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THE RISK OF SQUAMOUS CELL CARCINOMA ON HUMAN PAPILLOMAVIRUS TYPE-16 INFECTION IN BALI

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ABSTRACT

The high risk of human papillomavirus (HPV) have already known widely and accepted as a causative agent for cervical cancer. Epidemiologically, predominant high-risk is HPV-16 and squamous cell carcinomas (SCC) is the most common histological type. HPV genotype probably correlates to histologic type. This study aims to determine how many fold is the risk of SCC on HPV-16 infection. This is a case control with SCC HPV-16 positive as the cases and SCC HPV-16 negative as the controls. Tissues diagnosed as SCC and non SCC was paraffin-embedded. SPF-10 and specific E7-primer types by LiPA were employed for genotyping of HPV-16. χ^2 was applied to analyze the correlation. A number of 65 SCC consisted of 33 cases and 32 controls were observed in this study. The risk of SCC on HPV-16 infection was 3.40-fold (95% CI = 1.44-8.03; p = 0.004) compare with HPV-16 negative. Controls in this study consist of 18 (27.69%) of HPV-18, 9 (13.85%) of HPV-52, and 5 (7.69%) of other HPV types. The mean-age of case group and control group infected by HPV were 52.28 ± 12.43 and 47.70 ± 8.02 year, respectively (p = 0.02). HPV-16 infection caused SCC is 3.5 more than other high risk group.

Keywords: HPV-16, cervical, cancer, SCC, squamous

INTRODUCTION

Cancer still becoming health problems worldwide and cervical cancer is the second most common cancer in women in developing countries where 80-90% of cases occur.[1,2,3] Cervical cancer also remains the leading cause of mortality in developing countries.[4,5] The high risk of HPV have been well established as causative agent for cervical cancer. It can be detected in about 90% of all cervical cancers.[5,6,7] More than 100 different genotypes of HPVs have been identified.[2] The two predominant high-risk HPV types are HPV-16 and 18 associated with more than 90% of cervical cancers.[5,7,8] Squamous cell carcinomas (SCC) and adenocarcinoma were the first and second most common histologic types of the cervical cancer.[1,8] Several HPV genotypes may cause differentially progress from low-grade squamous intraepithelial lesion (LSIL) to malignancy so that HPV genotype may have potential use to predict the risk of cancer.[9]

Many study found that HPV-16 is more prevalent in SCC whereas HPV-18 is more prevalent in adenocarcinoma. The purpose of this study was to know the risk developing cervical SCC infected by HPV-16.

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MATERIAL AND METHODS

Data and specimen collection

This study was case-control study that was conducted during the years 2011-2012. As the material of this study were the paraffin-embedded tissue which have been diagnosed as cervical cancer at Department of Anatomical Pathology Faculty of Medicine Udayana University.

HPV DNA detection and typing

Paraffin-embedded tissue from cervical biopsies was sent for detection and genotyping of HPV DNA by PCR-based methods at Department of Pathology, Leiden University Medical Centre, the Netherland and Molecular Biology Unit, Faculty of Medicine, Udayana University. HPV DNA was detected in 2 steps. In the first step, the SPF10 primers at several dillution were used to amplify the DNA. In the second step, the positive products was performed using specific probes type-specific E7 primer by LiPA which detected 25 HPV types to know the evidence of HPV-16 or other types. A total of 185 cervical cancer biopsies were included in this study.

The samples of this study were SCC consist of case subjects i.e. women with SCC who infected by HPV-16 and control subjects i.e. women with SCC who infected by other types of HPV.

Statistical analysis

A 2 x 2 table was created and Pearson's χ^2 test was applied. Statistical significance for these tests was set at the 2-sided of 0.05 levels. Bivariate analysis was employed to calculate odds ratios (ORs) for the risk of cervical SCC associated with HPV-16 with 95% confidence intervals (CIs).

RESULTS

The mean-age and risk of developing SCC associated with HPV-16 display in Table 1 and 2.

