RESEARCH ARTICLE

Cervical Pathology in High-Risk Human Papillomavirus-Positive, Cytologically Normal Women

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Abstract

This study was undertaken to evaluate the prevalence of significant cervical pathology among women who are high-risk human papillomavirus (HR-HPV)-positive/cytology negative, the most common combination of positive co-tests. The records of 244 women HR-HPV-positive/cytology-negative who had undergone colposcopy at Srinagarind Hospital, Khon Kaen University during January 2010 and April 2014 were reviewed. Mean age was 46.4 years. Of these 224 women, 75 were positive for HPV types 16/18 (33.5%) and 123 were positive for non-16/18 types (54.9%). HR-HPV was not genotyped in the remaining 26 women (11.6%). Prevalence of significant lesions for the entire cohort was 2.4%, and 2.6% and 3.3%, respectively, for those with HPV 16/18 and other oncogenic HPV types. One woman with HPV 16/18 (1.3%) had invasive cervical cancer. Multiparous women were more likely to be infected with HPV 16/18 compared to nulliparous women (36.3% versus 17.6%, respectively). In conclusion, the prevalence of significant cervical lesion among our study population was 2.4%. Multiparous women were more likely to be infected with HPV 16/18 compared to nulliparous women.

Keywords: Human papillomavirus - high-risk HPV - genotyping - cervical pathology

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Introduction

Infection of high-risk human papillomavirus (HR-HPV) is a cause of cervical cancer (Suthipintawong et al., 2011; Siriaunkgul et al., 2012; de Sanjose et al., 2013; Sui et al., 2013; Natphopsuk et al., 2013; Hamzi Abdul Raub et al., 2014). This has led to incorporate HR-HPV testing into cytology screening methods, the so-called "cotests". In the 2012 guidelines for cervical cancer screening proposed by the American Society for Colposcopy and Cervical Pathology (ASCCP), cotests has been recommended as a preferred cervical screening method for women 30 to 64 years of age (Massad et al., 2013). Cotests has been serviced by several hospitals in Thailand. Nevertheless, the cost of the cotests is presently too high to be covered by a Thai government support program, Thai women who desire to undergo cervical screening using cotests have to afford this costly investigation by themselves.

The most common pattern of positive cotests is a HR-HPV-positive/cytology-negative results which ranges from approximately 4% to 9% (Castle et al., 2009; Wiley et al., 2012; Tabrizi et al., 2014; Carozzi et al., 2014; Saraiya et al., 2014). As compared to the results from areas with a low incidence of cervical cancer, Thai women with abnormal cervical cytology carry a higher risk of encountering significant cervical lesion (Kietpeerakool et al., 2009; Poomtavorn et al., 2011; Aue-Aungkul et al., 2011; Ingkapairoj et al., 2012). This finding emphasizes the potential need of particular management of abnormal cervical cancer screening results among Thai women. However, information regarding the prevalence of significant cervical pathology among women with cytology-negative/HR-HPV-positive, the most common combination of positive cotests, among Thai women is limited. Accordingly, this study was conducted to evaluate the prevalence of significant cervical pathology among women with HR-HPV-positive/cytology negative.

Materials and Methods

After receiving approval from the Research Ethic Committee of the Faculty, the medical records of women with cytology-negative/HR-HPV-positive who were referred to Colposcopy Clinic, Srinagarind Hospital, Khon Kaen University during January 2010 and April 2014 were reviewed. As mentioned earlier, prevalence of significant cervical pathology among women with cytology-negative/HR-HPV-positive in our setting is limited. Thus, it is our policy to recommend immediate colposcopy in all women with HR-HPV-positive/cytology negative irrespective of HR-HPV genotype. Abstracted data included baseline characteristics of patients, genotype of HR-HPV if

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available, colposcopic findings and cervical pathology.

Pregnant women were excluded from the present study, as well as women with a previous history of abnormal cervical cytology of any grade or cancer of any site.

Colposcopic examination was performed following the application of 5% acetic acid solution on the upper vagina and cervix. The severity of colposcopic findings was based on the density of acetowhite areas, sharpness of the lesion margins, and abnormal and atypical vascular patterns. A colposcopically-directed biopsy (CDB) was taken from the area of greatest abnormal appearance, and endocervical curettage (ECC) was carried out if endocervical lesion was suspected. Cervical conization was performed if the initial work-up results were positive for high-grade lesions.

The final histological diagnosis was made on the most severe histological results obtained after initial colposcopy. Women with normal colposcopic findings without CDB or ECC were categorized as having no significant lesion. Significant cervical pathology included cervical intraepithelial neoplasia (CIN) 2-3 and invasive cervical cancer. Women with invasive cervical lesions were clinically staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification. For each patient, surgical specimens were examined by the gynecologic pathologists at Khon Kaen University Hospital (P.K.).

