Natural History of Genital Warts: Analysis of the Placebo Arm of 2 Randomized Phase III Trials of a Quadrivalent Human Papillomavirus (Types 6, 11, 16, and 18) Vaccine

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Background. The placebo arm of human papillomavirus (HPV) vaccine trials helps define the natural history of genital warts (GW).

Methods. Women enrolled in the placebo arm (n = 8800) of 2 randomized trials of a quadrivalent vaccine were examined for the presence of GW for up to 9 visits over ~4 years. A comprehensive examination of the perianal area, vulva, and vagina prompted biopsy. Biopsy samples were analyzed by a blinded panel of up to 4 histopathologists and tested for 14 HPV genotypes (6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) by use of a polymerase chain reaction–based assay. Risk factors for the development of GW were assessed.

Results. Women were followed up for an average of 3.6 years (range, 0–4.9 years). Overall, 298 (3.4%) of 8800 participants developed GW related to HPV-6 or HPV-11 (incidence rate, 0.87 cases per 100 person-years-at-risk). In total, 520 distinct lesions were diagnosed as GW. HPV DNA was detected in 472 (90.8%) lesions, with HPV-6 and HPV-11 detected in 447 (86.0%) of these lesions (94.7% of 472 HPV DNA–positive lesions). We found high-risk HPV types in 161 (31.0%) of 520 lesions. Risk factors for HPV-6– and HPV-11–related GW included infection at baseline, acquisition of new sex partners, a higher number of sex partners, and DNA positivity at baseline for a high-risk HPV type.

Conclusions. We confirm the major role played by HPV-6 and HPV-11 in GW, as well as associated risk factors. A vaccine that includes these types of HPV could substantially reduce the overall burden of HPV disease.

Trial registration. ClinicalTrials.gov identifiers: NCT00092521 and NCT00092534

Anogenital human papillomavirus (HPV) infection is the most common sexually transmitted infection. The high-risk HPV types are the causative agent of virtually all cervical cancers as well as a significant proportion of vulvar, vaginal, and anal cancers and their respective intraepithelial dysplastic lesions. Worldwide, genotypes 16 and 18 are responsible for 70% of cervical cancer [1], 50% of high-grade cervical intraepithelial neoplasia (CIN2/3), and 25% of low-grade cervical intraepithelial neoplasia (CIN1) [2]. Low-risk genotypes also cause a significant amount of disease, with HPV-6 and HPV-11 being the causative agent of >90% of genital warts (GW) [3–8]; a proportion of low-grade cervical abnormalities; low- and high-grade disease of the vulva and vagina [2];
and virtually all cases of the rare, but debilitating, disease recurrent respiratory papillomatosis [9].

The prevalence of GW, otherwise known as condylomata acuminata, typically peaks in the early sexually active years, with two-thirds of the respective sexual partners complaining of warts [10–12]. The time from HPV infection to the development of clinical GW can be as little as 2–3 months [11–13]. In the United Kingdom, the number of reported cases of GW in 2004 represented a 32% increase over 1995 [14]. National cumulative prevalence estimates in the United States show that 5.6% of individuals 18–59 years old report ever having been diagnosed with GW [15]. The history of GW peaks among American women 25–35 years old and American men 35–44 years old. Data collected from the Australian Study of Health and Relationships show that 4.0% of men and 4.4% of women 16–59 years old reported a history of GW. This prevalence estimate translates into approximately 36,000 cases [16]. In a recent Nordic study of women 18–45 years old, 10.6% reported ever having been diagnosed with GW, with a reduced age of onset in younger birth cohorts [17].

GW cause psychosocial distress in individuals that is similar to that caused by high-grade dysplasia [18–20], and they carry a high and immediate financial burden given their recalcitrant response to conventional therapies [21]. In one US study, the direct costs associated with GW (including recurrence) were estimated at $167.4 million [22]. In British Columbia, 7% of all costs incurred from HPV disease are attributable to GW [23]. Treatment can be painful and is nonspecific, addressing the clinically evident lesion rather than the viral cause, and resulting in high recurrence rates and patient dissatisfaction [24]. Various modalities include office-based treatment (cryotherapy, electrocautery, laser, and/or surgery) or home-based treatment (chemotherapeutic agents or immunomodulatory therapy) [25].

