Can High Risk Human Papilloma Virus (HR-HPV) Testing Predict the High Grade Cervical Intraepithelial Neoplasia or Higher in Abnormal Liquid-Based Cervical Cytology?

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Objective: *To study the prevalence of HR-HPV, high grade cervical intraepithelial neoplasia (CIN2/3) and cancer diagnosis in women who had liquid-based cervical cytology (LBP) report with low grade and high grade squamous intraepithelial lesion (LSIL and HSIL) in the women who attended gynecological clinic for cervical cancer screening.*
Material and Method: *This retrospective study recruited participants who underwent co-testing (LBP with HPV testing) between July 2013 and June 2016 from medical records. Participants with abnormal Pap smear i.e., LSIL, HSIL, and malignancy were included. Data collected including age, Pap reports and HPV testing results. Cervical cytology, histopathological report from colposcopic directed biopsy and HR-HPV testing were analyzed.*
Results: *A total of 2,144 participants were enrolled. Prevalence of LSIL, HSIL and cancer from LBP were 1.4% (30), 1.07% (23) and 0.37% (8), respectively. CIN2+ in cases with LSIL and HSIL reports were 7.1% and 8.6%, respectively. There was no cancer in women who had LBP report of LSIL. In this study, there was no case of CIN2/3 in women with LSIL who had HR-HPV negative (negative predictive value; NPV 100%). All of women with HSIL reports had HR-HPV testing positive. Ninety percent of cases with HSIL reports had histopathological reports CIN2/3 and cancer.*
Conclusion: *In women with LSIL reports and negative HR-HPV testing, there was no silent CIN2/3. In the situation that colposcopy was not available, HR-HPV testing and LBP can assist the medical person to reduce the colposcopy referral.*

Keywords: *Cervical intraepithelial neoplasia, Cancer, Colposcopy, Pap, HPV testing*

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Cervical cancer is the second most common type of malignant cancer in Thai women[1]. In 2015, Ministry of Public Health reported 4,500 Thai women death due to cervical cancer and 8,000 new diagnosed cases per year. Since the progression of cervical cancer is very slow, an efficient screening method can provide early detection, proper management and reducing mortality rate[2].

High risk human papillomavirus (HR-HPV) infection is now known as a major cause of cervical intraepithelial neoplasia (CIN) and cervical cancer[3,4]. According to the international agency for research on cancer (IARC), 15 types of HPV are considered as high risk[5]. Cervical cancer screening are conventional Papanicolaou smear (CPP), liquid based Papanicolaou smear (LBP) and co-testing (combination of LBP and HPV genome testing).

The aim of this study was to determine the prevalence of HR HPV in women who had low grade and high grade squamous intraepithelial lesion (LSIL and HSIL) cytology and the prevalence of HR HPV in women diagnosed LSIL and HSIL who had pathological reports as normal or CIN1 and high grad precancerous lesion or cancer.

The prevalence of CIN2/3 and cancer diagnosis in women who had cervical cytology reports with LSIL and HSIL was reported.

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Material and Method

This retrospective study received the approval of the Ethics Committee on clinical Research of Faculty of Medicine, Thammasat University in year 2015.

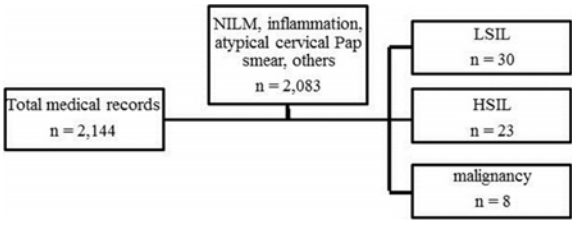
Data from all participants who underwent cervical cancer screening by LBP and HPV testing between July 2013 and June 2016 were reviewed using medical records from computerized hospital database. Patients who had previously been diagnosed of gynecologic cancer or CIN were excluded from this study.

Cervical cytology defined as Bethesda system 2014 terminology[6]. Patient who had abnormal cytology as LSIL or HSIL would then undergo colposcopic directed biopsy. Histologic diagnosis defined as normal, low grade (CIN1), high grade precancerous lesion (CIN2/3) and cancer.

