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PREVENTION OF CERVICAL CANCER IN RURAL LAOS

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ABSTRACT

Background

Cervical cancer, caused by high-risk human papilloma virus (HR-HPV), has a major impact on the lives of women worldwide, but particularly those in low-income countries. The disease can, however, be prevented by a variety of screening methods aiming to detect pre-cancerous lesions that can be treated. The most common method, cytological screening is expensive and is not available in many low-income countries like Laos. Alternative screening methods have been proposed for these settings.

Aims

The overall objective was to evaluate if it would be possible to introduce a cervical cancer prevention program in Laos.

Methods

The studies were conducted in rural areas of Laos between 2007 and 2010. Structured interviews regarding knowledge, attitudes and practice relating to cervix cancer and its prevention were carried out among rural women (n=800, study I) and health care providers from provincial to health centres (n=261, study II). Semi-structured interviews were conducted with 12 key policy makers regarding the magnitude of the problems of cervical cancer and preventative strategies (study II). The feasibility, safety and acceptability of a preventative approach to detect the precancerous lesions by using VIA followed by immediate treatment with cryotherapy was evaluated among 1926 rural women (study III). Cervical cells of 1922 women were also collected onto a filter paper medium for further human papillomavirus (HPV) analysis.

Results

Overall, about half of the women seemed to have some knowledge about cervical cancer and risk factors for developing the disease but only very small number of women (5%) knew about screening and its benefits. Risk factors and symptoms related disease was not known among the majority of these women (study I). Only about 5% of the women had ever had a Pap smear. The main information about cervical cancer was said to be from the media.

Nearly two thirds of health providers recognized that cervical cancer was the most common cancer in women (68%) and it is preventable (67%). Only 17% were able to correctly identify risk factors associated with cervical cancer. That early cervical cancer can be present without any symptoms was known only by 44% of providers. Only 24% of the female providers stated that they themselves had ever had a Pap smear. The key informants all stated that cervical cancer seems to be neglected in the health care system due to competing diseases, and a lack of data regarding the prevalence of the disease. They felt that it is necessary to draw the policy makers' attention to this issue in order to prioritize it within the reproductive health program. They believed that awareness needs to be raised among women and health providers and that they need to be committed to providing information as well as cervical cancer prevention and treatment services.

Among 1926 women VIA tested, 134 (7%) women were VIA positive and 113 (83%) were eligible for, and accepted, immediate treatment with cryotherapy. There was no report on major complication during or after treatment. Of those who had cryotherapy, 77 women (68%) returned for a one year follow up, and 68 (88%) were now VIA negative. VIA-positive women ineligible for cryotherapy, were referred for further investigation at the provincial hospital. Women stated that they found both VIA and cryotherapy highly acceptable (study III).

In the HPV testing study 123 of 1922 women (11%) were found to be HR-HPV positive. There was no different in distribution of HPV infection between age groups. The study also showed that the filter paper card was feasible and effective for collecting cervical cells for HPV-DNA analysis in this setting.

Conclusions

Our studies showed that there is a lack of awareness and knowledge among women, health care providers and policymakers in Laos regarding cervical cancer and its prevention. Despite of this, we demonstrated that women from rural areas had positive attitudes towards participation in the screening process in our study, using VIA and immediate treatment of appropriate lesions with cryotherapy. This approach proved to be acceptable to the women and feasible to perform in the rural setting, with no significant complication reported. Our findings may be of considerable importance when a screening program is being developed in Laos. Among the women in our study 11% were infected with some type of HR-HPV thus making them at risk for developing cervical cancer. If testing for HR-HPV would be an option for a preventative strategy in Laos, our study using the filter paper cards demonstrated that this could be a potential method in the tropical region.

Key words: Knowledge, attitudes, practices, women, health care providers, policy makers, VIA, HPV, Laos.

LIST OF PUBLICATIONS

- I. Keokedthong Phongsavan, Alongkone Phengsavanh, Rolf Wahlström, Lena Marions.
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Int J Gynecol Cancer 2010; 20: 821- 826.
- II. Keokedthong Phongsavan, Alongkone Phengsavanh, Rolf Wahlström, Lena Marions.
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- III. Keokedthong Phongsavan, Alongkone Phengsavanh, Rolf Wahlström, Lena Marions.
Safety, feasibility and acceptability of visual inspection with acetic acid and immediate treatment with cryotherapy in rural Laos.
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- IV. Keokedthong Phongsavan, Inger Gustavsson, Lena Marions, Alongkone Phengsavanh, Rolf Wahlström, Ulf Gyllensten.
Detection of human papillomavirus among women in Laos: feasibility of using filter card and prevalence of high risk types.
Submitted.

PREFACE

I was born and educated in Vientiane, Lao PDR. When I was eight years old, I was asked what would I like to be when I grew up? My answer was to be a teacher or a doctor, though I do not know why I said that. One experience that really affected me was seeing one of my cousin die from advanced stage of cervical cancer. She was in her mid fifties, but apart from the diagnosis no further information was given to her or her family about the cancer and nothing was done to make her life less miserable until her death. It was unbearable for us to watch her dying without any medical help.

I studied medicine in Laos and worked for five years in obstetrics and gynecology before receiving an Australian AUSAID scholarship to undertake a Masters degree in Medical Science in Obstetrics and Gynecology at the University of Tasmania. In the course of the masters degree I gained considerable experience in gynecological surgery and was able to do a further one year Fellowship in Gynecological Surgery at the Royal Hobart Hospital, where I learned to perform radical pelvic surgery as well as improving my skills in general gynecological surgery.

On my return to Laos I worked as a staff specialist in Obstetrics and Gynecology at Sethathirath Hospital, which at that time was the only University Hospital in Laos. Currently I am a member of the Committee of the Lao Association of Obstetrics and Gynecology, a faculty member of the University of Health Sciences and a supervisor for postgraduate students in Obstetrics and Gynecology.

In 2007, I was awarded a SIDA scholarship to undertake PhD work at the Karolinska Institutet. My choice of research topic was easy, when I considered the suffering of my cousin and the many women like her in Laos. Sadly, even if she had lived I doubt if she would have discussed the disease with me unless unbearable symptoms forced her to. It is my hope that the research reported in this Thesis will help change this situation for the better.

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LIST OF ABBREVIATIONS

ACCP	Alliance of Cervical Cancer prevention
ADB	Asian Development Bank
AIDS	Acquired immunodeficiency syndrome
ASCUS	Atypical squamous cells of undetermined significance
CIN 1-3	Cervical intraepithelial neoplasia grade 1-3
DH	District hospital
DNA	Deoxyribonucleic acid
DOH	Department of Health
HC	Health centres
HC 2	Hybrid Capture 2
HCPs	Health care providers
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR-HPV	High-risk HPV
HSIL	High grade squamous intraepithelial lesion
ICC	Invasive cervical cancer
IUD	Intra-uterine device
LBC	Liquid-based cytology
LEEP	Loop electrosurgical excision procedure
LSIL	Low grade squamous intraepithelial lesion
MCI	Mother and Child Institute
MOH	Ministry of Health
NGOs	Non government organizations
NSC	National statistics centre
OBGY	Obstetrics and Gynaecology
OC	Oral contraceptives
OR	Odds ratio
PH	Provincial hospital
PCR	Polymerase-chain reaction
STI	Sexual transmitted infection
TZ	Transformation zone
VIA	Visual inspection with Acetic acid
VILI	Visual inspection with Lugol's iodine
WHO	World Health Organization
WHO/ICO	World Health Organization/ in collaboration with the Institut Català d'Oncologia

1 INTRODUCTION

1.1 SCOPE OF THE PROBLEM

Cervical cancer is an important public health problem around the world (Ferlay et al, 2010; Jemal et al, 2011). Overall, it is the third most common cancer among women, accounting for 13% of malignancies, but it is the commonest cancer among women in low-income countries (Arbyn et al, 2011). It has been estimated that there were 529,000 new cases of cervical cancer around the world in 2008, and 275,000 deaths from the disease and that almost 90% of these cases occur in low-income countries. (Ferlay et al, 2010). Sub-Saharan Africa has the highest estimated age standardized incidence and mortality rates, followed by South-central Asia, South America and Melanesia (Figure 1) (Jemal et al, 2011).

In many low-income countries concerns about reducing high maternal mortality rates overshadow the issue of cervical cancer mortality, even though it is similar to, or even greater than, maternal mortality rates in some low-income countries (IARC, Globocan 2008).



Figure 1: Age-standardized cervical cancer incidence and mortality rates by world areas (from Jemal et al, 2011).

Death resulting from cervical cancer is particularly tragic because unlike many cancers, it develops slowly and has detectable precursor conditions, collectively known as cervical intraepithelial neoplasia (CIN) which are easily treatable, thus preventing the development of invasive cancer (Wellensiek et al, 2002). In high-income countries, cervical cancer incidence and mortality have been reduced by up to 80% through the use of cytological screening, and histological assessment, followed by treatment of precancerous lesions (Anttila et al 2006; Comber et al, 2004; Bray et al, 1995; Peto et al, 2004; IARC, 2008). However, in most low-income countries, cervical cancer screening is not widespread or even non-existent (Denny et al, 2006). Cytological screening in low-resource settings is mostly carried out in the context of opportunistic screening. Screening is often of poor quality and faces obstacles such as inadequate equipment and supplies, inadequate provider training, limited cytology services and difficulties in patient follow-up and treatment (Lazcano-Ponce et al, 1999). A substantial proportion of women at risk have never been screened, and low coverage is a critical issue (WHO library, 2002). In these settings women tend to seek medical care only after they are symptomatic and frequently present with advanced stage disease, rather than seeking screening as a preventative measure (Tebeu et al, 2008). It has been estimated that only 5% of women in low-income countries have been screened for cervical cancer in the past 5 years, compared with some 80% of women in high-income countries (WHO library, 2002).

1.2 ETIOLOGY AND NATURAL HISTORY OF CERVICAL CANCER

1.2.1 Human papillomavirus

It is now recognized that the basic cause of virtually all premalignant and malignant lesions of the cervix is persisting infection with one or more of the oncogenic strains of human papilloma virus (HPV), which is a common sexually transmitted infection (Bosch et al, 1995; Holowaty et al, 1999; Walboomers et al, 1999).

There are over 100 subtypes of HPV, of which 30 or more can infect the genital tract. In 2005 the International Agency for Research on Cancer (IARC) assessed the carcinogenicity of various strains of genital HPV infections and

listed 13 “high-risk” types (HR-HPV), namely HPV type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 (IARC, 2005; Bernard, 2005).

It is believed that almost all sexually active women under the age of 35 have been exposed to HPV infection (Burchell et al, 2006). It has been estimated that around the world 326 million adult women will have genital HPV infection at some time in their lives, but the majority will not develop significant cervical abnormalities (Bosch et al, 2000). Most infections clear spontaneously within 6-8 months, and about 90% within two years (WHO library, 2006). However, the 10% of the infections that persist longer are associated with a high risk of developing precancerous lesions or invasive cancer (Stanley et al, 2006; Paanoven et al, 2007a; Schiffman et al, 2011). Persistence may represent continuous infection with a single HPV type, with multiple HPV types, or re-infection (Schiffman et al, 2007).

Neoplastic changes are graded histologically by their extent in the cervical epithelium as cervical intraepithelial neoplasia grade 1 to 3 (CIN 1-3), where the ratio of the cell nucleus to the size of the cell is increased. The transient infections result either in no symptoms or mildly atypical cellular changes in the transformation zone (TZ) of the cervix or CIN 1.

Untreated CIN 1 is much more likely to regress to normal than to progress to cancer (Holowaty et al, 1999). The approximate likelihood of regression of CIN 1 is 60%, of persistence 30%, and of progression to CIN 3 is 10%, with progression to invasive cancer about 1%. The corresponding approximations of regression of CIN 2 are 40%, persistence 40%, progression to CIN 3 20%, and progression to invasion 5%, respectively (Ostor et al, 1993; Arends et al, 1998). The likelihood of untreated CIN 3 regressing is 33% and of progressing to invasion greater than 12% (Ostor et al 1993; Markowitz et al, 2007). Unlike CIN 1 and many CIN 2 lesions, CIN 3 represents a uniformly aneuploid condition which is truly a preinvasive lesion, capable of progressing to invasive cancer in a period as short as a year to 20 or more years (IARC, 2005, Campion, 2010).

