Journal of Rural Medicine

Original article

Progression of cervical intraepithelial neoplasia grade 2 lesions among Japanese women harboring different genotype categories of high-risk human papillomaviruses

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Abstract

Background: This study aimed to examine whether genotype categories of high-risk human papillomaviruses (HR-HPVs), when divided into HPV16/18, HPV 31/33/45/52/58, and HPV35/39/51/56/59/68, had an effect on the time required for and the proportion of cases that progressed to cervical intraepithelial neoplasia (CIN) grade 3 among women with CIN2.

Patients: A total of 160 women aged 20–49 years and having CIN2 were recruited between January 2008 and June 2018. The time required for progression to CIN3 was determined by Kaplan-Meier time-to-event analysis. HPV genotypes were determined using the Linear Array HPV genotyping test.

Results: During an average follow-up time of 22 months, 62 (39%) women with CIN2 progressed to CIN3, whereas 34 (21%) eliminated HR-HPVs and became cytologically normal. The majority (63%) of the women harboring HPV16/18 progressed to CIN3 with a 50% progression time of 11 months, whereas 26% of those harboring HPV31/33/45/52/58 progressed to CIN3 with a 50% progression time of 70 months.

Conclusion: For every patient diagnosed with CIN2, genotyping to distinguish HPV16/18 from other HR-HPVs should be performed. Therefore, electing a surgical treatment, such as conization, should be considered as the primary option for women who are positive for HPV16/18, particularly when they are likely to be lost for follow-up or are 40 years old or older. In contrast, follow-up cytology should be repeated every 12 months for women harboring non-16/18 HR-HPVs. Those who tested negative for HR-HPV may be followed at the maximum interval of 24 months.

Key words: human papillomavirus, genotype, CIN2, CIN3, progression

(J Rural Med 2021; 16(2): 91–97)

Introduction

Infection of the uterine cervix with human papillomaviruses (HPVs) causes a range of pathologic conditions, namely asymptomatic infection, low-and high-grade cervical intraepithelial neoplasia (CIN) and cervical carcinoma[1)].

Received: July 29, 2020
Accepted: December 8, 2020
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Certain HPVs, including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, are frequently detected in cervical carcinoma and are, thus, called high-risk (HR)-HPVs[2–5)]. Virtually all cervical carcinomas are caused by HR-HPVs through a stepwise progression from CIN1, to CIN2, CIN3, and, finally, to cervical carcinoma[1, 6)].

However, most HPV infections are transient, and even HR-HPVs are often eliminated, particularly in adolescents and young women[7–9)]. Thus, not all lower CIN lesions progress to higher CIN lesions, let alone cervical carcinoma. Cervical carcinoma occurs only in a tiny fraction of women who are persistently infected with HR-HPVs; hence, HR-HPVs are causally associated with carcinogenesis[6)]. HR-HPVs rarely persist in patients with CIN1, and the regression of histopathological conditions is a common event[10, 11)]. For this reason, women with CIN1 are placed under cytological follow-up, and no treatment is required. In contrast,

the vast majority of patients with CIN3 are likely to be persistently infected with HR-HPVs, having a higher probability of progression to invasive carcinoma than of regression. For example, Motamedi *et al*.[12] reported that 98% of women with CIN3 harbored HR-HPVs, and during an average of 8.9 weeks before surgical treatment, regression occurred only in 1.3% of the cases, whereas invasive carcinoma was found in 1.9% of the conization tissue. Thus, surgical excision of the transformation zone is indicated, regardless of the age or concern about future fertility[13].

The in-between condition, namely CIN2, is at a crossroads in clinical decision-making and its management options need to be carefully considered depending on each individual case. The guidelines implemented by the American Society for Colposcopy and Cervical Pathology state that the observation of CIN2 (as well as CIN3 or CIN2,3) with sequential cytology and colposcopy is unacceptable, except in young or pregnant women[13]. In contrast, the guidelines published by the Japan Society of Gynecology and Obstetrics state that women with CIN2 are to be followed at 3–6-month intervals with cytology/colposcopy, and that surgical intervention is acceptable only for non-pregnant women who do not regress for 1–2 years, which carry HR-HPVs (i.e., HPV 16, 18, 31, 33, 35, 45, 52, and 58), and who no longer desire to bear a child or are at risk of loss to follow-up[14].

