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Incident Cervical HPV Infections in Young Women: Transition Probabilities for CIN and Infection Clearance

Ralph P. Insinga[1], Gonzalo Perez[2], Cosette M. Wheeler[3], Laura A. Koutsky[4], Suzanne M. Garland[5], Sepp Leodolter[6], Elmar A. Joura[6], Daron G. Ferris[7], Marc Steben[8], Mauricio Hernandez-Avila[9], Darron R. Brown[10], Elamin Elbasha[1], Nubia Muñoz[11], Jorma Paavonen[12], and Richard M. Haupt; for the FUTURE I Investigators

Abstract

Background: We describe transition probabilities for incident human papillomavirus (HPV) 16/18/31/33/35/45/52/58/59 infections and cervical intraepithelial neoplasia (CIN) 1 lesions.

Methods: Women ages 16 to 23 years underwent cytology and cervical swab PCR testing for HPV at approximately 6-month intervals for up to 4 years in the placebo arm of an HPV vaccine trial. The cumulative proportion of incident HPV infections with diagnosed CIN, clearing (infection undetectable), or persisting without CIN, were estimated.

Results: Most incident infections cleared, without detection of CIN, ranging at 36 months from 66.9% for HPV31 to 91.1% for HPV59. There was little variation in the 36-month proportion of incident HPV16, 18, and 31 infections followed by a CIN1 lesion positive for the relevant HPV type (range 16.7%–18.6%), with lower risks for HPV59 (6.4%) and HPV33 (2.9%). Thirty-six–month transition probabilities for CIN2 ranged across types from 2.2% to 9.1%; however, the number of events was generally too small for statistically significant differences to be seen across types for this endpoint, or CIN3.

Conclusions: Some incident HPV types appear more likely to result in diagnosed CIN1 than others. The relative predominance of HPV16, vis-à-vis some other high-risk HPV types (e.g., HPV33) in prevalent CIN2/3, appears more directly associated with relatively greater frequency of incident HPV16 infections within the population, than a higher risk of infection progression to CIN2/3.

Impact: Nearly all incident HPV infections either manifest as detectable CIN or become undetectable within 36 months. Some HPV types (e.g., 16 and 33) appear to have similar risk of CIN2/3 despite widely varied incidence. *Cancer Epidemiol Biomarkers Prev; 20(2); 287–96. ©2011 AACR.*

Authors' Affiliations: [1]Merck Research Laboratories Merck and Co., Inc., North Wales, Pennsylvania; [2]Universidad del Rosario, Bogotá, Colombia; [3]Departments of Pathology and Gynecology, University of New Mexico Health Sciences Center, Albuquerque New Mexico; [4]Department of Epidemiology, University of Washington, Seattle, Washington; [5]Microbiology and Infectious Diseases Department, Royal Women's Hospital and Department of Obstetrics and Gynecology, University of Melbourne, Melbourne, Victoria, Australia; [6]Department of Gynecology and Obstetrics, Medical University of Vienna, Vienna, Austria; [7]Departments of Family Medicine and Obstetrics and Gynecology, Medical College of Georgia, Augusta, Georgia; [8]Direction Risques Biologiques et Santé au travail, Institut National de Santé Publique du Québec, Montréal, Québec, Canada; [9]Ministry of Health, Mexico City, Mexico; [10]Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana; [11]National Institute of Cancer, Bogotá, Colombia; and [12]Department of Obstetrics and Gynecology, University Central Hospital, Helsinki, Finland

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Current address for G. Perez: Merck and Co., Inc.

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Corresponding Author: Ralph P. Insinga, Merck and Co., Inc., UG1C-60, P.O. Box 1000, North Wales, PA 19454-10099. Phone: 267-305-7992; Fax: 267-305-6466. E-mail: ralph_insinga@merck.com

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Introduction

In countries with routine screening for cervical cancer, the diagnosis and treatment of precursor lesions or cervical intraepithelial neoplasia (CIN) can result in a substantial health and economic burden (1–3). The prevalence (4, 5) and estimated attribution (6) of individual human papillomavirus (HPV) types within CIN have been described in recent meta-analyses. In a previous study, we reported the risk of detection of biopsy-confirmed CIN grades 1, 2, and 3 (in the form of a probability of transition between infection and disease states) following incident HPV type 6, 11, 16, and 18 infections (7). However, a corresponding risk for other HPV types has not been reported. Current prophylactic HPV6/11/16/18 and HPV16/18 vaccines have recently been shown to confer a degree of cross-protection against some non-6/11/16/18 types (8–10) and, in the future, coverage of vaccines may be broadened to incorporate additional HPV types (11). Thus, an understanding of transition probabilities between infection and diagnosed

disease, and between individual diagnosed disease states (e.g., CIN1 and CIN2/3), will be particularly important for forthcoming policy evaluations of technologies such as HPV vaccines and HPV test–based screening programs, as they typically utilize data inputs in this format (12, 13).

This study describes transition probabilities for CIN, persistence, and clearance of incident HPV16/18/31/33/35/45/52/58/59 infections in young women. The importance of this group of HPV types is exemplified by their significant contribution to the risk of cervical cancer. Altogether, it has been estimated that more than 90% of cervical cancers worldwide are attributable to these types (14). We also describe transition probabilities for incident CIN1 lesions testing positive for these HPV types. Although in some natural history studies HPV infection and CIN1 lesions are considered as indistinguishable, the distinction between HPV infection with and without histologically diagnosed CIN1, 2, or 3 is consistent with how HPV infection is often conceptualized in policy evaluations of interventions to prevent and diagnose HPV disease, where economic and quality of life impacts may occur once an HPV-infected women has been diagnosed with CIN (15, 16).

