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PATTERNS OF PERSISTENT GENITAL HUMAN PAPILLOMAVIRUS INFECTION AMONG WOMEN WORLDWIDE: A LITERATURE REVIEW AND META-ANALYSIS

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Abstract

Persistent high-risk human papillomavirus (HR-HPV) infection is the strongest risk factor for high-grade cervical precancer. We performed a systematic review and meta-analysis of HPV persistence patterns worldwide. Medline and ISI Web of Science were searched through January 1, 2010 for articles estimating HPV persistence or duration of detection. Descriptive and meta-regression techniques were used to summarize variability and the influence of study definitions and characteristics on duration and persistence of cervical HPV infections in women. Among 86 studies providing data on over 100,000 women, 73% defined persistence as HPV positivity at a minimum of two time points. Persistence varied notably across studies and was largely mediated

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by study region and HPV type, with HPV-16, 31, 33 and 52 being most persistent. Weighted median duration of any-HPV detection was 9.8 months. HR-HPV (9.3 months) persisted longer than low-risk HPV (8.4 months), and HPV-16 (12.4 months) persisted longer than HPV-18 (9.8 months). Among populations of HPV positive women with normal cytology, the median duration of any-HPV detection was 11.5 and HR-HPV detection was10.9 months. In conclusion, we estimated that approximately half of HPV infections persist past 6–12 months. Repeat HPV testing at 12 month intervals could identify women at increased risk of high-grade cervical precancer due to persistent HPV infections.

Keywords

human papillomavirus; HPV; duration; persistence; clearance; natural history; repeat testing; literature review; screening; cervical cancer; meta-analysis

INTRODUCTION

Infection with high-risk human papillomavirus (HR-HPV) genotypes is considered necessary for the development of invasive cervical cancer (ICC)[1–4]. Despite the high prevalence of HR-HPV infections among women, the incidence of ICC is comparatively low, which highlights the importance of factors that may mediate progression to invasive cancer. Persistent HR-HPV infection has been consistently and strongly associated with cervical intraepithelial neoplasia (CIN) of grades 2 and 3[5] and is considered essential for the progression of cervical precancer to ICC[6]. The higher sensitivity of HPV testing but lower specificity, as compared with cytology for the detection of CIN2–3[7–9], suggest that co-testing with cytology and HPV could enhance accuracy in identifying women at high risk of cervical precancer and cancer[5, 10]. Recent ASC/ASCCP/ASCP guidelines for cervical cancer screening in women older than 30 years recommend that one option for women with normal cytology and a positive HPV testing is rescreening in one year with Pap smear and HPV co-testing[11]. Implementation of repeat HPV testing in screening requires a clinically relevant definition of HPV persistence and a better understanding of HPV persistence duration.

There has been wide variation in definitions of HPV persistence used in the literature. Given that aspects of the definition of persistence, such as the frequency and length of testing intervals, may affect the estimated risk of cervical precancer associated with HPV persistence[5], persistence and duration of HPV should be better understood to operationalize inclusion of repeat testing into future cervical cancer screening programs and for use as an endpoint in HPV vaccine trials and efficacy modeling. To date, there is no summary of the literature that examines definitions and estimates of HPV persistence across studies. Thus, we performed a systematic review and meta-analysis to determine the influence of HPV persistence definitions and study characteristics on estimated duration of HPV infection and proportion of women with persistently detectable HPV DNA over time.

METHODS

Eligibility and data abstraction

Studies published through January 1, 2010 were identified by searching ISI Web of Science, MEDLINE via PubMed, and the reference lists from eligible articles and relevant review articles, with no language restrictions. Only original peer-reviewed journal articles were included. Broad search term categories included HPV (e.g. HPV, human papillomavirus) and persistence (e.g. persistence, clearance, duration) (see online supplement for full set of terms).

To be included in this review, eligible articles had to present one or more measures of HPV persistence over time, regardless of study design. The overall prevalence of cervical abnormalities, as measured and defined by each study (generally atypical squamous cells of undetermined significance (ASCUS) or greater), at baseline in the study population had to be less than 15% to approximately reflect the characteristics of populations of average risk[12]. However, population-based studies that did not explicitly state the prevalence of cervical abnormalities were included. Only human immunodeficiency virus (HIV) negative study populations were included; articles that did not state HIV serostatus were assumed to be HIV negative and were included. Studies that tested for cervical or cervicovaginal HPV infections using polymerase chain reaction (PCR) or Hybrid Capture (HC; QIAGEN Gaithersburg, Inc.) DNA detection methods were included. We excluded serology-, male- and low-risk HPV (LR-HPV)-only studies, post-treatment studies, studies with less than three months of total study follow-up, and studies that included only buccal, nasopharyngeal, anal, vulvar or labial specimens. All search results were independently reviewed to ensure that no pertinent articles were omitted.

Abstracted persistence data included (i) proportion of HPV-positive (incident or prevalent) women with persistent infections and the standard error or confidence interval, (ii) median and/or mean duration of HPV infection, and (iii) HPV persistence estimates extracted from Kaplan-Meier survival curves. Variables used to define persistence were abstracted, which included HPV testing interval, number of HPV positive tests, minimum duration of HPV infection to be considered persistent, whether persistence was based on detection of the same HPV type at visit ‘v’ and ‘v+1’ (type-specific persistence) or detection of any HPV type at consecutive visits (non-type-specific), and HPV type (e.g., HPV-16) or HPV grouping (e.g., HR-HPV positivity)). Data were abstracted on population characteristics and study methods, including geographical region, study design, sample size, population and HPV detection method. All data were independently double-abstracted to ensure accuracy. Study authors were contacted if clarification of published information on HPV persistence was needed.

Selection of Persistence Estimates

Many articles that met the inclusion criteria were based on the same study population (28 articles from 11 populations). To maintain the independence of study results, the article from a given study population was chosen that used the most sensitive detection method (e.g., PGMY09/11 over MY09/11, GP5+/6+ over GP5/6)[13–15]. If HPV methods were similar, we chose the article with more women in the persistence analysis, or the most recent, if study sample sizes did not vary. If multiple articles from the same study population could contribute to separate analyses (e.g., persistence by baseline HPV status and persistence by HPV type), all relevant articles were included.

Most articles (n=57) presented multiple estimates for the proportion persistent or median duration of infection. A set of decision rules was applied to select one result for each meta-regression or meta-regression stratum: (i) choose the HR-group result first, then any-HPV, then single HR-HPV types based on worldwide HPV prevalence in ICC[16]: 16, 18, 33, 45, 31, 58, 52, 35; (ii) choose the type-specific result over the non-type-specific result; (iii) choose the result with the greatest number of visits used to define persistence unless substantially fewer (30%) women were tested at that visit; (iv) choose the result with mixed incident and prevalent HPV infections first, then incident, then prevalent; (v) if results are presented by age categories, choose the overall estimate first, then choose youngest to oldest; (vi) if results are presented by HPV type variants, choose the estimate for all variants combined or else the largest sample size; (vii) if results are presented by cytology method (e.g. thin-prep, conventional), choose the overall estimate, then the largest sample size.

Descriptive analyses

The number and proportion of persistence estimates were calculated for each category of a given study characteristic. If an article reported multiple results that fell into different categories of study characteristics, the article was included in all relevant categories so results could add to more than 100%. The median duration of HPV infection could not be formally analyzed by meta-regression because most studies did not provide a measure of random error. Instead, estimates of median HPV duration were graphed on a forest plot for HPV groups and HPV types with at least three estimates of median duration. The pooled duration for each HPV group and type was then calculated as the average, weighted by the number of women that were included in each result. Plotting symbols were sized in proportion to the number of women included in the calculation of median duration for each study. Articles that presented Kaplan-Meier curves or reported the proportion persistent at two or more time points were included in a figure to examine patterns of HPV persistence within and across HPV groups. To examine the effect of age on HPV persistence within study populations, any-HPV or else HR-HPV estimates were plotted by age. The mid-range of each reported age category was used to plot persistence, where grayscale symbols indicates the category of the reported mid-point. All figures were created using R version 2.10.1.

