Chapter 5

Secondary Prevention of Uterine Cervical Cancer

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Additional information is available at the end of the chapter

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Abstract

Secondary prevention by cervical cytology has clearly improved the mortality rate of uterine cervical cancer (CC) by enabling early detection and treatment of high-grade squamous intraepithelial lesion (HSIL) or cervical intraepithelial neoplasia (CIN), which is a precancerous lesion. In the past two decades, HPV-DNA testing, including HPV typing, has clearly brought about positive effects on secondary prevention of CC. However, in practice, CC remains a fatal disease and is the second leading cause of cancer deaths in women aged 20–39 years. Although elucidation of the mechanisms of HPV carcinogenesis and development of a prophylactic vaccine have made CC a preventable disease, eradication of CC is expected to take several decades. Therefore, primary screening to decrease the mortality rate of CC will remain important for a while. In addition, the clinical application of simple biomarkers to stratify HPV-positive women is important for maintenance of medical economy and avoidance of overtreatment in women in the reproductive age. Therefore, the development of an inexpensive therapy or vaccine that can be used worldwide is necessary to overcome cancer deaths due to CC.

Keywords: uterine cervical cancer, cervical intraepithelial neoplasia, secondary prevention, human papillomavirus, carcinogenesis, biomarker, therapeutic vaccine

1. Introduction

Secondary prevention with the use of cervical cytology has clearly improved the mortality rate and early treatment of uterine cervical cancer (CC) by enabling early detection of high-grade squamous intraepithelial lesion (HSIL) or cervical intraepithelial neoplasia (CIN), which is a precancerous lesion [1]. In practice, however, CC was estimated to have 12,820 newly diagnosed cases and 4210 women dying of the disease in 2017 [2]. Moreover, according to the United States data in 2014, CC is the second leading cause of cancer deaths in women aged 20–39 years [2]. Therefore, improvement of screening efficiency remains an important issue.

The etiology of CC is persistent uterine cervical infection with the high-risk human papillomavirus (hrHPV). Therefore, HPV-DNA testing or HPV testing, has become widely used for primary screening of CC. Compared with conventional cytology, HPV testing has higher sensitivity and reproducibility in detecting lesions [3]. However, the specificity of HPV testing is low, with an increase in the number of false-positives, especially in women in their twenties who are highly sexually active [3, 4]. Therefore, HPV testing has been adopted in cancer screening for women over 30 years old. In fact, in the United States (US), the guidelines created by the American Cancer Society, American Society for Clinical Pathology, and American Society for Colposcopy and Cervical Pathology suggested CC screening by cytology starting at the age of 21 and every 3 years until 30 years old; beyond the age of 30, combined HPV testing and cytology for every 5 years was recommended [5]. Based on data from large-scale, longitudinal, randomized-controlled trials in European countries, HPV testing has been adopted as the primary screening tool for CC in women aged 30 years or older [6–9]; in those who are tested positive for HPV, cytology is used as the triage test. In ASC-US cases, HPV testing is performed for triage in the management of CIN, based on the results of available large-scale clinical studies [10–13]. Furthermore, HPV typing has already been used as a biomarker for decisions on therapeutic interventions and subsequent follow-up of CIN [14–19]. Both the US and European guidelines recommended HPV testing to confirm the completion of treatment of CIN.

HPVs are classified according to carcinogenic potential. In general, the frequently reported high-risk types are HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 [20]. Among these, HPV 16 and 18 are the most common types that are related to carcinogenesis worldwide; both HPV types are controllable by prophylactic vaccines that contain virus-like particles with antigenicity [21, 22]. Bivalent vaccines for HPV 16 and 18 are commercially available, but quadrivalent vaccines are also available for HPV 6, 11, 16, and 18. Although these vaccines have some cross-protective effects [23, 24], these are basically ineffective for infection by all HPV types. To overcome these limitations, a nonavalent vaccine containing HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 has been launched [25, 26].