Methods

Study participants and procedures

The current evaluation focuses on women enrolled in the placebo arm of a multinational randomized double-blind clinical trial (Merck Protocol V501-012) of an HPV6/11/16/18 vaccine (Gardasil; Merck), an HPV16 vaccine, or a placebo. The primary study population and trial design have been described elsewhere (10, 17). Briefly, the placebo-arm population consisted of 1,788 women, who on day 1 of the trial were 16 to 23 years of age and did not report a history of clinical HPV disease (e.g., CIN or genital warts) or a lifetime total of more than 4 sex partners. The study was conducted in conformance with applicable federal and local requirements regarding ethical committee review and protection of human subjects participating in biomedical research. Women in the placebo arm received 3 intramuscular injections at day 1, month 2, and month 6 that were visually indistinguishable from vaccine.

Women underwent type-specific endocervical/ectocervical swab HPV polymerase chain reaction (PCR) testing for "high-risk" HPV16/18/31/33/35/45/52/58/59 infections at approximately 6-month intervals through 48 months of follow-up. The HPV testing methods utilized have been described in detail elsewhere (17–20). Briefly, swabs were prepared for multiplex PCR using a QIAamp DNA Blood kit (QIAGEN, Inc.). DNA was analyzed by qualitative PCR using type-specific and gene-specific primers. Beta-globin PCR assay was carried out to verify that purified samples contained a sufficient quality and quantity of DNA for PCR amplification. All PCR assays were carried out at Merck Research Laboratories.

Cervical samples were also collected for liquid-based cytology (ThinPrep; Cytyc) testing at day 1, month 7, and approximately 6-month intervals thereafter for 48 months. Women were referred for colposcopy if the cytology result showed (i) atypical squamous cells of undetermined significance along with a positive reflex Hybrid Capture II test (QIAGEN, Inc., formerly Digene) for high- and/or low-risk HPV types from residual ThinPrep material or (ii) low-grade squamous intraepithelial lesion or worse cytology. Of all women with normal cytology results up to the month 48 trial visit, those who had an abnormal Pap test at that visit were referred for colposcopy, with biopsy done if a CIN lesion was suspected. Women with CIN2 or worse or persistent CIN1 (CIN1 detected on at least 2 consecutive biopsies over a period of at least 1 year) were referred for definitive therapy. Cervical tissue specimens were processed and assigned histologic diagnoses for purposes of medical management by central laboratory pathologists, and were typed by PCR for HPV6/11/16/18/31/33/35/39/45/51/52/56/58/59.

Measures

Incident cervical HPV16/18/31/33/35/45/52/58/59 infections were identified on cervical swab or tissue specimens among women negative for the relevant HPV type on their first two study cervical swabs and any cervical biopsy specimens obtained on or before the second swab (Fig. 1). Consistent with our and others' earlier works (21–23), we assumed that HPV infections occurred at the mid-point between the initial positive test date and the previous negative swab.

Incident HPV infections were examined until either the detection of a CIN1–3 lesion for which the cervical tissue specimen tested PCR-positive for the relevant HPV type, or a negative cervical swab HPV test result(s) for that type ("clearance"—representing infection becoming undetectable; Fig. 1). In a few instances, an initial CIN result on a biopsy specimen (e.g., CIN2) was followed by a more severe CIN result (e.g., CIN3) shortly thereafter on a definitive therapy specimen. In these instances, we considered a more severe result observed within 60 days of the biopsy diagnosis to have been present at the time of the initial biopsy (but missed), rather than as a reflection of disease progression, and substituted the diagnosis and HPV typing information for the higher grade lesion within the analysis (11 substitutions made among 1,183 incident infections). Because women were required to have 2 consecutive negative swabs for a given HPV type before the start of an incident infection, if 2 consecutive negative swabs for that type were subsequently observed, the infection was assumed to have gone below detectable levels at the midpoint in time between the final positive test and first negative swab result. As previously reviewed in greater conceptual detail (22) for women with a positive swab or tissue sample(s) for a given type followed by only a single negative swab before the trial concluding or their withdrawal, it was assumed that the

