Cumulative risk of cervical intraepithelial neoplasia for women with normal cytology but positive for human papillomavirus: systematic review and meta-analysis

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List of abbreviations
CIN: cervical intraepithelial neoplasia
HR-HPV: high-risk human papillomavirus
HPV: human papillomavirus
HC2: Hybrid Capture 2
US: United States

Novelty and impact: Cervical cancer screening recommendations are based on risk benchmarks; we performed a meta-analysis of the prospective risk of precancer for women positive for human papillomavirus but cytology normal, the most common screen-positive result with HPV-based screening. We found that though the short-term risk of oncogenic progression is low, it is highly heterogeneous across populations and HPV types. Decision makers should consider the range of potential risks and HPV type distributions in their target screening population.

Abstract

Most women positive for human papillomavirus (HPV) are cytology normal. The optimal screen-management of these women is unclear given their risk of developing precancer. We performed a systematic review and meta-analysis of progression rates to precancer and cancer for HPV-positive, cytology normal women. We searched MEDLINE, EMBASE, and Scopus for prospective studies measuring the cumulative incidence of precancer and cervical cancer in HPV-positive, cytology/histology normal women. Record screening was performed independently by two reviewers. We modeled the cumulative incidence over time using a multilevel random-effects meta-regression model. We used the model to predict HPV type-specific risks of precancer and cancer over follow-up. Data from 162 unique records were used in our analysis. The average incidence rate of cervical intraepithelial neoplasia grade 3 or cancer (CIN3+) in high-risk HPV positive but cytology/histology normal women was 1.0 per 100 women-years (95% CI: 1.0 to 1.1). This corresponds to an average cumulative risk at 1, 3, and 5 years of 2.1% (95% prediction interval 0.0 to 9.5), 4.3% (95% prediction interval 0.0 to 11.5), and 6.4% (95% prediction interval 0.0 to 13.5). HPV type was a strong predictor of the risk of oncogenic progression. There was substantial heterogeneity in the background precancer risk across studies (p-value<0.0001). Our HPV type-specific progression risk estimates can help inform risk-based cervical cancer screening guidelines for HPV-positive women. However, precancer and cervical cancer risks are highly variable and may not be generalizable between populations.

Introduction

Tests for the human papillomavirus (HPV) are increasingly replacing cytology as the primary screening test for cervical cancer in many countries, such as the United States (US), Australia, and England.[1-3] Clinical trials have demonstrated that HPV tests are more sensitive and have a higher long-term negative predictive value than cytology.[4,5] However, these trials have also shown that more screen-positive women will require follow-up and management with HPV testing than with cytology.[6,7] The majority of HPV-positive women are cytology negative.[8,9] For example, 65% of women in the Australian screening program who are positive for any oncogenic HPV do not have any cervical abnormality.[10] While these women are at a lower risk of progressing to precancerous lesions than women with cytological abnormalities, they remain at a higher risk of developing precancerous lesions than HPV-negative women.[11] The management strategy for these women varies across guidelines.[1,2,12] Most guidelines recommend short-term follow-up rather than an immediate colposcopy referral for these women to avoid overwhelming colposcopy services and to reduce unnecessary harms, but the optimal follow-up management strategy for these women is unclear.

Increasingly, many guidelines use precancer risk benchmarking to determine the best course of action for different screening results.[2,12,13] The ASCCP is updating its screening guidelines in 2020 based on 5-year cervical intraepithelial neoplasia (CIN) grade 3 or higher risks.[13,14] Its preliminary draft guidelines recommend that women with a CIN3+ risk of ≤0.1% return for screening in 5 years, 0.2 to 0.5% return in 3 years, 0.6% to <4% return in 1 year, and that those with an immediate risk of ≥4% be referred to colposcopy. While risk-based guidelines promote transparency and equal management for equal risks, the choice of which population is used to inform the risk thresholds deserves careful attention. For example, the risk thresholds proposed by the ASCCP are heavily influenced by results from the Kaiser Permanente Northern California cohort.[13] Likewise, the results may also not be generalizable to other countries.

While previous reviews have analyzed precancerous lesion progression and regression rates, to our knowledge no systematic review has specifically examined HPV-positive, cytology normal women. Cantor *et al.* published in 2005 a meta-analysis of progression and regression risks between precancer lesion grades, but did not assess the risk of progression from normal cytology to precancer.[15] Insinga *et al*. reviewed the literature in 2009 and found scarce data on progression from infection to precancer.[16] Ting *et al.* published a review of precancerous lesion incidence rates in 2015 but did not restrict their analysis to cytology normal women.[17] HPV-positive, cytology normal women are of particular interest because they are the most common screen-positive result, and consequently their management will substantially influence screening costs and workload. Results of landmark studies on long-term infection progression risks have been published in the past few years,[18-21] suggesting that a systematic review specifically on the topic of oncogenic progression risks in HPV-positive, cytology normal women is timely.

Consequently, we performed a systematic review and meta-analysis of prospective observational studies and randomized controlled trials measuring the risk of progressing to histologically-ascertained precancerous lesions and cancer for women who are positive for HPV DNA but cytologically or histologically normal. We also examined women- and study- level risk factors that might influence the incidence of precancer in these women.

Methods

The initial review protocol was registered with the PROSPERO international prospective register of systematic reviews (registration number CRD42017064325) and can be accessed at https://www.crd.york.ac.uk/PROSPERO/.

Eligibility criteria

To be included, studies had to have a prospective design (randomized controlled trials, cohort and nested case-cohort studies) that allowed calculating cumulative risks of incident histologically-confirmed CIN or cancer over time. The report had to include an analysis that was restricted to women who were initially cytologically, colposcopy or histologically normal, but who had a vaginal or cervical sample positive for HPV DNA.

Records were excluded if the study design did not allow measuring prospective risks (cross-sectional, case-control studies, studies with ≤20 participants fitting the inclusion criteria); if HPV infection was detected using serology or mRNA; if they were non-research publications (e.g. commentaries, letters to the editor); and if the study was done exclusively in immunocompromised women (ex. women living with HIV, solid organ transplant patients, systemic lupus), as the risk of CIN may be different in these populations. However, if studies recruited both immunocompromised and non-immunocompromised women, the risks reported for the non-immunocompromised women were included. We excluded records reported in languages other than English or French. Due to the lower sensitivity of older nucleic acid hybridization assays (Southern blot, *in situ* hybridization, dot blot hybridization), we restricted our search to studies published from 1990 onwards and excluded studies that used these assays for HPV DNA detection, though they could be used for genotyping. There were no age or setting restrictions for the study population.

Information sources and search strategy

We searched the MEDLINE, EMBASE, and Scopus databases for relevant literature up to May 16, 2019. We searched the conference abstracts of EUROGIN (EUropean Research Organization on Genital Infection and Neoplasia) and International Papillomavirus conferences held from 2016 to 2018 for unpublished data. We also reviewed the reference lists of included papers and a review article identified through the search[17] for additional studies that might have been missed by the search strategy.

The search strategy was developed with the support of a Health Sciences Librarian with expertise in conducting systematic literature searches. The search strategy used a combination of database subject headings (e.g. MeSH) and text keywords relative to HPV infection, CIN, and prospective study designs. The full search strategy is presented in the Supplementary Appendix.

Study selection and data collection

Title and abstract screening of all identified records were done independently by two reviewers (TM, and SB or KV) using Rayyan.[22] The full text of potentially relevant records were independently reviewed and assessed against the eligibility criteria by two reviewers (TM and KV). Disagreements between reviewers at the screening and full-text review stages were resolved by consensus.

The data extraction sheet was piloted independently by three authors (KV, CL, MZ) on a small sample of 16 studies selected due to their high quality of reporting. Data extraction was performed by trained research assistants. All extracted data were verified by TM and subsequently re-verified by three other reviewers (KV, CL, MZ). Disagreements were investigated and resolved by TM. Extracted data included demographic information, study setting, study design, HPV DNA assay, follow-up length, follow-up losses, HPV types, whether HPV infection was prevalent or incident, infection persistence, and sample

size. We initially planned to contact corresponding study authors for missing data, but this was discontinued at an early stage given the poor response rate. To attempt to find information on data items that were missing from a record, we also searched other publications on the same study population.

Prevalent HPV infections were defined as HPV detected at study baseline, while incident HPV infections were defined as new HPV detections in women who were negative for that type at previous visits. We used the studies' own definitions of persistent infections. Generally, for type-specific analyses this was defined in studies as the detection at two consecutive visits of the same HPV type. For pooled high risk (HR)-HPV types, there was a mix of detection at two consecutive visits of the same HPV type or of any HR-HPV type, due to the lack of genotyping in many studies. The time between visits varied between studies. If studies used different methods to attribute lesions to HPV types, where possible we used the analysis where CIN lesions were attributed to all HPV types present; this was to ensure higher consistency across studies because the vast majority of studies did not use hierarchical attribution methods. This also corresponded to the analysis with the largest sample size, respecting our prioritization order detailed below.

