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Worldwide burden of cervical human papillomavirus (HPV) in women over 50 years with abnormal cytology: a systematic review and meta-analysis

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ABSTRACT

Introduction More than half of global cervical cancer cases occur among women older than 50. However, global estimates regarding the human papillomavirus (HPV) prevalence among this population are lacking, especially for women with abnormal cytology. Therefore, we conducted a systematic review and meta-analysis to estimate the worldwide HPV prevalence in women aged 50 and older with abnormal cytology.

Methods We searched PubMed, Scopus and Web of Science for quantitative studies reporting any or high-risk (HR)-HPV prevalence for women 50 years and older with abnormal cytology (atypical squamous cells of undetermined significance and higher). We extracted data on world region, subregion, cervical lesion type, recruitment setting, HPV test, year of study conduct and HPV prevalence from the included studies. We assessed the risk of bias of the included studies using a modified Newcastle-Ottawa scale. We estimated the pooled prevalence and 95% CIs of any-HPV and HR-HPV using random-effects models, considering the world regions. Additionally, we estimated the prevalence by HPV type, lesion type and age groups.

Results Overall, 113 studies met the inclusion criteria, of which 104 were included in the meta-analysis. Among women aged 50 and older with abnormal cytology, the estimated global pooled prevalence of any-HPV from 53 studies, including 14 585 women, was 54.5% (95%CI, 46.0 to 62.8%), and the HR-HPV prevalence from 85 studies, covering 33 672 women, was 43.0% (95%CI, 36.6 to 49.5%). There was a higher HR-HPV prevalence among women with high-grade lesions and women living in the African continent. No major differences in HR-HPV prevalence between the age groups of women over 50 years were found. The most common single HPV types worldwide were 16 and 52, with pooled prevalence estimates of 12.0% (95%CI, 8.0% to 17.7%) and 8.4% (95%CI, 4.4% to 15.4%), respectively.

Conclusion Our findings highlight the relevance of targeted screening interventions among women 50 years and older. To achieve the elimination of cervical cancer, age-inclusive screening strategies should be considered.

PROSPERO registration number CRD42021241365.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The majority of cervical cancer cases and deaths occur among women 50 years and older, disproportionately affecting women in low and middle-income countries (LMICs). Persistent human papillomavirus (HPV) infections are necessary for the development of cervical cancer; however, much is unknown about the HPV burden in older women in a global context, especially for those with abnormal cytology findings.

WHAT THIS STUDY ADDS

⇒ To our knowledge, this is the first systematic review and meta-analysis estimating global HPV prevalence among women over 50 with abnormal cytology. Analysing data from 14 585 and 33 672 women, we found a global any-HPV prevalence of 54.5% and a high-risk HPV prevalence of 43.0%, respectively. The highest HPV prevalence was found in Africa and the lowest primarily in Northern America and Europe.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The burden of HPV among older women with abnormal cytology highlights the relevance of cervical cancer screening and more age-inclusive cancer prevention policies worldwide. This age group has a high burden of cervical cancer and has not benefited from HPV vaccination.

INTRODUCTION

In 2022, 662 301 women were diagnosed with cervical cancer worldwide, with more than half of those cases diagnosed after age 50.[1] Older women also disproportionately died from cervical cancer, with more than 70% of the deaths occurring among those over 50 years old.[1] Despite global cervical cancer screening efforts and general decreases in incidence in the last decades, there are reports of stagnation of incidence and second peaks in cervical cancer incidence rates among older women in some regions.[2 3] This

pattern may be attributed to factors such as new acquisitions of human papillomavirus (HPV) infections in older age or reactivations due to declining immunity[4] and cohort effects, including changes in sexual behaviour, contraceptive use and inadequate participation in cervical cancer screening.[3]

Most guidelines in high-income countries recommend cervical cancer screening discontinuation between 60 and 70 years of age.[5] These recommendations are challenged due to the paucity of research conducted on women over 45 years to inform evidence-based decision-making.[6] In low- and middle-income settings, screening is usually recommended up to age 49 or no official recommendations exist,[5] despite cervical cancer contributing to the largest proportion of preventable cases and deaths among older women in these countries.[7] More than 60% of women worldwide have also never been screened between 30 and 49 years.[5] Older women are often excluded or are not participating in trials and studies.[8 9] The worldwide data regarding HPV prevalence among older women are scarce. Prior reports and meta-analyses have primarily estimated the HPV prevalence among women with normal cytology,[10–13] with a lesser focus on older women, especially those with abnormal cytological findings (atypical squamous cells of undetermined significance and higher, ASCUS+).

Therefore, we aimed to systematically review the literature and estimate the HPV prevalence among women 50 years and older with abnormal cytology worldwide, considering cervical lesion severity, age groups and HPV types.

METHODS

Our research was conducted based on the review protocol registered in PROSPERO (ID: CRD42021241365), following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analysis Of Observational Studies in Epidemiology guidelines. Overall, we aimed to investigate the HPV prevalence, screening participation and cervical cancer incidence among older women. Here, we present the analyses of HPV prevalence among women with abnormal cytology.

Eligibility criteria

We included quantitative studies from which the HPV prevalence could be extracted or calculated for women 50 and older with abnormal cytology findings. Abnormal cytology refers to changes in the cervix detected via cytology or cytopathology examinations.[12] These include atypical glandular cells of undetermined significance (AGUS); ASCUS; atypical squamous cells-cannot exclude HSIL (ASC-H); low-grade squamous intraepithelial lesion (LSIL); high-grade squamous intraepithelial lesion (HSIL); and corresponding lesion diagnoses of cervical intraepithelial neoplasia (CIN) 1, 2 and 3.[12] Women with cervical cancer and studies reporting only on subpopulations such as women with HIV were excluded. Reviews and meta-analyses were excluded. However, their references were hand-searched. Authors were contacted in case of unclear information on cytology or age group, and when the information was received, the studies were included.

