RESEARCH ARTICLE

Spatial and Temporal Analyses of Cervical Cancer Patients in Upper Northern Thailand

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Abstract

Background: Cervical cancer is a major public health problem worldwide. There have been several studies indicating that risk is associated with geographic location and that the incidence of cervical cancer has changed over time. In Thailand, incidence rates have also been found to be different in each region. **Methods:** Participants were women living or having lived in upper Northern Thailand and subjected to cervical screening at Maharaj Nakorn Chiang Mai Hospital between January 2010 and December 2014. Generalized additive models with Loess smooth curve fitting were applied to estimate the risk of cervical cancer. For the spatial analysis, Google Maps were employed to find the geographical locations of the participants' addresses. The Quantum Geographic Information System was used to make a map of cervical cancer risk. Two univariate smooths: x equal to the residency duration was used in the temporal analysis of residency duration, and x equal to the calendar year that participants moved to upper Northern Thailand or birth year for participants already living there, were used in the temporal analysis of the earliest year. The spatial-temporal analysis was conducted in the same way as the spatial analysis except that the data were split into overlapping calendar years. **Results:** In the spatial analysis, the risk of cervical cancer was shown to be highest in the Eastern sector of upper Northern Thailand (p-value <0.001). In the temporal analysis of residency duration, the risk was shown to be steadily increasing (p-value =0.008), and in the temporal analysis of the earliest year, the risk was observed to be steadily decreasing (p-value=0.016). In the spatial-temporal analysis, the risk was stably higher in Chiang Rai and Nan provinces compared to Chiang Mai province. According to the display movement over time, the odds of developing cervical cancer declined in all provinces. **Conclusions:** The risk of cervical cancer has decreased over time but, in some areas, there is a higher risk than in the major province of Chiang Mai. Therefore, we should promote cervical cancer screening coverage in all areas, especially where access is difficult and/or to women of lower socioeconomic status.

Keywords: Spatial and temporal analyses- quantum geographic information system- cervical cancer- Thailand

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Introduction

Cervical cancer is one of the most common cancers in women (National Cervical Cancer Coalition, 2016) and it is a major public health problem worldwide with, in 2012, an estimated 527,600 new cases and 265,700 deaths caused by the disease (World Health Organization, 2016). Of these, over 50% of the deaths occurred in Asia (144,400 deaths) (Torre et al., 2012). In Thailand between 2010 and 2014, the overall age standardized rate (ASR) of cervical cancer was 14.4 per 100,000 and 18.2 per 100,000 in Northern Thailand (Imsamran et al., 2015), and the mortality rate from cervical cancer was 5.9 per 100,000 in Thailand and 6.7 per 100,000 in Northern Thailand (National Economics and Social Development Board, 2016), both sets of figures indicating that there is a higher incidence of the disease in the Northern region.

Risk factors for the occurrence of cervical cancer have been identified and show that a higher risk of the disease is associated with age, Human Immunodeficiency Virus infection, several full-term pregnancies (Cancer Research UK, 2015), and smoking (American Cancer Society, 2015). Moreover, it has been found that geographical location is also associated with the risk of cervical cancer (Cheng et al., 2011; Ahmadi and Zahrani, 2013; Walter et al., 1994; Hernández et al., 2013). Cheng (2011) investigated geographical patterns of incidences and epidemiological characteristics of cervical cancer using geographically weighted Poisson regression, and found that incidence rates of cervical cancer varied spatially across England. Similarly, the National Cancer Institute reported that the incidence of cervical cancer was different

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in each region in Thailand based on data from the Cancer Registry located in various regions across the country (Imsamran et al., 2015).

Several studies have reported that trends of cervical cancer incidence vary over time (Vaccarella et al., 2013; Sriplung et al., 2014; Du et al., 2015). For example, Vaccarella (2013) assessed trends in cervical cancer across 38 countries in five continents. They found that during 1998–2002, ASRs decreased in several countries, except in Eastern European, Thailand, and Uganda.

