ORIGINAL ARTICLE

Epidemiology of, and behavioural risk factors for, sexually transmitted human papillomavirus infection in men and women in Britain

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ABSTRACT

Objectives Persistent infection with high-risk sexually transmitted human papillomaviruses (HR-HPVs) can lead to development of cervical and other cancers, while low-risk types (low-risk HPV) may cause genital warts. We explored the epidemiology of different HPV types in men and women and their association with demographic and behavioural variables.

Methods We analysed data collected for the British National Survey of Sexual Attitudes and Lifestyles, a cross-sectional survey undertaken in 1999–2001. Half of all sexually experienced male and female respondents aged 18–44 years were invited to provide a urine sample. We tested 3123 stored urine samples using an in-house Luminex-based HPV genotyping system.

Results HPV DNA was detected in 29.0% (95% CI 26.7% to 31.3%) of samples from women and 17.4% (95% CI 15.1% to 19.8%) from men. Any of 13 HR-HPV types was detected in 15.9% (95% CI 14.1% to 17.8%) of women and 9.6% (95% CI 8.0% to 11.6%) of men. HPV types 16/18 were found in 5.5% (95% CI 4.5% to 6.8%) of women and 3.0% (95% CI 2.1% to 4.3%) of men; and types 6/11 in 4.7% (95% CI 1.8% to 5.9%) of women and 2.2% (95% CI 1.5% to 3.1%) of men. In multivariate analysis, HR-HPV was associated with new partners, without using condom(s), and age at first intercourse.

Conclusions HPV DNA was detectable in urine of a high proportion of the sexually active British population. In both genders, HR-HPV was strongly associated with risky sexual behaviour. The minority of HPV infections were of vaccine types. It is important to monitor HPV prevalence and type distribution following the introduction of vaccination of girls.

INTRODUCTION

Persistent infection with certain types of sexually transmitted human papillomavirus (HPV) can lead to the development of cervical and other cancers, while other types cause the majority of genital warts. HPV types that infect the genital area are categorised as ‘high-risk’ HPV (HR-HPV) if known to cause cervical cancer or ‘low-risk’ HPV (LR-HPV) if not, albeit an imperfect categorisation.1 2 Infection with HR-HPV types is necessary but not sufficient for development of cervical cancer. Thirteen types are currently recognised by the WHO International Agency for Research on Cancer as ‘high risk’.3 HR-HPV is also implicated in the aetiology of some other anogenital cancers and of some oropharyngeal cancers.4 Types 16 and 18 are associated with >70% of cervical cancers worldwide.5 Infection with HPV types 6 or 11 is associated with the majority of cases of anogenital warts.6

Genital infection is often asymptomatic and undiagnosed. However, genital warts remain the most commonly diagnosed viral sexually transmitted infection in the UK, with around 91 000 cases diagnosed in genitourinary medicine clinics in 2009, an increase of 50% since 2000.7 Transmission is driven by the infectivity of the organisms, sexual behaviour and the effectiveness of control interventions. Once infected, it is estimated that 70% of women clear infection within 5 years.8 Surveillance of genital warts, detection of abnormalities by cervical screening and cancer registries give some measure of the impact of HPV infection but do not show the population prevalence or distribution of HPV types.

An HPV immunisation programme was introduced in the UK in 2003 for 12–13-year-old girls, with a catch-up programme to age 18.9 10 The programme, to protect against cervical cancer, uses the bivalent vaccine protecting against types 16 and 18, but not types 6 and 11, which the quadrivalent vaccine offers.