Search strategy and article screening

The systematic search was undertaken in Medline via PubMed, Scopus and Web of Science, considering initially studies from inception until 31 May 2022, with an updated search extending to 26 April 2024. Handsearching was also conducted using Google Scholar and on references of identified reviews and reports after the main search. The main search strategy can be seen in online supplemental table S1 in the supplement. All identified articles were managed via Endnote and screened using Rayyan for titles/abstracts and Excel for full text. VO, SR (title/abstract) and LH (full text) independently screened the studies, resolving discrepancies through discussion.

Data extraction

VO and MR independently extracted the following details from the individual studies: authors, publication year, study conduct year, study design, recruitment setting, world region and subregion, screening method (conventional or LBC), lesion type, HPV test used, number of HPV types tested, prevalence or number of participants, and number of women HPV positive. The United Nations (UN) geographic region classification was used to categorise the world's regions and subregions.[14] When reported, we recorded prevalence by lesion type, age groups and HPV types. Only the prevalence at baseline was extracted from longitudinal studies and RCTs. In cases of multiple HPV testing methods, we report results from validated tests like Hybrid Capture II (HC2, PCR GP5+/6+ or Cobas.[15]

Quality assessment

We applied a modified Newcastle-Ottawa Scale to assess the risk of bias, focusing on sample representativeness overall, representativeness for older women specifically, sample size, quality of reported methods and HPV test validity. Studies could score up to five points (one for each criterion); those scoring 3–5 points were classified as having a low risk for bias (Methods S1). A study was considered representative if it recruited women from the general population using random sampling, from population-based screening programmes or multiple clinics. Age-stratified samples or those oversampling older women were considered representative of the age group. Studies received points if they included over 100 women older than 50 with abnormal cytology and reported the methodology used regarding cytology, HPV testing and genotyping. Studies that used validated and partially validated tests[15 16] received one additional point. The assessment was performed by VO and TN, with any discrepancies addressed through discussion.

Statistical analyses

Using random-effects models in meta-analyses, we separately estimated the pooled any-HPV (from studies that tested for both high-risk (HR)- and low-risk (LR)-HPVs) and the HR-HPV prevalence with 95% CIs, only from studies reporting the population numbers or from which these could be estimated. HR-HPV types were considered those as informed by the studies and following the International Agency for Research on Cancer (IARC) 2012 classification,[17] including group 1 (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) and groups 2A and 2B (types 26, 30, 34, 53, 66, 67, 68, 69, 70, 73, 82, 85, 97). The proportions were calculated using the arcsine transformation, while the pooling was done using the inverse variance method. Prediction intervals (PIs) were also calculated and displayed in forest plots, alongside assessments of heterogeneity via the I^2 statistic. Publication bias was examined through funnel plots. Results are presented in forest plots for any-HPV and HR-HPV prevalence considering the world regions (Northern America, South and Central America, Africa, Asia, Europe).

We examined prevalence differences between world regions, subregions, lesion type, recruitment setting, HPV tests, number of HPV types, risk of bias (Methods S2) in subgroup meta-analyses and univariate meta-regressions considering the last year of study conduct for any-HPV and HR-HPV, separately. Differences were assessed using Q tests to evaluate whether the observed variations in prevalence across subgroups were greater than expected by sampling error alone, thereby indicating whether the assessed factors could account for the observed heterogeneity. All variables were included in multiple meta-regression models separately for any and HR-HPV to identify relevant predictors influencing the heterogeneity in the prevalence estimates. We considered the world subregion in the analyses, except for African and Oceanian studies, where the world region was considered due to a limited number of studies.

For studies reporting on HPV prevalence by cervical lesion grade (AGUS, ASCUS, ASC-H, LSIL or HSIL), we also estimated pooled HPV prevalence for both any and HR-HPV. CIN1 lesions were categorised as LSIL, while CIN2 and CIN3 were classified as HSIL for these analyses. Similarly, if studies reported the HPV prevalence by age group and HPV type, we also estimated the pooled prevalence for each category. We estimated the worldwide HPV prevalence by 10-year age groups (50–59 to 80–89). If the studies provided prevalence data for 5 year age groups, this data was included in the corresponding 10 year age group. Further, we calculated the pooled prevalence for each HPV IARC group 1 and 2A/B type, if reported, globally and by world region. Global estimates were calculated by pooling data of each HPV type across regions. The pooled prevalence of HPV 16/18, defined as the proportion of women positive for 16 and/or 18, was estimated by including the studies that reported only the combined prevalence of 16/18 and those that reported the prevalence of each type separately. Therefore, the pooled 16/18 prevalence was estimated by dividing 16/18+16+18 HPV positives with the tested population of interest. Finally, the HPV type prevalence was also estimated by lesion type (ASCUS, LSIL, HSIL). We used generalised linear mixed models for all three analyses. We conducted all analyses using R V.4.2.2 (meta-package).

Patient and public involvement

The patient and public involvement statement is not applicable in this paper since the patients or the public were not involved in our research's design, conduct, reporting or dissemination plans.