Statistical analyses

The proportion persistent was calculated in different ways in the literature: using either women or infections as the unit of analysis, and including all women or only women with infections in the denominator. To standardize the persistence results for inclusion in the same analyses, the total number of women with an HPV infection at baseline (prevalent persistence) and the total number of women who acquired an incident infection (incident persistence) was used as the denominator to calculate the proportion persistent. If both prevalent and incident infections were included in the persistence estimate, both were included in the denominator. If a persistence result was stratified or limited to a subset of the sample (e.g., women with a given HPV type), the number of women with an infection in that particular stratum was used as the denominator. For studies that did not report a standard error for the proportion persistent, it was calculated as the square root of $(p*(1-p))/n$, where p was the observed proportion persistent and n was the sample size. In cases where the proportion persistent was 0% or 100% and the standard error was undefined, the following adjustment[17] was made to calculate the standard error: the overall meta-regression model was first fitted without study characteristics using all studies with defined standard errors. Based on the summary estimate of 40% persistence at 6 months, the undefined standard errors were then estimated by adding 0.4 to the number of women who persisted and 0.6 to the number of women who did not persist (i.e. +0.4/+0.6 adjustment). If the standard error was not reported and could not be calculated, the result was not included in meta-regression analyses.

Random-effects meta-regression and stratification was used to formally compare differences in proportion persistent estimates across study characteristic categories (i.e., difference between estimates in each category compared to a common referent), with the among-study variance estimated by restricted maximum likelihood[18]. Stratified summary estimates allowed descriptive comparisons across individual categories of study characteristics (i.e., summary estimates and 95% confidence intervals for each category). Variation between estimates was evaluated by comparing Cochran's Q two-sided *P-value* with a 0.1 significance level[19]. The mean length of the testing interval multiplied by the number of HPV testing intervals used to define persistence was included in models, centered at 6 months, as a means to control for the time over which persistence was measured. If the mean testing interval was not reported, the interval specified in the study protocol or the minimum

time required to meet the authors' definition of persistence was used. For these analyses, at least three study estimates in each stratum were required. Studies were allowed to contribute to more than one category to reduce the influence of the decision rules on the distribution of study and population characteristics. When multiple results from the same study population were included an indicator variable for that study population was included in the model to account for the lack of independence. Methods and results for sensitivity analyses on adjustment method and choosing rules are presented in an online supplement. Meta-regression analysis was conducted in STATA version 11 (StataCorp, College Station, TX).

RESULTS

Descriptive results

Eligible studies—Of the 4,203 abstracts identified, 86 studies met the study inclusion criteria and reported non-duplicate results. These studies provided estimates of HPV persistence on over 100,000 women. Most studies were conducted in Europe (40%) and North America (29%), with few from each of the other world regions (Central or South America (20%), Asia (5%), Africa (3%) and Australia (1%)) (Table 1). Over half of the results were among women with an average age of 30 years or older, although average age was not reported in 14% of studies. Most studies (65%) were of populations where 100% of women had normal cytology at baseline and were screening-based cohort studies that employed PCR-based detection methods. MY09/11 alone or MY09/11 in combination with other methods was the most frequently used HPV laboratory detection protocol (43%).

Definitions and characteristics of HPV persistence—HPV persistence was most commonly defined as two or more HPV DNA positive time points (73%; Table 1), whereas other definitions included a minimum of three positive tests, infection duration, and persistent pairs (positive at any pair of visits, v and v+1). Consecutive HPV positive visits were generally required for HPV persistence, but intervening HPV DNA negative visits were allowed in 12 (14%) of the studies[20–27]. Minimum duration of HPV persistence, defined as the shortest time period of HPV positivity for a woman to be considered persistent, was 6 to <12 months for most studies (41%). The median time between HPV tests (i.e. the testing interval) was 6 months, although there was a wide range of testing intervals, from 1.3[28] to 117.6[29] months. Most studies reported type-specific HPV persistence (72%) and persistence among HPV infections that were prevalent at baseline (70%).

Median duration of HPV persistence—Including all estimates (N=119), regardless of HPV type or group, the average median duration of any-HPV was 9.8 months (Figure 1). There were 15 independent study results for estimation of median duration of any-HPV, which had the widest range estimated median durations, from 6.0 to 24.0 months. Weighted average median duration for any-HPV infection was 9.8 months. HR-HPV (n=15) had a slightly longer median duration at 9.3 months (range: 6.0–14.8) compared to LR-HPV (n=11) at 8.4 months (range: 4.3–13.3). Among the individual HPV-types, median duration was longest for HPV-31, with a weighted average of 14.4 months, followed by HPV-33 at 12.5 months, and HPV-16 at 12.4 months. Median duration of detection of all other high-risk HPV types ranged from 6.0 to 11.7 months. The median durations of any-HPV and HR-HPV from populations of women with 100% normal cytology at baseline were 11.5 and 10.9 months, respectively.

Time-specific HPV persistence—Forty-seven articles reported at least one estimate of HPV persistence at a standard 6 month interval for any-HPV (n=20), HR-HPV (n=22), LR-HPV (n=7), HPV-16 (n=16) (Figure 2). The thick gray curve in each panel represents the weighted summary of all study estimates across time. The curves for any-HPV and LR-HPV

were similar, with a rapid decrease in persistence within 6 months, followed by a slow decline through 36 months. There was a relatively slower, more uniform decrease in HR-HPV and HPV-16 persistence over time. Between studies, the variability in estimates differed by HPV type and by time. At 6 months, estimates of the proportion persistent ranged from 16–88% for any-HPV, 18–90% for HR-HPV, and 50–100% for HPV-16. At 12 months, the proportion persistent ranged from 10–68% for any-HPV, 24–63% for HR-HPV, and 0–97% for HPV-16.

Age-specific HPV persistence—Articles that presented estimates of persistence stratified by age were limited (n=14) (Figure 3). Estimates of any-HPV by age were most common (n=8), followed by HR-HPV estimates (n=5). Three of the HPV persistence results were based on incident infections[30–32]. There was no distinguishable trend of HPV persistence by age. The study with the shortest persistence follow-up (3 months)[33] found that women aged <25 years were more likely to persist compared to all older age groups. Three other studies found a similar trend: older women had lower persistence compared to younger women[34–36]. However, the study with the longest persistence follow-up (67 months)[37] found the opposite result: younger women had a lower proportion of persistent infections compared to older women, as did four other studies[30, 38–40].

Analytic results

Evaluation of study characteristics and persistence definitions—Of the 86 included articles, 4 did not report proportion persistent results (these estimated median duration of infection in Figure 1), thus the number of estimates included in each meta-regression could be more or less than 82 depending on whether estimates from the same study population entered into different study characteristic strata. After applying the inclusion and selection rules, 68 independent estimates produced a summary estimate for persistence at 6 month of 39% (95% confidence interval (CI): 34%, 45%).

The *p-value* for Cochran's Q statistic was less than 0.01 for all meta-analyses, indicating a large amount of variation among the proportion persistent estimates included in each meta-regression. Given the relatively small number of studies in each meta-regression stratum and the inclusion of several variables in each model, most meta-regression coefficient estimates were imprecise, as indicated by relatively wide confidence intervals. Compared to Europe, which had the highest proportion persistence at 6 months (49%; 95% CI: 40%, 57%), HPV persistence at 6 months was significantly lower among studies from North America (40%; 95% CI: 31%, 48%) and from Central and South America (28%; 95% CI: 8%, 48%) (Table 2). There was a slight difference in persistence between younger (<30) and older women (≥30) at 40% (95% CI: 32%, 48%) and 48% (95% CI: 41%, 535), respectively. HPV persistence was highest among the few studies that used pU1M/pU2M, L1C1/L1C2, GP5/6 or other L1 primers (56%; 95% CI: 40%, 72%) and Hybrid Capture 1/2 (46%; 95% CI: 36%, 55%).