Nationally representative epidemiological studies are needed to inform HPV immunisation policy and cervical cancer screening strategies and efforts to improve uptake. The frequency of HR-HPV types not present in current vaccines is an important baseline against which to monitor any indirect effect of vaccination on non-vaccine types (eg, type replacement or cross-protection). Here, we examine the proportion of men and women with detectable HPV infection in urine samples archived from a national probability sample survey of sexual attitudes and lifestyles (NatSAL-2) undertaken prior to the introduction of HPV vaccination in Britain and the relationship between infection and demographic and behavioural variables.11

METHODS

The second National Survey of Sexual Attitudes and Lifestyles (NatSAL-2) is a stratified probability
sample survey of the population aged 16—44 years, resident in Britain. Eleven thousand one hundred and sixty-one people, of whom 6399 were women, were interviewed between May 1999 and February 2001. Details of the methodology are published elsewhere.11 Briefly, a sample of 40,523 addresses was selected from the small-user Postcode Address File for Britain with a multistage probability cluster design, with oversampling in Greater London. Interviewers visited all selected addresses. One resident aged 16—44 years from every eligible household was invited after random selection to participate. Natsal-2 achieved a response rate of 65.4%. Interviewers conducted interviews in respondents’ homes. A face-to-face interview included questions on socio-demographics, health behaviours, and first sexual experience. Respondents who reported no sexual experience of any kind in the face-to-face interview and those aged 16 and 17 years with some heterosexual experience but no heterosexual intercourse or same-sex experience reported in screening questions were not given the subsequent computer-assisted self-interview. This included questions on the number and gender of sexual partners and sexual practices.

Five thousand and twenty-six respondents at alternate sampled addresses, aged 18—44 years, who reported at least one partner with whom they had sexual intercourse, were invited to provide a urine sample for initial testing for genital Chlamydia trachomatis (chlamydia) as previously reported.12 Three thousand five hundred and sixty-nine (71%) agreed and gave signed informed consent for chlamydia testing and storage for anonymous future testing, providing 10 ml of urine in a plastic sterile container containing 1 mg of boric acid. The interviewer posted the urine sample to a central laboratory. Following testing for chlamydia, samples were stored at −80°C.

Ethical approval

Natsal-2 obtained ethical approval from University College Hospital, North Thames Multicentre, and all local research ethics committees in Britain. Approval for HPV testing of the stored urine samples was obtained from St Mary’s Research Ethics Committee (Ref: 07/Q0405/9).

Laboratory methods

Three thousand four hundred and thirty-six urine samples stored at −80°C were available. Three thousand one hundred and twenty-three samples were adequate for testing using an in-house Lumixen-based genotyping assay for detection of HPV types 6, 11, 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73 and 82.13 Each 1 ml urine sample was subjected to centrifugation (15,000 rpm for 20 min) and the pellet suspended in 300 µl phosphate buffered saline before samples were lysed (40 µl Qiagen Protease and 265 µl Qiagen Buffer AL) and nucleic acids extracted on the BioRobot Universal platform (Qiagen; QIAamp® DNA Blood BioRobot® MDx kit, Qiagen Limited, Crawley, West Sussex, UK). Ten microlitres of the 100 µl eluted material was used for PCR amplification. HPV DNA (10 µl) was amplified using the in-house single-round multiplex PCR. The assay incorporated a control PCR to assess specimen integrity and resolved type-specific infections using a genotyping assay based on the Bio-Plex® (Lumixen xMAP®, Bio-Rad Laboratories, Hemel Hempstead, Hertfordshire, UK) platform.

Statistical methods

We did all statistical analyses in Stata (V 10).14 accounting for stratification, clustering and weighting of the sample. We used weighted data to correct for unequal selection probabilities and to match the age/sex population profile.11 We examined the relationship between HPV detection and socio-demographic and behavioural factors and used multivariate analyses to identify the factors associated with HR-HPV types detection. We defined HR-HPV as types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 according to WHO International Agency for Research on Cancer definition.13 We used stepwise logistic regression to model factors identified as statistically significant at p<0.10 in the bivariate analyses. The statistical significance threshold for inclusion in the final multivariate model was p<0.10. To account for differential demographic and behavioural response patterns in willingness to provide a urine sample, the data were given an additional weight, calculated by the inverse of the model-predicted probability of responding.12

RESULTS

Table 1 shows the prevalence of detectable HPV DNA by type in urine for men and women. Any HPV DNA was detected in 29.0% of samples from women and 17.4% from men. Any HR-HPV was detected in 15.9% of women and 9.6% of men. The detected prevalence of either HR-HPV type in current vaccines (HPV types 16 and 18) was 5.5% in samples from women and 3.0% from men, with 4.1% of women and 2.6% of men having these types only. 9.8% of women and 4.8% of men had one of the quadrivalent vaccine types (6, 11, 16 and 18). 3.4% of women and 2.6% of men had two or more HR-HPV types detectable.

