High-Risk and Multiple Human Papillomavirus Infections Associated with Cervical Abnormalities in Japanese Women

Toshiyuki Sasagawa, Walid Basha, Hiroshi Yamazaki, and Masaki Inoue

School of Health Sciences, Faculty of Medicine, Kanazawa University, Ishikawa 920-0942, and Department of Obstetrics and Gynecology, School of Medicine, Kanazawa University, Ishikawa 920-8641 [H. Y., M. I.], Japan

Abstract

To estimate the risk of human papillomavirus (HPV) infection for cervical malignancies, we conducted a case-control study in Japan. Abnormal cervical cell (366) and normal cell samples (1562) were tested for the presence of HPV DNA using a new PCR-based test (LCR-E7 PCR). When single HPV infections were considered, 26 different HPV types were identified in normal cervices and in low-grade squamous intraepithelial lesions (LSIL); whereas HPV-16, -18, -31, -33, -35, -45, -51, -52, -56, -58 and -67 were detected in high-grade squamous intraepithelial lesions (HSIL) and in squamous cell carcinoma (SCC) of the cervix, and HPV-16 and -18 were detected in cervical adenocarcinoma. HPV-6 and -11 were detected in condyloma acuminatum tissue. In HSIL and SCC, HPV-16 was the most prevalent type and HPV-51, -52, and -58 were the next most prevalent; whereas HPV-39, -59, and -68 were not detected. Analysis by odds ratio (OR) revealed that HPV-11, -39, -42, -44, -53, -59, -62, and -66 (HPV-66: OR, 139; 95% confidence interval (CI) = 6.7–168) were associated with LSIL; HPV-16, -18, -31, -51, -52, -56, -58 and -67 were detected in high-grade squamous intraepithelial lesions (HSIL) and in squamous cell carcinoma (SCC) of the cervix, and HPV-16 and -18 were detected in cervical adenocarcinoma. HPV-6 and -11 were detected in condyloma acuminatum tissue. In HSIL and SCC, HPV-16 was the most prevalent type and HPV-51, -52, and -58 were the next most prevalent; whereas HPV-39, -59, and -68 were not detected. Analysis by odds ratio (OR) revealed that HPV-11, -39, -42, -44, -53, -59, -62, and -66 (HPV-66: OR, 139; 95% confidence interval (CI) = 6.7–168) were associated with LSIL; HPV-16, -18, -31, -51, -52, -56, -58 and -67 were detected in high-grade squamous intraepithelial lesions (HSIL) and in squamous cell carcinoma (SCC) of the cervix, and HPV-16 and -18 were detected in cervical adenocarcinoma. Multiple HPV infection was associated with LSIL (OR, 94; 95% CI = 36–131) and SCC (OR, 83; 95% CI = 3.2–22), although the prevalence decreased with the grade of the lesions. All results suggest that HPV-6 and -11 are condyloma types, HPV-16, -18, -31, -51, -52, -58, and perhaps -33, -35, -45, -56, and -67, are the high-risk HPV types, and many other types are LSIL-associated types in Japan. HPV typing and detection of multiple HPV infections in clinical samples may be useful as surrogate markers for cervical cell abnormalities.

Introduction

Cervical cancer is the fifth most frequently seen cancer and the second most common cancer in women worldwide (1). zur Hausen et al. (2) first showed that HPV is closely associated with the development of cervical cancer. Many previous studies have shown that HPV-6 and -11 are associated with benign anogenital lesions, whereas HPV types 16 and 18 are associated with cervical cancer (3). Currently, more than 80 HPV types have been identified. More than 30 distinct HPV types are known to infect the genital tract, and at least 10 are associated with cancer (3). Therefore, the association between HPV infections and anogenital lesions is more complicated than expected. HPV types such as HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, and -68 are thought to be high-risk types because these types are identified in HSIL (4, 5) or invasive cervical cancer (6), whereas HPV-6, -11, -40, -42, -43, -44, and -55 are considered low-risk types (3, 7). Geographical differences in HPV types have been reported to exist between countries (6) and even within the United States (7, 8). Therefore, the HPV types prevalent in Japan may differ from those in Western countries (5, 9).