The commonest HPV type associated with cervical cancer is HPV 16, which is found in 50% of squamous carcinomas and 30% of adenocarcinomas

worldwide (Bosch & de Sanjose, 2007; Munoz et al, 2006). HPV 18 is the second most common HPV type found in association with invasive cervical cancer, being present in about 25% of cases worldwide. Overall HPV16 and 18 are the most prevalent of the oncogenic types and are linked to 70% of cervical cancers diagnosed throughout the world (Bernard, 2005; Schiffman et al, 2007; de Sanjose et al, 2010).

The distribution of HPV types varies between geographic regions, and although the dominant oncogenic type worldwide is HPV16 (Bosch et al, 1995; Walboomers et al, 1999). HPV18 has a higher incidence in cervical cancers in south Asia, while HPV45 is dominant in cervical cancers in sub-Saharan Africa and HPV39 and 49 are dominant in cervical cancers in Central and South America (Bosch et al, 1995; Munoz et al, 2003).

While persistent infection with high-risk HPV is a necessary feature for the development of cervical cancer, it alone is not sufficient in a woman with normal immune defences. It is clear that other cofactors are required for this transformation to take place.

1.2.2 Risk factors

The lifetime number of sexual partners of the woman or her partner, and early age at first intercourse are significantly associated with the risk of cervical cancer (International Collaboration of Epidemiological Studies of Cervical Cancer, 2009). High parity has been consistently found to increase the risk of squamous cell cervical carcinoma among HPV-positive women (Skegg et al, 2002; Munoz et al, 2002; Moreno et al, 2002; Franceschi et al, 2003). Several studies suggest that long-term use of oral contraceptives (≥ 5 years) increases the risk of cervical cancer by up to four-fold in women who are HPV positive (Skegg et al, 2002; Munoz et al, 2002; Moreno et al, 2002; Castellsague et al, 2003; International Collaboration of Epidemiological Studies of Cervical Cancer, 2009).

Tobacco smoking is known to be an important carcinogenic factor that increases the risks of many cancers. Women who smoke have approximately twice the risk of cervical cancer as non-smokers (Kapeu et al, 2009). Passive

inhalation of cigarette smoke also significantly increases the risk of both high grade premalignant lesions and invasive cancers in women infected with HR-HPV (Coker et al, 2002).

HIV infection is associated with high prevalence of HPV related-diseases. Yet, it is unclear whether HIV induced immune-suppression is a cofactor for progression of the diseases, or if it simply increases the prevalence and persistence of HPV (Odida et al, 2011). Patients on immunosuppressive agents following renal transplant have a rate of development of CIN that is up to 16 times higher than that of the general population (Sillman et al, 1984).

Women who are co-infected with HPV and other sexual transmitted agents such as Herpes simplex Virus type 2 (HSV-2) or Chlamydia trachomatis and Neisseria gonorrhoea are more likely to develop cervical cancer than are women who are not infected (Smith et al, 2002; Smith et al, 2004). The mechanism of this effect is not clear.

1.3 PREVENTION OF CERVICAL CANCER

1.3.1 Primary prevention by vaccination

The recognition of the central role of HR-HPV in the aetiology of cervical cancer worldwide has led to the development of prophylactic vaccination as a new means of cervical cancer prevention. There are currently two HPV vaccines available: one quadrivalent HPV vaccine (Villa et al, 2005) and one bivalent HPV vaccine (Paavonen et al, 2007b; Paavonen et al, 2009). Both vaccines offer protection against HPV16 and 18 (Smith et al, 2007). The cross-reactivity for HPV31, 33 and 45 suggest that an even higher percentage of cervical cancers might be prevented by vaccination (Paavonen et al, 2009). Quadrivalent HPV vaccine also protects against non-oncogenic HPV types 6 and 11, which are the cause of benign anogenital warts (Paavonen et al, 2009).

HPV vaccines are designed for prophylactic use only, as they do not clear existing HPV infection or treat HPV-related disease. Furthermore, regular screening is still necessary, because HPV vaccination is not effective against all oncogenic types. The introduction of vaccination is especially important in low-income countries, where invasive cervical cancer is most common and

the impact of screening has been limited (Bosch et al, 2007). The high cost of this vaccine has been a cause for concern. Several countries have or are considering programs to fund HPV vaccination (Ngan et al, 2011).

1.3.2 Secondary prevention

1.3.2.1 Cytology

Since its introduction in 1941 by George Papanicolaou, cervical cytology screening, known as Pap smear, has become an extremely successful preventative tool reducing the incidence of cervical cancer by 79% and decrease mortality by 70% over the past five decades in high-income countries (Ries et al, 2009; Saslow et al, 2002; Parkin et al, 2005; Arbyn et al, 2008). Until recently the Pap smear has remained the principal test for preventing cervical cancer worldwide. However this method has several limitations. Firstly it is subjective with wide variations in sensitivity in detecting CIN 1 -3 ranging from 30% to 87% and specificity ranging from 86% to 100% (Sankaranarayanan et al, 2005; Nanda et al, 2000). Furthermore, false negatives rate as high as 25% have been reported, that are thought to be due to sample preparation and misinterpretation of the cytology (Sawaya & Grimes, 1999). To improve the sensitivity of cytology attempts have been made to combine it with a second test or other tests (Sherris & Herdman, 1998; O'Meara, 2002).

An alternative method to the conventional Pap smear is liquid-based cytology (LBC). It is a technology that has been developed with the aim of improving the interpretation of cytology, which is normally carried out by cytotechnologists. By providing slides that display the collected cells much more clearly than the conventional smear this technique improves the accuracy of the Pap test, its main advantage has been to reduce the number of inadequate samples from around 9% to around 1% (O'Meara, 2002). This reduces the need to recall women for a further test. However, in a recent meta-analysis it was concluded that LBC is neither more sensitive nor more specific for detection of high-grade cervical intraepithelial neoplasia than the conventional Pap test (Arbyn et al, 2008).

In some low-income countries where cytological screening has been implemented, it has failed to reduce the mortality rate because of lack of infrastructure, inadequate equipment and laboratories, lack of trained personnel, inadequate patient follow-up and treatment and also low coverage of the high-risk population (WHO, 2002; Denny et al, 2006).

1.3.2.2 Visual inspection of the cervix with acetic acid (VIA) and with Lugol's iodine (VILI)

Due to the low success rates of cytological screening in low-income countries, an alternative screening method has been developed (Sankaranarayanan et al, 2001). Visual inspection with acetic acid (VIA) involves naked-eye inspection after application of 3-5% acetic acid to the uterine cervix for one minute. A higher concentration of intracellular proteins in cervical neoplasia leads to the dense aceto-whitening effect following the acetic acid application, close to the squamo-columnar junction or the cervical os (Blumenthal et al, 2005).

VIA can be effectively carried out by a variety of staff including trained nurses, midwives and doctors (Gaffikin et al, 2003; Sankaranarayanan et al, 2007; Blumenthal et al, 2007). Several studies indicate that it has a sensitivity ranging from 70 to 85% in detecting high-grade cervical intraepithelial neoplasia (CIN 2–3) and invasive cancer; its specificity ranges from 67 to 85% (University of Zimbabwe/JHPIEGO, 1999; Belinson et al, 2001; Sankaranarayanan et al, 2003; Sherris et al, 2003; Sangwa et al, 2006). Studies from India that was limited by the fact that not all cases were biopsied suggested that VIA detected 90% of the cases with high-grade disease with specificity of 92% (Sankaranarayanan et al, 1998; Sankaranarayanan et al, 2004).

Since VIA provides immediate results, it is possible to screen and treat women during the same visit, which is important because the inability to follow up women is a major problem in low-income countries (Mathers et al, 2005; Jeronimo et al, 2005).

Visual inspection with Lugol's Iodine (VILI) is another method for detection of precancerous lesions. When iodine is applied to the cervix, the normal cells

containing glycogen stain dark brown, but areas of CIN and invasive cancer do not take up iodine as they lack glycogen and appear as mustard yellow or saffron yellow areas (Sellors & Sankaranarayanan, 2003). Adding VILI to VIA has been shown to improve the sensitivity and specificity of VIA (Sankaranarayanan et al, 2004b). IARC studies in India and Africa reported that VIA and VILI was as good as cytology for detection of cervical neoplasia (Sankaranarayanan et al, 2004b; IARC, 2005).

1.3.2.3 HPV testing

Since HPV has been recognized as the necessary cause of cervical cancer, interest is focusing the potential of HPV testing in cervical cancer prevention. Several recent studies have demonstrated that HPV test results are more sensitive than Pap smears in detecting CIN 3 (Maryrand et al, 2007; Ronco et al, 2010), but less specific. Moreover, a number of studies showed that HPV testing is now a viable alternative or adjunct to the cytological smear because it identifies not only women who currently have high grade cervical disease but also women who are at greatest risk of developing the disease in the future (Kuln et al, 2000). There is also growing consensus that HPV testing is useful for the 'triage' of women with atypical squamous cells of undetermined significance (ASCUS) lesions and for the follow-up of women with low grade squamous intraepithelial lesion (LSIL) (ACOG, 2009; Schiffman et al, 2011). Several technologies exist for the molecular detection of HPV infection (Malloy et al, 2000). Presently, the two most widely used methods for the detection of genital types are the Digene Hybrid Capture assay (HCII) and polymerase chain reaction (PCR) with generic primers (Malloy et al, 2000; Villa et al, 2006). The sensitivity of both HCII and PCR are high and almost equal, for detection and post-treatment follow-up of CIN 2-3 (Soderlund-Strand et al, 2006; Huang et al, 2006).

Some studies in low-income countries have shown that providing a single round of HPV testing to women age 30-59 followed by appropriate treatment was associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervical cancer (Qiao et al, 2008; Sankaranarayanan et al, 2009). Efforts are underway to develop low cost HPV tests which might

be used for primary screening of women in low-income settings (Shi et al, 2011).

1.3.2.4 Treatment of precancerous lesions

Treatment of VIA-positive or precancerous lesions can be performed either by ablative methods such as cryotherapy and laser, or excisional methods such as loop electrosurgical excision, laser or cold knife excision (Carr et al, 2004; Blumenthal et al, 2005; Ngan et al, 2011). When resources are available biopsy and a histological examination should be performed. Several studies have demonstrated that a single examination with VIA followed by immediate treatment of the abnormal lesions have proven to be a safe, acceptable and feasible prevention method in low-income settings (Royal Thai College/JHPIEGO 2003; Blumenthal et al, 2007; Jacob et al, 2005). In addition, VIA can be life saving and it is affordable (Goldie et al, 2005; Sankaranarayanan et al, 2005).

Although a number of studies have demonstrated the safety and effectiveness of VIA followed by immediate cryotherapy as an approach to cervical cancer prevention in other low-resource settings, each country has its own characteristics which may influence the acceptability and appropriateness of such an approach. It was thought that the isolation, educational level, cultural beliefs and the variety of ethnic groups in rural Laos may mean that the approach was less likely to succeed than in other countries. It was far from certain that women would be willing to participate, and if they did, that they would find the testing and treatment acceptable. If women reported negative experiences it could inhibit the uptake of any further community screening program in the country. Furthermore, prior to this study nothing was known about the prevalence rates of VIA positivity, which, if very high would lead to a prohibitive number of women being treated. For all these reasons it was important to assess the appropriateness of this approach in rural Laos, prior to committing to a screening and prevention program.