In comparison to the summary estimate for any-HPV persistence at 6 months (43%; 95% CI: 37%, 48%), HR-HPV persistence was nearly identical (0.5%; 95% CI: −7%, 8%), whereas LR-HPV persistence was lower (−10%; 95% CI: −20%, – 0.1%). HPV-16 (54%; 95% CI: 48%, 60%), HPV-18 (48%; 95% CI: 40%, 56%) and HPV-33 (47%; 95% CI: 35%, 59%) had the highest proportion persistent. HPV-51 (30%; 95% CI: 19%, 42%) and HPV-66 (29%; 95% CI: 16%, 43%) had the lowest proportion of persistent infections at 6 months. Consistent with the trend observed in Figure 1, HPV-16 persistence (54%; 95% CI: 48%, 60%) was slightly higher than HPV-18 (48%; 95% CI: 40%, 56%).

There was a slight difference in the proportion HPV persistent when persistence was defined by a minimum of two time points (43%; 95% CI: 37%, 49%) compared to a minimum of

three time points (50%; 95% CI: 36%, 63%). There was also a slight increase in the proportion HPV persistent as the minimum duration of infection required to be considered persistent increased from 6 months or less (44%; 95% CI: 35%, 53%) compared to 12 months or more (52%95% CI: 41%, 62%). There was little difference between the summary estimates for HPV type-specificity: non-type-specific persistence was 44% (95% CI: 36%, 51%) and type-specific persistence was 43% (95% CI: 36%, 50%). Similarly, there was little difference in estimates of persistence by baseline HPV status: 45% (95% CI: 33%, 57%) for incident infections and 43% (95% CI: 36%, 49%) for infections that were prevalent at baseline.

DISCUSSION

This systematic literature review and meta-analysis of HPV persistence combined data on over 100,000 women from 86 studies to examine study characteristics that might affect the duration and likelihood of persistent HPV infection. We found that the median duration of HPV detection was slightly less than one year overall and among women with normal cytology. Given these findings, repeat HPV testing after one year follow-up is expected to have substantial utility for cervical cancer screening. Although most studies were similar in that they defined HPV persistence as HPV positivity at two or more time points (73%), not all required the same HPV type to be detected at consecutive visits (42% non-type-specific persistence). The proportion persistent at 6 months varied across studies and the heterogeneity in the estimates was largely a function of HPV type. The most persistent types were HPV-16, 31, 33 and 52 in the analysis of median duration, which were notably higher than the least persistent types HPV-35, 51, 66 and 68.

The median duration of any-HPV detection was approximately 10 months, whereas the duration of HR-HPV detection was slightly shorter, and that of LR-HPV infections even shorter. This pattern was consistent with the results from the meta-regression of HPV type. Previous reports comparing the duration of HPV-16 infection and HPV-18 infection have been inconsistent[41–44], which is confirmed by the variability in our results. Assuming that heterogeneous results can be combined, the estimated average median duration of HPV-16 detection in this systematic review was 12.4 months, compared to 9.8 months for HPV-18. Meta-regression revealed a similar pattern, where the proportion persistent for HPV-18 was 9% less than that for HPV-16 at 6 months. Among alpha-9 (genotypes (HPV-16, 31, 33, 35, 52, 58)[45], HPV-16, 31, 33 and 52 were the most persistent. Among alpha-7 genotypes (HPV-18, 39, 45, 59, 68, 70)[45], HPV-18, 39, 45, and 59 were the most persistent. Given the biological importance of persistent HPV infections in HPV-related invasive cervical cancer, the relatively longer persistence for HPV-31, 33 and HPV-52 infections supports their inclusion in next generation prophylactic HPV vaccines.

Although the observed patterns of HPV persistence were generally similar between the analyses of median duration and the proportion persistent, discrepancies in the absolute values were noted. For example, we found that the median duration of HR-HPV persistence, the time at which 50% of women had persistently detectable HR-HPV infections, was on average 9.8 months (N=15), whereas meta-regression indicated that 38% persisted at 6 months (N=41). The studies included in the two analyses differed; however, such discrepancies may also result from a potential underestimation of the proportion persistent in meta-regression analysis. The variable we used in meta-regression to control for the time at which persistence was measured corresponded to the interval between two study visits, unless the mean or median time at which persistence was measured was reported, because persistence is most commonly defined as two or more HPV positive visits. However, based on this common definition of HPV persistence, a woman could actually have had more than 2 positive visits, leading to a potential underestimation of how long her HPV infection

actually persisted. This would have affected estimates of the proportion persistent but not estimates of median duration, which would take into account the exact number of HPV positive study visits for each women over study follow-up. Also, an important point regarding testing intervals is that if future studies aim to estimate persistence with the highest degree of accuracy, for example down to the month, it would require sample collection at a minimum of weekly intervals, whereas the current literature tests, on average, every 6 months. Length of testing interval might also explain our observation of a higher proportion of women with persistently detectable HPV infections in studies with intervals of 12 months or more as compared to 6 months or less; more frequent testing internals would be expected to detect transient infections that may have been missed by testing with longer intervals. Furthermore, we found that most studies did not take into account in the definitions of persistence or clearance the potential for HPV latency[46], and thus did not permit the differentiation between true biological persistence and persistence as measured by detectable HPV DNA at the mucosal surface.

Given the limited data available for specific age groups, it is difficult to make definitive conclusions about the relation between age and HPV persistence. Although no distinct trend by age was observed across studies that presented age-stratified estimates, the proportion of women with persistently detectable HPV infections was slightly higher in meta-regression analysis among study populations with a mean age of 30 years and older compared to those with a mean age under 30. These data reflect the inconsistent results reported in the literature and suggest that the complex relationship between age and persistence is likely mediated by additional factors such as incident/prevalent infection status, study design, differences in immune response, and population-level characteristics such as number and type of recent and lifetime sexual partners. Recently, a large study found prevalent HPV infections were slower to “clear” (i.e., become non-detectable) in older compared to younger women, but no difference in persistence of incidence infections was reported by age[47]. Our descriptive figure was predominately comprised of prevalent HPV infections; thus, we were unable to reliably compare persistence of prevalent versus incident infections by age. In addition, although meta-regression did not identify differences between the proportion of incident and prevalent infections that remained persistent, it is important to note that the interpretation of these estimates are different. Prevalent infections are left-censored so true persistence is likely greater than measured persistence, whereas persistence of incident infections is estimated beginning from the first detection during the study.

HPV persistence within strata of individual study characteristics showed notable heterogeneity, potential evidence that the use of broad or heterogeneous categories may mask important associations between study variables. This complexity is not unexpected given that persistence estimates within a stratum may differ by several other characteristics including study region, HPV type, testing interval, or detection method. For example, each HPV detection assay has different sensitivities for the detection of individual HPV types, especially if multiple HPV types are present[48, 49]. In addition, previous studies suggest that most women with persistent HPV infections actually have type-specific infections even if non-type-specific persistence was measured[50], which may explain why we observed no difference between type-specific and non-type-specific HPV persistence. Although it is likely that the relation between such study characteristics and HPV persistence are multi-factorial, data were too sparse to examine several study characteristics simultaneously. Future reviews could consider obtaining individual-level study data for a pooled analysis approach.