Recent studies of a prophylactic quadrivalent HPV vaccine (types 6, 11, 16, and 18) have shown the vaccine to be highly effective in preventing disease associated with HPV types 6, 11, 16, and 18, including GW [26–29]. The longitudinal follow-up of the placebo arm provides a unique opportunity to examine the natural history of GW. Here, we describe the prevalence of 14 genotypes in biopsy-confirmed GW. We also approximate the time from the period of the vaccine containing a proprietary amorphous aluminum hydroxy-

phosphate sulfate (AAHS) adjuvant that is currently used in other vaccines, of which >300 million doses have been distributed globally. Protocols 013 and 015 (hereafter, “FUTURE-I” and “FUTURE-II”) were designed to investigate the prophylactic efficacy of the vaccine for cervical, vaginal, and vulvar disease related to HPV types 6, 11, 16, and 18, as described elsewhere [26, 27].

The trials enrolled healthy women who reported ≤4 lifetime sex partners. Women were excluded if they had a past history of GW or GW were present at the time of enrollment. The protocols were approved by the institutional review boards at participating centers, and written informed consent was obtained from all subjects. Both studies were designed to last for 4 years. Because of the high vaccine efficacy observed in FUTURE-I and FUTURE-II, the independent data and safety monitoring board recommended vaccination of women in the placebo group earlier than planned. The end-of-study data reported here reflect a mean follow-up time of ~3.6 years (25th and 75th percentiles, 3.5 and 3.9 years, respectively; range, 0–4.9 years).

Examination for GW was performed on day 1 and at months 7, 12, 24, 36, and 48 (in addition, examination was performed at months 3, 18, 30, and 42 for FUTURE-I only). Examinations included visual inspection of the perianal area, vulva, and vagina with the naked eye, a magnifying glass, or a colposcope. A clinical impression of any lesions was recorded (i.e., condylomata acuminata, flat wart, keratotic wart, papular wart, or other potentially HPV-related lesion). In cases for which multiple lesions were suspected to be HPV-related, a separate biopsy sample was obtained from each lesion that was morphologically and/or anatomically distinct. Follow-up biopsy samples were obtained only if new lesions appeared that were of differing morphology and/or in a different location.

Biopsy samples were first analyzed for diagnosis and management by pathologists at a central laboratory (Diagnostic Cytology Laboratories) and then analyzed for end point determination by a blinded panel of up to 4 pathologists, as described elsewhere [27]. Biopsy samples obtained at any time during the studies were tested for 14 HPV genotypes: the 4 vaccine genotypes (types 6, 11, 16, and 18) and 10 non-vaccine, high-risk genotypes (types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) by use of a polymerase chain reaction (PCR)–based assay [26, 27, 30].

Two swab samples were collected at each scheduled visit: an endo-ectocervical swab sample and a second combined labial-vulvar-perineal-perianal swab sample. Swab samples were tested for the 14 HPV types listed above on day 1 and tested for the 4 vaccine genotypes at month 3 (FUTURE-I only) and month 7. Mandatory tests for Chlamydia trachomatis and Neisseria gonorrhoeae infection were performed on day 1. Blood samples obtained on day 1 were measured for serum neutralizing antibodies to HPV types 6, 11, 16, and 18 by use of a competitive Luminex immunoassay [31–33]. In FUTURE-I and a subset of FUTURE-II, neutralizing antibodies were also assessed at months 7, 12 (FUTURE-I only), 24, and 48.

**METHODS**

**Study design and population.** Between December 2001 and May 2003, there were 17,622 women 15–26 years old enrolled in 1 of 2 randomized, placebo-controlled, phase III efficacy trials of an HPV (types 6, 11, 16, and 18) vaccine (Gardasil or Silgard; Merck); the vaccine contains a proprietary amorphous aluminum hydroxy-
Statistical analysis. This post hoc analysis was restricted to participants in the placebo arm who had \( \geq 1 \) follow-up visit. The objectives were as follows: (1) to describe the distribution of 14 genotypes in GW, as diagnosed by an expert pathology panel; (2) to approximate the period from the time that an individual became HPV DNA positive for an HPV genotype until the subsequent development of GW related to the same HPV genotype; and (3) to describe the risk of developing HPV-6– and/or HPV-11–related GW.