1.4 LAO PEOPLE'S DEMOCRATIC REPUBLIC

1.4.1 Economy and income

Laos is a low-income country situated in Southeast Asia that shares borders with Thailand, Myanmar, China, Vietnam and Cambodia. The total area is 236,800 square kilometres, and 65% is mountainous with cultivated floodplains along some reaches of the Mekong River and larger tributaries. Its population is approximately 5.6 million with an almost equal ratio between male (2.80 million) and female (2.82 million). The life expectancy of the Lao population at birth is 61 years (women 63 years) (MOH, 2006). About 50% of the population is currently less than 20 years (39% is below 15 years old, 57% aged 15-64 and 4% is 65 and older) (NSC, 2006). Women of reproductive age constitute 25% of the total of population and the total fertility rate is 4.5. Laos has the lowest population density in Asia, about 24 persons per square kilometres in 2005 (NSC, 2006; WHO, 2008).

Laos is ethnically diverse with a great variety of languages and customs: 49 ethnic groups are officially recognized by the government (World Bank, 2010). Fifty-five percent of the population is Lao, 11% Kmou and 8% Hmong (NSC, 2006; King et al, 2005). The official language is Lao. In most provinces a few ethnic groups make up most of the population. Almost three fourths of the populations (73%) lives in the rural areas and they depend heavily on agriculture of natural resources and the rearing of livestock for their livelihood (WHO, 2008). Seventy-one percent of the population live on less than two US dollars a day and 27% live on less than one dollar a day (Prasit et al, 2010). The main religion in Laos is Buddhism which represented 67% of the population, while 33% were Animists, Christians, Muslims or devotees to the Bahai faith (NSC, 2006; WHO, 2005a, King et al, 2005).

1.4.2 Health situation

National health indicators have been improving steadily over the past three decades, but despite the efforts of the national authorities, they remain well below international standards, being some of the lowest in the region (WHO, 2005a). Selected demographic and health indicators are shown in Table 1.

1.4.3 Organization and health system

The main network for health care service provision is the public system (MOH, 2006). There are four administrative strata in the health system: central (Ministry of Health, College of Health Technology and reference/specialized centres), provincial (Provincial Health Office, Provincial and Regional Hospitals, and Auxiliary Nursing Schools), district (District Health Offices and District Hospitals) and village (Health Centres) levels (figure 2).

Table 1. Selected health and socio-demographic indicators.

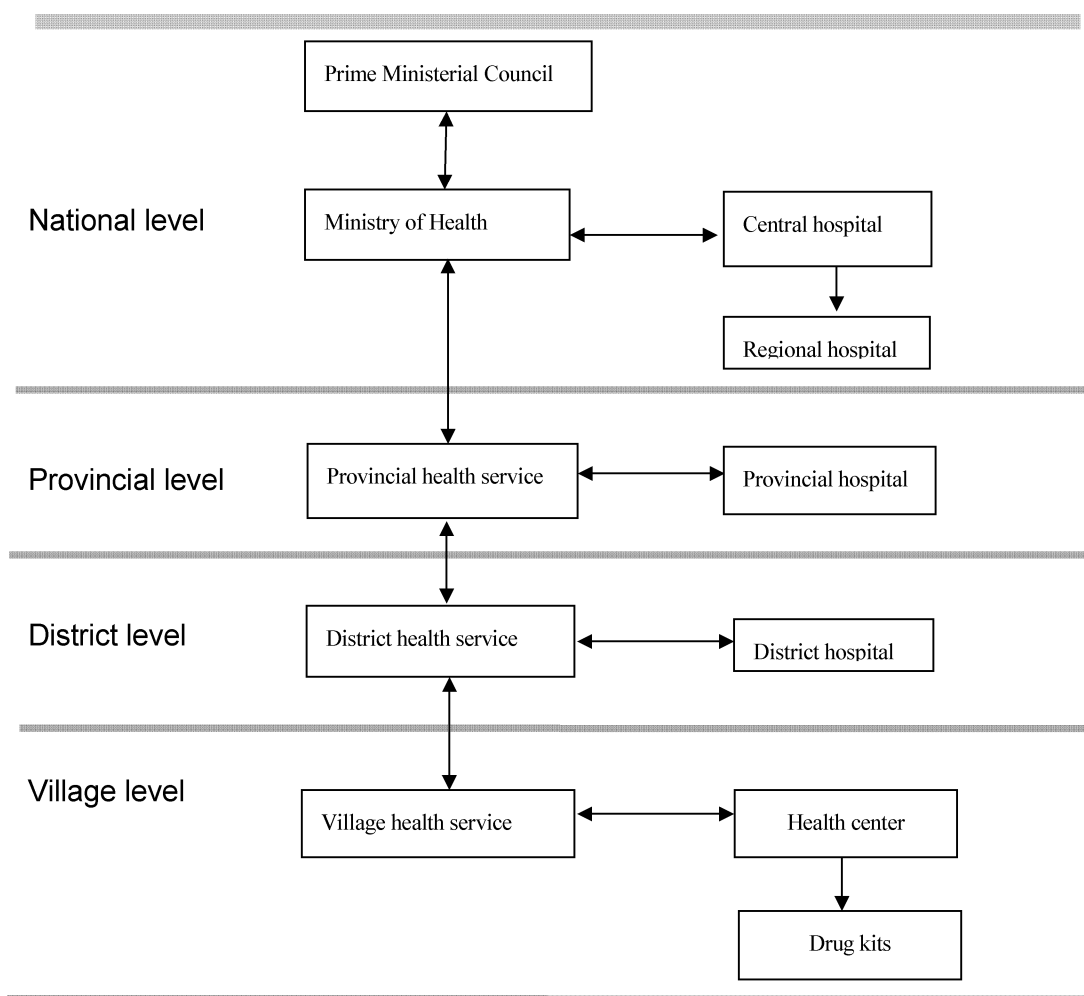
Indicators	1995*	2000**	2005*
Population (million)	4,58	5,20	5,62
Population density, person/sq km	19.3	22.0	23.7
Population growth rate (%)	2.8	2.6	2.1
Crude birth rate (/1000)	41.3	34.0	34.7
Crude death rate (/1000)	11.1	6.3	9.8
Total fertility (%)	5.4	4.9	4.5
HIV prevalence (%)	-	-	0.1
Life expectancy at birth (years), T (M/F)	51(50/52)	59 (57/61)	61 (59/63)
IMR (per 1000 live births)	104	82	70
U5MR (per 1000 live births)	170	107	90
MMR ((per 1 00,000 live births)	656	530	405
ANC	-	72	76
Supervised deliveries (%)	-	17	19
Contraceptive prevalence (%)	-	29	39
Adult literacy rate (%), T (M/F)	60 (74/48)	-	73 (83/63)
Average per capita income (\$)	-	395	441
Total health expenditure per person (\$)	-	-	12

* National Statistics Centres (NSC, 2006)

**Reproductive health survey (MOH, 2006)

HIV= Human immunodeficiency virus; IMR= infant mortality rate; U5MR= under five years mortality rate; MMR= maternal mortality rate; ANC= antenatal care; T(M/F)= total (men/women)

Figure 2. Organizational and management structure of the Lao public health system (Adopted from Phomtavong et al, 2005)



Drug kits= cabinets with selected drugs located in the villages and administered by the village health volunteers (Lao Health Master Planning Study Final Report).

1.4.4 Distribution of Health-care personnel

There are about 18,000 public sector health workers of which 70% are employed by the Ministry of Health and 30 % by the Ministries of National Security and National Defence. The overall ratio of health worker (doctors, nurses and midwives) per population in 2009 was 0.5 per 1,000 people; far lower than the 2.3 health workers per 1,000 people recommended by the World Health Organization (WHO, 2005a; ADB, 2009). Distribution of health workers is skewed in favour of urban areas. Furthermore, overall health worker capacity is reportedly weak due to deficiencies in the quality of training of health

providers. Low salaries combined with low levels of basic training inhibit the effectiveness of the health system (ADB, 2009; Asante et al, 2010). Because of this, the disparate geographic distribution of health workers has left many primary health care facilities grossly understaffed and unable to provide basic services leading to lack of interest in utilization. Only 63 per cent of medical staff work at health facilities (Asante et al, 2010). However, efforts are being made by the government to strengthen health worker education and increase training opportunities (Asante et al, 2011, United Nation. Economic and Social Commission for Asia and the Pacific). A recently formulated National Policy on Human Resources for Health places greater emphasis on providing and retaining health providers in remote and underserved areas (ADB, 2009; Asante et al, 2010).

1.4.5 Access to health-care and health-care delivery

In the whole country, there are four central hospitals, six special centres, 4 regional

And 13 provincial hospitals, 141 district hospitals, 740 health centres, and around 5,000 village drug kits. In total, there are around 5,000 hospital beds in the country (MOH, 2006). Each health centre covers about 7,000 people, but many centres serve less than 1,000 (Pradit et al, 2010). Each health centre serves as a focal service point for about eight villages, including for obstetric care (ADB, 2009).

There are no private hospitals, but 2,132 private pharmacies and 308 private clinics, mainly in urban areas (NSC, 2006; Phomtavong et al, 2005). Government services are underused, and a significant share of out-patient health-care is privately delivered (United Nation. Economic and Social Commission for Asia and the Pacific). Purchase of drugs in official or unofficial pharmacies is the first health-seeking behaviour. Public facilities, especially district and health centres, are poorly utilized, with only 0.2 curative contacts per capita per year, as reported at the National Health Conference in August 2007 (Asante et al, 2010). An effort to increase access through village volunteers and village revolving drug funds has reached 5,226 villages (Lao Health Master Planning Study Final Report; ADB, 2009). Coverage for preventive health services is also low.

Moreover, ethnic diversity presents a major challenge in health-care delivery and education due to cultural and linguistic barriers. Many taboos and superstitions persist. Seventy-eight percent of women practised food taboo after delivery (Thome et al, 2010; Phomtavong et al, 2005). Women have lower literacy rates than men and girls have lower school-completion rates than boys. The literacy rate in the age group 15-24 years was 88% (Pradit et al, 2010).

Furthermore travel can be very difficult between villages and districts where journeys are not counted in kilometres but in walking days. These constraints are an important barrier to accessibility of health services and other services. During the rainy season, the major constraint is the difficulty of land communication and transportation due to flooding and washing out of roads (Phomtavong et al, 2005).

1.4.6 Situation of cervical cancer in Laos

“A family’s well-being is strongly tied to the physical health of its members. When illness strikes one member, the entire family shares the burden.” (World Bank, 2010)

Information about cancer incidence in Laos is limited due to lack of population-based cancer registries. Reduction of the incidence of maternal deaths has been seen as the main concern nationwide and therefore, other diseases have been given far less prominence in the national health strategy (MOH, 2005; WHO, 2011). While Laos has a prevalence of HIV/AIDS with an estimated adult sero-prevalence of HIV of 0.1% (WHO, 2005b) and the country faces the difficulty of halting the spread of HIV and AIDS, at the time when higher HIV prevalence has been reported from neighbouring countries (Limpakarnjanarat et al, 1999; Kim et al, 2005; Beyrer et al, 2003). Communicable diseases (malaria, diarrhoea, tuberculosis, Dengue hemorrhagic fever, acute respiratory infection, measles and STI) remain common or are serious threats, however, non-communicable diseases are emerging and being recognized as significant and expanding problems (WHO, 2005a; ADB, 2009).

Since there are no cancer registries in Laos, a figure on the incidence of cervical cancer can only be a crude estimation extrapolated from the incidence of the disease in neighbouring countries (MOH, 2006). The World Health Organization estimated that in 2010 there were 1.77 million women aged 15 and older who are potentially at risk of developing cervical cancer and every year 491 women would probably be diagnosed with the disease and 270 would die from it (WHO/ICO, 2010). The mortality of the disease would be expected to be high due to presentations with advanced stage disease which could only be treated by radiotherapy, which is not available in Laos and unaffordable for the majority of Lao women seeking treatment in neighbouring countries.