This meta-analysis systematically described the patterns and characteristics associated with the persistence and duration of HPV infections in published studies. Our results confirm individual study findings that specific HPV types, particularly HPV-16, are more likely to

produce persistent infections with a longer duration of detection than other HR-HPV types. Repeat and possibly type-specific HPV testing would increase specificity over a one-time HPV test, thus improving clinical detection of cervical high-grade precancer by providing a higher sensitivity and similar specificity as compared to cytologic screening[5]. Current ASC/ASCCP/ASCP guidelines recommend a one-year repeat screening interval for women over 30 years who are HPV-positive with normal cytology. These guidelines are consistent with our systematic review, which indicates that the median duration of HPV detection was less than one year among women with normal cytology for both any-HPV and high-risk type infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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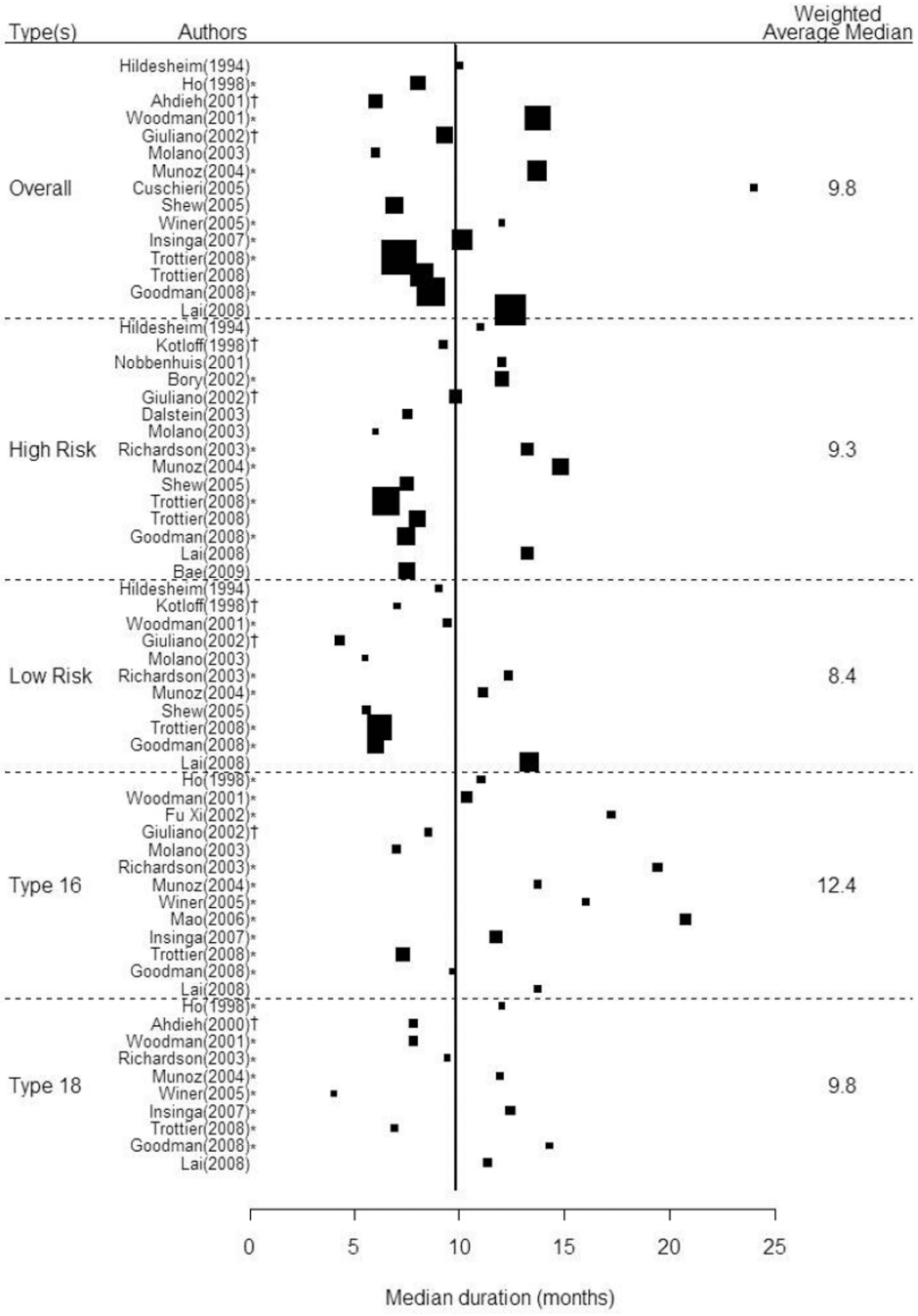
Impact statement

HPV persistence varied notably across studies and was largely mediated by study region, detection method, and HPV type. We estimated that approximately half of HPV infections persist past 6–12 months. Weighted median duration of any-HPV detection was 9.8 months and HR-HPV was 9.3 months. Repeat HPV testing at 12 month intervals could identify women at increased risk of high-grade cervical precancer due to persistent HPV infections.



