



Impact of universal health care and screening on incidence and survival of Thai women with cervical cancer: A population-based study of the Chiang Mai Province

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ABSTRACT

Universal Health Coverage (UHC) was implemented in Thailand in 2002. This study aims to compare cervical cancer incidence and survival before and after the implementation of UHC, including the national screening program, in the Chiang Mai population in Northern Thailand. Data of women diagnosed with *in situ* or malignant cervical cancer in Chiang Mai during 1998–2012 were used in our analysis. Annual age-standardized incidence rates (ASR) and age-adjusted relative survival (RS) were estimated for the following three diagnosis periods: period I: 1998–2002 (before UHC), period II: 2003–2007 (UHC implementation) and period III: 2008–2012 (after UHC). The ASR peaked in 2001 at 38 per 100,000, and then subsequently declined to 23 per 100,000 in 2012. The proportion of *in situ* and localized tumors increased in all age groups, while regional tumors declined. In all women (aged 15–89) with malignant cervical cancer or *in situ*, the 5-year RS in Period I, Period II and Period III was 73%, 74% and 77%, respectively; when only malignant cases were considered, the RS was 63%, 61% and 62%, respectively. In the screening target women (aged 30–59) with malignant or *in situ* tumors, the 5-year RS was 84%, 88% and 90%, respectively, in the three periods, while the RS was 71%, 74% and 75%, respectively, in only those with malignant cancers. The introduction of UHC including national cervical cancer screening program has likely reduced the magnitude and severity of cervical cancer and improved the survival of cervical cancer in the screening target age group.

1. Introduction

Cervical cancer screening has been shown to be effective in reducing incidence and mortality rates, even in low and middle income countries. In Thailand, cervical cancer was the top ranking cancer in women from 1998 to 2000, affecting 24.7 per 100,000 women. More recently, the incidence rate has dropped to 14.4 per 100,000 women from 2010 to 2012, which has been partly linked to screening programmes [1,2].

Originally, efforts were made to address cervical cancer through occasional screening campaigns on special occasions such as the birthday of the King and the Queen. In 2002, nationwide universal

health care (UHC) was established in Thailand. Since this health system facilitates a wide-range of health services to the population, it is expected to significantly improve health outcome, reduce occurrence of diseases that can be detected early such as cervical cancer, and may finally lead to an increase in (healthy) life expectancy [3].

In Thailand, UHC evolved over the last 40 years and in 2001 the government decided to implement a full population coverage (starting from 2002) with access to a comprehensive benefit packages including radiotherapy and chemotherapy for cancer as well as access to prevention program such as cervical cancer screening. The system used a primary care-based system where the primary care units act as gate-

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keepers with clear referral pathways for cancer patients and cancer treatment.

The Department of Medical Services of the Ministry of Public Health (MOPH) proposed to screen the entire population of women in Thailand at 5-year intervals from the ages of 35 to 60 years [4]. However, when the organized screening program were implemented under UHC in 2005, the screening recommendations were slightly modified so that only women aged 30–60 years had access to the organized screening program at 5-year intervals using Pap smear or visual inspection with acetic acid (*via*) [5–9]. In 2010, a major effort was subsequently made to scale up cervical cancer screening in Thailand when the MOPH launched the nationwide screening initiative to increase public awareness and the coverage of such programs. Whilst the results on adherence to the screening program are mixed [10–12], the decreasing cervical cancer incidence rates nationally, as well as the downshifting in the stage distribution of malignant tumors [13], suggest that strategies to attenuate the burden of cervical cancer can be considered as a success thus far.

Despite these improvements in the cervical cancer burden in terms of both incidence and mortality, it remains unclear whether the implementation of UHC with access to the organized screening program and cancer treatment has improved the survival of cervical cancer patients in Thailand. To date, there have been few studies that have reported cervical cancer survival in Thailand using a population-based data [14–16], and none of these studies reported cervical cancer survival before and after the implementation of UHC when access to the organized screening program and cancer treatment became widely available in Thailand [17]. Our study therefore aims to evaluate cervical cancer incidence and survival both before and after the implementation of UHC in the Chiang Mai population in Thailand.