The time to first development of HPV-6– or HPV-11–related GW was modeled with a Cox regression model [34]. The impact of each variable was assessed univariately and in a multivariate model that simultaneously assessed the impact of all covariates. Hazard ratios (HRs) and 95% confidence intervals (CIs) for each covariate were calculated on the basis of the estimates from these models. The hazard ratio from the multivariate model assesses the impact of each covariate after adjusting for the effect of all the other covariates in the model. There was no statistical selection procedure, and all covariates were included simultaneously.

The proportional hazards assumption was assessed for each variable in a model that included an interaction with time for that variable. For the variables that showed evidence of nonproportional hazards, hazard plots were examined to determine the relationship of the hazard over time and to allow for an appropriate additional term to be added to the model to account for the changing hazard over time.

All variables were measured at baseline, with the exception of the new cases of \( \text{C. trachomatis} \) infection detected during the study, only cases among those who were negative for \( \text{C. trachomatis} \) at baseline were considered. Since participants retrospectively reported at each visit whether they had had \( \geq 1 \) new partner since their last visit, we approximated that the participant acquired the new partner(s) at the midpoint between visits. We used a time-varying covariate to assess the impact of acquiring a new partner in the 12-month period prior to the development of GW.

RESULTS

Overall, 8812 women were randomized to the placebo arm of FUTURE-I \( (n = 2732) \) or FUTURE-II \( (n = 6080) \) [26, 27]. Of these, 8800 were included in these analyses because 12 women discontinued the study after randomization. The general baseline characteristics of the individuals in the placebo arm have been described elsewhere [35]. The mean age was 20 years, and the median lifetime number of sex partners was 2. Papanicolaou testing on day 1 showed that 970 (11.1%) of 8707 participants had a cytological abnormality. Of 8810 participants tested, 2861 (32.5%) were DNA positive for one of the 14 HPV types for which we tested. Of those with complete HPV DNA testing results and complete serology data for HPV-6 and HPV-11 on day 1, a total of 350 (4.0%) of 8708 and 55 (0.6%) of 8720 were positive for HPV-6 and HPV-11 DNA by PCR, respectively; 724 (8.2%) of 8791 and 181 (2.1%) of 8791 were positive for HPV-6 and HPV-11 by serologic testing, respectively.

Of 8800 participants, a total of 351 (4.0%) received a biopsy-confirmed diagnosis of GW during the course of the studies. Of these women, 298 (84.9%) had a lesion that was related to HPV-6 or HPV-11, with HPV-6 being the predominant type (figure 1). Among these 351 women, there were a total of 538
lesions considered HPV-related by the study investigator that were subsequently diagnosed by the pathology panel as GW. There were 18 lesions (involving 17 participants) for which PCR results were missing, typically owing to a sample that was inadequate for amplification. Of the remaining 520 lesions for which complete PCR testing results for 14 HPV types were available, HPV DNA was detected in 472 (90.8%). Because nearly 40 HPV genotypes are known to infect the anogenital tract, it is not known whether the lesions that were negative for these 14 HPV genotypes were in fact positive for a type for which we did not test, particularly as we did not test for other low-risk types apart from HPV-6 and HPV-11. HPV-6 and/or HPV-11 were detected in 447 (86.0%) of 520 lesions. Of the 472 HPV-positive lesions, HPV-6 and/or HPV-11 were detected in 447 (94.7%) (table 1), and 325 (68.9%) were positive for a single genotype. HPV-6 was the dominant genotype (268 [82.5%] of 325). Of the infections due to a single genotype, 22 (6.8%) of 325 were due to 1 of the 12 high-risk genotypes tested, with HPV-16 and HPV-18 accounting for 11 (50.0%) of 22. Two HPV genotypes were detected in 95 (20.1%) of 472 HPV-positive lesions, with the vast majority (92 [96.8%]) containing HPV-6 and/or HPV-11. In 52 of 472 lesions (11.0%), 3–5 genotypes were identified; all of these lesions contained HPV-6 and/or HPV-11 DNA.