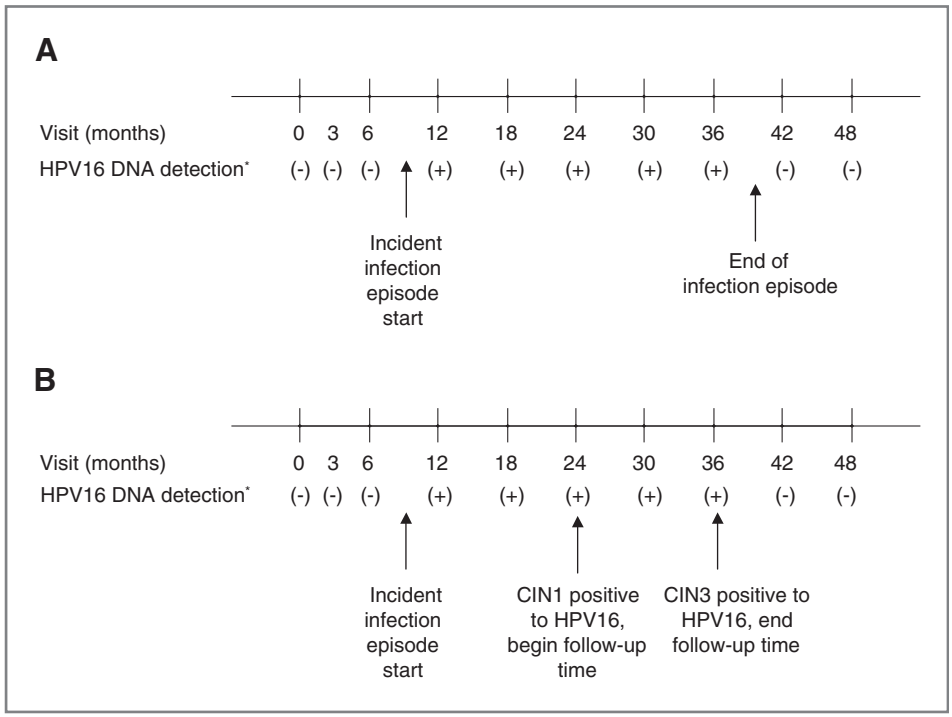

Figure 1. Examples of analyses of incident cervical infections without transition to CIN (A) and analyses of incident CIN1 with transition to CIN3 (B). A, incident infection duration begins at the midpoint between a prior negative swab and the first HPV positive test result, in this example, HPV16 detection at month 9. The HPV16 infection was assumed to have gone below detectable levels at the midpoint in time between the final positive test and first negative swab result; in this example, at month 39. B, the duration of a hypothetical HPV16 infection would be categorized within the modified Kaplan–Meier analysis. Women with incident infections who had a histologically confirmed CIN1 lesion testing positive for a given HPV type, in the absence of a preceding or concurrent diagnosis of more severe cervical pathology testing positive for that type, were eligible for the analyses of CIN1 transition probabilities.
* HPV16 DNA detected in endocervical/ectocervical swab or cervical tissue specimen.

infection had gone below detectable levels at the midpoint in time between the last positive sample and the negative swab. Positive swab or biopsy specimens, followed by a single negative swab, followed by a positive swab or biopsy specimen, were analyzed as persistent infections. Ongoing infections characterized by a positive test on the date of the final trial swab were evaluated as censored.

Women with incident infections who had a histologically confirmed CIN1 lesion testing positive for the relevant HPV type, in the absence of a preceding or concurrent diagnosis of more severe cervical pathology testing positive for that type, were eligible for the analyses of CIN1 transition probabilities (Fig. 1). Follow-up time was defined to begin with the date of the initial CIN1 diagnosis. Case definitions for detection of CIN2 or CIN3, clearance (of HPV), and persistence were analogous to those described for incident HPV infections earlier in the text, with the exception that women undergoing treatment for a CIN lesion (e.g., for a persistent CIN1 lesion) were censored at the time of treatment. During follow-up, there was 1 substitution of a more severe CIN diagnosis on a definitive therapy specimen observed within 60 days of an initial biopsy result, from among 155 incident CIN1 lesions.

Finally, the persistence of incident HPV infections was evaluated among women with infections observed on excisional treatment tissue specimens, who had at least one swab typing result available post-therapy. Women were considered to have persistent infections if their subsequent swab tested positive for the same HPV type observed at the time of therapy.

Statistical analysis

The cumulative proportion of incident HPV infections with a diagnosed CIN1, 2, or 3 lesion, clearing, or persisting without evidence of CIN, at 12, 24, and 36 months postinfection were estimated using modified Kaplan–Meier (K-M) methods, with analogous methods utilized for analyses of the natural history of CIN1 (24). Each outcome was mutually exclusive. For instance, once an endpoint of CIN1, 2, or 3 was observed, a woman was no longer at risk for contributing toward the cumulative risk of transitioning to other grades of CIN, and vice versa. Specifically, infections were modeled as persisting ("surviving") until either being censored (by end of follow-up) or transitioning to 1 of 4 outcomes (clearance, CIN1, CIN2, or CIN3). Incremental changes in the overall K-M product-limit survival estimate over time resulting from each of these 4 outcomes were identified and

summed cumulatively to estimate risks of specific outcomes, analogous to the marginal failure probabilities analysis in the presence of competing risks described by Andersen and colleagues (25). Ninety-five percent confidence intervals (95% CI) for cumulative proportions persisting without CIN, detected with CIN, and clearing were estimated through nonparametric bootstrapping of the K-M survivorship function with 1,000 replicates (26).

Two separate types of analyses for outcomes of incident HPV infections and CIN1 lesions were conducted. The first presumed that for CIN lesions testing positive for multiple HPV types, each HPV type detected was causally associated with that lesion. Results of these analyses are presented as supplementary material in the Appendix Tables 1A and 1B. For instance, if a woman with incident HPV6, 16, and 59 infections subsequently had an HPV6/16/59-positive CIN3 lesion detected, that lesion would fully contribute to the transition risk to CIN3 estimated for each of these HPV types. As discussed in detail in previous works (6, 27), in these cases there has been some evidence to suggest that just one of these HPV types was likely responsible for the lesion, and that according a full transition risk to each type individually would tend to overestimate the risk of higher-grade disease for one or more types (28, 29).

To better approximate the transition probabilities for each HPV type, in our primary analyses we have performed a statistical adjustment that assumes a fractional allocation for each individual HPV type with respect to the lesion of interest when evaluating multitype infected CIN lesions. In previous analyses conducted for prevalent CIN cases, this fractional allocation was based on the relative frequencies with which each HPV infection type was observed as a single-type infection in prevalent CIN lesions of a given grade, as information on risk of CIN following incident single-type HPV infections was unavailable (6). However, in this study, it was possible to compute a transition probability to CIN following incident HPV infections for certain types and, hence, a modified statistical adjustment procedure was utilized.