2. Methods

2.1. Study population and data

Cervical cancer cases diagnosed during the period of 1998–2012 were extracted from the population-based Chiang Mai Cancer Registry using the International Classification of Diseases 10th edition (ICD-10) codes C53 (malignant) and D06 (*in situ*) in order to assess incidence and survival during the 5-year period during the implementation of the UHC program and organized screening. Individual cancer registration records included patient profiles for all individuals of all ages, including date of birth, age at diagnosis, clinical diagnosis, pathological report, clinical extent of disease before treatment (SEER staging) [18], initial treatment, vital status, and date of death. Linkage to the national mortality database, in combination with active follow-up through scrutiny of patient's medical records, was performed to update vital status up to the end of the study period (31 December 2017). All data were verified, checked for duplication, and were coded and entered into CanReg5 software. Quality of data was assessed in terms of morphologically verified (%MV) and death certificate only (%DCO) cases, as well as completeness of follow-up.

2.2. Statistical analysis

Annual age-standardized incidence rates per 100,000 (ASR) and truncated ASRs (< 30, 30–59, 60+ years) were computed, with the former being plotted to visually illustrate the temporal trends with locally weighted scatterplot smoothing function. Person-years were estimated from census data in 1992, 2002, and 2012. Frequency distributions of age, extent of disease, and treatments were calculated, and differences in the distribution by these indicators in difference periods were tested using chi-square test. For the survival analysis, out of 6876 women recorded with *in situ* or malignant cervical cancer, 152 were excluded for the following reasons: 28 had no follow-up time because the diagnosis of those cases were from death certificate only (DCO) or

diagnosis date was the same as date of death, 4 were outside the study's age range (15–89 year old) and 120 were lost to follow-up with an unknown date of last contact. Relative survival (RS) was estimated using the Ederer II method [19] and adjusted for age according to the international standard as proposed by Corazziari et al. [20] Time-to-event was calculated from date of diagnosis to date of death by any causes. Abridged lifetables by sex and country were obtained from the WHO lifetable database [21]. Mortality rates were expanded using a Poisson regression model to obtain a complete lifetable by 1-year age group and period of diagnosis [21]. To investigate the change in survival over time, RS was estimated for the following three diagnosis periods: period I: 1998–2002 (before UHC), period II: 2003–2007 (UHC implementation) and period III: 2008–2012 (after UHC) and conducted for all females by three age groups: < 30 years old, 30–59 years old (the screening target women) and ≥ 60 years old. The cut-off point for the diagnostic periods was based on year of UHC establishment in 2002 (1998–2002) short-term after UHC implementation (2003–2007) and longer term after UHC implementation (2008–2012). The truncated ASRs for ages < 30, 30–59, and 60+ years were calculated based on the target screening age for women: < 30 years (too young for screening), 30–59 (screening group), and 60+ years (too old for screening). The vital status was updated until the 31 of December 2017 to complete 5-year follow-up on all cancer patients included in this study.

This study was approved by the Research Ethics Committee of Faculty of Medicine at Chiang Mai University.

3. Results

In total, 6876 women were diagnosed with *in situ* or malignant cervical cancer in Chiang Mai between 1998 and 2012, of which 3420 with malignant cervical cancer and 3456 with *in situ* cervical cancer (Table 1).

In general, the age distributions were similar between the periods for both malignant and *in situ* cervical cancer. However, differences by diagnosis period were observed for extent of disease and type of initial treatment at diagnosis among patients with malignant tumors; specifically, patients were more often diagnosed with localized cancers and treated using surgery only or in combination with radio- and/or chemotherapy more recently. The ASR of malignant cervical cancer decreased from 25 per 100,000 in the first period (1998–2002) to 18 per 100,000 in 2008–2012. In contrast, the incidence of cervical *in situ* increased from 17 per 100,000 to 24 per 100,000, respectively.

