RESEARCH ARTICLE

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Trends in the Incidence of Kaposi's Sarcoma and Non-Hodgkin Lymphoma in Northern Thailand during the Time Period of Universal Access to Antiretroviral Treatment, 1998-2017

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Abstract

Purpose: We evaluated the trends in incidence of Kaposi's sarcoma (KS) and Non-Hodgkin's lymphoma (NHL) over the two decades in northern Thailand during which access to antiretroviral treatments (ART) in Thailand was scaled up. **Methods:** This is retrospective observational study. Data from 1998 to 2017 of patients diagnosed with KS and NHL from three long-standing, population-based cancer registries in northern Thailand (Chiang Mai, Lampang and Lamphun) were used to describe trends in age-adjusted incidence rate (ASR) of these cancers. The annual percent change (APC) of incidence rates were evaluated over this timeframe. **Results:** The incidence of KS significantly increased from 1998 to 2017 in males (APC of 6.9%) and very low incidence for evaluating change in female. NHL incidence significantly increased from 1998 to 2017, 2.2% and 1.8% per year in males and females, respectively ($p<0.001$). **Conclusion:** In the last two decades, the incidence of KS in male and NHL in both sexes have increased in northern Thailand, while the incidence of KS in female remained low. The change in incidences in opposite to the decline in HIV prevalence and increase ART coverage rate supported that other associated factors attributable to the development of KS and NHL should be looked for i.e., environmental, occupational exposures and other infections.

Keywords: Incidence trends- Kaposi's Sarcoma- Non-Hodgkin Lymphoma- Universal health coverage

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Introduction

Kaposi's sarcoma (KS) and Non-Hodgkin's lymphoma (NHL) are two of the most common cancers in people living with human immunodeficiency virus (PLHIV) and those with Acquired Immune Deficiency Syndrome (AIDS) (Scadden, 2003), and both are AIDS-defining illnesses. The risk of developing KS increased by 200–1000-fold in patients with HIV/AIDS, while the risk of NHL was increased by a factor of 70–300 (Cote et al., 1997; Dal Maso et al., 2001; Frisch et al., 2001). In the era of combination antiretroviral treatment (cART), the incidence of these two cancers decreased (Collaboration of Observational et al., 2009; Borges, 2017) in HIV infected people.

After ARTs were introduced in 1992-1998, ART services in the clinical and public health research networks in Thailand started in 1998-2000. In 2002, Thailand established the new Universal Coverage Scheme (UCS) for the remaining 75% of Thai citizen who were not covered by any public health insurance schemes included the Civil Servant Medical Benefit Scheme (CSBMS) for government employees and retirees and their dependents and Social Health Insurance (SHI) for private-sector employees (Tangcharoensathien et al., 2018). ARTs were added to the UCS in 2003, with initial funding support from the Global Fund to Fight AIDS, Tuberculosis and Malaria. The Government Pharmaceutical Organization also began producing generic versions of HIV triple combination therapy in 2003, further expanding access to life-saving HAART. In 2005, antiretroviral treatment was fully reimbursement under UHS. The Thai government

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extended to cover all costs of HIV care from 2006, including antiretroviral medicines and other related services such as voluntary counselling and testing, viral load tests and viral resistance tests for Thai citizen (United Nation Developement program, 2017). The cancer diagnosis and treatment was not initially covered in 2002 but the same year for ART, cancer care such as screening, curative treatment such as surgery, chemotherapy, radiation was included under UHC due to high demand from 2005 (Akaza et al., 2016; Pittayapan, 2016).

HIV prevalence is declining in Thailand. Over half of new infections occurred in population groups with higher risk for contracting HIV, men who have sex with men (MSM) who account for around 40% of new infections each year including transgender people male sex workers, people who inject drugs (PWID) around 3.4%, and female sex worker around 3.2% of new infections (National Monitoring and Evaluation Unit Bureau of AIDS, 2018). The HIV prevalence have been high and not declining in MSM (8.0% in 2010 and 9.2% in 2014) and declining in male sex worker (MSW) but remains very high (16.0% in 2010 and 11.7% in 2014) while the HIV prevalence among female sex worker (FSW) has declined steadily from 2.7% in 2010 to 1.1% in 2014. HIV prevalence among PWID has been on the decline but remains high (21.9% in 2012 and 19.0% in 2014) (National AIDs Committee of Thailand, 2015).

