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LETTER

Anogenital human papillomavirus infection patterns by anatomical site and sexual orientation in Chinese men: a national multi-center study

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Human papillomavirus (HPV) is the most prevalent sexually transmitted infection worldwide[1]. More than 200 HPV genotypes have been identified and are classified as high-risk HPV (HR-HPV) or low-risk HPV (LR-HPV) according to their oncogenic potential. Persistent infection with HR-HPV is associated with cancers of the cervix, vagina, vulva, anus, penis, and oropharynx. In contrast, LR-HPV infections cause benign lesions, such as genital warts and recurrent respiratory papillomatosis.

In men, HPV has been implicated in nearly all anal squamous cell carcinomas and 52.9% of penile cancers[2]. The incidence of HPV-associated anal cancer has increased over the past two decades in several countries, including China[3,4]. Beyond causing benign and malignant pathologies in men, HPV-infected men may also serve as a reservoir for the virus, thus considerably contributing to HPV transmission and related disease risk in women[5,6]. Therefore, understanding the epidemiology of anogenital HPV infection in men is essential to better inform prevention and control strategies.

In China, the burden of HPV infection among men remains poorly investigated. To address this gap, we analyzed baseline HPV data from 9,000 human immunodeficiency virus (HIV)-negative men aged 18–45 years enrolled in a multicenter nonavalent HPV vaccine trial in China (CTR20223306). The study included 7,800 heterosexual men (HM) and 1,200 men who have sex with men (MSM), who were recruited from 17 centers across eight provinces between 2022 and 2023. The baseline analysis was aimed at assessing and comparing anogenital HPV prevalence and genotype distribution across anatomical sites, and was stratified by sexual orientation. Cytology samples were collected from the external genitalia, perineal–perianal area, and anal canal. HPV genotyping was performed with SureX HPV tests detecting 25 genotypes. A flowchart of the study procedures is presented in **Figure 1A**. Detailed descriptions of materials and methods are provided in the Supplementary material. Among the participants, HM were slightly older than MSM (28.9 ± 7.7 years *vs.* 26.6 ± 6.2 years, $P < 0.001$). MSM showed greater sexual activity and behavioral complexity than HM: whereas 83.6% of MSM engaged in only anal intercourse, 16.2% engaged in both vaginal and anal intercourse. Demographic and behavioral characteristics are presented in **Table S1**.

Anogenital HPV prevalence and infection patterns in HM and MSM

The total anogenital HPV prevalence was 33.7% in HM and 60.9% in MSM ($P < 0.05$) (**Table S2**). The anatomical distribution of HPV infections also significantly differed between groups. In HM, the prevalence of any HPV infection was highest at the external genitalia (26.1%), followed by the perineal–perianal area (16.6%) and anal canal (9.6%). In contrast, MSM exhibited the highest prevalence at the anal canal (45.1%) and perineal–perianal area (42.4%), and a lower prevalence at the external genitalia (21.2%). Similar patterns were observed for HR-HPV, LR-HPV, nonvalent vaccine subtypes (9v-HPV), HPV-16/18, and HPV-6/11 (**Figure 1B**). Single- and multiple-type HPV infections were also more frequent in MSM than in HM at the perineal–perianal region and anal canal. However, HM exhibited a higher prevalence of multiple HPV infections at the external genitalia than MSM (9.1% *vs.* 4.9%, $P < 0.001$) (**Figure S1**). This anatomical distribution of