As mentioned above, hrHPV testing has clearly brought about positive effects on early detection of CIN and prevention of CC in the past two decades [27–30]. Several researchers all over the world continue to pursue efforts to eradicate CC. **Figure 1** shows the schema of the natural

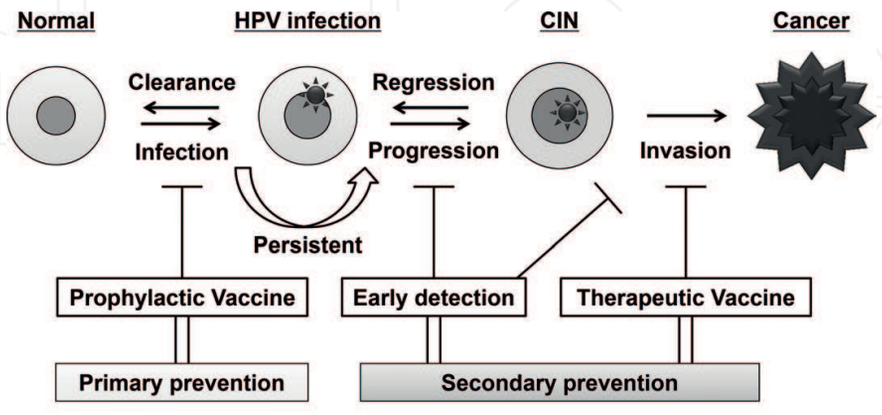

Figure 1. Natural history of HPV and prevention of cervical cancer. Persistent infection of the cervix with high-risk HPV causes cervical cancer (CC), which begins as cervical intraepithelial neoplasia (CIN). Primary prevention of CC can be achieved by prophylactic HPV vaccination. Secondary prevention consists of early detection of CIN and therapeutic vaccination to inhibit progression from CIN to CC.

history of HPV and CC prevention. In this chapter, we will describe the recent developments in secondary prevention of CC.

2. Biology and carcinogenesis of HPV

HPV is a virus with a double-stranded circular DNA in the icosahedral capsid. The genome size is about 8000 bases and contains eight protein-coding genes and a noncoding, regulatory long control region [31]. The early genes (E1, E2, E4, E5, E6, and E7) encode nonstructural proteins involved in replication, transcription, and transformation; whereas the late genes (L1 and L2) encode viral capsid proteins. Among these genes, E6 and E7 play a central role, particularly in carcinogenesis. Notably, a recent whole-genome sequencing study that assessed the risk of viral genetic variation showed that strict preservation of the 98 amino acids of E7, which destroys the function of the retinoblastoma protein (pRB), was critical for HPV 16 carcinogenesis and development of CIN and CC [32].

HPV can infect the epithelial cells of the human mucosa and skin at least once in most women's lives. In other words, HPV infection is a common sexually transmitted disease. Because prophylactic vaccines prevent only initial infection, its value in women is most effective before the first sexual contact [33]. In the early stages of HPV infection, the host is asymptomatic, and in most cases, the virus is eliminated by the immune system within a few years [34]. However, HPV infection can persist in some patients. The reported risk factors for progression of cervical HPV infection to CIN or CC include persistent hrHPV infection, immunosuppression, age over 30 years, and smoking [35].

Persistent hrHPV infection of the cervix is divided into three stages: latent, permissive, and transforming [36–38]. First, HPV invades the epithelial basal cells via minor breaches of the epithelium [39] and become latent as a nuclear episome; the infected cells usually die after virus multiplication. The E6 and E7 genes are rarely integrated into cellular DNA and cause HPV growth in the cells; however, this property also allows continued expression of E6 and E7 proteins at high levels. The expression of E6 and E7 oncogenes in basal cells is tightly controlled; therefore, HPV-infected cells can escape a host's immune defense. In fact, in a small percentage of HPV-infected women, HPV-specific antibodies and T cells are detected at low levels [40, 41]. Recently, it was suggested that the programmed death 1/programmed death 1 ligand (PD-1/PD-L1) pathway might be involved in the mechanism of this immune evasion [42–44].

