International Journal of Public Health (2018) 63:377–385
https://doi.org/10.1007/s00038-018-1077-7

ORIGINAL ARTICLE

Effect of the national screening program on malignancy status of cervical cancer in Northern Thailand

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Received: 13 July 2017 / Revised: 7 December 2017 / Accepted: 11 January 2018 / Published online: 23 January 2018

Abstract

Objectives Cervical cancer has posed a serious problem in Thailand for decades. In 2002, a systematic screening program was implemented under universal healthcare coverage for all Thai women. However, there has been little research on how screening affected particular aspects of cervical cancer, such as stage distribution. This screening program has a target group; therefore, it is necessary to assess stage and incidence trends by age of those within and outside the screening target group.

Methods Using trend analysis, we assess in situ and malignant cervical cancers in Northern Thailand to measure changes after implementation of the national screening program.

Results While incidence of malignant cancers is decreasing and incidence of in situ tumors is increasing across all age groups, women above age 60 still experience a high incidence of malignant tumors.

Conclusions The screening program is successful in the target group at downshifting the stage distribution of malignant tumors and reducing incidence of malignant tumors with in situ cases being captured. However, the high incidence of malignant tumors in women over age 60 will continue to be clinically relevant for cervical cancer management until younger generations undergoing screening enter this age group.

Keywords Cervical cancer · Screening · In situ · Malignant · Thailand

Introduction

Cervical cancer has posed a serious problem in Thailand for decades. It was the top cancer in women in Thailand with an age-standardized incidence rate (ASR) of 29.4 from 1998 to 2000. From 2001 to 2003, the ASR dropped to 18.1 due to intermittent screening strategies (Khuhaprema et al. 2007, 2010). Efforts were made to address cervical cancer through occasional screening campaigns. In 2002, a systematic screening program was implemented under universal healthcare coverage (UC) for all Thai women ages 30–60 years at 5-year intervals (Sriamporn et al. 2006) to reduce the burden of cervical cancer incidence (Khuhaprema et al. 2012). However, coverage was low until 2005 when the National Health Security Office (NHSO) established a contract with the Ministry of Public Health to provide both Pap smear and visual inspection with acetic acid (VIA) as eligible benefits under the universal healthcare coverage (Hengrasmee et al. 2004;

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International Health Policy Program 2008). After phase 1 of the program ended in 2008, the Ministry of Public Health scaled up the screening program and increased coverage by promoting reimbursement for Pap smears and VIA for women ages 30–60 years and allowing health providers to choose the approach they considered most appropriate for their setting (Sangrajrang 2016; Yothasamut et al. 2010).

National targets for the percent of women aged 30–60 years screened for cervical cancer once in the previous 5 years were 20% in 2010, 60% in 2011, 70% in 2012 and 80% in 2013 (Ministry of Public Health 2013). Reports on adherence to targets are mixed. Several surveys indicated that coverage was between 38 and 63% between 2003 and 2006 (Joseph et al. 2010; National Statistical Office of Thailand 2010). However, one study suggested that coverage with Pap smears and VIA was 11 and 8%, respectively, of the target population in 2005 (Tangcharoensathien et al. 2008). Results of the 2010 Thai Behavioral Risk Factor Surveillance System (BRFSS) suggested that the 2010 and 2011 targets were reached (Joseph et al. 2010).

Despite conflicting reports on coverage, national efforts to attenuate the burden of malignant cervical cancer can be regarded as a success. The overall success of the screening program was demonstrated by the decreasing rates of cancer incidence nationally. By 2012, cervical cancer incidence reached an ASR of 14.4 (Imsamran 2015). While coverage is improving, there is little research on how screening is affecting specific aspects of cervical cancer. Important measures of screening, such as stage distribution, have not been assessed. In addition, it is important to assess stage and incidence trends by age of those within and outside the screening target group.

Screening varies by region and it is likely that screening outcomes vary also. Here, we assess stage distribution and trends and provide projections of cervical cancer incidence in Northern Thailand.