In figure 2, the 520 lesions diagnosed as GW are categorized according to the most common high-risk genotypes that were observed in conjunction with HPV-6 or HPV-11. For all lesions with \( > 1 \) HPV genotype detected, HPV-52 and HPV-16 were the types most commonly observed in conjunction with HPV-6. HPV-16 and HPV-56 were the types most commonly observed in HPV-11–related GW. The least common high-risk HPV genotypes observed were HPV-45 and HPV-35. Although coinfection with high-risk genotypes was common, HPV-6 and HPV-11 were also often found together as coinfections.

After controlling simultaneously for the impact of all the covariates, multivariate analysis of the risk for developing GW related to HPV-6 or HPV-11 (table 2) revealed the strong impact of an HPV-6 or HPV-11 infection at baseline, with a hazard ratio of 29.1 for the first year of follow-up. Of the women positive for an HPV-6 or HPV-11 infection at baseline, with a hazard ratio of 29.1 for the first year of follow-up. Of the women positive for an HPV-6 or HPV-11 infection at baseline, with a hazard ratio of 1.47.)

Figure 3 shows the time to development of an HPV-6– or HPV-11–related GW, stratified by a woman’s PCR status from day 1 through month 7. To appear in figure 3A, a woman had to be negative by PCR for the HPV genotype that subsequently led to the development of GW, in all swab samples obtained from day 1 through month 7. The time to development of GW was counted from the date of the first positive PCR result until the time to the first development of GW positive for that same type. The median interval from infection to detection of HPV-6– and HPV-11–related GW was 6.0 and 4.9 months, respectively. We also calculated the time to development of HPV-6–related GW among women who were HPV-6 DNA negative on day 1, but HPV-6 DNA positive at month 3 or month 7 (\( n = 30 \)). For this group, the median interval from infection to detection of HPV-6–related GW was 5.0 months. We did not perform this same analysis for HPV-11 because of the small number of participants available (\( n = 7 \)).

Women with antibodies to HPV-6 at enrollment had a risk of developing GW similar to that of those who were seronegative (23 [3.2%] of 724 vs. 328 [4.1%] of 8067; \( P = .242 \), by \( \chi^2 \) test). In the cohort seropositive for HPV-6 (\( n = 724 \)), 23 women developed GW, and 18 (78.3%) of 23 developed lesions that were positive for HPV-6. Of these 18 women, 5 (27.8%) had been HPV-6 DNA negative at baseline. Of the 181 women who were HPV-6 DNA negative on day 1, but HPV-6 DNA positive at month 3 or month 7, 18 (78.3%) of 23 developed lesions that were positive for HPV-6.

Anti-HPV antibody levels were measured during the entire follow-up period for all participants in FUTURE-I. Of 2530 women in the placebo arm who were seronegative for HPV-6 on day 1, there were 314 (12.4%) who developed antibodies to HPV-6 during the follow-up period. Of those, 61 (19.4%) received a diagnosis of GW during the course of the study, with 55 (90.2%) of 61 positive for HPV-6. Of 2663 women who were seronegative for HPV-11 on day 1, there were 102 (3.8%) who developed antibodies to HPV-11 during the follow-up period. Of those, 20 (19.6%) were diagnosed with GW during the course of the study, with 18 (90.0%) of 20 developing lesions that were positive for HPV-11.

DISCUSSION

These large multinational studies with a relatively long duration of follow-up help to define the incidence and risk factors for GW in a population of young women (age range, 15–26 years) who had a mean of 2 sex partners. Given that 298 (3.4%) of 8800 women developed a case of HPV-6– or HPV-11–related GW...
during the follow-up period, the incidence rate in this minimally experienced population was 0.87 cases per 100 person-years-at-risk. Of women who were positive by PCR for HPV-6 or HPV-11, but without a lesion at baseline, 44 (12.6%) of 350 and 3 (5.4%) of 55 developed HPV-6- or HPV-11–related GW, respectively. At a time when many countries are preparing to launch their HPV vaccine programs, it is reassuring to find that

Table 1. Distribution of human papillomavirus (HPV) genotypes in biopsy samples from lesions diagnosed as genital warts.