3.1. Trends in cervical cancer incidence

When assessed annually, the malignant cervical cancer ASR decreased in all age groups, with the overall ASR declining from 42 to 21 per 100,000 in 2000 and 2012, respectively (Fig. 1a). By age group, truncated rates peaked in 1999 for women aged < 30 years at an ASR of 5 per 100,000 and continuously declined until an ASR of < 1 per 100,000 in 2012. In the screening target women, the rates peaked at 65 per 100,000 in 2000, and continuously declined to an ASR of 31 per 100,000 in 2012. In women aged 60 and older, the rates peaked in 2003 (66 per 100,000) and continuously declined to an ASR of 37 per 100,000 in 2012.

In contrast, for *in situ* cervical cancer, the ASR increased in all age groups (Fig. 1b). In women aged < 30 years, the *in situ* cervical cancer rates peaked in 2010 (11 per 100,000) and became stable thereafter. For the screening target women, *in situ* cervical cancer peaked in 2004 at 64 per 100,000 and became stable around 60 per 100,000. In women aged 60 and more, the ASR peaked in 2004 (16 per 100,000) and slightly drop to 14 per 100,000 in 2012.

Table 1
Characteristics of patients diagnosed with *in situ* and malignantcervical cancer in Chiang Mai Thailand, between 1998 and 2012.

Characteristics	Malignant N = 3456			p-value	<i>In situ</i> N = 3420			p-value
	Period I N = 1,127 ASR = 25	Period II N = 1,215 ASR = 23	Period III N = 1,114 ASR = 18		Period I N = 834 ASR = 17	Period II N = 1,236 ASR = 23	Period III N =,1350 ASR = 24	
Age group				0.076				0.338
15-29	29 (3%)	23 (2%)	11 (1%)		47 (5%)	59 (5%)	88 (7%)	
30-59	849 (75%)	906 (75%)	844 (76%)		748 (90%)	1115 (90%)	1188 (88%)	
≥ 60	249 (22%)	286 (23%)	259 (23%)		39 (5%)	62 (5%)	74 (5%)	
Extent of disease				< 0.001				
Localized stage	444 (39%)	563 (46%)	531 (48%)					
Regional stage	597 (53%)	561 (46%)	508 (46%)					
Distant stage	41 (4%)	53 (5%)	62 (5%)					
Missing	45 (4%)	38 (3%)	13 (1%)					
Initial treatment				< 0.001				< 0.001
No treatment	131 (12%)	224 (19%)	83 (8%)		141 (17%)	427 (35%)	311 (23%)	
Surgery only	262 (23%)	367 (30%)	393 (35%)		669 (80%)	793 (64%)	1029 (76%)	
Radiotherapy only	451 (40%)	244 (20%)	168 (15%)		6 (1%)	5 (< 1%)	0 (0%)	
Surgery + RT/CT or other	283 (25%)	380 (31%)	470 (42%)		18 (2%)	11 (1%)	10 (1%)	

Period I covers cases diagnosed in 1998–2002, period II in 2003–2007 and period III in 2008–2012; ASR: Age-standardised incidence rate per 100,000 women; p-value from Chi-square test.

Note: Missing treatment data were considered as no receiving any treatment (No treatment).

3.2. Extent of disease

Fig. 2 shows the distribution of disease extent by age group for each diagnosis period. The proportion of *in situ* and localized tumor increased in all age groups while regional tumors declined. Distant tumors also decreased in women aged < 30 years, but was stable in the screening target women and increased in women aged 60 or more.