Recent progress in molecular biology techniques prompted us to use a highly sensitive HPV DNA test as a supplementary test for cervical cancer screening, and to follow-up women with low-grade cervical lesions, such as LSIL (10), ASCUS, and AGUS (11–13). The clinicopathological grading of HPV types according to their ability to promote cancer is now the most important issue for many clinicians who use such HPV tests in cancer screening programs. However, the introduction of a highly sensitive assay revealed multiple HPV infections in women with abnormal cytology, and even in normal women (14, 15). Multiple HPV infections may cause confusion in determining which HPV types are responsible for the development of cervical lesions. We recently established a PCR-based system that is able to detect the E6-E7 DNA of more than 36 mucosal HPV types (16). Using this assay, we conducted a case-control study in Hokuriku, Japan, to elucidate the risk of individual HPV types for cervical cancer. In this study, we examined the prevalence of infection with a single HPV type or with multiple HPV types to clarify the association between HPV infection patterns and the stage of cervical lesions.

Materials and Methods

Study Population. Women were recruited to participate in a cervical cancer-screening program at four hospitals in the Hokuriku area of Japan (Fukui, Ishikawa, and Toyama prefec-

Received 7/12/00; revised 10/2/00; accepted 10/18/00.

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1 To whom requests for reprints should be addressed, at School of Health Sciences, Faculty of Medicine, Kanazawa University, 5-11-80 Kodatsuno, Kanazawa, Ishikawa 920-0942, Japan. Phone: 81-76-265-2000, extension 5231; Fax: 81-76-234-4266; E-mail: tsasa@med.kanazawa-u.ac.jp.

2 The abbreviations used are: HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesions; UC, uncharacterized type; ADCA, adenocarcinoma; SCC, squamous cell carcinoma of cervix; LSIL, low-grade intraepithelial lesions; NCX, normal cervices; OR, odds ratio; CI, confidence interval; CIN, cervical intraepithelial neoplasia.
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were added to a 50-mmol/L mucosal HPV types. One hundred ng of sample DNA above. Four degenerate LCR forward primers (LCRF1, LCRF2, included in the numbers of case and control samples mentioned samples ineligible for the study, and these samples are not 1

ASTEC PCR Thermal Cycler PC 707-02 (ASTEC, Fukuoka, Japan) using the alkaline transfer method. The blotted membrane was hybridized with a mixture of four fluorescence-labeled, HPV-degenerated oligoprobes. The sequences of these probes were as follows: (a) HPV-16R-AS, AATTGCTCA-TARCAGTAKAGRTCA; (b) HPV-18R-AS, TCWYTAA-AWGCAAATTCAWATACCTC; (c) HPV-51/56-AS, AATTGTYCTRWGCATTGAGTTC; and (d) HPV-6b/11-AS, CAATGDAARCAGCCACCTTCCA (R, A/G; K, G/T; W, A/T; Y, C/T; D, G/A/T). Hybridized HPV DNA was visualized using an enhanced chemiluminescence detection kit for fluorescence-labeled probes (Amersham, Japan). HPV typing was performed by an RFLP method using amplified DNA stained with ethidium bromide. HPV typing was performed by RFLP analysis on gels stained with ethidium bromide. The details of the RFLP typing method were as described previously (16). We performed RFLP analysis using hybridization on some samples, which had shown too-faint signals, with a mixture of E6-E7 DNA probes of HPV types 11, 16, 18, 31, 51, 52, 56, 72, and 73. Most of the E6-E7 DNA probes were amplified with LCR-E7 PCR from cloned wild-type HPV DNA, and only E6-E7 of HPV51 from a clinical sample. An amplified DNA probe from each type was cloned into a pgEM vector, and the sequence was confirmed by autosequencer. Southern blot hybridization was performed under the moderate-stringency condition (Tm = −30°C). Labeling and detection of the E6-E7 DNA probe was performed using the ECF Random-Prime Labeling and Detection system (Amersham Pharmacia Biotech, Tokyo, Japan). Undetermined HPV types with RFLP analysis were cloned into a pgEM vector. HPV typing was performed on these clones by sequence analysis. The samples that could not be typed by RFLP and sequence analysis were classified as UCs. HPV 62 was determined with MY09/11-PCR and RFLP method established by Manos et al. (18) because we have no sequence data for E6-E7 genes of HPV62.

Statistical Analysis. The χ² test was used to compare the prevalence of HPV infection. We used the crude OR with the 95% CI to estimate the relative risk of each HPV type for cervical lesions. All cases and controls infected with single and multiple HPV infections were evaluated for this analysis.

