

## Genital Warts - Current Issues

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### ABSTRACT

*Clinical genital warts represent only the tip of the iceberg of genital human papillomavirus infection. The causal relationship of HPV infection and cervical cancer has been well established. However, the effect of chronic cigarette smoking on genital warts and cervical dysplasia are more controversial. This is reviewed with emphasis on the possible therapeutic implication. Old regime with podophyllin to new immune modifier with imiquimod in the treatment of genital warts are also discussed.*

**Keywords:** genital warts, human papillomavirus, smoking, cervical cancer, immune modulation

### INTRODUCTION

Human papillomavirus (HPV) infection is a common problem in dermatology and venereology. The incidence of genital warts has been increasing in the past ten years and is now the second commonest sexually transmitted disease in Hong Kong.

Besides being the cause of warty lesions on skin and mucus membrane, HPV has been implicated in many forms of human cancers, especially those of the uterine cervix. With advances in molecular biology, more has been learnt about the virology, the mechanisms of keratinocyte transformation and its role in oncogenesis.

Treatment of genital warts has been for many years a challenge to venereologists. Although podophyllin has been used for years and has been proven to be a safe treatment when administered by a trained personnel, the cure rate is only a disappointing 20-40%. Surgical modalities, including laser surgery, have not been shown to be any superior in terms of cure rate. The combination of interferon with surgical treatment may give better results. Imiquimod, which is introduced recently for

treatment of genital warts, acts by immune modulation. This new concept for treatment of viral infection has reawakened our interest in this old disease.

#### 'The tip of the iceberg'

The exact prevalence of genital warts is difficult to determine, but it is definitely a very common sexually transmitted disease. The incidence appears to be increasing in recent years (Table 1). But what is more alarming is that clinical warts only represent 'the tip of the iceberg' of genital HPV infection.<sup>1</sup> It has long been known that not all patients infected with HPV actually develop genital warts. In some population-based studies, evidence of HPV infection can be detected in many patients without prior history of genital warts. This is more important in female patients undergoing Papanicolaou smear examination. Many of these patients with koilocytes present in Papanicolaou smear do not have history of genital warts.<sup>2</sup> With the advances in the diagnostic techniques like Southern blot hybridization and polymerase chain reaction, the number of patients diagnosed with HPV infection would be much higher than previously thought.

#### Genital warts, cervical cancer and smoking

Cervical cancer is a common malignancy in women throughout the world. The World Health Organization estimates that the annual worldwide incidence of cervical carcinoma is about 450,000 cases. In some Nordic countries there has been a dramatic decline in incidence since 1950, attributable to the

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**Table 1. Annual incidence and trends of genital wart (Annual statistics of Social Hygiene Service 1998, Hong Kong)**

Year	1990	1991	1992	1993	1994	1995	1996	1997	1998
No. of cases	1727	1810	1666	1898	2418	2995	3168	3124	3641

effectiveness of their screening program. In Hong Kong the incidence was 445 in 1996.<sup>3</sup> It was the third commonest cancer in female under the age of 50.

There is very strong epidemiological evidence that cervical cancer and cervical dysplastic condition are associated with an infectious agent that is transmitted sexually.<sup>4</sup> HPV has long been implicated as they had been demonstrated to have oncogenic potential in animals. Both genital warts and cervical cancer are common in women with multiple sex partners and early coitarche.<sup>5</sup> However, the finding of high prevalence of HPV in women with cytologically and colposcopically normal cervixes has cast doubt on the relevance of this association. Some has suggested that other events are needed to initiate the carcinogenic process.

DNA hybridization studies of tumour tissue and cervical cancer cell-lines showed that most genital cancers harbour a specific HPV type and the HPV prevalent rates in different studies vary between 84 and 100%. HPV 16 and 18 appeared to be the most prevalent HPV detected, with the latter being more aggressive. Depending on the prevalence of HPV types in cervical cancer, HPV can be divided into high risk and low risk (Table 2). There is also a close relationship between the degree of dysplasia and the rate of isolation of high risk HPV. Women with persistent oncogenic HPV infection are at greater risk to progression to cancer. Identification of the presence or absence of high risk HPV has highly significant prognostic implication. Those patients with persistent high risk HPV and cervical dysplasia should be referred promptly to gynaecologist for management.