3.3. Survival by period and target population

Figs. 3a and b show the RS for malignant and *in situ* tumours according to the three periods and target groups. Overall, for women aged 15–89 years, the combined RS (malignant and *in situ*) was similar between the two first periods, but substantially higher in the last period (2008–2012). For instance, while the RS estimates in the first period (1998–2002) was 88.8% at 1-year, 77.8% at 3-years and 73.0% at 5-years post-diagnosis, the RS estimates increased to 90.3%, 80.5% and 77.0%, respectively, in the most recent period (2008–2012). In the

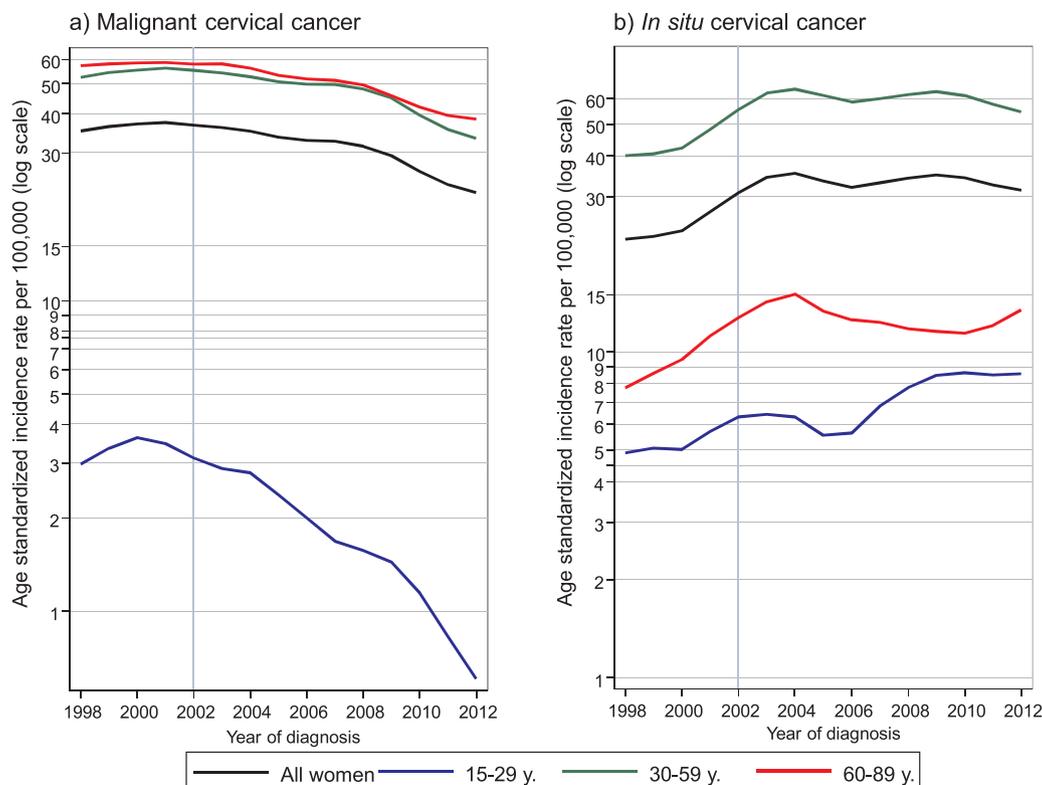


Fig. 1. Age-standardized incidences rate by age groups (in log scale). Grey vertical line indicates year of implementation of universal health care in 2002. a) Malignant cervical cancer b) *In situ* cervical cancer.