Statistical analysis

Outcomes and prioritization

The primary outcome was the cumulative incidence of histologically confirmed precancerous lesions (CIN2+, CIN3+) or invasive cervical cancer. Invasive cancer cases were included in CIN2+ and CIN3+ outcomes. We also evaluated CIN1 as a secondary outcome; while CIN1 is generally considered to be a proxy for active HPV infection rather than true precancer, it may be of interest as a marker of progression from HPV detection to active HPV infection. For records where the cumulative incidence was not explicitly reported, we calculated it based on the available information in one of the following ways. If only the number of events or Kaplan-Meier figures were provided, we calculated the crude incidence proportions based on the number of events divided by the total population at risk. If the incidence rate, rather than the cumulative incidence proportion, was reported, we used the formula below to impute cumulative incidence over the cohort's follow-up, where λ is the incidence rate, t is the average follow-up time per person, and $p(t)$ is the cumulative incidence at time t:

$$p(t) = 1 - e^{-\lambda t}$$

If the cumulative incidence was reported for the total observation time of a cohort without specifying a time point, we imputed the time based on the average follow-up time per person. If the average follow-up time was not specified, we imputed it based on the protocol's screening intervals. If confidence intervals (CI) and/or variances were not provided for proportions, exact binomial CIs were calculated using the number of events.

We anticipated that we would find multiple records that reported risks based on the same study population. For this reason, we performed a meta-regression analysis that allowed the use of cumulative incidences from multiple time points from the same population, while accounting for the correlation between estimates (see meta-regression section). We extracted all cumulative incidence estimates stratified by follow-up time, age group, HPV type and persistence, and whether the HPV infection was prevalent or incident. When multiple cumulative incidence estimates existed for the same population and outcome, HPV type, time point, age group, persistence, and prevalence definition, we prioritized by selecting in order the estimate that was: 1) calculated using methods accounting for loss to follow-up (e.g. Kaplan-Meier), 2) reported in the most recent publication, or finally 3) calculated in the analysis with the largest sample size.

Meta-regression

We modeled the cumulative incidence of CIN and cancer over time using a generalized linear multilevel random-effects meta-regression model with the R package metafor.[23] The outcome of this model was the log-transformed survival (1-cumulative incidence of CIN), with time as a continuous fixed-effect predictor, and with random effects for each study population:

$$\log\left(1 - p\left(t_{ij}\right)\right) = \alpha CIN_{ij} + \lambda_1 t_{ij} HPV_{ij} \times CIN_{ij} + \lambda_2 t_{ij} Covariates_{ij} \times CIN_{ij} + u_j + e_{ij}$$

where t_{ij} is the time point of observation *i* in population *j*; $p\left(t_{ij}\right)$ is the cumulative incidence of CIN at time t_{ij} in population *j*; α is the average prevalence at baseline of a given CIN grade; CIN_{ij} is the lesion grade (CIN1, CIN2+, CIN3+); λ_1 and λ_2 are progression incidence rates from normal to CIN; HPV_{ij} is the HPV type; $Covariates_{ij}$ is a vector of covariates; u_j are the random effects for each study population *j*; and e_{ij} is the residual error. This model uses cumulative incidences from studies to estimate the average incidence rate of progression from normal infection to CIN. The underlying assumptions are that the incidence rate of progression from infection to each outcome (CIN1, CIN2+, CIN3+) is constant over time and does not change between populations after conditioning on HPV type and the other study covariates we assessed (infection persistence, infection incidence, detection assay, mean/median participant age, baseline normal test type, study design, follow-up interval, and loss to follow-up). The random effect in this model represents the variation in the background prevalence of CIN in different study populations that is not accounted for by HPV type and study-level covariates. This model can accommodate multiple observations from the same population over time while accounting for their correlation with the random effects. The observations were weighted in the model using a generic inverse-variance method, using the delta method to calculate the standard errors for log-transformed proportions.[24] Incidence rates and incidence rate ratios along with their 95% CIs were calculated using the ratios of linear combinations of model parameters with their variance-covariance matrix.[25] The effect of study-level covariates on progression rates was assessed separately in models that adjusted only for HPV type, and in a multivariable model that adjusted for all study-level covariates simultaneously. Progression rates to all CIN grades were fit using the same model; however, since fewer studies reported cancer outcomes, progression rates to cancer were fitted in a separate model with only HPV type as a predictor.

We used the regression models with only HPV type as a covariate to predict the average cumulative risks of CIN2+, CIN3+, and cancer at 1 year, 3 years, and 5 years after baseline. Results were stratified by HPV type. For risk estimates, we calculated prediction intervals rather than CIs to assess uncertainty: while CIs represent the uncertainty due to sampling variability in the estimation of the average progression incidence rate, prediction intervals also include uncertainty due to heterogeneity in the background risk of CIN across studies (the random effect).[26] Consequently, prediction intervals better represent the range of likely cumulative risks across different settings.

Since the model assumed a log-normal distribution of error, it was possible for CIs and prediction intervals to include negative risks; we truncated negative risks and rates at 0. We used Cochran's Q to test whether there was residual heterogeneity across studies that was not accounted for by study characteristics included as model covariates.[27]

Study influence and risk of bias

Individual studies' influence in the analysis was evaluated using Cook's distance.[28] To assess the risk of bias within studies, we included as predictors in the regression model study characteristics that we hypothesized might be associated with study quality; these included HPV detection assay, proportion of women lost to follow-up, follow-up intervals, and whether follow-up was based on a study protocol or

screening registry. To assess publication bias, we used a funnel plot of the standard error of study estimates compared with the standardized residuals from the meta-regression.

Results

Study selection and characteristics

We screened 4035 records identified through the database search and an additional 33 records included in a review of CIN incidence rates.[17] We further identified 17 records through the manual search of reference lists and 12 conference abstracts. There were 162 unique records reporting on 87 independent study populations that met the inclusion criteria (Figure 1). The primary reasons for exclusion were either because the analysis was not restricted to women who were cytology or histology normal at baseline, or because the analysis was not restricted to HPV DNA positive women.

The study characteristics and references for all included records are reported in full in the Supplementary Appendix Table S1. The vast majority of included records used cytology (95.1%) rather than colposcopy/histology (4.9%) as the baseline test to establish cervical status. More than half of the records (54.3%) used Hybrid Capture 2 (HC2) to detect HPV DNA. Although study participants were located in many different regions of the world, most studies were performed in European (51.2%) or North American (27.8%) populations. The type of study design from which the data originated was distributed among registry (30.2%), observational studies (41.4%) and randomized controlled trials (27.8%). Many studies did not report the number of participants who were lost to follow-up, and 38.0% reported <20% of the study participants lost to follow-up.

Results of individual studies

Cumulative incidence estimates for all outcomes and HPV types combined are presented in the Supplementary Appendix Figure S1. The cumulative incidence estimates for CIN2+ and CIN3+ in women positive for any high risk (HR) HPV type are presented in Figure 2. There was statistically significant heterogeneity in the baseline CIN2+ and CIN3+ risk across studies ($p<0.0001$). Smaller studies with large standard errors were more likely to report high cumulative incidences of CIN2+ and CIN3+ (>10%) during their first 5 years of follow-up than larger studies (Figure 2).

Incidence rates and study-level predictors

The estimated average incidence rate of CIN3+ in HR-HPV positive women who were cytology or histology normal at baseline is 1.0 CIN3+ per 100 women-years (95% CI: 1.0-1.1) (Table 1). HPV type was a statistically significant predictor of CIN incidence, with HPV 16/18 positive women having a 2.6 (95% CI: 2.1-3.2) times higher rate of progression to CIN3+ than women positive for any HR type. Studies restricting analyses to women whose HPV was persistently detected in at least two visits had a 2.1 (95% CI: 1.8-2.4) times higher rate of progression to CIN3+ than studies where HPV positivity was only assessed once (persistence unknown). Studies using non-commercial DNA tests to detect HR-HPV estimated higher CIN3+ progression risks than studies that used HC2 to detect HR-HPV. Studies with shorter follow-up intervals reported on average lower CIN3+ progression rates. On average, studies with lower loss to follow-up reported higher CIN3+ progression rates after adjusting for other study variables listed in Table 1. Although mean participant age was a predictor of progression in univariate analyses, it was no longer statistically significant in the multivariable model, suggesting that observed differences among studies with different age distributions might be attributable to HPV type, persistence, and other study features. On average, studies published in 2006 or later reported a lower incidence rate in HR-HPV positive women of 1.0 CIN3+ per 100 women-years (95% CI 1.0-1.1) compared to studies published before 2006 (1.4 per 100 women-years, 95% CI: 1.3-1.6).

The estimated average incidence rate of CIN2+ in women HR-HPV positive who were cytology or histology normal at baseline was 1.6 CIN2+ per 100 women-years (95% CI: 1.6-1.6). The results of regression analyses were very similar for CIN2+ (Table 2). The main difference was that studies with shorter follow-up intervals reported on average lower CIN3+ progression rates, but higher CIN2+ progression rates. The estimated average incidence rate of cervical cancer in HR-HPV positive women who were cytology or histology normal at baseline was 0.21 cancers per 100 women-years (95% CI: 0.20-0.22). HPV16 positive women had a 3.03 (95% CI: 2.87-3.19) times higher rate of progression to cancer than women positive for any HR-HPV type.

Cumulative risk estimates

The weighted average risks of CIN2+ at 1, 3, and 5 years in women who were baseline HR-HPV positive but cytology or histology normal were 3.9%, 7.0%, and 9.9% (Figure 3). The weighted average risks of CIN3+ at 1, 3, and 5 years in women who were baseline HR-HPV positive but cytology or histology normal were 2.1%, 4.3%, and 6.4%. The weighted average risks of cervical cancer at 1, 3, and 5 years in women who were baseline HR-HPV positive but cytology normal were 0.8%, 1.2%, and 1.6%. Results for other HPV types, including HPV16, HPV18, and HR-HPV excluding HPV16/18 are presented in Table 3. The 95% prediction intervals for these risks were very wide due to large variability in the background risks between the different study populations (Table 3, Figure 2).