Methods

Region

Chiang Mai, Thailand is a northern province occupying an area of 7763 square kilometers located 700 km north of Bangkok. It is the main base of a variety of hill tribes living in the surrounding mountains. This region is covered under the national UC system, which provides healthcare access to 97% of the population (Virani et al. 2017). Population characteristics and demographics can be found in previous work (Virani et al. 2017).

Cancer registry

The Chiang Mai registry covers 25 districts in Northern Thailand and accounts for 15% of the northern population. The population of Chiang Mai Province at the 2010 census was approximately 1.7 million, of which 51% were females. This registry actively compiles cancer cases from all hospitals in the province. The capture-recapture technique was used to monitor completeness of the cancer registry (Suwanrungruang et al. 2011). All data are verified, checked for duplication, coded and entered into CanReg5 software.

Data

Cases were extracted from the Chiang Mai Cancer Registry from 1989 through 2013 using ICD-10 codes 53.X. Information included age and date of diagnosis. Data quality, in terms of percent morphologically verified and percent of death certificate only, for cervical cancer was high from 1989 to 2012 (1988–1991: %MV 96.3, %DCO 0.2; 2010–2012: %MV 98.3, % DCO 0.5; Imsamran 2015; Vatanasapt et al. 1993).

Population numbers used to calculate incidence rates were retrieved from population censuses conducted in 1990, 2000 and 2010 (1990 Population and Housing Census 1994; 2000 Population and Housing Census 2002; Carstensen et al. 2013). Intercensus populations were estimated using a log-linear function between two consecutive censuses. Population numbers beyond 2010 were estimated and reported by the Office of the National Economic and Social Development Board (Office of the National Economic and Social Development Board of Thailand 2013).

Age-specific incidence rates were calculated for 18 age groups (0–4, 5–9, …, 80–84 and $\geq$ 85).

Trend analysis

Age-adjusted cervical cancer incidence rates in Chiang Mai, Thailand, from 1989 to 2013 were standardized to Segi's world population (Doll 1976; Segi 1960). Incidence trends were evaluated using the Joinpoint-Regression Program version 4.2.0.2, utilizing a Monte Carlo permutation method to identify statistically significant trend change points (joinpoints) and the rate of change (annual percent change) in each trend segment (Kim et al. 2000). Statistical significance was determined at $\alpha = 0.05$. Analyses were conducted for invasive + in situ, in situ only, and invasive only cases of cervical cancer to assess differences in incidence trends by invasion status. Trends were assessed for women below age 35, age 35–60 years

and 60 years and above to assess differences by age group as targeted by the national screening program.

To investigate the effects of age, calendar year and birth cohort on the incidence of cervical cancer, we fit age-period-cohort (APC) models for 5-year age groups to incidence rates, as described previously (Tassanasunthornwong et al. 2015; Virani et al. 2014). Briefly, a Poisson distribution was fit in a log-linear model to address the non-identifiability problem. Two effects models (age-period and age-cohort)] were fit to determine the effect influencing incidence trends. The remaining effect (cohort or period) was then fit constrained to be 0 on average with a 0 slope (Carstensen et al. 2013). These are referred to as the APC and age-cohort-period (ACP) models. Analysis was performed using the Epi package (Carstensen et al. 2013) for R statistical software version 3.3.2 (R Core Team 2016).

Projections

An APC model with a power5 link function was fit using case and population data aggregated over 5-year intervals and 18 age groups. Projected trends were based on either all observed data (historical trend) or limited to the most recent 10 years (recent trend). Dampening of the linear drift was used to limit the continuous linear increase present over time. We used a combination of methods from Møller et al. (2002) and Mistry et al. (2011) by projecting the first 5 years with 0% attenuation, followed by geometric dampening at a rate of 8% each year until 2030. Projected rates were calculated for incidence of all cervical cancers, in situ cancers only and invasive cancers only. Natural splines were fit to 5-year ASR values to obtain ASRs for each single year in each group.

