

## The Human Papillomavirus Vaccine and its Relevance in Israel

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The human papillomavirus may cause a great variety of benign and malignant lesions in the anogenital area as well as in other organ systems. HPV is the most common sexually transmitted infection, with an estimated 80% lifetime risk of acquiring it at least once [1]. Of the more than 100 HPV types about 40 are sexually transmitted and affect the squamous epithelium and mucosa of the anogenital region, i.e., the vulva, perineal and perianal areas, crural folds, vagina, cervix and urethral meatus in females, and the penis, scrotum, and perianal areas and crural folds in males [2]. Persistent infection with the non-oncogenic, so-called low risk, types (mainly types 6 and 11) may cause genital warts (condylomata acuminata) and the oncogenic, so-called high risk, types (mainly types 16, 18, 31 and 45) may cause premalignant and malignant lesions of the uterine cervix, the vagina and vulva in women [3-7], and the penis in men [8,9]. HPV-6 and 11 are responsible for about 90% of genital warts and HPV-16 and 18 are responsible for about 70% of cervical cancers [6]. Analysis of almost 1000 cervical cancer specimens from women in 22 countries indicated that worldwide HPV prevalence in cervical carcinomas is 99.7% [10] and is similar in different regions [11]. Extragenital infections causing diverse, but much less common, similar lesions in other organ systems such as lesions in the conjunctiva, the larynx, and the oropharyngeal cavity may also occur [12-16].

Worldwide, overall HPV-related lesions are a considerable health problem since infections and benign lesions are common [17] and the incidence of cervical cancer is high in certain populations, being more than 80/100,000 in some areas [18]. The advent of vaccines against HPV infection is a major breakthrough in medicine. Such vaccines are expected to reduce HPV-related health hazards considerably. Data on the high efficacy of two vaccine kinds have been published. One is a bivalent virus-like particle vaccine against HPV-16 and 18 [19,20] and the other a quadrivalent VLP vaccine against HPV types 6, 11, 16 and 18 [21,22]. Both vaccine kinds have a seroconversion rate of over 98%, both effectively reduce targeted HPV type-related morbidity, and both are safe and well tolerated [23].

The incidence of cervical cancer in Israeli Jewish women is persistently very low: about 4–6/100,00 [24]. Data on other HPV-related lesions in Israel are scarce. This paper will review the existing data concerning HPV infection in the Israeli popula-

tion and attempt to assess whether the HPV types involved in HPV-related lesions are the same as in other populations and whether the vaccine is relevant in Israel. An English-language literature search cited in MEDLINE was conducted using the terms Israeli Jewish women, Israeli population, Israeli men, and HPV. All relevant articles are cited.

### What is the prevalence of HPV in the general population?

No data are available with regard to the prevalence of the various HPV types in the general Israeli population. In one study [25] the prevalence of HPV-16 and 18 in a selected, non-population-representative group of 1434 Israeli Jewish women aged 17–60 years was assessed by filter *in situ* hybridization. These women comprised different population groups. The prevalence was 1.8% in 742 healthy government employees, 0% in 153 kibbutz and moshav residents, and 21% in women attending a gynecological clinic. Overall, HPV-16 and 18 DNA was detected in 22.8% of the women. Interestingly, this overall rate is higher than that reported from other countries, such as Canada [26] and Holland [27] where it is 13% and 4.6% respectively.

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*Vaccines against HPV infection effectively reduce targeted HPV type-related benign, premalignant and malignant lesions and are safe and well tolerated*

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### Is Israeli youth exposed to HPV infection?

The foremost behavioral risk for the acquisition of an HPV infection is non-penetrative and penetrative sexual contact [28]. In the United States in 2003, 46.7% of high school students had ever had sexual intercourse [29]. In Washington State, the cumulative incidence of first-time infection at 24 months in 603 female university students followed at 4 month intervals between 1990 and 2000 was 32.3% [30].

In Israel, a study of teenage sexual behavior found that 25.9% of boys and 12.5% of girls have had sexual intercourse by the age of 17 [31]. Moreover, sexual intercourse with two partners or more was reported by 15.4% and 6.4% of boys and girls respectively. These percentages are lower than in the USA, nevertheless they are not negligible.

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HPV = human papillomavirus  
VLP = virus-like particle

### **Which HPV types are associated with condylomata acuminata in Israel?**

Only one study on this issue could be identified [32]. In that study tissue specimens or cervical, vulvar or penile swabs were obtained from genital condylomata of Jewish Israeli patients and examined for HPV DNA by blot hybridization. By this relatively insensitive method, HPV-6 and 11 was present in 16 (61.5%) of 26 cervical lesions, in 22 (75.8%) of 29 vulvar lesions, and in 5 (62.5%) of 8 penile lesions. Although the exact overall prevalence of condylomata acuminata in Israel is not known, my impression and that of many of my colleagues is that in all likelihood many thousands of men and women are affected by this lesion.

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*In Israel the HPV types involved in HPV-associated lesions seem to be the same as in other countries.*

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### **Is there a correlation between condylomata acuminata and cervical abnormalities in Israel?**

A comparison was made between Israeli women with clinically evident condylomata acuminata and asymptomatic women attending a colposcopy clinic [33]. Among 74 women with condylomata acuminata, 10 (13.5%) had an abnormal cervical cytology (Pap) smear and 8 (10.8%) had a biopsy showing cervical intraepithelial neoplasia. Among 88 asymptomatic women, only 2 (2.3%) had an abnormal Pap smear and none had CIN. These differences were statistically significant ( $P < 0.05$ ). Thus, a correlation between condylomata acuminata, caused by HPV, and cervical cytological abnormalities and CIN is present in Israeli women as well.