Heterogeneity and risk of bias

Substantial heterogeneity ($p<0.0001$) remained among studies even after adjustment for the variables listed in Tables 2 and 3, suggesting that those variables did not explain all the variation in CIN2+ and CIN3+ risk among studies. Cook's distance analyses (not shown) suggested that larger studies with longer follow-up durations were the most influential in the meta-regression analysis. The observations with the highest Cook's D values came from large screening registries and databases in the US,[13,29-31] Taiwan,[32] Korea,[33] Denmark,[18,34] as well as results from the POBASCAM trial[35] in the Netherlands and the Costa Rica HPV vaccine trial[36].

The funnel plot did not suggest a publication bias (Supplementary Appendix Figure S2). While there were few small studies estimating very low progression risks, this was expected because large sample sizes are required to have sufficient precision to measure low progression risks. Smaller studies had little weight in the analysis compared to the large studies described above, so they are unlikely to have substantially impacted the results.

Discussion

In this systematic review and meta-analysis, we pooled results from 162 records to estimate the progression rates to precancer (CIN2+, CIN3+) and cervical cancer for women who present as HPV-positive but cytology or histology normal. HPV type and infection persistence were important predictors of whether a woman was at a higher risk of precancer. The mean age of study participants was not a statistically significant predictor of progression after accounting for other study features. We found that studies that used the HC2 genotyping assay and those with a high loss to follow-up (>20%) estimated lower progression rates than studies that used other HPV DNA assays and studies that had a lower loss to follow-up. Studies with shorter follow-up intervals tended to detect more CIN2+ but fewer CIN3+. There was very high heterogeneity among studies in the background risk of precancer and cancer which could not be accounted for by HPV type, persistence, age, or any other study design feature we assessed.

Of all women who screen HR-HPV positive, the majority will have normal cytology results.[8,9] The decision of how to manage these women will have substantial impacts on colposcopy referrals, follow-up appointments, costs, and harms of over screening. These results can help inform the management of these women in screening programs. Some researchers have advocated for risk-based management to guide screening recommendations.[11] These risk thresholds, by extension, reflect societies' tolerance for risk. Notably, while the ASCCP proposes a 4% immediate CIN3+ risk as the threshold for referral to colposcopy,[14] the Netherlands have instead used a 20% CIN3+ risk at 2 to 3 year as the threshold for referral to colposcopy.[12] In our analysis, a HR-HPV positive, cytology normal woman had on average a 6.4% risk of CIN3+ within 5 years, but her 1-year risk of CIN3+ was less than 4%. The implication is that these women should be referred for a follow-up retest in 1 year based on both risk thresholds.

HPV genotyping could be considered for further risk-stratification. Due to HPV vaccination programs, the HPV type distribution is changing over time. Consequently, the risks reported in past studies for women positive for pooled HR HPV+ types may therefore no longer be applicable. For example, in our study we observed that studies published in 2006 or later estimated on average lower progression rates to CIN3+ for HR-HPV positive women than studies published before 2006; this potentially reflects changes in HPV type distribution over time. The results for pooled HR-HPV types may in particular not be as applicable to younger women in HPV vaccinated cohorts, who are expected to have a lower HPV16/18 prevalence. For these reasons, we estimated type-specific risks, which are less affected by changes in HPV type distribution over time and across populations. HPV tests with genotyping capabilities may therefore be desirable for screening programs to preserve their positive predictive value over time and implement more individualized risk management. Our model estimated that HPV16/18 positive women have an average 1-year CIN3+ risk of 3.5%. Nonetheless, the large prediction intervals (0.0-10.8%) suggest that in some populations HPV16/18 positive women could have a sufficiently high risk to warrant immediate colposcopy referral in risk-averse societies such as the US. Interestingly, HPV18 positive women had a lower risk of CIN2+ but a higher risk of CIN3+ compared to all pooled HR-HPV types. This may reflect the higher contribution of HPV18 to invasive cancer, particularly adenocarcinoma, compared to lower lesion grades.[37] This finding supports triaging of HPV18 positive women to colposcopy due to its high oncogenic potential. The low estimated risk of CIN3+ in cytology negative women positive for HR-HPV excluding 16/18 supports not immediately referring these women to colposcopy, in line with current guidelines in countries that have implemented HPV genotyping.

Another motivation for this study was to define plausible intervals for oncogenic progression rates in natural history models of HPV and cervical cancer. The probability of oncogenic progression from infection to precancer and eventual cancer over time is a considerable source of uncertainty in models of the natural history of cervical cancer.[16,38] The rate of progression from infection to precancer is a

crucial parameter because it determines the ages at which models predict that precancerous lesions will be detected during screening. This question is important as more decision models examine the impact of which age to start screening with HPV testing and the appropriate intervals for rescreening. These models are used to inform screening guidelines in many countries.[39,40] Since the distribution of HPV types will likely change in the future due to the impact of vaccination, HPV type-specific progression rates, like the ones we calculated, will be needed to model how screening will perform in the future.

Our analysis suggests that some study features may lead to underestimating the risk of precancer over time. Studies with a high loss to follow-up tended to estimate lower progression risks; this may be because women who do not return for follow-up screening are at a higher risk of precancer. Also, studies that excluded women with previously abnormal results reported, on average, lower CIN3+ progression risks than studies not excluding these women. Since the general population includes women with previous abnormal cytology results, studies that exclude these women may underestimate progression risks in the general population. While follow-up intervals were also associated with progression rates, the relationship was inconsistent across lesion grades.

In order to pool results from studies with different follow-up times, we used a parametric model to assess the relationship between time and progression risk. However, there are caveats to this approach. Firstly, the model estimates risks based on the assumption that progression rates from infection to precancer are constant over time. The assumption of constant rates is often made in many models and in other oncogenic progression reviews[15,16] for interpretability because it leads to the estimation of a single incidence rate. Predictions assuming constant progression rates are roughly consistent with the observations from most individual studies included in our review when we assumed a baseline prevalence of disease (Figure 2). However, other researchers have suggested that models where rates can change over time (e.g. logistic-Weibull models) may fit the data better.[41] Secondly, the model specification assumes a log-normal distribution of the error for risks and rates. While this provided a good fit for most observations, very small and large risks were not well fitted by the model due to data skewness, and lower CIs were not bounded by 0. Thirdly, several studies with larger sample size highly influenced the results and thus model predictions mostly reflected the observations from those studies. However, these large studies generally had concordant results (Figure 2); the outliers tended to be smaller studies which had very little influence in our analysis. Another limitation of our analysis was that, due to differences in reporting of age categories across studies, it was not possible to calculate age-stratified rates or to control for participants' age beyond their mean or median age. However, other studies have suggested that different age groups have comparable progression risks over time after conditioning on HPV type[34,42].

We found substantial heterogeneity of the background risk of disease between populations that was not accounted for by HPV type or other variables in our analysis. The average estimated risks are therefore not necessarily generalizable to all populations; for this reason, we included prediction intervals to provide a range of plausible risk values. The implication is that decision-makers should pay particular attention when choosing studies to base guidelines on because the risk of precancer and cancer in HPV positive, cytology normal women differs between populations even within the same country. For example, a risk comparison of the Kaiser Permanente North California cohort with another large US population from New Mexico suggested that cytology normal women have significantly different 3- and 5- year CIN3+ risks between populations.[43] A joint European cohort study also found cytology negative HPV positive women had 5-year risks ranging from 3-10% between different European countries, though this difference was not statistically significant.[44] We hypothesize that the heterogeneity we observed may be due to differences in the sensitivity of cytology, which varies across settings;[45] consequently the negative predictive value of a normal cytology result likely varies between populations. There may also

be differences in the sensitivity of colposcopy across studies.[46] Disease ascertainment is often more thorough in clinical trials than in observational data, which could in part explain the slightly higher risks we estimated for clinical trials. There might also be differences in screening adherence and quality between populations that influence the background risk of precancer; it was not possible to control for these variables in our analysis as these are not study design features.

In conclusion, our progression risk estimates and their prediction intervals can help inform the screen-management of HPV-positive women, development of guidelines, and models of the natural history of cervical cancer. However, the large observed heterogeneity among studies suggests that we should be cautious in generalizing the risks between different populations. While the natural history of HPV is unlikely to vary between immunocompetent populations, other features such as the quality of screening programs may lead to differences in the background prevalence of disease and the predictive value of screening tests.

Contributions

TM and SB developed the search strategy. TM drafted the manuscript and data extraction forms, as well as developed and performed the statistical analysis. CL, KV, and MZ piloted the data extraction forms. TM, SB, and KV screened records for inclusion and exclusion. TM, CL, KV, and MZ performed data extraction and validation. ELF provided team supervision and advice. All authors read, provided feedback, and approved the final protocol and manuscript.