Results

There were 9794 total cases (invasive + in situ) of cervical cancer diagnosed in Chiang Mai Province from 1989 to 2013. Median age of onset was 46 years. Of these, 5447 (55.6%) cases were invasive. Approximately 4% of all cases were found in women below age 30, of which 66% were in situ. The target screening group of women ages 30–60 years accounted for 80.5% of all cases, of which 48.7% were in situ cases. Women above age 60 represented approximately 15.3% of all cases, of which 15.6% were in situ. Median age of onset was 42 years for in situ tumors and 49 years for malignant tumors.

Stage distribution

ASRs per 100,000 person-years (PY) by stage show the incidence of regional tumors decreased from 33.2 in 1989 to 8.1 in 2013, while in situ and localized tumors increased from 12.7 to 25.3 and 0 to 15.3 from 1989 to 2013, respectively, for all ages (Fig. 1). Separating incidence of each stage by age group shows that women in the target screening group drive these trends. In these women, in situ cases had the highest incidence starting from 1998, when it surpassed the incidence of regional tumors. The incidence of in situ tumors doubled from 2001 to 2002, increasing from 30.5 to 64.4. By 2013, the incidence of in situ, localized and regional tumors reached ASRs of 45.6, 26.5 and 8.7, respectively.

In women less than 30 years, the incidence of in situ and localized cases increased slightly, reaching ASRs of 6.6 and 3.1 in 2013, respectively. Incidence of regional cases for this age group dropped to 0.9 in 2013. Conversely, for women above age 60, regional tumors decreased over time, but continued to have the highest incidence compared to all other stages with an ASR of 22.6 in 2013. Incidence of in situ and localized tumors reached ASRs of 7.0 and 9.5 in 2013, respectively.

Trend analysis

Cervical cancer incidence in all women increased by 3.5% annually until 2004 when it decreased by 3.4% per year (Table 1; Fig. 2). In the target screening group, incidence increased by 4.4% annually until 2004 and then decreased by 3.6% per year. In women above 60 years, incidence decreased by 4.3% annually starting in 2003. Incidence in women younger than 30 years remained constant.

Incidence of in situ only cases increased by 10.6% per year for all women until 2003, when it decreased by 1.8% annually. Women less than 30 years had a 2% annual increase in incidence of in situ cancers, whereas women in the target screening group and women above age 60 had annual increases of 11.6 and 12.4%, respectively, until 2003.

Incidence of malignant cases in all women began decreasing in 2008 by 8.4% annually. However, in women younger than 30 years, an annual decrease of 3.4% was exhibited earlier, from 1989 to 2011. In contrast, women in the target screening group and women above age 60 exhibited decreases in incidence of malignant cancers in 2008 and 2003, respectively, by 8.6 and 4.9% annually.

APC analysis revealed both period and cohort effects shaped cervical cancer incidence trends (Fig. 3a). Significant reduction in residual deviance (indicates the goodness of fit of modeled to observed values) was achieved when comparing the age-only model [residual deviance (RD) 681.1, degrees of freedom (*df*) 336] to the APC model (RD: 448.3, *df*: 325). However, the age-period model (RD: 507.0, *df*: 333) had better fit compared to the age-cohort model (RD: 582.9, *df*: 327). This indicates that although