There is a gradient of relative frequencies at which each of the HR-HPV genotypes was found in cervical squamous cell carcinoma[4, 5, 15]; HPV16 and 18, for which vaccines are globally licensed, account for approximately 70% of cervical squamous carcinomas, HPV 31, 33, 45, 52, and 58 account for approximately 20%, and the rest refers to HPV 35, 39, 51, 56, 59, and 68. However, it is not adequately studied whether the genotype category of HR-HPVs to which a woman with CIN2 belongs makes any difference in the probability of and the time required for progression to CIN3.

Thus, the aim of this study was to examine the time and proportion of progression to CIN3 among women diagnosed with CIN2, according to the three genotype categories of HR-HPVs. Furthermore, we aimed to apply the observed differences, if any, on the management of CIN2 patients, including the follow-up visit intervals and the decision to elect a surgical intervention.

Patients and Methods

Patient recruitment

The study subjects were selected from the women who visited the outpatient department of Obstetrics and Gynecology, at Yuri-Kumiai General Hospital, Akita, Japan, between January 2008 and June 2018. Specifically, women diagnosed as having CIN2 at the first visit, and those who progressed to CIN2 during the follow-up visits were asked to participate if they were 20–49 years of age. Informed consent was obtained from those who agreed to participate. This study was approved by the Institutional Review Board and Ethics Committee of Yuri-Kumiai General Hospital.

Histological examination

Women who had an abnormal cytology or tested positive for the hybrid capture II assay or both were subjected to colposcopy. Two to four punch-biopsy specimens were collected from the lesions where abnormality was observed under colposcopy. For the unambiguous cases, a CIN2 diagnosis was made on the biopsied specimens by an in-house pathologist after hematoxylin-eosin staining; however, for borderline cases, specimens were examined by two pathologists. In addition, immunohistochemistry with anti-p16 antibody was performed whenever necessary. The pathologists were informed of the cytological and colposcopic findings of the patients.

HPV detection, genotyping, and categorization of HR-HPV genotypes

Samples for HPV detection and genotyping were scraped from the cervix with a Cervex Brush® (Rovers Medical Devices B.V., 5347 KV Oss, The Netherlands), suspended in the PreservCyt® solution (Hologic, Inc., Marlborough, MA, USA), and sent to Medical and Biological Laboratories, Co., Ltd. or SRL, Inc. (Tokyo, Japan) for the hybrid capture II assay® (Qiagen) or for the Linear Array HPV genotyping test® (Roche Molecular Diagnostics), respectively.

The HR-HPVs defined in this study were the HPVs whose genotypes were included in the hybrid capture II assay, i.e., HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. After the genotype(s) of HR-HPVs in the sample of a given patient was (were) identified by the Linear Array HPV genotyping test®, the patient was categorized into any one of the three genotype categories, namely, HPV16/18, HPV31/33/45/52/58, and HPV35/39/51/56/59/68. Patients harboring HPV16/18 are defined as those in whom, at least, HPV16 or HPV18 was present, irrespective of the presence of other genotypes. Thus, multiple infection cases were included in HPV16/18 if either HPV16 or HPV18 was detected in the sample. Patients harboring HPV31/33/45/52/58 were defined as those in whom any one of the genotypes 31, 33, 45, 52, and 58 was present, but neither HPV16 nor HPV18 was present. Patients harboring HPV35/39/51/56/59/68 were defined as those in whom any one of the genotypes 35, 39, 51, 56, 59, and 68 was present, but none of the genotypes 16, 18, 31, 33, 45, 52, and 58 was present.