First, follow-up of all incident HPV16/18/31/33/35/45/52/58/59 infections, for which detection of a CIN lesion testing positive for multiple HPV types was observed, was censored at the time of the CIN diagnosis and labeled as persistent infection at that time point. Second, the 36-month risk of CIN1, 2, and 3 lesions testing positive for the HPV type observed in the incident infection was estimated. This corresponds to the CIN transition risk for each incident HPV type as relates to single-type infected lesions only. These probabilities were then compared across HPV types and used to fractionally allocate risks for CIN for multitype infected lesions on the basis of the relative magnitude of risk observed for each type, for a given grade of CIN lesion. For instance, if the transition risk to single-type infected CIN2 lesions for HPV16 was computed to be 10%, and for HPV45 to be 5%, then an HPV16 and 45 coinfected CIN2 lesion would be allocated in two-third portion [10%/(10%+5%)] to HPV16 and one-third portion [5%/(10%+5%)] to HPV45, in estimating an overall transition probability for these types.

Unfortunately, this method of allocation of transition risk was not always possible, as swab testing for HPV6/11/39/51/56 was not conducted for specimens collected over the full duration of the trial, and it was not possible to compute an HPV transition risk for these types. Instead, when 1 of these 5 HPV types was observed in a multitype infected CIN lesion (22.7%, 14.9%, and 26.7% of all types observed in incident CIN1, 2, and 3 lesions, respectively), a modified adjustment procedure was employed. This involved first computing the fractional allocation for any of the 5 HPV types noted in the text using the former methods for prevalent CIN described in Insinga and colleagues (6) and allocating the other types (HPV16/18/31/33/35/45/52/58/59) to the remaining portion of risk to be allocated on the basis of the incidence-based approach just described. Data for calculating attribution on the basis of a cross-sectional evaluation of CIN cases were derived from the placebo arms of all phase III trials of the quadrivalent HPV6/11/16/18 vaccine (8) conducted in young women. The prevalence of HPV6/11/16/18/31/33/35/39/45/51/52/56/58/59 infections in CIN1–3 lesions was estimated on the basis of PCR typing from the first histologic diagnosis of CIN observed in the trial for a given woman. Only the first date with a CIN biopsy specimen was chosen to avoid selecting data for the same lesion multiple times in cases in which more than one biopsy specimen was taken during the course of follow-up. If multiple grades of CIN were observed for a woman on a given date, the most severe histologic diagnosis was selected. HPV typing results for these lesions are summarized in the Appendix in fully disaggregated form (Appendix Table 2A) and for specific combinations of types currently targeted by HPV vaccines (Appendix Table 2B). For an example of this latter method, consider an HPV16/45/51 infected CIN2 lesion. Using the figures provided in the previous example for the incidence-based method of allocation and data in Appendix Table 2A, the fractional allocation would be computed as 15.8% [20/(103+3+20)] for HPV51, 56.1% for HPV16 [(1–15.8%)×(2/3)], and 28.0% for HPV45 [(1–15.8%)×(1/3)]. In the analyses of outcomes of incident CIN1 lesions, these adjudication methods were used to estimate both attribution for incident CIN1 lesions testing positive for more than one HPV type and for subsequently observed CIN2 or 3 lesions positive for multiple types.

Results

Of the 1,788 women in the placebo arm of the trial who underwent endocervical/ectocervical swab HPV testing at day 1, 1,694 were potentially eligible for one or more analyses of type-specific HPV incidence (i.e., had $\geq$3 trial visits with satisfactory swab PCR test results for a given HPV type). From this group, there were 1,183 incident

HPV16/18/31/33/35/45/52/58/59 infections originating from 676 women. The age range among these women at the time of their incident infections was 16 to 27, and women most commonly resided in North America, followed by South/Central America. Roughly one-third of these women were active users of tobacco products.

The estimated probabilities of incident type-specific HPV infections transitioning to diagnosed CIN1, 2, or 3 testing positive for the relevant HPV type, clearing, or persisting in the absence of detected CIN, by 12, 24, and 36 months following the date of incident infection are reported in Table 1. The mean available observation window following incident HPV infection ranged from 19.0 months for analyses of HPV35 to 22.8 months for HPV18. Estimates of infection outcomes are based on adjudication of CIN lesions testing positive for multiple HPV types as described in the Methods section. Without such adjudication, the estimated probabilities of infection transition to CIN would generally be higher (Appendix Table 1A). A complete listing of HPV types observed in incident CIN1, 2, and 3 lesions testing positive for a concordant HPV type as observed in a previous or

Table 1. Transition probabilities (12, 24, and 36 months) for incident HPV16, 18, 31, 33, 35, 45, 52, 58, and 59 infections (with adjudication of CIN lesions infected with multiple HPV types)

