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REVIEW

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Risk factors for human papillomavirus infection and disease: A targeted literature summary

Marta del Pino[1] | Alex Vorsters[2] | Elmar A. Joura[3] | John Doorbar[4] | Marta Haniszewski[5] | Irene Asensio Gudina[6] | Petya Kodjamanova[7] | Christine Velicer[8] | Rosybel Drury[9]

[1]Department of Obstetrics and Gynecology, Hospital Clínic of Barcelona, University of Barcelona, Barcelona, Spain

[2]Vaccine & Infectious Disease Institute, Centre for the Evaluation of Vaccination, University of Antwerp, Antwerp, Belgium

[3]Department of Gynaecology and Obstetrics, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

[4]Division of Virology, Department of Pathology, University of Cambridge, Cambridge, UK

[5]Amaris Consulting, Toronto, Canada

[6]Amaris Consulting, Barcelona, Spain

[7]Amaris Consulting, Sofia, Bulgaria

[8]Global Medical and Scientific Affairs, Merck & Co., Inc., Rahway, New Jersey, USA

[9]Global Medical and Scientific Affairs, MSD, Lyon, France

Correspondence
Marta del Pino, Gynecology Oncology Unit, Clinical Institute of Gynecology, Obstetrics and Neonatology (ICGON), Hospital Clínic de Barcelona, Universitat de Barcelona, c/Villarroel, 170, 08036 Barcelona, Spain.
Email: MDELPINO@clinic.cat

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Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

Abstract

Adolescents are the primary cohort for routine human papillomavirus (HPV) vaccination, but unvaccinated adults may also benefit. A lack of consensus on which adults to target and the presence of reimbursement barriers likely contribute to the lag in adult vaccinations, highlighting missed prevention opportunities. Understanding factors contributing to risk of HPV infection and disease could help in decision making on vaccination. This review summarizes existing literature on risk factors for HPV infection and disease and includes 153 studies reporting relative risks or odds ratios for factors associated with HPV infection or disease in adults, published between 2009 and 2020. Despite inconsistent design and reporting of risk factors across studies, this review confirmed several risk factors associated with adult infection, including human immunodeficiency virus positivity, number of sex partners, and smoking. These findings can support policymaking, guideline development, and clinical decision making for HPV vaccination and screening of high-risk adult groups.

KEYWORDS

human papillomavirus, papillomavirus, sexually transmitted disease, vaccine

1 | INTRODUCTION

Human papillomavirus (HPV) infection is the most common sexually transmitted infection (STI) worldwide.[1] While most HPV infections clear, some persist and may progress to premalignant lesions and cancer.[2,3] Globally, approximately 690 000 new cases of HPV-related cancer occurred in 2018, comprising mostly cervical cancer (approximately 570 000 cases).[4] In addition, approximately 29 000 new anal, 11 000/14 000 new vulvar/vaginal, 18 000 new penile, and 42 000 new head and neck cancer cases were attributable to HPV infection.[4] Furthermore, millions of precancers and genital warts cases are reported each year;[1,5–7] however, the number of cases is likely to be underreported given the lack of genital wart registries in most countries. These data demonstrate the high global burden of both cervical and noncervical HPV-related disease.

Strategies for the prevention of HPV-related diseases include both primary prevention of infection and secondary prevention through screening for and treatment of precancerous lesions.[8–10] Availability of and access to cervical screening is limited for women in many parts of the world,[8,11,12] and screening is not performed for other HPV-related cancers, such as vulvar and oropharyngeal cancers. Therefore, primary prevention of HPV infection through vaccination remains the most efficient approach to reducing the burden of HPV-related disease.

HPV vaccines are highly effective in preventing vaccine-type HPV infection and associated diseases for which they are indicated.[13–16] Because these vaccines confer maximum protection when administered before HPV exposure, individuals aged 9–14 years are the recommended target population for routine HPV vaccination in many countries.[17–19] Adults are also at risk for HPV infection and disease,[20] and the efficacy of HPV vaccination against vaccine-type HPV infections in adults has been demonstrated in randomized clinical trials and immunobridging studies.[21–26] This has led some countries to recommend catch-up HPV vaccination for individuals through age 26 years (e.g., the United States, Sweden, Spain, and the United Kingdom).[17,18,27] However, vaccination of adults has not been universally recommended nor funded. Furthermore, HPV vaccine uptake in adolescent primary cohorts varies worldwide,[27–29] and vaccination programs were disrupted due to the COVID-19 pandemic, resulting in deficits of uptake in many countries.[30] Therefore, many adults residing in countries with low vaccine uptake remain unprotected from HPV infection.