RESULTS

Search strategy findings

Overall, we identified 10 730 studies and an additional 194 through hand searching (online supplemental figure S1). 113 studies were included in the qualitative review and 104 in the meta-analysis.

Study characteristics

Forty-six (40.7%) studies were conducted in Asia,[18–63] 31 (27.4%) in the Americas[64–94] and 30 (26.5%) in Europe[95–124] (table 1 and online supplemental table 2). Only five studies were identified from Africa[125–129] and one from Oceania.[130] Studies were conducted mainly in Eastern Asia (n=29; 25.7%), Northern America (n=14; 12.4%), Southern America (n=11; 9.7%) and Southern Europe (n=11; 9.7%). The majority were cross-sectional studies (90.3%). Fifty-two (46.0%) studies recruited participants from clinics and hospitals, 40 (35.4%) from screening programmes and databases and 21 (18.6%) from the general population. Eighty-five studies (75.2%) were conducted from 2006, and more than half involved more than 50 women older than 50 years with abnormal cytology. Various HPV tests were used, with HC2 applied in 22 (19.5%) studies, followed by PCR GP5/6 or GP5/6+ in 20 (17.7%) studies. Roughly 60% of the studies had a low risk of bias (online supplemental figure S2). The main quality issues were representativeness for women older than 50 and low sample sizes for these populations.

Any human papillomavirus (HPV) prevalence

Overall, 55 studies reported on any-HPV prevalence among women with abnormal cytology, with prevalence ranging from 0% to 100%. Two studies with missing population numbers presented an any-HPV prevalence of 72.7%[63] and 88.1%.[62] From the remaining 53 studies, we estimated a global any-HPV pooled prevalence of 54.5% (95%CI, 46.0 to 62.8%) among 14 585 women 50 and older with abnormal cytology (I^2=98%, p=0; PI=7.2%–96.7%) (figure 1). No evidence of publication bias could be noted (online supplemental figure 3). The highest any-HPV prevalence was found in Africa (83.7%, 95%CI, 65.9 to 95.8%) and South and Central America (66.7%, 95%CI, 48.8 to 82.5%) and the lowest in Northern America (42.1%, 95%CI, 7.3 to 82.5%) (Q=21.3, p=0.0007; figure 1 and online supplemental

Table 1 Summary of the key characteristics of the included studies (n=113)

Study characteristics	Number (%)
World region	
Americas	31 (27.4)
Africa	5 (4.4)
Asia	46 (40.7)
Europe	30 (26.5)
Oceania	1 (0.9)
World subregion	
Northern America	14 (12.4)
Southern America	11 (9.7)
Central America	6 (5.3)
Northern Africa	1 (0.9)
Middle Africa	1 (0.9)
Western Africa	2 (1.8)
Eastern Africa	1 (0.9)
Western Asia	7 (6.2)
Southern Asia	7 (6.2)
Southeastern Asia	3 (2.7)
Eastern Asia	29 (25.7)
Northern Europe	7 (6.2)
Western Europe	8 (7.1)
Southern Europe	11 (9.7)
Eastern Europe	4 (3.5)
Melanesia	1 (0.9)
Study design	
Cross-sectional	102 (90.3)
Longitudinal	8 (7.1)
Case control	1 (0.9)
RCT	2 (1.8)
Recruitment setting	
Clinical setting*	52 (46.0)
General population	21 (18.6)
Screening†	40 (35.4)
Year of study conduct‡	
Before 2000	5 (4.4)
2000–2005	23 (20.4)
2006–2010	30 (26.5)
2011–2015	30 (26.5)
2016–2022	25 (22.1)
Sample size: women 50 years and older	
<50	51 (45.1)
50–100	15 (13.3)
101–300	23 (20.4)
301–500	4 (3.5)
>500	11 (9.7)
Not reported	9 (8.0)
HPV testing method	
PCR GP5/6 or GP5/6+	20 (17.7)
PCR MY09/11 or PCR PGMY09/11	12 (10.6)
PCR GP5/GP6+and MY09/11 or PGMY09/11	6 (5.3)
HC2	22 (19.5)
Linear Array HPV Genotyping Test	8 (7.1)
Cobas HPV Test	8 (7.1)
Anyplex II	3 (2.7)
Hybribio GenoArray	4 (3.5)
PCR L1	11 (9.7)
PCR E6/E7	8 (7.1)
Other§	11 (9.7)
HPV prevalence: quantitative analyses¶	
Any-HPV prevalence	53 (46.9)
HR-HPV prevalence	85 (75.2)
Lesion-specific prevalence**	76 (67.3)
Age-specific prevalence††	43 (38.1)
Type-specific prevalence‡‡	30 (26.5)
HPV prevalence: qualitative only§§	
Any-HPV prevalence	2 (1.8)
HR-HPV prevalence	9 (8.0)
Risk of bias based on NOS	
Low	67 (59.3)
High	46 (40.7)

Note: Percentages may not add up to 100% due to rounding;
World regions and sub-regions have been defined based on the UN Standard Country or Area Codes for Statistical Use.
Any HPV, both high and low-risk HPV.
*Studies recruiting participants from gynaecological clinics and hospitals.
†Screening databases, laboratories and population-based screening programmes.
‡Based on the last year of study conduct.
§Includes studies using other methods such as in situ hybridisation, dot blot or southern blot analysis.
¶These do not add up to the total number of studies because some studies reported on both any-HPV and HR-HPV prevalence or in any combination with genotyping and prevalence by age groups.
**Studies reporting prevalence based on individual abnormal lesion types.
††Studies reporting on prevalence for any age groups 50+ for any-HPV or HR-HPV prevalence.
‡‡Studies reporting on genotyping information for women older than 50 with abnormal cytology findings.
§§Studies reporting on any-HPV or HR-HPV prevalence only and not reporting population numbers for women older than 50 with abnormal cytology findings. These do not add up to the total number of studies that did not report on population numbers because some reported on both any and HR-HPV prevalence.
HC2, Hybrid Capture II; HR-HPV, high-risk HPV; NOS, Newcastle–Ottawa scale; RCT, randomised controlled trial.