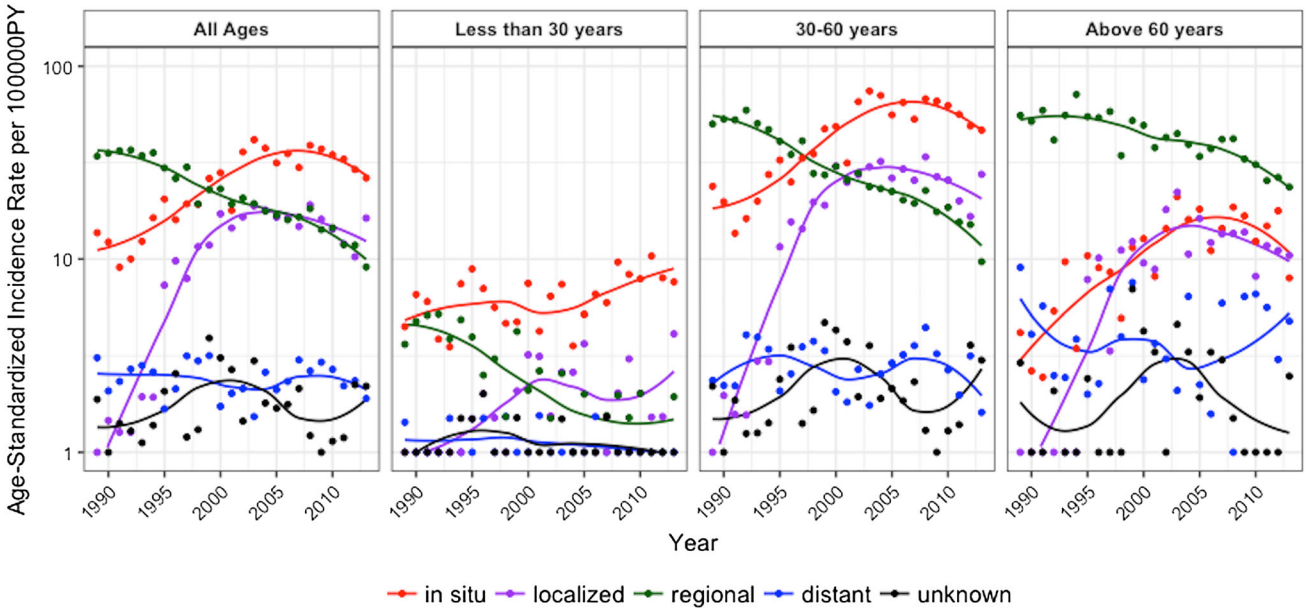

Fig. 1 Age-standardized incidence rates of cervical cancer by stage for each age group in Northern Thailand from 1989–2013

Table 1 Trend analysis from 1989 to 2013 in Northern Thailand

	Trend 1		Trend 2	
	Years	APC^{+} (%)	Years	APC^{+} (%)
All cases				
All ages	1989–2004	3.5*	2004–2013	−3.4*
Less than 30 years	1989–2013	0.4		
30–60 years	1989–2004	4.4*	2004–2013	−3.6*
Above 60 years	1989–2003	1.9	2003–2013	−4.3*
In situ cases only				
All ages	1989–2003	10.6*	2003–2013	−1.8
Less than 30 years	1989–2013	2*		
30–60 years	1989–2003	11.6*	2003–2013	−2.3
Above 60 years	1989–2003	12.4*	2003–2013	−2.4
Malignant cases only				
All ages	1989–2008	− 0.5	2008–2013	−8.4*
Less than 30 years	1989–2012	− 3.4*	2012–2013	30.4$^{\pm}$
30–60 years	1989–2008	−0.3	2008–2013	−8.6*
Above 60 years	1989–2003	0.4	2003–2013	−4.9*

*p-value < 0.05

$^{+}$Annual percent change in age-standardized incidence rates

$^{\pm}$Although this annual percent change is high, is it not significant due to the low number of data points

the best fit was found for the full model, the period effects were found to be more important than the cohort effects in terms of model fit (Table 2). Separating incidence by malignancy status reveals similar findings in terms of model fit; however, period and cohort effects are more prominent based on malignancy status. In situ and malignant incidence trends have both a period and cohort effect. However, period effects were found to be slightly more important in in situ trends, whereas cohort effects were slightly more important in malignant trends (Table 2).