The level of risk for an HPV infection is not equal for all adults.[17] As a result, HPV vaccination recommendations and clinical guidelines vary among local and national professional societies[17,27,31–35] based on factors including age of first sexual activity, age-specific prevalence of HPV infections, vaccine delivery strategies, and the acceptance of vaccination by the target group[18] While guidelines in some countries, such as Spain and Germany, provide guidance for physicians to facilitate vaccination decisions in nonadolescent cohorts at high risk of HPV infection and disease (e.g., human immunodeficiency virus [HIV]-infected patients, men who have sex with men [MSM], etc.),[18,36–39] consensus between guidelines is limited and decisions are often at the discretion of the physician and patient. Therefore, understanding factors that contribute to higher risk could help patients, healthcare providers, and payers prioritize the need for vaccination on an individual level.[32,40]

Observational studies can contribute important information on factors associated with increased risk of HPV infection and disease, which can help guide data-driven decision making. Numerous factors can increase the risk of HPV infection and persistence and subsequently the risk of high-grade lesions and HPV-related cancers. However, the sheer volume and variety of data from observational studies on this topic are difficult to interpret, highlighting an unmet need to better synthesize these data. To address this concern, our review aimed to summarize scientific literature regarding factors associated with increased risk of HPV infection and/or disease.

2 | METHODS

The main objectives of this targeted literature review were (1) to identify and summarize groups of individuals at increased risk for acquiring HPV infection and developing related diseases (compared with the general population) and (2) to identify and summarize sociodemographic, clinical, and behavioral characteristics associated with risk of HPV infection and diseases in adults. Except for those involving people living with HIV, studies of risk factors for people with immunocompromised conditions (e.g., systemic lupus erythematosus) were outside the scope of this review. Given the unique nature of immunocompromised conditions and the importance of fully delineating the study population's clinical course of disease and current and past treatments, a high-level targeted literature review may not be the most useful way to describe their risk factors.

2.1 | Search strategy and selection criteria

A structured electronic search (2009–2020) of the MEDLINE, MEDLINE-IN-PROCESS, and EMBASE databases (via embase.com) was performed to identify peer-reviewed, English-language publications of observational studies (prospective and retrospective) that included patient population(s) at risk of developing primary (first time infected) or secondary (infected after being treated and having tested negative) HPV infection and associated diseases. A measure of risk (relative risks [RRs], rate ratios, relative rates, and/or odds ratios [ORs]) for at least one of the prespecified factors in adult males and females also had to be reported in the study. Additional peer-reviewed publications were identified through supplemental searches in Google Scholar and by cross-referencing the bibliographies of key identified publications; nonpeer-reviewed publications (i.e., conference abstracts) were excluded.

Selection criteria for identifying relevant studies were outlined using the Population, Intervention, Comparison, Outcome and Study type framework (Supporting Information S1: Table S1), and exact search terms are summarized in the Supporting Information S1: Table S2. Briefly, the population(s) assessed comprised those at risk of HPV infection and associated diseases (i.e., anogenital warts, cervical cancer and premalignant lesions, anogenital cancers and premalignant lesions other than cervical cancer/premalignant lesions, recurrent respiratory papillomatosis, and head and neck cancer).

Studies conducted during the prevaccine era (initiated before 2006, when the first HPV vaccine was approved) and the vaccine era were considered. For studies during the vaccine era, only unvaccinated subjects were included in this analysis.

The titles and abstracts of identified studies were assessed independently by two reviewers; full text of relevant articles was then evaluated according to prespecified inclusion/exclusion criteria. Discrepancies were discussed between the two reviewers, and if necessary, a third reviewer was involved. Data abstracted from selected studies included citation details, study objective, sample size, follow-up period, patient demographics and clinical/behavioral characteristics, and risk outcome measures (i.e., RRs, ORs, HPV incidence/prevalence). Duplicate publications were excluded using the duplicate detection features in EndNote reference manager and during the reviewer screening process.

2.2 | Data analysis

No formal assessment of study quality or quantitative analysis of the data was planned given the heterogeneity of the methodologies used in the studies. Descriptive statistics and qualitative approaches were used to synthesize the data.

For the overall population of adults, we developed a graphical display of the risk-factor literature by using bubble plots of the reported risk magnitudes, with bubble size providing a sense of the corresponding sample size in the original study. The colors of the bubbles indicate whether the risk factor was from a univariate or multivariate analysis, and the shading of the bubble indicates if the measure of association reached statistical significance in the original study. These distinctions were made to help visualize potential confounding of the reported associations. Risk magnitudes were reported for different characteristics based on multivariate-adjusted analyses conducted in the original studies. When multivariate analyses were not conducted, univariate associations were used.

Patient groups already known to be at risk of developing primary or secondary HPV infection and/or HPV-related diseases that are identifiable by physicians (e.g., women/men, HIV status, heterosexual males [HM]/MSM) were identified a priori. For each patient group, a comprehensive set of demographic, clinical, and behavioral risk factors identified in the literature was summarized (Supporting Information S1: Table S3).

3 | RESULTS

Overall, 4472 studies were identified, comprising 4299 studies identified via electronic database searches, two studies identified through manual searches, and 171 additional studies identified through rerunning of the Embase search (Supporting Information S1: Figure S1). After removal of duplicates, 4444 unique publications were obtained, 3928 of which were excluded after screening of the title and abstract (Supporting Information S1: Tables S1 and S2, Figure S1). Of the remaining 516 full-text articles, 365 were excluded for the following reasons: "not outcome of interest" (331 articles); "not population of interest" (23); "not study type of interest" (8); "not language of interest" (1); and "duplicate" (2). As a result, 153 unique studies met the prespecified selection criteria and were included in the targeted literature review.