table S3). There were significant differences by subregion (Q=113.0, p<0.0001), lesion type (Q=747.0, p<0.0001), HPV test (Q=32.4, p<0.0001) and the number of HPV types tested (Q=117.1, p<0.0001) (online supplemental table S3). No differences were found based on risk of

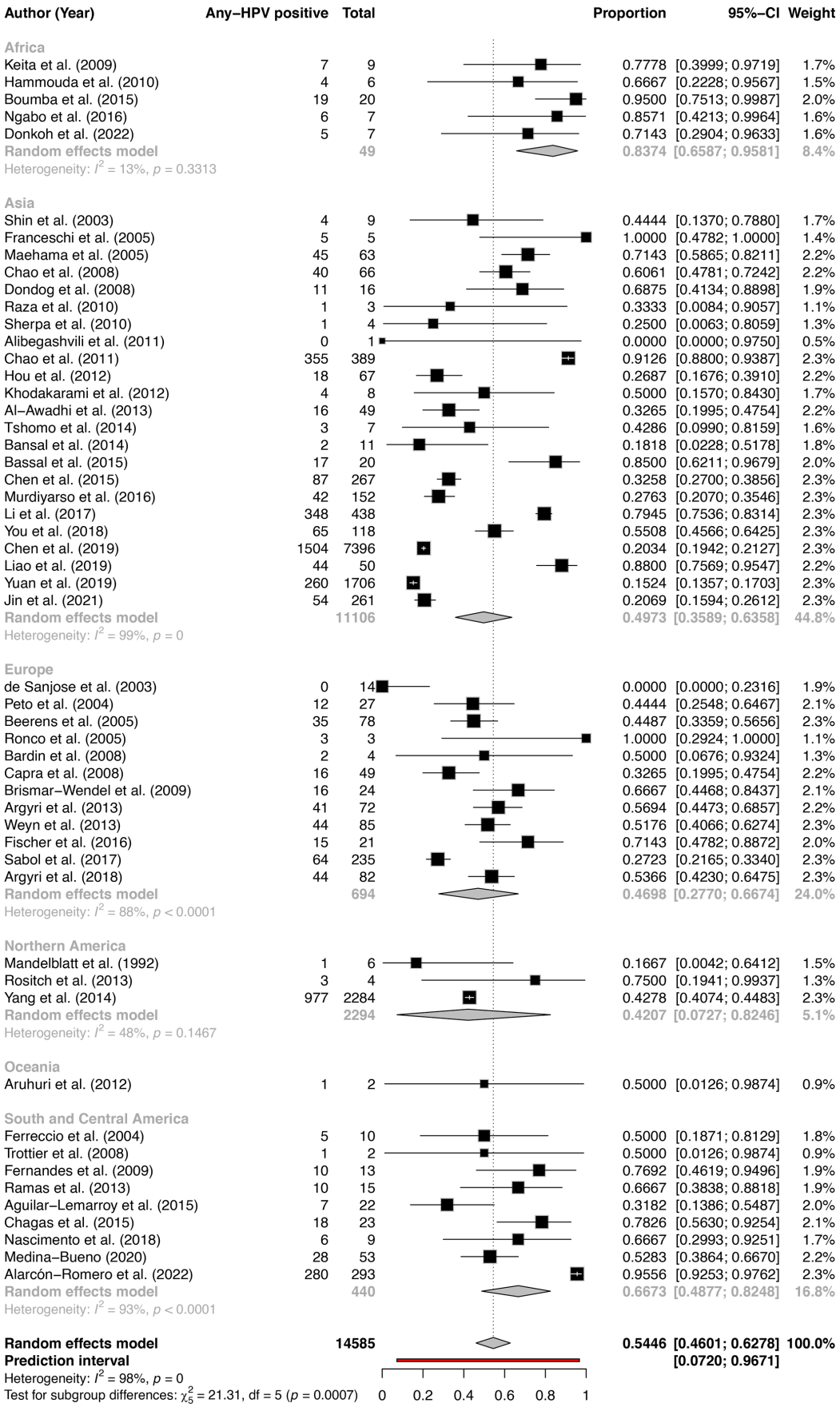

Figure 1 Meta-analysis results on the any human papillomavirus (any-HPV) prevalence among women 50 years and older with abnormal cytology by world region and ranked based on the publication year (n=53).

bias, recruitment setting and year of study conduct. In the multiple meta-regression, only subregional differences remained significant, with Western Asia having a significantly lower prevalence compared with Africa (online supplemental figure S4).