Statistical analysis

Kaplan-Meier time-to-event analysis was used to determine the time to progression from CIN2 to CIN3, stratified by the three genotype categories of HR-HPVs (i.e., HPV16/18, HPV31/33/45/52/58, and HPV35/39/51/56/59/68).

Kaplan-Meier time-to-event analysis was performed by using STATA ver. 13 (Stata Corp., College Station, TX, USA). Student's t-test was used to compare the average visit intervals between women with HPV16/18 and those with non-16/18 HR-HPVs. The Wilcoxon test was used to examine the statistical differences in the Kaplan-Meier curves between HPV16/18 and HPV31/33/45/52/58, and between HPV16/18 and HPV35/39/51/56/59/68.

Results

Among the 1,217 women who were initially diagnosed as having atypical squamous cells of undetermined significance or worse (ASC-US+) by routine cytology testing and/or tested positive for HR-HPVs by the hybrid capture II assay® during a 10.5-year period between January 2008 and June 2018, 1,117 women underwent cervical biopsy (Figure 1). Of those, 158 (13.0%) women were diagnosed as having CIN3 or worse (CIN3+) and were excluded from the study. Cervical intraepithelial neoplasia 2 was found in 140 (11.5%) women. During the follow-up of the women who initially had CIN1 (n=657) or no CIN (non-neoplastic lesions or normal histology; n=168), 77 women developed CIN2 lesions. The number of women with CIN2 was 217, of whom 160 were women aged 20–49 years and who harbored one or more genotypes of HR-HPVs identified by the Linear Array HPV genotyping test®. They were enrolled in the study after informed consent was obtained (Figure 1). The women with CIN2 were followed for an average of 22 months (range: 1–136 months), and the total observation time was 3,557 months.

Table 1 and lower panel of Figure 1 show the clinical outcomes of the women who were diagnosed with CIN2 at some points during the study period. Overall, 62 (38.8%) of the 160 women progressed to CIN3, whereas 34 (21.3%) eliminated HR-HPVs and became cytologically normal. The remaining 64 (40.0%) women had CIN2 or regressed to milder lesions during an average of 22 months of observation time. When the results were stratified according to the genotype categories of HR-HPVs, those women who harbored HPV16/18 comprised one-third of the subjects (54/160). The proportion of progression of the women who harbored HPV16/18, HPV31/33/45/52/58, and HPV35/39/51/56/59/68 were 63.0%, 31.0%, and 9.1%, respectively (P=0.0005). Thus, the majority of women harboring HPV16/18 progressed to CIN3, whereas the women harboring HPV35/39/51/56/59/68 rare-