Studies spanned >50 countries; 47 studies were conducted in the Americas, 46 in Europe, 37 in Asia, 21 in Africa, and two in Oceania (Supporting Information S1: Figure S2). Of the 153 studies, 91 (60%) had a sample size of >500 participants and 53 (35%) had 100–500 participants (Supporting Information S1: Figure S2). The association between risk factors for HPV infection/incidence/prevalence was reported more commonly (136 studies) than the association between risk factors for HPV-associated diseases (30 studies) (Supporting Information S1: Figure S3). The most commonly reported measure of association between HPV infection and risk factors was OR.

A total of 29 risk factors were identified, comprising seven demographic factors, 13 clinical factors, and nine behavioral factors (Supporting Information S1: Table S3).

3.1 | Graphical distribution of the association between HPV infection and risk factors, overall adult population (bubble plots)

ORs for HPV infection based on demographic, clinical, and behavioral risk factors are summarized in Figure 1, which provides an overview of all data points collected in the analysis, showing the distribution of ORs of any HPV infection (i.e., cervical, vaginal, anal, oral) by risk factor studied.

The association between increasing age and infection had an unclear pattern, with the exception of age ≤50 years (vs. >50 years), in which the older population appears to be at higher risk. Lesbian orientation (vs. heterosexual female) was associated with lower odds of HPV infection, while MSM or men who have sex with both men and women orientation had higher risk (vs. HM) (Figure 1A). Consistent condom use (vs. no condom use) was associated with significantly decreased odds of HPV infection. However, other contraceptive methods as well as no contraceptive methods seemed to be associated with an increase in HPV infection. Furthermore, prior abortion/miscarriage appeared to be associated with a higher risk of HPV infection as well. Current/history of other STI and history of prior HPV-related disease (cervical lesion, abnormal Papanicolaou [Pap] smear results, genital/anal warts) were also associated with increased risk/odds of HPV infection (Figure 1B). While HIV positivity was clearly associated with increased risk of infection, when HIV was asymptomatic, CD4 count was high. When HIV infection was controlled with highly active antiretroviral therapy (HAART), the presence of an association was less clear. Frequent use of alcohol and recreational drugs generally showed an increased risk of HPV infection, although the data spread was wide, and results were often not statistically significant (Figure 1C). A more consistent relationship was seen between smoking (tobacco) and HPV infection. Factors that directly measure sexual activity (higher number of sex partners, female sex work, younger age at first sexual activity, anal sex, and oral sex) and type of sex (Figure 1C) were consistently associated with increased risk of infection.

FIGURE 1 Odds of any HPV infection by (A) demographic, (B) clinical, and (C) behavioral risk factors. The type of statistical analysis used (univariate or multivariate) and the significance level (significant or nonsignificant) are indicated by the colors of the circles, and the size of each data point represents the relative size of the study population. AIDS, acquired immune deficiency syndrome; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HPV, human papillomavirus; IUD, intrauterine device; MSM, men who have sex with men; MSMW, men who have sex with men and women; Pap, Papanicolaou; STI, sexually transmitted infection.

Factors depicted in the bubble plots that showed no clear association with HPV infection included ethnicity, education, employment status, circumcision, parity, dental issues, and marital/relationship status.

3.2 | Factors associated with HPV infection and diseases by study population and endpoint

We reviewed each study and categorized risk factors in distinct patient populations (women, HIV-positive women, men, HIV-positive men, MSM, HIV-positive MSM) and more specific HPV endpoints (cervical, vaginal, anal, oral, and penile infections; cervical and anal lesions; seroprevalence; and seroincidence). These findings are summarized in Tables 1–4 (additional analysis is included in the Supporting Information S1: Tables S4–S15).

3.2.1 | HIV-negative women (Table 1; Supporting Information S1)

Among HIV-negative women, factors associated with increased risk of cervical or vaginal HPV infection included sexual activity, history of STIs or genital warts, condomless sex, use of hormonal contraception, being perimenopausal, smoking, and younger age (20–40 years). Risk factors associated with cervical HPV infection in female sex workers were similar to those in the general female population (i.e., younger age, smoking, condomless sex, and STIs); however, these factors were not stratified by HIV status. In contrast, factors associated with oral HPV infection included number of oral sexual partners, self-inoculation (placing hand/object onto genitals and then into mouth), and smoking (for HIV-positive and HIV-negative women), whereas anal chlamydia or gonorrhea were the only factors identified in the reviewed literature as being associated with anal infection in women.

Factors associated with HPV seropositivity among HIV-negative women were similar to those associated with cervical HPV infection (i.e., history of STI, number of lifetime sex partners [LSPs], use of hormonal contraception, and history of genital warts), although no association was identified for smoking because no records were found in the literature. In addition, a high-risk HPV infection (current infection as well as past history of infection), smoking, and the use of hormonal contraception were associated with the development of high-grade cervical intraepithelial neoplasia or worse (CIN2+).

