ORIGINAL RESEARCH—MEN'S SEXUAL HEALTH

Impact of the Quadrivalent HPV Vaccine on Disease Recurrence in Men Exposed to HPV Infection: A Randomized Study

Enis Rauf Coskuner, MD, FECSM,* Tayyar Alp Ozkan, MD,† Ayhan Karakose, MD,‡ Ozdal Dillioglugil, MD,† and Ibrahim Cevik, MD‡

*Department of Urology, Acibadem University School of Medicine, Istanbul, Turkey; †Department of Urology, Kocaeli University School of Medicine, İzmit, Turkey; ‡Department of Urology, Yeni Yuzyil University School of Medicine, Istanbul, Turkey

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ABSTRACT

Introduction. Human papillomavirus (HPV) is one of the most common sexually transmitted infections and is the cause of several different diseases in men and women. Although little is known about HPV infection in men, they are also in the risk group of HPV infection and play an important role in transmitting the virus to women.

Aim. To define the efficacy of the HPV vaccine through cross-immunization and its role in clearance of HPV infection, and to assess infection-associated factors in men.

Methods. This prospective randomized clinical study enrolled 171 evaluable men with genital warts between June 2009 and October 2013. After the initial treatment intervention, 91 patients were randomly assigned to receive HPV vaccine in three doses. Eighty patients were in the control (unvaccinated) group. One hundred-eleven men were single and 60 men were married. Patients who had previous treatment for pre-existing warts and medical disorders that needed chronic treatment or immunosuppression were not included in the randomization. Also 29 men with follow-up less than 12 months and incomplete vaccination were not included.

Main Outcome Measures. The patients were assessed regarding age, condom use, marital status, number of visible genital warts, and smoking status. Post-treatment follow-up was monthly up to 12th month.

Results. Mean age was 34 ± 7.6. One hundred fifteen patients were smokers. For the recurrence of warts, age, smoking, vaccination status were insignificant and marital status was significant in the univariable analysis; only marital status preserved significance (HR: 2.0 CI:1.29–3.12 $P = 0.002$) in the multivariable analysis including vaccination status, marital status, and smoking.

Conclusion. Among the investigated factors vaccination status was not but marital status significantly influenced wart recurrence. Married men had more recurrences in our population. Larger multicenter randomized clinical trials are lacking and seriously required to investigate the therapeutic effect of current quadrivalent HPV vaccine in genital warts. **Coskuner ER, Ozkan TA, Karakose A, Dillioglugil O, and Cevik I. Impact of the quadrivalent HPV vaccine on disease recurrence in men exposed to HPV infection: A randomized study. J Sex Med 2014;11:2785–2791.**

Key Words. HPV; Vaccine; Men; Recurrence; Gardacil

Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections and is the cause of several different diseases in men and women [1,2]. Although cancers of the cervix, vagina, vulva, penis, oral cavity, head and neck, and anal canal are attributable to HPV infection, anogenital warts are the most common outcome of it [3]. There are 148 recognized HPV types and among them high-risk subtypes HPV 16 and 18 account for 70% of cervical cancers in females, and low-risk subtypes HPV 6 and 11 account for 90% of genital warts found in male and females [4,5]. Jemal et al. reported that HPV-associated cancers accounted for 3.3% of all

cancers in women and 2% of the total cancers in men in 2009 [6]. Men also play an important role in transmitting the virus to women. Improved understanding of the HPV infection course in men has an essential role to solve the problems related with the disease. Genital HPV infection is a sexually transmitted disease and it is predictable that male immunization may help prevent HPV transmission and this will reduce the load of HPV infection and HPV related diseases in women. Although the health authorities of most Western European countries introduced HPV vaccination especially for adolescent girls, immunization rates are not very impressive compared with other childhood vaccinations. The low immunization rates in women shows the importance of extending vaccination to males in order to achieve the greatest possible protection from cervical cancer [7].