Models for in situ incidence trends show age effects that exhibit increasing risk until ages 35–40 years. The age effect in the APC model drops rapidly after 35–40 years, whereas the age effect in the ACP model remains stable. The cohort effect of the ACP model exhibits higher relative risk (reference year: 1962) of in situ tumors for younger

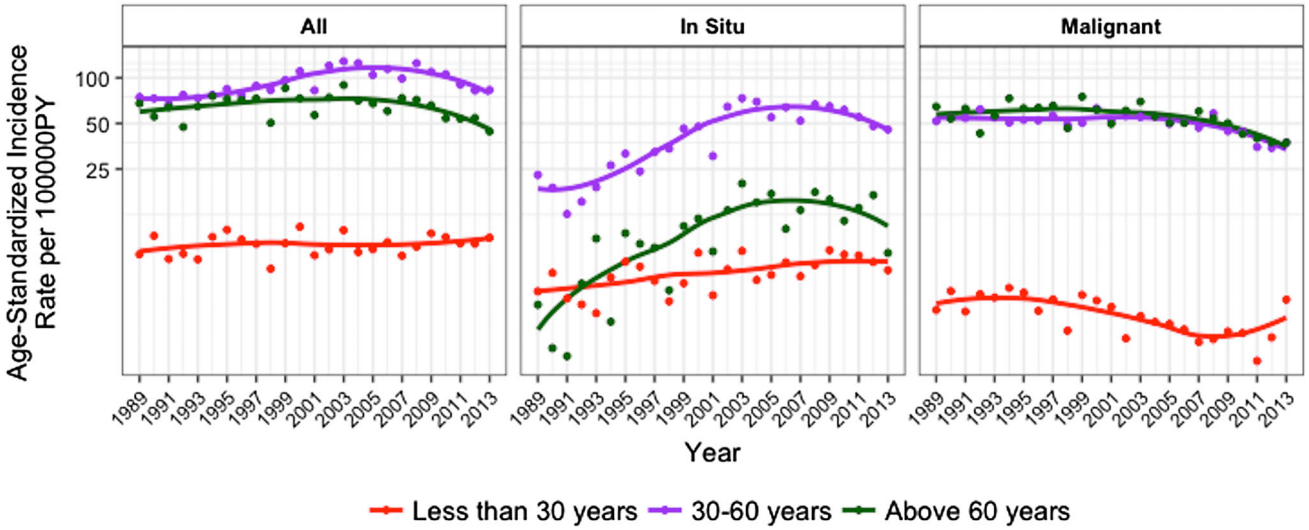

Fig. 2 Age-standardized incidence rates of all cervical cancers and by malignancy status by age group in Northern Thailand from 1989–2013

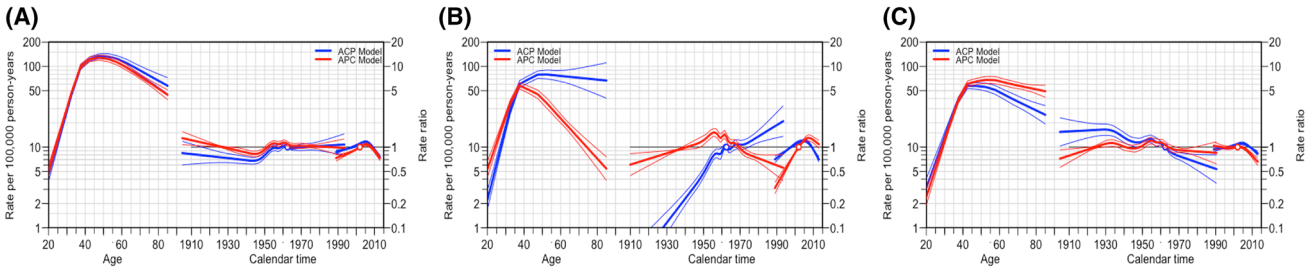

Fig. 3 Age-period-cohort (APC) modeling of **a** all cervical cancer, **b** in situ cancers only and **c** malignant cancers only. Comparative modeling using Age-cohort-period (ACP; blue) and APC (red) models are shown and illustrate age (left), cohort (center) and period (right) effects for women in Northern Thailand from 1989–2013 (colour figure online)