Our study is the first to consider geographic location and time together as factors associated with risk of cervical cancer using data collected from the Chiang Mai Cancer Registry and Department of Obstetrics & Gynecology, Faculty of Medicine, Chiang Mai University. This source of data provides geocoded residential histories and information on confounders, creating an important dataset to use for a spatial-temporal analysis of participants' residency over five decades. The aim of our study is to ascertain cervical cancer risk during 2010-2014 in upper Northern Thailand according to geographical location using spatial-temporal analysis.

Materials and Methods

Study area and data

In this study, participants were women who lived in upper Northern Thailand and received cervical screening at Maharaj Nakorn Chiang Mai Hospital between 1 January 2010 and 31 December 2014. Data from the Chiang Mai Cancer Registry and Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University were used in the analysis. For this study, we focused on data from upper Northern Thailand, which has eight provinces: Chiang Mai, Lamphun, Lampang, Phrae, Nan, Phayao, Chiang Rai, and Mae Hong Son.

Sample size calculation was performed by using Rosner's formula (Rosner, 2000) with parameters:

$p_1 = p_{(exposure|case)} = 0.016 \quad p_2 = p_{(exposure|control)} = 0.080$

$$\bar{p} = \frac{p_1 + p_2 r}{1 + r} = 0.048$$

$$\bar{q} = 1 - \bar{p} = 0.952$$

$$r = \frac{n_{control}}{n_{case}} = 1$$

$\alpha = 0.1$ and $\beta = 0.2$.

Then a minimum sample size of 1,000 women including 500 cases and 500 controls were needed, where cases were women with cervical cancer diagnosed and controls were women without cervical cancer during 2010-2014. We used simple random sampling to select the cases from the list at the Chiang Mai Cancer Registry (100 cases in each year). The controls were randomly selected from OPD-cards. Five participants who had received cervical screening at Maharaj Nakorn Chiang Mai Hospital were randomly chosen daily for 20 working days according to the year of screening.

Variables

The characteristics variables included in this study were age at cervical screening (years), weight (kg.), height (cm.), number of sexual partners, number of pregnancies, smoking (yes/no), and alcohol consumption (yes/no).

The variables for spatial, temporal, and/or spatial-temporal analyses were age at cervical screening, weight, number of sexual partners, number of pregnancies, smoking status, alcohol consumption, location of participant address (latitude, longitude), earliest year (the year a participant moved to upper Northern Thailand or birth year for participants already living there), and residency duration (the difference between the date of cervical screening and earliest year in the study area) (years). All variable values were extracted from the literature and available in the database.

Comparison of the characteristic variables between the case and control groups

Baseline characteristics of women were compared between case and control groups using Chi-square tests for discrete variables and Wilcoxon rank-sum (Mann-Whitney) tests for continuous ones. A p-value of less than 0.05 indicates a significant difference between the case and control groups.

Generalized additive models

Generalized additive models (GAMs) were used to estimate the risk of cervical cancer during the time period 2010–2014 for the spatial, temporal, and spatial-temporal analyses. Participants who moved away from the study area and later returned were excluded from the study.

A GAM is a non-parametric/semi-parametric regression method that is able to analyze binary data while adjusting for confounders (Hastie and Tibshirani, 1999) and can be written in the form

Logit $[p(x_1, x_2)] = S() + \gamma' Z$

Where Logit $[p(x_1, x_2)]$ is the natural log of odds, $S()$ is the Loess smooth function (univariate smooth $S()$ or bivariate smooth $S(x_1, x_2)$), Z is a vector of covariates, and γ is a vector of parameters (Vieira et al., 2008).

In the spatial analysis, bivariate smooth with x_1 = latitude, x_2 = longitude was used (Vieira et al., 2005; Vieira et al., 2008). Results from the GAM were exported from R and loaded into the Quantum Geographic Information System to generate the map of cervical cancer risk. The results on the cervical cancer risk map were reported for 23 zones determined by geography, transportation, communication, population number, and number of schools (Donprasit, 2016).