The only available preventative activity has been to use opportunistic screening of women when they come to the health units for other reasons. According to reports on the health status of Laos, only 2.4 percent of women aged 18 to 69 years had ever been screened for cervical cancer and those women were living in the urban and central region (MOH, 2006). Pathology services are severely limited in Laos with only a few pathologists in the country, and the few cytologists who are poorly trained. Furthermore, there is no quality control in provided services. All the pathology laboratories are in the capital city. Patients pay a significant fee for cytology, and are responsible for delivering the slides to the laboratory and collecting the reports, which is a considerable expense for the majority of the population, and especially for those from rural areas.

2 AIMS OF THE STUDY

The overall objective was to evaluate the possibility to introduce a cervical cancer prevention program in Laos.

The specific aims were:

To describe knowledge, awareness and attitudes regarding cervical cancer among rural women in Laos (Study I).

To explore knowledge, attitudes and practices among health providers and policy makers regarding cervical cancer and its prevention in Laos (Study II).

To evaluate the safety, acceptability, and feasibility of a preventative approach to reduce the risk of cervical cancer among rural Lao women using VIA followed by immediate treatment with cryotherapy (Study III).

To determine the suitability of filter paper cards (FTA Elute Micro Card™) for collection of cervical cells in a tropical climate followed by human papillomavirus analysis and to estimate the prevalence and distribution pattern of high-risk viral strains in Lao women (Study IV).

3 MATERIALS AND METHODS

3.1 STUDY DESIGN

All four studies of the thesis were cross-sectional using quantitative methods, although Study II also included a qualitative section. The first two studies were conducted in order to explore the perception of cervical cancer prevention among women in the community of two provinces (Study I) and the opinions of policy makers and health care providers regarding cervical cancer and its prevention (Study II). Study III and IV were performed in order to evaluate alternative options of cervical cancer prevention program among women in rural Laos. The study design, participants, methods and time periods are summarized in Table 2.

Table 2. Study design, participants, methods and time periods.

Study	Setting site	Study design and data collection methods	Participants	Time period
I	LuangPrabang and Champassack provinces	Quantitative study -Structured-interviews	-800 women 18-55 years old	May to June, and August to September 2008
II	LuangPrabang and Champassack provinces	Quantitative and qualitative study -Structured-questionnaire -Key informants interviews	-291 health care providers -12 policy makers	May to September 2008 and July to September 2010.
III	LuangPrabang and Champassack provinces	A demonstration study -Structured-interviews	1926 women 25-45 years	-February to April and June to August 2009. -March to April and May to June 2010.
IV	LuangPrabang and Champassack provinces, Vientiane Capital	Quantitative study -Clinical examination -Laboratory analysis	1922 women 25-48 years	February to April and June to August, 2009.

3.2 STUDY SETTING AND STUDY POPULATION

3.2.1 Study setting

All four studies were conducted in the communities of two provinces (LuangPrabang and Champassack) of Laos, although in Study IV, women from Vientiane Capital city were also included (Figure 3). The two provinces were chosen due to demographic and administrative concerns. They have among the highest maternal death rates in Laos and the tertiary hospital of each region is located within the province (MOH, 2006). Vientiane city was included in Study IV for logistic reasons and to increase the statistical power of the sample size.

LuangPrabang province is one of the seven provinces that are situated in the northern region of Laos, with a population of 405,949 inhabitants. It consists of 11 districts, 855 villages and 55 health centres. It is estimated that there are 97,100 women of reproductive age among a total of 220,700 women in the province (NSC, 2006).

Champassack province is one of the five provinces that are located in the southern region with a population of 603,880 inhabitants. From the 305,340 female in the population, about 147,100 women are estimate to be reproductive age. It comprises 10 districts, with 924 villages and 58 health centres. The socioeconomic situation is not different from LuangPrabang (NSC, 2006).

Vientiane city has a population of 698,318. It is estimated that there are approximately 57,767 women of reproductive age. It consists of 9 districts, with 499 villages and 68 health centres (NSC, 2006).

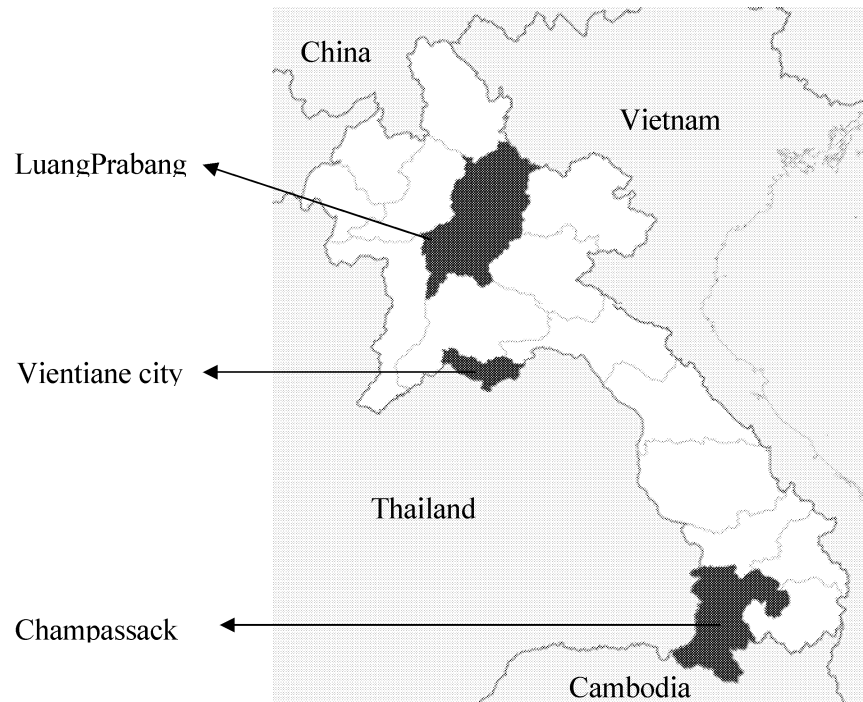


Figure 3. Map of Laos and location of the study settings.

(<http://en.wikipedia.org/wiki/>)

3.2.2 Study population and data collection

The data collection methods included structured questionnaires (Study I, II, III, IV), semi-structured interviews (Study II), clinical examinations, collection of cervical cells samples and laboratory tests (Study III, IV).

Study I

A total of 800 women aged 18 to 55 years participated. Based on the assumption that 40% of the women had knowledge about cervical cancer (Gatune et al, 2007), with a precision of 5%, a confidence interval of 95% and allowing for 10% of non-respondent rate, it was estimated that 400 participants from each province were needed.

In each province, two districts were randomly selected and from each district, four villages with health centres and four without were selected by the district health officer independently of the researchers. In each village, 50 women were

recruited by the head of the village or by the head of the Lao Women's Union in the village.

Data was collected from May to June and August to September 2008, using a structured questionnaire with mostly pre-coded questions with "yes", "no", or "not sure" as alternatives, but included also some multiple choice alternatives and some open-ended questions. The questionnaire contained questions on socio-economic status, reproductive history (age at the first delivery and live births), prior knowledge of cervical cancer, personal perception of risk factors, awareness and attitudes toward cervical cancer and its prevention. The questionnaire was administered during face to face interviews, conducted by medical staffs (two gynaecologists and two nurses) who had been trained before the data collection. All interviews were conducted and read out to the respondents in Lao and the answers were translated to English for reporting.

Study II

For the first part of Study II, self-administered questionnaires with closed and open-ended questions were given to the health-care providers (HCPs) of the two provinces from May to June and from August to September, 2008. The questionnaires covered information about personal characteristics and had specific questions regarding knowledge, attitudes and practice with respect to cervical cancer and its prevention. Knowledge related to causes, risk factors symptoms and screening interval, attitudes and practice towards screening or not screening patients, and referring or not referring patients for screening. Female providers were also asked if they themselves were ever screened.

In total, 291 HCPs (doctors, medical assistants, nurses and nurse assistants) from provincial health officers to employees of health centres in the two provinces were listed and invited to participate in the study (in each province: two from provincial health office, two from the provincial hospital, two from district hospital and one or two for all of the health centres). In order to reach the HCPs in each facility of these two provinces, the provincial health officer and district health officer were the key persons who distributed and collected the questionnaires from each facility. An official letter about the study was sent to the provincial health office four weeks in advance in order to inform them

about the study objectives before providing the survey questions to the health officer.

The qualitative part of the study was conducted from July to September 2010. Semi-structured interviews regarding the significance of cervical cancer and its prevention were conducted with twelve key informants: two from the Ministry of Health (MOH), two from Mother and Child Institute in Vientiane (MCI), three from each of the provinces [one senior Health Officer (HO), the Director of the Provincial Hospital (DOH) and the head of the hospital's department of Obstetrics and Gynaecology (OBYG)] and two from Non-Government Organizations (NGOs) in Vientiane involved in women's health care projects. The interviews were conducted by two research assistants, who were trained during a pilot study and a refresher course before the interviews. All of the interviews were conducted in Lao and lasted from 20-45 minutes. A tape recorder was used with the consent of the persons interviewed. All the interviews took place in the key informant's office as it was convenient and comfortable for the respondents.

Study III and IV

Women aged 25–45 years with an intact uterus, no history of cervical cancer, and not pregnant were invited to participate in the study. Based on the results from a study from neighbouring Thailand (Royal Thai College/JHPIEGO, 2003), we estimated that approximately 13% would be VIA positive, and with a precision of 5%, a confidence interval of 95%, a sample size of 174 VIA-positive women was calculated. Therefore the target number of women would be 1740, giving a minimum of 10% test positive rate.

In each province, two districts were randomly selected, and in each district, the district health officer chose ten villages independently of the researchers. With the help of the heads of village and the Lao Women's Union, all women fulfilling the criteria were invited. The number of women fulfilling the criteria was estimated to be about 2,408 in LuangPrabang province and about 2,160 in Champassack province (NSC, 2006). Eligible women attending the study sites for any reason during recruitment were also invited to participate.

VIA training

All of the staff (doctors and nurses from provincial and district hospital) involved in the study (each province: one from provincial hospital; three from district hospitals) were trained on VIA and cryotherapy for a period of ten days in an intensive course, using manuals developed by the Alliance for Cervical Cancer Prevention (ACCP) (Sellors & Sankaranarayanan, 2003). Training included lectures dealing with anatomy and physiology of the female genital tract, the pathology of cervical neoplasia, the technique of speculum examination, and the performance of VIA, together with discussions, review of photographs of the normal and abnormal cervix, and clinical sessions to observe and provide sufficient clinical practice for every trainee. The training course was strictly supervised by experienced consultants.

After training, the trained staff members were assigned to two teams. One team referred as the first team, were responsible in interviewing the women before and after the tests. The second team was responsible for the examinations and the tests.

Providing information about VIA and treatment to the participants

Information about cervical cancer (risk factors, possible symptoms and prevention), the benefits and potential complications of VIA and cryotherapy treatment was initially provided to the participating women by the first team. A structured questionnaire was then employed to collect data for demographics, personal information and reproductive health issues after obtaining informed consent from the women.

HPV and VIA procedures

Collecting cervical cells samples for HPV testing (Study IV)

Prior to the examination, a second verbal consent was obtained. The procedure was performed by one of three gynaecologists and two nurses. The participants then underwent a direct visual inspection of the cervix and cervical cells were collected with a cytobrush rotated 360 degrees in the endocervix. The cervical cells were then applied onto the FTA Elute Micro Card™ (GE Healthcare, United Kingdom) which was the same size as the glass slide used for Pap smears (Gustavsson et al, 2009b). Filter cards were allowed to dry at

room temperature (29°C) overnight or dried with a hair dryer before folding the cover and being placed into auto-seal (zip lock) bags on the following day. All FTA cards were stored in an air-conditioned office (25-26° C) in Vientiane before being sent by air-freight to the Department of Immunology, Genetics and Pathology, Rudbeck Laboratory, University of Uppsala, Sweden, for HPV typing.