High-risk human papillomavirus (HR-HPV) prevalence

Ninety-four studies reported on HR-HPV prevalence among women with abnormal cytology, with prevalence ranging from 0% to 100%. Nine studies did not provide population numbers with HPV prevalence ranging from 18.0% to 92.2%.[26 38 50 54 55 62 63 71 93] From the remaining 85 studies and among 33 672 women 50 and older with abnormal cytology, the pooled HR-HPV prevalence was 43.0% (95%CI, 36.6 to 49.5%; PI=2.7%–91.0%; I^2=98%, p=0) (figure 2). There was no evidence of publication bias (online supplemental figure S5). The highest HR-HPV prevalence was in Africa (69.2%, 95%CI, 54.3 to 82.3%) and the lowest in Northern America (33.3%, 95%CI, 20.0 to 48.2%) and Europe (36.8%, 95%CI, 26.7 to 47.5%) (Q=29.6, p<0.0001; figure 2 and online supplemental table S4). Significant differences were observed across subregions (Q=113.4, p<0.0001), lesion types (Q=61.8, p<0.0001), HPV tests (Q=21.9, p=0.0155), by year of study conduct (p=0.0098) and risk of bias (Q=3.9, p=0.0483). There were no differences in prevalence based on the number of HPV types tested and recruitment setting (online supplemental table S4).

Based on the meta-regression results, significant geographical differences remained. HR-HPV prevalence for all European subregions (except Southern Europe), Northern and South America, and Western Asia was lower than Africa's estimates after controlling for the rest of the predictors (online supplemental figure S6). Similarly, HPV prevalence among women with HSIL was higher compared with those with ASCUS. Additionally, the HPV prevalence in studies with a low risk of bias was lower than in those with a high risk of bias.

Human papillomavirus (HPV) prevalence by lesion type

In total, 76 studies presented HPV prevalence by single lesion types, of which 38 provided any-HPV prevalence and 65 HR-HPV prevalence. The any-HPV and HR-HPV pooled prevalence increased progressively with the severity of cervical lesions (figure 3; online supplemental table S5). The any-HPV and HR-HPV prevalence were lowest among women with AGUS, at 24.7% (95%CI, 19.1% to 31.4%) and 12.7% (95%CI, 8.7% to 18.3%), respectively. The highest prevalence was observed in women with HSIL, with pooled estimates of 87.9% (95%CI, 76.0% to 94.3%) for any-HPV and 76.6% (95%CI, 66.9% to 84.2%) for HR-HPV (figure 3; online supplemental table S5).

Human papillomavirus (HPV) prevalence by age

Fourteen studies reported any-HPV prevalence, and 35 studies provided HR-HPV prevalence for at least one age group over 50 years. The pooled any-HPV prevalence was above 48% across all age groups, while HR-HPV prevalence remained over 34% (figure 4; online supplemental table S6). An increase in HPV prevalence with increasing age can be noted; however, there is high uncertainty due to small population numbers, especially for those over 70 years (figure 4; online supplemental table S6).

Human papillomavirus (HPV) genotype prevalence

Thirty studies reported the prevalence of at least one HPV type for women 50 and older with abnormal cytology. Most studies reported on the types HPV16, 18, 31, 33, 35, 52 and 58. The most commonly identified types worldwide were 16, 52 and 53, with a pooled prevalence of 12.0% (95%CI, 8.0% to 17.7%), 8.4% (95%CI, 4.4% to 15.4%) and 5.8% (95%CI, 4.1% to 8.0%), respectively (figure 5; online supplemental tables S7-S12). The pooled global prevalence of 16/18 was 14.0% (95%CI, 9.5% to 20.1%).

The prevalence of the single HPV types varied by lesion type (online supplemental figure S7). The HPV 16/18 prevalence increased with the severity of the lesions, from 6.2% (95% CI, 4.1% to 9.4%) among women with ASCUS to 17.3% (95%CI, 10.6% to 26.8%) and 35.9% (95%CI, 22.9% to 51.4%) among women with LSIL and HSIL, respectively. For women with HSIL, the prevalence of HPV 16 and 52 was 28.4% (95%CI, 17.3% to 43.0%) and 15.2% (95%CI, 8.8% to 24.9%), respectively. For ASCUS, HPV 16 and 52 prevalence were lower at 4.3% (95%CI, 2.2% to 7.9%) and 2.5% (95%CI, 0.9% to 6.4%), respectively. The HPV 53 prevalence was lower among women with HSIL (3.8%; 95%CI, 2.6% to 5.6%) than those with LSIL findings (6.8%; 95%CI, 4.2% to 10.9%).

DISCUSSION

We aimed to assess the burden of cervical HPV infections among women 50 years and older with abnormal cytology. We estimated that worldwide, over half of those women had detectable any-HPV types, and 43% had HR-HPV infection. Based on the multiple meta-regression results, the any-HPV prevalence was higher in Africa compared with Western Asia. The HR-HPV prevalence was highest among African women compared with Eastern, Western, and North European; South and North American; and those from Western Asia. Higher HR-HPV prevalence was also seen among women with HSIL compared with those with ASCUS.

Globally, we estimated that over half of the women with LSIL and about 77% of those with HSIL had HR-HPV infection. The any-HPV prevalence was higher, with approximately 88% of women with HSIL infected with HPV. This aligns with the overall HPV prevalence of 85% found in a prior meta-analysis analysing women of all ages with HSIL.[131] The latest global HPV Information Centre report showed an HPV 16/18 prevalence for women of all ages with LSIL and HSIL of 25.8% and 51.9%, respectively.[12] In comparison, our estimates for HPV 16/18 among women over 50 years were lower, at 17.3% for women with LSIL and 35.9% for women with