Currently available HPV vaccines target the late protein 1 (L1) in the protein shell of DNA molecules of the virus, which is necessary for viral replication and assembly of newly formed virus particle in infected cells [8]. The U.S. Food and Drug Administration (FDA) approved a quadrivalent HPV vaccine against types 6, 11, 16 and 18 for females in aged 9–26 years in 2006 [9]. The HPV vaccine has also been shown to be preventive and safe in men. The vaccine is 85.6% effective at preventing persistent infection with HPV types 6, 11, 16, and 18 in men who are vaccinated before HPV exposure with these types and 90.4% effective at preventing anogenital lesions related to these types [10]. As a result, in 2009, FDA recommended the quadrivalent HPV vaccine for the prevention of external genital lesions caused by HPV 6, 11, 16, or 18 in males aged 9–26 years [11]. In 2010, the FDA included prevention of anal cancer in men and women as an additional indication for use of the quadrivalent HPV vaccine. HPV vaccines are most effective when given before exposure to HPV through sexual contact; however, individuals who may have already been exposed to HPV should still be vaccinated [12]. It has been shown that HPV vaccination is likely to induce neutralizing antibodies across HPV species [13].

The high prevalence of HPV infection and its serious medical, psychosexual, and relationship consequences make the prevention of HPV infection important for the field of sexual medicine [14]. Unfortunately current vaccination research has largely focused on females. After recent approval of quadrivalent HPV vaccine for males, the implementation of gender-based vaccination provides more argument. But there is still no randomized study about HPV vaccine for males known to have been exposed to HPV virus.

Aim

Our purpose in this randomized study was to define the importance of immunization and its role in clearance of HPV infection and to assess infection-associated factors in men. We tried to answer the question whether quadrivalent HPV vaccination can prevent HPV recurrence in men already exposed to this virus.

Methods

This prospective randomized clinical study enrolled 200 men with new onset genital warts living in the same area for at least 1 year, between June 2009 and October 2013. Genital warts were visibly diagnosed with magnifying glass after aceto-white test application whenever deemed necessary. Pathologic examination was performed in suspicious cases. Initial treatment is local excision with electrocautery (in larger pedunculated lesions) or electrocautery alone (in flat broad based lesions) with local anesthetic agent in all patients. Patients who had previous treatment (local or systemic) for pre-existing warts and medical disorders that needed chronic treatment or immunosuppression (including HIV positive patients) were not included in the randomization. A total of 292 patients were evaluated for eligibility. Seventy two patients were excluded because they met exclusion criteria, 19 patients declined to participate, 1 patient declined to provide informed consent, resulting in 200 patients. After the initial treatment intervention, 100 patients were randomly assigned with computerized block (block size 4) randomization table to receive a quadrivalent HPV vaccine (Gardasil® by Merck & Co. Inc.) in three doses at the day of intervention, and at months 2 and 6. Vaccine was administrated by intramuscular injections in the deltoid region of the upper arm. The primary immunogenicity objective is to assess the clinical antibody response to quadrivalent HPV vaccine after administration of three-doses. Hundred patients were also similarly randomized to the control (unvaccinated) group. All men were circumcised and reported only female sexual partners. Twenty-nine men were excluded if they had follow-up (F/U) less than 12 months and incomplete vaccination. Finally, 171 consecutive evaluable patients were included in the study analysis; 91 men in the vac-