People infected with HIV have a markedly higher risk of KS and NHL compared with uninfected people. Sriplung et al studied trends in the incidence of malignancies related to HIV/AIDS in Thailand during the period 1989–2001, prior to universal access to antiretroviral treatment, using population-based cancer registry in Thailand and found that KS incidence rate slightly increased from 1989–1991 to 1995–1997 while a marked increase in the incidence NHL, from 2.7 per 100,000 for the period 1989–1991 to 4.8 per 100,000 for the period 1999–2001(Sriplung and Parkin, 2004). The data from cancer in Thailand also reported the results in the same direction, incidence rate was stable low for KS and slightly increase from 2001-2003 to 2013-2015 for NHL in male (from 5.0 to 5.7) and in female (from 3.2 to 4.5).

However, the trends in incidence of these HIV-related cancers in different period of time during the expansion of access of ART in Thailand have not been reported. Our study aims to estimate incidence of Kaposi's sarcoma and non-Hodgkin lymphoma in Northern Thailand over two decades during the expansion of access of ART in Thailand.

Materials and Methods

Study design and population

This is population-based retrospective cross-sectional study. Kaposi's sarcoma and non-Hodgkin lymphoma cases diagnosed during the period of 1998-2017 were derived from the population-based cancer registries in three provinces of upper northern Thailand, Chiang Mai from Chiang Mai cancer registry, Lampang and Lamphun from Lampang cancer registry. To calculate disease incidence, the following International Classification of Diseases 10th edition (ICD-10) was used to extract individual data of cancer cases from the cancer registries, C46 for Kaposi's sarcoma cases and C82-85 and C96 for non-Hodgkin lymphoma cases. All data included patient's profiles for example age at diagnosis, clinical diagnosis, pathological report, clinical extent of disease were verified, checked for duplication, coded and entered into CanReg5 software by the trained cancer registrars. The data quality was evaluated based on proportion of cancer diagnosis that have been morphologically verified (MV%) and proportion of cancer diagnoses from death certificate only indicate (DCO%). MV% more than 80% and lower than 5% of DCO was considered satisfactory (Bray and Parkin, 2009).

Data from the Global Health Observatory, WHO (The Global Health Observatory; The Global Health Observatory) were used to described trends in the number of people living with HIV (all ages) and percent of antiretroviral therapy coverage among people living with HIV in Thailand, from 2005 to 2019.

Statistical analysis

The age at cancer diagnosis of patients were reported as median and interquartile ranges (IQRs) and as counts and percentages for sex, histologic classification, anatomic sites of cancer. Annual age-standardized incidence rates (ASR) per 100000 person-years were computed and plotted to illustrate temporal trends using the denominators (person-years) that were estimated from census data in 1992, 2002, and 2012. Using a Monte Carlo permutation method (Kim et al., 2000), a Joinpoint regression model was used to identify statistically significant change of trends and the annual percent change (APC) in each trend segment. All reported P-values are 2 sided and P-values <0.05 was considered statistically significant. The STATA software version 14 (Stata Corp, College Station, TX) was use to performed the data management and descriptive statistical analyse and R program was used to plot all incidence trends.

Ethics statement

The study was approved by the institutional review board at the Research Institute for Health Sciences, Chiang Mai University (Certificate approval number 53/2020).