Statistical analysis was carried out with SPSS software (IBM, Armonk, NY, USA). Descriptive statistics were used for reporting demographic data, genotype of HR-HPV, and prevalence of significant cervical pathology. A 95% confidence interval (CI) of the prevalence of significant pathology was calculated to determine the precision of data.

Results

The records of 224 women were reviewed. Mean age was 46.4 years. Thirty-four (15.2%) were nulliparous. One hundred and forty (62.5%) women were in premenopausal period. Table 1 displays the baseline characteristics of all women in this study.

Of these 224 women, 75 were positive for HPV type 16/18 (33.5%; 95% CI, 27.3-40.1%), 123 were positive for non-16/18 type (54.9%; 95% CI, 48.1-61.5%) and 26 (11.6%) were not genotyped. Table 1 shows baseline characteristics of women stratified by type of HR-HPV.

CDB and/or ECC were carried out in 200 women. Four women underwent loop electrosurgical excision procedure without intervening histological diagnoses because of unequivocally suspected high-grade disease

Table 1. Characteristics of Women Stratified by Types of HR-HPV

Characteristics		All patients N=224	Genotype of HR-HPV Not specify N= 26	16/18 N=75	Non-16/18 N=123
Mean age, SD (years)		46.4, 9.7	45.5, 7.4	47.2, 9.8	46.1, 10.2
Parity status					
	Nulliparous	34 (15.2)	7 (26.9)	6 (8.0)	21 (17.1)
	Multiparous	190 (84.8)	19 (73.1)	69 (92.0)	102 (82.9)
Menopausal status					
	Premenopause	140 (62.5)	20 (76.9)	42 (56.0)	78 (63.4)
	Postmenopause	84 (37.5)	6 (23.1)	33 (44.0)	45 (36.6)
Education attainment					
	Primary school	14 (6.3)	1 (3.8)	4 (5.3)	9 (7.3)
	High school	37 (16.5)	9 (34.6)	9 (12.0)	19 (15.5)
	Bachelor or higher	224 (77.2)	16 (61.5)	62 (82.7)	95 (77.2)
Current contraception					
	None	99 (44.2)	12 (46.2)	34 (45.3)	53 (43.1)
	Tubal resection	95 (42.4)	11 (42.3)	30 (40.0)	54 (43.9)
	Condom	8 (3.6)	1 (3.8)	2 (2.7)	5 (4.1)
	OCPs	6 (2.7)	1 (3.8)	2 (2.7)	3 (2.4)
	IUD	5 (2.2)	0 (0)	3 (4.0)	2 (1.6)
	DMPA	4 (1.8)	0 (0)	2 (2.7)	2 (1.6)
	Vasectomy	4 (1.8)	1 (3.8)	2 (2.7)	1 (0.8)
	unknown	3 (1.3)	0 (0)	0 (0)	3 (2.4)

Data are present as number (percentage); Abbreviation: HR-HPV, high-risk Human Papillomavirus; OCPS, oral combined pills; IUD, intrauterine device; DMPA, depot medroxyprogesterone acetate

Table 2. Final Pathology Results Cross-tabulated with Genotypes of HR-HPV

Pathology	All patients N=224	Genotype of HR-HPV Not specify N= 26	16/18 N=75	Non-16/18 N=123
CIN 2-3	5 (2.2)	0 (0)	1 (1.3)	4 (3.3)
Cancer	1 (0.4)	0 (0)	1 (1.3)	0 (0)
CIN 1	57 (25.4)	4 (15.4)	23 (30.7)	30 (24.4)
No significant lesion	141 (62.9)	16 (61.5)	44 (58.7)	81 (65.9)
Normal colposcopy	20 (8.9)	6 (23.1)	6 (8.0)	8 (6.5)

Data are present as number (percentage); Abbreviation: HR-HPV, high-risk Human Papillomavirus; CIN, cervical intraepithelial neoplasia

Table 3. Characteristics of Six Patients Found to have CIN 2-3+

Variables	Patient number					
	1	2	3	4	5	6
Age (years)	29	26	32	53	56	56
Parity no.	0	0	2	2	0	0
Current contraception	None	None	DMPA	None	None	None
HR-HPV type	16/18	Non16/18	16/18	Non16/18	Non 16/18	Non16/18
Colposcopic diagnosis	Cancer	HGL	LGL	LGL	unknown	HGL
Pathology results	Cancer	CIN 2-3	CIN 2-3	CIN 2-3	CIN 2-3	CIN 2-3

Abbreviation: CIN, cervical intraepithelial neoplasia; HR-HPV, high-risk human papillomavirus; DMPA, depot medroxyprogesterone acetate; HGL, high-grade lesion; LGL, low-grade lesion

on colposcopy. Twenty women who had normal colposcopic examination were advised to follow-up without histological examination performed.