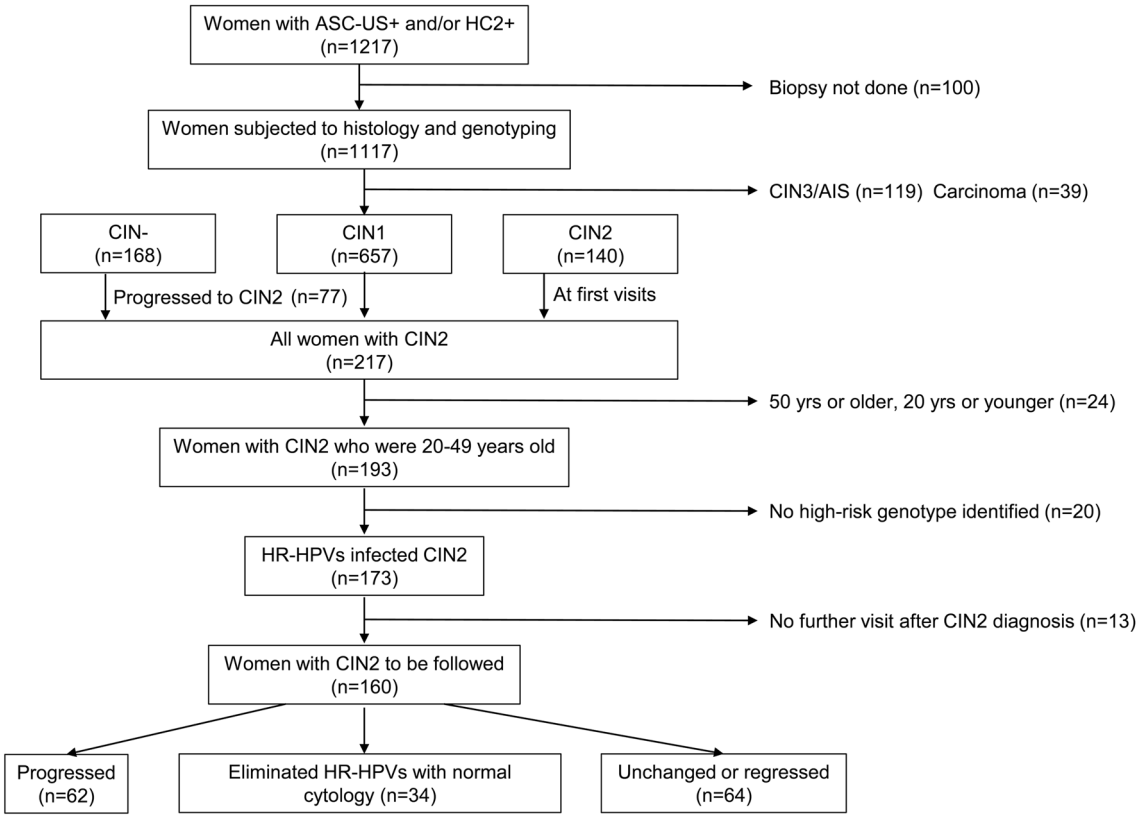

Figure 1 The selection process of the women with CIN2 who were followed in this study, and their clinical outcomes.
HR-HPV: High-risk human papillomavirus; CIN: Cervical intraepithelial neoplasia; ASC-US+: Atypical squamous cells of undetermined significance or worse; HC2+ Hybrid capture II assay positive; AIS: adenocarcinoma *in situ*.

ly progressed to CIN3 (Table 1). To examine whether the progression to CIN3 among women harboring HPV16/18 was an age-dependent phenomenon, the clinical outcome in these women was stratified according to the three age groups, namely, 20–29, 30–39, and 40–49 years (Table 2). Meanwhile, the vast majority (47/54) of the CIN2 women harboring HPV16/18 were between 20 and 39 years of age; 27 (57.4%) of the 47 women in this age group progressed to CIN3, but all seven women who were aged 40–49 years, progressed to CIN3, although the number was low. In sharp contrast, those women who eliminated the virus and had a normal cytology were all in the age group of 20–39 years (Tables 1, 2).

Kaplan-Meier's time-to-event curves visualize how rapidly the CIN2 women progressed to CIN3, according to the genotype categories of HR-HPVs (Figure 2). Women harboring HPV16/18 progressed more rapidly to CIN3 than those harboring either HPV31/33/45/52/58 (P<0.0001, by

Table 1 Clinical outcome of the women diagnosed with CIN2 at some points during the study period stratified by the genotype categories of HR-HPVs they harbored

	Progressed to CIN3	Eliminated HR-HPV with normal cytology	Unchanged or regressed	Overall
Overall	62 (38.8%)	34 (21.3%)	64 (40.0%)	160 (100%)
HPV16/18	34 (63.0%)	8 (14.8%)	12 (22.2%)	54 (100%)
HPV31/33/45/52/58	26 (31.0%)	18 (21.4%)	40 (47.6%)	84 (100%)
HPV35/39/51/56/59/68	2 (9.1%)	8 (36.4%)	12 (54.5%)	22 (100%)

Table 2 Clinical outcome of women diagnosed with CIN2 and harboring HPV16/18 stratified by the three age groups