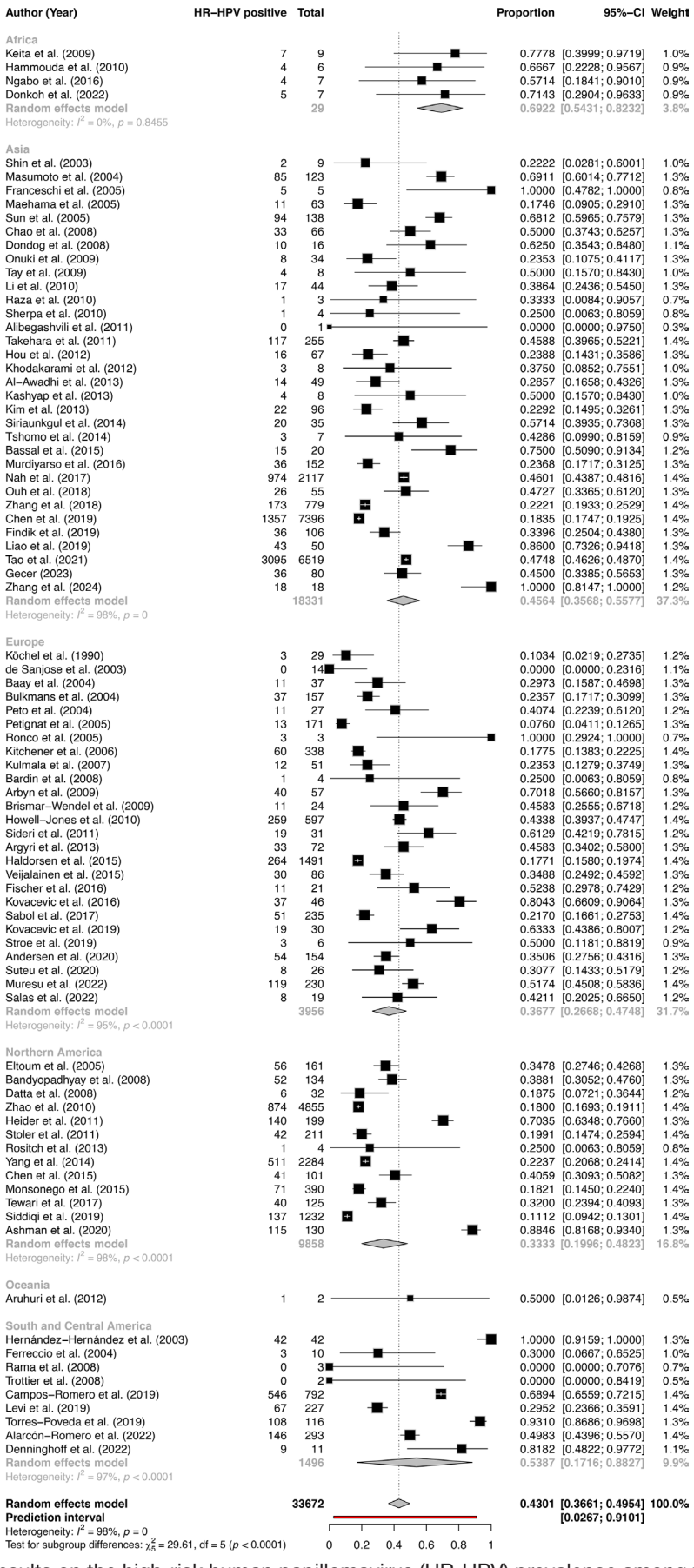

Figure 2 Meta-analysis results on the high-risk human papillomavirus (HR-HPV) prevalence among women 50 years and older with abnormal cytology by world region and ranked based on the publication year (n=85).

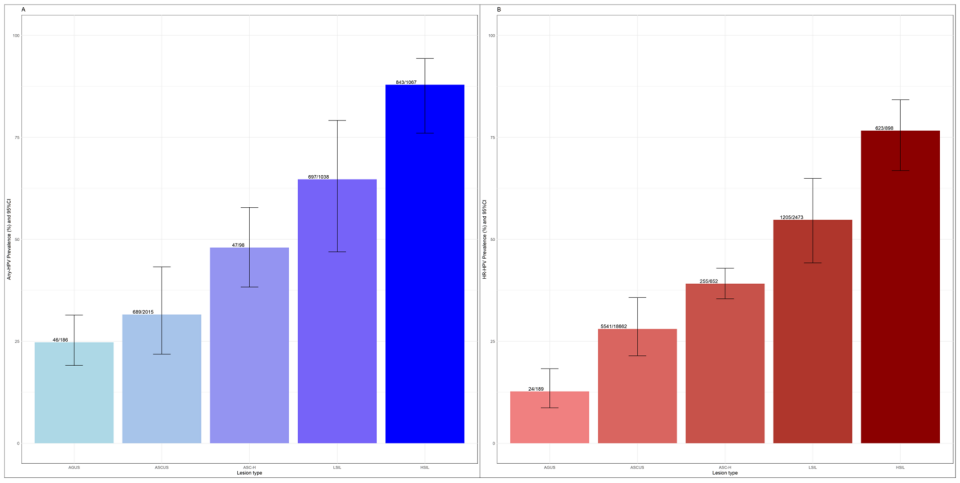

Figure 3 Any-HPV and HR-HPV pooled prevalence by lesion type (n=38 for any-HPV, n=65 for HR-HPV). AGUS, atypical glandular cells of undetermined significance; ASC-H, atypical squamous cells-cannot exclude; ASCUS, atypical squamous cells of undetermined significance; HR-HPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

HSIL. Prior reviews have shown that types other than 16/18 might be overrepresented in cervical lesions[131 132] which might partly explain the lower prevalence among older women with LSIL and HSIL seen in our analysis, who had a high any-HPV prevalence. Other factors, such as the studies analysed, geographical regions of included studies, HPV testing methods and their performance in different settings, could influence the differences.