Patient and Public Involvement statement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Study population

Fifty-one patients diagnosed with KS were included in this analysis, 42 (82%) male and 9 (18%) female, all diagnosed in three provinces of northern Thailand (Chiang Mai, Lampang and Lamphun) between 1998 and 2017. The median age was 34 years (IQR: 25 to 44 years). There were 3,612 patients diagnosed with NHL in the same time period and study areas, 2,014 (56%) males and 1,598 (44%) were females, with a median age of 59 years

Table 1. Characteristics of Patients Diagnosed with Kaposi's Sarcoma Non-Hodgkin Lymphoma in northern Thailand, 1998-2017

Characteristics	1998-2002	2003-2007	2008-2012	2013-2017	Total
Kaposi's Sarcoma					
Number of case	5	9	17	20	51
Sex					
Male	4 (80)	5 (56)	15 (88)	18 (90)	42 (82)
Female	1 (20)	4 (44)	2 (12)	2 (10)	9 (18)
Median age (IQR), year	33 (24-44)	27 (20-33)	23 (21-37)	32 (26-46)	34 (25-44)
Non-Hodgkin Lymphoma					
Number of case	611	811	1,005	1,185	3,612
Sex					
Male	350 (57)	449 (55)	559 (56)	656 (55)	2,014 (56)
Female	261 (43)	362 (45)	446 (44)	529 (45)	1,598 (44)
Median age (IQR), year	55 (40-68)	58 (45-70)	58 (47-71)	60 (51-72)	59 (46-70)
Histology					
Large B-cell, diffuse	265 (43)	510 (63)	653 (65)	795 (67)	2,223 (62)
Burkitt lymphoma	18 (3)	13 (2)	11 (1)	17 (1)	59 (2)
Others	328 (54)	288 (35)	341 (34)	373 (32)	1,330 (37)
Anatomic sites					
Lymph node	378 (62)	440 (54)	504 (50)	611 (52)	1,933 (54)
Head, face and neck	175 (29)	213 (26)	272 (27)	342 (29)	1,002 (28)
Intrathoracic	4 (1)	3 (<1)	11 (1)	10 (1)	28 (1)
Intra-abdominal	29 (5)	22 (3)	22 (2)	34 (3)	107 (3)
Axilla and arm	29 (5)	23 (3)	31 (3)	35 (3)	118 (3)
Inguinal region or leg	22 (4)	46 (6)	58 (6)	67 (6)	193 (5)
Pelvic	5 (1)	13 (2)	9 (1)	1 (<1)	28 (1)
Multiple regions	3 (<1)	0 (0)	2 (<1)	2 (<1)	7 (<1)
Not otherwise specified	111 (18)	120 (15)	99 (10)	120 (10)	450 (12)
Non-lymph node	233 (38)	371 (46)	501 (50)	574 (48)	1,679 (46)

(interquartile range: 46 to 70 years). The main histologic types of NHL found in this population was diffuse (62%). Two percent of patients were diagnosed with Burkitt lymphoma. The most common location of NHL was in the lymph nodes of the head, face and neck (28%) (Table 1).

Trends in incidence of NHL and KS

The Zero join point model was the best fit for describing the incidence trend of NHL and KS. In males, KS incidence rates significantly increased, from an estimated ASR of 0.09 per 100,000 person-years in 1998