Age group	Progressed to CIN3	Eliminated HR-HPV with normal cytology	Unchanged or regressed	Overall
20–29	14 (53.8%)	5 (19.2%)	7 (26.9%)	26 (100%)
30–39	13 (61.9%)	3 (14.3%)	5 (23.8%)	21 (100%)
40–49	7 (100%)	0 (0%)	0 (0%)	7 (100%)
Overall	34 (63.0%)	8 (14.8%)	12 (22.2%)	54 (100%)

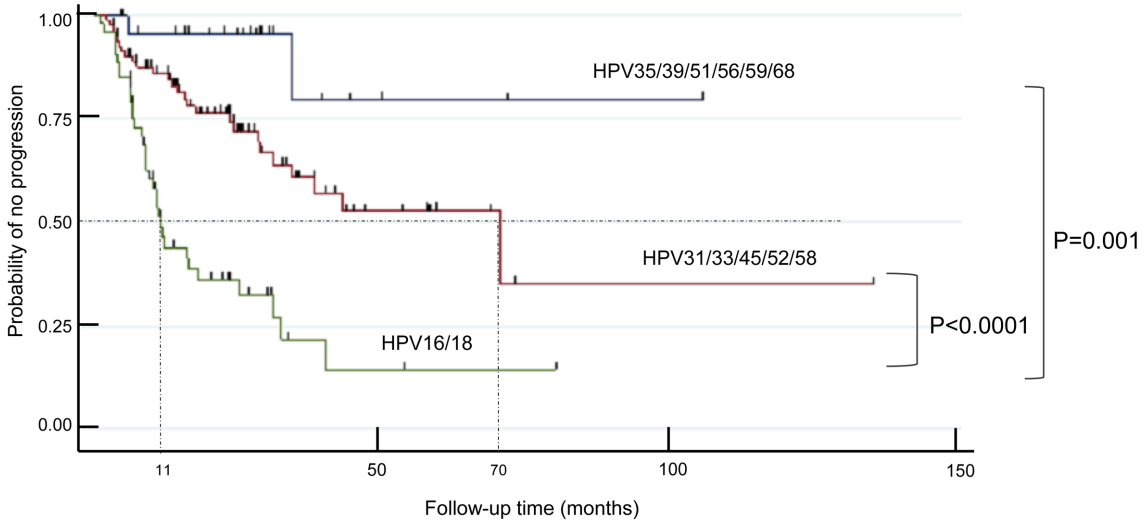

Figure 2 Kaplan–Meier's time-to-event curves showing how rapidly the CIN2 women progressed to CIN3, according to the three genotype categories of HR-HPVs; i.e., HPV16/18, HPV31/33/45/52/58, and HPV35/39/51/56/59/68. P-values shown between two HPV groups were obtained using Wilcoxon test.
HR-HPV: High-risk human papillomavirus; CIN: Cervical intraepithelial neoplasia; ASC-US+: Atypical squamous cells of undetermined significance or worse; HC2+ Hybrid capture II assay positive; AIS: adenocarcinoma *in situ*.

Wilcoxon test) or HPV35/39/51/56/59/68 (P=0.0001, by Wilcoxon test). The time at which the probability of progression to CIN3 was 50% was 11 months. In contrast, the time at which the probability of progression to CIN3 was 50% was 70 months for the women harboring HPV31/33/45/52/58. Women harboring HPV35/39/51/56/59/68 showed the slowest progression, and the probability of progression to CIN3 remained at 21% at the end of the study period (Figure 2).

Discussion

When a practicing gynecologist has received a diagnosis of CIN2 on a patient, the most important decision that the gynecologist needs to make is whether to perform a surgical intervention or to place the patient under active surveillance at frequent follow-up visit intervals. The most important information to make this decision is the probability of progression to CIN3 and how rapidly this progression may occur. According to a recent systematic review[16], the pooled proportion of progression to CIN3 at 24 months was 18% (95% confidence interval [CI]: 11–27%), whereas the pooled proportion of regression was 50% (95%CI: 43–57%). Furthermore, among women aged less than 30 years, the progression and regression proportions were 11% (95%CI: 5–19%) and 60% (95%CI: 57–63%), respectively, justifying that young women with CIN2 should be placed under active surveillance instead of undergoing immediate intervention. Thus, the key question is what genotype of HR-HPVs the woman with CIN2 harbors, rather than whether the woman is infected with HR-HPV, which helps predict the clinical outcome and, if progression is expected, the pace at which the patient will progress to CIN3.