VIA procedure (Study III)

After collection of samples for HPV testing, VIA was performed on all women. A cotton ball soaked in 5% acetic acid was applied to the cervix and after one minute the cervix was inspected under good illumination. The test was considered positive if a well-defined acetowhite lesion was visible close to the squamocolumnar junction. Polyps, ectropions, or lesions of doubtful acetowhite change were considered negative. Where positive or doubtful lesions were found Lugol's iodine was applied to achieve further clarification (Sellors & Sankaranarayanan, 2003; Blumenthal et al, 2005). Women were told the results immediately. If the test was positive and the lesion occupied less than 75% of the cervix, did not extend onto the vaginal wall or more than 2 mm beyond the cryotherapy probe, and was not suspicious of cancer, cryotherapy was offered. VIA-positive women, who were ineligible to immediate treatment, were referred to the provincial hospital for investigation and treatment. No further action was taken if the test was negative and there was no visual indication of malignancy.

Immediate treatment with cryotherapy (Study III)

For women choosing immediate treatment with cryotherapy, the steps involved in the treatment procedure were explained in detail while preparing the cryotherapy equipment. Waiting time was between 5 - 30 minutes due to the need to sterilize the tip of the cryoprobe. Some VIA-positive women chose to return on the following day for the treatment.

Cryotherapy was performed with carbon dioxide using the double-freeze technique (Blumenthal et al, 2005) with a 19-mm shallow nipple probe (Wallach LL-100 cryotherapy gun, Wallach Surgical Devices, Orange, CT, USA). After cryotherapy, the women remained under observation for 15–20 minutes and

were informed that they might experience mild cramps for several days and a light bloodstained watery discharge for up to 6–8 weeks after treatment. They were advised not to insert anything into the vagina or use douches and to abstain from sexual intercourse for four weeks. They were instructed to return to or contact the district hospital in case of fever for more than two days, severe lower abdominal pain, foul-smelling or pus-coloured vaginal discharge, or heavy bleeding for more than two days and to return for a one year follow-up. Condoms were also provided to all treated women for use if intercourse was unavoidable.

Interviews regarding satisfaction of VIA testing (study III)

After leaving the examination room, all women tested were interviewed again by the first team regarding their willingness to participate and acceptance of the test. They were also asked about their attitudes toward and understanding of cryotherapy (if treated) and their satisfaction with a single visit approach and the attitudes of the staff providing the service.

Follow-up of women treated with cryotherapy (study III)

The women, who had received the treatment with cryotherapy, were asked to come back for follow-up after one year. All of them were asked about their post-cryotherapy experiences and a new VIA examination was performed. Women who were still VIA-positive and eligible for cryotherapy were offered immediate treatment, whereas women with lesions unsuitable for cryotherapy were referred to the provincial hospital.

HPV DNA extraction (study IV)

The filter papers were punched by a 3 mm Harris micro-punch (Whatman, Inc., Clifton, NJ). Six punches from each sample were then transferred to a single well in a 96-well plate and washed once by vortexing 3×5 seconds in 200 μ l distilled water. The water was then carefully removed with a pipette. The DNA elution was performed in 50 μ l distilled water at 95°C for 30 minutes in a heating block (with heated lid). Three microliters of the DNA extract was used as template in each real-time PCR.

HPV analyses (study IV)

The typing of HPV was performed as described previously using a real-time PCR-based assay (Gustavsson et al, 2009a). This assay detects and quantifies a human single copy gene (house keeping gene) (HMBS, Homosapiens hydroxymethylbilane synthase; GenBank accession no M95623.1) and the following HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. The threshold for a positive sample was set to 10 copies in the PCR both for the human single copy gene and for HPV. The results are presented as individual types, except for HPV18 and 45 which are detected as a group and HPV33, 52, and 58 which are also detected as a group.

3.2.3 Data analysis

Quantitative part

The data were coded and analyzed using the STATA program (StataCorp, LP, College Station, Texas, USA) in all quantitative studies (Study I, II, III, IV). Basic descriptive statistics and frequency calculations were performed on all variables. The Chi-square or Fisher exact test was used when appropriate (Study I, II, III, IV). Odds ratios (ORs) or adjusted ORs(AOR) and their 95% confidence intervals (CI) were used to measure strength of associations, considering HPV infection as the dependent variable (Study IV).

Qualitative part

All twelve interviews (study II) were analyzed using content analysis (Graneheim & Lundman, 2004). All of the interviews were transcribed from the audio tape and note taking by the interviewer after each interview and then translated from Lao into English. The transcripts of the discussions and the interviews were read several times to obtain a sense of the whole. Key words and phrases were underlined, condensed meaning units were identified and then the codes were formed. Once coded, the data was analyzed for common themes, and findings were summarized.

3.2.4 Ethical aspects

All four studies were approved by the National Ethics Committee for Health Research, Ministry of Health of Laos (No 175/ NECHR and No 299/NECHR)

and for Study IV by the Regional Research Ethics Committee in Stockholm, Sweden (2010/787-31/1).

Informed consent was obtained from all the subjects, emphasizing that refusing to participate or leaving the study at any time, would not adversely affect any care provided and would not influence future care. Participation was voluntary. All study personnel were trained regarding the importance of strict confidentiality regarding information and data. All collected information was handled anonymously.

4 RESULTS

4.1 WOMEN'S KNOWLEDGE, AWARENESS AND ATTITUDES RELATING TO CERVICAL CANCER (STUDY I)

The median age of the 800 women was 34 years (range 18 to 55 years). Nine out of ten were married (91%) and three out of four engaged in farming (74%). Seventy three percent of the participating women were Buddhists, 13% were Christian, and 10% animist or others.

More than half (58%) claimed to have heard about cancer of the cervix. Among those women, 70% expressed a concern about developing the disease, and 34% of them believed that they were at risk. Sixty-two percent believed that the disease could be prevented and 59% thought it can be cured.

Vaccination was considered as one method of prevention by 61%, of the 62% of the women who believed that cervical cancer can be prevented. Seventy percent thought that frequent vaginal douching would prevent the development of cervical cancer. Of the respondents overall, 14% correctly identified all of the risk factors. The most commonly selected symptoms likely to indicate cervical cancer as listed to the women were a foul vaginal discharge (64%) and inter-menstrual bleeding (52%).

Only 37% of the women reported having had a gynaecological examination at some point in the past, most commonly as part of the investigation and management of vaginal discharge (38%), pregnancy related problems (24%) or pelvic pain (18%), while 14% had had an examination as part of a routine health check. Only 36 (4.5%) of the women studied had ever had a Pap smear performed. Among those, 30 of them believed the test to be a way of preventing cancer or detecting it at a curable stage, while six women thought it was a test for sexually transmitted infections.

With respect to what prevented them from having gynaecological examination, 78% stated that since they felt healthy there was no need for it. Thirty percent said they could not cope if they were given a diagnosis of cancer and 20%

expressed feelings of embarrassment and fear of pain during examination. Lack of money or distance to health facility was only reported by nine women.

The main sources of knowledge about cervical cancer were reported to be the media (47%), health care providers (30%) and friends (23%). When asked whether they would like to know more about cervical cancer, 83% agreed.

4.2 OPINIONS OF HEALTH CARE PROVIDERS AND POLICY MAKERS

4.2.1 Survey of knowledge, attitudes and practices of health care providers (study II)

A total of 261/291 (90%) of the survey forms were returned. The majority of respondents (74%) were midwives, nurses or nurse assistants, one-fifth (21%) were medical assistants and a small proportion (5%) were medical doctors. About three out of four (77%) worked at health centres, and two-thirds (62%) of them had been in practice for over 10 years. The mean age was 36 years (SD 7.9) and 58% were female.

About two thirds of the respondents (68%) believed that cervical cancer was the most common cancer in low-income countries, and that it was preventable by changing sexual behaviour (67%). Well under half of the respondents believed cervical cancer could be cured by early detection of the cancerous lesion (29%), or by hysterectomy (40%). Seventeen percent of the respondents correctly identified three of the five risk factors (early age at first sexual intercourse, multiple sexual partners, smoking, multiparity and sexually transmitted infections), and 13% did not recognize any of them.

About six out of ten of the respondents answered that the possible symptoms of early cervical cancer were heavy vaginal bleeding (61%), postcoital and intermenstrual bleeding (58%), whereas 44% believed that there were no symptoms. Almost half of the respondents (46%) believed that the Pap smear was a test to detect cervical cancer, while 39% thought it was a test to detect precancerous lesions. Sixteen per cent thought the test was for detecting sexually transmitted infections.

More than half of the respondents (57%) said they had performed vaginal examinations. Only 36/151 (24%) of the female respondents stated that they

themselves had ever had a Pap smear. Seventy-nine percent of health care providers never advised or referred women for screening. In total 72% of the respondents felt that they had an important role in cervical cancer prevention, although 63% of them felt that their knowledge about cervical cancer was inadequate.

4.2.2 Interviews with key informants (Study II)

Five themes were identified: a) lack of data regarding to cervical cancer in Laos, b) perceptions, regarding the increase in the incidence, c) lack of a national policy for screening, d) lack of public awareness and e) prioritization of women's health issues in government planning.

Lack of data regarding cervical cancer

A common and recurrent theme was that there was no data regarding the incidence of any form of cancer in the country. More than half of the senior health administrators explained that there was no data collected at the central hospitals, let alone in the provincial or district facilities, and felt that one should start with getting databases in the central hospitals as a first step to a country-wide audit. One respondent believed that if such a survey showed there was a significant problem with cervical cancer, then either the Ministry of Health or a foreign aid organization would take up the challenge:

"I can't say anything about the frequency or mortality of any cancer: we do not have any information. We need to start collecting data when women come to hospital for any problem relating to reproductive health. Lack of data is a real problem."(MCI 1)

A number of respondents pointed out that part of the problem relating to lack of data was that pathological examinations were rarely undertaken on surgical specimens, as stated by the director of a provincial hospital:

"...the big problem is that there are a lot of operations done for cancer in women but we don't know the exact types of cancer because tests were not sent for pathology."(MOH1)

None of the respondents elaborated on the reasons why pathology was not done, and none seemed to consider that it was an important part of the treatment of the patient.

Perceptions regarding the increase in the incidence of cervical cancer

There was a strong feeling among respondents that, even though hard data was not available, cervical cancer, or at last female genital cancer, was increasing in incidence.

“...the number of non-communicable diseases is increasing and at the top of the list [recently] is female cancer, second to liver cancer...as you can see when you go to the hospitals, there are more cancer patients admitted....especially breast cancer, cancer of the liver, cervical cancer... (MOH2, MCI 2)

The assumption regarding the increasing incidence of cervical cancer was often related to the belief that there was an increasing incidence of hysterectomies, which most respondents believed were frequently performed to treat cancer:

“It seems like the trend of cancer is on the rise, because there are a lot of hysterectomies done. Cancer may have originated from the cervix but it does not indicate what types of cervical cancer they were done for.” (MOH1)

Lack of a national policy for screening

Most respondents commented on the lack of any national policy on screening for cervical cancer. They commented that screening was only practised in central hospitals and even there in a haphazard way.

“We don’t have a policy or strategy specifically related to cervical cancer prevention...but the health professionals who are dealing with this issue, [have attempted to] investigate and diagnose the disease... according to their own training without any policy or guidelines [from the ministry];...each hospital provides the screening according to their own experience which is different between hospitals.... they should work and share ideas in order to make proper guidelines....” (MOH2)

On the other hand, respondents from provincial areas pointed out the logistical problems of providing services outside the capital:

“With regard to pap smears and biopsy to make a diagnosis, it can only be done in the central hospitals due to the fact that there are only a few cytologists in the country who can interpret the slides and they are at the central hospitals ...”(DOH2)

Lack of public awareness

Many of the respondents made reference to the need to increase public awareness of cervical cancer and its prevention. One stated that this was part of an existing, but unimplemented part of a national reproductive health policy:

“The policy said that every woman should have access to the screening and treatment of cancer of genital tract including... with a view to preventing the diseases. Because the incidence of these problems is rising we want every woman ... to be aware of the issues and to provide examination for breast cancer and cervical cancer for them.”(MCI 1)

The fact that cervical screening must be done in health care facilities and involved an intimate examination was seen by some respondents to make increased public awareness a critical issue.