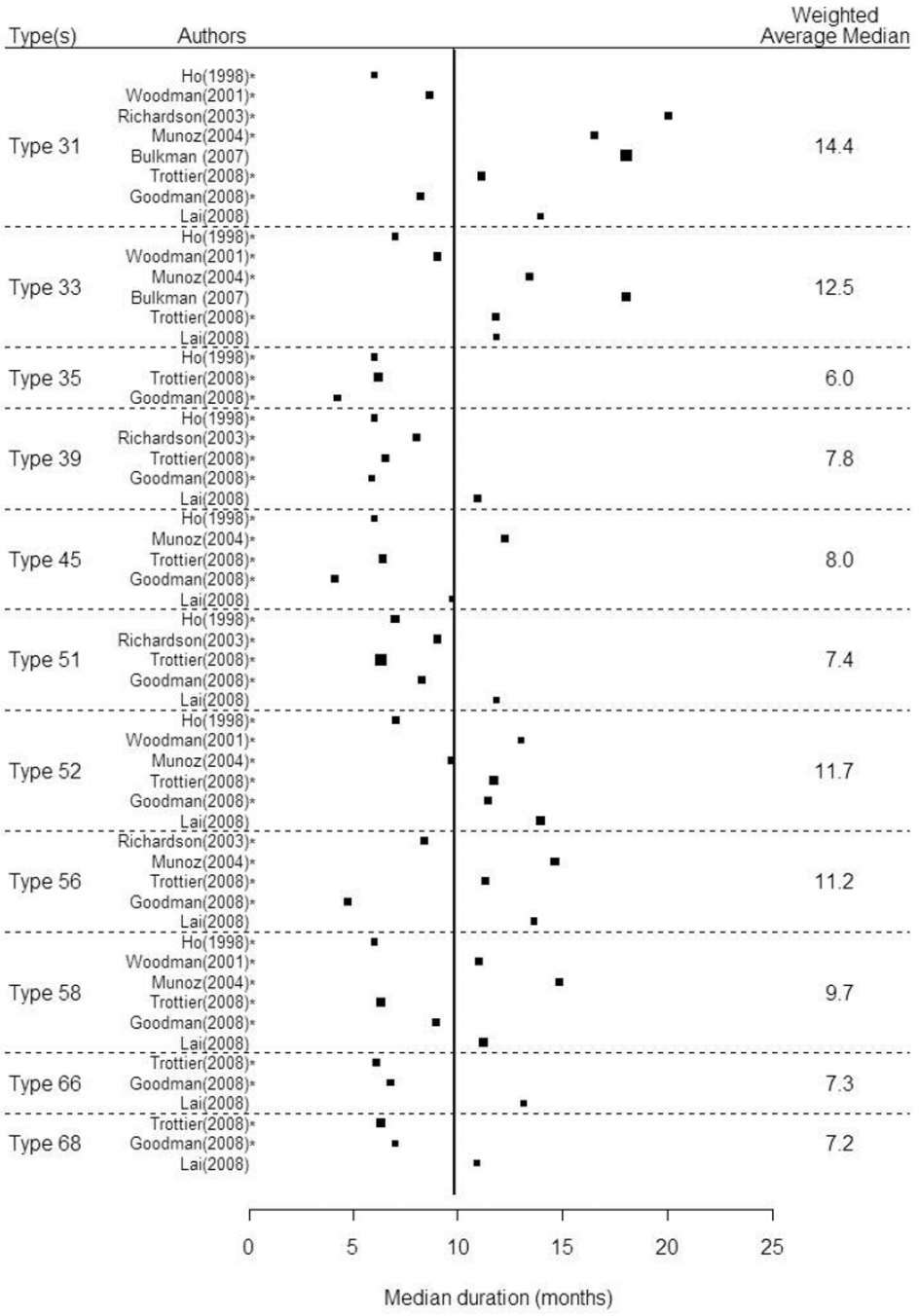
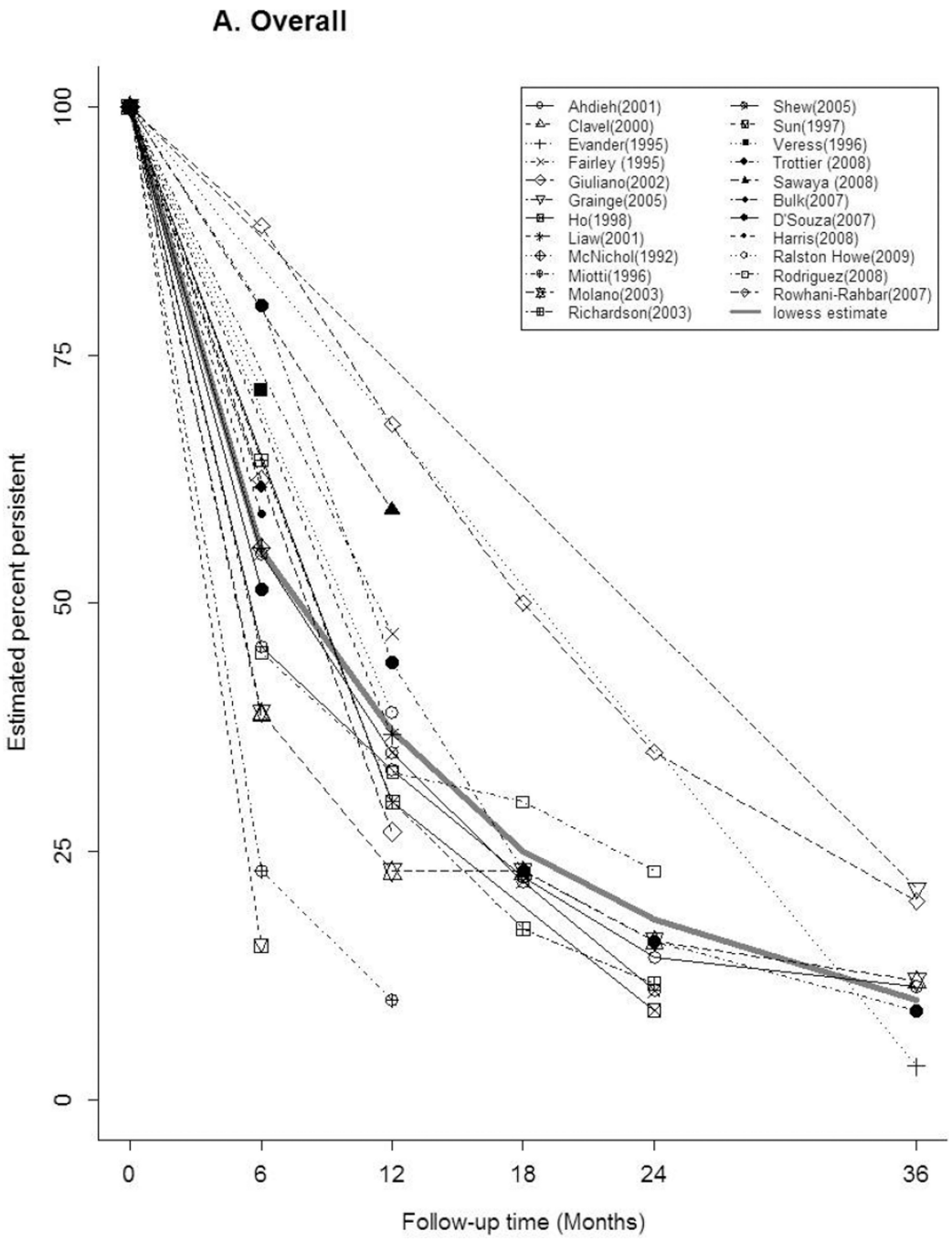
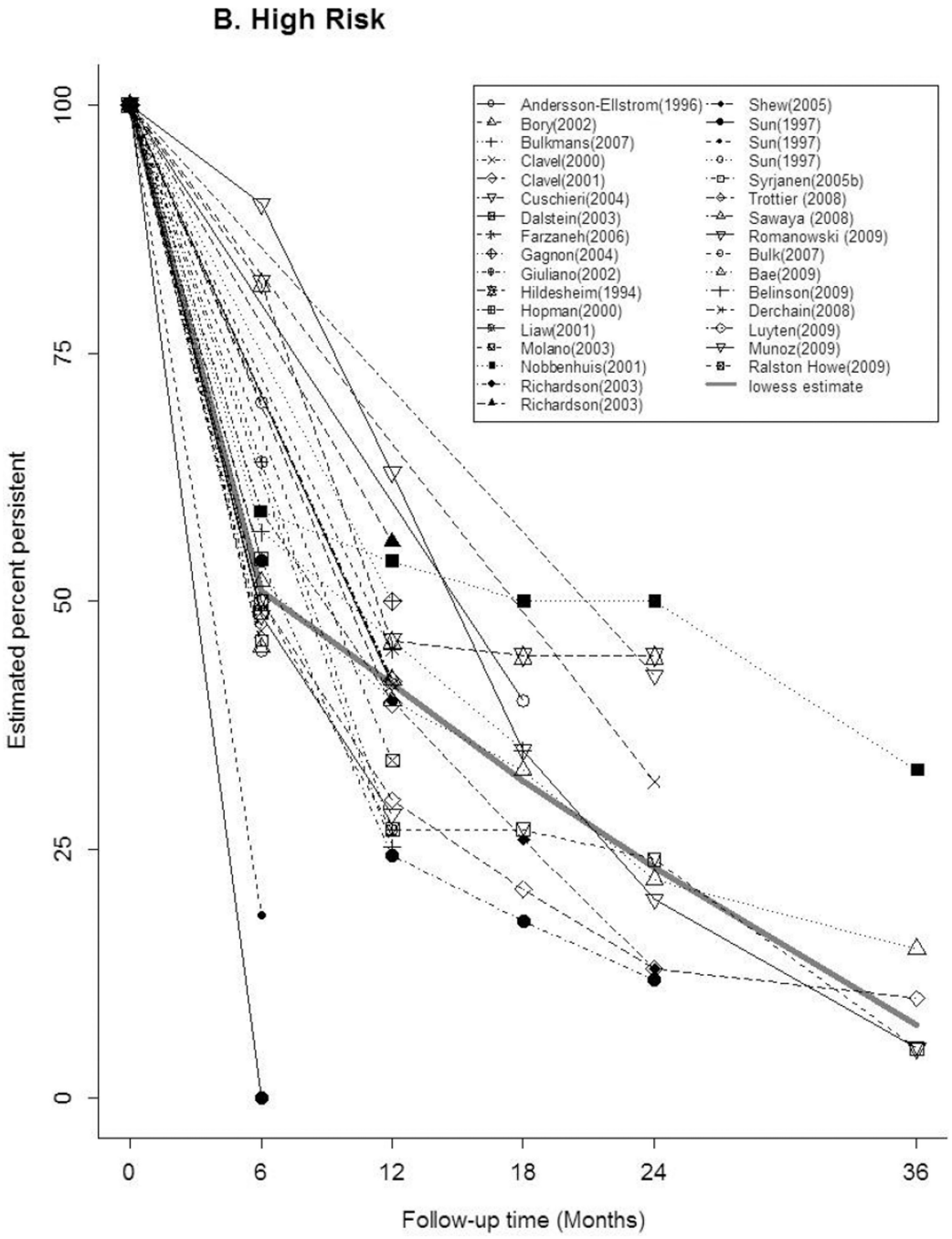
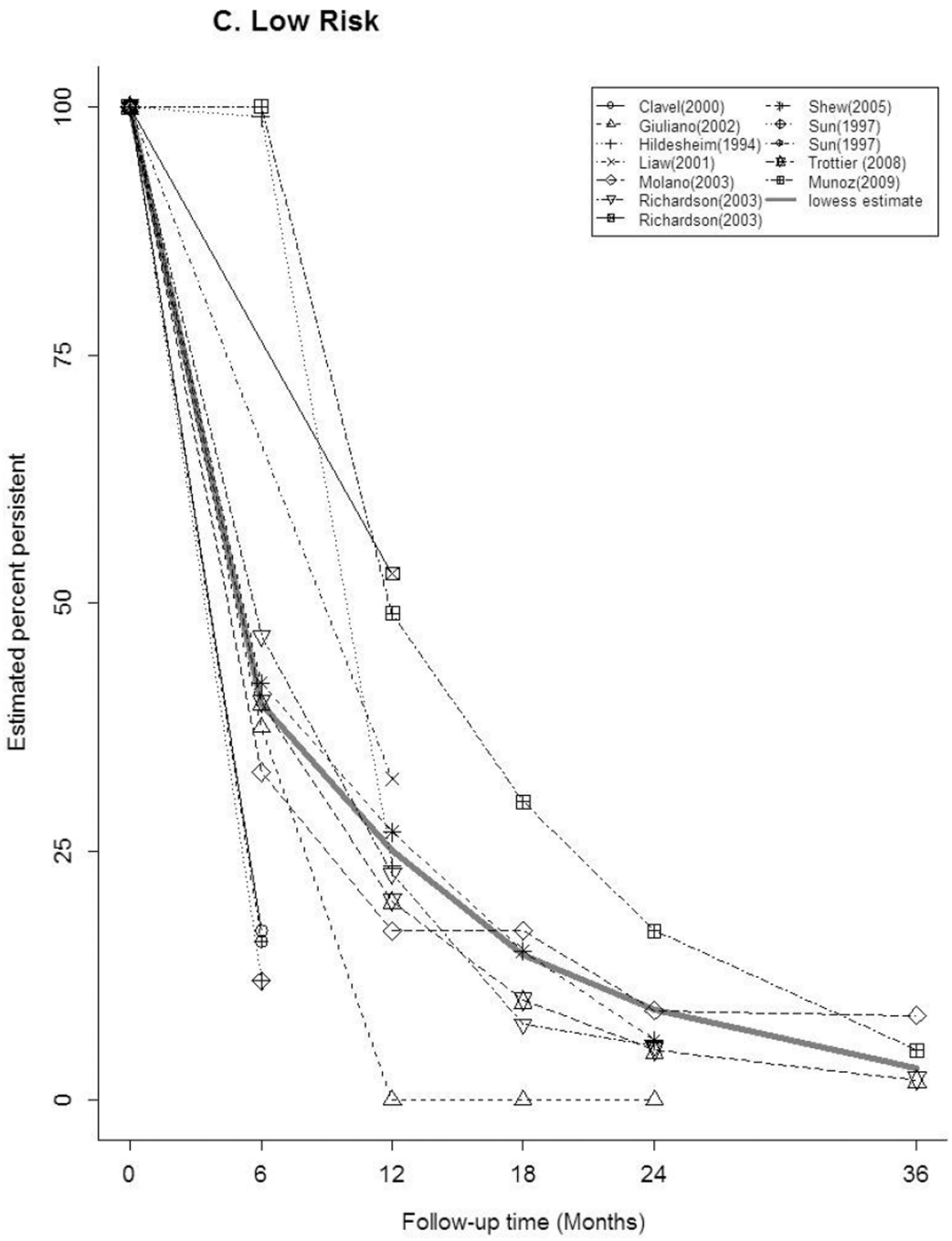