3.2.2 | HIV-positive women (Table 2; Supporting Information S1)

Among HIV-positive women, factors associated with cervical or vaginal HPV infection include smoking (current smoker), low CD4 count (<200 cells/μL), and high HIV viral load (>100 000 copies/mL),

TABLE 1 HIV-negative women: Factors associated with increased risk of HPV infection and disease.[a,b]

Variables	Cervical or vaginal infection	Oral infection	Anal infection	Seropositivity	CIN2 +
Sexual activity: number of LSPs, recent SPs, number of SPs before age 21, number of anal SPs, number of oral SPs, and/or younger age at sexual debut	X	NA	NA	X	NA
Lifetime number of oral sex partners	NA	X	NA	NA	NA
Self-inoculation[c]	NA	X	NA	NA	NA
Condomless sex	X	X	NA	X	NA
History of STIs or genital warts	X	NA	NA	X	NA
History of or current anal chlamydia or gonorrhea	NA	NA	X	NA	NA
Younger age (e.g., 20s, possibly with second peak in infection at ages 50s/60s)	X	NA	NA	X	NA
Use of hormonal contraception	X	NA	NA	X	X
Menopausal status	X	NA	NA	NA	NA
Smoking	X	X	NA	NA	X
High-risk HPV infection	NA	NA	NA	NA	X

Abbreviations: HIV, human immunodeficiency virus; HPV, human papillomavirus; LSP, lifetime sex partner; NA, not assessed; OR, odds ratio; SP, sex partner; STI, sexually transmitted infection.

[a]Most studies were cross-sectional in design, reporting baseline covariate associations for the odds of HPV infection and/or disease. As a result, factors associated with increased risk of HPV infection and/or disease were defined as OR > 1.

[b]Table cells with "X" indicate that the factor was associated with HPV infection or disease. Table cells with "NA" indicate that the factor was not assessed in studies that were reviewed; it is still possible for such factors to be associated with infection/disease.

[c]Placing hand/object onto genitals and then into mouth.

TABLE 2 HIV-positive women: Factors associated with increased risk of HPV infection and disease.[a,b]

Variables	Women with HIV			Women with and without HIV[c]	
	Cervical or vaginal infection	Anal infection	Anal lesions	Cervical or vaginal infection	Anal, oral, cervical, or vaginal infection
Sexual activity: number of LSPs, recent SPs, number of anal SPs, number of oral SPs, age at sexual debut	NA	X	NA	X	X
Receptive anal sex	NA	NA	X	NA	NA
Condomless sex	NA	NA	NA	NA	NA
History of STIs or GW	NA	NA	NA	X	NA
Younger age (20s and 30s)	NA	NA	NA	X	NA
Hormonal contraception	NA	NA	NA	X	NA
History of HPV-positive anal lesions	NA	NA	X	NA	NA
Smoking	X	X	NA	X	NA
HIV-positive status	NA	NA	NA	X	NA
Low CD4 count	X	X	X	X	NA
High viral load	X	NA	NA	NA	NA

Abbreviations: GW, genital warts; HIV, human immunodeficiency virus; HPV, human papillomavirus; LSP, lifetime sex partner; NA, not assessed; OR, odds ratio; SP, sex partner; STI, sexually transmitted infection.

[a]Most studies were cross-sectional in design, reporting baseline covariate associations for the odds of HPV infection and/or disease. As a result, factors associated with increased risk of HPV infection and/or disease were defined as OR > 1.

[b]Table cells with "X" indicate the factor was associated with HPV infection or disease. Table cells with "NA" indicate that the factor was not assessed in studies that were reviewed; it is still possible for such factors to be associated with infection/disease.

[c]Reported as a single group.

whereas oral HPV infection in this group was associated with smoking, oral sexual partners, and self-inoculation, and anal infection was associated with a history of or current anal chlamydia or gonorrhea. Furthermore, cervical, vaginal, anal, and/or oral HPV infection (combined into a single variable) was associated with the amount of sexual activity (i.e., LSPs) in HIV-positive women.

This group also included studies that combined HIV-positive and HIV-negative women as a single, unstratified analysis population. In this mixed population, factors associated with cervical HPV infection were similar to those in HIV-negative women (i.e., younger age [20–40 years], LSP, use of hormonal contraception, genital warts), with the exception of low CD4 count (<200 cells/μL).

3.2.3 | HM (Table 3; Supporting Information S1)

Among HIV-negative HM, factors associated with penile HPV infection were similar to those associated with cervical HPV infection for women (i.e., sexual activity, condomless sex, history of STIs/genital warts, younger age [20–40 years], and smoking [in a study that combined HIV-positive and HIV-negative HM]), in addition to other factors related to relationship status (long-term partner with cervical dysplasia, genital warts, or HPV infection). With regards to oral HPV infection, an association was observed for younger age (20–40 years) and a history of oral disease. Furthermore, HPV seropositivity among HIV-negative HM was associated with sexual exposure and younger age.