In temporal analysis, univariate smooth with x = residency duration was used in the temporal analysis of residency duration and x = calendar year that participants moved to upper Northern Thailand or birth year for participants already living there was used in the temporal analysis of earliest year. The optimal span size in the temporal analysis of the earliest year was used to determine the timeframe of the spatial-temporal analysis, with the size of the span being optimal for each dataset. Too small a span size produces a 'spikey' line which causes errors in the model, whereas too wide a span results in a model with important local trends omitted (Fielding, 2015).

A GAM was used in the spatial-temporal analysis

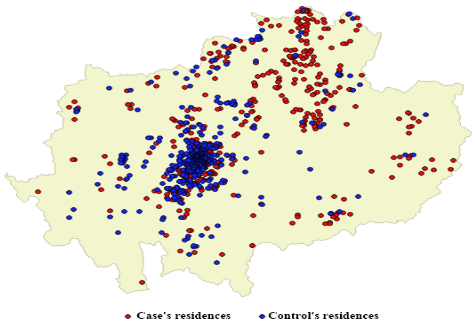

Figure 1. Point Map of the Distribution of Participants in the Study Area

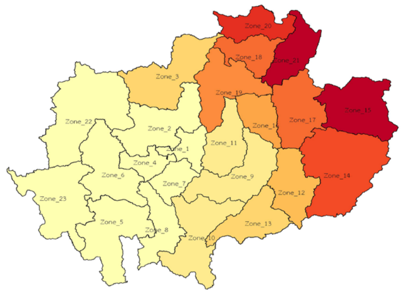

Figure 2. Spatial Analysis of Cervical Cancer Risk During 2010- 2014 in Upper Northern Thailand

in much the same way as in the spatial analysis, but the data were split into overlapping calendar years over a 30-year timespan (determined by the span size from the temporal analysis of the earliest year). The first timeframe was 1936–1965, the second timeframe 1937-1966, and moved year by year until the last timeframe 1962-1991, producing a total of 27 timeframes. The optimal span size from the first timeframe was used for all timeframes. After this, the maps of cervical cancer risk were made for each timeframe. The results on a cervical cancer risk map in a spatial-temporal analysis were reported by 7 provinces instead of 23 zones (district groups) because there was a lack of data for many of the zones when we moved the time frames.

The optimal span size was identified using a deviance test used to compare the models with and without the smooth term, where the null hypothesis is that the model fits versus the alternative hypothesis that the model does not fit. Many models were built, each with a different span size (0.25-0.95 in increments of 0.05). The best model (optimal span size) has the lowest residual deviance, and the null hypothesis was that the risk of cervical cancer does not depend on the smooth term (Webster et al., 2006).

Geographical Information System

Residential addresses collected from OPD-card were used for the spatial analysis. Some participants lived at more than one address in upper Northern Thailand. In this study, the participants consisted of 1,000 women; 14 of these had two and one had three residential addresses during the cervical screening year. Therefore, 1,016 records of residence address were used in the spatial analysis. Residential addresses that were outside of upper Northern Thailand for part of this period were excluded from the study.

Google Maps was used to find the participants' addresses using the geographic coordinate system (latitude, longitude) to pinpoint their location to the nearest village. The spatial analysis included all locations (n = 1,016) from the residential history.

Results

Baseline characteristics

The results in Table 1 show that the characteristic attributes of the case and control groups were statistically different except for height. The median age and weight of the controls was higher than those of the cases, and more than three quarters of the cases had one partner, with less of the controls having had one partner, and more than three quarters of cases and controls had been pregnant between 1 and 4 times. Nearly all of the cases and controls did not smoke or consume alcohol.