Table 2 Goodness of fit for age-period-cohort models for women in Northern Thailand from 1989–2013

Model	All tumors		In situ only		Malignant only	
	Residual degrees of freedom	Residual deviance	Residual degrees of freedom	Residual deviance	Residual degrees of freedom	Residual deviance
Age	336	681.2	275	913.4	323	498.2
Age-drift	335	646.6	274	590.5	322	432.3
Age-cohort	327	582.9	266	470.8	314	391.7
Age-period	333	507.0	272	438.2	320	397.2
Age-period-cohort	325	448.3	264	350.4	312	361.8

generations, and the period effect of the APC model exhibits low relative risk of in situ tumors prior to 2002 (reference year: 2002) and increased relative risk after this year (Fig. 3b). Age effects in models for malignant incidence trends exhibit increasing risk until ages 40–45. Cohort effects from the ACP model show younger generations have relatively lower risk of malignant tumors while period effects from the APC model exhibit lower relative risk of malignant tumors after 2002 (Fig. 3c).

Projections

Projections are based on all observed data (historical projections) or the previous 10 years (recent projections) to account for the implementation of the national screening program. These models provide a range of expected incidence in the future. For all women, cervical cancer incidence is expected to reach an ASR between 23.2 (recent) and 39.7 (historical) by 2030. In terms of malignancy,

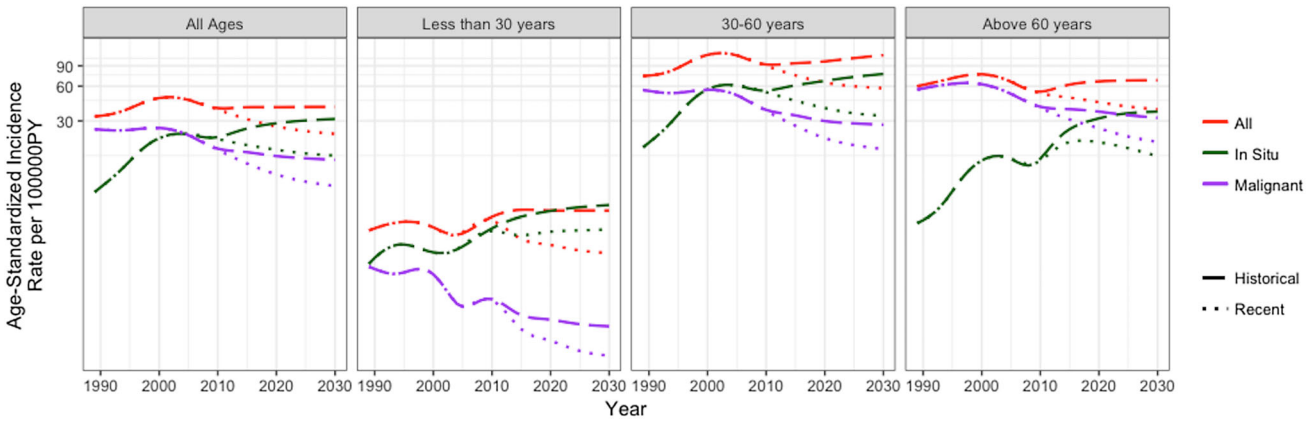

Fig. 4 Rate projections of all cancers, in situ only and malignant only cancers by age group for women in Northern Thailand from 1989–2013. Historical projections are based on all observed data. Recent projections are based on observed data from the last 10 years

in situ incidence is expected to reach 15–31.2 cases per 100,000 PY, while malignant tumor incidence is expected to decrease to an ASR between 8.2 and 13.8 (Fig. 4).