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Conflicts of Interest

TM, KV, SB, CL declare no conflicts of interest. ELF has served as occasional consultant to Merck and GSK on HPV vaccines, to Roche and BD on HPV diagnostics. His institution has received unrestricted grants from Merck. MZ and ELF hold a patent related to the discovery “DNA methylation markers for early detection of cervical cancer”, registered at the Office of Innovation and Partnerships, McGill University, Montreal, Quebec, Canada (October, 2018). A provisional utility patent application before the United States Patent & Trademark Office was also filed (November, 2018).

Data availability

The data that support the findings of this study come from published records; a full reference list of the records contributing data to this analysis can be found in the Supplementary Appendix.

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Table 1. CIN3+ incidence rates predicted by a meta-regression model for women who were cytology/histology normal but HPV-positive at baseline.

Progression predictors	Adjusted for HPV type only*		Multivariable model†	
	Incidence rate per 100 women-years (95% CI)‡	Incidence rate ratio (95% CI)‡	Incidence rate per 100 women-years (95% CI)‡	Incidence rate ratio (95% CI)‡
HPV type				
HR-HPV	1.0 (1.0 to 1.1)	1.00 (ref)	0.8 (0.6 to 1.0)	1.00 (ref)
HPV16/18	2.4 (2.1 to 2.7)	**2.30 (2.00 to 2.60)**	2.1 (1.7 to 2.5)	**2.58 (2.12 to 3.21)**
HR excluding 16/18	0.4 (0.4 to 0.5)	**0.42 (0.38 to 0.46)**	0.3 (0.1 to 0.5)	**0.36 (0.17 to 0.49)**
HPV16	2.3 (2.2 to 2.4)	**2.19 (2.09 to 2.30)**	2.0 (1.8 to 2.2)	**2.47 (2.17 to 2.92)**
HPV18	1.3 (1.2 to 1.4)	**1.25 (1.12 to 1.37)**	1.0 (0.8 to 1.2)	**1.23 (1.06 to 1.42)**
HPV31	1.5 (1.4 to 1.6)	**1.47 (1.36 to 1.58)**	1.2 (1.0 to 1.5)	**1.53 (1.36 to 1.76)**
HPV33	1.7 (1.5 to 1.9)	**1.66 (1.49 to 1.83)**	1.4 (1.2 to 1.7)	**1.74 (1.49 to 2.07)**
HPV35	1.1 (0.8 to 1.5)	1.10 (0.76 to 1.45)	0.8 (0.4 to 1.2)	0.98 (0.52 to 1.44)
HPV45	1.0 (0.8 to 1.1)	0.95 (0.80 to 1.10)	0.6 (0.4 to 0.9)	**0.76 (0.53 to 0.96)**
HPV51	1.0 (0.9 to 1.1)	0.94 (0.84 to 1.04)	0.6 (0.4 to 0.8)	**0.70 (0.52 to 0.84)**
HPV52	1.0 (0.9 to 1.1)	1.00 (0.90 to 1.11)	0.7 (0.4 to 0.9)	**0.81 (0.65 to 0.96)**
HPV58	1.0 (0.7 to 1.2)	0.94 (0.71 to 1.16)	0.8 (0.5 to 1.0)	0.93 (0.62 to 1.23)
HPV59	1.0 (0.8 to 1.1)	0.95 (0.81 to 1.09)	0.6 (0.4 to 0.8)	**0.76 (0.55 to 0.94)**
HPV infection persistence				
Baseline assessment only	1.1 (1.1 to 1.1)	1.00 (ref)	0.8 (0.6 to 1.0)	1.00 (ref)
Persistent infection	1.7 (1.6 to 1.9)	**1.60 (1.49 to 1.71)**	1.7 (1.5 to 1.9)	**2.07 (1.83 to 2.44)**
HPV detection event				
Incident	0.0 (0.0 to 0.1)	**0.00 (0.00 to 0.09)**	0.0 (0.0 to 0.2)	**0.00 (0.00 to 0.18)**
Prevalent	1.1 (1.1 to 1.1)	1.0 (ref)	1.0 (0.8 to 1.2)	1.0 (ref)
HPV detection assay				
HC2	0.9 (0.9 to 1.0)	1.00 (ref)	0.7 (0.5 to 0.9)	1.00 (ref)
Commercial§	1.1 (0.9 to 1.4)	1.19 (0.92 to 1.47)	0.8 (0.5 to 1.2)	1.20 (0.73 to 1.72)
Other	1.2 (1.1 to 1.2)	**1.27 (1.21 to 1.33)**	1.3 (1.0 to 1.6)	**1.88 (1.40 to 2.52)**
Mean/median participant age				
<30y	1.2 (1.1 to 1.2)	1.00 (ref)	0.9 (0.7 to 1.1)	1.00 (ref)
≥30y	1.0 (1.0 to 1.0)	**0.88 (0.83 to 0.95)**	0.8 (0.6 to 1.0)	0.91 (0.81 to 1.03)
Missing	1.0 (0.9 to 1.0)	**0.84 (0.78 to 0.90)**	0.7 (0.5 to 0.9)	**0.76 (0.61 to 0.93)**
Baseline normal test				
Cytology	1.0 (1.0 to 1.1)	1.00 (ref)	0.9 (0.8 to 1.0)	1.00 (ref)
Colposcopy/histology	0.9 (0.4 to 1.3)	0.82 (0.39 to 1.26)	0.6 (0.1 to 1.1)	0.65 (0.13 to 1.17)
Excluded women with history of abnormal results				
Yes	1.1 (1.1 to 1.1)	1.00 (ref)	0.6 (0.4 to 0.8)	1.00 (ref)
No	0.9 (0.9 to 1.0)	**0.83 (0.80 to 0.87)**	0.8 (0.7 to 1.0)	**1.30 (1.10 to 1.62)**
Study type				
Registry data	1.0 (0.9 to 1.0)	1.00 (ref)	0.8 (0.6 to 1.0)	1.00 (ref)
Observational study	0.6 (0.4 to 0.8)	**0.60 (0.40 to 0.80)**	0.0 (0.0 to 0.2)	**0.00 (0.00 to 0.24)**
Randomized controlled trial	1.2 (1.1 to 1.2)	**1.24 (1.18 to 1.30)**	0.7 (0.4 to 1.0)	0.89 (0.53 to 1.30)
Follow-up intervals (protocol)‖				
<6 months	0.2 (0.0 to 0.6)	**0.21 (0.00 to 0.65)**	0.2 (0.0 to 0.8)	**0.29 (0.00 to 0.87)**
6 months	0.4 (0.2 to 0.5)	**0.39 (0.26 to 0.51)**	0.5 (0.2 to 0.8)	**0.60 (0.33 to 0.82)**
12 months	1.3 (1.0 to 1.5)	**1.31 (1.05 to 1.57)**	1.3 (0.7 to 1.8)	1.54 (0.97 to 2.13)
>12 months	0.5 (0.4 to 0.7)	**0.56 (0.40 to 0.72)**	0.4 (0.0 to 0.8)	**0.47 (0.00 to 0.93)**
Passive (registry)	1.0 (0.9 to 1.0)	1.00 (ref)	0.8 (0.6 to 1.0)	1.00 (ref)
Loss to follow-up¶				
<20%	1.1 (1.1 to 1.2)	1.02 (0.97 to 1.06)	1.1 (1.0 to 1.3)	**1.53 (1.33 to 1.84)**
≥20%	1.1 (1.1 to 1.1)	1.00 (ref)	0.8 (0.6 to 1.0)	1.00 (ref)
Missing	0.9 (0.8 to 0.9)	0.80 (0.76 to 0.84)	0.8 (0.6 to 1.0)	1.02 (0.83 to 1.27)

CI=confidence interval; CIN=cervical intraepithelial neoplasia; HC2=hybrid capture 2; HPV=human papillomavirus; HR=high risk.

* Except for results by HPV type, all rates are estimated for a woman who is HR-HPV positive at baseline.

† Adjusted for all variables included in the table. Except for results by HPV type, all rates are estimated for a woman who is HR-HPV positive at baseline.

‡ Negative incidence rates and ratios predicted by the model are truncated at 0.0 for coherence.

§ Commercial tests included the Abbott RealTime High-Risk HPV assay, Cervista HPV HR assay, CLART HPV 2, cobas 4800 HPV Test, APTIMA, MyHPV DNA microchip, and PCR-RDB HPV Genotyping Kit.

‖ Interval between baseline and first follow-up visit in the protocol of observational studies and randomised controlled trials.

¶ Loss to follow-up between the baseline and second visit, where reported. If only overall loss to follow-up was reported, then this value was used as a proxy.

Table 2. CIN2+ incidence rates predicted by a meta-regression model for women who were cytology/histology normal but HPV-positive at baseline.