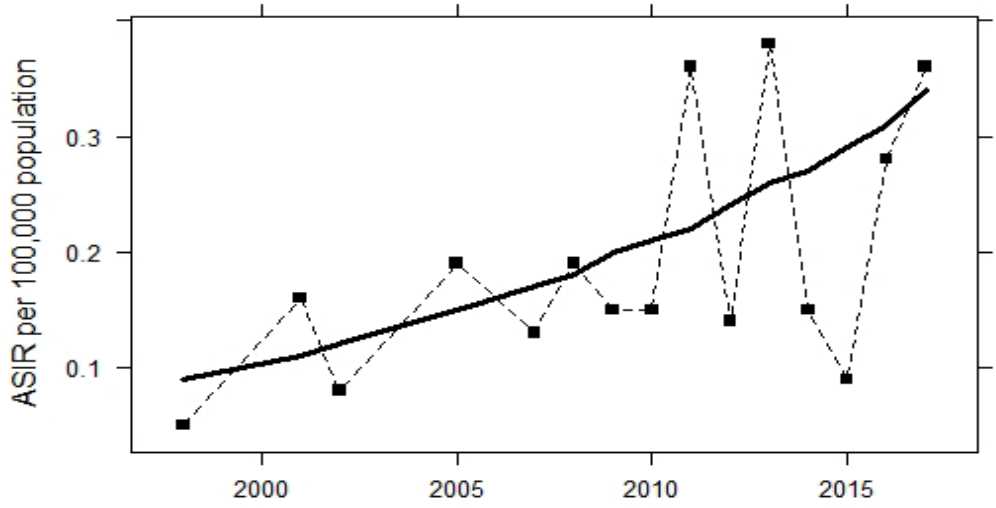

Figure 1. Trends in Incidence of Kaposi's Sarcoma in Male

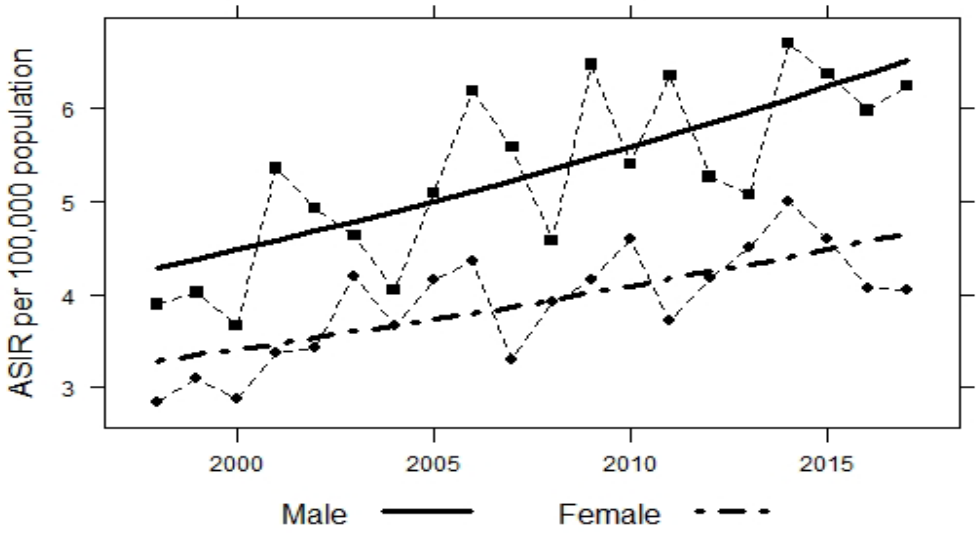

Figure 2. Trends in Incidence of Non-Hodgkin Lymphoma by Gender

to 0.34 cases per 100,000 person-years in 2017, an APC of 6.9% (95%CI: 1.8%, 12.3%) (Figure 1). Trends in KS incidence rate in females could not be properly estimated owing to the very low numbers of females diagnosed with the disease during the study period.

Estimated NHL incidence rates significantly increased in males, from an ASR of 4.29 cases per 100,000 person-years in 1998 to 6.51 cases per 100,000 person-years in 2017, an APC of 2.2% (95%CI, 1.2%-3.3%). Significant increases in NHL incidence was also found in females, an APC of 1.8% (95%CI, 0.9%-2.8%), from 3.29 cases per 100,000 person-years in 2002 to 4.65 cases per 100,000 person-years in 2017 (Figure 2).

For the incidence trend of the most common histological type of NHL, diffuse increased from an ASR of 1.75 cases per 100,000 person-years in 1998 to 3.49 cases per 100,000 person-years in 2017, an APC of 3.8% (95%CI, 2.1%-5.5%). During this same timeframe, the incidence of Burkitt lymphoma did not significantly increase (p=0.4) (Figure 3).

Trends in HIV prevalence and ART coverage

The estimated ART coverage among Thai people living with HIV after the establishment of universal health coverage based on data from WHO has been increasing, 16% in 2005, 36% in 2010, 56% in 2015 and 80% in 2019 (Supplementary Figure 1). The estimated number of people living with HIV (all ages) decreased from 720,000 in 2000 to 470,000 in 2019 (Supplementary Figure 2).