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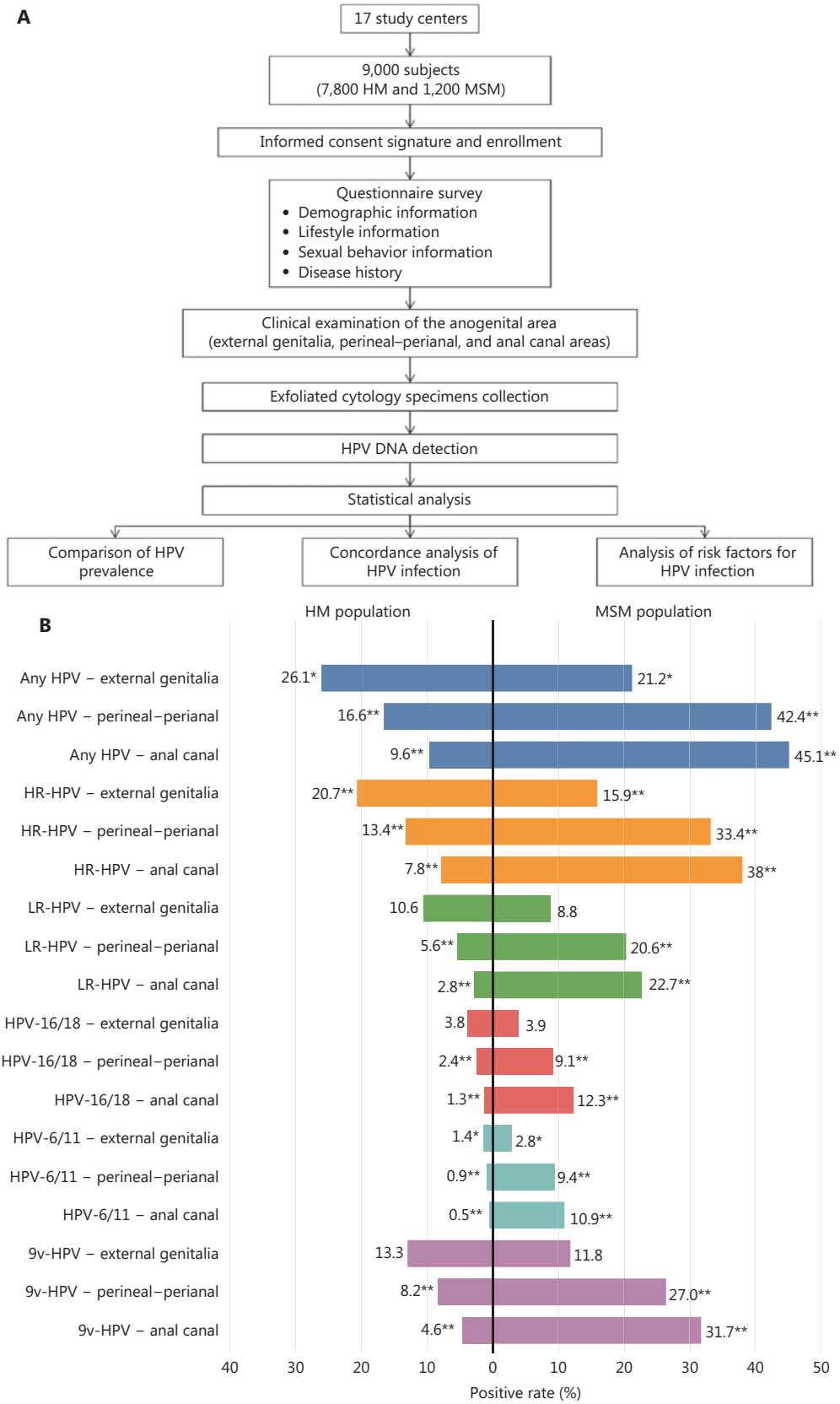