When considering projections by age group, incidence of in situ and malignant cervical cancers are lowest in women younger than 30 years and expected to be the lowest out of all the age groups in 2030. Incidence of all cervical cancers is expected to reach between 2.2 and 5.0 cases per 100,000 PY. Incidence of in situ cancers is expected to be between 3.5 and 5.6 cases per 100,000 PY, while incidence of malignant cancers is expected to reach 0.3–0.5 cases per 100,000 PY in 2030. The target screening group of women ages 30–60 years is expected to have the highest incidences of in situ and malignant tumors of all age groups in the future. Cervical cancer incidence in the target screening group is expected to reach an ASR between 57.6 and 111.2. Specifically, in situ tumor incidence has expected ASRs of 33.2 and 76.5, while malignant tumor incidence has expected ASRs of 17.1 and 27.8. Finally, women above 60 years are expected to have cervical cancer incidence reach an ASR between 37.8 and 67.6 in 2030. In situ-only incidence is expected to reach between 14.8 and 36.1 cases per 100,000 PY, while malignant tumor incidence is expected to reach an ASR between 19.7 and 31.9 in 2030.

Discussion

In this paper, we show cervical cancer incidence decreased significantly after screening shifted from occasional campaigns to a more consistent screening program that was continually amended to expand coverage. In situ and localized tumor incidence increased while incidence of regional tumors decreased, indicating overall success. In addition, we see the expected increase and subsequent decrease in incidence between 2000 and 2010 as prevalent cases are captured and cases are detected earlier before reducing the incidence of malignant cases. It is important to consider these trends by age. The national screening program targets women ages 30–60 years. Our findings show that the effects of this program are clearly seen in these women. Incidence of in situ tumors is highest in this age group. Although trends for malignant tumors are similar in this group and women above age 60, women in the target screening group were down-staged after the screening program started in 2002 as incidence of regional tumors decreased and localized tumors increased. Conversely, while the incidence of in situ tumors increased in women above 60 years, this group continued to have the highest incidence of malignant regionally staged tumors. Finally, women younger than 30 years had the lowest incidence of cervical cancer and exhibited an increase in in situ cancers and a decrease in malignant tumors. Women in this age group have low risk of cervical cancer. Although the reason for the decrease in incidence of malignant tumors is unclear, it is possible that widespread importance of screening promotes opportunistic screening in this group, particularly among those who are sexually active.

Trends exhibit clear effects related to screening. Period effects for in situ tumor trends show increased risk of incidence after the screening program was established due to higher probability of detection, and cohort effects illustrate the higher risk of in situ tumors in younger generations. The opposite is seen for malignant trends where period effects show reduced risk after the screening program and cohort effects show reduced risk of malignancy in younger generations. These findings show that as younger generations pass through the screening program, they are more likely to be diagnosed with in situ tumors than malignant tumors.

Women older than 60 years have the highest incidence of regionally staged tumors. This is expected due to physiological reasons. The transformation zone is an area of the cervix where columnar cells are constantly changing into squamous cells. Most cervical cancers begin in the transformation zone. In premenopausal women, this zone is located on the outer surface of the cervix and is accessible for screening. In postmenopausal women, this zone shifts to the inner canal of the cervix, making screening difficult (Sankaranarayanan and Wesley 2003). However, our findings show incidence of regionally staged malignant tumors in this age group decreased in recent years. It is expected that with consistent screening, women will pass through the target screening group and cases will be captured earlier, addressing the cancer burden in women above age 60 years.

Projections indicate that when historical data are considered, incidence of in situ tumors is expected to increase while incidence of malignant tumors is expected to plateau. When data from the past 10 years are considered, incidences of both in situ and malignant tumors are expected to decrease. These approaches to projections consider various situations. Occasional screening campaigns existed before the national screening program. For example, campaigns were promoted on special occasions, such as the Queen's birthday. Also, postpartum Pap smear was recommended to all women after delivery. These practices, although not standardized, allowed for down-staging tumors and capturing in situ cases prior to 2005. Historical projections provide predictions based on this scenario. The national screening program was fully phased in around 2005 and expanded in 2008. The recent projections provide predictions based on this standardized program. It is likely that true future incidences will fall somewhere in these ranges.