When infected cells begin to differentiate in the epidermis, the E6 proteins degrade the tumor suppressor protein p53, while the E7 proteins inhibit the function of the pRB; these processes reactivate DNA synthesis and replication of the HPV genome. The cells with integrated E6 and E7 genes will have uncontrolled cell cycles because p53 and pRB are major cell cycle regulators. Furthermore, apoptosis and the tumor suppressor pathway are repressed. During this process, accumulation of genetic mutations and genomic instability ensue [45–50]. As a result, a large number of clones with intratumor heterogeneity are produced, some of which might be able to avoid the host antitumor response [51–54]. Ultimately, with the addition of external factors, these cells will be immortalized and can become cancerous [55].

3. Biomarker for early detection and triage

HPV testing has been introduced for primary screening for CC; it is highly sensitive, but its false-positive rate is high due to the low specificity. Therefore, the need to stratify HPV-positive women with or without abnormal cytology has become a very important issue [56]. At present, HPV-positive women undergo cytology tests and HPV retesting, with colposcopy and tissue biopsy correlations at frequent intervals; however, the precision of this process remains unclear. More objective indicators are required to prevent unnecessary procedures and treatment. As the understanding of the molecular mechanisms of cervical carcinogenesis by HPV has progressed, various biomarkers that predict patient outcomes have been developed not only for early detection but also for triage.

As mentioned earlier, persistent HPV infection of cervical cells leads to tumor formation through several stages. Since HPV infection is often transient, detection of the stage when HPV infection shifts from permissive to transforming is clinically important for cancer screening. Similarly, the histopathologic and molecular diagnostic processes for CIN focus on detection of malignant transformation in HPV-infected cells [57, 58]. The function of HPV-transformed cells is critically dependent on E6 and E7 oncogenes and related molecules such as $p16^{INK4a}$ [59, 60]. Therefore, E6/E7 mRNA and $p16^{INK4a}$ are important targets for early detection and triage. In addition, genetic or epigenetic changes in HPV-transformed cells have been attracting attention as biomarkers for screening of CC, in the triage of HPV-positive women, and as targets of treatment. Because, such new biomarkers can be analyzed from preserved liquid-based cytology (LBC) specimens, their use may be further expanded [61].

3.1. HPV typing

HPV 16 and 18 account for 70% of the causes of CC. The other reported HPV types related to CC are 31, 33, 35, 45, 52, and 58 [62]. Furthermore, the risk of developing CC has been reported to differ according to the type of hrHPV [63]. A cohort study to estimate the risk of disease progression among the HPV genotypes in 570 Japanese women with cytologic low-grade squamous intraepithelial lesion (LSIL) and histologic CIN1/2 showed that the cumulative probability of CIN3 within 5 years was higher in HPV 16, 18, 31, 33, 35, 52, and 58 than in the other hrHPV types [64]. Another Japanese cohort study on cytologic abnormalities, including ASC-US, LSIL, and HSIL (≤CIN2), reported that infection with HPV types 16, 18, and 33 posed a high risk of developing CIN3 [65]. The Japanese gynecologic guideline 2017 recommended HPV typing to evaluate the risk of disease progression for patients with histologically proven CIN1/2 (**Figure 2**). Taken altogether, HPV typing in CIN patients is useful for risk assessment of disease progression [66].