<table>
<thead>
<tr>
<th>Denominator*</th>
<th>Women % (95% CI)</th>
<th>Men % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any HPV</td>
<td>29.0 (26.7 to 31.3)</td>
<td>17.4 (15.1 to 19.8)</td>
</tr>
<tr>
<td>Any high risk†</td>
<td>15.9 (14.1 to 17.8)</td>
<td>9.6 (8.0 to 11.6)</td>
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<tr>
<td>2+ high-risk types †</td>
<td>3.4 (2.6 to 6.6)</td>
<td>2.6 (1.3 to 4.9)</td>
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<tr>
<td>High-risk type(s) 16 and/or 18</td>
<td>5.5 (4.5 to 6.8)</td>
<td>3.0 (2.1 to 4.3)</td>
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<tr>
<td>High-risk type(s) 16 and/or 18 only</td>
<td>4.1 (3.1 to 5.2)</td>
<td>2.6 (1.8 to 3.9)</td>
</tr>
<tr>
<td>Low-risk type(s) 6 and/or 11</td>
<td>4.7 (3.8 to 5.9)</td>
<td>2.2 (1.5 to 3.1)</td>
</tr>
<tr>
<td>Types 6/11/16/18</td>
<td>9.8 (8.4 to 11.3)</td>
<td>4.6 (3.7 to 6.3)</td>
</tr>
<tr>
<td>LR HPV-6</td>
<td>3.1 (2.3 to 4.2)</td>
<td>1.1 (0.7 to 1.9)</td>
</tr>
<tr>
<td>LR HPV-11</td>
<td>2.4 (1.8 to 3.3)</td>
<td>1.2 (0.7 to 2.0)</td>
</tr>
<tr>
<td>HR HPV-16</td>
<td>4.2 (3.3 to 5.3)</td>
<td>2.3 (1.5 to 3.5)</td>
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<tr>
<td>HR HPV-18</td>
<td>1.4 (0.9 to 2.2)</td>
<td>0.7 (0.3 to 1.4)</td>
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<tr>
<td>LR HPV-26</td>
<td>0.9 (0.5 to 1.6)</td>
<td>0.3 (0.1 to 1.0)</td>
</tr>
<tr>
<td>LR HPV-31</td>
<td>0.6 (0.3 to 1.1)</td>
<td>0.3 (0.1 to 0.9)</td>
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<tr>
<td>HR HPV-33</td>
<td>0.9 (0.6 to 1.5)</td>
<td>0.4 (0.1 to 0.9)</td>
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<tr>
<td>LR HPV-35</td>
<td>1.0 (0.6 to 1.6)</td>
<td>1.0 (0.5 to 1.8)</td>
</tr>
<tr>
<td>HR HPV-39</td>
<td>1.0 (0.6 to 1.6)</td>
<td>0.7 (0.3 to 1.5)</td>
</tr>
<tr>
<td>LR HPV-45</td>
<td>0.7 (0.4 to 1.2)</td>
<td>0.8 (0.4 to 1.6)</td>
</tr>
<tr>
<td>LR HPV-51</td>
<td>1.9 (1.3 to 2.7)</td>
<td>1.5 (1.0 to 2.4)</td>
</tr>
<tr>
<td>HR HPV-52</td>
<td>2.3 (1.7 to 3.2)</td>
<td>1.1 (0.6 to 1.9)</td>
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<tr>
<td>LR HPV-53</td>
<td>2.0 (1.4 to 2.8)</td>
<td>0.8 (0.4 to 1.5)</td>
</tr>
<tr>
<td>HR HPV-56</td>
<td>1.4 (0.9 to 2.1)</td>
<td>0.9 (0.5 to 1.9)</td>
</tr>
<tr>
<td>HR HPV-58</td>
<td>1.7 (1.2 to 2.4)</td>
<td>0.9 (0.3 to 1.5)</td>
</tr>
<tr>
<td>HR HPV-59</td>
<td>1.0 (0.5 to 1.8)</td>
<td>0.2 (&lt;0.01 to 0.6)</td>
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<tr>
<td>LR HPV-66</td>
<td>0.9 (0.5 to 1.5)</td>
<td>0.6 (0.3 to 1.2)</td>
</tr>
<tr>
<td>HR HPV-68</td>
<td>1.8 (1.2 to 2.7)</td>
<td>0.9 (0.5 to 1.7)</td>
</tr>
<tr>
<td>LR HPV-70</td>
<td>1.0 (0.6 to 1.6)</td>
<td>0.4 (0.1 to 0.9)</td>
</tr>
<tr>
<td>LR HPV-73</td>
<td>0.9 (0.6 to 1.5)</td>
<td>0.4 (0.2 to 1.0)</td>
</tr>
<tr>
<td>LR HPV-82</td>
<td>&lt;0.01 (&lt;0.01 to 0.3)</td>
<td>&lt;0.01 (&lt;0.01 to 0.6)</td>
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</table>