After the first phase of the screening program, many aspects were critiqued and areas for improvements were noted (International Health Policy Program 2008). As the program continued to improve, our findings illustrate its beneficial impact on the cervical cancer burden. The success of the national cervical cancer screening program highlights the importance of healthcare infrastructure and health systems. Thailand has a universal healthcare system that covers 99% of the population (Tangcharoensathien et al. 2016). Cervical cancer screening is covered under this system, allowing access and providing better equity in coverage. The major health facilities providing Pap smear and VIA services are health centers and district hospitals, respectively. These infrastructures were established in the 1980s and have been expanded since to provide access to services even throughout rural areas.

The healthcare system and process of cancer registration in terms of data collection and variable coding revisions is constantly evolving. A limitation of this study is the missing information on how these changes might affect the cancer trends reported here. For example, there is little information available on how many VIAs are conducted compared to Pap smears. This is an important consideration as VIA does not collect tissue which can be pathologically verified to provide information for the registry and can impact incidence estimations. In addition, coverage of this screening program is assessed with the population census. Therefore, there is little information after 2010 as the next population census will be collected in 2020. Finally, precise information on the extent and magnitude of the occasional screening campaigns limits the extent to which we can attribute past changes in cervical cancer incidence to these strategies. Despite this, the trends reported here fit well with the overall changes in the healthcare system, validating our findings.

Screening programs in other countries have shown similar findings to those presented here. In Nordic countries, where occasional screening campaigns were established prior to a national screening program, the effects of screening on decreasing malignant cervical cancer incidence were seen earlier than expected (Vaccarella et al. 2014). This is similar to our study where a decrease in malignant incidence was seen shortly after implementation of the national screening program, likely due to presence of occasional screening campaigns prior to the national campaign. An important consideration in understanding our projections is the potential for cohort-specific risk to increase due to risk factors. Our projections are based on present cohort risk. This might change due to population-wide changes in sexual behavior and transmission of human papilloma virus (HPV), particularly in younger cohorts. This is seen in almost all European countries, Japan and China, where younger women exhibit increased risk for invasive cervical cancer risk (Vaccarella et al. 2013). Currently, there are ongoing studies in Thailand to assess the cost-effectiveness and feasibility of implementing HPV testing as a primary cervical cancer screening in Thailand, which will serve to limit this expected cohort-specific risk. Although we do not have mortality data in this study, previous studies have shown cervical cancer screening programs have a large impact on mortality as well as incidence due to downshifting of the stage distribution (Landy et al. 2016). However, a study in Sweden found that survival within stages remained constant after introduction of screening (Gustafsson et al. 1997). This is an important point when considering that although malignant tumor incidence is decreasing in women above age 60, the highest proportions of patients still present at regional stages. This could continue to prevent improved survival in this age group. However, women with negative screens between ages 50–64 years have one sixth of the risk of cervical cancer at age 65–83 years, suggesting that

consistent screening might attenuate this issue over time (Castanon et al. 2014).

The success of the screening program has been documented in Southern Thailand by the declining trend of cervical cancer (Sriplung et al. 2014). However, there were some regional variations. For example, the decline in incidence in the south began in 2000, whereas here we report incidence declined in the north beginning in 2004. This is probably due to regional variation in implementation of screening. Regardless, the overall declining trend of cervical cancer is now confirmed in the northern and southern regions of Thailand. To confirm the effect is countrywide and to assess regional variations, comparable studies should be conducted in the remaining regions.

Acknowledgements Dr. Sriplung acknowledges the support from the National Research University Fund, Prince of Songkla University (MED580635S). Dr. Virani acknowledges the Fogarty International Center (04R25TW009345).

Funding This study was funded by the National Research University Fund, Prince of Songkla University (MED580635S) and the Fogarty International Center (04R25TW009345).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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