Demographic data were analyzed with descriptive statistics in term of mean and standard deviation (SD). Chi-square test was used for categorical data. The *p*-value <0.05 was considered statistically significant. All analyses were performed by using statistic program (SPSS version 17, SPSS Inc., Chicago, USA).

Results

Data from a total of 2,144 women with LBP and HPV testing at Thammasat University Hospital were enrolled. There were 30 (1.4%), 23 (1.07%) and 8 (0.37%) cases of LSIL, HSIL and cancer, respectively (Fig. 1).



NILM = negative for intraepithelial lesion or malignancy; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion

Fig. 1 Medical records reviewed in this study.

Women with HSIL report were older than those with LSIL significantly (51.4±16.1 and 43.5±11.5 years, *p* = 0.043). While the other characteristics as occupation or incomes were not difference.

In LSIL group, there were two patients who denied undergoing colposcopic directed biopsy. Among 28 cases of LSIL group, there were two cases (7.1%) of CIN2/3. There was no cervical cancer in LSIL group. Among 23 cases of HSIL group, there were 19 (82.6%) and 2 (8.6%) cases of CIN2/3 and cervical cancer, respectively (Table 1).

Among 28 cases of LSILgroup, one-quarter of cases (8/28) had negative HR-HPV testing. All of them had histopathological reports equal or less than CIN1. There are 2 cases of CIN2/3 in this group and both of them had positive HR-HPV tests. One case had positive test of HPV type 16&18 while another case had negative test of HPV type 16, 18&45 (Table 2).

All 23 cases of HSIL had positive result of HR-HPV testing. Ninety percent of cases (21/23) in this group had histopathological report equal or more than CIN2 (CIN2+). Only one case had negative histopathological diagnosis and another one case had diagnosis of CIN1. Both patients had HR-HPV test positive of non 16, 18&45 types.

In this study, there were 9 cases of CIN2/3 underwent LEEP and both cases of cervical cancer underwent radical hysterectomy. The pathological results confirmed as colposcopic biopsy reports.

Discussion

Early detection of the precancerous condition is the main strategy of cervical cancer control[2]. Cervical cytology by Papanicolaou smear is the gold standard screening method[2]. At Thammasat

Table 1. Cervical histopathologic results for LSIL and HSIL

Histopathologic results	LSIL* (n = 28)	HSIL* (n = 23)	*p*-value
Normal, cervicitis	17 (60.7)	1 (4.35)	<0.001
CIN1	9 (32.1)	1 (4.35)	
CIN2/3	2 (7.2)	19 (82.6)	
Cervical cancer	0	2 (8.7)	

* n (%), LSIL = low grade squamous intraepithelial lesion; HSIL = high grade squamous intraepithelial lesion; CIN1 = cervical intraepithelial neoplasia grade 1; CIN2/3 = cervical intraepithelial neoplasia grade 2/3

Table 2. Comparison of HPV test for detection of abnormal cervical cytology and histopathology

	HR-HPV		CIN2+ prediction				
	negative	positive	Sensitivity*	Specificity*	PPV*	NPV*	Accuracy*
LSIL			100	30.8	10	100	35.7
≤CIN 1	8	18					
CIN 2+	0	2					
HSIL			100	0	91	0	91.3
≤CIN 1	0	2					
CIN 2+	0	21					

LSIL = low grade squamous intraepithelial lesion; HSIL = high grade squamous intraepithelial lesion; CIN1 = cervical intraepithelial neoplasia grade 1; CIN2+ = CIN2/3 and cervical cancer; PPV = positive predictive value; NPV = negative predictive value; * = percent

University Hospital, LBP was used since 2009[7]. Co-testing (combination of LBP and HPV genome testing) is currently used in approximately 10 percent of cases who came in for cervical screening at Thammasat University hospital. However Thammasat University Hospital's HPV testing routine has been changed from HPV DNA detection to HPV mRNA detection since June, 2014.

