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Association between Human Leukocyte Antigen Polymorphism and Human Papillomavirus Infection in Brazilian Women

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Abstract

Background: Human papillomavirus (HPV) infection is a necessary cause for cervical cancer, but the majority of genital HPV infections clear spontaneously. Human leukocyte antigen (HLA) polymorphism influences immune response and genetic susceptibility, and its association with cervical cancer was extensively investigated, but few reports focused on HPV infection.

Methods: We performed molecular typing of *HLA-A*, *-B*, *-DQB1,* and *-DRB1* genes as well as of HPV in 1226 women enrolled in the Ludwig-McGill cohort study and investigated the influence on cumulative HPV positivity. HPV types were grouped according to Alphapapillomavirus subgenera that exhibit similar tissue tropism and biological behavior concerning cancer risk. The associations between HLA polymorphisms and HPV infections were estimated using unconditional logistic regression analysis adjusted for age and race.

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CONFLICT OF INTERESTS

ELF and LLV report grants and personal fees from Merck outside of the submitted work. ELF and MZ hold a patent related to the discovery “DNA methylation markers for early detection of cervical cancer”, registered at the Office of Innovation and Partnerships, McGill University, Montreal, Quebec, Canada (October, 2018). No conflict reported by the other authors.

MEETING PRESENTATION

Part of this work was presented in part at 3rd ICGEB Workshop on Human Papillomavirus and Associated Malignancies, São Paulo, Brazil, September, 2017.

Results: *HLA-B**08 and *HLA-DRB1**15:01 were negatively associated with HPV positivity, and similar effects were observed for HPV Subgenus 2 only, which includes HPV16. *HLA-DRB1**08:07 was associated with overall HPV infection and Subgenus 2 positivity. The haplotypes *HLA-B**08-*DRB1**03:01-*DQB1**02:01 and *HLA-DRB1**08:07-*DQB1**04:02 were negatively and positively associated with cumulative HPV positivity, respectively.

Conclusions: Our data suggest that HLA class I and II polymorphism can influence HPV natural infection.

SUMMARY:

A prospective study of human papillomavirus infections and risk of cervical neoplasia in Brazilian women found that human leukocyte antigen polymorphisms may influence the natural history of these infections.

Keywords

Human Papillomavirus (HPV); Human Leukocyte Antigens (HLA); genetic susceptibility; polymorphism; cohort study

INTRODUCTION

While the majority of genital human papillomavirus (HPV) infections clear spontaneously, persistent infection with high-risk types is necessary for progression to cervical precursor lesions and cancer.[1] The importance of immune response in viral clearance has been demonstrated, and genetic susceptibility to cervical cancer has been widely investigated.[2]

Due to the essential role of the highly polymorphic Human Leukocyte Antigen (HLA) molecules in antigen presentation and consequently in mediating an adaptive immune response, several studies have investigated a possible association between HLA and cervical cancer.[3] HLA class II *HLA-DQB1* and *HLA-DRB1* were the most investigated genes; positive associations were reported between each of HLA-DQB1*03, *HLA-DQB1*06:02*, *HLA-DRB1*15*, *HLA-DRB1*11*, *HLA-DRB1*04* and *HLA-DRB1*07* and squamous cervical cancer (SCC) in case-control studies [3]. Conversely, an inverse association was consistently found between *DRB1**13 and SCC [3]. Less investigated were HLA class I genes; one study found an association between HLA-B7 and SCC[4] and another between *HLA-A**01:01-*B**08:01-*C**07:01-*DRB1* 03:01-DQB1* 02:01* haplotype and SCC.[5]

Although studies suggested a possible association between HLA polymorphism and the development of cervical cancer, only few reports considered genetic susceptibility to HPV infections.[6–9] We report in the current study the associations between HLA class I and II alleles and HPV infections in Brazilian women enrolled in the Ludwig-McGill cohort study, a prospective natural history study of HPV infections and risk of cervical neoplasia in Brazilian women.