3.2. $p16^{INK4a}$

The $p16^{INK4a}$ is a cyclin-dependent kinase inhibitor that blocks the phosphorylation of various cyclins that control the cell cycle. In many human cancers, including colon and breast, the function of the $p16^{INK4a}$ gene is lost by gene deletions, mutations, or epigenetic silencing. In CC,

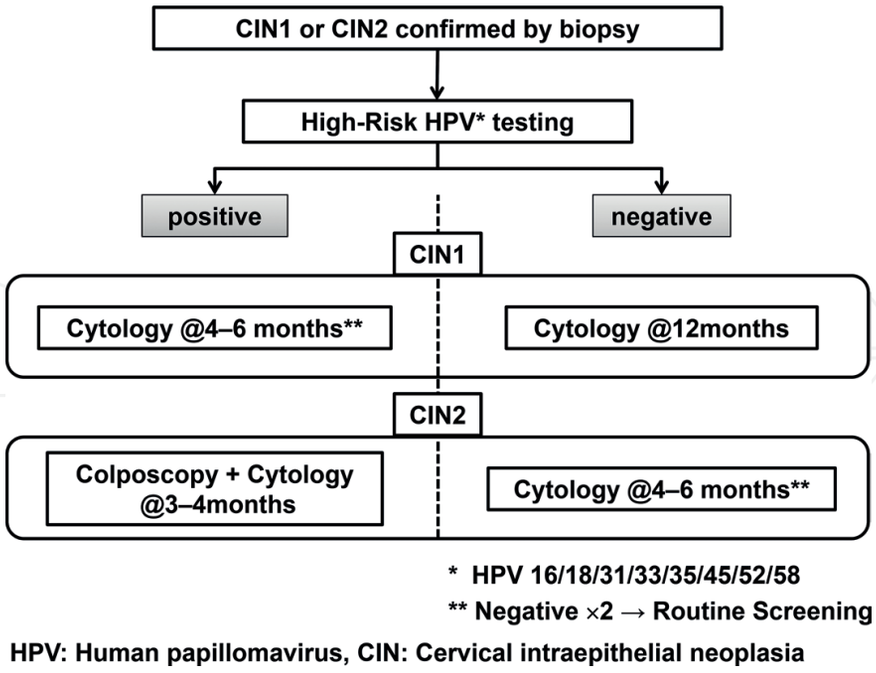

Figure 2. HPV typing for CIN1 and CIN2 in Japan. The Japanese gynecologic guidelines in 2017 recommend HPV typing to evaluate the risk of disease progression in patients with histologically proven CIN1/2. Patients who are positive for high-risk HPV receive more intensive management compared with negative patients.

however, a high level of intracellular E7 expression eliminates the inhibitory methylation mark encoding the CDKN2A gene promoter from $p16^{INK4a}$, resulting in overexpression of the $p16^{INK4a}$ protein [67]. In addition, since E7 inactivates pRB, there is proliferation of cells that highly express $p16^{INK4a}$. In other words, high expression of $p16^{INK4a}$ reflects the high expression of E7, which is a good indicator of CIN3 and CC. For this reason, $p16^{INK4a}$ is widely accepted as a valuable surrogate biomarker for the transforming properties of HPV infection [68]. Based on this fact, a therapeutic peptide vaccine using $p16^{INK4a}$ as the antigen has been developed [69]. Moreover, $p16^{INK4a}$ has been used for dual-staining with p16/Ki-67 cytology (p16/Ki-67); this would complement the low sensitivity of cytology and the low specificity of the HPV test for secondary prevention of CC [70–72].

In Europe, p16/Ki-67 was compared with Papanicolaou (Pap) cytology and HPV testing for screening high-grade CIN (CIN2+) in 27,349 women aged 18 years or older; the p16/Ki-67 had high sensitivity and comparable specificity for CIN2 detection, compared with the other tests [73]. This suggested the utility of p16/Ki-67 as a screening method in young women with high HPV infection rates. Other studies showed the effectiveness of p16/Ki-67 as a triage test for CIN2+ detection in Pap-negative and HPV-positive women ≥30 years old [74]. In addition, the usefulness of p16/Ki-67 for follow-up of patients after CIN treatment was suggested [75]. In Germany, a recent study revealed that combined HPV 16/18 testing and p16/Ki-67 resulted in lower cost and clinically efficient CC screening, compared with conventional annual Pap cytology [76]. As described earlier, several evidences on the utility of p16/Ki-67 have accumulated; therefore, p16/Ki-67 will definitely play an important role in the secondary prevention of CC.