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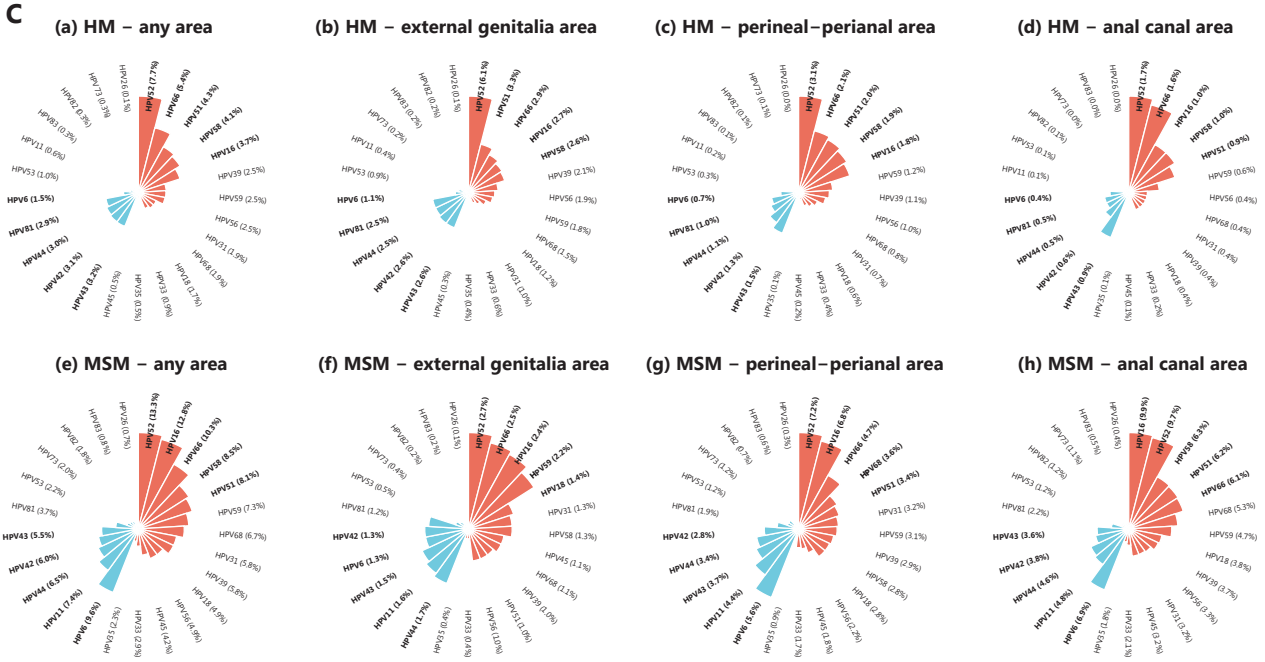


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HPV infection might reflect the primary sites of HPV exposure during heterosexual intercourse. During penile–vaginal intercourse, HPV might invade basal epithelial cells through microabrasions, thereby facilitating penile HPV infection[7]. The anal epithelium consists primarily of squamous cells and lacks a keratinized barrier. Receptive anal intercourse can cause minor trauma to the anal epithelium, thereby increasing the likelihood of viral entry into basal cells and increasing HPV infection risk among MSM[8]. Moreover, the high prevalence of multi-HR-HPV infections in the anal canal among MSM (12.5%) is particularly concerning, because concurrent infection with multiple high-risk HPV types has potential to synergistically increase the risk of anal carcinogenesis.

HPV genotype distribution by population and anatomical site

Across all anogenital sites combined in HM, the most prevalent HR-HPV types were HPV-52 (7.7%), HPV-66 (5.4%), HPV-51 (4.3%), HPV-58 (4.1%), and HPV-16 (3.7%), whereas the most common LR-HPV types were HPV-43 (3.2%), HPV-42 (3.1%), HPV-44 (3.0%), HPV-81 (2.9%), and HPV-6 (1.5%). At each anatomical site, the five most prevalent HR-HPV and LR-HPV types remained consistent: HPV-52 and HPV-43 were consistently the most prevalent HR-HPV and LR-HPV types, respectively. The predominance of HPV-52 in HM aligns with the HR-HPV genotype profile reported in cervical cancer studies among Chinese women, where HPV-52 is also the most common type[9].

Among MSM, across all anogenital sites combined, the most prevalent HR-HPV types were HPV-52 (13.3%), HPV-16 (12.8%), HPV-66 (10.3%), HPV-58 (8.5%), and HPV-51 (8.1%), whereas the most common LR-HPV types were HPV-6 (9.6%), HPV-11 (7.4%), HPV-44 (6.5%), HPV-42 (6.0%), and HPV-43 (5.5%). The anal canal and perineal–perianal area exhibited a similar genotypic profile, with HPV-52 and HPV-16 predominating at both sites for HR-HPV, and HPV-6 and HPV-11 dominating for LR-HPV. At the external genitalia, the most prevalent HR-HPV types were HPV-52 (2.7%), HPV-66 (2.5%), HPV-16 (2.4%), HPV-59 (2.2%), and HPV-18 (1.4%), whereas the most prevalent LR-HPV types were dominated by HPV-44 (1.7%), HPV-11 (1.6%), HPV-43 (1.5%), HPV-6 (1.3%), and HPV-42 (1.3%) (**Figures 1C and S2**).