<table>
<thead>
<tr>
<th>Number of HPV genotypes detected, particular genotype identified</th>
<th>Lesions, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HPV genotypes detected</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>48 (9.23)</td>
</tr>
<tr>
<td>Exactly 1 HPV genotype detected</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>325 (62.50)</td>
</tr>
<tr>
<td>6</td>
<td>268 (51.54)</td>
</tr>
<tr>
<td>11</td>
<td>35 (6.73)</td>
</tr>
<tr>
<td>18</td>
<td>6 (1.15)</td>
</tr>
<tr>
<td>16</td>
<td>5 (0.96)</td>
</tr>
<tr>
<td>31</td>
<td>3 (0.58)</td>
</tr>
<tr>
<td>58</td>
<td>2 (0.38)</td>
</tr>
<tr>
<td>59</td>
<td>2 (0.38)</td>
</tr>
<tr>
<td>52</td>
<td>2 (0.38)</td>
</tr>
<tr>
<td>45</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>51</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>Exactly 2 genotypes detected</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>95 (18.27)</td>
</tr>
<tr>
<td>6, 52</td>
<td>16 (3.08)</td>
</tr>
<tr>
<td>6, 51</td>
<td>14 (2.69)</td>
</tr>
<tr>
<td>6, 16</td>
<td>11 (2.12)</td>
</tr>
<tr>
<td>6, 31</td>
<td>8 (1.54)</td>
</tr>
<tr>
<td>6, 11</td>
<td>8 (1.54)</td>
</tr>
<tr>
<td>6, 18</td>
<td>5 (0.96)</td>
</tr>
<tr>
<td>6, 33</td>
<td>4 (0.77)</td>
</tr>
<tr>
<td>6, 39</td>
<td>4 (0.77)</td>
</tr>
<tr>
<td>6, 45</td>
<td>3 (0.58)</td>
</tr>
<tr>
<td>6, 56</td>
<td>3 (0.58)</td>
</tr>
<tr>
<td>6, 58</td>
<td>3 (0.58)</td>
</tr>
<tr>
<td>6, 59</td>
<td>3 (0.58)</td>
</tr>
<tr>
<td>11, 16</td>
<td>3 (0.58)</td>
</tr>
<tr>
<td>11, 18</td>
<td>2 (0.38)</td>
</tr>
<tr>
<td>11, 31</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>11, 45</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>11, 51</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>11, 52</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>11, 59</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>16, 56</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>31, 56</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>51, 52</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>Exactly 3 genotypes detected</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>34 (6.54)</td>
</tr>
<tr>
<td>6, 11, 59</td>
<td>3 (0.58)</td>
</tr>
<tr>
<td>6, 18, 52</td>
<td>3 (0.58)</td>
</tr>
<tr>
<td>6, 11, 16</td>
<td>2 (0.38)</td>
</tr>
<tr>
<td>6, 16, 52</td>
<td>2 (0.38)</td>
</tr>
<tr>
<td>6, 45, 56</td>
<td>2 (0.38)</td>
</tr>
<tr>
<td>6, 52, 59</td>
<td>2 (0.38)</td>
</tr>
<tr>
<td>6, 11, 18</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>6, 16, 31</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>6, 16, 33</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>6, 16, 39</td>
<td>1 (0.19)</td>
</tr>
</tbody>
</table>

(continued)
in this multinational study (there were 16 countries included in FUTURE-I and 14 countries included in FUTURE-II) the prevalence of HPV-6 and HPV-11 in GW was very close to what was anticipated in previous studies, that is, 90%. The substantial burden of GW might therefore be reduced by a prophylactic vaccine that contains HPV genotypes 6 and 11 [15].

The study has some limitations. We enrolled young healthy women with ≤4 lifetime sex partners. Therefore, we may have underestimated the incidence of GW in the general population. The study is also limited by the lack of HPV DNA testing for swab samples collected after month 7. To estimate the time to development of GW, we stratified women by their PCR status from day 1 through month 7. Among those positive for HPV-6 or HPV-11 DNA from day 1 through month 7, the time to development of GW was 6.0 and 4.9 months, respectively. In addition, in FUTURE-I, women were examined for the presence of GW at 6-month intervals, whereas in FUTURE-II, the interval between visits was 1 year. Nonetheless, these data are consistent with those from previous, albeit smaller, studies [11–13]. In a study of 603 American women 18–20 years old who were examined at 4-month intervals, the median time between detection of incident HPV-6 or HPV-11 infection and detection of any GW