Results

Detection and Typing of HPV in Clinical Samples Using LCR-E7 PCR. To determine the prevalence of HPV infection in different cervical lesions in Japanese women, we examined the presence of HPV DNA in cervical cytology samples using the LCR-E7 PCR method, which we recently developed. This new method is able to amplify the E6-E7 DNA of more than 36 mucosal HPV types (16). We tested 1562 normal controls and 366 cases with abnormal cervical cells. In the study, 9.7% (151 of 1562) and 9.7% (151 of 1562), 77% (111 of 145), 91% (125 of 137), 93% (67 of 72), and 67% (8 of 12) were positive for any HPV type in NCX, LSILs, HSILs, SCCs, and ADCAs, respectively (Table 1). When we tested condyloma tissues, 100% (16 of 16) of condyloma samples were positive for HPV-6 or -11 DNA. HPV typing using RFLP and sequence analysis revealed two patterns of infection: single HPV infection and multiple HPV infection. Multiple HPV infection was suspected in some samples that showed an overlay of type-specific bands in the RFLP analysis. Correct typing with RFLP was sometimes very difficult in the samples with multiple infection if the band signals were weak or if the samples contained more than three distinct HPV types. HPV types of such cases were determined by sequence analysis on cloned HPV DNA from the PCR products.

In condyloma tissue, HPV-6 was the predominant type (88%, 14 of 16), and only two cases were HPV-11. Nine of 10 (90%) condyloma patients also showed positive for HPV DNA in their cervixes too. Surprisingly, the HPV types identified in...
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<td>Vulva and vagina</td>
<td>Any types</td>
<td>No.</td>
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<td>Con. T (n = 16)</td>
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<td>NCX (n = 1562)</td>
<td>151</td>
<td>9.7%</td>
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<td>LSIL (n = 145)</td>
<td>111</td>
<td>77%</td>
<td>30</td>
<td>21%</td>
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<td>HSIL (n = 137)</td>
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<td>SCC (n = 72)</td>
<td>67</td>
<td>93%</td>
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<td>ADCA (n = 12)</td>
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aPhylogenetic classification of HPV types by Bernard et al. (19).

bHPV type was not characterized.

CCon. T, condyloma tissue; Con. CX, cervical cells from condyloma patients.

dNumber of women with multiple HPV infections.

The prevalent HPV types in the genital areas of Japanese women.
their cervixes differed from those detected in the condyloma tissue in most of these cases (Table 1). HPV-18, -51, -58, and -66 were detected as a single HPV types, and HPV-6, -31, -42, -44, -52, and -56 were detected as multiple HPV infections in the cervixes (Table 1).

In the cervical samples that were positive for HPV infection, single infection was found in 8.6% (134 of 1562) of normal, 56% (81 of 145) of LSILs, 76% (104 of 137) of HSILs, and 81% (58 of 72) of SCCs (Table 1). HPV-11, -16, -18, -31, -33, -35, -39, -42, -44, -51, -52, -53, -56, -58, -59, -61, -62, -66, -67, -68, -72, and -73 were identified as single HPV types in NCX and in LSILs, whereas HPV-16, -18, -31, -33, -35, -45, -51, -52, -53, -54, -55, -56, -58, -59, -61, -62, -66, -67, -68, -72, and -73 were identified as single HPV types in NCX and in LSILs, whereas HPV-16, -18, -31, -33, -35, -45, -51, -52, -53, -55, -56, -58, and -67 were identified in HSILs and SCCs, and HPV-16 and -18 were identified in ADCA of the cervix. Of the HPV types thought to be cancer-associated types in a previous study (6, 8), HPV-39, -59, and -68 were not detected in HSILs and SCCs, and HPV 56 were not detected in SCCs.