Progression predictors	Adjusted for HPV type only*		Multivariable model†	
	Incidence rate per 100 women-years (95% CI)‡	Incidence rate ratio (95% CI)‡	Incidence rate per 100 women-years (95% CI)‡	Incidence rate ratio (95% CI)‡
HPV type				
HR-HPV	1.6 (1.6 to 1.6)	1.00 (ref)	1.8 (1.4 to 2.2)	1.00 (ref)
HPV16/18	2.9 (2.7 to 3.0)	**1.78 (1.69 to 1.88)**	3.0 (2.6 to 3.5)	**1.70 (1.55 to 1.92)**
HR excluding 16/18	0.4 (0.4 to 0.5)	**0.27 (0.22 to 0.30)**	0.8 (0.4 to 1.2)	**0.43 (0.26 to 0.54)**
HPV16	2.8 (2.6 to 3.0)	**1.73 (1.61 to 1.86)**	2.5 (2.0 to 2.9)	**1.38 (1.23 to 1.57)**
HPV18	1.0 (0.7 to 1.2)	**0.61 (0.44 to 0.78)**	1.3 (0.8 to 1.8)	**0.72 (0.54 to 0.88)**
HPV31	1.8 (1.3 to 2.2)	1.09 (0.83 to 1.36)	1.9 (1.3 to 2.5)	1.06 (0.81 to 1.33)
HPV33	1.9 (1.4 to 2.5)	1.22 (0.85 to 1.58)	2.1 (1.4 to 2.8)	1.16 (0.82 to 1.53)
HPV35	0.7 (0.5 to 0.9)	**0.43 (0.29 to 0.58)**	1.1 (0.6 to 1.6)	**0.62 (0.43 to 0.76)**
HPV45	0.8 (0.5 to 1.1)	**0.50 (0.32 to 0.68)**	1.1 (0.6 to 1.6)	**0.62 (0.42 to 0.79)**
HPV51	0.7 (0.5 to 0.9)	**0.45 (0.32 to 0.59)**	1.1 (0.6 to 1.5)	**0.59 (0.41 to 0.73)**
HPV52	1.0 (0.7 to 1.2)	**0.60 (0.44 to 0.75)**	1.3 (0.8 to 1.7)	**0.71 (0.54 to 0.86)**
HPV58	1.0 (0.6 to 1.3)	**0.60 (0.39 to 0.81)**	1.3 (0.8 to 1.8)	**0.74 (0.53 to 0.94)**
HPV59	0.7 (0.5 to 1.0)	**0.44 (0.30 to 0.60)**	1.1 (0.6 to 1.5)	**0.61 (0.42 to 0.75)**
HPV infection persistence				
Baseline assessment only	1.6 (1.5 to 1.6)	1.00 (ref)	1.8 (1.3 to 2.2)	1.00 (ref)
Persistent infection	4.1 (3.9 to 4.3)	**2.56 (2.42 to 2.70)**	4.6 (4.1 to 5.1)	**2.62 (2.29 to 3.13)**
HPV detection event				
Incident	0.0 (0.0 to 0.2)	**0.02 (0.00 to 0.11)**	0.1 (0.0 to 0.5)	**0.03 (0.00 to 0.23)**
Prevalent	1.7 (1.6 to 1.7)	1.00 (ref)	1.9 (1.5 to 2.3)	1.00 (ref)
HPV detection assay				
HC2	1.6 (1.6 to 1.6)	1.00 (ref)	1.8 (1.4 to 2.2)	1.00 (ref)
Commercial§	2.1 (1.9 to 2.3)	**1.32 (1.17 to 1.47)**	2.4 (1.9 to 2.9)	**1.35 (1.17 to 1.56)**
Other	1.6 (1.5 to 1.7)	1.01 (0.95 to 1.08)	1.5 (1.0 to 2.0)	0.86 (0.66 to 1.04)
Mean/median participant age				
<30y	2.4 (2.2 to 2.6)	1.00 (ref)	1.9 (1.4 to 2.4)	1.00 (ref)
≥30y	1.3 (1.3 to 1.4)	**0.55 (0.50 to 0.61)**	1.7 (1.2 to 2.1)	0.87 (0.71 to 1.05)
Missing	1.8 (1.7 to 1.9)	**0.74 (0.69 to 0.81)**	1.7 (1.2 to 2.1)	0.87 (0.72 to 1.05)
Baseline normal test				
Cytology	1.6 (1.6 to 1.7)	1.00 (ref)	1.6 (1.4 to 1.8)	1.00 (ref)
Colposcopy/histology	1.8 (1.3 to 2.4)	1.14 (0.80 to 1.48)	1.9 (1.3 to 2.5)	1.20 (0.84 to 1.57)
Excluded women with history of abnormal results				
Yes	1.6 (1.5 to 1.7)	1.00 (ref)	1.6 (1.1 to 2.0)	1.00 (ref)
No	1.6 (1.6 to 1.7)	1.03 (0.99 to 1.08)	1.8 (1.4 to 2.2)	1.14 (1.00 to 1.35)
Study type				
Registry data	1.6 (1.5 to 1.6)	1.00 (ref)	1.9 (1.5 to 2.3)	1.00 (ref)
Observational study	1.3 (1.1 to 1.5)	**0.81 (0.70 to 0.93)**	0.8 (0.2 to 1.3)	**0.42 (0.15 to 0.65)**
Randomized controlled trial	1.8 (1.7 to 2.0)	**1.16 (1.08 to 1.24)**	1.4 (0.9 to 1.9)	**0.76 (0.55 to 0.96)**
Follow-up intervals (protocol)‖				
<6 months	2.7 (2.3 to 3.2)	**1.69 (1.40 to 1.98)**	3.1 (2.3 to 3.9)	**1.77 (1.36 to 2.27)**
6 months	1.3 (1.1 to 1.5)	**0.81 (0.71 to 0.90)**	2.8 (2.3 to 3.3)	**1.60 (1.41 to 1.86)**
12 months	2.2 (1.9 to 2.4)	**1.35 (1.20 to 1.49)**	2.1 (1.5 to 2.7)	1.22 (0.96 to 1.51)
>12 months	1.2 (1.0 to 1.4)	**0.76 (0.65 to 0.86)**	1.6 (1.0 to 2.2)	0.93 (0.66 to 1.20)
Passive (registry)	1.6 (1.6 to 1.7)	1.00 (ref)	1.7 (1.3 to 2.2)	1.00 (ref)
Loss to follow-up¶				
<20%	1.6 (1.6 to 1.7)	**1.1 (1.1 to 1.2)**	2.1 (1.7 to 2.5)	**1.30 (1.19 to 1.46)**
≥20%	1.5 (1.4 to 1.5)	1.0 (ref)	1.6 (1.2 to 2.1)	1.00 (ref)
Missing	1.7 (1.6 to 1.8)	**1.2 (1.1 to 1.2)**	2.1 (1.7 to 2.6)	**1.32 (1.14 to 1.57)**

CI=confidence interval; CIN=cervical intraepithelial neoplasia; HC2=hybrid capture 2; HPV=human papillomavirus; HR=high risk.

* Except for results by HPV type, all rates are estimated for a woman who is HR-HPV positive at baseline.

† Adjusted for all variables included in the table. Except for results by HPV type, all rates are estimated for a woman who is HR-HPV positive at baseline.

‡ Negative incidence rates and ratios predicted by the model are truncated at 0.0 for coherence.

§ Commercial tests included the Abbott RealTime High-Risk HPV assay, Cervista HPV HR assay, CLART HPV 2, cobas 4800 HPV Test, APTIMA, MyHPV DNA microchip, and PCR-RDB HPV Genotyping Kit.

‖ Interval between baseline and first follow-up visit in the protocol of observational studies and randomised controlled trials.

¶ Loss to follow-up between the baseline and second visit, where reported. If only overall loss to follow-up was reported, then this value was used as a proxy.

Table 3. Model-predicted average cumulative risk of CIN2+, CIN3+, and cancer for women who were cytology/histology normal but HPV-positive at baseline, with 95% prediction intervals.

HPV type	1 year (95% prediction interval)	3 years (95% prediction interval)	5 years (95% prediction interval)
	Cumulative CIN2+ risk (%)*		
HR-HPV	3.9 (0.0 to 11.2)	7.0 (0.0 to 14.0)	9.9 (2.5 to 16.8)
HPV16/18	5.1 (0.0 to 12.3)	10.4 (3.1 to 17.2)	15.4 (8.5 to 21.9)
HR excluding 16/18	2.8 (0.0 to 10.2)	3.7 (0.0 to 11.0)	4.6 (0.0 to 11.8)
HPV16	5.0 (0.0 to 12.2)	10.2 (2.8 to 17.0)	15.1 (8.1 to 21.6)
HPV18	2.6 (0.0 to 10.0)	3.1 (0.0 to 10.4)	3.5 (0.0 to 10.8)
HPV31	4.1 (0.0 to 11.4)	7.5 (0.0 to 14.6)	10.8 (3.2 to 17.8)
HPV33	4.3 (0.0 to 11.6)	8.1 (0.3 to 15.2)	11.7 (4.0 to 18.8)
HPV35	3.0 (0.0 to 10.4)	4.5 (0.0 to 11.7)	5.8 (0.0 to 13.1)
HPV45	3.2 (0.0 to 10.5)	4.8 (0.0 to 12.1)	6.4 (0.0 to 13.6)
HPV51	3.1 (0.0 to 10.4)	4.6 (0.0 to 11.8)	6.0 (0.0 to 13.2)
HPV52	3.3 (0.0 to 10.6)	5.2 (0.0 to 12.4)	7.1 (0.0 to 14.2)
HPV58	3.3 (0.0 to 10.6)	5.2 (0.0 to 12.5)	7.1 (0.0 to 14.3)
HPV59	3.1 (0.0 to 10.4)	4.5 (0.0 to 11.8)	6.0 (0.0 to 13.2)
	Cumulative CIN3+ risk (%)*		
HR-HPV	2.1 (0.0 to 9.5)	4.3 (0.0 to 11.5)	6.4 (0.0 to 13.5)
HPV16/18	3.5 (0.0 to 10.8)	8.1 (0.5 to 15.1)	12.6 (5.3 to 19.3)
HR excluding 16/18	1.5 (0.0 to 9.0)	2.5 (0.0 to 9.9)	3.4 (0.0 to 10.7)
HPV16	3.3 (0.0 to 10.6)	7.6 (0.1 to 14.6)	11.8 (4.5 to 18.5)
HPV18	2.3 (0.0 to 9.7)	4.9 (0.0 to 12.1)	7.3 (0.0 to 14.4)
HPV31	2.6 (0.0 to 9.9)	5.5 (0.0 to 12.7)	8.4 (0.9 to 15.4)
HPV33	2.7 (0.0 to 10.1)	6.1 (0.0 to 13.2)	9.3 (1.8 to 16.2)
HPV35	2.2 (0.0 to 9.6)	4.4 (0.0 to 11.7)	6.6 (0.0 to 13.9)
HPV45	2.0 (0.0 to 9.5)	4.0 (0.0 to 11.3)	6.0 (0.0 to 13.1)
HPV51	2.0 (0.0 to 9.5)	4.0 (0.0 to 11.3)	6.0 (0.0 to 13.1)
HPV52	2.1 (0.0 to 9.5)	4.2 (0.0 to 11.5)	6.3 (0.0 to 13.4)
HPV58	2.0 (0.0 to 9.4)	4.0 (0.0 to 11.3)	5.8 (0.0 to 13.1)
HPV59	2.1 (0.0 to 9.5)	4.1 (0.0 to 11.3)	6.0 (0.0 to 13.2)
	Cumulative cervical cancer risk (%)*,†		
HR-HPV	0.8 (0.0 to 8.3)	1.2 (0.0 to 8.7)	1.6 (0.0 to 9.1)
HPV16	1.2 (0.0 to 8.7)	2.5 (0.0 to 9.9)	3.7 (0.0 to 11.0)