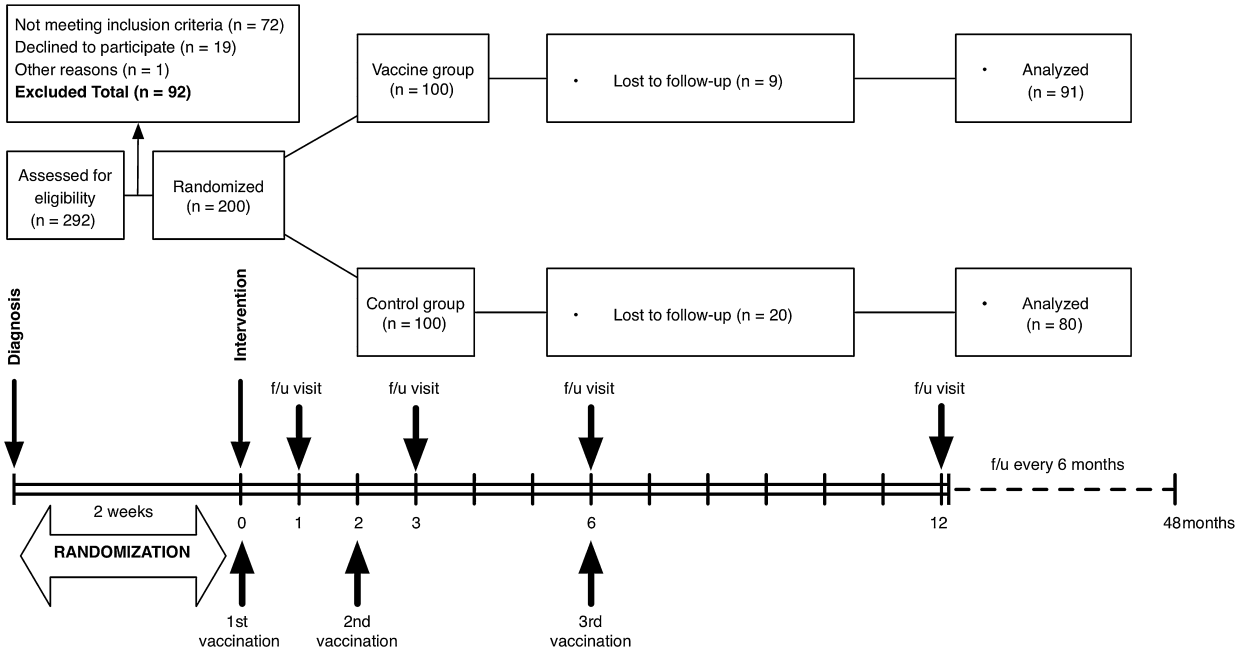

Figure 1 Randomization flow chart on the study design.

cinated group and 80 men in the control group. One hundred-eleven men were single and 60 men were married, and all married men declared that they were monogamous.

Written informed consent was obtained from all patients. The patients were assessed regarding age, marital status, number of visible genital warts under magnifying glass, condom use, and smoking status in their initial visits and at each follow-up. A post-treatment follow-up was performed in the 1st, 3rd, 6th and 12nd month after the treatment for the evaluation of wart recurrence as primary outcome measure (Figure 1). In the vaccinated group, although failures (recurrences) did occur before 12th month of follow-up, they were not considered as failure because development of enough antibody response after completing the 3-dose series requires at least 12 months. Patients' charts and commercially available database (MS Access) was used for data collection.

We assumed that HPV vaccine injection result in 20% reduction in wart recurrence. When power set to 80%, minimum number of patients needed to reject the null hypothesis per group was calculated 69, total 138 patients. With minimum 30% dropout rate a total of 200 patients were randomized. Results were expressed as means (standard deviation [SD]) and median (interquartile range [IQR]). All variables, except age were categorical. Patients were considered as failed if they had a recurrence. Kaplan–Meier method and Log- rank test was used for time to recurrence analyses and to compare the differences between groups, respectively. Univariate and multivariable cox proportional regression analysis was performed to assess the association of variables. All analysis was performed using STATA 12.0 statistical software package (Stata Corp, TX, USA). Statistical significance was set at 0.05, all tests were two-tailed, and effect size was 0.2.

Main Outcome Measures

The present study asseses the efficacy of HPV vaccination on previously HPV infected men. HPV infected men were randomly assigned to HPV vaccinated or control groups. The primary outcome measure was recurrence in both vaccinated and control groups. Secondary outcome measures included evaluation of the influence of modifying co-factors; marital status, smoking, condom use and the number of lesions.