3.3. HPV E6/E7 mRNA

The usefulness of HPV E6/E7 mRNA testing in secondary prevention of CC has already been established [77, 78]. Combined testing of LBC cytology and APTIMA® HPV (AHPV) has already been used in the US and Europe. HPV E6/E7 mRNA testing is useful because it can detect HPV infection and the transformation properties of cervical cells. In fact, HPV E6/E7 mRNA testing was reported to detect high-grade CIN with high sensitivity and specificity [79–81].

ASC-US and LSIL on cytology are mainly caused by low-grade cervical lesions that often resolve spontaneously [82]. Currently, the HPV test is used for triage of women with ASC-US and LSIL; however, its low specificity has increased the number of unnecessary examinations and treatment [83]. On the other hand, HPV E6/E7 mRNA testing enables stratification of the risk of developing CIN2+ in women with both hrHPV-positive and hrHPV-negative cytology [84]. A recent meta-analysis to confirm usefulness of HPV E6/E7 mRNA testing for triage revealed that a positive HPV E6/E7 mRNA testing in women with mild cytology findings, such as ASC-US and LSIL, necessitates immediate colposcopy and intensive follow-up because the risk of carcinogenesis is high [85].

3.4. Epigenomic alterations

Epigenetic events in the host and in viral genomic regions and genes are necessary during HPV-mediated cellular transformation and carcinogenesis [86]. DNA methylation is a typical epigenetic change and characterizes the molecular, cellular, and clinical features of HPV-associated neoplasia. Because hypermethylation is a stable and reversible process, detection of methylation marks is used for diagnosis. In addition, new targeted therapies with demethylating compounds have been developed [87].

Combined testing with DNA methylation and hrHPV is one of the promising screening options for CC. The Triage and Risk Assessment of Cervical Precancer by Epigenetic Biomarker (TRACE) study was conducted to examine the usefulness of human epigenetic biomarker testing in the primary prevention of CC. In this study, methylation of the POU4F3 promoter, which is a promising marker for CIN3, showed significantly higher sensitivity and similar specificity for detecting CIN3+, compared with LBC [88]. This finding suggested that detection of POU4F3 methylation is useful for early detection of CIN3. Another study assessed the correlation between CpG methylation of the HPV16 L1 gene and CC in 145 HPV 16-infected Uyghur women who were divided into five groups, as follows: transient infection (n = 32), persistent infection (n = 21), CIN1 (n = 21), CIN2–3 (n = 33), and CC (n = 38) [89]. After quantifying each CPG methylation by pyrosequencing, results revealed that methylation increased at 13 CpG sites in advanced lesions and that high methylation levels were associated with the risk of developing CIN2+ [89]. These findings may be applied to CC screening.

4. Therapeutic vaccine for CIN

Currently, the standard therapy for CIN is surgical excision such as conization or LEEP. Although these treatments are very effective from the viewpoint of removing HPV-induced

precancerous lesions, these can cause infertility and menstrual disorders secondary to stenosis of the cervix. In addition, the existing CC prophylactic vaccines are ineffective for HPV-infected women and nontargeted HPV types. Therefore, development of a therapeutic vaccine using immunotherapy as a nonsurgical treatment for CIN is an important strategy for the prevention of CC.

The development of therapeutic vaccines has been mainly targeted for HPV E6 and E7 [90], because these proteins are essential for the malignant transformation of HPV-infected cells and are permanently expressed in CIN. In order to induce an E6 or E7 antigen-specific T cell immune response, several kinds of vaccines have been developed; these include adoptive transfer of tumor-specific T cells, chimeric virus-like particle vaccines, dendritic cell, DNA vaccines, peptide vaccines, protein vaccines, and viral or bacterial vector vaccines. Among these, protein vaccines are the most common therapeutic vaccines for HPV 16 because of the simplicity of the method and the lack of HLA restriction [91]. However, there are currently no available therapeutic HPV vaccines against CIN.