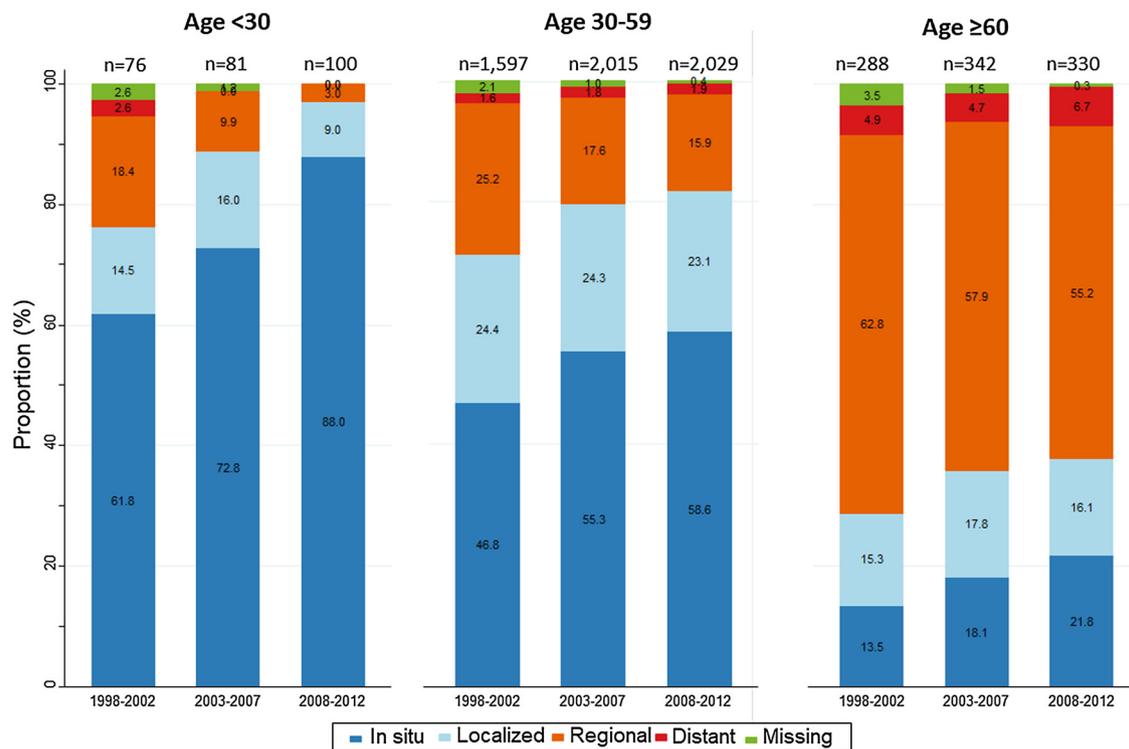


Fig. 2. Distribution of disease extent (in proportion, %) by age groups over three periods of diagnosis 1998–2002, 2003–2008 and 2009–2012.

screening target women, the RS of cervical cancer dramatically improved in period II (1-year RS = 96.5%, 3-year RS = 90.6% and 5-year RS = 88.5%) compared to period I (1-year RS = 93.5%, 3-year RS = 86.3% and 5-year RS = 83.9%), and continued improving in period III (1-year RS = 96.9%, 3-year RS = 92.4 and 5-year RS = 90.4%).

Finally, Figs. 3c and d show the RS estimates only for malignant cases, in all women (15–89 years-old) and for the screening target group (30–59 years-old) by period. The screening target women had higher survival estimates than all ages combined. In all ages combined, the RS was similar in all periods; specifically, the 1-year, 3-year and 5-year RS were 85%, 70% and 63%, respectively in period I, and 86%, 68% and 61%, respectively in period II and 86%, 70%, and 62%, respectively in period III (Fig. 3c). In the screening target women, the RS of cervical cancer improved in period II (1-year RS = 93%, 3-year RS = 80% and 5-year RS = 74%) compared to period I (1-year RS = 89%, 3-year RS = 76% and 5-year RS = 71%), and continued improving in period III (1-year RS = 92%, 3-year RS = 81% and 5-year RS = 75%) (Fig. 3d). The RS of women age < 30 and age ≥ 60 are presented as supplementary files.