Concurrence and concordance of HPV infection across anatomical sites

The findings regarding HPV infection concurrence and concordance across anatomical sites are presented in **Table S2** and **Figure 1D**. Among HM, the prevalence of concurrent HPV infection in at least two anatomical sites was 15.4% for any HPV, 11.8% for HR-HPV, and 5.3% for LR-HPV. The prevalence was lower when all three sites were positive: 6.2% for any HPV, 4.6% for HR-HPV, and 2.0% for LR-HPV (**Table S2**). Concordance analysis of these HPV categories across anatomical sites in HM revealed moderate agreement between the external genitalia and perineal–perianal area (kappa range: 0.45–0.52) and between the perineal–perianal region and anal

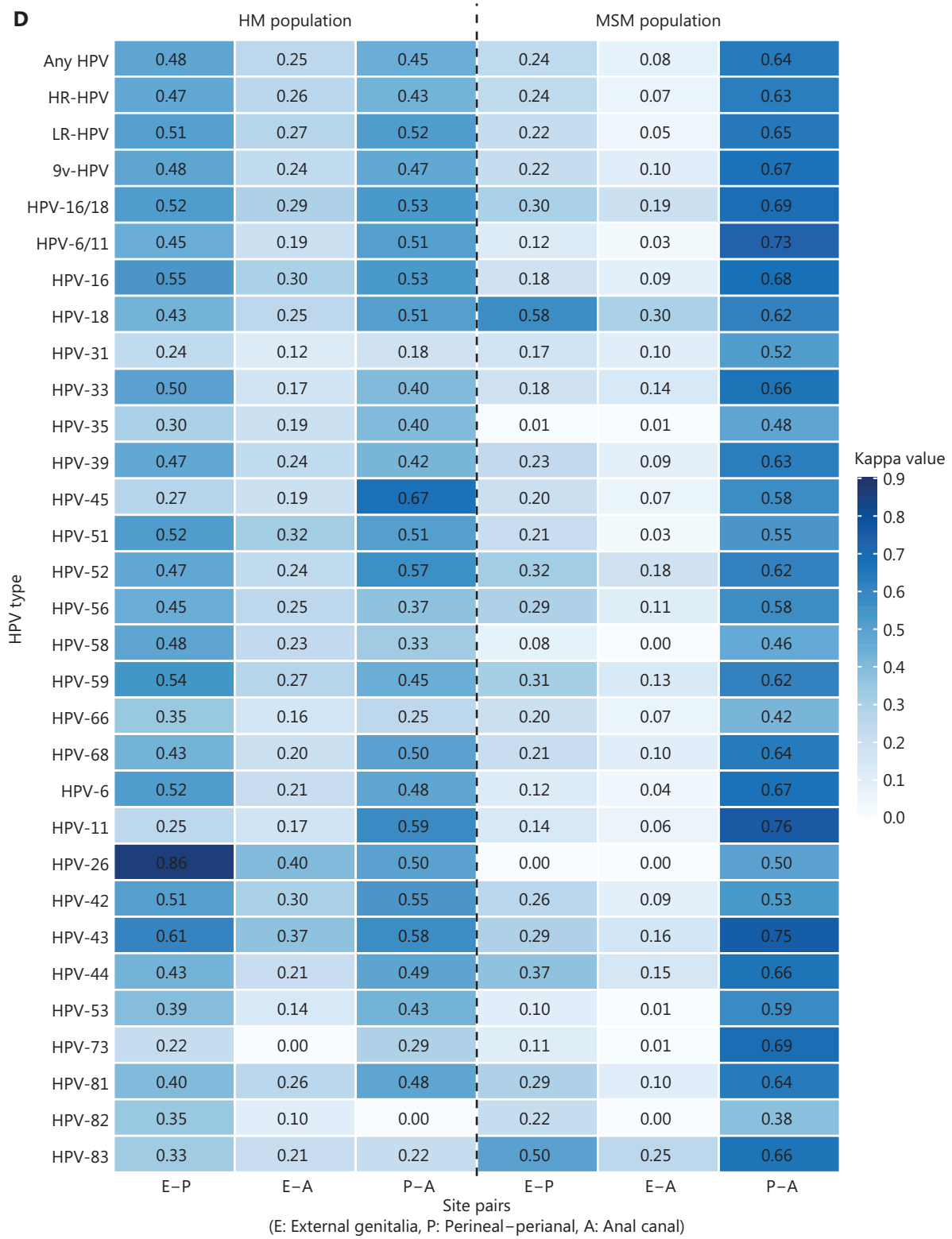


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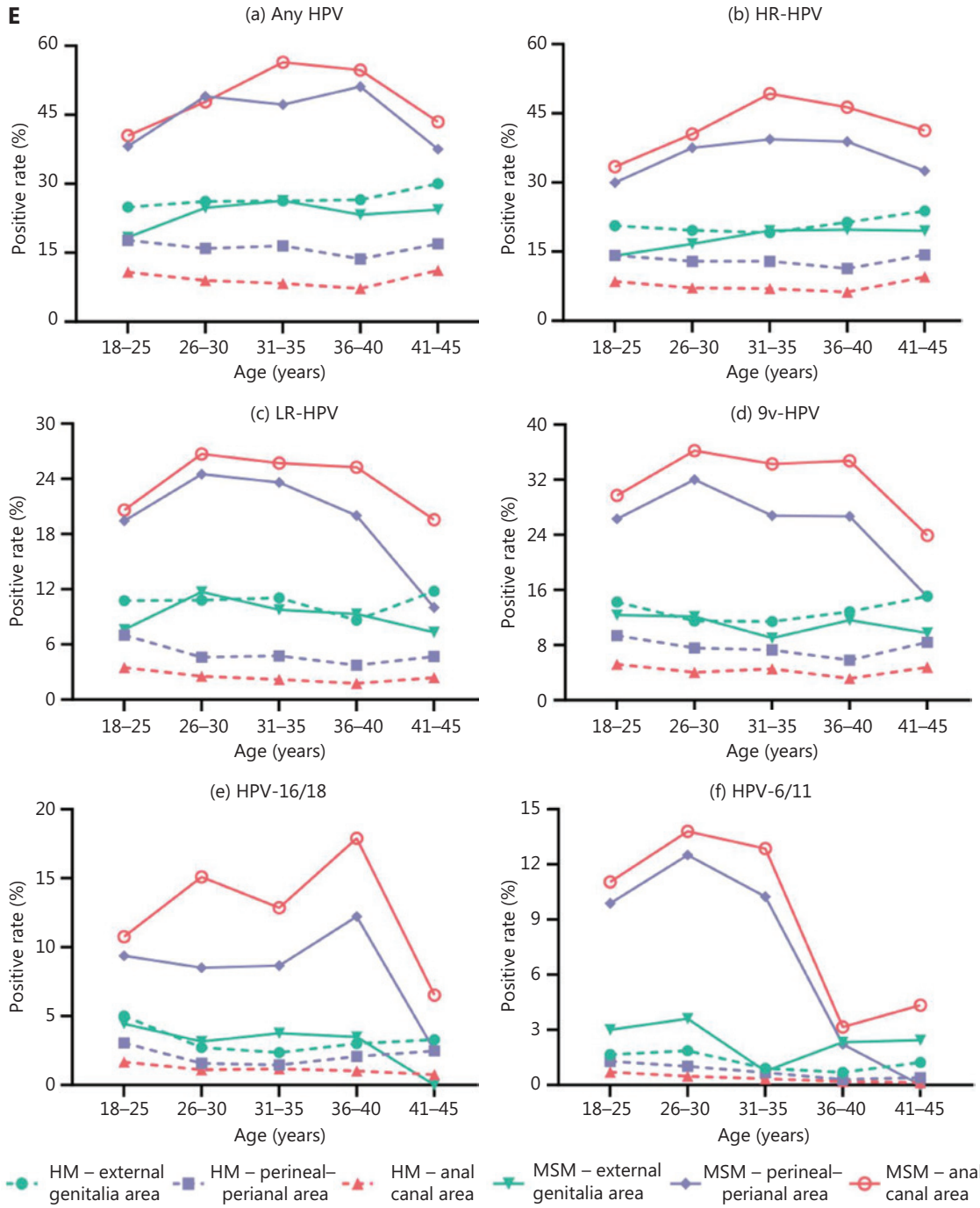