Figure 2. Distribution of high-risk human papillomavirus (HPV) types in the 520 lesions diagnosed as genital warts, categorized according to the most common high-risk genotypes that were observed in conjunction with HPV-6 or HPV-11 (adapted from table 1). The no. of types detected is the no. of genotypes detected in a given lesion.
was 2.9 months (interquartile range, 0–5.7 months) [11]. In our study, among women who were negative by PCR for HPV-6 or HPV-11 from day 1 through month 7, the time to development of HPV-6–or HPV-11–related GW was approximately 2 years. However, the exact time from incident infection to the development of GW in these women could not be determined. The long latent period may reflect detection of low viral loads well before lesion development and clinical manifestation of GW.

Other, smaller studies have reported the contribution of HPV-6 and HPV-11 to GW. Two studies conducted in the United States found HPV-6 or HPV-11 in 100% of GW analyzed (samples from 37 and 41 participants, respectively) [3, 4]. In another US study, HPV-6 or HPV-11 was detected in 74% of GW (samples from 42 participants) [36]. In this multinational study of 351 participants with GW, HPV-6 and HPV-11 were detected in 447 (86.0%) of 520 lesions diagnosed as GW and in 94.7% of the 472 HPV-positive lesions. Differences in the findings between these studies could be attributed to sample sizes, regional variations in HPV prevalence, or differences in HPV DNA detection methods.

We identified a single genotype in 325 (68.9%) of 472 HPV-positive lesions, with HPV-6 being the dominant type (268 [82.5%] of 325). Individuals who have visible GW are frequently infected or colonized simultaneously with multiple HPV genotypes. HPV 16, 18, 31, 33, and 35 have been found in visible GW and are associated with cervical, vaginal, vulvar, penile, and anal neoplasia or cancer, as well as some head and neck cancers [37]. We found high-risk HPV genotypes in 161 (31.0%) of 520 lesions, with HPV-52 and HPV-16 the types most commonly observed in HPV-6–related GW and HPV-16 and HPV-56 the types most commonly observed in HPV-11–related GW. This result is consistent with previous studies, in which 20%–50% of lesions were found to be colonized or coinfected with high-risk HPV types [3, 14]. As we did not evaluate the presence of other low-risk genotypes that are known to cause GW, such as HPV-40 and HPV-42, one