*Weighted, unweighted denominator defined as respondents in Natsal-2 providing a urine sample.
† Defined as HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68.
HR HPV, high-risk human papillomavirus; LR HPV, low-risk human papillomavirus.
Epidemiology

Further analyses examine the factors associated with HR-HPV types. In both women and men, prevalence of detectable HR-HPV declined with age from over one-quarter of women aged 18–24 years to less than a tenth of women aged 40–44 years (supplemental table, available online). HR-HPV was least frequent among those who were married but was not associated with either educational status or social class. Since over 90% of the sample was of white ethnicity, sample sizes for ethnic variations.

In bivariate analysis, prevalence of HR-HPV was strongly associated with sexual behaviour in men and women (supplemental table, available online). Prevalence fell with rising age at first intercourse, more markedly for men than women. HR-HPV was strongly associated with increasing numbers of lifetime partners, and, in the last year, the total number and new partners, partners without a condom and partner concurrency (ie, where dates of sex overlapped between the most recent partner and the second most recent partner and/or the second most recent partner). As an example, prevalence rose from 11.5% of women with no new partner in the last year to 42.3% of those with two or more new partners in the last year (unadjusted OR 5.77 (95% CI 3.72 to 8.94)). Reporting ever having a same-sex partner was associated with HR-HPV, with prevalence of 28.3% (95% CI 15.6% to 49.9%) and 9.2% (95% CI 7.5% to 11.2%) in men and without chlamydial infection, respectively, detected in their urine (unadjusted OR 3.91 (95% CI 1.50% to 10.14%)) and 39.5% (95% CI 24.4% to 56.9%) and 15.4% (95% CI 13.7% to 17.4%) in women with and without chlamydial infection, respectively, (unadjusted OR 3.57 (95% CI 1.74 to 7.34)).

We undertook a stepwise regression analysis to identify the demographic and behavioural factors most strongly associated with HR-HPV. Table 2 shows that for women, in the final model, HR-HPV remained significantly associated with younger age, being unmarried, increasing numbers of new sexual partners in the last year and concurrency between the most recent sexual partners in the last year. For men (table 3), HR-HPV remained significantly associated with younger age at first sex, increasing numbers of sexual partners without a condom in the last year and the number of new sexual partners in the last year.