This investigation found the prevalence of 6.5% abnormal cervical cytology, 1.4% LSIL and 1.07% HSIL. The finding is in the similar percentage with the work reported by Tangjitgamol et al[8] of 6.28% and 1.82% abnormal Pap and LSIL, respectively. When CPP result was focused, this investigation reported higher prevalence than LSIL and HSIL prevalence at 0.29 and 0.14%, reported by the study of Anantaworapot et al respectively[9]. When compared to LBP in pregnant women's study by Pranee et al[10], her prevalence of abnormal cervical cytology was 6.5% but the prevalence of LSIL in the pregnant women was higher than the result of our study. The prevalence of abnormal Pap in Thailand has a wide range (Table 3) because of the difference of population and screening technique. Nonetheless, the prevalence of CIN2+ diagnosis in women who had cervical cytology reported with LSIL and HSIL of the present investigation is concordance to Kanjanavirojkul's study[11].

This report found that 28.6% of LSIL cases had negative HR-HPV test. This finding is not agreeing with Jovanoviae's study in Serbian population that showed 70.15% HR-HPV negative in LSIL population[12]. This study reported no case of CIN2+ in women with LSIL who had HR-HPV negative (negative predictive value; NPV 100%) while there were 10% of LSIL cases who had HR-HPV positive diagnosed CIN2+.

This investigation revealed that 91% of HSIL cases had diagnosis of CIN2+ and all cases of HSIL cases had positive HR-HPV test.

Conclusion

Therefore, HR-HPV test may have no role in women who had HSIL cytology. However, HR-HPV test possibly might be valuable for reducing referral to colposcopy in LSIL group in some institutes where there is a limitation of colposcopy resource. Nonetheless, the limitation of the small number of cases in this report suggests a further future investigation.

Ethical approval

The study was approved by Ethics Committee, Faculty of Medicine, Thammasat University, and study protocol numbers MTU-EC-OB-2-178/58.

What is already known on this topic?

High risk human papillomavirus (HR-HPV) infection is now known as a major cause of cervical intraepithelial neoplasia (CIN) and cervical cancer. According to the international agency for research on cancer (IARC), there are 15 types of HPV considered as high risk. Cervical cytology is a worldwide tool for cervical cancer screening. There are conventional Papanicolaou smear (CPP), liquid-based Papanicolaou smear (LBP) and co-testing (combination of LBP and HPV genome testing). Even though, co-testing is more expensive, but it seems to improve the efficacy of cervical cancer screening.

What this study adds?

This study demonstrated 91% of HSIL cases

Table 3. Comparison of abnormal Pap smear in Thailand

	Khaengkhor[10]	Suwannarurk[7]		Kanjanavirojkul[11]	Kituncharoen[13]		Lertcharernrit[14]	Tangjitgamo[6]]	Parkpinyo[15]	Anantaworapot[9]	Present
Year	2011	2011		2012	2015		2016	2016	2016	2016	2016
Subject	Preg	Non preg		Non preg	Non preg		Preg	Non preg	Preg	Preg & non	Non preg
Type	LBP*	CPP	LBP*	CPP/LBP*	CPP	LBP**	CPP/VIA	LBP**	LBP***	CPP	LBP*
Number	143	5,835	497	15,345	11,179	11,851	414	4,442	655	2,098	2,144
Cytology											
Abnormal Pap€	7.0	2.6	4.0	1.9	8.1	12.3	6.0	6.28	3.4	4.4	6.5
LSIL€	3.5	0.84	1.81		1.7	3.1	2.65	1.82	1.1	0.29	1.4
HSIL€	0.7	0.43	0		0.8	0.9	0.48	0.36	0.2	0.14	1.07
LSIL€											
≤CIN1	100			90.91							92.9
CIN 2/3	0			9.09							7.1
HSIL€											
≤CIN1	0			16.0	32.0	39.2	100				8.7
CIN 2/3	100			84.0	48.6	36.3	0				82.6
cancer	0			0	19.4	24.5	0				8.7

€ = (%); Pap = Papaniculaou smear; LSIL = low grade squamous intraepithelial lesion; HSIL = high grade squamous intraepithelial lesion; CIN1 = cervical intraepithelial neoplasia grade 1; CIN2/3 = cervical intraepithelial neoplasia grade 2/3; CPP = conventional cervical Pap smear; LBP = liquid based cytology; VIA = visual inspection with acetic acid; * = ThinPrep®; ** = SurePath®; *** = Siriraj liquid-based solution; preg = pregnancy

had diagnosis of CIN2+ and all cases of HSIL cases had positive HR-HPV test. Therefore, HR-HPV test may have no role in women who had HSIL cytology. HR-HPV test possibly will valuable for reducing referral to colposcopy in LSIL group.