Table 2. Risk of developing genital warts (GW) related to human papillomavirus (HPV)–6 or HPV-11.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Overall (n = 8800)</th>
<th>Univariate model, HR (95% CI)</th>
<th>Multivariate model, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White race, vs. non-white race</td>
<td>6103 (69.4)</td>
<td>1.11 (0.86–1.43)</td>
<td>0.84 (0.63–1.13)</td>
</tr>
<tr>
<td>Hormonal contraceptive use on day 1, yes vs. no</td>
<td>5159 (58.6)</td>
<td>0.77 (0.62–0.97)</td>
<td>0.80 (0.61–1.06)</td>
</tr>
<tr>
<td>Contraception on day 1 was male condom, yes vs. no</td>
<td>2164 (24.6)</td>
<td>1.28 (0.99–1.64)</td>
<td>0.93 (0.69–1.26)</td>
</tr>
<tr>
<td>DNA-positive for HPV-6 or HPV-11 at baseline, yes vs. no</td>
<td>400 (4.6)</td>
<td>Impact during first follow-up year 31.29 (18.73–52.27)</td>
<td>29.10 (17.00–49.89)</td>
</tr>
<tr>
<td>DNA-positive for other type(s) of high-risk HPV and negative for types 6 and 11, yes vs. no</td>
<td>2467 (28.0)</td>
<td>1.23 (0.96–1.57)</td>
<td>1.47 (1.12–1.92)</td>
</tr>
<tr>
<td>Chlamydia trachomatis infection on day 1, yes vs. no</td>
<td>360 (4.1)</td>
<td>1.72 (1.11–2.68)</td>
<td>1.32 (0.61–2.88)</td>
</tr>
<tr>
<td>History of C. trachomatis infection, yes vs. no</td>
<td>503 (5.7)</td>
<td>1.54 (1.03–2.31)</td>
<td>1.06 (0.52–2.14)</td>
</tr>
<tr>
<td>New case of C. trachomatis infection for those negative for C. trachomatis at baseline, yes vs. no</td>
<td>870 (9.9)a</td>
<td>1.67 (1.09–2.55)</td>
<td>1.34 (0.87–2.05)</td>
</tr>
<tr>
<td>History of Neisseria gonorrhoeae infection, yes vs. no</td>
<td>24 (0.3)</td>
<td>1.23 (0.17–8.77)</td>
<td>0.81 (0.11–5.84)</td>
</tr>
<tr>
<td>Current smoker, yes vs. no</td>
<td>2391 (27.2)</td>
<td>1.61 (1.28–2.04)</td>
<td>1.17 (0.91–1.50)</td>
</tr>
<tr>
<td>History of smoking, yes vs. no</td>
<td>696 (7.9)</td>
<td>0.82 (0.52–1.30)</td>
<td>0.84 (0.53–1.35)</td>
</tr>
<tr>
<td>ASCUS or worse on day 1, yes vs. no</td>
<td>955 (10.8)</td>
<td>2.30 (1.24–4.25)</td>
<td>1.12 (0.60–2.10)</td>
</tr>
<tr>
<td>Impact after first follow-up year</td>
<td>2.0 ± 2.0</td>
<td>0.93 (0.61–1.42)</td>
<td>0.78 (0.50–1.20)</td>
</tr>
<tr>
<td>History of pregnancy, yes vs. no</td>
<td>1972 (22.4)</td>
<td>0.77 (0.57–1.03)</td>
<td>0.94 (0.68–1.31)</td>
</tr>
<tr>
<td>Age at enrollment, years</td>
<td>20.0 ± 2.0</td>
<td>0.83 (0.78–0.88)</td>
<td>0.84 (0.79–0.89)</td>
</tr>
<tr>
<td>Number of lifetime sex partners on day 1</td>
<td>2.0 ± 1.2</td>
<td>1.15 (1.05–1.27)</td>
<td>1.15 (1.04–1.27)</td>
</tr>
<tr>
<td>New sex partner within a year prior to developing a case of GW, yes vs. no</td>
<td>4578 (52.0)b</td>
<td>2.89 (2.3–3.6)</td>
<td>2.38 (1.87–3.02)</td>
</tr>
</tbody>
</table>

**NOTE.** For categorical covariates, data are no. (%) of participants with the characteristic; for continuous covariates, data are mean (±SD). In the Cox regression model, 2 baseline variables failed to meet the proportional hazard assumption (DNA positivity for HPV-6 and/or HPV-11 and a Papanicolaou test result of atypical cells of undetermined significance [ASCUS] or worse). Parameters were added to the model to account for the increased hazard associated with these covariates in the first year relative to later in the follow-up period.

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a A total of 870 participants (9.9%) were negative for *C. trachomatis* on day 1 but positive for *C. trachomatis* at some time during follow-up. Of the 298 individuals who developed GW, 42 (14.1%) had a new positive *C. trachomatis* test result during follow-up, with 24 of those new *C. trachomatis* infections occurring prior to developing a case of GW. Of the 8802 participants who did not develop GW, 828 (9.7%) had a positive *C. trachomatis* test result sometime during follow-up.

b A total of 4578 participants (52.0%) reported acquiring a new partner during the study. The number who reported acquisition of a new partner during years 1, 2, 3, and 4 of follow-up were 28.1%, 25.2%, 22.8%, and 16.4%, respectively. Of the 298 participants who developed GW, 150 (50.3%) reported acquiring a new partner in the 12-month period prior to developing GW.
cannot suggest ascertainment of these high-risk HPV types to be causative in these lesions.