Spatial analysis

A point map of the distribution of participants in the study area is shown in Figure 1. Figure 2 Spatial analysis of cervical cancer risk during 2010- 2014 in upper Northern Thailand shows the predicted odds ratio (OR) ranging from 1.00 to 26.60 after adjustment for weight, smoking status, alcohol consumption, age at cervical screening, number of partners, and number of pregnancies. The optimal span for this analysis was 60%. OR values were found to be highest in the East of upper Northern Thailand (Zone_14 to Zone_21). A test for deviance from the null hypothesis that the risk of cervical cancer

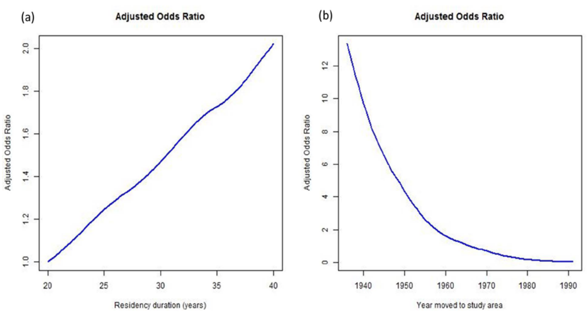

Figure 3. Temporal Analysis of (a) Residency Duration and Temporal Analysis of (b) Earliest Year

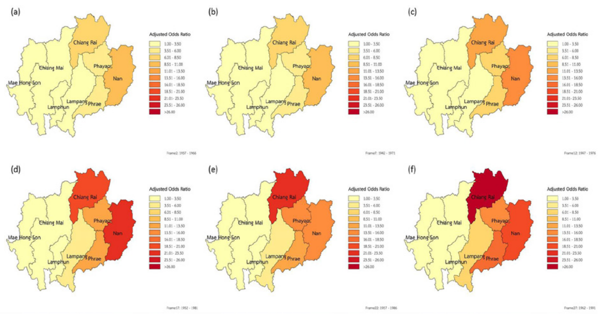

Figure 4. Spatial-Temporal Analysis of Cervical Cancer Risk During 2010- 2014 in Upper Northern Thailand

Table 1. Baseline Characteristics of Individuals

Demographics	Control group	Case group	p-value
Age at cervical screening (years)	n= 500	n= 500	
Median (IQR)	48.0 (37.5 to 55.5)	52.0 (46.0 to 60.8)	<0.001**
Weight (kg.)	n= 500	n= 500	
Median (IQR)	56.0 (48.0 to 60.0)	53.0 (46.0 to 59.3)	<0.001**
Height (cm.)	n= 133	n= 400	
Median (IQR)	154.0 (150.0 to 158.5)	154.0 (149.0 to 157.0)	0.126**
Number of partners	n= 408	n= 496	
Never have sex	44 (11%)	4 (1%)	<0.001*
1 person	315 (77%)	315 (64%)	
more than 1 person	49 (12%)	177 (35%)	
Number of pregnancy	n= 483	n= 497	
Never have pregnancy	101 (20%)	6 (1%)	<0.001*
1- 4 times	379 (79%)	443 (89%)	
more than 4 times	3 (1%)	48 (10%)	
Smoking	n= 500	n= 500	
Yes	2 (1%)	65 (13%)	<0.001*
No	498 (99%)	435 (87%)	
Alcohol drinking	n= 500	n= 488	
Yes	13 (3%)	42 (9%)	<0.001*
No	487 (97%)	446 (91%)	
Residency duration (years)	n= 500	n= 500	
Median (IQR)	48.0 (32.0 to 64.0)	52.0 (36.3 to 67.8)	<0.001**
Earliest year	n= 500	n= 500	
Median (IQR)	1964 (1948 to 1980)	1960 (1945 to 1975)	<0.001**

IQR, Interquartile range; *p-value from Chi-square test; **p-value from Wilcoxon rank-sum (Mann-Whitney) test

does not depend on location yielded a p-value < 0.001, which means that there is a highly significant association between location and risk of cervical cancer.

