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The Prevalence of High Risk Human Papilloma Viral Infection and Abnormal Cervical Cytology in Faculties of Medicine and Nursing, Chiang Mai University Population

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ABSTRACT

Objective: To evaluate the prevalence of high risk HPV infection and abnormal liquid based cytology (LBC) in healthcare population of Faculty of Medicine and Nursing, Chiang Mai University.

Material and Method: Healthcare population who aged ≥ 30 years and no history of preinvasive or invasive cervical cancer from both faculties were invited. LBC was done by collecting a specimen into Thin Prep Pap test solution and Cobas® 4800 was used for high risk HPV testing. The persons with abnormal cytology and /or HPV type 16/18 positive were referred for colposcopy.

Results: Between September, 2012 and April, 2013, 261 persons joined this project. Sixteen persons (6.1%) revealed abnormal cytology that consisted of ASCUS ten persons, LSIL four persons and HSIL two persons. Positive HPV test were also found in 16 persons (6.1%). Twelve persons (4.6%) showed positive only in the cytology or HPV tests while four persons tested positive in both methods. HPV type 16 was detected in one person and HPV type 18 was detected in two persons. With 17 persons who were referred for colposcopy, the colposcopic-directed biopsy and conization were done in seven and three persons, respectively. Of these persons, the histology showed chronic cervicitis in three persons, LSIL in four persons and HSIL in three persons. One HSIL person revealed only HPV type 16 positive without abnormal cytology.

Conclusion: The prevalence of high risk HPV infection and abnormal cytology seems to be minimal in healthcare population. Infected HPV type 16/18 persons should be referred for colposcopy even with normal cytology.

Keywords: Human papilloma virus, liqid based cytology, colposcopy, LSIL, HSIL

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Introduction

Cervical cancer is the most common gynecologic cancer in Thailand and it ranked as the third most common female cancer in the world[1]. The etiology of cervical cancer is the persistent mucosal infection with an oncogenic human papilloma virus (HPV) genotype especially type 16 and 18 that comprises 70% of cervical cancer[2]. Conventional cytological screening is the initial method frequently used in many countries. However, this screening method revealed a problem of high false negatives and is labor intensive[3]. Thus, in the decade of 2000-2010, liquid-based cytology (LBC) is an innovation which decreased the problem of inadequate smears with comparable sensitivity and specificity as conventional cytology[4]. Another advantage of LBC is that it enables the physician to identify the high risk HPV type on the same material. The combination LBC plus high risk HPV test will increase the accuracy of a cervical cancer screening method with the sensitivity of 100% and the specificity of 92.5%[5]. The American Cancer Society (ACS) recommends LBC plus a high risk HPV test in women over 30 years of age to detect persistent HPV infections. If both results are negative, the interval of repeat screening test can be postponed to five year intervals[6]. Four high risk HPV tests were approved by United States Food and Drug Administration (US-FDA) consisting of Hybrid Capture 2, Cervista® HPV high risk test, Cervista® HPV type 16,18 and Cobas® 4800 HPV test. The latter two HPV tests could be specified as HPV type 16,18 separate from other high risk HPV type[5,7,8].

Our center adopted LBC plus a high risk HPV test as the standard cervical cancer screening method in recent years. Although, this screening method presents a high accuracy, it was not popular in our healthcare population. This might be from the high cost (37 US-dollars per test). Thus, we applied the funding from our research committee to partially support the test with the primary aim to identify the prevalence of high risk HPV infection and abnormal LBC in the healthcare population older than 30 years of age who worked in Faculty of Medicine and Nursing. The second aim was to follow the final results after further investigation when abnormal tests were found.