Among HIV-positive HM, the development of anal lesions was associated with low CD4 count (<200 cells/mm^3) and a history of anal lesions. Additionally, studies that included a mixed HM population (HIV-positive and HIV-negative combined) also reported an association between penile HPV infection and having an HIV-positive partner or low CD4 count (<350 cells/mL).

3.2.4 | HIV-negative and HIV-positive MSM (Table 4; Supporting Information S1)

Among HIV-negative MSM, sexual activity, receptive anal sex, drug use, and abnormal anal Pap smear results were associated with anal HPV infection. Additionally, the incidence of HPV seropositivity was associated with no circumcision, condomless sex, and younger age (20–40 years), while HPV seroprevalence was associated with age older than 25 years, history of genital warts and STIs, sexual activity, and anal sex (current and in the last 6 months).

Among HIV-positive MSM, penile HPV infection was associated with drug use, no circumcision, a history of anal warts, less education (≤8 years), HIV-associated opportunistic infections, AIDS (vs. latent HIV), treatment with HAART, and low CD4 count (<200 cells/mm^3). In contrast, anal HPV infection was associated with factors such as

TABLE 3 HM: Factors associated with increased risk of HPV infection or disease.[a,b]

Variables	HM without HIV			HM with HIV	HM (HIV positive and HIV negative)
	Penile infection	Oral infection	Seropositivity	Anal lesions	Penile infection
Sexual activity: number of LSPs, recent SPs, number of anal SPs, number of oral SPs, and/or age of sexual debut	X	NA	X	NA	NA
Condomless sex	X	NA	NA	NA	NA
History of STIs or GW	X	NA	NA	NA	NA
Age (20s and 30s)	X	X	X	NA	NA
History of HPV-related anal lesions	NA	NA	NA	X	NA
History of oral disease	NA	X	NA	NA	NA
Long-term partner with cervical dysplasia, GW, or HPV	X	NA	NA	NA	NA
Partner who is HIV positive	NA	NA	NA	NA	X
Partner with low CD4 count	NA	NA	NA	NA	X
Sex with female sex worker	X	NA	NA	NA	NA
Smoking	X	NA	NA	NA	NA
Low CD4 count	NA	NA	NA	X	NA

Abbreviations: GW, genital warts; HIV, human immunodeficiency virus; HM, heterosexual males; HPV, human papillomavirus; LSP, lifetime sex partner; NA, not assessed; OR, odds ratio; SP, sex partner; STI, sexually transmitted infection.

[a]Most studies were cross-sectional in design, reporting baseline covariate associations for the odds of HPV infection and/or disease. As a result, factors associated with increased risk of HPV infection and/or disease were defined as OR > 1.

[b]Table cells with "X" indicate the factor was associated with HPV infection or disease. Table cells with "NA" indicate that the factor was not assessed in studies that were reviewed; it is still possible for such factors to be associated with infection/disease.

sexual activity, anal insertive LSP, receptive anal sex, condomless sex, a history of HPV-related anal lesions or anal warts, less education (high school or less), smoking, no treatment with HAART, and low CD4 count. Furthermore, HPV seroprevalence was associated with low CD4 count (<50 cells/μL).

With regard to factors associated with the development of HPV-related disease, anal lesions were associated with a history of HPV-related anal lesions, younger age (<45 years), low CD4 count (<200 cells/mm^3), and multiple infections with high-risk HPV types. Penile lesions were also associated with low CD4 count (<200 cells/mm^3).

3.2.5 | Inconsistent evidence for additional factors not listed

There was insufficient evidence and the presence of too many caveats for several factors that were primarily derived from small-scale studies. As a result, accurate conclusions could not be drawn for associations between HPV infection and some factors, such as age at first menstruation, dental hygiene, transgender women, risky behavior among HIV-positive MSM, and religion. These factors are listed in the Supporting Information S1: Tables S4–S6.

4 | DISCUSSION

To date, the implementation of universal adult HPV vaccination has been hampered by several factors, even though clinical efficacy of HPV vaccines in these age groups has been demonstrated.[41–48] Therefore, HPV vaccination of this age group would likely provide health benefits at the population level, and the indications for three HPV vaccines (2-valent HPV vaccine [Cervarix®]; 4-valent HPV vaccine [Gardasil®]; 9-valent HPV vaccine [Gardasil® 9]) have no upper age limit in some countries.[13–15] Nonetheless, the cost-effectiveness of targeting specific adult groups at higher risk of HPV infection for vaccination has not been assessed, except among MSM.[49–51] Furthermore, there is no consensus on which high-risk adult patient groups could benefit most from HPV vaccination. Although guidance for the vaccination of certain high-risk populations (e.g., MSM, HIV-infected patients, immunocompromised individuals) has been provided in some guidelines,[18,36–39] there is a general lack of consensus among global and European guidelines on which high-risk nonadolescent populations physicians should target for vaccination. While HPV vaccination of young individuals (i.e., adolescents before start of sexual activity) will most likely continue to provide the best return on investment at the population level, our review highlights the need to better define patient groups in the adult population who are at higher risk of HPV infection and