	Persistence	Clearance	CIN1	CIN2	CIN3
HPV16 ($n = 273$)					
12 Months	57.4 (50.6–63.7)	27.7 (22.0–33.6)	8.0 (4.4–11.8)	5.1 (2.5–8.5)	1.7 (0.0–3.8)
24 Months	22.6 (16.4–28.9)	57.3 (50.0–64.3)	12.6 (7.6–17.8)	5.9 (3.0–9.3)	1.7 (0.0–3.8)
36 Months	5.4 (0.0–11.2)	67.4 (59.1–75.9)	17.9 (11.3–24.9)	7.6 (3.8–12.4)	1.7 (0.0–3.8)
HPV18 ($n = 113$)					
12 Months	43.8 (33.8–53.8)	42.5 (32.9–52.2)	12.0 (5.8–19.1)	1.6 (0.0–4.8)	0.0 (-)
24 Months	12.7 (5.3–21.4)	69.5 (58.9–79.9)	14.3 (7.1–22.7)	3.4 (0.0–8.7)	0.0 (-)
36 Months	2.5 (0.0–7.8)	76.8 (65.9–86.1)	16.7 (8.2–25.9)	4.0 (0.0–9.9)	0.0 (-)
HPV31[a] ($n = 157$)					
12 Months	53.4 (44.0–62.4)	32.2 (25.0–40.1)	8.4 (3.5–14.0)	4.5 (1.3–8.6)	1.5 (0.0–4.4)
24 Months	24.4 (16.2–33.2)	54.5 (44.7–64.5)	14.1 (7.6–21.1)	5.4 (1.6–9.9)	1.5 (0.0–4.4)
36 Months	5.8 (0.0–13.0)	66.9 (57.4–77.7)	18.6 (9.5–28.1)	5.4 (1.6–9.9)	3.2 (0.0–8.8)
HPV33 ($n = 57$)					
12 Months	55.4 (40.9–69.4)	39.7 (26.6–54.0)	0.2 (0.0–2.3)	4.7 (0.0–11.2)	0.0 (-)
24 Months	18.9 (7.6–31.4)	69.1 (54.3–83.0)	2.3 (0.0–7.3)	5.5 (0.0–12.8)	4.1 (0.0–10.5)
36 Months	3.0 (0.0–17.6)	80.9 (63.4–94.8)	2.9 (0.0–10.7)	9.1 (0.0–22.8)	4.1 (0.0–10.5)
HPV35 ($n = 52$)					
12 Months	46.0 (30.4–61.7)	48.3 (32.4–63.4)	4.1 (0.0–12.2)	1.6 (0.0–7.6)	0.0 (-)
24 Months	7.3 (0.0–18.7)	76.7 (61.7–90.9)	4.1 (0.0–12.2)	8.3 (0.0–19.7)	3.7 (0.0–12.4)
36 Months	3.6 (0.0–12.3)	76.7 (61.7–90.9)	7.8 (0.0–19.1)	8.3 (0.0–19.7)	3.7 (0.0–12.4)
HPV45 ($n = 77$)					
12 Months	44.9 (31.1–57.4)	43.6 (30.9–56.9)	9.2 (2.7–16.6)	2.2 (0.0–7.2)	0.0 (-)
24 Months	15.8 (5.3–27.0)	72.7 (59.7–85.0)	9.2 (2.7–16.6)	2.2 (0.0–7.2)	0.0 (-)
36 Months	3.5 (0.0–17.1)	83.2 (70.1–95.4)	9.2 (2.7–16.6)	2.2 (0.0–7.2)	0.0 (-)
HPV52 ($n = 173$)					
12 Months	57.7 (48.1–65.8)	34.4 (26.2–42.8)	5.7 (2.1–10.3)	2.2 (0.0–5.0)	0.0 (-)
24 Months	24.1 (15.7–32.9)	62.0 (52.5–71.4)	11.6 (5.6–17.9)	2.2 (0.0–5.0)	0.0 (-)
36 Months	14.2 (5.9–23.4)	70.2 (60.1–79.0)	13.4 (6.5–22.0)	2.2 (0.0–5.0)	0.0 (-)
HPV58 ($n = 109$)					
12 Months	56.5 (45.7–66.8)	30.8 (20.9–41.3)	9.7 (3.4–17.9)	2.1 (0.0–5.8)	0.9 (0.0–2.8)
24 Months	23.2 (11.7–35.5)	58.5 (46.1–71.2)	12.0 (5.0–20.9)	5.4 (0.0–12.9)	0.9 (0.0–2.8)
36 Months	12.6 (0.0–29.6)	69.1 (50.9–87.3)	12.0 (5.0–20.9)	5.4 (0.0–12.9)	0.9 (0.0–2.8)
HPV59 ($n = 172$)					
12 Months	39.2 (31.4–47.8)	55.9 (47.5–63.8)	4.3 (1.3–8.2)	0.6 (0.0–1.8)	0.0 (-)
24 Months	7.0 (2.3–12.5)	86.1 (78.6–92.3)	6.4 (2.3–11.7)	0.6 (0.0–1.8)	0.0 (-)
36 Months	0.1 (0.0–1.5)	91.1 (84.5–96.1)	6.4 (2.3–11.7)	2.4 (0.0–6.8)	0.0 (-)

NOTE: All values are given in % (95% CI).

[a]Persistent infection with the longest follow-up time was censored before 36 months (at month 34).

concurrent incident HPV16/18/31/33/35/45/52/58/59 infection may be found in Appendix Table 3A. Overall, 44.9% (61 of 136) of CIN1, 40.0% (20 of 50) of CIN2, and 63.6% (7 of 11) of CIN3 lesions tested positive for multiple HPV types. HPV types 16 (37.5%), 31 (29.5%), 51 (25.0%), 52 (22.7%), and 56 (25.0%) were each observed in 20% and more of the lesions testing positive for multiple HPV types ($n = 88$).

Across all incident HPV types examined, a small percentage was estimated to persist for greater than 36 months without either the detection of a CIN lesion testing positive for the relevant type or infection clearance, ranging from 0.1% for HPV59 to 14.2% for HPV52. Most infections eventually cleared, without detection of CIN, ranging at 12 months from 27.7% for HPV16 to 55.9% for HPV59, and at 36 months from 66.9% for HPV31 to 91.1% for HPV59. Differences in persistence and clearance rates observed between HPV types reported for the upper and lower ends of these ranges were statistically significant (i.e., $P < 0.05$).