We also examined the relationship between receptive oral sex and HPV. Receptive oral sex in the last year was commonly reported by women (cunnilingus) (77.9%, 95% CI 75.8% to 80.0%) and by men (fellatio) (79.0%, 95% CI 76.2% to 81.6%). HR-HPV DNA positivity was higher in those reporting receptive oral sex, in men only (supplemental table, available online). This indicates considerable potential for HPV transmission to oropharyngeal sites of partners. The prevalence of reporting receptive oral sex did not vary by age group among men but declined significantly among women aged 35–44 years. Heterosexual anal sex in the last year was reported by 12.7% (95% CI 10.9% to 14.8%) of men and 11.7%,
(95% CI 10.2% to 13.4%) of women. Women (only) reporting this behaviour were more likely to be detectable HR-HPV DNA positive.

For completeness, we also carried out analysis of the relationship between HPV 16 and/or 18 and demographic and behavioural variables (data not shown). Given the lower prevalence, we had less power than for the analysis of any HR type, but this analysis was broadly consistent with that for all HR-HPV types (supplemental table, available online).

Of those found to have HPV 6 and/or 11, the types predominantly associated with genital warts, only 1.9% (95% CI 0.6% to 6.2%) of women and 4.8% (95% CI 0.7% to 27.7%) of men reported that they had been informed by a doctor that they had genital warts/HPV infection.

The median age at first intercourse was 17 for both women and men. In an analysis of the time since first intercourse (figure 1A,B), infection appears to be acquired in a high proportion of young women within a year of first intercourse, with a greater

**Figure 1** (A) Detection of any high-risk human papillomavirus (HPV) by years since first sexual intercourse: Females denominator: Sexually experienced respondents aged 18–44 years in Natsal-2, 3-point moving average. (B) Detection of any high-risk HPV by years since first sexual intercourse: Males denominator: Sexually experienced respondents aged 18–44 years in Natsal-2, 3-point moving average. This figure is produced in colour in the online journal—please visit the website to view the colour figure.
Epidemiology

lag among men. This may reflect gender differences in the age of first sexual partners, as women tend to have first intercourse with partners who are older and who are more likely to be sexually experienced.\textsuperscript{15} Alternatively, or additionally, this may reflect increased biological susceptibility to HPV infection of the immature transformation zone in young girls.

**DISCUSSION**

This is the first population-based probability sample study of the distribution of sexually transmissible HPV types in Britain with detailed analysis of the relationship with demographic and behavioural variables, and including men. We have shown that sexually transmissible HPV is highly prevalent in the population with HPV DNA detectable in 29\% of urine samples from women and 17\% of samples from men. However, of those infected, less than one-third had HPV 16/18.

The overall HPV prevalence is similar to that observed for women by the National Health and Nutrition Examination Survey (NHANES) study in the USA in 2003–2004, which used self-taken vaginal swabs (27\% in women aged 14–59 years). However, prevalence of HPV 16 DNA was higher in Natsal-2 (4.2\%) than in NHANES (1.5\%), as was HPV 18, at 1.4\% in Natsal-2 and 0.8\% in NHANES.\textsuperscript{16} This may in part be explained by the younger age of the Natsal-2 participants and the exclusion of participants with no sexual experience.

In common with other studies,\textsuperscript{17} we detected HPV DNA less frequently in samples from men than from women. This may reflect genuine difference in prevalence. However, urine is known to be an imperfect sample for detection of genital HPV infection. In validation studies comparing HPV detection in paired samples from urine and genital swabs from men and urine and liquid-based cytology samples from women, we have shown urine samples to have lower sensitivity, particularly in men, although specificity approaches 100\%,\textsuperscript{15} consistent with the work of others.\textsuperscript{16}\textsuperscript{18}\textsuperscript{19} Taking account of the long period of storage of samples in this survey and the lower sensitivity of HPV assays in urine than in vaginal or urethral swabs, our results are likely to be minimum estimates.\textsuperscript{15}

Men are key to the transmission of HPV to women, but relatively little is known about HPV infection in men. The sexual behaviour data in this population-based study allowed us to demonstrate, despite the reduced sensitivity of the HPV measure in men, which may lead to misclassification, that similar associations with behavioural characteristics are seen for men as women. The prevalence in men is lower than that in the recent paper by Giuliano et al.\textsuperscript{20} but participants in that study were drawn from a non-random sample in a number of countries and testing was based on genital swabs so a direct comparison is not possible here.