Material and Method

After the proposal was accepted from our faculty research fund and approved by the local ethics committees, we invited the healthcare population in the Faculties of Medicine and Nursing of Chiang Mai University who were equal to or over 30 years old and would like to have cervical cancer screening. All invited participants should not have a history of treated cervical intraepithelial neoplasia or cervical cancer and never underwent hysterectomy or conization. We excluded the pregnant participants. Each participant required approximately 21 US dollars per test. After informed consent, the participants were requested to report personal information such as their latest cytology test, gynecologic symptoms, onset of sexual intercourse, the number of times married, smoking habits and the menopausal status. Pelvic examinations were performed on all of the participants by a gynecologist with the cervical epithelial cells collected in two steps by using Ayre spatula to collect from the ectocervical region and the cervical cytobrush to collect the endocervical epithelial cells. Afterward all the specimens collecting devices were dipped in Thin Prep Pap test solution and sent to the Department of Pathology to prepare the slides and process the high risk HPV testing by utilizing the Cobas® 4800 method. The cytology and further histology were interpreted by two pathologists (K.S, J.S) with using the term low grade squamous cell intraepithelial lesion (LSIL) for represent cervical intraepithelial (CIN) I and high grade squamous cell intraepithelial lesion (HSIL) for CIN II, III histology. This terminology was recommended by the Lower Anogenital Squamous Terminology Standardization project (The LAST project)[9].

Table 1. The Basic Personal Data (N = 261)

Mean age (range)	**46.9 (30-63)**	
Mean age of first sexual intercourse (range)	**25.5 (17-45)**	
	N	**%**
Interval from the previous pap smear (year)		
≤ 1	56	21.4
2	87	33.3
3	60	22.9
4	11	4.2
5	12	4.5
> 5 - 26	24	9.2
No previous Pap	3	1.1
Unable to remember	8	3.0
Symptom		
None	206	78.9
Leukorrhea	17	6.5
Dysmenorrhea	16	6.1
Pelvic pain	5	1.9
Pruritus vulva	5	1.9
Other	12	4.6
Parity		
Nulliparous	32	12.2
Multiparous	229	87.7
Current contraception		
None	76	29.1
Tubal resection	101	38.7
Condom	24	9.2
Oral contraceptive pill	22	8.4
Safety period	13	5.0
Vasectomy	11	4.2
Depo-medroxy progesterone acetate (DMPA)	7	2.7
Intra uterine device (IUD)	4	1.5
Coitus interruptus	3	1.1
Number of times married		
None	5	1.9
1	230	88.1
2	25	9.6
3	1	0.4
Smoking		
None	261	100
Menopause	78	29.9

The participants who tested negative for both the cytology and high risk HPV test were recommended to repeat the screening test in the next three to five years while the participants whose cytology was positive were referred for a colposcopy. In addition, the participants who tested positive only for high risk HPV were scheduled to have a repeat cytology test in the next six months and repeat the high risk HPV test annually. However, in the participants who had HPV type 16,18 positive were referred for a colposcopy even if the cytology showed a negative result.

The personal data, the cytology and high risk HPV test results, the final outcome after further investigation in the participants who showed abnormal outcomes were collected and analyzed as descriptive data by using SPSS version 17.0

Results

Between September, 2012 and April, 2013, 261 persons met the inclusion criteria and joined this project. The basic personal data were listed in Table 1. The mean age of participants was 46.9 years old with approximately 30% menopausal. The initial mean age of onset of sexual intercourse of the participants was 25.5 year old and nearly 90% of them were multiparous. About one-half of the participants had their last Pap smear within the past two years and about 9% had their most recent Pap smear longer than five years ago. Eighty percent of the participants did not show any symptoms at the screening time. About 90% of the participants been married only once and none of them were smokers.

The screening results were noted in Table 2. About 90% (233 persons) revealed negative results for both the cytology and high risk HPV test. However, positive only cytology or high risk HPV test were found in 12 persons (4.6%) and four persons (1.5%) showed both cytology and high risk HPV positive. In addition, HPV type 16 and 18 were positive in one and two participants, respectively. One participant showed HSIL with positive high risk HPV test but non type 16 or 18. None of the participants revealed invasive cervical cancer in their screening reports. Seventeen persons who revealed abnormal cytology or HPV high risk type 16/18 positive were referred for colposcopy and the results were noted in Table 3. In ten persons who had cytology reported as atypical squamous cell of undetermined significance (AS-CUS), only one person showed evidence of HPV type 18 infection. The final results of these persons were negative for dysplastic lesion except one person who showed only LSIL in the biopsy specimen. This case had negative high risk HPV test while one case that had HPV positive type 18 showed normal finding from colposcopic examination.