CIN=cervical intraepithelial neoplasia; HPV=human papillomavirus; HR=high risk.

* Negative risks predicted by the model are truncated at 0.0 for coherence.

† Results reported only for HPV types assessed in more than one study.

Figures

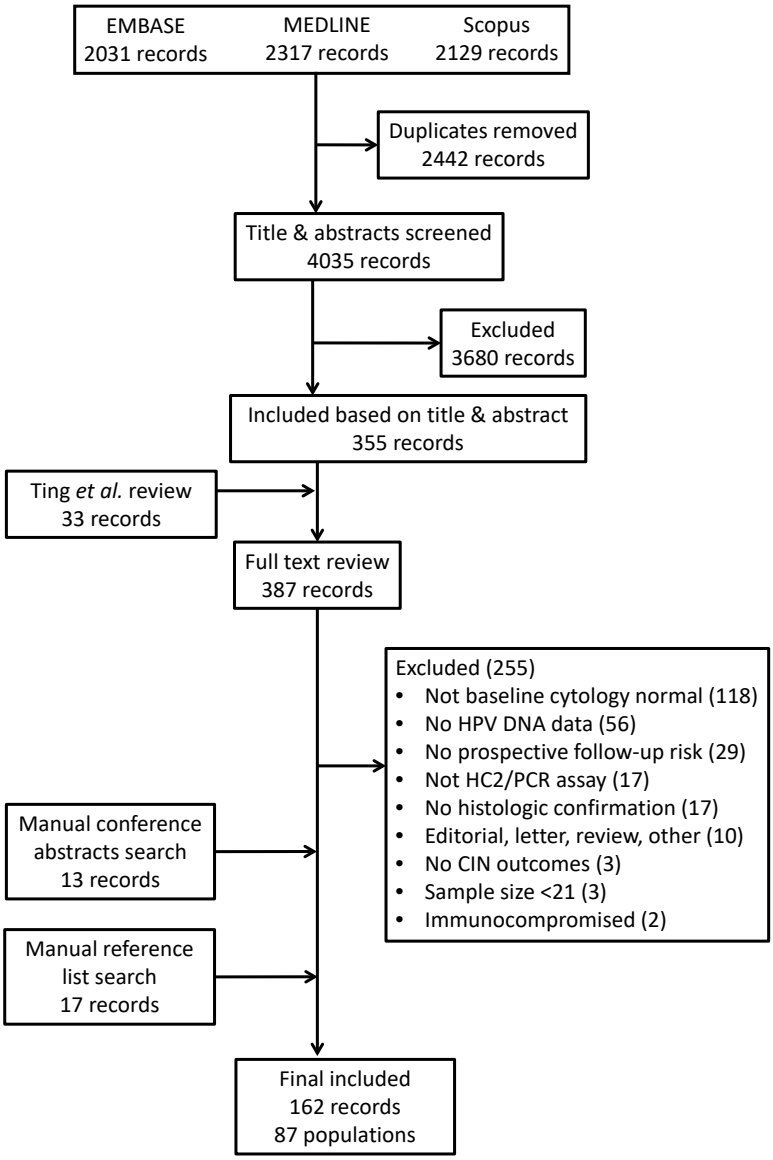

Figure 1. Flowchart of study selection. CIN=cervical intraepithelial neoplasia; HC2=Hybrid Capture 2; HPV=human papillomavirus; PCR=polymerase chain reaction.

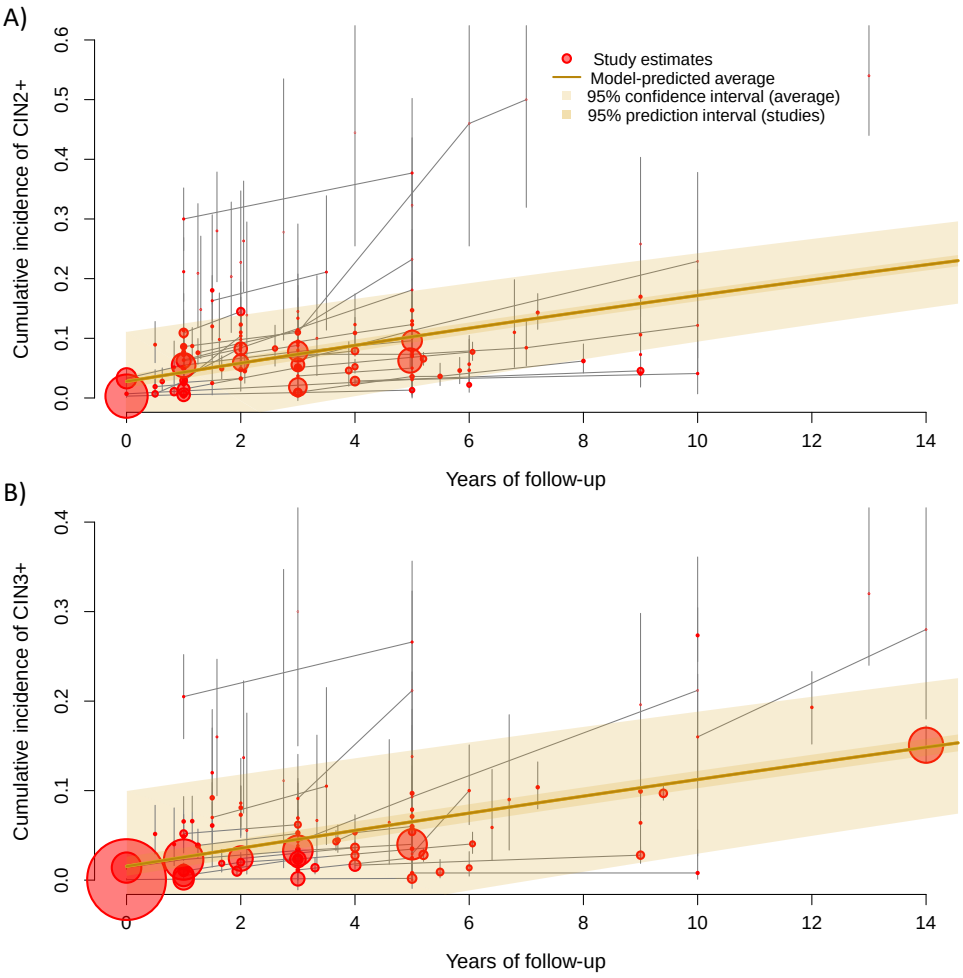

Figure 2. Cumulative incidence of A) CIN2+ and B) CIN3+ in women positive for any HR-HPV type and cytology/histology normal at baseline. Circles: estimates from individual studies; the circle size is inversely proportional to the standard error. Vertical error bars: 95% CI of individual study estimates. Horizontal grey lines: connection of study estimates from the same publication. Thick dark grey line: the model prediction for the weighted average cumulative risk of CIN2+ and CIN3+ across studies. Dark shaded region: 95% CI for the model-predicted average. Light shaded region: 95% prediction interval for individual study estimates. CI=confidence interval; CIN=cervical intraepithelial neoplasia; HR-HPV=high risk human papillomavirus.