Results

Mean age was 34.05 ± 7.61. All men were circumcised and heterosexual. Of those, 111 (65%) men were single and 60 (35%) were married. Among them, only 56 (32.7%) were nonsmokers; 115 (67.3%) were smokers (Table 1). Genital warts were determined predominantly in coronal sulcus, shaft of penis, pubic and perianal area. Number of

Table 1 Demographic data of patients

	Unvaccined (n = 80)	Vaccined (n = 91)
Age, mean ± SD	36.3 ± 7.6	32.1 ± 7.1
Martial status		
Single, n (%)	55 (68.25)	56 (61.54)
Married, n (%)	25 (31.25)	35 (38.46)
Smoke		
Nonsmoker, n (%)	12 (15)	44 (48.35)
Smoker, n (%)	68 (85)	47 (51.65)
Condom use		
No-condom	56 (70)	70 (76.92)
Condom	24 (30)	21 (23.08)
Number of warts, mean ± SD	11.96 ± 6.11	10.84 ± 5.34
Recurrence		
No	45 (56.25)	46 (50.55)
Yes	35 (43.75)	45 (49.45)

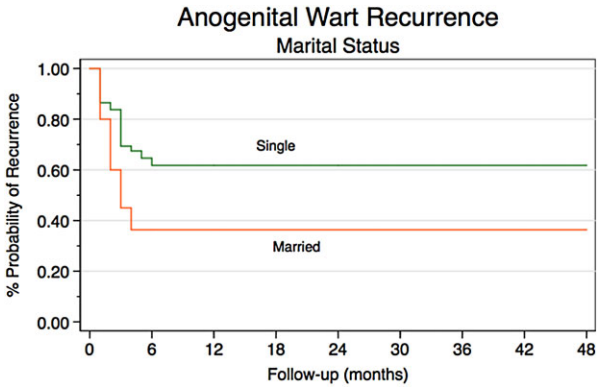

Figure 3 Kaplan–Meier analysis for the relationship between marital status and anogenital wart recurrence ($P < 0.001$).

cauterization sessions changed between 1 to 15 in four years in all men in both groups. Development of recurrence had been associated with increased number of genital warts determined during the initial patient visit. Mean follow-up time in the whole group, vaccinated and unvaccinated group were 46.1 ± 8.7 months, 46.3 ± 7.1 months and 45.4 ± 10.2 months ($P > 0.05$), respectively. In the univariate analysis age, smoking and vaccination status (Figure 2) were not significantly associated with recurrence. However only marital status (Figure 3) was associated with recurrence of genital warts ($P < 0.001$). However, the number of lesions (<10 vs. ≥10) had significant impact ($P < 0.001$) on recurrence regardless of vaccination status (Figure 4). The impact of condom use on recurrence has also been examined in the whole group ($P = 0.551$), according to marital status [$P = 0.737$ (married men), $P = 0.630$ (single men)], and only in married men ($P = 0.757$), and statistical significance was not found in any of them. In multivariable analysis marital status ($P = 0.002$, HR: 2.005) was, but vaccination ($P = 0.454$) and smoking ($P = 0.389$) were not independent covariates. Recurrence hazard ratio was about 2 in married men; they have 2 times higher recurrence rate. We did not observe any complication that resulted in discontinuation of the vaccine or required additional treatment.

Discussion

HPV has been linked to various benign and malignant lesions occurring in mucosal and skin epithelia. Most HPV infections are transient and asymptomatic. Men have higher likelihood of HPV cure rate than women. Almost 75% of HPV infection in men cleared within 1 year [15]. But persistent infection with high-risk types can prog-

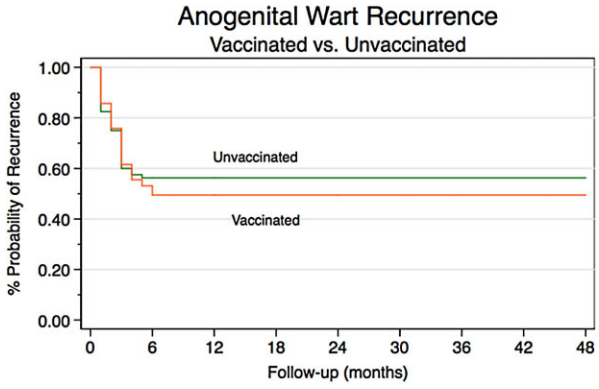

Figure 2 Kaplan–Meier analysis for the relationship between vaccination status and anogenital wart recurrence ($P = 0.591$).