Table 2. Outcome of Liquid-based cytology and high risk HPV testing

Cytology outcome / HPV testing	Negative	ASCUS	LSIL	Could not be excluded HSIL	HSIL	Total
Negative	233	9	3	-	-	245
HPV type 16 positive	1	-	-	-	-	1
HPV type 18 positive	1	1	-	-	-	2
Non 16,18 HR HPV type positive	10	-	1	1	1	13
Total	245	10	4	1	1	261

AS-CUS = Atypical squamous cell of undetermined significance, LSIL = Low grade squamous cell intraepithelial lesion, HSIL = High grade squamous cell intraepithelial lesion, HPV = Human papilloma virus, HR = High risk

Table 3. The further management outcome of the persons whose cytology abnormal or positive HPV type 16/18

	SN	Age (year)	HR-HPV	Cytology	Colposcopic diagnosis	Pathology (CDB/LEEP)	Further management
1	16	51	Negative	ASCUS	Normal	-	FU pap smear annually
2	23	53	Negative	ASCUS	LSIL	LSIL	FU pap smear every 6 months
3	54	38	Negative	ASCUS	LSIL	Chronic cervicitis	FU pap smear annually
4	80	50	Negative	LSIL	LSIL	R/O LSIL	FU pap smear every 6 months
5	92	57	Negative	LSIL	LSIL	R/O LSIL	FU pap smear every 6 months
6	100	40	Negative	ASCUS	Normal	-	FU pap smear annually
7	103	40	Negative	ASCUS	Normal	-	FU pap smear annually
8	105	46	Negative	ASCUS	Normal	-	FU pap smear annually
9	148	38	Positive (non type 16,18)	HSIL	HSIL	LEEP=HSIL	FU pap smear every 6 months
10	149	37	Positive (non type 16,18)	LSIL	LSIL	LSIL	FU pap smear every 6 months
11	168	39	Positive (non type 16,18)	R/O LSIL,HSIL	HSIL	LEEP=HSIL	FU pap smear every 6 months
12	169	42	Negative	ASCUS	Normal	-	FU pap smear annually
13	195	32	Negative	ASCUS	Normal	-	FU pap smear annually
14	208	38	Positive type 18	ASCUS	Normal	-	FU pap smear every 6 months
15	210	45	Negative	ASCUS	LSIL	Chronic cervicitis	FU pap smear every 6 months
16	246	40	Negative	LSIL	LSIL	Chronic cervicitis	FU pap smear every 6 months
17	111	44	Positive type 16	Negative	HSIL + LSIL	LEEP = HSIL	FU pap smear every 6 months

SN = Serial number, ASCUS = Atypical squamous cell of undetermined significant, LSIL = Low grade squamous cell intraepithelial lesion, R/O = Rule out, HSIL = High grade squamous cell intraepithelial lesion, HPV = Human papilloma virus, HR = High risk, CDB = Colposcopic directed biopsy, LEEP = Loop electrosurgical excision procedure, FU = Follow up

Four persons who had cytology report as LSIL, one person had positive non type 16,18 high risk HPV. Three of them showed LSIL while the rest showed chronic cervicitis on the colposcopic directed biopsy (CDB). Persons with LSIL from cytology and high risk HPV test positive revealed LSIL on CDB result. Moreover, one person who had cytology as HSIL and one who had cytology as could not be excluded HSIL revealed positive non type 16,18 high risk HPV test. Both of them were confirmed HSIL from final histology

with conization specimen. In addition, about one person who had only HPV positive type 16, the colposcopic finding suggested HSIL plus LSIL. However, the final histology on conization specimen was HSIL. The conization method used in this study was the loop electrosurgical excision procedure (LEEP).

All persons who had abnormal results either cytology or high risk HPV test were to follow up every six months.

Discussion

The prevalence of abnormal cytology or positive high risk HPV test in healthcare population of the Faculties of Medicine and Nursing in the present study was equally 4.6%. This result was similar to the previous report that found the prevalence of HPV infection about 5% in women age over 30 years old[10]. The prevalence of high risk HPV infection was related to current smoking, current oral contraceptive use, and increasing cumulative number of sexual partners[11]. Moreover, the prevalence of positive high risk HPV test increased with decreasing age but most of high risk HPV infection in young age group was transient[11,12]. Thus, American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines recommend screening cervical cancer with high risk HPV test in women aged over 30 years old for the most benefit in terms of being cost-effective[6]. When considered for the risk factor of cervical cancer in our participants, we found that the majority of them were low risk. The mean age of onset of sexual intercourse was 25 years old. All of them were non-smoking and nearly 90% of them had a single partner. However, we still found three persons diagnosed with HSIL in this study.