The Relative Risk of Each HPV Type for Cervical Lesions. Table 2 shows the crude OR for the prevalence of each HPV type associated with various cervical lesions. The OR was calculated for all cases of single and multiple HPV infection. For LSIL, the OR was significantly high for HPV types 6, 11, 16, 31, 33, 35, 42, 44, 51, 52, 53, 56, 58, 59, 62, 66, and 68, with magnitudes between OR, 7.0 (95% CI = 2.3–22) for HPV-42 and OR, 139 (95% CI = 6.7–168) for HPV-66. For HSIL, statistically significant associations with risk were detected for HPV types 16, 31, 33, 35, 45, 51, 52, 56, and 58, with magnitudes between OR, 4.3 (95% CI = 1.1–17) for HPV-33 and OR, 43 (95% CI = 24–75) for HPV-16. For SCC, statistically significant risk estimates were observed for HPV types 11, 16, 18, 31, 51, 52, 53, and 58, with magnitudes between OR, 5.0 (95% CI = 1.8–14) for HPV-18 and OR, 69 (95% CI = 36–131) for HPV-16. For ADCA, statistically significant risk estimates were observed for HPV types 11, 16, and 18, with magnitudes between OR, 24 (95% CI = 2.6–212) for HPV-11 and OR, 94 (95% CI = 28–317) for HPV-18. Because HPV-6 and -68 in LSIL, HPV-45 in HSIL, HPV-11 and -53 in SCC, and HPV-11 in ADCA were not identified as single HPV types, these types are not considered to be associated with these lesions. From these findings, we conclude that HPV-11, -39, -42, -44, -53, -62, -66, -67, -68, -72, and -73 were identified as single HPV types in NCX and in LSILs, whereas HPV-16, -18, -31, -33, -35, -45, -51, -52, -53, -55, -56, -58, -59, -61, -62, -66, -67, -68, -72, and -73 were identified as single HPV types in NCX and in LSILs, whereas HPV-16, -18, -31, -33, -35, -45, -51, -52, -53, -55, -56, -58, and -67 were identified in HSILs and SCCs, and HPV-16 and -18 were identified in ADCA of the cervix. Of the HPV types thought to be cancer-associated types in a previous study (6, 8), HPV-39, -59, and -68 were not identified in HSILs and SCCs, and HPV 56 were not detected in SCCs.
-59, -62, and -66 are LSIL-associated types, HPV-16, -18, -31, -51, -52, and -58 were cervical cancer (SCC) -associated types, and HPV-33, -35, and -56 were considered high-risk types. The magnitude of OR for HPV-16 dramatically increased with malignancies of cervical lesions, whereas ORs for other HPV types did not, suggesting that HPV-16 is the most malignant type. The risk of other HPV types, such as HPV-6, -30, -54, -55, -61, -67, -68, -70, -72, and -73, were not determined in the present study. However, HPV-6 was identified in condyloma tissue, HPV-54, -61, and -73 were detected as single-infection in LSIL, HPV-45 in SCC and HPV-67 was in LSIL and SCC, suggesting that HPV-6 is condyloma type, HPV-54, -59, -61, and -73 may be LSIL-associated types, and HPV-45 and -67 may be high-risk types. HPV-11 is likely to be associated with both condyloma and LSIL of the cervix. On the other hand, HPV-30, -55, -68, -70, and -72 were undetermined for the risk of any cervical lesions.

High-Risk and Multiple HPV Infections in Cervical Lesions.

Multiple HPV infection in LSIL (27%, 30 of 111) was a little more frequent than in HSIL (17%, 21 of 125; \( P = 0.056 \)) and significantly more frequent than in SCC (13%, 9 of 67; \( P = 0.033 \); Table 1). The OR for multiple HPV infection was significantly higher for LSIL (OR, 24; 95%CI = 13–44), HSIL (OR, 16; 95%CI = 8.4–32), and SCC (OR, 8.3; 95%CI = 3.2–22), suggesting that multiple infection is associated with all stages of cervical lesions (Table 2).

Next, we tried to identify all of the HPV types involved in multiple infection, although we failed to characterize HPV types in 16 cases (1 normal, 8 LSILs, 5 HSILs, and 2 SCCs; Fig. 1). HPV-6 and -70 were not identified as single types, but as one of multiple types in cervical cell samples. In multiple infection, the high-risk HPV types were identified as one of multiple types in 82% (14 of 17) of NCX, 60% (18 of 30) of LSILs, 95% (20 of 21) of HSILs, and SCCs (9 of 9), and all ADCAs (1 of 1). In contrast, condyloma types (HPV-6 and -11), LSIL-associated types (HPV-39, -42, -44, -53, -54, -59, -61, -62, -66, and -73), and the undetermined risk types (HPV-30, -55, -68, -70, -72) were identified in 65% (11 of 17) of NCX, 90% (27 of 30) of LSILs, 89% (8 of 9) of SCCs, and all (1 of 1) ADCAs. This analysis also revealed that the high-risk types included in multiple infection cases increased in percentage according to the grade of cervical lesions.