MATERIALS AND METHODS

Subject Recruitment

The study design and procedures of the Ludwig–McGill cohort study have been previously described.[10] Briefly, this cohort included 2439 women attending a comprehensive maternal and child health program for low-income families at a public hospital (Hospital e Maternidade Vila Nova Cachoeirinha). Women with permanent residence in the city of Sao Paulo, Brazil, were recruited between 1993 and 1997 and followed until 2005. They were between 18 and 60 years old, had an intact uterus, no current referral for hysterectomy, and did not report treatment for cervical disease in the previous 6 months. Cervical cell specimens were collected for cytologic and HPV DNA analyses and blood samples were taken at each of four visits, 4-months apart, in the first year, followed by annual and semester visits thereafter for HPV16 serology and cervical sampling, respectively. Information on sociodemographic, lifestyle, sexual, reproductive, and contraceptive characteristics were collected using a nurse-administered questionnaire. All subjects signed an informed consent prior to participation in the study. The study protocol was approved by institutional ethical and research review boards of the participating institutions in Canada and Brazil.

HPV DNA detection and genotyping

DNA was extracted from ecto- and endo- cervical samples, and DNA quality was assessed by amplification of a 268-bp β-globin gene fragment.[11] MY09/11 and PGMY09/11 PCR protocols were used for HPV detection.[12,13] Each PCR reaction included negative and positive controls. HPV typing was performed by hybridization with individual oligonucleotide probes and ambiguous results were confirmed by restriction fragment length polymorphism analysis of the L1-amplified fragment using a set of restriction enzymes. Genotyping was done for high oncogenic risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and 82, and low oncogenic risk types 6, 11, 26, 32, 34, 40, 42, 44, 53, 54, 57, 61, 62, 67, 69, 70, 71, 72, 81, 83, 84, and 89 (unknown types were considered as low risk).[14,15] HPV testing was performed blindly, and precautions were taken to prevent contamination. Samples that were negative for both HPV and β-globin were considered inadequate for analysis.

HLA typing

In a preliminary report, we studied *HLA-DQB1* and *HLA-DRB1* polymorphisms in a subset of 620 women enrolled in the cohort study.[9] In the current analysis, we expanded our HLA class II investigation to a total of 1226 women genotyped for *HLA-DQB1* and *HLA-DRB1* genes. We also performed HLA class I analysis: 647 and 466 women were genotyped for *HLA-A* and *HLA-B*, respectively. HLA typing, performed on cervical swabs, was done by PCR-based methods. *HLA-A*, *HLA-DRB1* and *HLA-DQB1* PCR and hybridization reaction protocols, primers, and probes followed recommendations of the 12th International Histocompatibility Workshop and Conference guidelines.[16,17] *HLA-B* genotyping was performed using a commercial kit (Luminex LABType SSO–One Lambda Inc. Canoga Park, CA, USA) according to the manufacturer's recommendations. *HLA-A* (n=647) and *HLA-B* (n=466) typing was performed in women included in our previous report of HLA

class II and HPV infection.[9] *HLA-DQB1* and *DRB1* typing was performed in additional 579 samples, totalizing 1226 women. The HLA class II high-resolution typing results were translated into groups of alleles with equal amino acid sequences (e.g., *DRB1**09:01:01 and *DRB1**09:01:02 alleles were grouped as *DRB1**09:01). When required, genotyping results were translated into alleles that resemble the detection spectrum of HLA serology (e.g., *DRB1**15:01, *15:02, and *15:03 alleles were grouped as *DRB1**15). HLA haplotypes were inferred from known linkage disequilibrium patterns between *HLA-A*, *HLA-B*, *HLA-DRB1* and *HLA-DQB1* alleles in the Brazilian population.[18–20]