In the present study, we used LBC to screen cervical cancer. Although, the data from systematic review and meta-analysis showed that LBC displayed similar sensitivity and specificity to detect HSIL when compared with the conventional Pap smear[13], the greater benefit of LBC than conventional Pap test was that LBC could utilize the same specimen to identify high risk HPV type. The previous study suggested that LBC plus high risk HPV test increased the accuracy of the screening test[5]. In our results, one person who showed only HPV type 16 positive revealed HSIL in their final histology. Thus, this case would be missed if screened with cytology alone.

Four types of high risk HPV tests were approved by US-FDA for standard testing which consisted of Hybrid Capture 2 test, Cervistra HPV/HR test, Cervistra® HPV 16/18 and Cobas® 4800 HPV test. The last one was just approved in 2011[5,8]. Cervistra® HPV 16/18 and Cobas® 4800 HPV test are the tests that not only can identify the high risk HPV type but also specifies the genotype of HPV 16 /18 too. However, Cobas® 4800 HPV test is more convenient than the Cervistra test because this test could identify both high risk HPV test and simultaneously determine the specific genotype of HPV 16/18 while the Cervista test required two steps. One step is to identify high risk HPV type and after that the positive specimens need the further process to identify genotype of HPV 16/18. Moreover, Cobas® 4800 test showed a high accuracy too[14]. Thus, in our research we used Cobas® 4800 test for determining the high-risk HPV type.

The clinical application of high risk HPV test included the following: triage of women with equivocal or low grade cytological abnormalities, follow up of women with abnormal screening results who were negative at colposcopic finding, prediction of the therapeutic outcome of treatment of preinvasive disease, primary screening of cervical cancer with or without cytology[15]. In the present study, we used a high risk HPV test with LBC to screen cervical cancer and found that in persons who showed a negative high risk HPV test, nobody developed HSIL. In addition, in participants who revealed high risk HPV test negative but had equivocal result of cytology such as AS-CUS, no HSIL was found. The recent international guidelines from ASCCP suggested that these women who revealed negative high risk HPV test whose cytology was abnormal as AS-CUS could be rescreened with cytology in the next three years[6]. Furthermore, all three participants who showed final diagnosis as HSIL revealed positive high risk HPV type. With the HPV genotype test, women who identified positive HPV type 16/18 need to be investigated further with a colposcopy if a negative lesion was seen, these women should be

closely followed up especially in women whose HPV type 18 was positive due to the high probability to develop an adenocarcinoma precursor lesion[15]. In our study, one person showed HPV type 18 positive with cytology abnormal as AS-CUS. However, her colposcopic examination was satisfactory and she will have rescreening in the next six months.

The strength of our study was the initial study regarding the prevalence of positive cytology plus high risk HPV testing in healthcare population in Thailand. This group of participants would be more reliable for follow up. However, the small number of healthcare population that participated in this research was the main problem. This might be from the cost of test or that in the Asian culture women are ashamed to receive the pelvic examination.

In conclusion, small number of the healthcare population of the Faculties of Medicine and Nursing showed abnormal cytology or positive high risk HPV test. Further investigation is required in the women who revealed only HPV type 16/18 positive while the women whose cytology showed ASCUS without high risk HPV infection showed the most severe lesion as only LSIL. These women seem to be safe for omitting the colposcopic examination.

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Conflict of interest

This study is no conflict of interest

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ความชุกของการติดเชื้อ Human papilloma virus ชนิดความเสี่ยงสูงและความผิดปกติทางเซลล์วิทยาของปากมดลูกในบุคลากรคณะแพทยศาสตร์และคณะพยาบาลศาสตร์ มหาวิทยาลัยเชียงใหม่

วิทวัส เชยพันธุ์, ประภาพร สู่ประเสริฐ, กรกนก สุขพันธ์, จงกลณี เศรษฐกร

วัตถุประสงค์ *: เพื่อหาความชุกของการติดเชื้อ HPV ชนิดความเสี่ยงสูงและความผิดปกติทางเซลล์วิทยาของปากมดลูกในบุคลากรคณะแพทยศาสตร์และคณะพยาบาลศาสตร์ มหาวิทยาลัยเชียงใหม่ ที่มารับการตรวจคัดกรองด้วยวิธี liquid-based cytology (LBC) และ HPV test*