Figure 1.

Forest Plots of the Median Duration of Infection by Human Papillomavirus Group or Type. Estimates are for human papillomavirus infections prevalent at baseline unless otherwise indicated, where * denotes incident infections and † denotes a mixture of prevalent and incident infections. The vertical line represents the overall, weighted median of 9.8 months.







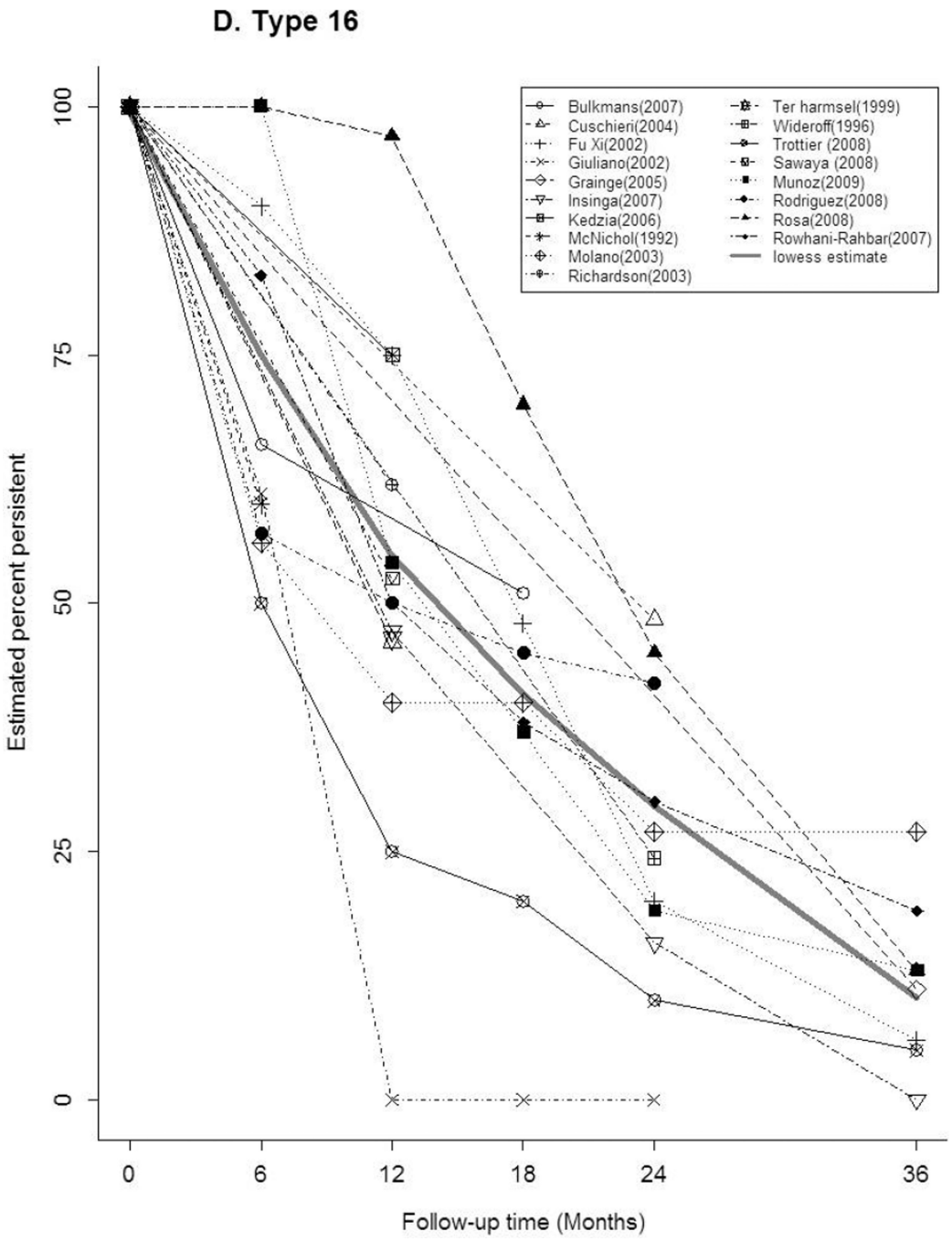


Figure 2.

Estimates of the Proportion of Infections Persisting across Time for A) any-HPV, B) high-risk HPV, C) low-risk HPV, D) HPV type 16. The legend in each panel provides the references for articles that contributed data to each figure. The thick gray curve is a locally weighted polynomial regression (lowess) estimate based on data from all studies over all time points.