Figure 1 (A) Flowchart of the study procedure. (B) Anogenital HPV prevalence between HM and MSM populations. (C) Prevalence of HPV genotypes by population group and anogenital site, including the (a) prevalence of 25 HPV genotypes among HM at any anogenital site (combined external genitalia, perineal–perianal, and anal canal areas), (b) prevalence of 25 HPV genotypes among HM at the external genitalia, (c) prevalence of 25 HPV genotypes among HM at the perineal–perianal area, (d) prevalence of 25 HPV genotypes among HM at the anal canal area, (e) prevalence of 25 HPV genotypes among MSM at any anogenital area (combined external genitalia, perineal–perianal, and anal canal areas), (f) prevalence of 25 HPV genotypes among MSM at the external genitalia, (g) prevalence of 25 HPV genotypes among MSM at the perineal–perianal area, and (h) prevalence of 25 HPV genotypes among MSM at the anal canal area. Red indicates high-risk HPV, and blue indicates low-risk HPV. The five most prevalent high-risk and low-risk HPV genotypes at each anatomical site are indicated in bold. (D) Concordance of HPV genotype distribution across anogenital sites. The x-axis represents the following pairs of anatomical sites: E–P (external genitalia *vs.*

perineal–perianal area), E–A (external genitalia *vs*. anal canal area), and P–A (perineal–perianal *vs*. anal canal area). The y-axis lists the HPV genotypes. Each cell represents the kappa value (range 0–1) for agreement in infection with a specific HPV genotype between the indicated site pair. The color intensity is proportional to the kappa value: darker colors indicate higher concordance (kappa closer to 1), whereas lighter colors indicate lower concordance (kappa closer to 0). (E) Age distribution of HPV prevalence by population group and anogenital site, including (a) age-specific prevalence of any HPV, (b) age-specific prevalence of high-risk HPV, (c) age-specific prevalence of low-risk HPV, (d) age-specific prevalence of nonavalent vaccine HPV types (9v-HPV), (e) age-specific prevalence of HPV-16/18, and (f) age-specific prevalence of HPV-6/11. For all panels, the x-axis represents age group (18–25, 26–30, 31–35, 36–40, and 41–45 years), and the y-axis represents HPV prevalence (%). Each panel includes six lines representing HM and MSM populations across three anatomical sites (external genitalia, perineal–perianal area, and anal canal), distinguished by line color and style, as indicated in the legend. HM, heterosexual men; MSM, men who have sex with men; HPV, human papillomavirus; HR-HPV, high-risk HPV, including HPV-16/18/31/33/35/39/45/51/52/56/58/59/66/68; LR-HPV, low-risk HPV, including HPV-6/11/26/42/43/44/53/73/81/82/83; 9v-HPV, HPV type covered by the nonavalent HPV vaccine, including HPV-6/11/16/18/31/33/45/52/58. *indicates statistical significance between HM and MSM ($P < 0.05$); **indicates statistical significance between HM and MSM ($P < 0.001$).

canal (kappa range: 0.43–0.53), but weak to very poor agreement between the external genitalia and anal canal (kappa range: 0.19–0.29) (**Table S3**). A similar concordance pattern was observed for the most prevalent HR-HPV and LR-HPV types (**Table S4, Figure S3**).

MSM, compared with HM, had a substantially higher prevalence of concurrent HPV infection in at least two anatomic sites: 41.4% for any HPV, 32.3% for HR-HPV, and 19.8% for LR-HPV. For infections involving all three anatomical sites, the prevalence was 11.5% for any HPV, 7.4% for HR-HPV, and 2.6% for LR-HPV (**Table S2**). Concordance analysis of these HPV categories in MSM indicated weak to very poor agreement between the external genitalia and perineal–perianal area (kappa range: 0.12–0.30), very poor agreement between the external genitalia and anal canal (kappa range: 0.03–0.19), and good agreement between the perineal–perianal area and anal canal (kappa range: 0.63–0.73) (**Table S3**). Similarly, type-specific HPV concordance analysis demonstrated moderate to good agreement between the perineal–perianal area and anal canal but unfavorable agreement between the external genitalia and the other two sites (**Table S5, Figure S4**). Notably, MSM demonstrated strong concordance between the perineal–perianal region and anal canal (kappa = 0.64 for any HPV), thus suggesting that these adjacent sites function as a unified ecological niche, because of shared exposure during receptive anal intercourse.