In NHANES, prevalence was highest in women aged 20–24 years and when the sexually inactive were excluded, and, as in Natsal-2, prevalence then declined with increasing age.\textsuperscript{16} Previous studies in England have shown that prevalence of cervical squamous cell carcinomas in recent years seem to be attributable to increasing HR-HPV (HPV 16/18 in particular) and increasing practice of orogenital sex.\textsuperscript{23} In the first National Survey of Sexual Attitudes and Lifestyles undertaken in 1990–1991, we documented a considerable increase in orogenital contact through the latter half of the 20th century.\textsuperscript{24} Given the high prevalence of orogenital contact\textsuperscript{11} and of HR-HPV in the Natsal-2 sample, there is substantial potential for transmission of HR-HPV from genital to oral sites of infection.

The high proportion of young women with detectable HPV and the finding that many are infected within a year or two from first intercourse underscores the importance of delivering HPV vaccination programmes before girls become sexually active. Our analysis of HPV16/18 demonstrated similar risk factors to those for all HR types and supports the existing policy to offer HPV vaccination to all young women (younger than 18 years) in the UK and may help to inform decisions about vaccination of some older women. It is striking that despite the lower sensitivity of urine

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**Key messages**

- **Our data from a representative cross-sectional sample survey of the British population allow for the first time direct comparison between men and women and the risk factors for HPV acquisition.**
- **Sexually transmissible HPV is highly prevalent in the population with HPV DNA detectable in 29\% of urine samples from women and 17\% of samples from men. However, of those infected, less than one-third had HPV 16 or 18.**
- **There is a very strong relationship in both men and women between recent sexual partner change and HPV DNA and rapid acquisition in women after first intercourse. Condom use has some protective effect even after taking account of numbers of sexual partners.**
- **Our data provide evidence for the ongoing debate on the cost-effectiveness of HPV vaccination in young men given the increasing number of cancers, which are thought to be related to HPV and the importance of continued sexual transmission of HPV when only women are vaccinated.**
samples in men for detecting HPV, it could be detected in a relatively high proportion. This finding provides evidence for the ongoing debate on the cost-effectiveness of vaccinating young men.

These estimates of sexually transmissible HPV frequency prior to introducing vaccination in girls provide a baseline to measure changes in vaccine- and non-vaccine-type HPV, in vaccinated women and unvaccinated women and in men who should benefit from ‘herd immunity’ effects due to reduced transmission of infection. HPV 16/18 vaccination has been shown to confer some cross-protection against some closely related non-vaccine HPV types, particularly HPV 31, 33 and 45.26

HPV vaccination is an expensive public health intervention, and it will be important to examine whether vaccination of women reduces the prevalence of infection, in both genders. We are currently undertaking on a third National Survey of Sexual Attitudes and Lifestyles in which urine samples will be collected and self-reported urine sample uptake measured. Fieldwork is scheduled to be completed in 2012 and will allow comparative estimates between the two surveys a decade apart.

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**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** Natsal-2 study obtained ethical approval from University College London, North Thames Multicentre, and all local research ethics committees in Britain. Approval for HPV testing of the stored urine samples was obtained from St Mary’s Research Ethics Committee (Ref: 07/Q0403/9).

**Contributors** AMJ and KAF were responsible for the study design of Natsal-2 and oversaw the collection of urine samples. CML, KS and AMJ were responsible for the study design and secured funding for the present study. SB and NSD were responsible for the HPV testing. RH-J and SD were responsible for data management at the HPA. CHM undertook all statistical analyses. All authors contributed to the design and interpretation of the data. AMJ wrote the first draft of the manuscript, but all authors contributed to revising the manuscript and approved the final version of the manuscript.

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**REFERENCES**