To answer this question, this study was undertaken by recruiting women diagnosed with CIN2 who visited or referred to a teaching hospital providing services to a defined administrative region of an approximate population of 110,000 people, over a 10.5-year period. When the HR-HPVs were grouped into three genotype categories, this study showed that 63% of the women with CIN2 and harboring HPV16/18 progressed to CIN3 with a 50% probability of progression occurring at 11 months, 31% of women with CIN2 and harboring HPV31/33/45/52/58 progressed to CIN3 with a 50% probability of progression occurring at 70 months, but only 9% of the women harboring HPV35/39/51/56/59/68 progressed to CIN3.

These results are important for practicing gynecologists to whom women with CIN2 are referred, as the proportion and time required for a CIN2 lesion to progress to CIN3 are substantially different depending on which of the three genotype categories of HR-HPVs a woman with CIN2 belongs to. While the guidelines by the American Society for Colposcopy and Cervical Pathology discourage the observation of CIN2 (as well as CIN3 or CIN2,3) patients with sequential cytology and colposcopy, except in young or pregnant women[13], the guidelines by the Japan Society of Obstetrics and Gynecology recommend the active surveillance of women with CIN2 at 3–6-month intervals with cytology/colposcopy, and an immediate surgical excision is restricted only to special cases[14]. The authors believe that the difference in the pace, as well as the proportion, of CIN2 lesions to progress to CIN3+ between the first two genotype categories of HR-HPVs, should be reflected in the interval between the follow-up visits. However, in the Japanese guidelines, no distinction is made between the women harboring HPV16/18 and those harboring HPV31/33/45/52/58 regarding the follow-up visit intervals, between which this study showed a substantial difference in the proportion of progression and the pace at which the lesion progressed. According to the Japanese guidelines, once a woman with CIN2 tests positive for HPV16/18/31/33/35/45/52/58, the patient should be placed under active surveillance with follow-up visits every 3–4-months. If a woman tests positive for any of the remaining genotypes of HR-HPVs, the patient should be followed at a 6-month interval. Therefore, in terms of reflecting the genotype difference in clinical practice, the Japanese guidelines draw the major distinction, not between HPV16/18 and HPV31/33/35/45/52/58, but between HPV16/18/31/33/35/45/52/58 and HPV39/51/56/59/68.

However, the results of this study led us to claim that there may be little practical significance in distinguishing HPV31/33/45/52/58 from HPV35/39/51/56/59/68, but it cannot be emphasized enough that women infected with HPV16/18 need to be taken care of separately from women infected with other types of HR-HPVs.

Regarding the proportion and the pace of progression from CIN2 to CIN3 for the women harboring HPV16/18, the results from this study are in good agreement with those of Hosaka *et al*[17]. About 60% of women who tested positive for HPV16/18/33 progressed from CIN2 to CIN3 in two years. Approximately 30% of women who tested positive for HPV31/35/52/58 progressed to CIN3. The corresponding percentages in our study were 63.0% and 31.0%, respectively; hence, the results of these two studies are very similar, despite the difference in the age ranges of the women recruited, from less than 29 to more than 70 years of age in the study by Hosaka *et al*.[17] vs. between 20 and 49 years of age, in this study. In addition, an interesting observation from the cumulative incidence curve is that the median progression time from CIN2 to CIN3 of women infected with HPV16/18/33 was about 12 months, which is very similar to the 50% probability of progression from CIN2 to CIN3, which was obtained in this study (11 months). However, the reason for putting HPV16, 18, and 33 into a single category has not yet been described[17]. Combining HPV16/18 and HPV33 together into a single category and exploring its effect using the Kaplan-Meier time-to-event analysis was

not performed here, because of the very small number of women harboring HPV33.