4. Discussion

Our study noted a peak in cervical cancer incidence in 2001 with an ASR of 38 per 100,000, which then subsequently declined to 23 per 100,000 in 2012. Conversely, we observed a substantial increase in the rate of *in situ* cervical carcinoma, particularly in the screening target women. These findings are similarly exemplified when the proportion of cervical cancers by stage is assessed, with the proportion of *in situ* and localized tumors increasing after 2002. The absence of an immediate increase in incidence after an organized screening program suggests an adequate coverage of opportunistic screening before its implementation. A high incidence was found before UHC appeared in 2002 in our study and the series of Cancer in Thailand [22,23].

Although, we could not directly report on the impact of screening because unavailability of individual data of screening participation, the

increasing proportion of *in situ* and localized cervical cancer, and also higher proportion of treatment for early stage tumor, suggest that these improvements are likely linked to increased UHC coverage, including screening [24]. Unfortunately, there was no information of screening participation prevalence right after the establishment of UHC. Yet, we have incorporated information on the improvement in the screening program's coverage from 51% in 2007 (Period II) to 68% in 2009 (Period III) which were reported based on the analysis of nationally representative household surveys may be related to the further reduction of malignant cervical cancer cases after 2009 observed in our study [12]. Decreasing trends in malignant cervical cancer have been previously reported in southern Thailand since 2000 [25]; this study confirms similar trends in the Northern part of the country, suggesting the wide-ranging impact of UHC including screening. However, some influential factors on cervical cancer incidence *i.e.* education level and socioeconomic conditions, and religion need to be taken into account for strengthening this finding.

In terms of survival, our study observed similar estimates in the different periods assessed among all women with malignant cervical cancer, but an improved survival was found when *in situ* cases were included, with notable increases noted in the latest period of 2008–2012. These findings are likely mainly related to the introduction of the UHC system, coupled with the national screening program which increases the detection of *in situ* tumors that have a better prognosis, as well as better access to adequate treatment and care. Before the introduction of nation-wide UHC, there were several UHC initiatives that only covered at a maximum of 71% of the population with differing care packages [17]. Cancer patients benefited from access to cancer treatments, but the type of treatment and care coverage was lower compared to what was offered after the establishment of UHC.

Using the same sources of data as this current study but for the earlier period of 1993–1997, Sumitsawan et al [14] reported RS of several types of cancer, and found that the 3- and 5-year RS of cervical cancer patients was 68% and 60%, respectively. Continuing the observation reported by Sumitsawan et al, our study found continuous improvement in cervical cancer survival in more recent periods