TABLE 4 HIV-negative and HIV-positive MSM: Factors associated with increased risk of HPV infection or disease.[a,b]

HIV-negative MSM				
Variables	**Anal infection**	**Abnormal anal Pap smears**	**Seroincidence**	**Seroprevalence**
Sexual activity: number of LSPs, recent SPs, number of anal SPs, number of oral SPs, age at sexual debut	X	NA	NA	X
Anal sex	NA	NA	NA	X
Anal sex in last 6 months	NA	NA	NA	X
Drug use	X[c]	NA	NA	NOT
Receptive anal sex	X	NA	NA	X
Uncircumcised (mostly among males who favor insertive position)	NA	NA	X	NA
Condomless sex	NA	NA	X	NOT
History of STIs or GW	NA	NA	NA	X
Age < 35 years	NA	NA	X	NOT
Age > 25 years	NA	NA	NA	X
Anal HPV infection	NA	X	NA	NA
No casual SPs in the last 6 months	NA	NA	NA	NA

HIV-positive MSM					
Variable	**Penile infection**	**Penile lesions**	**Anal infection**	**AIN**	**Seroprevalence**
Sexual activity: number of LSPs, recent SPs, number of anal SPs, number of oral SPs, and/or age at sexual debut	NA	NA	X	NA	NA
Anal insertive LSP	NA	NA	X	NA	NA
Drug use	X	NA	X[d]	NA	NA
Receptive anal sex	NA	NA	X	NA	NA
Uncircumcised	X	NA	NA	NA	NA
Condomless sex	NA	NA	X	NA	NA
Multiple infections with HR HPV types	NA	NA	NA	X	NA
History of HPV-related anal lesions	NA	X	X	X	NA
History of anal warts	X	NA	X	NA	NA
Less education	X	NA	X	NA	NA
Younger age (e.g., 20s and 30s)	NA	X	NA	X	NA
HIV-associated opportunistic infections	X	NA	NA	NA	NA
AIDS vs. latent HIV	X	NA	NA	NA	NA
Smoking	NA	NA	X	NA	NA
No HAART use	NA	NA	X	NA	NA

HIV-positive MSM					
Variable	Penile infection	Penile lesions	Anal infection	AIN	Seroprevalence
Use of HAART	X	NA	NA	NA	NA
Low CD4 count	X	X	X	X	X

Abbreviations: AIDS, acquired immunodeficiency syndrome; AIN, anal intraepithelial neoplasia; GW, genital warts; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HPV, human papillomavirus; HR, high risk; LSP, lifetime sex partner; MSM, men who have sex with men; NA, not assessed; OR, odds ratio; Pap, Papanicolaou; SP, sex partner; STI, sexually transmitted infection.

[a]Most studies were cross-sectional in design, reporting baseline covariate associations for the odds of HPV infection and/or disease. As a result, factors associated with increased risk of HPV infection and/or disease were defined as OR > 1.

[b]Table cells with "X" indicate the factor was associated with HPV infection or disease. Table cells with "NA" indicate that the factor was not assessed in studies that were reviewed; it is still possible for such factors to be associated with infection/disease. Table cells with "NOT" indicate that the factor was not associated with the outcome in studies that were reviewed.

[c]Rectal drug use.

[d]This analysis combined MSM irrespective of HIV status; oral, anal, and external genital sites were combined; results were attenuated, but point estimates were still elevated in multivariate analyses that controlled for HIV status. Another study found that cannabis use (unspecified route of administration) was associated with oral infection in MSM, irrespective of HIV status.

associated disease to complement existing HPV vaccination guidelines and, potentially, adaptation of screening guidelines.

Although factors associated with HPV infection and disease have been previously reported in the scientific literature, to our knowledge, this targeted literature review is the first comprehensive qualitative overview of these factors in adults. Several well-known factors were consistently associated with HPV infection and associated disease.

By using bubble plots as visual representations of the data, we present a complex and abundant data set of diverse studies from around the world in a more user-friendly manner, where the distribution of the bubbles illustrates trends derived from the publications available to date. Through this visualization of complex data sets, these bubble plots can guide future research aimed at confirming trends and addressing gaps and inconsistencies. Results show that the quantity of evidence was greater and more diverse for the effect of clinical and behavioral factors on HPV infection and/or associated disease, compared with studied demographic factors. Clinical and behavioral factors such as the level of sexual activity (e.g., number of LSPs); having a history of prior HPV infections, genital warts, STIs, or cytological abnormalities; smoking (HIV-positive or HIV-negative individuals); condomless sex; and low CD4 count among HIV-positive individuals showed consistent associations with HPV infections and/or associated disease across patient subgroups. In contrast, few demographic risk factors outside of younger age or sexual orientation showed a strong/consistent effect.