Temporal analysis

The results of the temporal analysis of residency duration are presented in Figure 3 Temporal analysis of (a) residency duration. Predicted ORs range from 1.00 to 2.11 after adjustment by age at cervical screening, weight, smoking status, alcohol consumption, number of partners, and number of pregnancies. The optimal span was 50%, and the risk of cervical cancer during 2010–2014 was found to be steadily increasing. A test for deviance from the null hypothesis that the risk of cervical cancer does not depend on duration produced a p-value = 0.008, which indicates a significant association between residency duration and risk of cervical cancer.

The results of temporal analysis of earliest year are shown in Figure 3 Temporal analysis of (b) earliest year. Predicted ORs range from 0.03 to 13.3 after adjustment for age at cervical screening, weight, smoking status, alcohol consumption, number of partners, and number of pregnancies. The optimal span was 60%, and the risk of cervical cancer during 2010–2014 was found to be steadily decreasing. A test for deviance from the null hypothesis that risk of cervical cancer does not depend on the earliest year a participant lived in the study area produced a p-value of 0.016, proving a significant association between earliest year and risk of cervical cancer.

Spatial-temporal analysis

The data was split into overlapping calendar years over a 30-year timespan. The first timeframe was between the years 1936 and 1965, and was moved a year at a time until 1962- 1991, for a total of 27 map timeframes. The optimal span size for all timeframes was 70%. Figure 4 Spatial-temporal analysis of cervical cancer risk during 2010- 2014 in upper Northern Thailand shows the risk of cervical cancer during 2010-2014 in upper Northern Thailand selected at random from (a) to (f) to: 2nd, 7th, 12th, 17th, 22nd, and 27th timeframes. Selected timeframes show changing values and position of cervical cancer in upper Northern Thailand based on participants' historical residences.

Figure 4 (a) shows that predicted ORs range from 1.0 to 9.6 for timeframe 2 (1937-1966) with the highest incidence being in Nan province (p-value < 0.001). Figure 4 (b) indicates that predicted ORs span 1.0 to 10.3 for timeframe 7 (1942-1971) with the highest incidence once again being in Nan province (p-value < 0.001). Figure 4 (c) reveals that predicted ORs ranged from 1.0 to 13.7 for timeframe 12 (1947-1976) and were highest yet again in Nan province (p-value < 0.001). Figure 4 (d) shows that predicted ORs range from 1.0 to 22.5 for timeframe 17 (1952-1981) and are once more highest in Nan province (p-value < 0.001). Figure 4 (e) discloses predicted ORs range from 1.0 to 21.9 for timeframe 22 (1957-1986) with the highest being in Chiang Rai province this time (p-value < 0.001). Figure 4 (f) shows predicted ORs range from 1.0 to 28.0 for timeframe 27 (1962-1991) with the highest once again being in Chiang Rai province (p-value < 0.001).

All selected timeframes show highly significant associations between location and the risk of cervical cancer. In particular, the risk was stable higher in Chiang Rai and Nan provinces compared to Chiang Mai province. According to the display of movement across time, odds declined in all provinces.

Discussion

The results of our spatial-temporal analysis show that cervical cancer risk is highly significantly associated to geography location during all timeframes. In particular the risk was stable higher in Chiang Rai and Nan provinces compared to Chiang Mai province. According to the display of movement across time, the odds of contracting cervical cancer declined in all provinces.

Pap smear screening is likely to be a major factor in reducing the occurrence of cervical cancer because cervical screening is used to identify pre-cancerous lesions which can easily be treated to prevent the occurrence of invasive cervical cancer (Peirson et al., 2013). In Thailand, five-yearly pap smear screening has been recommended to test Thai women between 35 and 60 years old by the Ministry of Public Health. However, some hill tribes cannot access this program because some of them have not obtained Thai citizenship. Moreover, because of lack of knowledge, poor socioeconomic conditions, and/or prohibition by their religion, these hill tribes groups may refuse pap smear screening (Aguettant, 1996).