Risk factors for anogenital HPV infection by population and anatomical site

Univariable and multivariable analyses identified age, smoking, sexual behavior, and sexually transmitted diseases (STD) history as factors associated with HPV infection; however, notable differences were observed by sexual orientation and anatomical site (**Tables S6–9**). At the external genitalia, older age (36–45 years *vs.* 18–25 years) was associated with elevated HPV risk in HM (aOR = 1.26–1.60), whereas in MSM, elevated risk was concentrated among those aged 26–35 years (aOR = 1.56–1.68). In the perineal–perianal area, MSM aged 26–40 years had significantly elevated risk (aOR = 1.58–2.06), whereas HM showed no significant age-related differences. At the anal canal, HM aged 36–40 years had relatively low HPV prevalence (aOR = 0.74), whereas MSM aged 31–40 years had elevated risk (aOR = 1.85–1.96) (**Figure 1E**). Regarding behavioral factors, older age at sexual debut was protective across most anatomical sites in both populations (aOR range: 0.33–0.85). In addition, among HM, external genital HPV infection was significantly associated with smoking, having multiple sexual partners, the partner's HPV infection history, and STD history (aOR range: 1.46–3.42). In contrast, among MSM, only occasional smoking reached statistical significance (aOR = 2.03). At the perineal–perianal area, HM HPV infection was associated with regular smoking and having multiple sexual partners (aOR range: 1.30–1.99), whereas circumcision was found to be protective (aOR = 0.79). At the anal canal, circumcision remained protective in HM (aOR = 0.80), whereas in MSM, having multiple sexual partners and an STD history was associated with elevated risk (aOR range: 1.97–2.43).

To our knowledge, this study is the largest national multi-center epidemiological investigation of anogenital HPV infection among HIV-negative men in China. The overall anogenital HPV prevalence was 33.7% in HM and 60.9% in MSM, and distinct site-specific prevalence patterns were observed between populations. HPV-52 was the most prevalent genotype in both populations. Whereas MSM displayed substantially higher prevalence of HPV-16 and HPV-6/11, HM demonstrated higher prevalence of HPV-43 and HPV-42. The substantial anogenital HPV burden in both HM and MSM supports inclusion of men in HPV vaccination strategies. The high prevalence of HPV-52 across both populations, coupled with elevated HPV-16 and HPV-6/11 in MSM, underscores the potential protective value of the HPV vaccine targeting these genotypes. In conclusion, our findings demonstrated substantial variation in HPV infection profiles by sexual orientation and anatomical site, thus providing key evidence to

inform individualized prevention and screening strategies for HPV and related lesions, particularly among MSM.

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Conflict of interest statement

Hongyang Yu, Douhong Li, and Yongjiang Liu are current employees of Beijing Health Guard Biotechnology Inc. Hongyang Yu and Yongjiang Liu own stocks in Beijing Health Guard Biotechnology Inc. All other authors declare no competing interests.

Author contributions

Shangying Hu, Huan Yang, Jinyu Zhang, Hongyang Yu, Douhong Li, Xuelian Zhao, Yongjiang Liu, and Fanghui Zhao contributed to the study design. Shangying Hu, Jinyu Zhang, Yutong Li, Qiaoyun Du, Yu Cui, and Fanghui Zhao contributed to data collection and laboratory analyses. Shangying Hu, Huan Yang, Jinyu Zhang, Xuelian Zhao, and Fanghui Zhao were the core team for data analysis and manuscript preparation. All authors critically reviewed and verified the drafts of the manuscript, and approved the final version. The corresponding author had final responsibility for the decision to submit for publication.

Data availability statement

Since the trial is ongoing and individual-level data remain masked, these data will be available to investigators upon reasonable request after trial completion and publication of the final results.

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