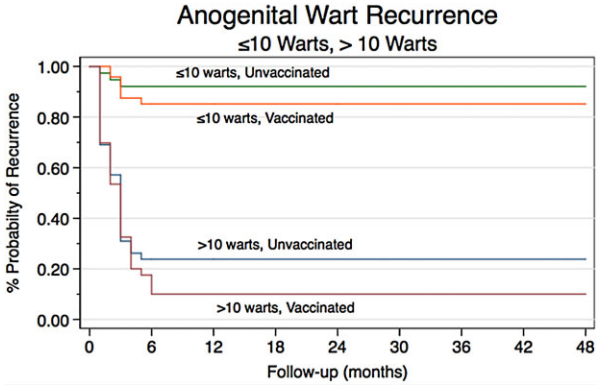

Figure 4 Kaplan–Meier analysis for the relationship between vaccination status and number of anogenital wart recurrence ($P < 0.001$).

ress to a precancerous lesion and eventually to cancer. HPV 16 and 18 account for 70% of cervical cancers in females, and low- risk subtypes HPV 6 and 11 account for 90% of genital warts found in male and female [4,5,16].

Results of the FUTURE II trial helped widespread use of HPV vaccination among physicians. The aim of this study was to assess the effect of quadrivalent vaccine on HPV types 16 and 18 on women. Randomization included 12.167 women randomized to vaccine and placebo arms. The study showed that quadrivalent vaccine is prophylactic (preventive), but not therapeutic for HPV 16 and 18 associated lesions that are implicated in cervical cancer [17]. On the other hand, the impact of prior vaccination on recurrent genital warts and low- grade disease was assessed in the post-hoc subset analysis of FUTURE I and II trials in women. Although vaccination was associated with less recurrence of genital warts by 46.8% in women followed for recurrent genital warts, results were not statistically significant to show therapeutic efficacy [18]. Similar to the lack therapeutic effect of vaccination on women in this trial, we also could not show any therapeutic effect of HPV vaccine in males in the present study.

There are two case reports of warts treated successfully with quadrivalent HPV vaccine [19,20]. One of the reported patients has had imiquimod treatment before vaccine. As authors discussed it is not clear that only quadrivalent HPV vaccine had been effective for the treatment, or it was the delayed effect of imiquimod treatment [20]. In the other reported case there were multiple cutaneous warts in both hands. In this report a 31 years old male was previously treated with several agents (podophilin, sail-cylic acid, oral cimetidine). This case became wart free 8 months after vaccination. Both treatment successful case reports were flawed by previous treatments. On the other hand, these two debated results were seriously criticized in a case series of Kreuter et.al all which included six patients (5 male 1 female) [21]. According to this series all had recurrence after quadrivalent HPV vaccine treatment. The present study results also showed that HPV vaccine had no effect on preventing recurrence.

Male's tolerability and immunogenity of quadrivalent HPV vaccine was assessed in a randomized trial. 4,065 males aged 16 to 26 were randomized to quadrivalent vaccine and placebo arm. One month after 3rd dose of vaccine, seroconversion for vaccine HPV types were 97.4% of vaccinated males. Adverse events were similar in both study arms. On the other hand, this study also showed a decreased incidence of genital warts with a reported observed efficacy of 67.2%. As a result, this randomized trial proved that quadrivalent HPV vaccine is safe, had similar immunoresponse and decreased the incidence of wart development in men [22]. Vaccine was also safe in our hands and did not result in either discontinuation of the drug or required additional treatment.