There have been many reports on the association of smoking and cervical cancer, but a definite causal

**Table 2. Oncogenic potential of mucosotropic HPV types**

Oncogenic potential	HPV types
Low	6,11,40,42,43,44,57
High	16,18,30,31,33,35,39,45,51,52,56

relationship has yet to be established. Some has argued that the association may be confounded as there is a strong link between cigarette smoking, multiple sexual partners and early coitarche in women. However, there is now increasing scientific evidence that smoking may be a cofactor in the aetiology of cervical cancer. Chemical carcinogens in tobacco smoke, like nitrosamine and polyaromatic hydrocarbons, might account for a high rate of mutagenicity of the cervical mucus of smokers. Indeed, nicotine and cotinine are present in the cervical mucus of smokers, the level in the mucus being 45 and 3.6 times respectively more concentrated than the serum level. There seemed to be a dose-response relationship for nicotine in mucus with number of cigarette per day.<sup>6</sup> Similarly, there is also a dose dependent relationship between the amount of cigarette intake and the decrease in number of Langerhan's cell in the cervix of smokers.<sup>7,8</sup>

There is evidence that at least in patients infected with high risk HPV, smokers are at a greater risk of progression to high grade cervical dysplasia. Buerger et al has shown a dose dependent effect of cigarette smoking on the occurrence of oncogenic HPV.<sup>9</sup> Szarewski et al demonstrated that quitting smoking may result in a reduction in the size of low-grade cervical lesions.<sup>10</sup> These two studies have further strengthened a causal link between smoking and cervical disease.

The relation between smoking and genital warts is also interesting. Although smoking has been suspected to be related to cervical cancer since 1977, little has been done on smoking and exophytic warts. Feldman et al had shown a three fold increase in risk of developing exophytic warts in women who smoke.<sup>11</sup> The risk increases to 5.2 times after adjusted for other variables. Interestingly the risk of acquisition of other sexually transmitted diseases did not increase in their study. Similarly the risk of developing anal HPV infection and intraepithelial neoplasia, a counterpart of cervical intraepithelial neoplasia in male patients, has also been shown to increase in both HIV-positive and HIV-negative smokers.<sup>12</sup> In a study completed recently in the Social Hygiene Service in Hong Kong, it is also

found that smoking has a negative effect on treatment of genital warts in male patients.<sup>13</sup> In this study, 57 of 72 (79%) male non-smokers with genital warts were cleared of lesions after 2 months therapy with topical 25% podophyllin, whereas only 30 of 83 (36%) male smokers responded.

From all the available data, there is strong evidence that smoking increases the risk of developing genital warts in women. For female patients with genital warts, smokers are at greater risk of progression to high grade cervical dysplasia and cervical cancers. Quitting smoking could have a beneficial effect on early cervical disease and therefore every effort should be made to encourage these patients to stop smoking.

### **Podophyllin and Podophyllotoxin**

Podophyllin has been employed for treatment of genital warts for almost 50 years. It is a plant-derived resin originating from either of two *Podophyllum* species: *Podophyllum peltatum* and *Podophyllum embodi*, and is composed of several cytotoxic compounds in unpredictable ratios. The most active of these is podophyllotoxin. Quercetin and kaepherol are the two mutagenic substances present in podophyllin mixture that account for its toxicity. In one study, it was found that quercetin and kaepherol constituted 2.5-3.8% and 6.0-6.4% of dry substance respectively in three batches of podophyllin.<sup>14</sup> Since these substances are mutagenic and infection with HPV is known to be associated with genital neoplasia, the use of podophyllin in treatment of genital warts has raised concern. However, it must be emphasized that up till now there is no evidence that treatment of genital warts with podophyllin increases the risk of genital neoplasm. But many would agree that it is best to be avoided in the treatment of vaginal as well as cervical warts. Since it has to be applied by a trained personnel and only has a cure rate of around 40% at 6 weeks of therapy, it is not a very cost-effective treatment.

Podophyllotoxin is a lignan of podophyllin and has been purified for clinical use. Since it contains little or no quercetin and kaepherol, it has a very low toxicity when compared with podophyllin. It can therefore be applied by the patients themselves.<sup>15</sup> In clinical studies, podophyllotoxin has shown much higher cure rate than podophyllin.<sup>16</sup> Krogh has reported high cure rates after only one treatment cycle, that is twice daily treatment

for three consecutive days in one week. A very high cure rate of 80% was achieved with 6 treatment cycles in his studies. Local side effects like erosion and erythema are less common and less severe than with podophyllin. An optimal dosage formulation has been worked out as 0.5% podophyllotoxin in ethanolic solution.<sup>17</sup> Cream formulation is also available recently which is especially suitable for treatment of external genital warts in female patients.<sup>18</sup>

Although podophyllotoxin is safer and more effective than podophyllin, it is more expensive and has a recurrence rate very much similar to podophyllin.