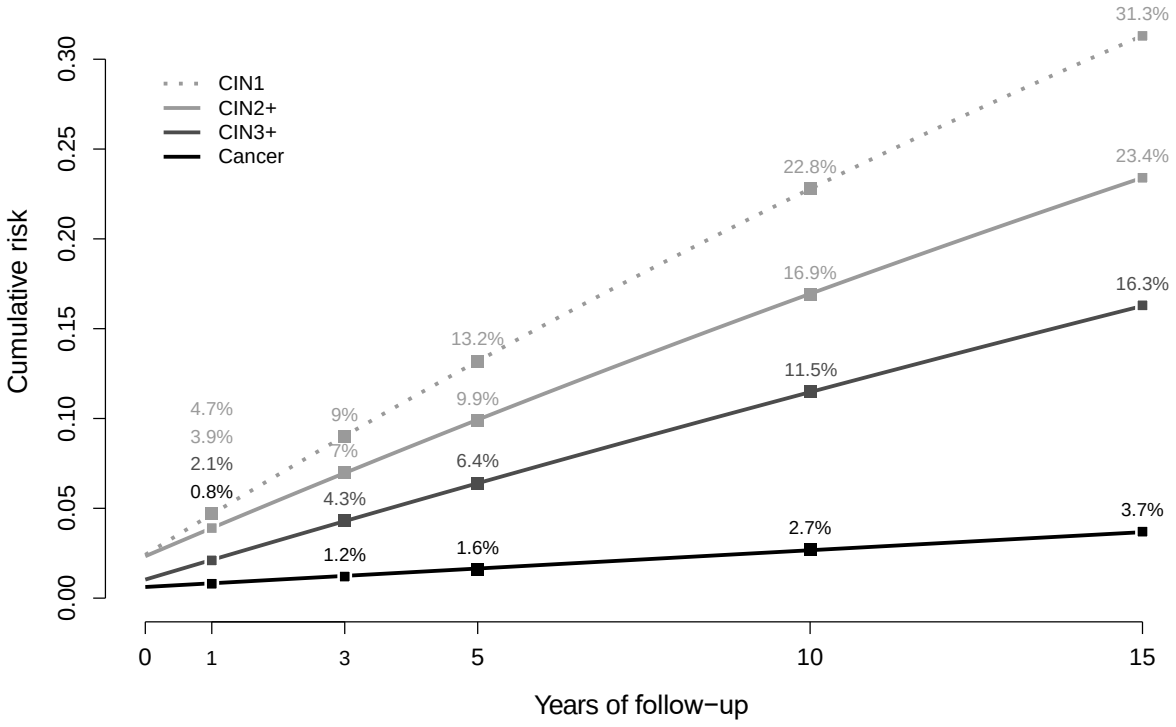

Figure 3. Model-predicted average cumulative risk of CIN and cancer in women who are HR-HPV positive but cytology/histology normal at baseline. CIN=cervical intraepithelial neoplasia; HR-HPV=high risk human papillomavirus.

Supplementary appendix

Cumulative risk of cervical intraepithelial neoplasia for women with normal cytology but positive for human papillomavirus: systematic review and meta-analysis

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Supplementary References 8

Search strategy for MEDLINE

1	papillomaviridae/
2	alphapapillomavirus/
3	Papillomavirus Infections/
4	DNA Probes, HPV/
5	human papillomavirus.ab,kf,kw,ti.
6	HPV.ab,kf,kw,ti.
7	Papillomaviridae.ab,kf,kw,ti.
8	Alphapapillomavirus.ab,kf,kw,ti.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	Cervical Intraepithelial Neoplasia/
11	exp Uterine Cervical Dysplasia/
12	*Uterine Cervical Neoplasms/
13	(Cervical Intraepithelial Neoplas* or CIN or CIN2* or CIN 2* or CIN3* or CIN 3*).ab,kf,kw,ti.
14	cervical dysplasia.ab,kf,kw,ti.
15	10 or 11 or 12 or 13 or 14
16	exp Cohort Studies/
17	Follow-Up Studies/
18	exp clinical trial/
19	Public Health Surveillance/
20	(cohort stud* or follow up or followup or follow-up or followed up or longitudinal stud* or prospective or clinical trial*).ab,kf,kw,ti.
21	*risk factors/
22	(progression adj2 risk).ab,kf,kw,ti.
23	(risk adj2 management).ab,kf,kw,ti.
24	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25	*risk factors/
26	Risk Factors/
27	Risk Management/
28	risk management.ab,kf,kw,ti.
29	risk-based management.ab,kf,kw,ti.
30	longitudinal.ab,kf,kw,ti.
31	risk factor*.ab,kf,kw,ti.
32	prospective.ab,kf,kw,ti.
33	disease progression/
34	progression.ab,kf,kw,ti.
35	Incidence/
36	incidence.ab,kf,kw,ti.
37	((Cervical Intraepithelial Neoplas* or Cervical Intra-epithelial Neoplas* or CIN or CIN2* or CIN 2* or CIN3* or CIN 3* or cancer*) adj3 risk).ab,kf,kw,ti.
38	genotype-specific risk*.ab,kf,kw,ti.
39	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40	9 and 15 and 24 and 39

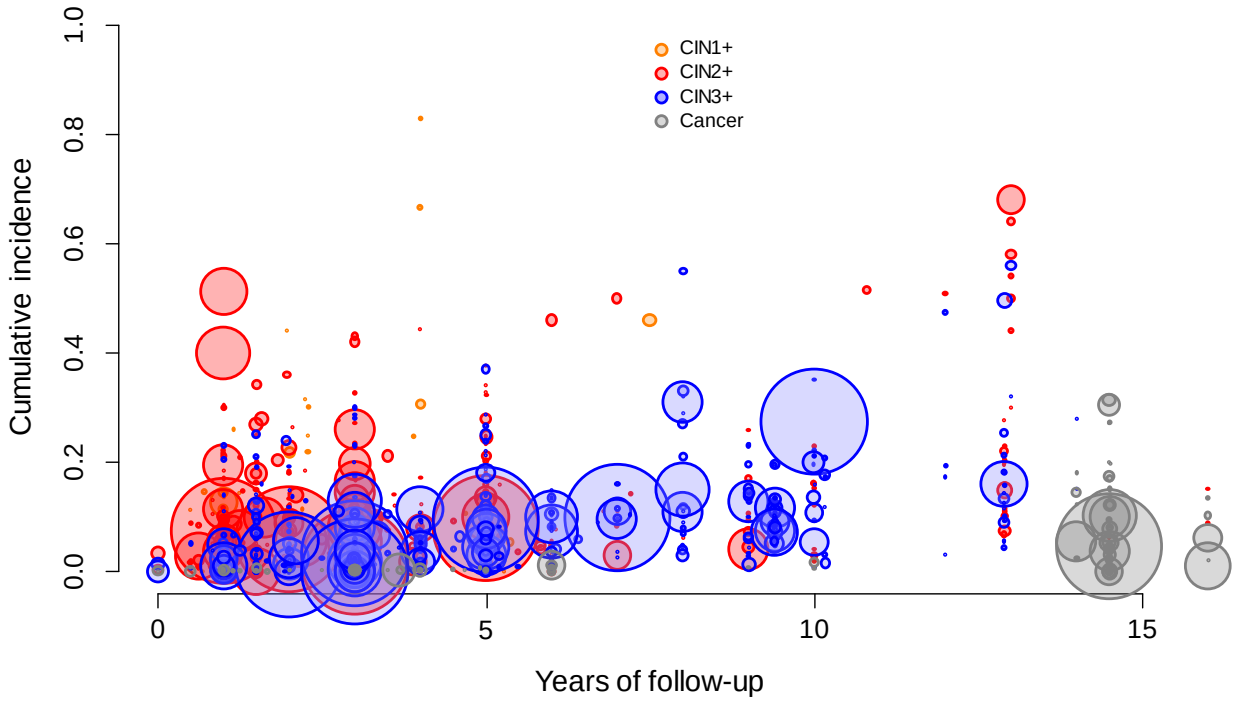
41	Animals/
42	Humans/
43	41 not 42
44	40 not 43
45	limit 44 to (english or french)
46	limit 45 to yr="1990-Current"

Appendix Table S4. Characteristics of the study records (N = 162) included in the systematic review.