Discussion

Over two decades, the incidence of KS and NHL have increased in northern Thailand. Our study found a higher incidence of KS in males compared to females in northern Thai population during a period from 1998 to 2017. Globally, it has been reported that KS incidence was 2–3- fold higher in men than in women (Cook-Mozaffari et al., 1998). In addition, the incidence rate of this disease in males increased from ASR of 0.09 to 0.34 cases per 100,000 person-years during the study period, 1998-2017,

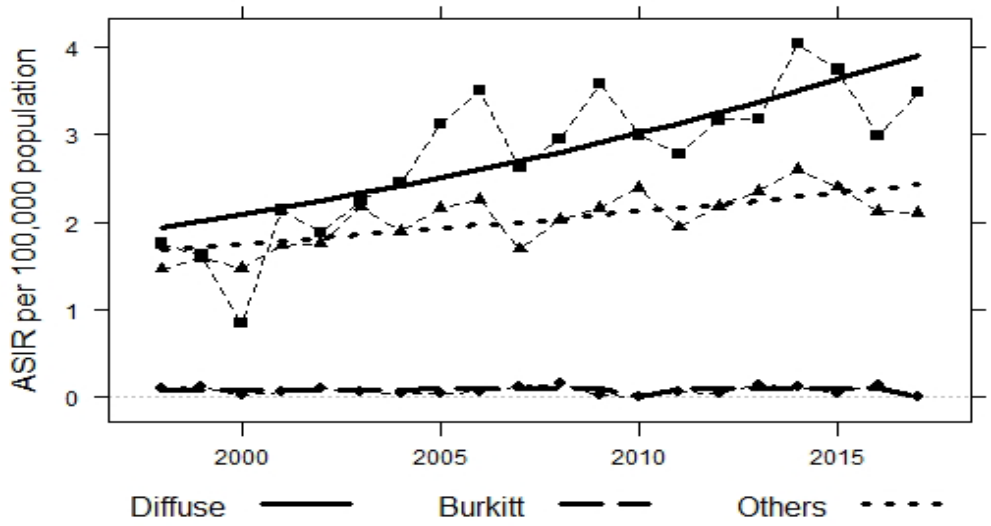

Figure 3. Trends in incidence of Non-Hodgkin Lymphoma by Subtype

while this malignancy in females remained very rare, an event too low to reliably describe incidence trends. The incidence of HIV in Thailand is also higher in males in particular in MSM than females (National Monitoring and Evaluation Unit Bureau of AIDS, 2018).

NHL is the most complication found in people who living with HIV (Chaisson et al., 1998). Although, a systematic review study showed that the widespread use of HAART could reduce the incidence KS and NHL in HIV-infected people (International Collaboration on and Cancer, 2000), risk of AIDS-defining NHL such as Burkitt lymphoma continuously elevated in HIV infected people (Gibson et al., 2014). Moreover, the decrease incidence of NHL was not observed in a multicenter cohort study of HIV infected homosexual/bisexual men (Jacobson et al., 1999). Thus, it was not clear whether the ART reduce NHL incidence.

In the general Thai population, a study using population-based data from registries in different regions of the country, Chiang Mai and Lampang in the north, Khon Kaen in the northeast and Songkla in the south of Thailand and the metropolitan area of Bangkok reported that trends in the incidence of KS and NHL increased during 1989-2001, the period prior to implementation of universal access to ART in 2006 (Sriplung and Parkin, 2004), similar to what was found in other Asian countries including the Republic of Korea, and Japan (Miranda-Filho et al., 2019). In our study, the significant increase in incidence of NHL were found in both genders during 1998-2017, in three provinces of northern Thailand while the decrease of estimated number of people living with HIV (all ages) was shown in Thai population (Supplementary Figure 2). This decrease of HIV was possibly because of the wider coverage of antiretroviral therapy in Thailand (Supplementary Figure 1). The decrease of HIV/AIDS incidence also found in northern Thailand from 1997 to 2006 in Chiang Mai province (Sriwattanapongse W et al., 2010). The incidence of NHL may not specifically link with HIV in the era of cART in Northern Thai population.