HPV infection was consistently associated with factors related to sexual activity (i.e., number of LSPs, number of recent/oral/anal sex partners, age of sexual debut) across patient groups. However, patients may not accurately report sexual history for various reasons (e.g., embarrassment, lack of knowledge, not knowing a partner's sexual history), suggesting the need to understand surrogates for sexual activity (e.g., history of prior STIs). Indeed, the strong correlation between history of STIs or genital warts (anal warts among MSM) and high-risk HPV infection may reflect cumulative lifetime sexual behavior and an individual's immune status. Genital warts develop when an individual is unable to clear an HPV infection (either low or high risk), which suggests dysregulation of the immune system,[52] making them vulnerable to other HPV infections and the development of persistent infections and lesions/diseases. Furthermore, hormonal contraceptive use among women was associated with HPV infection and CIN2+, which may be indicative of women who are more sexually active, or of a potential hormonal effect in an individual's capacity to naturally defend against and clear HPV infection.[53] Smoking was also associated with HPV infection and CIN2+ in women and HPV infection in some men (HIV-negative HM and HIV-positive MSM); this may be a marker of sexual activity or impaired immune function and damage to host DNA, which may increase susceptibility to infection and/or disease progression.[54] Finally, low CD4 count was associated with HPV infection and HPV-related disease among HIV-positive women and men (both HM and MSM), suggesting that HIV-induced immunosuppression may result in an inability of the immune system to control the expression and replication of HPV, thus leading to persistent HPV infection and a consequent increase in the risk of progression to HPV-related precancerous lesions/cancer.[55,56] These factors may be helpful for decisions regarding HPV vaccination.

This literature review also highlighted areas in which biological mechanisms remain unclear or results were inconsistent. For example, it is possible that HPV infection measured in peri- or postmenopausal women could be indicative of a new infection (e.g., from a new partner); however, menopause may also be a marker for

decreased immune surveillance resulting in the potential for increased risk of infection acquisition or reactivation of latent infections.[57,58] Inconsistent results were also observed for condomless sex, with condom use among those at higher risk being more likely but less consistent, and results being affected by inaccurate responses from young women responding to questions on condom use. Age is also complex, particularly in women where it is confounded by other factors (i.e., hormonal changes in menopause). Although increasing age is associated with decreased odds of HPV, increased early exposure to high-risk HPV infection and a weakened immune response after menopause, women's perception that continued cervical screening following menopause is no longer needed, or a combination of both, may lead to re-emergence of latent HPV infections, resulting in a second HPV peak in older women.[59–61] In addition, some factors associated with HPV infection may not necessarily be risk factors, but rather "surrogates" for some other behavior that increases the risk of HPV infection. For example, a low education level itself is not a risk factor of HPV infection but may be linked to poor awareness of HPV and sexual behaviors that place the individual at a higher risk of infection. Finally, more research is required for factors that were too broadly defined in the original research. For example, the association between recreational drug use and risk of HPV infection appears inconsistent with the use of high-level definitions, such as "illegal drug use," "drug abuse," and "IV drug use."

There are many other studies that could not be included in our review because there was no statistical analysis on the level of risk for the factor studied, and it is possible that certain risk factors may have been missed in our review because they were not captured in the search terminology. In addition, several studies included ethnicity-specific or geography-specific factors (e.g., region of residence or occupation-related regions of residence or migration patterns) that may be associated with HPV infection and disease. However, we did not report these in the main manuscript (see Supporting Information S1) because there was no distinct pattern, and these factors are highly specific to each study. This highlights the importance of understanding unique factors within a given population of interest. Future studies with statistical analysis of the level of risk for different and new factors should help us enhance our knowledge of risk groups for HPV infection and disease. Furthermore, as HPV testing moves toward being the preferred method for primary screening, more data sets will become available that could help enlighten this area of research.

In many countries, HPV vaccination rates, especially in adults, are still low. For many of these countries, a full catch-up of the entire adult population is likely difficult to attain because of several factors, including lack of access (mainly related to insurance coverage)[62] and the lack of evidence demonstrating the population-level health benefits of vaccinating older adults.[63] In other cases, even with wide recommendations for HPV vaccinations, boys and girls may have missed their immunization because of communication issues or other causes, such as the recent COVID-19 pandemic, which has dramatically reduced the coverage rates of HPV vaccination in the younger targeted (recommended and funded) cohorts.[64] Understanding later age groups not currently recommended for routine HPV vaccination who could greatly benefit from HPV vaccination (and for those who have access to screening) would help identify who to target for HPV vaccination. This in turn, may help to reach the World Health Organization's elimination goals for cervical cancer and to reduce and control other HPV-related diseases in women and men.

The strengths of this targeted literature review should be recognized. This study is a large-scale and widely encompassing review of risk factors identified in studies from around the world. A granular analysis of the relationship between risk factor and patient subgroup status and HPV infection was undertaken, highlighting the need to consider both risk factor exposure and underlying risk factors (e.g., sex, HIV status, sexual orientation) on consequent HPV infection, persistence, and disease risk. The narrative synthesis of a large number of studies related to HPV infection will allow researchers to identify how strongly related the most commonly reported risks and the most commonly studied populations are to HPV infection.