Recently, a randomized, double-blind, placebo-controlled phase 2b trial on CIN2/3 patients showed promising results on the efficacy and safety of VGX-3100, which is a synthetic plasmid targeting human HPV 16 and HPV 18 E6 and E7 proteins (ClinicalTrials.gov Identifier: NCT01304524). In the study, the primary endpoint for efficacy was regression to CIN1 or normal pathology at 36 weeks after the first dose. This study enrolled 167 people who were randomized (3:1) to the VGX-3100 group (n = 125) and the placebo group (n = 42); the rate of histopathologic regression was significantly higher by 18.2% [95% CI 1.3–34.4] in the VGX-3100 group, compared with the placebo group (48.2% vs. 30.0%; p = 0.034). The incidence of erythema at the injection site was significantly higher in the VGX-3100 group than in the placebo group (78.4% vs. 57.1%, p = 0.007). On the other hand, there was no significant increase in the number of severe side effects that could interfere with the performance of vaccine therapy [92]. Therefore, this vaccine might be a nonsurgical therapeutic option for CIN2/3, but further research and development are needed in this field. A clinical trial on HPV therapeutic vaccines was detailed in a recent review [93].

5. Discussion

The mathematical model by a German group estimated that the incidence and mortality of CC will drastically decrease in the next 30 years due to the increasing number of screening participants since the 1990s [94]. Furthermore, even at a vaccination rate of only 50%, more than 40% of CC is considered to be preventable in the next 100 years [94]. Nevertheless, more effective primary prevention is necessary to eradicate CC. Currently, an effective vaccine can be used to inhibit a part of the hrHPV infection process that leads to cancer. However, several individuals cannot receive vaccination due to economic or geographical problems. In order to solve this problem, international cooperation and national policy are necessary to construct a CC prevention system. One possible problem in the future would be the changes in the distribution of hrHPV types due to an increase in the number of vaccinated cohorts; this would

likely decrease the efficiency of the current screening system. Therefore, it may be necessary to monitor the distribution of hrHPV in each country and region, and to develop screening methods that are suitable for each situation.

Secondary prevention remains important because vaccines only prevent infection with a limited number of HPV types. In order to reduce the mortality rate of CC, the coverage of a screening program needs to be increased and include patients with advanced CC. To address this issue, the usefulness of self-sampling for HPV testing has been studied [95, 96]. The US National Health and Nutrition Examination Survey in 2007–2010 on women aged 18–59 years revealed a 41.9% prevalence of genital HPV infection [97]. Multivariate analysis in this cohort revealed that HPV infection was related to age, number of sexual partners, smoking, educational level, income, and insurance status [97]. Similar results on the risk of persistent HPV infection have been confirmed in other studies [98, 99]. Therefore, populations with these risk factors require more rigorous and continuous monitoring for effective prevention; in these cases, self-sampling may be particularly useful. Importantly, the hrHPV detection rate by continuous self-sampling of vaginal fluid for 28 days was reported to be consistent regardless of the hormonal cycle [100]. In other words, hrHPV detection by self-sampling can be adapted to all women, even those in the nonmenstrual period, including menopause. A recent meta-analysis of 37 studies including 18,516 women revealed that HPV-DNA sampling screening was highly accepted compared with clinician's sampling. In the future, the importance of self-collection method will increase, especially from the viewpoint