The histopathologic results of the 224 women were as follows: CIN 2-3, 5 (2.2%, 95% CI, 0.7%-5.1%); invasive squamous cell carcinoma, 1 (0.4%, 95% CI, 0.01%-2.5%); CIN 1, 57 (25.4%); and no lesions, 161 (71.8%). The prevalence of significant lesion (CIN 2-3 and invasive lesion) was 2.4% with a 95% CI of 0.9%-5.3%. Table 2 shows the association between final pathology results and types of HR-HPV. One woman who had invasive lesion was in FIGO stage IB1.

Characteristics of six women who found to have CIN 2-3 and invasive cervical lesion are displays in Table 3.

Discussion

In this study, we evaluated the prevalence of significant cervical pathology among women with cytology-negative/HR-HPV-positive who had undergone colposcopy. Our findings have direct implications for determining an appropriateness of cervical cancer prevention among the study population. Nevertheless, this study has to be cautiously viewed in that approximately two-third of women in this study had Bachelor or higher level of educational attainment. As mentioned earlier, cotests will be carried out only among Thai women who are able to pay for this costly test by themselves. Thus, our findings represent data derived from women at high level of socioeconomic status and may be different from data on women of other settings.

For women with positive cotest results, management guidelines are tailored to the level of risk associated with the specific combination of cytologic and HPV test results. In the recent consensus guidelines updated by the ASCCP, if possible, cytology-negative/HR-HPV positive women should be genotyped for HPV 16/18. With this option, women who have HPV 16/18 infection are recommended to undergo colposcopy whereas for those without these two high-risk types are for cotest to be repeat after 1 year (Massad et al., 2013). In our study, the considerably low prevalence of CIN 2-3 (3.3%) among women with cytology-negative who infected with non-HPV 16/18 oncogenic types lend support to the recommendation of repeat cotests in 1-year interval for our population if good patient's compliance is ascertained.

Although the significant cervical lesion among women infected with HPV 16/18 genotypes in this study was found in only 2 women which accounted for 2.6% of the cases, however, a 29-year old woman in this group was found to have invasive cervical cancer. This finding was in line with previous study which noted that the majority of cervical cancer observed among women below 35 years caused by HPV 16/18 (de Sanjose et al., 2013). Immediate colposcopy thus appears to be appropriate for women positive with HPV 16/18 to prevent some invasive lesions go unnoticed.

Some patient's characteristics have been noted to impact on the genotype of oncogenic HPV infection. In Taiwanese women who had high-grade squamous intraepithelial lesion (HSIL) smears, HPV 16/18-infected women were significantly younger than those with other oncogenic types (39.8 versus 48.6 years). However, among women with low-grade squamous intraepithelial lesion (LSIL) smears, the mean age between women with HPV 16/18 positive and those who infected with other oncogenic HPV was comparable (45.6 versus 42.2 years) (Chiang et al., 2013). Although the actual reasons about the higher rate of HPV 16/18 related HSIL smears among young women remains unknown, this could be the results of rapid progression of these types. In the recent study conducted in Italy, differences in HPV genotype distribution related to geographically close populations but not to age (Carozzi et al., 2014).

In our study, mean age of women infected with HPV 16/18 was 47.2 years which was similar to that of 46.1 years among women with other oncogenic HPV genotypes. Interestingly, our study found that nulliparous women were less likely to be infected with HPV 16/18 compared to multiparous women (17.6% versus 36.3%, respectively). This finding and underlying mechanism of increasing risk of HPV 16/18 infection among multiparous women should be confirmed and verified from further large scale study.

This study has some limitations. First, population in this study appears to be a group of high socioeconomically women, our results therefore may not be able to generalize to other populations with different background risk. Second, this study contains a relatively small sample size. Third, because of a retrospective data collection, some potential factors associated with the background risk of cervical cancer among the study population-particularly history of previous cervical cancer screening- could not assessed. Finally, details of laboratory methods used for HPV testing and genotyping were unknown.

In conclusion, prevalence of significant lesion for the entire cohort was 2.4%. The rate of significant lesion among women infected with HPV 16/18 and those

with other oncogenic HPV types was 2.6% and 3.3%, respectively. One woman with HPV 16/18 (1.3%) had invasive cervical cancer. Multiparous women were more likely to be infected with HPV 16/18 compared to nulliparous women (17.1% versus 8.0%, respectively).

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