Several limitations should be considered when interpreting the findings of this targeted literature review. First, because of the comprehensive nature of this review, the studies included were too heterogeneous to summarize with quantitative methods; therefore, the analysis focused on descriptive data with no formal assessment of the magnitude of risk. Moreover, there is potential bias associated with observational studies and limitations of data sources used in the different studies included. Second, some groups were underrepresented, with most of the evidence obtained from healthy women. For example, this review did not address immunocompromised patients other than people living with HIV (e.g., patients with transplants or autoimmune disorders, patients under immune modulator treatments, healthcare providers exposed to HPV such as dermatologists or obstetricians/gynecologists, sex workers). The importance of HPV vaccination in immunocompromised individuals is well-known, but risk factors in this group may differ from those of the general population. Third, our analysis identified strong associations between several clinical and behavioral factors; however, quality data for other potential risk factors, such as history of abortions, history of circumcision (except for HIV-positive MSM), and transgender women status, were insufficient to define a clear trend. Additionally, the quantity of evidence evaluating factors associated with HPV-related diseases was low, with <20% of studies/publications being linked to HPV-related diseases (the rest related to HPV infection). Fourth, risk related to HPV infection does not indicate risk of HPV diseases since the only accepted virological surrogate of HPV-related cancer is persistent infection (at 6 or 12 months), not prevalent or single-time incident infection. As a result, the data related to incident infection should be confirmed by data on persistent infection, lesions/dysplasia, or cancer itself. Finally, there was no formal assessment of study quality using validated checklists, and analyzed studies were limited to English-only publications.

Our study summarizes important factors that place some populations at higher risk for HPV infection and HPV-associated

disease. Further research should confirm whether the risk groups identified through HPV infection do translate to persistent infection, lesions, or cancer. A finer analysis for some factors may also be required to provide a more quantitative understanding of their importance/relevance (e.g., is a factor's influence limited to a specific age range or does it span all ages). This final step would bolster evidence-based guidance.

5 | CONCLUSIONS

Our literature review provided data-driven confirmation of some risk groups and risk factors (e.g., MSM, HIV-positive status, sexual activity, and smoking) associated with adult HPV infection. Nonetheless, the main risk factor for HPV infection and disease for all adults is sexual activity. The use of bubble plots to represent complex sets of data helped to identify trends, inconsistencies, and data gaps. For specific patient populations, some factors consistently associated with HPV infection and related lesions were identified, defining groups that may benefit from specific primary and secondary HPV prevention strategies. In addition, areas that may benefit from future research to better understand underlying biological mechanisms were identified. As HPV testing moves toward being the preferred method for primary screening, more data sets will become available that could help enlighten this area of research. The real-world applications of this study are critical because rapid identification of these risk groups in clinical practice is necessary to inform decisions more comprehensively regarding which patients should be offered primary prevention (HPV vaccination), secondary prevention (screening), or both, in addition to those already covered by immunization programs, which currently focus on primary cohorts of adolescents. Further research is needed to contextualize our results and provide the insight needed to formulate tools for data-driven decisions that can support policy-making and clinical decision making for adult HPV vaccination and screening.

AUTHOR CONTRIBUTIONS

Marta del Pino, Alex Vorsters, Elmar A. Joura, John Doorbar, Marta Haniszewski, Christine Velicer, and Rosybel Drury contributed to conceptualization of the manuscript. Christine Velicer contributed to data curation of the manuscript. Marta Haniszewski, Petya Kodjamanova, Christine Velicer, and Rosybel Drury contributed to formal analysis of the manuscript. Rosybel Drury contributed to funding acquisition and project administration for the manuscript. Irene Asensio Gudina and Christine Velicer contributed to investigation of the manuscript. Alex Vorsters, Marta Haniszewski, Irene Asensio Gudina, Petya Kodjamanova, Christine Velicer, and Rosybel Drury contributed to the methodology of the manuscript. Marta del Pino and Rosybel Drury contributed to supervision of the manuscript. Marta Haniszewski, Irene Asensio Gudina, and Petya Kodjamanova contributed to the visualization of the manuscript. All authors contributed to reviewing and editing of the manuscript. M. Chang and M. Grzywacz (medical writers, ApotheCom) contributed to editing of the manuscript. Rosybel Drury and Christine Velicer had direct access and verified the underlying study data reported in the manuscript. All authors approved the final version of the manuscript.

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CONFLICTS OF INTEREST STATEMENT

Marta del Pino has received personal fees for scientific advisory committee meetings and speaking fees from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), for work outside this publication. Alex Vorsters has received organizational grants and speaking fees from GlaxoSmithKline Biologicals and MSD for work outside this publication. Elmar A. Joura received personal fees for scientific advisory committee meetings and speaking fees from MSD for work outside this publication. John Doorbar has received speaking fees from MSD for work outside this publication. Marta Haniszewski received consulting fees from MSD and was an employee of Amaris Consulting during this study. Petya Kodjamanova has received consulting fees from MSD and is an employee of Amaris Consulting. Christine Velicer is an employee of MSD. Rosybel Drury is an employee of and holds shares in MSD. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to Data Access mailbox.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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