The most common single HPV types among older women with abnormal cytology were 16 and 52. The same genotypes have been found among women of all ages with LSIL and HSIL results worldwide.[12] The HPV types

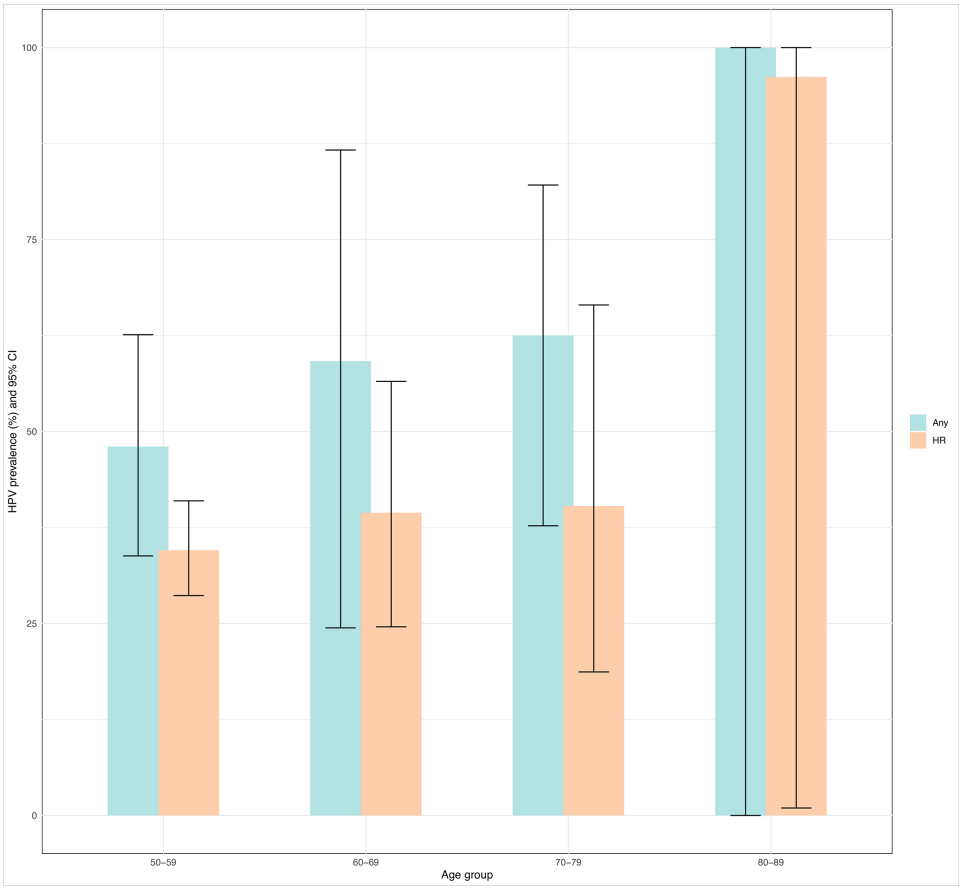

Figure 4 Any-HPV and HR-HPV pooled prevalence by 10-year age group (n=14 for any-HPV, n=35 for HR-HPV). HPV, human papillomavirus.

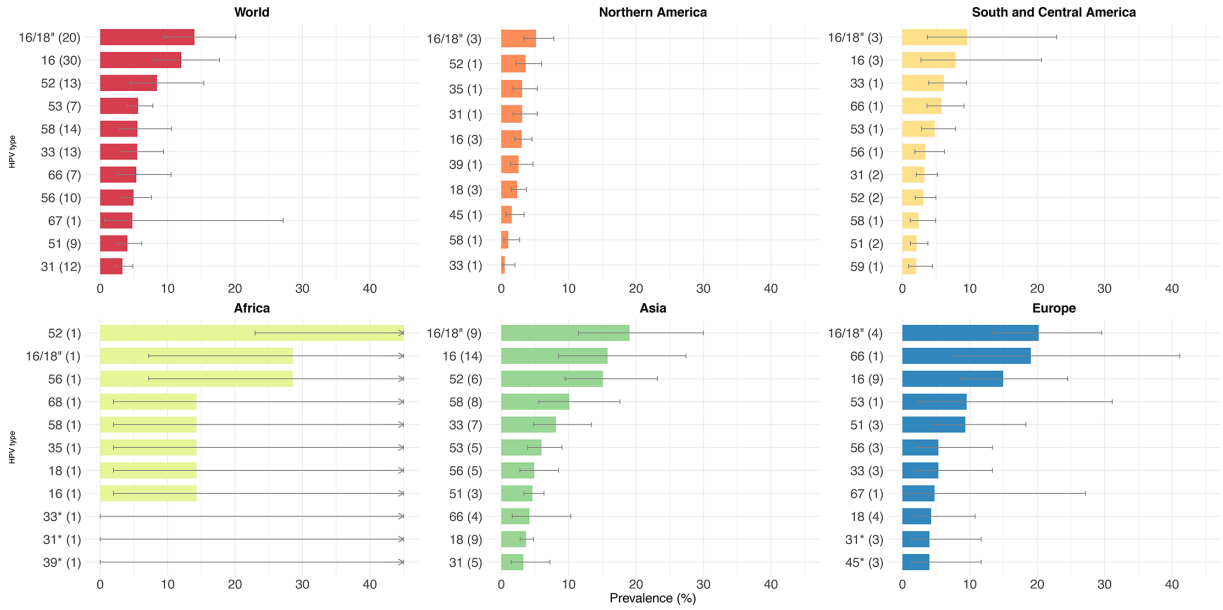

Figure 5 Pooled prevalence of human papillomavirus (HPV) 16/18 and the 10 most common single types worldwide and by world region (n=30). Note: for Northern America, there was information only for nine single genotypes. "The pooled prevalence of HPV 16/18, defined as positivity for either type, was estimated by including studies that reported both types together and those that reported them separately, calculated as 16/18+16+18 divided by the population of interest. *The HPV genotype prevalence is the same for HPV types 45, 51 and 66 as for types 31, 33 and 39].