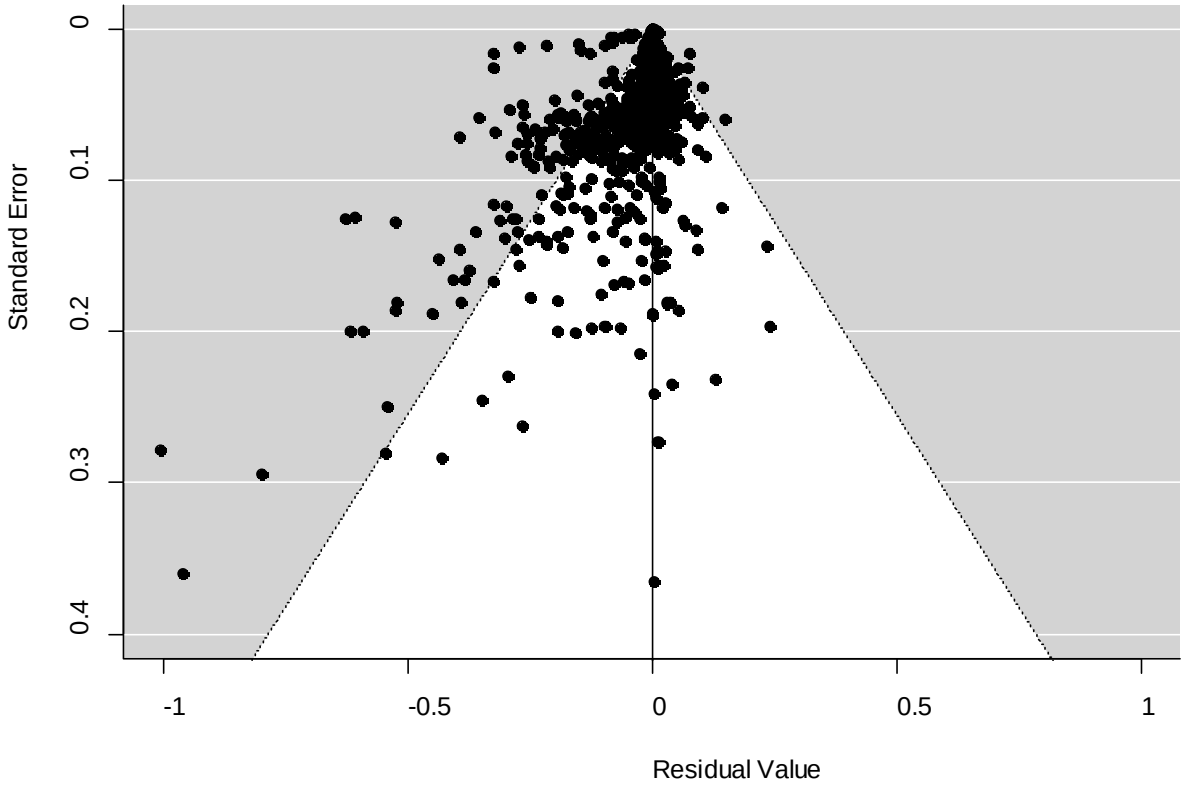
Study characteristic	n (%)	References
Baseline normal test		
Cytology	154 (95.1%)	1-154
Colposcopy/histology	8 (4.9%)	155-162
Mean/median participant age[a]		
<30y	22 (13.5%)	32,34,40,43,47,48,50-52,62,63,70,74,104,107,115-117,147,148,155,161
≥30y	108 (66.3%)	1-12,14-16,18-23,26,28,30,35-39,41,42,44-46,56-58,62,64,66-69,71-73,75,76,78,80-102,105,106,108-112,114,118,120-122,125-127,129-131,133-135,137,138,140,143,144,149-152,156,158-160,162
Missing	33 (20.2%)	13,17,24,25,28,29,31,33,49,53-55,59-61,65,77,79,103,123,124,128,132,136,139,141,142,145,146,153,154,157
HPV DNA detection method		
HC2	88 (54.3%)	1-3,5,11,12,17,19-25,32-37,39,43,46,49-55,57,59-65,67,68,72-75,78,80,81,83,85,87,88,93-96,98-100,103-106,108,109,115,117,118,120,121,123-125,127,128,133,138,140,145,146,148,151,152,155,157-159,161,162
Commercial[b]	14 (8.6%)	10,38,58,101,119,126,130,131,136,139,141,142,144,153
Other	59 (36.4%)	4,6-9,13-16,18,26-31,40-42,44,45,47,48,56,66,69-71,76,77,79,82,84,86,89-92,97,102,107,110-114,116,122,129,134,135,137,143,147,149,150,154,156,160
Missing	1 (0.6%)	132
Study region		
Asia	21 (13.0%)	3,15,18,58,64,66,67,69,92-94,99-101,125,126,131,152,158,159,162
Central and South America	10 (6.2%)	14,16,35-37,41,43,76,84,137
Europe	83 (51.2%)	1,4-9,17,19-21,23,24,26-31,34,42,44-46,50-52,62,63,68,70-75,77,79-82,86-91,102-104,106,108-114,116,119,122,123,127-130,132,134-136,138-140,142,143,145,146,149,150,153,156,157,160
North America	45 (27.8%)	2,10-13,22,25,32,33,38,39,47,49,53-57,59-61,65,78,83,85,95-98,105,115,117,118,120,121,124,133,141,144,147,148,151,154,155,161
Multi-region	3 (1.9%)	40,48,107
Excluded women with history of abnormal results		
Yes	68 (42.0%)	3-9,11,12,16,19,20,22-24,26,27,37,40,42,44-49,56,64,75,78,79,82,84-91,93,94,97,100,101,104,107-114,119-122,124,128,129,131,133,135,140,143,149,158
No	92 (56.8%)	1,2,10,13-15,17,18,21,25,29-36,38,39,41,43,50-55,57-63,65-72,74,76,77,80,81,83,92,95,96,98,99,102,103,105,106,115-118,123,125-127,130,132,134,136-139,141,142,144-148,150-157,159-162
Missing	2 (1.2%)	28,73
Study type		
Registry data	49 (30.2%)	2,9,11-13,15,18,23,25,33-36,38,39,50-55,57,62,63,65,67,69,74,78,83,90,91,95-98,101,103-105,118,120,121,124,138,142,151,154,157
Observational study	67 (41.4%)	3,5,14,16,17,19-21,24,30,37,41,44-46,56,58,64,66,68,70-73,76,79-81,84,85,87-89,92-94,99,100,102,106,108,109,116,119,123,125-128,130-132,136,137,139,140,145-147,149,150,152,153,158-160,162
Randomized controlled trial	45 (27.8%)	1,4,6-8,10,22,26,27,29,31,32,40,42,43,47-49,59-61,75,77,82,86,107,110-115,117,122,129,133-135,141,143,144,148,155,156,161
Meta-analysis[c]	1 (0.6%)	28
Follow-up intervals (protocol)[a,d]		
<6 months	9 (5.5%)	3,16,40,48,70,84,92,147,158
6 months	51 (31.3%)	4-8,14,19-21,24,26,32,37,40-42,44,45,47,56,58,66,68,72,73,76,80,81,86,89,100,102,106,107,114-117,119,122,126,134,135,143,148-150,155,156,160,161
12 months	29 (17.8%)	17,22,29,31,43,49,64,71,77,85,87,88,93,94,108,109,123,128,131-133,136,139,140,144-146,153,159
>12 months	11 (6.7%)	10,30,46,59-61,99,125,127,152,162
Passive (registry)	62 (38.0%)	1,2,9,11-13,15,18,23,25,27,33-36,38,39,50-55,57,62,63,65,67,69,74,75,78,79,82,83,90,91,95-98,101,103-105,110-113,118,120,121,124,129,130,137,138,141,142,151,154,157
Missing	1 (0.6%)	28
Mean/median length of follow-up[a]		
<2 years	26 (16.0%)	3,5,20,21,24,26,31,32,38,48,49,66,72,73,81,87-89,92,96,102,118,134,143,150,153
2 to <5 years	29 (17.8%)	1,9,16,19,25,40,43-45,67,70,77,83,84,90,98,101,107,112,116,119,120,124,130,140,147,156,157,159
5 to <9 years	26 (16.0%)	7,23,27,30,41,49,59,61,64,75,76,91,93,94,97,104,108,109,111,113,114,128,131,133,137,160
≥ 10 years	8 (4.9%)	15,18,34,50,51,62,63,69
Missing	74 (45.4%)	2,4,6,8,10-14,17,22,28,29,33,35-37,39,42,46,47,52-58,60,65,68,71,74,78-80,82,85,86,95,99,100,103,105,106,110,115,117,121-123,125-127,129,132,135,136,138,139,141,142,144-146,148,149,151,152,154,155,158,161,162
Loss to follow-up[a,e]		
<20%	62 (38.0%)	1,3,9,11,14,16,22-24,27,30,32,41,44,47-49,56,70-72,75,76,81,82,84,92,99,103-105,107-113,115,120,121,123,125,127,131,133,134,137,138,143,144,146,148,149,151,152,155-157,160-162
≥20%	63 (38.7%)	4-8,10,12,15,17,18,20,26,28,29,31,34-39,42,45,46,50-52,59-64,66-69,74,77-79,83,85-88,90,93,94,101,102,114,116-119,124,128,135,140,141,145,159
Missing	38 (23.3%)	2,13,19,21,25,33,40,43,49,53-55,57,58,65,73,80,89,91,95-98,100,106,122,126,129,130,132,136,139,142,147,150,153,154,158

CIN=cervical intraepithelial neoplasia; HC2=hybrid capture 2; HPV=human papillomavirus.
a The counts sum to >162 because three of the 162 records reported on multiple study populations with more than one characteristic.

b Commercial tests included the Abbott RealTime High-Risk HPV assay (1), Cervista HPV HR assay (1), CLART HPV 2 (1), cobas 4800 HPV Test (9), APTIMA(1), MyHPV DNA microchip (1), and PCR-RDB HPV Genotyping Kit (1).
c Meta-analysis of observational studies and trials fitting the eligibility criteria. The meta-analysis was included as it reported an analysis of three studies not published elsewhere.
d Interval between baseline and first follow-up visit in the protocol of observational studies and randomised controlled trials.
e Loss to follow-up between the baseline and second visit, where reported. If only overall loss to follow-up was reported, then this value was used as a proxy.



Appendix Figure S1. Cumulative incidence of CIN1+, CIN2+, CIN3+, and cancer in women positive for HPV and cytology/histology normal at baseline, all HPV types. Estimates from individual studies are shown in circles, with the size of the circle being inversely proportional to its standard error. CIN=cervical intraepithelial neoplasia.



Appendix Figure S2. Funnel plot of estimated standard errors compared with standardized residuals from the meta-regression model. A positive residual means that the observed risk was lower than the one predicted by the model, while a negative residual means that the observed risk was larger than the one predicted by the model.

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