Kritpetcharat (2012) examined the prevalence of cervical cancer in Chiang Rai province using the results of pap smear screening. Their study compared the prevalence of cervical cancer in Akha hill tribe and urban women, and the results showed that the prevalence of abnormal pap smears was higher in Akha women (12.2% vs. 4.5%, p-value <0.05) where the risk factors were marriage at an early age (≤ 17 years old), high pregnancy frequency, multiple partners, and no/low education level. In our analysis, the risk of cervical cancer was found to be high in upper Chiang Mai province and Chiang Rai province, where many hill tribes reside, especially the Akha (Highland Research and Development Institute, 2009).

Several studies have shown a relationship between cervical cancer occurrence and socioeconomic status whereby the incidence of cervical cancer is higher in women of low socioeconomic status (Adler and Ostrove, 1999; Clegg et al., 2009; Froment et al., 2014). In our study, a higher risk of cervical cancer was found in Nan, Phayao, and Chiang Rai provinces where the socioeconomic status of the population is generally lower compared to the reference zone (Chiang Mai). According to economic status in terms of income, expenditure and debt in these three provinces, the average income per household is close to the average expenditure, which means that little remains from the income of households in these provinces for saving. Indeed, in Nan province, average expenditure is higher than income, which has led to increased debt over the five years prior to the period of diagnosis (2010-2014) (National Statistical Office, 2015).

The National Statistical Office reported that women aged between 35 and 59 tend to migrate to others regions; for instance, the number of migrants was 23,334 in 2007, 24,872 in 2008, and 27,113 in 2009 (National Statistical Office, 2015). Since the information on migration by age group during 1936-1991 has not been previously reported, we hypothesize that migration was also prevalent in this study period in women of this age range, which could have affectively decreased the number of cervical cancer cases in upper Northern Thailand. In addition, the pap smear test has been in use since 1952 (Jontasopeepun et al., 2012), and so the increased coverage of pap smear screening could have reduced the occurrence of cervical cancer in Thailand, including the upper Northern part of the country (Wiwanitkit, 2006). In our study, the risk of cervical cancer was shown to be steadily decreasing when reviewing data from the earliest year of the period 1936-1991 onwards.

Retrospective data was used in this study and unfortunately some useful demographic variables, including family history and socioeconomic status, were not available for our analysis. Future research with alternative data sources would be able to address the possible relationship between other covariates and cervical cancer occurrence.

The risk of cervical cancer has been steadily decreasing compared to the past, but in some areas, a higher risk is indicated when compared to Chiang Mai. Therefore, we should promote cervical cancer screening coverage in all areas, especially in those with difficult access and/or with populations of low socioeconomic status.

List of abbreviations

GAMs: Generalized Additive Models
ASR: Age Standardized Rate
HIV: Human Immunodeficiency Virus
DES: Diethylstilbestrol
NCI: National Cancer Institute
OPD: Out Patient Department
QGIS: Quantum Geographic Information System
GIS: Geographical Information System
OR: Odds Ratio

Ethics approval and consent to participate

This study received ethical from Faculty of Medicine, Chiang Mai University Ethics Committees.

Consent for publication

Not applicable

Availability of data and material

This study use data from Chiang Mai Cancer Registry and Department of Obstetrics & Gynecology, Faculty of Medicine, Chiang Mai University. Request for using their data should be addressed to Faculty of Medicine, Chiang Mai University Ethics Committees.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

1.Natthapat Thongsak contributed in literature search, data collection, performed the data analyses and the writing of the manuscript.

2.Imjai Chitapanarux and Prapaporn Suprasert contributed in study design, data collection and reviewing the manuscript.

3.Sukon Prasitwattanaseree contributed in study design and reviewing the manuscript.

4.Walaithip Boonyatisai and Patumrat Sripan contributed in literature search, and reviewing the manuscript.

5.Patrinee Traisathit had primary responsibility for literature search, study design, performed the data analyses and the writing of the manuscript.

All authors contributed to critical revisions of the manuscript and approved the final submitted version.

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