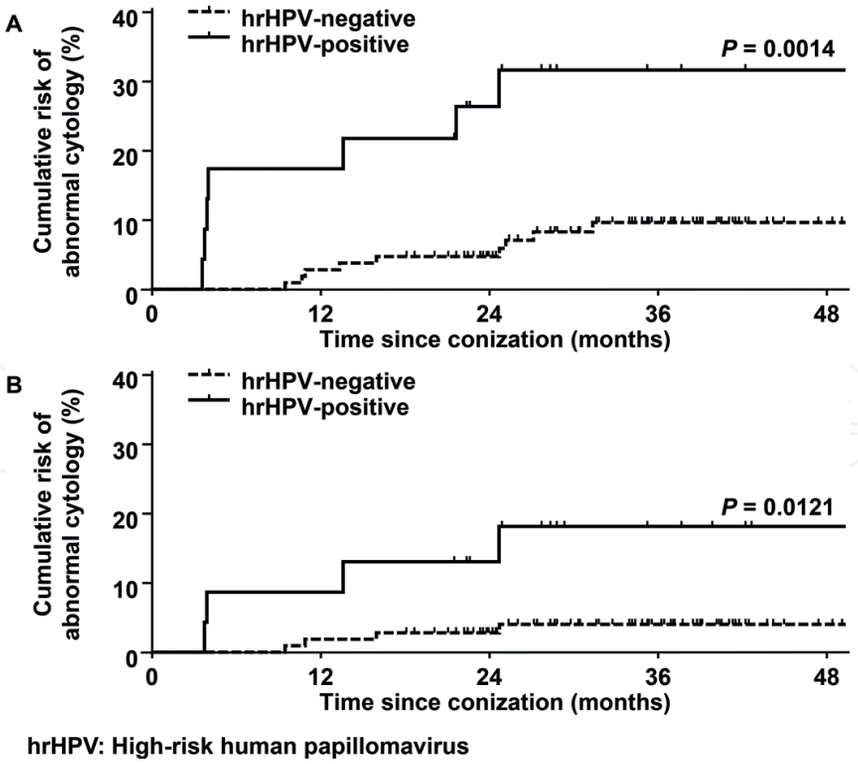

Figure 3. Postoperative infection with high risk (hr) HPV and risk of abnormal cytology. The cumulative risk curves for (a) atypical squamous cells of undetermined significance (ASC-US) or higher and (b) low-grade squamous intraepithelial lesion (LSIL) or higher show that the cumulative risks for recurrence of abnormal cytology and LSIL or higher were significantly increased in postoperative hrHPV-positive patients than in hrHPV-negative patients.

of cost-effectiveness and expansion of screening services [101]. Therefore, HPV-DNA testing by self-sampling has the potential to become the mainstream in cancer prevention.

CIN frequently regresses spontaneously within months or a few years [102, 103]. However, there is no biomarker to predict spontaneous regression of CIN. The standard treatment for CIN is still surgical resection such as conization; for a long time, there had been no other options for treatment. Although surgical excision is successful for CIN treatment most of the time, HPV infection cannot be completely eliminated. We reported that postsurgical hrHPV infection was a positive predictor of the recurrence of abnormal cytology (**Figure 3**). Furthermore, surgical procedure can lead to complications such as pregnancy problems, infertility, incontinence, and sexual dysfunction [104–106]. At the very least, overtreatment of women with fertility must be avoided. With the progression of CC screening, the importance of these problems has increased. In order to overcome this problem, development of a therapeutic vaccine as a new treatment option without surgery is urgently needed. The availability of low-cost therapeutic vaccines for patients with CIN or stage IA CC in the future will lead to a long-term reduction in medical costs [107].

6. Conclusions

Although elucidation of the mechanisms of HPV carcinogenesis and development of a prophylactic vaccine have made CC a preventable disease, eradication of CC is expected to take several decades. To decrease the mortality rate of CC, early detection by screening will remain important for a while. The clinical application of simple biomarkers to stratify HPV-positive women is important for maintenance of medical economy and avoidance of overtreatment of women in the reproductive age. To overcome cancer deaths due to CC, the development of inexpensive treatment options or therapeutic vaccines that can be readily used worldwide is necessary.

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