### **What HPV types are associated with cervical pre- and invasive genital cancer in Israeli women?**

Two Israeli studies address this issue. In one, tissue specimens of cervical, vulvar or vaginal pre-invasive and invasive lesions were obtained and examined for the presence of HPV-16/18 DNA by blot hybridization [32]. Presence of HPV DNA was found in 2 of 4 CIN-3 samples, in 5 (38.5%) of 13 invasive cervical carcinoma samples, in 2 of 2 vulvar intraepithelial neoplasia samples, and in 1 of 3 vaginal carcinoma samples. None of six invasive vulvar carcinoma samples were positive for HPV-16/18. In the other study [34], the presence of HPV-16/18 was ascertained by a sensitive polymerase chain reaction amplification method in tissue sections from formalin-fixed paraffin-embedded blocks of women with pre-invasive and invasive genital lesions. Positive HPV DNA was detected in 8 (80%) of 10 patients with CIN-3, in 23 (79.3%) of 29 patients with invasive cervical squamous cell carcinoma, in 2 of 3 patients with invasive cervical adenocarcinoma, and in

CIN = cervical intraepithelial neoplasia

9 (64.3%) of 14 patients with squamous vulvar carcinoma. The authors concluded that the prevalence of HPV in Israeli Jewish women with cervical and vulvar neoplasia is similar to that in other populations, suggesting that the etiological factors are probably also alike.

### **How many tests and invasive procedures are performed countrywide due to HPV-associated lesions in women?**

The exact total number of Pap smears performed yearly in Israel is not known. However, there is no doubt that tens of thousands of women throughout the country undergo a Pap smear each year. One study [35] assessed the rate of abnormal Pap smears obtained in one laboratory during a 10 year period. Of almost 300,000 Pap smears, 8% were abnormal – 7.7% had minor and 0.3% major abnormalities. In Israel, almost all patients with Pap smear abnormalities are referred for colposcopy. Therefore, by simple arithmetic it can be calculated that this cohort had about 24,000 colposcopies during the study period, or 2400 colposcopies/year. The total number of colposcopies and subsequent cervical biopsies and conizations performed countrywide is also not known. It is reasonable to estimate that more than a thousand conizations are performed yearly.

### **What is the prevalence of HPV infection in Israeli males, and of extra-genital lesions?**

The prevalence of HPV infection in the general population of Israeli males is not known. Two studies assessed the prevalence in male partners of Israeli women with HPV-related lesions. One study [36] assessed the prevalence of penile condylomata in 63 males who were regular sexual partners of women with proven genital HPV infection; 15 (24%) were found to have histological evidence of condylomata. In a similar study [37], 322 males underwent colposcopic examination of the anogenital area followed by colposcopically guided biopsies from the most representative lesions, when present. The histological prevalence of HPV among the male partners was 86.6% (185 of 213 biopsies). HPV-6/11 and 16/18 DNA sequences were found in 17 (35.4%) of the 48 males who had *in situ* hybridization. In a more recent study of coexistent sexually transmitted diseases in 169 men, about 40% had condylomata acuminata [38].

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*While the very low incidence of premalignant and malignant cervical lesions in Israel may not justify mass vaccination, the considerable number of the other HPV-associated conditions may render it cost-effective*

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Only one study regarding the presence of HPV in extra-genital lesions could be identified. In that study [39] the possible causal association of HPV with transitional cell carcinoma of the urinary

bladder in Israeli Jewish patients was assessed. Histopathological transitional cell carcinoma sections were examined by the peroxidase anti-peroxidase method and HPV capsid antigen was demonstrated in 19 (17.3%) of 110 cases examined. HPV-DNA sequences, determined by *in situ* DNA-DNA hybridization at high stringency wash, were present in 24 cases (21.8%): 16 cases (14.5%) proved to be positive for HPV-6/11 and 8 (7.3%) for HPV-16/18. Sixteen samples known to be positive by *in situ* hybridization were reconfirmed by PCR. The authors concluded that HPV in transitional cell carcinoma of the bladder is detected at a relatively high frequency and might be involved in the pathogenesis of this tumor in the Jewish population in Israel.

In summary, the available limited evidence indicates that in Israel the HPV types involved in HPV-associated lesions are the same as in other countries and that there is no reason to assume that different HPV types act in the Israeli population.

As in other populations, objections to the introduction of the vaccine may be encountered [40]. Parents and physicians may be reluctant to discuss issues of sexual activity and sexually transmitted diseases with children and young adolescents, and religious groups may object because they do not acknowledge extramarital sexual activity.

An effective vaccine is expected to reduce substantially the incidence of the type-targeted HPV-associated benign, premalignant and malignant lesions, the prevalence of abnormal Pap smears, the prevalence of additionally required examinations (colposcopies, biopsies, conizations, etc.), and extragenital benign and malignant lesions. While the very low incidence of premalignant and malignant cervical lesions in Israel may not justify mass vaccination, the considerable number of the other HPV-associated conditions, may render it cost-effective. While the effect of a vaccine will be evident only in the distant future, its current introduction to Israel should be seriously considered by the medical establishment.

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PCR = polymerase chain reaction

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