At the upper end of observed risks, there was relatively little variation between HPV types 16, 18, and 31 (range 16.7%–18.6%) in the 36-month proportion of incident HPV infections followed by a CIN1 lesion testing positive for the relevant HPV type, with transition probabilities for HPV59 (6.4%) and HPV33 (2.9%) falling well below 10%. Although these differences attained statistical significance for CIN1, the number of events was generally too small for statistically significant differences to be observed between HPV types for transition probabilities to CIN2 or CIN3. Nonetheless, it is interesting to note that although incident HPV types 33 and 35 each occurred at a frequency of approximately one-fifth that of HPV16, the nominal transition probabilities observed for CIN2 and CIN3 were comparable to or more than those for HPV16.

Although these transition data reflect instances in which a CIN lesion was observed, which tested positive for the corresponding type observed in the incident infection, it is worth noting that there were many cases in which a CIN lesion was observed during the post-incident infection follow-up period that did not test positive for the given HPV type. Overall, there were fewer instances in which at least one subsequent CIN1 ($n = 205$) or CIN2/3 ($n = 83$) lesion was observed testing positive for the same HPV type as in the incident infection ($n = 1{,}183$), as compared with instances in which at least one CIN1 ($n = 406$) or CIN2/3 ($n = 104$) lesion was observed not testing positive for that incident infection type. For incident HPV16 infections ($n = 273$), the corresponding figures for positive lesions were $n = 57$ for CIN1 and $n = 29$ for CIN2/3, versus $n = 98$ for CIN1 and $n = 21$ for CIN2/3 for HPV16-negative lesions.

The estimated proportions of incident untreated type-specific CIN1 lesions transitioning to CIN2 or 3 testing positive for the relevant HPV type, clearing that HPV type, or persisting with the HPV type by 12 and 24 months following the date of detection of the CIN1 lesion are reported in Table 2. A complete listing of HPV types observed in incident CIN2 and 3 lesions testing positive for a concordant HPV type as observed in a previous incident HPV16/18/31/33/35/45/52/58/59-positive CIN1 lesion may be found in Appendix Table 3B. Overall, 37.5% (3 of 8) of CIN2 and 75.0% (3 of 4) of CIN3 lesions tested positive for multiple HPV types.

From among the incident CIN1 lesions testing positive for the HPV types reported in Table 2, nearly half (48.7%) had no evidence of HPV infection by PCR testing for the relevant type within 12 months. The number of cases was too small to permit differentiation in the probability of transitioning to CIN2 or CIN3 across HPV types. However, overall, 10.8% of incident CIN1 lesions transitioned to CIN2 positive for the relevant type within 12 months, with a relatively high proportion of HPV16 infected CIN1 lesions (18.7%) transitioning to CIN3 within 24 months. The 24-month transition risk to HPV16-positive CIN2/3 was observed to be higher following incident HPV16-positive CIN1 (46.2%) than incident HPV16 infection in the absence of CIN1 (7.6%; $P = 0.01$). Of all incident CIN1 lesions, 25.5% (39 of 153) were censored with persisting CIN1/HPV infection due to receipt of treatment.

There were 69 instances in which incident infection HPV types were observed within excisional treatment tissue specimens, for which at least one endocervical/ectocervical swab HPV typing result was available post-therapy (mean interval 4.4 months). Overall, 34.8% of women had persisting HPV infections of the same HPV type on their posttreatment cervical swab. Among women with HPV16- or HPV18-positive specimens ($n = 26$), the proportion persisting was 42.3%, as compared with 30.2% among women with HPV31/33/35/45/52/58/59-positive specimens ($n = 43$).

Discussion

To our knowledge, this is the first study to report transition probabilities for incident type-specific cervical HPV infections, and CIN1 lesions, for individual HPV types other than 6, 11, 16, or 18. Although in some natural history studies, HPV infection and CIN1 lesions are considered as indistinguishable, for health economic studies and other types of policy evaluations the actual diagnoses provided to women in clinical practice are generally preferred (whether highly reproducible or not), as they will determine quality of life and cost outcomes for the women. These data can be especially helpful for policy evaluations of future generations of HPV vaccines and the modeling of cross-type protection conferred by existing vaccines (8–10).

An important feature of the study was the ability to correlate HPV types observed in incident swab-detected infections with those detected in subsequent CIN lesion tissue specimens, when linking swab-detected infection and subsequent disease detection. This has very often not been possible in previous natural history studies of HPV infection and disease, and confirms previous findings that women are frequently infected

Table 2. Transition probabilities (12 and 24 months) for incident HPV16, 18, 31, 45, 52, and 58[a] infected CIN1 lesions following adjudication of CIN lesions positive for multiple HPV types

