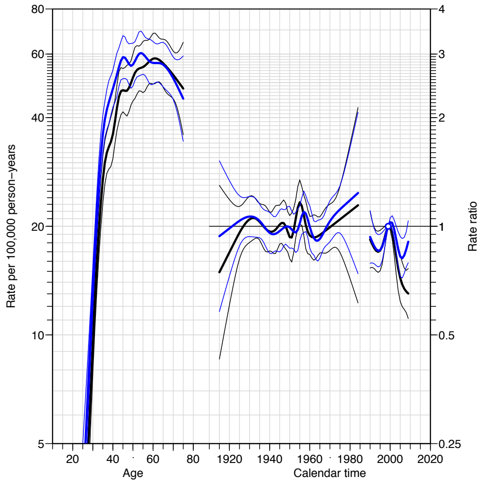

Figure 6. APC Trend Analysis, AP-C Models, for Invasive Plus *in situ* (blue) and Invasive Only (Black) Tumors. Adding *in situ* to invasive cancers causes an increase in incidence in early ages and raise in rate ratio among younger birth cohorts and in later years

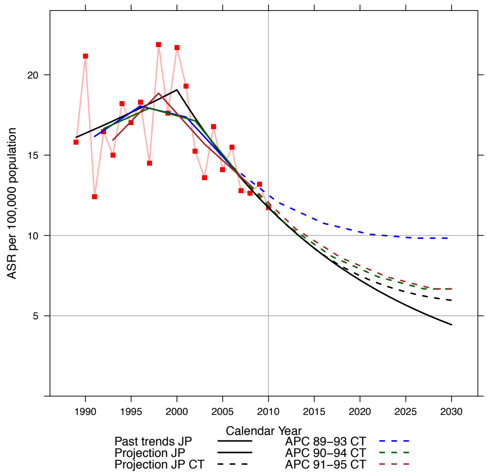

Figure 7. Cervical Cancer Incidence Trend Projections to 2030. JP is the line obtained from joinpoint analysis. The line segments after the year 2010 are projected lines. APC lines are obtained by the Nordpred package which uses age period cohort analysis with a 5-year interval. Nordpred takes the change in population age structure in the future into account in ASR computation

marked drop in age-specific incidence rates in almost all age groups in the period 2005-2009 (AP plot). The PA plot demonstrates a general drop of incidence in all age groups with a spike in young to middle age groups in two periods: 1995-1999 and 2000-2004. This phenomenon corresponds to the peaks seen in Figure 1. It is indicated in Figure 5 that both AC-P and AP-C models show the peak rate ratio (RR) of the period (the lines on the right) at the year 1999 (at the middle of the peaks in 1998 and 2000 in Figure 1) and a continuous drop in RR after that. However, after 2006 the RR seems to increase again. The cohort effect shown in the middle portion of the graph, suggests a slight increase in RR among younger birth cohorts, especially in the AP-C (red) line. In interpretation of both the period and cohort together, it seems to have a deceleration of the declining trend in the overall ASR in the last few years in the data set and such the deceleration may continue in the near future.

There are two points to mention regarding the age effect in the APC model. Both AC-P and AP-C models show the same fact that the incidence of cervical cancer in Songkhla peaks around peri-menopausal to early elderly age groups (Figure 5). APC plot of AP-C models for invasive tumors (black) and invasive plus *in situ* tumors (blue) in Figure 6 clearly demonstrate that *in situ* tumors caused an increase in incidence in early ages. For cohort and period effects, the plot shows that *in situ* tumors are increasing drastically among younger cohorts in later years.

Figure 7 compares the future trends predicted by joinpoint and APC analysis using the Nordpred package using 3 starting 5-year periods: 1989-1993, 1990-1994, and 1991-1995. With the same method of APC analysis and cut trend as described above, we can observe the difference in ASRs projected by changing the starting 5-year period. The results obtained by using 1989-1993 (blue) as the first 5-year period give the highest projected ASRs while the lines of the other two periods (green and brown) were quite similar and close to, but still higher than, that of the joinpoint method (black).

Discussion

The analysis of trends in incidence of cervical cancer in Songkhla demonstrated initial increases in incidence until 1998-2000 which was before the start of the countrywide systematic screening coverage program in 2002 (Figure 2). In countries where systematic national cervical cancer screening program were used, the incidence of the cancer increased due to extensive case finding and dropped down to the initial rate within an interval of approximately 10 years and the variation was dependent on the frequency and coverage of screening program (Laara et al., 1987; Sigurdsson 1999).