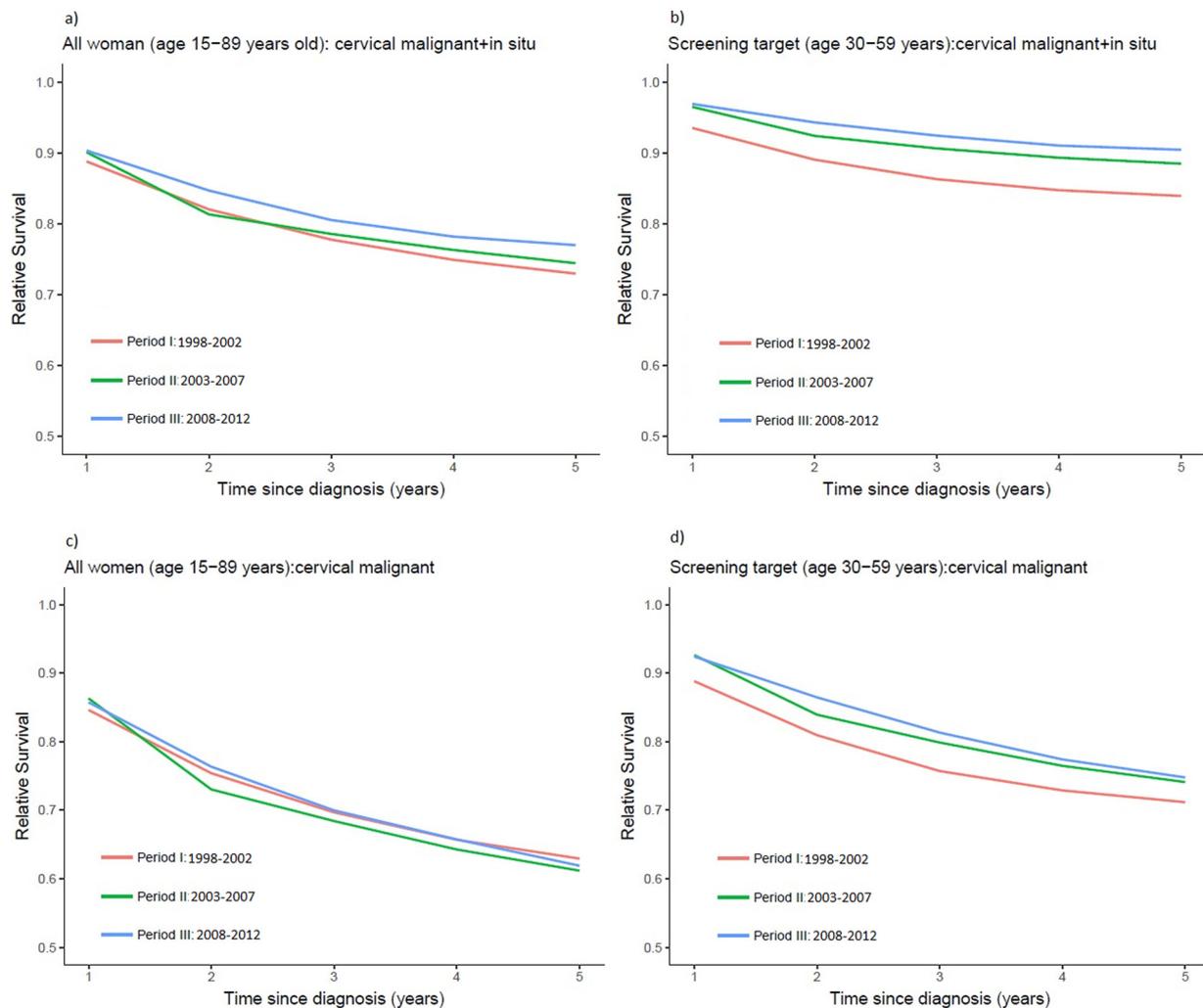


Fig. 3. Relative survival of women diagnosed with insitu and malignant cervical cancer in Northern Thailand by periods of diagnosis: before (Period I: 1998–2002), during (Period II: 2003–2008) and after (Period III: 2009–2012) implementation of Universal Health Coverage, including screening in malignant and *in situ* cases combined (top) and only malignant cases (bottom). a) and c) all ages b) and d) screening target women.

[14,15]. Improvement in survival was seen in both screening targeted women and women outside of the screening age group; this is likely due to the improved stage distribution across age groups, as well as improved access to treatment with the introduction of UHC. Additionally, UHC might influence opportunistic screening participation for women outside of the screening age group.

One limitation of our study is that we cannot distinguish the role of national screening and UHC regarding lead time bias. Although, stage shift and longer survival were found in our study, only data of initial treatment were available and observed. We therefore could not take into account compliance to treatment and improved coverage of the effective treatment protocols which also play important roles in survival time. The observed improvement in survival of cervical cancer in our population is probably due to both national screening and UHC.

There are well-known benefits of cervical cancer screening, but screening has also negative physical and psychological consequences. Although having only small negative impact, the harms of cervical cancer screening need to be mentioned. For example pap smears have been reported to lead to false positive results that further lead to unnecessary follow-up tests and treatments causing anxiety and potential further side effects on these women [26,27]. Treatment of pre-cancerous cervical lesions can also lead to adverse pregnancy outcomes, such as preterm birth [28]. As implementation of screening differs by countries the harms (and also benefits) differ, continuous surveillance

and quality assessment are therefore important to ensure best harm-benefit balance. The new guidelines for HPV screening to prevent cervical cancer are expected to bring further change that still needs to be studied.