When FUTURE-I and FUTURE-II were considered together, vaccine efficacy for CIN associated with HPV types 6, 11, 16, and/or 18 (i.e., CIN1, CIN2/3, or cervical adenocarcinoma in situ) and GW associated with HPV types 6, 11, 16, and 18 was 96% and 99%, respectively [38]. Our data confirm that prophylactic vaccination with an HPV vaccine that includes HPV-6 and HPV-11 will prevent the majority of GW cases and will also eliminate high-risk types that are commonly observed as coinfections. As peak attack rates are known to occur in women 16–24 years old and men 20–29 years old [39, 40], our population may reflect a catch-up population for vaccination but may not correspond to what would be considered a high-risk population that may already have been exposed to many of these HPV genotypes. However, a recent study that used the same clinical trial population (FUTURE-I and FUTURE-II) has shown that women who are infected with HPV-6 or HPV-11 prior to vaccination are still protected from GW due to the HPV type(s) to which they were naive (93% efficacy [95% CI, 79.3%–98.7%]) and are protected from CIN2 or worse due to HPV-16 and HPV-18 (100% efficacy [95% CI, 78.6%–100.0%]), which suggests that the HPV-6 and HPV-11 components of the vaccine do not mitigate the high vaccine efficacy observed for low-risk and oncogenic HPV genotypes [35]. Immunogenicity studies have also confirmed that the inclusion of several antigens in an AAHS-adjuvanted HPV vaccine does not result in a reduction of the immune response to the individual antigens [41, 42].

We also use both multivariate and univariate analyses to describe the risk of developing HPV-6– or HPV-11–related GW. Not surprisingly, multivariate analysis revealed the strongest impact from an HPV-6 or HPV-11 infection at baseline, with a hazard ratio of 29.1 for the first year of follow-up. The hazard ratio associated with infection with a high-risk HPV type (for those negative for HPV-6 or HPV-11 at baseline) was 1.47, a correlate for HPV infection in general. We found other risk factors that are commonly associated with sexually transmitted infections. Seropositivity at baseline did not predict risk of development of GW, and some women who presumably had cleared an HPV-6 infection in the past (i.e., women who were HPV seropositive and HPV DNA negative), went on to develop HPV-6–related GW. This could represent reactivation of infection or perhaps HPV DNA that was missed at baseline. The vaccine for HPV types 6, 11, 16, and 18 has recently been shown to induce an anamnestic response in those women who are seropositive; thus women who have cleared an HPV infection in the past may benefit from a vaccine that increases antibody levels over those that result from natural infection [42, 43].

Data extracted from the placebo arm of these large, multinational trials may help physicians to better counsel individuals about GW and their prevention. GW are highly infectious, with a transmission rate of ~65% [14]. They are associated with a high economic burden soon after onset and with psychological morbidity and feelings of shame [44]. Consistent condom use may reduce the risk for genital HPV infection [45]; however, HPV infection can occur in areas that are not covered or pro-

Figure 3. Time to development of genital warts (GW) related to human papillomavirus (HPV)–6 or HPV-11. A, Participants who were DNA negative for HPV-6 or HPV-11 at months 0, 3 (protocol 013 [FUTURE-I] only), and 7 and subsequently developed GW due to the HPV type for which they had tested negative. The time to development of GW was counted from the date of the month 7 visit (i.e., the last recorded visit with a swab sample negative for the relevant HPV type) until the development of GW positive for the relevant type. B, Participants who were DNA positive for HPV-6 or HPV-11 at months 0, 3 (FUTURE-I only), or 7 and subsequently developed GW due to the same HPV type for which they were DNA positive. The time to development of HPV-6– or HPV-11–related GW was counted from the date of the first positive polymerase chain reaction (PCR) result until the development of GW positive for that same HPV type. Of 351 participants who received a biopsy-confirmed diagnosis of GW, 23 (7.7%) were not included for the following reasons: 8 women had a lesion that tested positive for both HPV-6 and HPV-11; 3 women had had GW recorded prior to that time at which we began counting (either month 7 or after the first positive PCR result); 7 had a missing PCR result at either day 1, month 3, or month 7; and 5 had a missing PCR result for the biopsy sample. Thus, 275 (92.3%) of 298 women with GW contributed to the analyses in figure 3, with no woman contributing to more than one row.
ected by a condom (e.g., the scrotum, vulva, or perianal region). We have shown that in a population of healthy women 15–26 years old with ≤4 lifetime sex partners, the incidence of GW was considerable. Overall, testing for only 14 genotypes, 472 (90.8%) of 520 lesions were HPV DNA positive; among these, HPV-6 and/or HPV-11 were detected in 447 (94.7%). Therefore, a vaccine that prevents anogenital disease due to HPV-6 and HPV-11, as well as oncogenic HPV types, has the potential to substantially reduce the clinical and societal burden of HPV disease.

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References