Before 2000, cervical cancer screening in Thailand was implemented as an occasional campaign on special occasions. This sporadic screening caused a marked increase in some years such as in 1990 followed by a deep drop in the following years. After the organized screening program had been set up in 2002, health centers and governmental hospitals were assigned target populations under their coverage for screening once in 5 years, thus, continuous screening activities were settled and fluctuation in incidence was obviously reduced.

One of the suspected outcomes in the shift of cancer towards early stages was not evident in Songkhla (Figure 3). The suspected phenomenon seems to occur before 2002 but the picture seems to be different afterwards with a drop in *in situ* tumors, increase in localized (stage I) and unknown stage cancers. Changes in a countrywide health care system may underlie this finding, however, the mechanism is not clearly known.

The APC models (Figure 4 and 5) showed the increase in cancer detection corresponding to the increase in proportion of *in situ* and localized tumors (Figure 3). Together with the overall rise in incidence during 1989 to 2000, the evidences showed the success of opportunistic early detection strategy by using Pap smear screening. In Thailand, in addition to cervical screening campaign on special occasions such as the Queen's birthday, a postpartum Pap smear was recommended to all women after delivery. This strategy could detect a few cases with cellular abnormalities since women at delivery were usually too young to develop cancer, but it could make women familiar with regular Pap smear screenings afterwards and could increase health awareness and screening rate among women from 35 to 60 years of age. A comparison of incidence rates of invasive cervical cancer and invasive plus *in situ* cancer (Figure 6) illustrated that women in young age groups, recent birth cohorts, and later age groups, joined screening both opportunistic and countrywide systematic screening programs. Thus, it can be concluded that both opportunistic and systematic screening programs worked but it is difficult to determine the magnitude of each screening scheme.

With various projection procedures (Figure 7), the decreasing trend in cervical cancer incidence seems to continue into the future. The black solid line beyond 2010 is the projected ASRs without a cut trend. Each dashed line represents the results of APC projection method using Nordpred, except the black dashed line being the cut trend result of the joinpoint method. In the APC method, 5-year periods are to be clearly defined. Selection of different starting 5-year periods, 1989-1993,1990-1994 and 1991-1995 produces different results. The slowest decline in incidence is observed when the starting 5-year period was 1989-1993. Thus, in a disease where an abrupt change in incidence during the time course is obvious, a trial in varying the 5-year periods on the calendar time frame is important. In this study, both joinpoint and APC methods predict decreasing trends. Varying the 5-year time frame also results in the declining trend but with different rates and the predicted ASR at a given future time point.

The coverage of implementeding a screening program plays a role in incidence and should be maintained at the least same level (Hakama and Louhivuori, 1988). The crude coverage of the screening program surveyed in 2009 by the Health Intervention and Technology Assessment Program (HITAP) was 68% (Sirisamutr et al., 2010) which is in between that of developing and developed countries (Gakidou et al., 2008).The screening participation rate is very good in suburban and rural areas where primary health care facilities have long been settled. With this degree of screening coverage, the projection is ensured when there is no major change in factors affecting the screening scheme in the near future.

Thus, it can be concluded that the decreasing trend in cervical cancer incidence was observed in Songkhla from the year 2000 and the incidence continues to decline into the future. The predicted ASR at 2030 varies from 5 to 10 per 100,000 women with different projection methods. Cervical screening has proven its success both areas of opportunistic and systematic.

Analysis of a population-based cancer registry data is the best way to understand the nature of a disease in a population. Usually the data set is designed as a minimum data that is easy for the registrar to complete with completeness and reliability, thus, it misses variables to answer specific research questions. In this case, the definite timeline of opportunistic screening campaigns of previous times could not be identified and hard to recall by health officers. For this reason, we missed some information for explaining the trend. Changes in the health care system, data collection procedures, and coding convention especially when the hospital information system and codes of various variables, was revised might have interfered with the trends. However, major changes in incidence and trends in this study seem to fit well with the overall health care system in the country, thus, our findings and conclusions should be valid.

The declining trend in cervical cancer incidences must be maintained to achieve the predicted goal of ASRs below 10 or even 5 per 100,000 women by 2030. For public health planning, maintenance and improvement of the screening process to ensure high coverage of systematic; screening in Songkhla should be continued. Since this is the first report to document the success of cervical cancer screening in Thailand, the same method of APC and joinpoint analysis must be reported from other population based cancer registries in Thailand, to confirm that the effect is countrywide and variations in different regions in the country could be observed.

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