Table 1
Mean-age of Case and Control Group

	Case (n = 33)		Control (n = 32)		*p**
	Mean	SD	Mean	SD	
Age (years)	52.28	12.43	47.70	8.02	0.02

*significant $p < 0.05$
SD = standard deviation

The mean-age of case group infected by HPV was 52.28 ± 12.43 and control group was 47.70 ± 8.02 (p=0.02). This mean-age was statistically significant different. The youngest patient infected by HPV-16 was 29 years old and the oldest patient was 80 years old. Table 2 displays the presence of HPV-16 infection was statistically significant associated with an increase of 3.40-fold in the risk of SCC compared with women who had SCC infected by other HPV types (95% CI = 1.44-8.03; p = 0.004).

DISCUSSION

A total of 185 cervical cancer samples were included in this study. Of these, the overall HPV DNA prevalence was 108 (58.38%) and 77 (41.62%) were negative for HPV DNA. Some study found overall HPV prevalence was 90-98% in cervical cancer.[4,10,11]
A total of 15 different HPV types were detected, but HPV-16 and 18 were the first and the second most common types. These two types were present in 56.48 % of the patients. Other HPV types were 11, 31, 33, 35, 39, 45, 51, 52, 53, 54, 58, 59, and 66. Several study also found HPV-16 and 18 as the first (57.4%) and the second (16.6%) most common types.[2,12,13] Study by Helena et al (2009) found more than 90 per cent of cases were HPV-16, 18, 31, and 45, and about half of these cases were infected by HPV-16.[14,15] In Jakarta, Indonesia, HPV infection was found 95,9% in patient with cervical carcinoma. The most common type were HPV-16 (35%) and HPV-18 (28%).[16] Study by Schellekens (2004) found the three most common types were HPV-16 (44%), 18 (39%) and 52 (14%).[4] Study in three regions in Indonesia, Jakarta, Tasikmalaya and Bali found the most prevalent types were HPV-52 (23,2%), HPV-16 (18%), HPV-18 (16,1%) and HPV-39 (11,8%). In Bali the most prevalent types were HPV-52 (18%), HPV-16 (15%) and HPV-18 (12%).[17] Of the 108 specimens positive for HPV DNA, 42 (38.89%) diagnosed histopathologically as adenocarcinoma, 65 (60.19%) were SCC and 1 (0.92%) was adenosquamous carcinoma. About 90% of cervical cancer was squamous cell carcinoma origin from squamous metaplastic epithelium at transformation zone, the remain 10% was adenocarcinoma origin from cylindrical epithelium of endocervix.[1]

Table 2
Correlation between HPV-16 to SCC

		Squamous cell carcinoma		OR	CI	*p*
		Positive	Negative			
HPV16	Positive	33	10	3.40	1.44-8.30	0.004
	Negative	32	33			

The mean-age of case group infected by HPV was 52.28 ± 12.43 and control group was 47.70 ± 8.02 (p=0.02). The youngest patient infected by HPV-16 was 29 years old and the oldest patient was 80 years old. Study by Xavier et al (2004) found HPV-16 was detected slightly more frequently in women older than 50 years than in women aged 50 years or younger among HPV-positive case patients, 62% and 46%, respectively, whereas HPV-18 was more frequently detected in younger case patients than in older patients, 46% and 26%, respectively.[8]

In this study HPV-16 was more common in squamous cell carcinoma 33 (78.57%) than in adenocarcinoma 9 (21.43%). The statistically significant result also found by Nubia et al (2004) 54.4% vs 41.6% for HPV-16 and 37.3% vs 11.3% for HPV-18. [2] Other study by Xavier et al (2004) found the same results, the prevalence of HPV-18 in adenocarcinomas (39%) is statistically significantly greater (p<0.001) than that in SCC (18%).[8] The prevalence of HPV-16 is increased in SCC compared to normal cytology, whereas HPV-18 is more prevalent in adenocarcinoma and its precursor.[18,19] HPV-18 is the most prevalent type in

cervical adenocarcinomas (55%), followed by HPV-16 (32%) and HPV-45 (10%).[11,14]

Risk of developing SCC associated with HPV-16 in this study was statistically significant with an 3.40-fold increase (95% CI = 1.44-8.03; p = 0.004). Study by Xavier et al (2004) and Bulk et al (2006) found that HPV-16 confers the greatest risk for SCC.[18] HPV-16 was associated most strongly with SCC (ORs 30; 95% CI, 12-77). [20]

CONCLUSION

Infection by HPV-16 was statistically significant associated with an 3.5-fold increase in the risk of cervical SCC (95% CI = 1.44-8.03; p = 0.004).

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