	Persisting as CIN1/HPV	Clearing HPV	CIN2	CIN3
HPV16 ($n = 38$)				
12 Months	42.9 (19.3–67.1)	34.9 (11.7–58.8)	11.5 (0.0–29.3)	10.7 (0.0–27.5)
24 Months	10.0 (0.0–43.9)	43.8 (18.2–70.2)	27.5 (0.0–61.0)	18.7 (0.0–43.5)
HPV18 ($n = 18$)				
12 Months	60.1 (32.4–85.7)	30.0 (6.3–55.0)	9.8 (0.0–33.7)	0.0 (-)
24 Months	NA[b]	NA[b]	NA[b]	NA[b]
HPV31 ($n = 28$)				
12 Months	17.1 (0.0–55.1)	67.4 (29.3–100.0)	15.4 (0.0–51.6)	0.0 (-)
24 Months	10.5 (0.0–49.4)	74.0 (33.4–100.0)	15.4 (0.0–51.6)	0.0 (-)
HPV45 ($n = 9$)				
12 Months	36.6 (0.0–76.2)	63.3 (23.8–100.0)	0.0 (-)	0.0 (-)
24 Months	NA[b]	NA[b]	NA[b]	NA[b]
HPV52 ($n = 22$)				
12 Months	26.3 (0.0–75.0)	50.1 (11.1–88.2)	23.5 (0.0–79.4)	0.0 (-)
24 Months	15.5 (0.0–70.0)	60.9 (14.3–100.0)	23.5 (0.0–79.4)	0.0 (-)
HPV58 ($n = 16$)				
12 Months	54.2 (15.8–86.7)	45.7 (12.9–83.8)	0.0 (-)	0.0 (-)
24 Months	NA[b]	NA[b]	NA[b]	NA[b]
HPV59 ($n = 13$)				
12 Months[c]	34.0 (0.0–87.5)	65.9 (12.5–100.0)	0.0 (-)	0.0 (-)
24 Months	NA[b]	NA[b]	NA[b]	NA[b]

NOTE: All values are given in % (95% CI).

[a]Data are not reported in the table for CIN1 lesions positive for HPV33 ($n = 3$) or HPV35 ($n = 5$) due to the small numbers of observations; however, none of these individuals were observed to transition to CIN2 or 3 lesions positive for these types within the available follow-up.

[b]Individual(s) with longest follow-up time(s) were censored before 24 months postincident CIN1.

[c]The longest available follow-up time for HPV59-positive CIN1 lesions was 11 months.

with a number of different HPV types simultaneously and sequentially (30, 31), and even for particularly virulent HPV types (e.g., HPV16) and endpoints of CIN2/3, there is often a lack of correspondence between the HPV types seen to contribute to a subsequent CIN lesion and that being evaluated as the preceding infection (7). Nevertheless, although HPV typing of tissue specimens can significantly enhance the ability to attribute CIN lesions to specific HPV types, current PCR-based methods do not fully resolve the issue of causality, as many lesions will still test positive for multiple HPV types (32). Thus, additional analytical methods, such as laser microdissection and *in situ* PCR or the adjudication approach described herein, are needed for more refined estimations of disease attribution.

Several conclusions may be drawn from the analysis results. First, nearly all incident HPV16/18/31/33/35/45/52/58/59 infections either manifested as detectable CIN lesions or went below the limit of PCR detection within 36 months. The fair proportion of all CIN lesions observed within the first 12 months following infection incidence suggests that a long period (e.g., >1 year) of infection persistence is often not required before CIN development. However, this is not necessarily inconsistent with the notion that CIN development is characterized by persistent HPV infection, given that infections may persist for some time following the initial point at which CIN is detected. Second, even with the relatively frequent cytologic screening schedule employed in this study (routine screening typically every 6 months, and coinciding with swab collection for HPV DNA detection and typing), most incident infections, including for particularly carcinogenic types such as HPV16, do not result in clinically detected CIN. Third, it appears that some incident HPV types (e.g., HPV16 and HPV31) might be more likely to result in clinically diagnosed CIN1 lesions than others (e.g., HPV33 and HPV59), independent of differences in the underlying frequency of incident infection. Fourth, for at least some HPV types (e.g., HPV16), transition risks to CIN2/3 may be greater following diagnosed CIN1, than following incident HPV infection in the absence of diagnosed CIN1. This could relate to a higher absolute risk of progression due to increased duration of previous infection at the time of CIN1

diagnosis, diagnostic misclassification of the CIN1 biopsy result, and/or relatively more intensive follow-up of diagnosed CIN1.

Fifth, the relative predominance of HPV16 infections, vis-à-vis some high-risk HPV types, as observed in meta-analyses of population-based studies of HPV prevalence in CIN2/3 lesions (5, 6), appears to be more directly associated with the relatively greater frequency of incident HPV16 infections within the population, than a higher risk of infection progression to CIN2/3. For instance, the risk of progression of incident HPV16 infections to CIN2/3 (applying the 36-month transition probability from incident infection and 24-month transition probability from incident CIN1 lesions) is estimated from this study to be 17.6%, as compared with 13.2% for HPV33. However, given that incident HPV33 infections were approximately one-fifth as common as HPV16 infections, it is not surprising that HPV33 has been observed in a relatively small proportion of prevalent CIN2/3 lesions. A recent study of HPV types in carcinoma *in situ*/adenocarcinoma *in situ* cases and population controls similarly found a relative risk for HPV16 analogous to that for HPV33 (33). On the contrary, for HPV52, the corresponding CIN2/3 progression risk was 5.3%, which appears, at least nominally, to be lower than for HPV16, although incident HPV52 infection was observed in excess of three-fifth of the frequency of HPV16. It has recently been postulated that an observed relative predominance of HPV16, vis-à-vis other carcinogenic HPV types, among CIN2-positive lesions in younger versus older women, is the result of a stronger carcinogenicity for HPV16 (34). An alternative explanation is that at older ages the proportion of women at risk for less common HPV types is much larger than for HPV16 (for which many more women have already been infected, cleared, and become immune), and that this explains, at least in part, the distributional shift.