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Potential conflicts of interest

None.

References

1. Khuhaprema T, Attasara P, Srivatanakul P, Sangrajrang S, Muwonge R, Sauvaget C, et al. Organization and evolution of organized cervical cytology screening in Thailand. Int J Gynaecol Obstet 2012; 118: 107-11.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-86.
3. Wilbur DC, Nayar R. Bethesda 2014: improving on a paradigm shift. Cytopathology 2015; 26: 339-42.
4. ICO (Institut Catala d'Oncologia) Information Centre on HPV and Cancer. Human papillomavirus and related cancers, Fact sheet 2016. Canada: ICO Information Center on HPV and Cancer; 2016.
5. The International Agency for Research on Cancer (IARC). Human papillomaviruses. IARC Monographs on the evaluation of carcinogenic risks to humans. Lyon, France: IARC Press; 2009.
6. Jovanovic AM, Dikic SD, Jovanovic V, Zamurovic M, Nikolic B, Krsic V, et al. Correlation of human papilloma virus infection with cytology, colposcopy and histopathological examination of the bioptic tissue in low- and high-grade intraepithelial lesions. Eur J Gynaecol Oncol 2012; 33: 512-6.
7. Khaengkhor P, Mairaing K, Suwannarurk K, Thaweekul Y, Poomtavorn Y, Pattaraarchachai J, et al. Prevalence of abnormal cervical cytology by liquid based cytology in the antenatal care clinic, Thammasat University Hospital. J Med Assoc Thai 2011; 94: 152-8.
8. Suwannarurk K, Bhamarapravatana K, Thaweekul Y, Mairaing K, Poomtavorn Y, Pattaraarchachai J. A 1-year experience with liquid-based and conventional Papanicolaou smear in Thammasat

University Hospital. J Med Assoc Thai 2011; 94 (Suppl 7): S47-51.
9. Tangjitgamol S, Kantathavorn N, Kittisiam T, Chaowawanit W, Phoolcharoen N, Manusirivithaya S, et al. Prevalence and associated factors of abnormal cervical cytology and high-risk HPV DNA among Bangkok metropolitan women. Asian Pac J Cancer Prev 2016; 17: 3147-53.
10. Kituncharoen S, Tantbirojn P, Niruthisard S. Comparison of unsatisfactory rates and detection of abnormal cervical cytology between conventional Papanicolaou smear and liquid-based cytology (Sure Path(R)). Asian Pac J Cancer Prev 2015; 16: 8491-4.
11. Parkpinyo N, Inthasorn P, Laiwejpithaya S, Punnarat T. Benefits of cervical cancer screening by liquid-based cytology as part of routine antenatal assessment. Asian Pac J Cancer Prev 2016; 17: 4457-61.
12. Kanjanavirojkul N, Muanglek R, Yanagihara L. Accuracy of abnormal Pap smear at Thammasat University Hospital. J Med Assoc Thai 2012; 95 (Suppl 1): S79-82.
13. Lertcharernrit J, Sananpanichkul P, Suknikhom W, Bhamarapravatana K, Suwannarurk K, Leaungsomnapa Y. Prevalence and risk assessment of cervical cancer screening by papanicolaou smear and visual inspection with acetic acid for pregnant women at a Thai provincial hospital. Asian Pac J Cancer Prev 2016; 17: 4163-7.
14. Anantaworapot A, Manusook S, Tanprasertkul C, Lertvutivivat S, Chanthasenanont A, Bhamarapravatana K, et al. Clinical factors associated with specimen adequacy for conventional cervical cytology in Thammasat University Hospital, Thailand. Asian Pac J Cancer Prev 2016; 17: 4209-12.
15. Garcia F, Hatch KD, Berek JS. Intraepithelial disease of the cervix, vagina, and vulva. In: Berek JS, editor. Berek& Novak's gynecology. 15th ed. Philadelphia: Lippincott Williams & Wilkins; 2012: 574-606.
16. Miller C, Elkas JC. Cervical and vaginal cancer. In: Berek JS, editor. Berek& Novak's gynecology. 15th ed. Philadelphia: Lippincott Williams & Wilkins; 2012: 1304-39.