Transmission can occur between many anatomic sites but the cervix is the most common reported site. In a study, transmission was almost 3 times as likely to occur from cervix to penis as penis to cervix [23]. As a sexually transmitted disease, the most common proposed sites of anogenital warts are the areas of micro-trauma within the skin and mucosal surfaces of anogenital region. Because of the reasons that are poorly understood, HPV transmission does not occur in every intercourse. Transmission of HPV infection between sexual partners ranges from 40% to 60% and most common risk factors include the length of sexual relationship, frequency of intercourse, condom use, and increased number of lifetime sexual partners [24–26]. Another study showed that women who had been in a relationship for 12 months or less were less likely to be HPV positive than women in relationship for more than 12 months [27]. We did not evaluate the length of marriage and the extramarital relationship of our patients in our study. We accepted marriage as the regular sexual relationship only with one partner. Frequent intercourse in a regular partnership in a period of time may be the main cause of statistically high recurrence rates of genital warts of our married patients in uni- and multivariable analysis.

In 2011 National Health and Nutrition Examination Survey in the United States, the prevalence of HPV was lowest among females 14–19 years of age and highest among women 20–24 years of age [28]. A second peak HPV prevalence appears in postmenopausal period of women [29]. In contrast to women, the prevalence of HPV infection in men was not significantly affected by age [28,29], similar to the finding in the present study.

Association between smoking and HPV infection is not clear. Two different studies have shown that while in some studies HPV infection prevalence was increased in smokers [30,31], another study showed that nonsmokers or former smokers had less risk for HPV load [32]. In the present study, we did not compare the viral loads. However, a statistically significant correlation was also not

identified between smoking and HPV recurrence in our study.

In present analysis, our experiences with the prophylactic quadrivalent HPV vaccine for treating genital warts are less promising. At the end of 1-year follow-up the vaccination had no beneficial impact on rate of lesion recurrence compared with the control group. But the current study has some limitations. First, the number of patients was small in our groups for a strong conclusion. And second, we did not assess the vaccine-type antibodies or DNA at baseline for both groups to show the exact difference between them. In our literature review, this study will be the first randomized trial with control group in men for current vaccine that is used for therapeutic aim. The study was designed for the assessment of the clinical efficacy of the quadrivalent HPV vaccine in patients with recurrent genital warts. It is also not clear whether vaccination would benefit men with prevalent infection by increasing their immunologic resistance against reinfection with the same viral type in the future or HPV related other diseases.

Conclusion

Among the investigated factors vaccination status was not but marital status significantly influenced wart recurrence. Married men had more reccurrences in our population. Larger multicenter randomized clinical trials are lacking and seriously required to demonstrate the therapeutic effect of current quadrivalent HPV vaccine in genital warts.

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Corresponding Author: Enis Rauf Coskuner, MD, FECSM, Department of Urology, Acibadem University School of Medicine, Halit Ziya Usaklıgil Cad. No:1, Bakirkoy, Istanbul 34140, Turkey. Tel: +905424215550; Fax: +902124145140; E-mail: enisraufcoskuner@hotmail.com

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Statement of Authorship

Category 1

(a) Conception and Design
Erik Rauf Coskuner; Tayyar Alp Ozkan; Ayhan Karakose; Ozdal Dillioglugil; Ibrahim Cevik

(b) Acquisition of Data
Erik Rauf Coskuner; Tayyar Alp Ozkan; Ayhan Karakose; Ibrahim Cevik

(c) Analysis and Interpretation of Data
Erik Rauf Coskuner; Tayyar Alp Ozkan; Ozdal Dillioglugil; Ibrahim Cevik

Category 2

(a) Drafting the Article
Erik Rauf Coskuner; Tayyar Alp Ozkan; Ibrahim Cevik

(b) Revising It for Intellectual Content
Erik Rauf Coskuner; Tayyar Alp Ozkan; Ayhan Karakose; Ozdal Dillioglugil; Ibrahim Cevik

Category 3

(a) Final Approval of the Completed Article
Erik Rauf Coskuner; Tayyar Alp Ozkan; Ayhan Karakose; Ozdal Dillioglugil; Ibrahim Cevik

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