สถานที่ทำวิจัย *: หน่วยมะเร็งวิทยานรีเวช ภาควิชาสูติศาสตร์และนรีเวชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ ระหว่างเดือนกันยายน 2555 ถึงเดือนเมษายน 2556*

กลุ่มตัวอย่าง *: สตรีอายุเท่ากับหรือมากกว่า 30 ปี ที่เป็นบุคลากรในคณะแพทยศาสตร์และ คณะพยาบาลศาสตร์ มหาวิทยาลัยเชียงใหม่ ที่ไม่มีประวัติการรักษามะเร็งปากมดลูกทั้งระยะลุกลามและก่อนลุกลาม โดยที่ยังมีมดลูกอยู่ และต้องการรับการตรวจคัดกรองมะเร็งปากมดลูก*

วิธีการทำวิจัย *: บุคลากรที่มีคุณสมบัติเข้าเกณฑ์การวิจัย จะได้รับการตรวจคัดกรองมะเร็งปากมดลูก โดยสูติแพทย์ ด้วยวิธี LBC ซึ่งใช้น้ำยา Thin Prep Pap test solution ในการเก็บรักษาเซลล์ และใช้ HPV test ชนิด Cobas® 4800 เพื่อหาเชื้อ HPV ชนิดความเสี่ยงสูง สตรีที่ตรวจพบความผิดปกติทางเซลล์วิทยาของปากมดลูก และ/หรือพบเชื้อ HPV ชนิด 16/18 จะได้รับการตรวจต่อด้วยกล้องส่องตรวจช่องคลอด colposcopy*

ผลการวิจัย *: มีสตรีเข้าร่วมโครงการวิจัย 261 คน พบมีความผิดปกติทางเซลล์วิทยาของปากมดลูก 16 คน (6.1%) แบ่งเป็น ASC-US 10 คน, LSIL 4 คน และ HSIL 2 คน และมีสตรี 16 คน (6.1%) ที่พบการติดเชื้อ HPV ชนิดความเสี่ยงสูง โดยมีสตรี 12 คนที่ตรวจพบเฉพาะความผิดปกติทางเซลล์วิทยาของปากมดลูกหรือมีการติดเชื้อ HPV ความเสี่ยงสูงอย่างใดอย่างหนึ่ง ส่วนสตรีที่มีความผิดปกติทางเซลล์วิทยาของปากมดลูกร่วมกับติดเชื้อ HPV ความเสี่ยงสูง มี 4 คน และพบสตรีมีการติดเชื้อ HPV ชนิด16 จำนวน 1 คน และชนิด18 จำนวน 2 คน มีสตรี 17 คนที่ได้รับการตรวจต่อด้วยกล้องส่องตรวจช่องคลอด ในจำนวนนี้มีสตรี 7 คน ได้ทำการตัดชิ้นเนื้อผ่านการตรวจด้วยกล้องส่องตรวจช่องคลอด และสตรี 3 คนได้รับการทำ LEEP โดยผลตรวจทางพยาธิวิทยา เป็น chronic cervicitis 3 คน, LSIL 4 คน และ HSIL 3 คน โดย 1 ใน 3 คนที่เป็น HSIL มีผลการตรวจคัดกรองพบเพียงการติดเชื้อ HPV ชนิด16 เท่านั้น โดยไม่พบความผิดปกติทางเซลล์วิทยาของปากมดลูก*

สรุป *: ความชุกการติดเชื้อ HPV ชนิดความเสี่ยงสูงและความผิดปกติทางเซลล์วิทยาของปากมดลูกในบุคลากรของทั้งสองคณะมีเพียงเล็กน้อยเท่านั้น และสตรีที่ตรวจพบว่าติดเชื้อ HPV ชนิด16/18 ควรได้รับการตรวจต่อด้วยกล้องส่องตรวจช่องคลอด ถึงแม้ว่าจะไม่พบความผิดปกติทางเซลล์วิทยาของปากมดลูก*