การตรวจเชื้อไวรัสเอชพีวีชนิดความเสี่ยงสูงสามารถทำนายภาวะซ่อนเร้นของภาวะก่อนมะเร็งปากมดลูกชั้นสูงหรือมะเร็งปากมดลูกได้หรือไม่

อธิตา จันทเสนานนท์, สุภาเพ็ญ เลิศวุฒิวิวัฒน์, ธีระพัฒน์ เมืองโต, เด่นศักดิ์ พงศ์โรจน์เผ่า, ต้องตา นันทโกมล, กรกาญจ์ ภมรประวัติธนะ, คมสันติ์ สุวรรณฤกษ์

วัตถุประสงค์: เพื่อศึกษาถึงความชุกของการติดเชื้อ HPV กลุ่มเสี่ยงสูงและภาวะซ่อนเร้นของภาวะก่อนมะเร็งปากมดลูกชั้นสูงหรือมะเร็งปากมดลูกในสตรีที่มีผลการตรวจคัดกรองมะเร็งปากมดลูกแบบแผ่นบางเป็น LSIL และ HSIL ที่มารับการตรวจที่หน่วยตรวจนรีเวช โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ

วัสดุและวิธีการ: เป็นการศึกษาย้อนหลังของการตรวจคัดกรองมะเร็งปากมดลูกแบบแผ่นบางและตรวจหาเชื้อ HPV กลุ่มเสี่ยงสูงในสตรีที่มารับการตรวจในระหว่างเดือนกรกฎาคม พ.ศ. 2556 ถึง เดือนมิถุนายน พ.ศ. 2559 โดยสตรีที่มีผลการตรวจคัดกรองตั้งแต่ ASC-US ขึ้นไป จะได้รับการตรวจด้วยกล้องส่องขยายปากมดลูกและตัดชิ้นเนื้อ ผลทางพยาธิวิทยาและการติดเชื้อ HPV ชนิดความเสี่ยงสูงถูกนำมาวิเคราะห์

ผลการศึกษา: จำนวนสตรีที่ได้รับการตรวจคัดกรองมะเร็งปากมดลูกแบบแผ่นบางและตรวจหาเชื้อ HPV กลุ่มเสี่ยงสูง จำนวน 2,144 ราย พบความผิดปกติชนิด LSIL, HSIL และมะเร็งปากมดลูกคิดเป็นร้อยละ 1.4 (30 ราย), 1.07 (23 ราย) และ 0.37 (8 ราย) ตามลำดับ และพบผลทางพยาธิวิทยาเป็น CIN2/3 และมะเร็งปากมดลูกในสตรีที่มีผลการตรวจคัดกรองเป็น LSIL และ HSIL ร้อยละ 7.1 และ 8.6 ตามลำดับ โดยไม่พบมะเร็งปากมดลูกในสตรีที่มีผลการตรวจคัดกรองเป็น LSIL และในการศึกษานี้ยังพบว่าในสตรีที่มีผลการตรวจคัดกรองเป็น LSIL และมีผลทางพยาธิวิทยาเป็น CIN2/3 นั้น ทุกรายมีการติดเชื้อ HPV ชนิดความเสี่ยงสูง ในขณะที่สตรีที่มีผลการตรวจคัดกรองเป็น HSIL นั้นทุกรายมีการติดเชื้อ HPV ชนิดความเสี่ยงสูง และร้อยละ 90 ของกลุ่มนี้ มีผลทางพยาธิวิทยาเป็น CIN2/3 หรือมะเร็งปากมดลูก

สรุป: ในสตรีที่มีผลการตรวจคัดกรองเป็น LSIL และไม่พบการติดเชื้อ HPV ชนิดความเสี่ยงสูงนั้น พบว่าผลทางพยาธิวิทยาไม่เป็น CIN2/3 ดังนั้นในบางสถาบันที่ไม่สามารถทำการตรวจด้วยกล้องส่องขยายปากมดลูกและตัดชิ้นเนื้อได้ การตรวจคัดกรองมะเร็งปากมดลูกแบบแผ่นบางร่วมกับตรวจหาเชื้อ HPV ชนิดความเสี่ยงสูง สามารถช่วยลดการส่งต่อผู้ป่วยไปรับการตรวจด้วยกล้องส่องขยายปากมดลูกได้