Sixth, as observed in a number of previous studies, persistence of HPV infection following excisional treatment for CIN is not uncommon (35–37). The actual degree to which excisional treatment eliminates the presence of active HPV infection is unknown. However, it does appear likely that there is some disruptive impact. For instance, in this study, 42% of HPV16/18 infections continued to persist at an average of 4 months posttreatment, as compared with 65% to 70% of these infections within 12 months following diagnosis of an HPV16/18-positive CIN1 lesion. Because most treated cases in the analysis reflected lesions of greater severity than CIN1, the actual persistence of these infections in the absence of treatment could well be even greater.

Our analysis has several limitations. First, although routine cytologic screening was conducted at frequent intervals (typically every 6 months), colposcopy was not done on a routine basis throughout the trial as has been done in some previous studies of the natural history of incident HPV infection (38, 39) and, as a result, some CIN lesions may have been missed. Neither of these tests, nor HPV testing, has perfect sensitivity/specificity. Second, swab HPV testing results were not available for types beyond HPV6/11/16/18/31/33/35/39/45/51/52/56/58/59. Although these reflect the vast majority of HPV types observed in cervical cancers and CIN2/3 lesions (5, 6, 40), it is possible, particularly for CIN1 cases, that other nontyped HPV infections contributed to lesion development, which could have resulted in some missed coinfections within this analysis. Third, although a statistical adjudication method was used, which may serve as a reasonable proxy for HPV type-specific attribution when multiple types are observed in a single CIN lesion tissue specimen, it is not an exact method for identifying which HPV type or types are responsible for a given lesion. For instance, it is possible that an apparent multitype infection could represent single infections in adjacent lesions (of the same grade, e.g., CIN2). However, a previous analysis of vulvar and vaginal lesions using *in situ* hybridization techniques found that multitype infections did not represent contiguous lesions, but rather single lesions with multiple HPV types within which a single type was pathogenic (28). The method also did not adjust for duration of previously detected infection. Fourth, the exact timing when infection occurs or goes below detectable limits is unknown. In this analysis, we assumed that these events occurred at the midpoint between observed data points. Fifth, as has generally been the case in other natural history studies, we could not be fully certain that CIN lesions positive for a given HPV type that were observed at different time points represented the same lesion (e.g., in the analyses of CIN1 natural history), and this was an assumption of the analysis. Sixth, infections were analyzed by individual type and we did not evaluate the influence of coinfection on natural history. Finally, the natural course of HPV infections may differ from that described in this article in subpopulations that are substantially different in their characteristics (e.g., HIV-infected women, organ transplant recipients), may be modified by other factors not analyzed here (e.g., smoking, oral contraceptive use, coinfection), and our study population was limited to young women (41).

Although a relatively large number of studies have been conducted describing the distribution of HPV types in prevalent CIN lesions (4, 5), relatively few data have previously been available on the course of incident type-specific HPV infections in the development of CIN lesions. This analysis has documented some variation in the frequencies and transition probabilities for different incident high-risk HPV types. However, much remains unknown with respect to these HPV types, including the potential for differences in the risk of transmission between infected partners, the likelihood of persistence, progression, and clearance of incident CIN2 and CIN3 lesions associated with each type and degree/duration of naturally acquired immunity following infection.

Disclosure of Conflicts of Interest

G. Perez has received lecture fees and consultancy fees from Merck and Co., Inc. and Sanofi Pasteur MSD, and is now an employee of the sponsor, Merck and Co., Inc. C.M. Wheeler has received funding through her institution for reagents and equipment for Roche Molecular Systems in support of HPV genotyping studies and to conduct HPV vaccine studies for GlaxoSmithKline. D.G. Ferris has received consultancy, lecture, and advisory board fees from Merck and Co., Inc. and has received funding through his institution to conduct HPV studies for GlaxoSmithKline. S.M. Garland has received advisory board fees and grant support from Commonwealth Serum Laboratories and GlaxoSmithKline, lecture fees from Merck and Co., Inc., and research funds through her institution to conduct HPV vaccine studies for GlaxoSmithKline. S.M. Garland is a member of the Merck Global Advisory Board and the Merck Scientific Advisory Committee for HPV. S. Leodolter has received lecture fees from Merck and Sanofi Pasteur MSD. E.A. Joura has received advisory board fees from Merck and Sanofi Pasteur MSD, and has received funding through his institution to conduct epidemiological HPV studies for GlaxoSmithKline, and has received lecture fees from Merck and Co., Inc., Sanofi Pasteur MSD, and GlaxoSmithKline. D.R. Brown has received lecture fees, advisory board fees, and intellectual property fees from Merck and Co., Inc. M. Steben has received lecture fees and grant support from Merck and Co., Inc. M. Hernandez-Avila has received lecture fees and grant support from Merck and Co., Inc. J. Paavonen has received consultancy fees, advisory board fees, and lecture fees from Merck and Co., Inc. In addition, M. Hernandez-Avila, G. Perez, C.M. Wheeler, D.G. Ferris, L.A. Koutsky, S.M. Garland, S. Leodolter, E.A. Joura, M. Steben, D.R. Brown, and J. Paavonen have received funding through their institutions to conduct HPV vaccine studies for Merck. R.P. Insinga, E. Elbasha, and R.M. Haupt are employees of Merck and potentially own stock and/or stock options in the company. N. Munoz has received lecture fees and advisory board fees from Merck and Co., Inc. and Sanofi-Pasteur MSD.

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Ralph P. Insinga, Gonzalo Perez, Cosette M. Wheeler, et al.

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