### **Interferons**

Immune response plays an important role in the control of HPV infection. The most convincing evidence is the observation of an altered clinical course of HPV infection among those with immune deficiencies. Moreover cell mediated cytotoxicity reactions, rather than humoral immunity, are responsible for eradication of HPV-infected cells and are involved in lesion regression. The body immune system is slow to produce an effective immune response against the HPV infection because the virus has adopted a strategy to prevent effective presentation of viral antigens to the host immune system. Firstly, there is no systemic phase in HPV infection. Secondly, papillomavirus infection is non-lytic, and so, there is little release of viral antigen to antigen presenting cells. Lastly, no local inflammation is induced by HPV infection which would produce the cytokines. The use of interferon is the first attempt to eradicate the virus by boosting the immune response.

Topical interferon has the advantage of being free of symptomatic side effects especially systemic toxicity. Despite early favorable reports, it fails to show a beneficial effect over placebo in controlled studies. Systemic administration by subcutaneous or intramuscular injection produces better results. In a multicentre study, use of both 1MU and 2MU gamma interferon cyclic therapy have significant better responses over placebo (50% and 45% respectively versus 27%). Nevertheless, parenteral alpha interferon has not been shown to be superior to conventional therapy with podophyllin.<sup>19</sup> There is substantial adverse effects of systemic interferon including fever and neutropenia.

Intralesional alpha interferon is the only form of interferon therapy approved by the Food and Drug Administration (FDA) for the treatment of genital warts.<sup>20</sup> It is relatively effective as compared with other forms of interferon therapy. However, as there is no beneficial effect on the non-injected lesions, this has no significant advantage in comparison to conventional therapies for treatment of widespread lesions. Also, subclinical warts may be missed and these in part account for the high recurrence rate of this form of therapy in some studies. The procedure is time consuming, painful, and only a limited number of lesions can be treated at each session, requiring patients to make multiple visits for treatment.

The role of adjuvant therapy with interferon in surgical treatment of genital warts is very controversial. This has been reviewed by Lassus.<sup>16</sup> Continuous subcutaneous interferon adjuvant therapy appears to have no effect on the recurrence rate. Local adjuvant therapy, either as perilesional or as gel application, reduces recurrence after surgical therapy.

### **Imiquimod**

Imiquimod, a new compound that is classified as immune response modifier, has been found to be useful in the treatment of genital warts. The drug has no direct antiviral effect by itself. It is believed that its antiviral and antitumour properties are results of immune response modulation. In preclinical studies in animals, imiquimod induced the local production of cytokines, including interferon alpha and tumor necrosis factor alpha when applied locally to the skin. Studies in human also confirmed its ability to induce these cytokines.<sup>21</sup>

Imiquimod 5% cream has been shown to be effective in clearing genital warts as compared with placebo in clinical studies. In one study, among the 109 patients treated with imiquimod application 3 times per week for 16 weeks, 54 patients had total clearance of their warts at the end of the study, whereas among the 100 patients receiving placebo only 11 had their warts cleared. Female patients seem to be responding better than male patients. Recurrence occurred in 13% of patients whose warts cleared with 5% imiquimod.<sup>22</sup> This compared favorably with other forms of therapy, recurrence rates of which ranged between 30-80%. Further studies with this relatively new agent would be required to confirm its effectiveness.

So far, no systemic side effect has been reported with imiquimod. The drug is much safer to be used when compared with podophyllin, and it can be applied by patients themselves. It is applied overnight in a three-times-per-week cycle. More frequent application may result in more severe reaction without any increase in therapeutic response. Minor local irritation is fairly common, including erythema and pruritus. Occasionally, severe erosion can occur which can happen very early in the course of treatment, therefore patient should be warned to suspend the therapy in case of irritation. Only a minority of patients discontinued treatment because of side effects. There seems to be no relationship between local reactions and therapeutic response.

## **CONCLUSION**

Genital HPV infection very often is sub-clinical and latent, and there is no specific therapy against the virus. Treatment should aim at clearing visible warts and not eradication of the virus. These patients, besides suffering from the physical symptoms, often have substantial psychosexual disturbance.<sup>23</sup> Most patients reported that treatment was associated with pain, discomfort, and embarrassment. Aggressive surgical procedures that may cause scarring and pain should be avoided. Female patients are at greater risk of developing cervical cancer especially for those infected with high risk HPV, and should be followed up by regular Papanicolaou smear. Podophyllotoxin remains as the first line of treatment for genital warts at present for its safety and effectiveness. It is an acceptable form of therapy for most patients, but there is still a fairly high recurrence rate. Preliminary experience with imiquimod has shown that the drug is better in this aspect. This form of therapy employing immune modulation, would open a new way to treatment of viral infection, if its efficacy can be confirmed in future studies.

### ***Learning points:***

***DNA hybridization studies of tumour tissue and cervical cancer cell-lines showed that most genital cancers harbour a specific human papillomavirus type. HPV 16 and 18 appeared to be the most prevalent HPV detected, with the latter being more aggressive.***

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