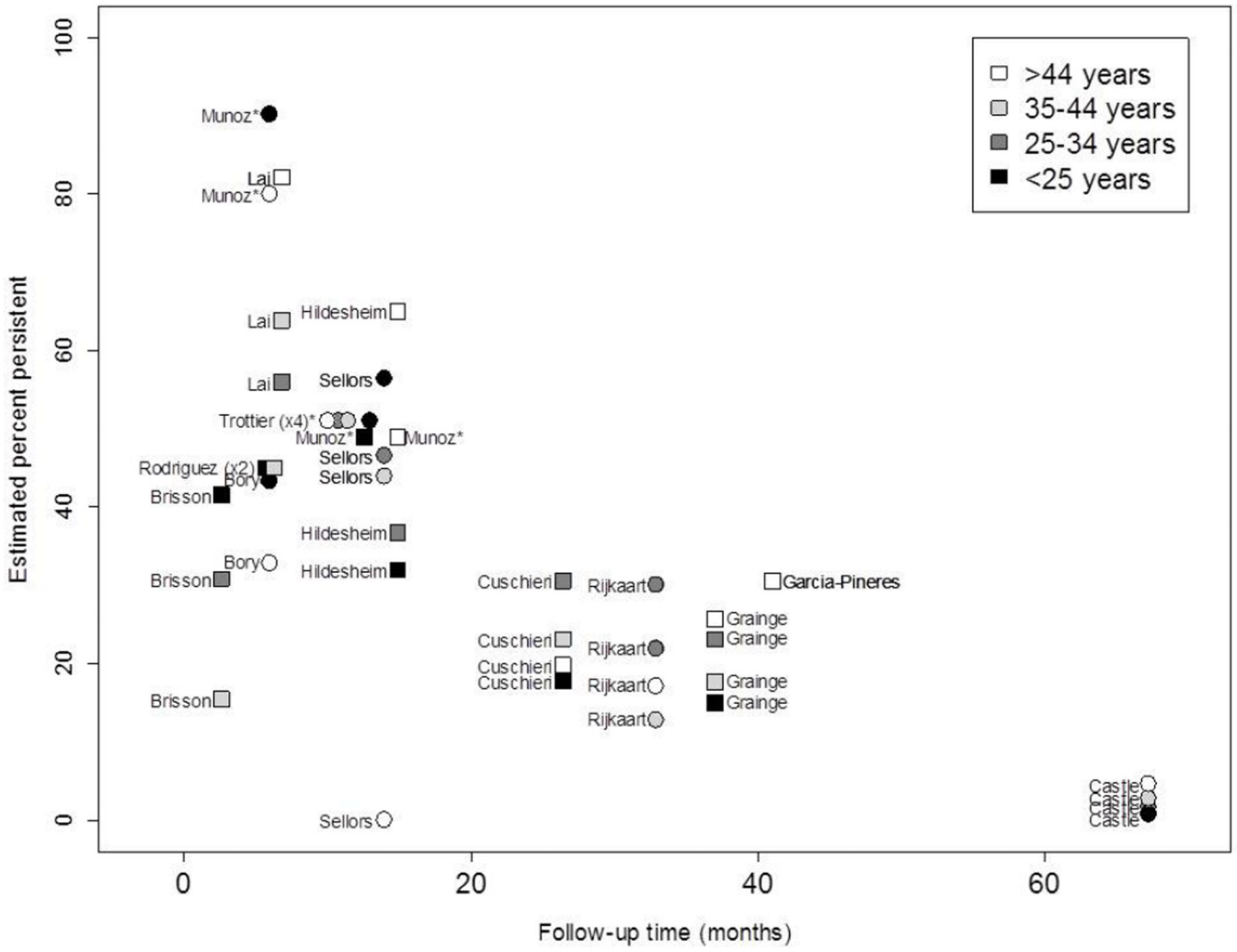


Figure 3.

Age-Specific HPV Persistence. Estimates of the proportion of women with persistent human papillomavirus (HPV) infection by time are presented for any-HPV (squares) or high-risk HPV (circles). All results were based on prevalent infections unless otherwise noted, where* indicates HPV persistence based on incident infections. Some points were dithered slightly to avoid overlap.

Table 1

Characteristics of Human Papillomavirus (HPV) Persistence Studies and Results from Published Studies through January 1st, 2010

	No. of results	% of results	References
Study region			
Europe	34	39.5	24, 27–29, 34, 36, 39, 43, 51–76
North America	25	29.1	21–23, 26, 33, 35, 38, 41, 42, 77–92
Central/South America	17	19.8	20, 25, 30–32, 37, 44, 93–102
Africa, Asia, Australia[a]	8	9.3	40, 103–109
Multicenter[b]	2	2.3	110, 111
Mean age of women			
< 30.0 years	33	38.4	23, 24, 27, 28, 30, 33–39, 41–44, 51, 57, 58, 62, 63, 67, 70, 78, 80, 82, 83, 86, 89, 98, 106, 110, 111
≥ 30.0 years	50	58.1	20, 21, 25, 26, 29–40, 53–57, 59–61, 64–66, 68, 69, 71–76, 79, 87, 90–93, 96, 99, 101–104, 107, 108, 112
Not stated	12	14.0	22, 52, 81, 84, 85, 88, 94, 95, 97, 100, 105, 109
Baseline abnormal cytology[c]			
0% abnormal	56	65.1	21, 23, 24, 26–31, 33, 34, 36, 38–40, 42–44, 51, 52, 54–61, 63, 65–71, 73–76, 78, 79, 81, 82, 84, 88–91, 93, 94, 104, 105, 107, 110, 111
1–15% abnormal	8	9.3	53, 59, 62, 65, 77, 83, 106, 109
Not stated	24	27.9	20, 22, 25, 32, 35, 37, 41, 64, 72, 80, 85–87, 92, 95–103, 108
HPV DNA detection method			
MY09/11 ± other primers	37	43.0	20, 21, 23, 25, 26, 32, 33, 37, 38, 41, 42, 51, 53, 61, 62, 73, 78, 79, 81, 82, 85, 87–91, 96–103, 108, 109, 112
SPF10, PGMY09/11, GP5+/6+	19	22.1	30, 31, 39, 40, 43, 44, 54, 57, 58, 64, 65, 67–69, 75, 80, 86, 110, 111
pU1M/pU2R, L1C1/L1C2, GP5/6 ± type-specific, other L1 primers	7	8.1	27, 36, 66, 71, 95, 105, 106
Type-specific primers	10	11.6	22, 24, 28, 39, 52, 72, 83, 84, 92, 104
Hybrid Capture 1/ 2	14	16.3	29, 34, 35, 55, 56, 59, 60, 63, 70, 74, 76, 93, 94, 107
HPV type[d]			
Any-HPV	49	57.0	20–23, 25–27, 30, 32, 33, 37–44, 53, 56, 57, 61, 62, 67, 72, 73, 75, 80–82, 84, 86, 87, 89–92, 96–103, 106, 108, 109, 112
HR-HPV	56	65.1	20, 23–25, 29–38, 40, 41, 44, 51, 54–60, 63–65, 67–70, 73–76, 79, 80, 82, 85–87, 91–95, 99–102, 104, 106, 107, 110, 111
HPV-16	39	45.3	20, 22, 24, 25, 28, 30–33, 37–44, 52, 54, 57, 58, 66, 71, 72, 78, 80, 83, 84, 88, 89, 91, 95, 96, 100, 105, 106, 108, 110, 112
HPV-18	26	30.2	20, 22, 25, 30–33, 39–43, 54, 57, 58, 72, 80, 82, 84, 89, 91, 100, 106, 108, 110, 112
LR-HPV	20	23.3	20, 23, 25, 30–32, 37, 38, 40, 41, 44, 56, 57, 80, 82, 86, 87, 91, 101, 102
HPV persistence definition[e]			
≥2 positive visits	63	73.3	20, 23–29, 33, 34, 36–39, 41, 51, 55–62, 64–67, 69, 70, 72–76, 78, 80–85, 87–90, 92–94, 96–101, 103, 104, 106, 109–112
≥3 positive visits	12	14.0	36, 42, 52, 56, 71, 79, 83, 97, 99, 105, 111
Clearance or duration	19	22.1	22, 30, 31, 35, 40–44, 53, 54, 63, 68, 86, 91, 93, 95, 108, 112
Persistent pairs	2	2.3	21, 102
Minimum HPV persistence duration			
< 6 months	27	31.4	20, 23, 25, 28, 32–34, 55, 56, 60, 64, 68, 74, 78, 80, 83, 86, 87, 89, 91, 98, 99, 101, 102, 104, 107, 108
6 to <12 months	38	44.2	21, 22, 27, 30, 31, 34–38, 40–42, 44, 51, 53, 54, 59, 62, 67, 70–72, 75, 82–85, 90, 92, 94, 95, 99, 105, 109–112