In contrast, it is difficult to compare the results by Matsumoto *et al.*[18] with those of this study because of the difference in the cervical lesion starting point (CIN1/2 vs. CIN2) and that in the genotype categorization (HPV16/18/31/33/35/45/52/58 and HPV39/51/56/59/68 vs. HPV16/18, HPV31/33/45/52/58 and HPV35/39/51/56/59/68).

The reasonable recommendations drawn from this study are as follows: electing a surgical treatment, such as conization, should be considered as the primary option for women who harbor HPV16/18, particularly those women who are likely to be lost for follow-up or who are ≥40 years of age. Nevertheless, young women (aged 20–29 years) with CIN2 and infected with HPV16/18 may be followed every 3 months, particularly those who plan to have a baby in the future.

Follow-up cytology should be repeated every 12 months for women who harbor non-16/18 HR-HPV (HPV35/39/51/56/59/68 and HPV31/33/45/52/58). Those who tested negative for HR-HPV may be followed at a maximum interval of 24 months.

There are a few limitations in this study. First, this study originated from a routine clinical practice in a teaching hospital providing services to a broad, yet defined, administrative region. As such, recruitment of cases took an extended period of time, resulting in heterogeneity concerning the length of observation periods from case to case. While two human papillomavirus vaccines were introduced during the study period, none of the women with CIN2 had ever received the vaccine. Therefore, it is unlikely that the introduction of the vaccine affected the outcome of this study. Knowledge on the HPV infection status and the genotypes might unknowingly affect the follow-up practice of the recruited patients, particularly the lengths of the intervals between visits, causing biases in calculating the progression time. However, when the average follow-up intervals between those who harbored HPV16/18 and those who harbored non-16/18 HR-HPVs were compared, no statistically significant difference was observed (2.7 months vs. 3.3 months, P=0.149). Thus, knowledge on the infection status is unlikely to affect the calculation of the progression time.

Second, 51 (32%) women were infected with multiple genotypes of HR-HPVs among the 160 women with CIN2. It is a common observation in clinical practice that approximately one-third of women who are diagnosed with CIN2 have more than one HR-HPVs[19]. These multiple infection cases were grouped into the HR-HPV categories according to the genotype(s) with the highest risk associated, and this study did not distinguish between multiple and single infection cases. This treatment might have added an unknown bias to this study, but the presence of multiple infections is a rule, rather than an exception, in a real-world setting. Thus, exclusion of multiple infection cases may not be the right thing to do.

Third, because this study was performed as part of routine clinical practice in the hospital, biopsied samples were examined under routine histological diagnosis conditions; an in-house pathologist made the diagnosis from unambiguous specimens, whereas diagnosis from borderline specimens was made by two pathologists using the p16 immunohistochemical staining, when necessary. The pathologists had knowledge about the patient's cytology and colposcopic findings. This may have caused potential biases, but the authors do not believe that the information provided to the pathologists made the histological diagnosis less accurate.

Fourth, an emphasis is placed on the progression from CIN2 to CIN3, and less weight is placed on the probability of regression. While the authors do not deny the meaning of addressing spontaneous regression, particularly in young women, progression to CIN3+ is a far more important concern for both gynecologists and patients, in clinical practice.

Conclusion

For every patient who is histologically diagnosed as having CIN2, genotyping to distinguish HPV16/18 from the rest of HR-HPVs should be performed. Therefore, electing surgical treatment, such as conization, should be considered the primary option for women who are positive for HPV16/18, particularly for women who are likely to be lost for follow-up or who are ≥40 years old. In contrast, follow-up cytology should be repeated every 12 months for women infected with non-16/18 HR-HPVs. Women tested negative for HR-HPV may be followed up at the maximum interval of 24 months.

Acknowledgement

The authors owe Osamu and Toyoko Nakagomi for an immense debt of gratitude for their encouragement and penetrating intellect they have given during this study.

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