53, 66 and 67, classified as probably carcinogenic, were among the 10 most common in older women. However, the prevalence of HPV 53 decreased with increasing lesion severity. This suggests that while these types can be present in cervical lesions, their presence is not necessarily associated with the development of cervical cancer.

We also found overall geographical differences in the HR-HPV prevalence among women with abnormal cytology. These might be explained by possible variations in HPV type distribution, disparities in access to screening services, screening practices and HPV testing methods. HPV type 52 was the most common single type in Northern America and Africa; however, the prevalence was based on only one study each for those regions. Given that most HPV 16/18 positives, which had the highest prevalence in all world regions but Africa, are HPV 16 positives, HPV 16 is likely the most prevalent. As previously documented, we also found a higher prevalence of HPV 52 and 58 among cervical lesions in Asia compared with other regions.[132 133]

Regarding access to screening, in many African countries, cervical cancer screening remains limited,[5] which could lead to more high-grade cervical lesions, explaining the high prevalence of HR-HPV types. Contrastingly, European and North American countries have established screening programmes with good coverage, some starting as early as the 1960s.[134] The early detection through screening and treatment of cervical lesions might have contributed to fewer HPV infections seen later in life.

No major age group differences in HPV prevalence were found. While an increase in the HPV estimates can be seen with increasing age, the data for women 70 years and older were scarce, limiting interpretation. The most robust estimates were those for HR-HPV prevalence for the age groups 50 to 69, for which we do not see significant differences. This highlights the continued risk of older age groups developing cervical cancer. Prior research found that among women aged 55 and older with persistent infection, the cumulative risk of cervical cancer was higher (18.1%) compared with those aged 45–54 (14.4%) and 30–44 (5.5%). However, the risk was low across age groups for new infections.[135] Conversely, other studies reported no major differences in the risk of progression[136] or cumulative CIN2+ risk[137] between younger and older women with HPV-positive findings and minor abnormalities. Other research indicated a lower risk of progression in older age groups with HPV-positive findings overall, except for women with HSIL findings, where the risk remained similar across age groups.[138 139] These findings underline the relevance of screening older women.

Most countries worldwide still use cervical cytology as their primary or co-testing method (with HPV testing) for cervical cancer screening.[5] For postmenopausal women, however, cytology has a lower sensitivity due to physiological changes at the portio.[140] The transformation zone moves upward in the cervical canal, making it difficult to get adequate cervical samples.[140] False negatives increase with age, leading to less protection from screening.[140] Improved physician training, HPV testing and investigation of multiple strategies, including diagnosis via methylation markers,[141] might be relevant for older women in different settings, considering the lack of HPV vaccination, potentially higher persistence of infections in comparison to younger women and higher cervical cancer mortality rates.

Further, more data are needed on the burden of HPV infections among older women, especially in Africa, Oceania and Southern Asia. In light of increasing life expectancy worldwide, future research should consider including representative samples of older women to investigate the prevalence of HPV types in cervical lesions and their progression to cervical cancer to accurately predict cancer risk.

Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis of the HPV burden among older women with abnormal cytology worldwide. We analysed data from 51 countries globally and included more than 30 000 women older than 50 years of age in our HR-HPV analyses.

However, the between-study heterogeneity is one limitation. We conducted subgroup analyses and meta-regression models to investigate this variability, where the world region, cervical lesion type, recruitment setting, HPV test, HPV categories, year of study conduct and risk of bias were considered. The heterogeneity in HR-HPV prevalence was, for the most part, attributed to regional differences and lesion type. These influences should be considered when interpreting the pooled estimates. On the other hand, the estimates from Africa, Oceania and women over 70 in the age group analyses should be interpreted cautiously due to the few studies identified. The risk of bias influenced the observed heterogeneity, with a higher prevalence seen in studies with a high risk of bias, likely due to various sources of bias (selection of participants, sample size, reporting) in these studies. However, the overestimation appears minimal, as the overall pooled HR-HPV prevalence (43.0%) is close to that of low-risk of bias studies alone (38.3%). Additionally, there are no standard procedures for screening and classification across settings, which could have led to some misclassification of lesion types. The data by HPV type among different lesions were limited and should also be interpreted with caution.

CONCLUSION

The burden of HPV among older women with abnormal cytology is high, with no significant differences by age group, which highlights the relevance of continued screening for those aged 50 years and older worldwide. Additionally, in light of the increasing size of the global elderly population and improved life expectancy, countries should evaluate the cost-effectiveness of extending the screening age or offering a catch-up HPV test to older women who are not HPV vaccinated. To achieve a cervical cancer incidence of four per 100 000, as defined by the WHO for the elimination of cervical cancer,[142] older women should be part of the prevention efforts and screening strategies worldwide.

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