“Performing breast examination is something external and can be done by the woman herself, but the cervix, that is inside and hiddenand most of the cervical cancer patients come at a late and untreatable stage. Women must be taught the importance of being screened before there are symptoms.”(MCI 2)

There a few suggestions were a “national cervical cancer awareness” day:

“There should be a national policy for the women to come for the Pap smear on a particular day such as March 8 of each year which is the Women’s Day. The government should emphasize this to the women in remote area because the majority of city women are educated and they will come for the health check each year” (MOH1)

The respondent did not give any thought to the logistics of such a project, particularly if all women were encouraged to come on a single day. This probably indicates a lack of understanding of what is involved in cervical

screening. One respondent believed that a very important part of a national awareness campaign would be to involve the Lao Women's Union which has committees in all villages around the country and has the potential to be a significant political voice for women.

Women health issues in government planning

Several of the key informants highlighted that cervical cancer does not feature as prominently as other conditions when considered in terms of health priorities:

“Up to the present time, reproductive health issues have focused on family planning, ...because Lao women have too many children which leads to complications during pregnancy or labour, often causing maternal mortality, so we have tried to focus on reducing this risk” (NGO1)

Most of the key informants stated that a key challenge for prioritizing cervical cancer prevention is the lack of available data on disease prevalence and that no-one had any realistic plan for obtaining such data.

“Get the data about cervical cancer for the whole country and it can be used as an evidence base in order to inform the Ministry of Health to recognize the real situation of cervical cancer in Laos, how big or small numbers of cancer...”(NGO2)

Half of the key informants pointed out this problem needs to be brought to the attention of the policy makers and authorities concerned about cervical cancer because this cancer can be prevented with proper screening and treatment:

“They take care of the women during pregnancy and delivery in order to reduce maternal mortality, but without thinking that cervical cancer is also a cause of death of both young and old women. In the past, women never had health checks, so we knew nothing... this is really one of the important issues that health programs should pay attention to as well.” (MCI 2)

In addition to this, a few suggestions stated that there is a real need for a greater professional commitment from health staff in order to achieve the given task.

“... The performance always has disrupted because the trained staff has always moved to other job...even though before moving you have to find somebody to take over the work... teach and train the new staff how to do the work properly before leaving or you have to come back and train the new staff...” (OBGY2).

4.3 SAFETY, FEASIBILITY AND ACCEPTABILITY OF VIA AND IMMEDIATE TREATMENT (STUDY III)

The mean age of the 1926 participating women was 34 ± 6 years (range 25–45 years), and most of them were engaged in farming. Average of parity was three with a wide range of 1-15. Nearly half of the participants (46%) had finished secondary schools and four out of five were Buddhists (86%).

Ninety-six percent of the participants indicated that they had come specifically for the screening and treatment program and 74% had discussed participation with their husband. Forty percent of these women had never had a gynaecological examination. About half of them had undergone between one and seven abortions, and 83 (4%) women were smokers.

Some eight percent of the women reported having had more than one sexual partner (range 2–9). Seventy percent of them believed that their husband had sex with other women, and 30% of these women believed that their husband used condoms in extramarital relationships.

Among the 1926 women tested, 134 (7%) women were VIA-positive. Of these, 113 (84%) were eligible for, and accepted, treatment with cryotherapy on the day of VIA testing. Treatment was performed on a later day for 14 women (12%) because they wished to talk to their husband (4%) or because of lack of equipment (8%). There were no major complications during or immediately after cryotherapy.

The twenty-one VIA-positive women who were ineligible for cryotherapy were referred for biopsy and large electrosurgical excision procedure (LEEP) at the provincial hospital. The pathology results of these lesions was cancer in four cases, cervicitis in six, high-grade squamous intraepithelial lesion (HSIL) in five,

low-grade squamous intraepithelial lesion (LSIL) in four, condyloma in one, and metaplasia in one.

One year follow-up

Of the 113 women treated with cryotherapy, 77 (68%) returned after 1 year as scheduled. No major complications were reported, but 63 (82%) reported having had a watery vaginal discharge during the first four weeks after treatment. Mild to moderate cramps for 2–3 days had been experienced by 14 women (18%). No woman had been hospitalized. The vast majority (90%) reported to have strictly followed the home care instructions.

Among those who returned for follow-up, 68 women (88%) were VIA-negative, seven (9%) were VIA-positive and while two women have had hysterectomy due to fibroid and ovarian tumour. Those who were not eligible for cryotherapy were sent to the provincial hospital for further investigation. Nearly all women were satisfied with their decision to be tested and would recommend VIA to friends or relatives. All women were very pleased (91%) or pleased (9%) with the services and the healthcare providers.

4.4 DETECTION OF HUMAN PAPILLOMAVIRUS AMONG WOMEN IN LAOS: FEASIBILITY OF USING FILTER PAPER CARD AND PREVALENCE OF HIGH-RISK TYPES (STUDY IV)

There were 1,922/1933 women (99%) with sufficient cellular material on the FTA card for subsequent HPV typing analysis. The mean age was 34 years (SD 6.1).

Overall, 11% (213/1,922) of the women were positive for HR-HPV. The prevalence of HR-HPV varied markedly between the three populations. Vientiane had the highest prevalence of 14% compared to 12 % in LuangPrabang province and only 4% in Champassack province. Most infected women (85%, n=182/213) were either infected by a single HPV type, such as HPV16, or one of a group detected by the same fluorophore, such as HPV33/52/58 or HPV18/45. Thirty-one women (1.6%) were positive for several HR-HPV types, most commonly the group HPV33/52/58 and HPV16 (Table 3).

The prevalence of HR-HPV infection did not differ between age groups, either in the overall study population or in any of the provinces (Table 4 and Table 5). Women with one or two children had a reduced risk of HR-HPV (Table 5). Farmers and women with only primary school education had significantly lower HR-HPV prevalence (Table 5). Neither age at first intercourse, number of lifetime sexual partners, or smoking, which was very rare in these women, were associated with higher prevalence of HR-HPV (Table 4). Fifty-four percent of the women had used some form of modern contraception most commonly oral contraceptives (24%). The majority of the participants (85%) had never had a Pap smear.

Among 1922 women, 131 (7%) women were VIA-positive. Of those women, 23/131 (18%) were HR-HPV positive. Although VIA positivity was associated with infection by HR-HPV in the univariate analysis, the effect was not seen when using adjusted OR. The most common HR-HPV infection in VIA-positive women was HPV16 (30%) and the group of HPV33/52/58 (22%).

In the multivariate analysis, when all the variables significantly related to HPV infection were included (Table 4), living in Vientiane city (OR=4.15, 95% CI: 2.34-7.35) and LuangPabang provinces (OR=4.52, 95% CI: 2.55-8.02) showed a four times increased risk for HPV infection compared to living in the Champassack province. Women with one or two children (OR=0.52, 95% CI: 0.31-0.89) and women engaged in farming (OR=0.56, 95% CI: 0.34-0.94) were less likely to get infected with HPV than other women in the study.

Table 3. Frequency of single and multiple HR-HPV type infection among HPV positive women of the three provinces and overall.

HPV subtypes ^a	Number of women (%) with single or multiple of HR-HPV				HPV prev
	Luangprabang n (%)	Vientiane n (%)	Champassack n (%)	Overall n (%)	n (%) of 1922
Single type					
16	20 (2.3)	19 (3.0)	4 (1.0)	43 (2.2)	59 (3.1)
18/45	13 (1.5)	8 (1.2)	1 (0.3)	22 (1.1)	28 (1.5)
31	6 (0.7)	3 (0.5)	-	9 (0.5)	15 (0.8)
33/52/58	28 (3.2)	29 (4.5)	4 (1.0)	61 (3.2)	83 (4.3)
35	-	2 (0.3)	-	2 (0.1)	3 (0.15)
39	9 (1.0)	4 (0.6)	-	13 (0.7)	14 (0.7)
51	3 (0.3)	1 (0.2)	-	4 (0.2)	7 (0.3)
56	5 (0.6)	9 (1.4)	4 (1.0)	18 (0.9)	26 (1.4)
59	8 (0.9)	2 (0.3)	-	10 (0.5)	16 (0.8)
Multiple types					
16,31	1 (0.11)	-	-	1 (0.05)	
16, 33/52/58	4 (0.45)	2 (0.31)	2 (0.5)	8 (0.40)	
33/52/58,56,59	1 (0.11)	-	-	1 (0.05)	
16, 33/52/58,56	1 (0.11)	-	-	1 (0.05)	
31, 33/52/58,56	1 (0.11)	-	-	1 (0.05)	
16,59	1 (0.11)	-	-	1 (0.05)	
51,59	1 (0.11)	-	-	1 (0.05)	
16,51	1 (0.11)	-	-	1 (0.05)	
18/45, 33/52/58,56	1 (0.11)	-	-	1 (0.05)	
16, 18/45,31	1 (0.11)	-	-	1 (0.05)	
33/52/58,59	1 (0.11)	1(0.16)	-	2 (0.10)	
33/52/58,56	1 (0.11)	2 (0.31)	-	3 (0.20)	
31, 33/52/58	-	2 (0.31)	-	2 (0.10)	
16,51,59	-	1 (0.16)	-	1 (0.05)	
18/45, 31	-	1 (0.16)	-	1 (0.05)	
18/45, 33/52/58	-	1 (0.16)	-	1 (0.05)	
31, 33/52/58, 35	-	1 (0.16)	-	1 (0.05)	
39,56	-	1 (0.16)	-	1 (0.05)	
16, 18/45	-	1 (0.16)	-	1 (0.05)	
16, 18/45, 33/52/58	-	1 (0.16)	-	1 (0.05)	
Total	107 (12.1)	91 (14.1)	15 (3.8)	213 (11.1)	

Table 4. ORs and 95% CI for HPV DNA positivity by provinces

Characteristics	LPB (n=886)			VTE (n=645)			CPX (n=391)		
	Total	N (%)	HPV+ OR	Total	N (%)	HPV+ OR	Total	N (%)	HPV+ OR
Age groups									
25-29	281	31 (11)	0.83 (0.47-1.48)	144	22 (15)	1.10 (0.60-2.01)	89	4 (4)	1.79 (0.39-8.20)
30-34	216	28 (13)	0.99 (0.55-1.80)	128	18 (14)	0.99 (0.52-1.90)	80	2 (2)	0.97 (0.16-5.97)
35-39	212	25 (12)	0.89 (0.49-1.63)	182	24 (13)	0.92 (0.51-1.67)	105	6 (6)	2.30 (0.56-9.45)
40-48	177	23 (13)	1	191	17 (9)	1	117	3 (3)	1
Marital status									
Married			1	654	91	-	369	14 (4)	1
Separated or divorce			1.87 (0.74-4.68)	0	0	-	22	1 (4)	1.20 (0.51-9.62)
Parity									
None	74	15 (20)	1	21	4 (19)	1	32	3 (9)	1
1-2	440	44 (10)	0.44 (0.22-0.83)	390	58 (15)	0.74 (0.24-2.30)	171	5 (3)	0.29 (0.66-1.29)
3-4	273	36 (13)	0.60 (0.31-1.61)	209	27 (13)	0.63 (0.19-2.01)	154	7 (4)	0.46 (0.11-1.89)
> 5	99	12 (12)	0.54 (0.24-3.24)	25	2 (8)	0.36 (0.06-2.26)	34	0	-
Occupation									
Housewife	86	11 (13)	1	194	33 (17)	1	82	3	1
Farmer	451	42 (9)	0.70 (0.34-1.42)	33	2 (6)	0.31 (0.71-1.38)	50	0	-
Vendors or labourers	197	32 (16)	1.32 (0.63-2.76)	139	15 (11)	0.59 (0.30-1.13)	140	6	1.18 (0.29-4.84)
Government officer	152	22 (14)	1.15 (0.53-2.51)	279	41 (15)	0.84 (0.51-1.38)	119	6	1.39 (0.34-5.76)
Education									
No school	128	18 (14)	1.02 (0.55-1.92)	40	4 (10)	0.65 (0.22-1.93)	12	0	-
Primary (1-5 years)	357	29 (8)	0.55 (0.32-0.95)	115	13 (11)	0.74 (0.39-1.45)	70	0	-
Secondary (6-8 years)	183	30 (16)	1.22 (0.71-2.13)	194	31 (16)	1.11 (0.78-1.85)	136	4	0.45 (0.134-1.43)
Graduate or college	218	30 (14)	1	296	43 (14)	1	173	11	1
Age at first intercourse									
12-15	111	14 (13)	1.01 (0.45-2.26)	4	0	-	4	0	-
16-18	340	38 (11)	0.88 (0.45-1.72)	123	17 (2)	0.84 (0.45-1.65)	48	1 (2)	0.57 (0.62-5.28)
19-24	331	42 (13)	1.01 (0.52-1.98)	339	46 (14)	0.85 (0.51-1.40)	227	10 (4)	1.24 (0.38-4.06)
≥ 25	104	13 (12)	1	179	28 (16)	1	112	4	1
Number of partners									
1	817	99 (12)	1	634	88 (14)	1	364	14 (4)	1
2	61	7 (11)	0.94 (0.42-2.12)	11	3 (27)	2.32 (0.60-8.94)	24	1 (4)	1.09 (1.37-8.63)
>3	8	1 (12)	1.04 (0.13-8.50)	0	0	-	3	0	-

Table 5. ORs and 95% CI for HPV DNA positivity by provinces and selected characteristics among 1922 studied women.