Further improvements in early detection and survival in non-target age groups could be achieved through increased awareness and education of the signs of cervical cancer, particularly among women above 60 years age as they continue to have the highest proportion of regional and distant stage of cancers. Furthermore, women aged > 60 years may see improvements in the future if they undergo regular screening when they are younger (screening target age range). In our study, we included women diagnosed with cervical cancer at age 60 in the not-screened group while this is not the case in Thailand. However, the proportion of women diagnosed with cervical cancer at this age is relatively small, only 3% out of those aged 30–60, so the inclusion of this group will not substantially change our conclusion.

In Thailand, the optimal strategies to detect early stage of cervical cancer have been investigated. A study found that primary HPV testing is more cost-effective than cytology testing for cervical cancer with 5-year intervals of screening in Thai women [29]. However, HPV testing has not been established for cervical cancer screening in Thailand. This may be due to limited resources and competing demands for screening for other common cancer sites such as colorectal cancer, which has been included in the national screening program since 2018 using fecal

immunochemical test (FIT) [30].

Indeed Thailand has an important sexually transmitted disease (STD) control actions, which include prevention of HIV and HPV. The prophylactic quadrivalent vaccine that could additionally prevent cervical cancer in Thai population is likely cost-effective [31]. However, the HPV vaccine has been licensed in Thailand since 2007, only a very small proportion of parents have actually vaccinated their daughters *i.e.* 3% [32]. The government of Thailand has recently started rolling out a free [33], nationwide HPV immunization program for only a specific young woman aged 11 years since in 2018.

Regardless of the test utilized in the cervical cancer program, additional work is needed to increase the coverage of UHC including screening. Although, the UHC in the region was the same across Thailand, the Chiang Mai population is diverse in geography, ethnicity, culture and lifestyle, and thus there are some groups, such as the hill tribes, that cannot access medical care and cervical cancer screening because of lack of knowledge, low socioeconomic conditions, and prohibition by their religion [34]; indeed, mortality declines have been shown to vary depending on the geographical area assessed [35]. Thus, improving coverage throughout the Chiang Mai region and Thailand overall will be a critical step for improving the cervical cancer burden and patient outcomes in the future.

The results of this study are based on only population-based data from the Chiang Mai province in Northern Thailand, which represents only 15% of the Northern Thai population. Moreover, an increase in findings may due to an improvement of the registry systems and the pathological evaluation. However, our analysis is based on population-based data that were collected by the active method since 1986. Therefore, the data is generally considered high quality, with more than 95% of histology verification (%HV) and less than 1% of death certificate only case (%DCO) and the percent of completeness of follow up were more than 85%. Moreover, the cancer *in situ* were also regularly recorded for common sites included the cervix uteri.

5. Conclusion

In this study, we show reducing incidence and improvements in the RS of cervical cancer, particularly in screening target women (women age 30–60), using population-based data from Chiang Mai in Northern Thailand. These improvements is likely to be due to the implementation of UHC including the national cervical cancer screening. Further work is needed to evaluate the current health care system and screening programs, as well as to improve coverage of the cervical cancer screening program to further improve the health impact on the population.

Authors' contributions

Patumrat Sripan contributed to the conception and design, performed the statistical analysis, interpreted results and drafted the manuscript.

Isabelle Soerjomataram and Imjai Chitapanrux contributed equally to the conception and design, interpreted results and drafted the manuscript.

Donsuk Pongnikorn and Ekkasit Tharavichitkul contributed interpretation of data and revised the manuscript.

Miranda M Fidler-Benaoudia, Adalberto Miranda-Filho and Aude Bardot contributed to the conception and design and revised the manuscript.

Narate Waisri, Chirapong Hanpragopsuk and Puttachart Maneesai performed clinical data acquisition and revised the manuscript.

All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.canep.2019.101594>.

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