The proportion of HPV infection patterns in each lesion is demonstrated according to the classification of HPV types with the risk for cancer in this study (Fig. 2). The proportion of single high-risk HPV infections increased with the malignant grade of the lesion and was 56, 49, 75, and 78% for NCX, LSIL, HSIL, and SCC, respectively. In contrast, condyloma, LSIL-associated, and undetermined-risk types were positive in 19% (28 of 151) and 17% (19 of 111) of NCX and LSILs, respectively, although none of these types was found as single infections in HSILs and SCCs. Combining single and multiple infections, high-risk types were identified in 91% (114 of 125) of HSILs, 91% (61 of 67) of SCCs, and 100% (8 of 8) of ADCAs, whereas they were only detected in 65% (72 of 111) of LSILs, and 65% (98 of 151) of NCX. In either analysis of single infection or the combining one, high-risk HPV types were significantly prevalent in HSIL and SCC than in NCX and LSIL (\( P < 0.03 \)).
High-Risk HPV Infection in Cervical Lesions in Japan

Discussion

Our new PCR test (16) identifies most mucosal HPV types; both the spectrum of detectable HPV types and the sensitivity are equivalent to the MY09/11-PCR method (15). Using this test, we conducted a case-control study in the Hokuriku area of Japan. We found that 9.7% (151 of 1562), 77% (111 of 145), 9% (125 of 137), 93% (67 of 72), and 67% (8 of 12) of NCX, LSILs, HSILs, SCCs, and ADCAs were positive for HPV, respectively (Table 1). The prevalence of HPV in various cervical lesions in this study was quite similar to the results of many previous studies. Most of our results concur with the results of many previous studies. However, HPV-39, -59, and -68 were not identified in HSIL and SCC, although these types are thought to be associated with cancer (6). The risk of HPV-30, -55, -68, -70, and -72 for cancer were not determined in the present study. Additional study is needed to clarify whether these uncommon types are actually high-risk types or others.

There were many multiple HPV infections in our clinical samples. Multiple infection appears to be a characteristic of women with cervical abnormalities, inasmuch as it showed statistically significant associations with the risk for LSIL, HSIL, and SCC in this study. Multiple infection was more frequent in LSILs than in malignant lesions (HSILs and SCCs; P < 0.05). This may represent a segregation of certain HPV types in cancer cells.

When we examined the HPV types involved in multiple infection, high-risk types were identified as one of the types in most HSILs and in all cervical cancers, whereas 60% of LSILs had high-risk types. For single-HPV infection and combining single and multiple infections, high-risk types were more prevalent in HSILs and in SCCs than in NCX and in LSILs (P < 0.03). All of our findings support the idea that there are two different groups of cervical lesions: (a) low-risk HPV-associated lesions; and (b) high-risk HPV-associated lesions. A previous study showed that the pathological grade shift from CIN I to III in the same cases was associated with infection by different HPV types (21). The higher-grade lesions (CIN II or III) were infected with HPV types 16 or 18, whereas the lower grade lesions (CIN I) were infected with HPV 11 in the report. Thus, lower-grade cervical lesions can be induced by low-risk or high-risk HPV types or both, whereas high-risk HPV infection alone promotes cancer. Two recent studies also showed that high-risk HPV infection persists longer than low-risk HPV types (14, 22). The cervix may deal with low-risk HPV-associated lesions easily, whereas high-risk HPV-associated lesions may resist host immunity and persist longer. In the present study, high-risk types alone appear to be segregated in HSIL and in SCC, suggesting that high-risk HPV-associated lesions are able to persist and progress to HSIL and SCC. This may fit the model of multistep carcinogenesis of the uterine cervix supported by many pathologists. In contrast, the low-risk HPV-associated lesions are merely HPV-induced transient lesions.
The reasons why a high-risk HPV infection is able to persist longer than a low-risk HPV infection remain to be investigated in the future.

A recent study found that multiple HPV infection is a factor in persistent HPV infection in normal young women (14). Some studies also indicate that persistent HPV infection is important for the development of cervical dysplasia (14, 23). Combining these results, multiple HPV infection is likely to be associated with the development of cervical neoplasia. Multiple HPV infection may produce conditions that confer immunological protection for persistent infection of HPV, or women with multiple HPV infections may be susceptible to HPV infection, although additional study is needed to elucidate these hypotheses.

Our findings suggest that it is important to identify HPV types and HPV infection patterns to predict the outcome in women with HPV DNA in their cervix. Accumulated data for the high-risk HPV types from different countries help determine the clinicopathological grading of HPV types. Under a consensus of clinicopathological grading of HPV types, HPV tests could be clinically useful for laboratory quality control and adjudication of ASCUS.

Acknowledgments

We thank Drs. Miwa, S. Satake, H. Funamoto, T. Nakano (Toyama Prefectural Central Hospital), Dr. T. Harada (Fukui Prefectural Hospital), Dr. K. Uchide, and Dr. N. Suzuki (Department of Obstetrics and Gynecology, Kanazawa University) for collecting clinical samples.

References


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Toshiyuki Sasagawa, Walid Basha, Hiroshi Yamazaki, et al.