	No of women	HR-HPV+		OR
		n	%	(95% CI)
Provinces				
Luangprabang	886	107	12.1	3.44 (1.97-5.99)
Vientiane	645	91	14.1	4.12 (2.34-7.22)
Champassack	391	15	3.8	1
Age				
25-29	514	57	11.1	1.01 (0.68-1.51)
30-34	424	48	11.3	1.04 (0.69-1.57)
35-39	499	55	11.0	1.00 (0.66-1.51)
40-48	485	53	10.9	1
Occupation				
Housewife	362	47	12.9	1
Farmer	534	44	8.2	0.60 (0.39-0.93)
Vendors & workers	476	53	11.1	0.84 (0.55-1.28)
Government officer	550	69	12.5	0.96 (0.65-1.42)
Education				
No school	180	22	12.2	1.00 (0.60-1.65)
Primary	542	42	7.7	0.60 (0.41-0.89)
Secondary	513	65	16.7	1.04 (0.60-1.64)
Graduate or college	687	84	12.2	1
Age at first intercourse				
< 15 years	119	14	11.8	0.96 (0.51-1.82)
16-18 years	511	56	10.9	0.92 (0.51-1.67)
19-24 years	897	98	10.9	0.92 (0.49-1.72)
> 25 years	395	45	11.4	1
No. of sexual partners				
1	1815	201	11.1	1
2	96	11	11.5	1.04 (0.54-1.98)
>3	11	1	9.1	0.80 (0.10-6.30)
Parity				
None	127	22	17.3	1
1-2	1,001	107	10.7	0.57 (0.35-0.94)
3-4	636	70	11.0	0.59 (0.35-0.99)
> 5	158	14	8.9	0.46 (0.23-0.95)
Contraceptive used				
None	875	90	10.3	1
Pills	459	53	11.5	1.13 (0.79-1.63)
DMPA	181	19	10.5	1.02 (0.61-1.73)
IUD	142	18	12.7	1.27 (0.74-2.17)
Condoms	164	28	17.1	1.80 (1.13-2.85)
Tubal ligation	101	5	4.9	0.45 (0.18-1.15)

5 DISCUSSION

It is generally accepted that well-organized community-wide cervical cancer prevention programs based on screening for precancerous lesions lead to impressive reductions in cervical cancer rates in high-income countries (Parkin et al, 2005; Arbyn et al, 2008). Cervical cytology has for decades been a cornerstone of cervical cancer screening but screening can only be effective if there is a well-organized system of follow up, diagnosis and treatment (WHO Library, 2006). Clearly the knowledge, attitudes and practice of women and of health care providers are important aspects of the acceptance and success of such preventative programs (Agurto et al, 2004; Wright et al, 2010).

1. Knowledge and attitudes of women

Awareness is of the utmost importance in getting women to undertake preventative health measures (Ajayi et al, 1998; Swaddiwudhipong et al, 1999; Gichangi et al, 2003). Where there is a lack of knowledge and information, screening behaviour is not undertaken (Diggman et al, 1996; Wright et al, 2010). Our study demonstrated that more than half of the women claimed to have prior knowledge of cervical cancer (58%) and two-thirds of these women believed that cervical cancer can be prevented through vaccination (61%). However, it is most unlikely that these women had heard of HPV vaccines. Probably, their beliefs are rather a reflection of the number of vaccination projects that have been carried out over the years throughout the country, mainly for the prevention of infectious diseases in children. Similar perceptions have been found in Mexico (Moraros et al, 2006).

Regarding perception of the risk factors, one in ten women was able to identify five of them (multiple partners, STI, early marriage, high parity, and smoking). This finding was similar to that from a study done in Nigeria (13%) (Wright et al, 2010). Importantly, misinformation or misconceptions about induced abortion and IUD use as causing the development of cervical cancer were common held beliefs among the Lao women. Similar perceptions have been reported from Cameroon and Kenya (Tebeu et al, 2008; Gatune et al, 2005). Vaginal douching was also believed to be a preventative measure to avoid the

development of cervical cancer, which is similar to beliefs of Vietnamese women living in the USA (Gardner et al, 1991). Such misapprehensions could be a major problem causing increased risks rather than benefits (Martino et al, 2002) and they may endanger the use of valuable contraceptive techniques which are of great importance for women's health in a country like Laos.

A large number of women had never had a gynaecological examination but the fear that they might be reluctant to do so turned out to be groundless. Despite this, lack of awareness of the risk factors for cervical cancer, considering oneself not to be at risk of developing the disease, and fear of being found to have it, were major barriers preventing women from seeking care, which is consistent with reports from Kenya and South Africa (Were et al, 2011; Bailie et al, 1996; Wellensiek et al, 2002). This may be due to lack of health education or information about cervical cancer in the public domain (Wright et al, 2010).

The fact that most of the women who claimed to know about cervical cancer said they gained their information from media sources and only one third from health-care providers, indicates that the media can play an important role in educating women regarding cervical cancer in Laos. Similar findings have been reported from Nigeria (Ajayi et al, 1998; Nwankwo et al, 2010).

Lack of knowledge or lack of awareness of the disease was suggested to be a barrier in cervical cancer screening and prevention. Therefore, health education and particularly education about cervical cancer and its prevention needs to be carried out throughout the community. Media campaigns have been widely used in low-income countries, such as health campaigns on National Cancer Day like in South Africa (Mosavel et al, 2009). Another approach has been used in Thailand where a mobile team promoted cervical cancer screening program and provided health education as well as extending invitations for screening to the target population (Swaddiwudhipong et al, 1999).

2. Knowledge attitudes and practice of health care providers (HCPs)

Both HCPs and policy makers acknowledged that cervical cancer is a major public health problem. Their beliefs were largely based on anecdotal

observations of increasing numbers of women presenting with the disease at hospitals, even though there was no data to support this belief.

The majority of the participating HCPs in Study II were nurses and auxiliary nurses working in health-care centres. The educational level of the respondents was very low, with only 4% having qualifications beyond primary school. This clearly limits their knowledge and skills. In contrast a study from neighbouring Thailand showed that 76% of the health professionals had obtained diploma or similar qualification (Oranatanaphan et al, 2010). A major goal of the Ministry of Health must be recognising and addressing this problem, because it impacts all aspects of community health care.

It is of great concern that more than one-third of the HCPs believed that cervical cancer could not be treated, although this is similar to the figure of 39% from Uganda (Mutya et al, 2006). This may be a reflection of the late stage of presentation of many women with the disease and the lack of appropriate knowledge and skills among gynaecologists in the country. The belief that the disease is untreatable may well lead to a lack of interest in discussing it with women. While two-thirds of HCPs believed the disease to be preventable there was little evidence that they really understood how. Twenty percent could identify three of the risk factors but ten percent had no idea at all which is comparable to the figure in a study done in Thailand (Oranatanaphan et al, 2010). Moreover, 42% believed incorrectly that abortion is one of the causes of cervical cancer, while only 6% recognized smoking as a risk factor, which is fewer than found in studies done in Thailand (56%) and in Turkey (76%) (Nganwai et al, 2007; Yaren et al, 2007).

In this study, nearly half of the HCPs (44%) were aware of the possibility that early cervical cancer may occur without any symptoms, a figure which is much higher than in Thailand (2.6%) (Pianmongkhon et al, 2011). This figure is rather surprising and may have resulted from the framing of the question rather than because of actual knowledge.

Only 46% recognized the Pap smear as a test to detect precancerous lesions or to detect cancer, which was less than in other low-income countries

(Ghargoro et al, 2006; Mutyaba et al, 2009, Thanappapasr et al, 2010). About one out of four female providers in Laos had undergone screening themselves, which is consistent with finding in studies from Uganda and Thailand (Mutyaba et al, 2009; Oranatanaphan et al, 2010) but a higher rate than in Nigeria (7-9%) (Ayinde et al, 2003; Anya et al, 2005). It is therefore unlikely that those HCPs, who had not screened themselves, would then feel motivated to screen others or even advise women to be screened. We do not know why they had not sought screening: it may have been because lack of access to screening or because they did not feel vulnerable to the disease.

3. Policy makers' opinions

The most common concern among policy-makers was that there was no data relating to the incidence of any form of cancer in the country. Awareness was limited regarding the burden of the disease because of lack of information to the health facilities. Therefore, it was suggested that there is a need to get started with databases in the central hospitals as a first step to a country-wide audit. This challenge would need to be met by either the Ministry of Health or a foreign aid organization willing to take charge of this responsibility. One needs to be aware that it is very likely that only a small proportion of women with the disease ever get to a central hospital. There was a strong feeling that since more patients were being seen or diagnosed with the disease in hospitals, that the incidence is high and increasing even though there is no data available and the assumption may be wrong.

Clearly Laos needs a national program but the approach must be realistic if it is to be implemented and applicable in relation to the demographics of the country. One key respondent in this study stated that a policy advocating cervical cancer screening exists, but there is no strategy or action plan for implementing it. She felt that even though some services have provided cervical screening or treatment without any guidance, national guidelines on cervical cancer prevention and management should be provided. There is a need to draw the policy makers' attention to this issue because cancer of the cervix can be prevented, and treated effectively if detected at an early stage, which would cost less and can save the life of a mother and the mainstay of the family which is not greatly different from preventing a maternal death.

4. The feasibility of a see and treat approach

The most common method for cervical cancer prevention is cytological screening but there are technical, human resources and financial constraints which make it difficult to implement such programs in low-income countries.

We found VIA followed by immediate treatment with cryotherapy to be an attractive approach because it is simple and requires minimal infrastructure for service delivery and by offering immediate treatment it decreases the risk of loss to follow-up (study III). A study from Peru (Jeronimo et al, 2005) reported that 40% of VIA-positive women did not return for planned examination and treatment whereas in our study none of the VIA-positive women declined treatment. For the planned follow-up, one year after the treatment, three out of four of the women returned as instructed. Some of the reasons for not returning may be that women had moved, changed phone numbers, or were engaged in work in the rice fields. Women in rural Laos are obliged to participate in family work, an obligation which is of greater importance than their own wellbeing, and this must be considered when planning a prevention program for these women.