Our results showed a stable trend of Burkitt lymphoma in the northern Thai population. As NHL is one of several cancers that arise from a suppressed immune system, particularly Burkitt lymphoma. The increasing NHL incidence could be induced by immunosuppression and a causal link between infectious agents, and lymphomagenesis has also been determined, particularly for human T-cell leukemia/lymphoma virus type 1 (HTLV-1), Epstein-Barr virus (EBV), and Helicobacter pylori infections (Knowles, 2003; Muller et al., 2005; Wong et al., 2022). However, the prevalence of those infectious agents in the northern Thailand have not been reported.

The other potential factor is the environmental exposures that cause immunosuppression and may be associated with the increased incidence of NHL. The relationship between NHL and occupational exposure to agricultural pesticide has been found especially with phenoxy herbicide exposure (Dich et al., 1997; Mao et al., 2000; Schinasi and Leon, 2014), which is associated with diffuse large B-cell lymphoma (Schinasi and Leon, 2014). From 2008 to 2017, Thailand increased its annual imports of pesticides in particular herbicide such as paraquat, glyphosate, 2,4-D, ametryn, and atrazine. The total cost of all import pesticide increased from 19812 million Thai Baht in 2008 to 26,298 million Thai Baht in 2019 (Laohaudomchok et al., 2021). This potential environmental exposure may be particularly relevant for northern Thailand, where people are heavily dependent on agriculture as their main source of income (National Statistics Office, 2020). However, the increasing of NHL incidence may be partially linked to better diagnosis and complete registration overtime. The results in the more recent time could be more reliable. Future research should be conducted to explain the association of NHL and other potential factors such as EBV infection and environmental exposure.

One limitation of our study is the HIV status was not available in the cancer registry database that is a set of data about cancer including patient history, diagnosis, treatment, and status for every cancer patient. We therefore could not directly describe the association of HIV incidence and its associated malignancies. The other limitation of our study is the missing of cancer cases who lived with HIV and died from other opportunistic infections. Although, the analysis of incidence trends was based on data from three long-standing, population-based cancer registries in upper northern Thailand in which the data quality was generally satisfactory (Supplementary Table 1), the very low DCO% for KS and NHL (0% for KS and 0.1% for NHL) reflexed that some cancer cases may not be registered because the underlying cause of death could be HIV/AIDs rather than cancer and then was not account in the cancer registry database especially in the early period before inclusion of ARTs to UHS .

In conclusion, while the incidence of KS was stable low in female, the increase of its incidence in male may be related with the rising rate of HIV in male. The incidence of NHL increased in both sex while the incidence of HIV declined. In the era of cART in Northern Thailand, NHL link with HIV may be fading and our findings encourage to further examine the influencing factors of NHL for instance on the role of other infections and environmental exposures in this population.

Author Contribution Statement

PS contributed to the conception and design, performed the statistical analysis, interpreted results and drafted the manuscript. LA contributed to the conception and design, interpreted results and drafted the manuscript. AR, DP, IC, AT, KS, and WU contributed to the interpretation of data and revised the manuscript. KD, NW, PM performed clinical data acquisition and revised the manuscript. All authors read and approved the final manuscript.

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the Human Experimentation Committee of Research Institute for Health Sciences, Chiang Mai University. PS contributed to the conception and design, performed the statistical analysis, interpreted results and drafted the manuscript. LA contributed to the conception and design, interpreted results and drafted the manuscript. AR, DP, IC, AT, KS, and WU contributed to the interpretation of data and revised the manuscript. KD, NW, PM performed clinical data acquisition and revised the manuscript. All authors read and approved the final manuscript. The authors declare that they have no competing interests.

Declarations

Ethics approval and consent to participate

The study was approved by the Human Experimentation Committee of Research Institute for Health Sciences, Chiang Mai University (Certificate approval number 53/2020).

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

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