	No. of results	% of results	References
≥12 months	27	31.4	24, 26, 29, 34, 36, 38, 39, 52, 56–58, 61, 63, 65, 66, 69, 73, 76, 79, 81, 93, 97, 99, 100, 103, 106, 111
Not stated	3	3.5	43, 88, 96
Mean testing interval			
< 6 months	20	23.3	20, 25, 28, 32, 33, 56, 68, 78, 80, 83, 86, 89, 91, 99, 101, 102, 104, 105, 107, 108
6 to <12 months	35	40.7	21–23, 27, 30, 31, 34, 38, 40–44, 51, 54, 59, 60, 64, 70–72, 74, 75, 79, 84, 85, 87, 90, 94, 95, 98, 109–112
≥12 months	30	34.9	24, 26, 29, 35–37, 39, 52, 53, 55, 57, 58, 61–63, 65–67, 69, 73, 76, 81, 82, 88, 92, 93, 97, 100, 103, 106
Not stated	1	1.2	96
Type-specific HPV persistence			
Type-specific	62	72.1	20–25, 27, 28, 30–33, 37–44, 51, 52, 54, 57, 58, 61, 62, 64, 66–69, 71–73, 78–80, 82–89, 91, 92, 95–98, 100–102, 105, 106, 108, 110–112
Non-type-specific	36	41.9	24, 26, 29, 34–36, 38–40, 53, 55–57, 59, 60, 63, 65, 67, 70, 73–76, 81, 90, 93, 94, 98, 99, 101, 103, 104, 106, 107, 109, 112
Baseline HPV infection status			
Prevalent	60	69.8	23, 27–29, 32–41, 44, 53–71, 73–76, 81, 82, 84, 86–88, 90, 92–97, 100, 101, 103–109
Mixed prevalent and incident	13	15.1	22, 23, 28, 30, 34, 41–43, 78, 83, 89, 90, 110
Incident	19	22.1	20, 21, 26, 28, 31, 32, 51, 52, 72, 79, 80, 85, 90, 91, 98, 99, 102, 111, 112
Not stated	2	2.3	24, 25

HPV: human papillomavirus; LR: Low-risk; HR: High-risk

[a] Africa[106, 108, 109], Asia[40, 104, 105, 107], Australia[103]

[b] Multicenter: North/South/Central America[110, 111] Australia, Belgium, Brazil, Canada, Finland, Germany, Italy, Mexico, Philippines, Spain, Taiwan, Thailand, UK, and USA

[c] Classification based on individual study definitions of abnormal cytology but generally included ASCUS or greater

[d] Any-HPV: any and all HPV types detected; HR-HPV: HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68; LR-HPV: all other genital HPV types.

[e] Persistent pairs: any pair of two consecutive positive visits (v, v+1)

Table 2

Meta-Regression Estimates of the Proportion Persistent and Persistence Differences at 6 Months by Study Characteristics

	N	Summary % persistence[a] (95% CI)		% persistent differences (95% CI)	
Study region					
Europe	31	48.6	39.9, 57.3	0	0
North America	22	39.5	30.6, 48.4	−9.1	−20.9, −2.7
Central/South America[b]	7	28.2	8.4, 48.0	−20.4	−41.5, 0.6
Africa, Asia, Australia	8	45.2	32.6, 57.9	−3.4	−18.6, 11.8
Mean age of total study population					
< 30.0 years	29	40.1	32.3, 48.0	0	0
≥ 30.0 years	40	47.6	40.6, 54.6	7.5	−2.3, 17.2
HPV DNA detection method					
MY09/11 ± other primers	26	40.7	31.7, 50.0)	0	0
SPF10, PGMY09/11, GP5+/6+	14	40.7	28.6, 52.7	−0.04	−14.4, 14.4
pU1M/pU2R, L1C1/L1C2, GP5/6 ± type-specific, other L1 primers	6	56.4	40.4, 72.3	15.7	−2.1, 33.5
Type-specific primers	10	41.2	28.5, 53.8	0.5	−14.6, 15.5
Hybrid Capture 1/2	14	45.6	35.8, 55.4	4.9	−7.9, 17.8
HPV type					
Any-HPV	35	42.5	36.9, 48.2	0	0
LR-HPV	14	32.4	23.6, 41.3	−10.1	−20.2, −0.08
HR-HPV	41	43	37.8, 48.2	0.5	−6.6, 7.5
HPV-16	31	53.8	47.5, 60.0	11.2	3.3, 19.1
HPV-18	21	47.7	39.6, 55.8	5.1	−4.3, 14.5
HPV-31	13	43.9	33.5, 54.3	1.3	−9.9, 12.6
HPV-33	11	46.6	34.6, 58.7	4.1	−8.7, 16.9
HPV-35	9	34.1	20.3, 47.9	−8.4	−22.9, 6.0
HPV-39	8	42.8	30.0, 55.7	0.3	−13.4, 13.9
HPV-45	10	37.9	25.9, 50.0	−4.6	−17.3, 8.1
HPV-51	9	30.5	19.0, 42.0	−12.1	−24.3, 0.2
HPV-52	8	43.8	31.3, 56.3	1.2	−12.0, 14.4

	N	Summary % persistence[a] (95% CI)		% persistent differences (95% CI)	
HPV-56	9	41.9	29.4, 54.5	−0.6	−13.9, 12.7
HPV-58	9	37	24.8, 49.3	−5.5	−18.6, 7.5
HPV-59	7	40	24.8, 55.2	−2.6	−18.4, 13.3
HPV-66	7	29.4	16.1, 42.7	−13.2	−27.2, 0.8
HPV-68	6	33.2	18.0, 48.4	−9.3	−25.2, 6.5
HPV persistence definition					
≥2 positive visits	51	43.1	36.9, 49.4	0	0
≥3 positive visits	11	49.7	36.1, 63.4	6.6	−12.6, 11.9
Clearance or duration	15	42.8	32.0, 53.5	−0.4	−12.6, 11.9
Persistent pairs	2	52.7	25.0, 80.5	9.6	−18.4, 37.6
Minimum HPV persistence duration					
< 6 months	20	44	35.3, 52.6	0	0
6 to <12 months	36	46	38.9, 53.1	2	−8.9, 13.0
≥12 months	25	51.7	41.2, 62.3	7.8	−5.8, 21.3
Mean testing interval					
< 6 months	15	43	32.3, 53.7	0	0
6 to <12 months	28	45.6	37.7, 53.5	2.6	−10.7, 15.9
≥12 months	26	42.3	30.7, 53.9	−0.7	−16.6, 15.2
Type-specific HPV persistence					
Type-specific	47	42.7	35.8, 49.6	0	0
Non-type-specific	33	43.6	36.1, 51.1	0.9	−7.8, 9.5
Baseline HPV infection status for persistence					
Prevalent	52	42.6	36.2, 49.1	0	0
Mixed prevalent and incident	13	42.5	29.5, 55.4	−0.2	−14.0, 13.7
Incident	13	45.1	33.2, 57.1	2.5	−10.6, 15.6

CI: confidence interval; HPV: human papillomavirus; LR: low-risk; HR: high-risk

[a]Estimates are adjusted for persistence follow-up, which was centered at 6 months, and for study populations that contributed to more than one stratum.

[b]Includes multi-center studies.