The disadvantage with this “see and treat” model is that since the sensitivity of VIA is high but the specificity is relatively low there is a risk of overtreatment. Cryotherapy is considered to be safe in the hands of experienced providers (Jacob et al, 2005; Blumenthal et al, 2005, Sankaranarayanan et al, 2007) and this was confirmed in our study. It has been estimated that performing VIA with immediate cryotherapy in women with a positive test result once in a lifetime may have the potential to reduce the incidence of cervical cancer by 25% and the mortality by 35% (Sankaranarayanan et al, 2007). While methods other than VIA will be more accurate in identifying precancerous lesions, offering women a gynaecological examination can also reduce the incidence of advanced disease. In our study four cases of histologically confirmed early stage cervical cancer were found and referred for further management.

The overall findings showed that despite insufficient knowledge women were very positive towards participation in our studies. On several occasions there

were more women coming for the screening more than our resources to possibly cope with them during one day. We estimate that of the number of the reproductive aged women invited in the two provinces, about 55% actively took part in the studies (study III and IV).

5. HPV in cervical cancer prevention

A possible method for cervical cancer prevention is vaccination against HPV. The vaccine is available in many settings but is at present expensive. It protects against the two most common HR-HPV types found in cervical cancer, HPV 16 and 18. However the distribution pattern of HR-HPV differs in different geographical regions. When new vaccines are being developed it is important to consider these differences between populations (Bosch et al, 1995; Walboomers et al, 1999; Munoz et al, 2003). Among women included in our analysis we showed that 11% were infected with some type of HR-HPV and thus at risk of developing invasive cancer. It is however important to bear in mind that most infections clear spontaneously, and do not develop into cancer (Bosch et al, 2000). HPV testing could also be used as a screening method; like VIA it has a high sensitivity but lower specificity. In many resourceful settings today it is used in combination with cytology to increase the specificity of screening (ACOG, 2009; Schiffman et al, 2011). A rapid test, giving the result immediately, in combination with VIA would probably reduce the number of women needed to be treated (Ngan et al, 2011). Recently, a rapid and affordable HPV test has been developed which gives promising results for low-recourse settings (Qiao et al, 2008; Shi et al, 2011).

Among the HR-HPV positive women, one out of ten was found to be VIA-positive. Given that this was a one-off testing of the women many of the HR-HPV positive women are likely to have transient infections which do not lead to CIN or cancer.

Detecting high risk HPV using filter paper medium

This study also showed that use of a filter paper card was feasible, durable and suitable in collecting genomic HPV-DNA for PCR-based analysis in Lao settings. Like other Asian countries, the temperature in Laos is warm all year round and with high humidity (75%). Storage conditions were far from optimal

before the specimens reached the air-conditioned office in the capital, often requiring drying with a hair dryer. Almost all yielded useable samples of genomic DNA to perform the HPV analysis, comparable results to the estimates for samples collected in other studies (Gustavsson et al, 2009b). Until recently, to our knowledge, there were only a few studies that reported the use of filter paper cards to collect HPV-DNA for analysis. One study from Uganda has shown that the detection rate of HPV-DNA from paper smear was lower than when cells were collected in phosphate buffer saline (Banura et al, 2009). In contrast, three studies showed that using filter paper card as a collection medium was equivalent to liquid based media or the dry cytobrush medium in detecting HPV-DNA types (Khailash et al, 2002; Gustavsson et al, 2009b, Lenselink et al, 2009). In the Uganda study a sterile cotton swab was used. It is likely that the different collecting techniques may explain the difference between that study and the others, including our.

6. Methodological considerations

a. Quantitative methods

The strength of our studies was the large sample size with high response rates (90-100%). Most of the women showed willingness to participate in Study I even though they had never heard about the tests before (Study III, IV). Furthermore, seven out of ten of the women treated with cryotherapy (Study III) returned for follow-up, one year later.

Despite the fact that these studies were limited to selected districts of two provinces, the validity of the study was strengthened as the women were randomly selected from the list provided by the heads of village or the Lao Women Union, independently from the researcher (Study I, III, IV). The target age range for the women in our studies was limited because our intention was to focus on prevention of cervical cancer programs rather than to detect cancer (Study III, IV).

The questionnaires were adapted and modified from other studies and then piloted among 50 women who were not part of the study sample. The questionnaire was designed to be clear and easy to administer consistently. After some modifications, these questionnaires were reviewed by HCPs at the

central hospitals in Vientiane and at the Division of Postgraduate Training and Research at the University of Health Sciences. As in all questionnaire-based surveys, this study relies only on the participant's self-reporting which may not represent their actual practice in sensitive areas such as age at first intercourse, number of sexual partners and other risk factors. In a face-to-face interview women may have found it difficult to answer such questions honestly, which may lead to underestimation of the real situation. To minimize this bias (Study I, III, IV), the interviewers were trained before data collection and used standardized closed-ended structured questionnaires to collect all information at baseline and follow-up. The reliability of the questionnaire as performed on knowledge and attitudes in Study I which Cronbach's Alpha coefficient values at 0.78 and 0.55 respectively.

All VIA examinations were performed in a consistent manner by the researchers and when VIA positivity was found, a double check was made by a second person, who repeated the examination and took a photograph. The major strengths of VIA include its simplicity and low cost, the real time availability of results and the potential for immediate linkage with further investigations and treatment. There are consistent estimates of its accuracy, and of the feasibility of using it in low-resource settings. Another advantage is the possibility of rapid training of providers.

The major limitations of VIA include: low specificity (generally less than 85%), which can lead to over-investigation and over-treatment of VIA-positive women and the lack of standardized methods of quality control, training and competency evaluation. Furthermore, it is limited in its ability to detect endo-cervical disease.

With respect to structured questionnaires, women are likely to report that they feel satisfied with the services that they have received and may not speak negatively about the services or the health providers. In addition to this, the collection of information about complications one year after treatment might have led to recall bias. However, the treatment event in itself was unique in the lives of the women and it can be reasonably assumed that they would at least remember major complications. Women who were VIA-negative were not

followed up. It would have been of added value to assess these women at one year, but this was impossible given the available resources. Finally, the gynaecologists were involved in the performance of VIA in this study for the purpose of training, which might reduce the generalizability of the findings as the intent would be to use nurses in the future preventative program.

This is the first study conducted in order to determine the prevalence of HR-HPV infection in Laos. It was thought that the storage of the samples would be extremely important in order to avoid damage or degradation of the DNA cell sample from the filter paper card for further analysis. Drying the FTA card was the main problem and often required the use of a hair dryer. Even so, the sample still contained sufficient HPV-DNA for analysis as frequently as was found in other studies in far more favourable environments. (Gustavsson et al, 2009b).

The analysis of HPV-DNA typing was done in an established laboratory (Rudbeck Laboratory, Uppsala University, Sweden) by experienced technicians. Highly sensitive PCR assay was used in this lab to detect the high risk HPV types. However, some of the high-risk types were detected as a group by the same fluorophore, such as HPV33/52/58 or HPV18/45. Therefore, those types could have been under-estimated in this study. We could have further analyzed it but whatever happens all of the women who have had positive results for these group types were classified as a high-risk group. Women who have had a single infection or a group of HR-HPV infections would have been at risk of developing cervical cancer when compared the HPV-negative women (Schiffman et al, 2011) and they need attention.

Even though all of the four studies incorporated in the thesis involved a large proportion of the women of reproductive age in the selected rural villages, the studies cannot be generalized to the overall rural population, because Laos is a country with 49 different ethnic groups with their own beliefs, cultural values and local conditions. In Study IV, there were only 391 women invited to participate from Champassack province due to a shortage of cytobrushes for collecting cervical cells for HPV testing. Therefore women from Vientiane city

were included in order to increase the statistical power calculation of the sample size from 91 to 99% (Lenth, 2006-9).

Regarding Study II, all health centres of the two provinces were included. Distribution and collection of the questionnaire was done through the district health officer and then the provincial health officer before reaching the research team. Because this is a structured questionnaire that relied heavily on self-reporting or was self-administered, it might not correlate with actual knowledge and practice. It is not possible to be certain whether what the health care providers reported was an accurate description of their real practice.

b. Qualitative research methods

Key informant interviews

Key informant interviews with policy makers were added in the second part of study II in order to explore more about the nature and magnitude of the problems. Content analysis was used. The selection of the key informants in this study was purposive sampling.

Trustworthiness

Three issues should be considered in order to evaluate and generate the findings: credibility, dependability and transferability. Credibility was enhanced by means of a thorough analysis and by verifying the transcripts with the co-author to ensure the consistency of the transcribed content. Then one author separately coded the interviews and the other co-authors took part in discussions on the emerging codes, categories and themes until consensus was reached.

The finding of the study, which aimed at exploring the opinion of policy makers, cannot be transferred to other settings. However, the findings can be applied in a similar situation to enhance understanding of the actual situation.

7. Implications for future research

Based on the research findings presented in this thesis, the following topics are recommended for future research:

1. Determining the most effective means of increasing the awareness of women in the community about their role in preventing the disease.
2. Intervention studies on health education approaches in the general population, particularly in rural communities.
3. Evaluating the most appropriate ways of implementing a cervical cancer prevention strategy.
4. Exploring the knowledge and practices regarding cervical cancer prevention among health-care providers throughout the country in order to improve and integrate the prevention program and to plan guidelines for the whole country.
5. The most appropriate ways of strengthening the curriculum for undergraduate and postgraduate training relating to cervical cancer and its prevention.
6. Investigations of the most effective ways to deliver continuing professional development to improve the practice and skills of the diverse groups of health professionals who need to be involved in screening and prevention
7. More research is needed regarding population-based cervical cancer statistics in order to inform policy makers about the disease and also to strengthen the existing policies, and ensure their proper implementation.
8. To investigate the hypothesis that programs for cervical cancer prevention will also result in a greater awareness of cancer services as a whole and therefore contribute significantly to the health of the population.
9. To further investigate the prevalence of high risk HPV infection in other parts of the country, and in particular in association with biopsy proven cervical intraepithelial neoplasia and cancer.

6 CONCLUSION

Lao women in rural settings have limited knowledge about cervical cancer and even less about screening and prevention. There is a need to educate the general community about the disease and its prevention. Such an educational program would need to be linked to an appropriate screening and treatment program. It was encouraging that most of the interviewed women expressed an interest in knowing more about the disease and expressed willingness to come to either a district or a provincial hospital for health check and for screening if any is provided.

This study has also revealed poor knowledge of cervical cancer and prevention as well as low level of supportive attitudes and practice of screening among these health care providers in rural areas of Laos. Health professionals need to be properly informed or educated about cervical cancer screening and prevention in order to become motivate to encourage screening and health checks. The health providers in partnership with concerned authorities are important as the frontline staff for any campaign of the cervical cancer prevention. For a successful introduction of a future general screening program appropriate training of providers involved in women's health is needed. An informed attention policy maker is needed in order to prioritize such a campaign as an important issue of the country.

VIA is an attractive test in low-resource settings like Laos, being simple and requiring minimal infrastructure. Results are immediate, making it possible to offer treatment during the same visit, decreasing the chance of loss to follow up. Cryotherapy is an effective treatment option, which is also feasible in low-resource settings. The equipment is cheap and a supply of carbon dioxide is readily available at affordable prices in provincial centres and easily transportable to the study sites. This study has shown that it is affordable, safe and feasible in the context of rural Laos, where the need is the greatest. Therefore, a preventive program, based on VIA and cryotherapy, constitutes a viable method at the primary care level of health services. However, it should be born in mind that all women with risk to develop cervical cancer will not be detected by one VIA examination. A future screening program needs to consider age groups and time intervals for offering the service.

This study has also shown that infection with HR-HPV infection was similar to other Asian countries. Infection with the virus types included in presently available vaccines (HPV16 and 18) was seen in only about one third of the HR-HPV positive women. There are, however, no studies on the association between HR-HPV types and diagnosed cervical neoplasia. Future studies should be performed to determine this association. The knowledge produced will constitute important information for planning and establishing approaches for primary and secondary prevention of cervical cancer in Laos.

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