Statistical Analysis

We compared characteristics of the study population by race using Pearson chi-square tests and Wilcoxon signed-rank test, when appropriate. We used logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between HLA polymorphisms and HPV infections. Models were adjusted for age (18–22, 22–29, 30–39 and ≥40 years) and race (white and non-white). We applied the following criteria for inclusion of alleles in association testing: *HLA-A* and *HLA-DQB1* alleles with a frequency ≥ 10%; *HLA-B* and *HLA-DRB1* with a frequency ≥ 5%; a *P* value lower than 0.01 in crude associations with overall HPV positivity; or alleles considered *a priori* to be associated with HPV or cervical cancer. To estimate the effect of each allele, comparisons were made between subjects positive and those negative for a particular HLA allele. For haplotypes, comparisons were made between subjects with neither of the alleles that comprise the specific haplotype and subjects carrying that haplotype.

Analyses were performed for any HPV infection, which included subjects who had at least one positive test for HPV at any time during the study, and for infections grouped according to *Alphapapillomavirus* species within subgenera that exhibit similar tissue tropism and biological behavior concerning cancer risk.[21] Subgenus 1 included HPV types 6, 11, 32, 40, 42, 44, and 54, from species α1, α8, α10, and α13. Subgenus 2 included HPV types 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82, from species α5, α6, α7, α9, and α11. Subgenus 3 included HPV types 57, 61, 62, 71, 72, 81, 83, 84 and 89, from species α3, α4, and α14. HPV types in Subgenus 1 (low-risk types) and Subgenus 3 (commensal) are not carcinogenic, whereas types in Subgenus 2 (high-risk types) are mostly carcinogenic.

For analyses by subgenus, women with infections by types from that subgenus were first compared to a floating control group of those who did not have infections with types of that specific subgenus. Similarly, for any HPV positivity, the referent group consisted of women who had no HPV infection during the entire follow-up. This approach is referred to as unrestricted analysis. For construct validity purposes, we then performed two additional analyses as above, both by restricting the referent group to HPV-negative women who had at least 4 follow-up visits (n=472). In the second of these restricted analyses, we further restricted the referent group to women who were above the 35% percentile in a propensity score based on the probability of acquiring an HPV infection (n=306). For this, we computed a propensity score using a multivariate logistic regression model for HPV infection that included as putative predictors *a priori* baseline characteristics of the study

population (age, race, education, smoking, age at menarche, age at first intercourse, number of pregnancies, number of lifetime sex partners, number of sex partners in the last 5 years, number of sex partners in the last year, oral contraceptive use, condom use, and history of sexually transmitted infections) and follow-up covariates (highest grade of cytology and cumulative number of new sex partners). The goal of these restrictions was to include in the referent groups women who had follow-up that was long enough to permit HPV detection (both restrictions) and substantial exposure opportunity to HPV infection (the second restriction).

For alleles associated with Subgenus 2 positivity, an analysis considering only women infected exclusively with Subgenus 2 types was also performed. Due to sample size limitation, a similar analysis could not be performed for Subgenus 1 and Subgenus 3. To investigate if the effect observed for the associated alleles could differ according to homozygosity or heterozygosity, we also performed a genotype analysis. The alleles selected for this analysis were those having risk estimates in the unrestricted analyses similar to those in the restricted analyses, and those which presented at least 5 homozygous carriers. Due to linkage disequilibrium found among HLA loci, we also considered the haplotypes containing the alleles associated with HPV positivity. This haplotype analysis compared women positive for the haplotype with women negative for all alleles of the haplotype.

As all the comparisons were hypothesis-driven, no corrections for the number of associations expected by chance were applied. Analyses were carried out using Stata version 13 (StataCorp, College Station, TX, USA).

RESULTS

The Ludwig–McGill cohort study included 2439 women, but only 1226 participants were genotyped for any HLA locus. For efficiency gains, the HLA-tested group was enriched to include women with long-term follow-up and HPV infection outcomes. Table S1 shows the differences between groups according to HLA testing status. Distortions found were related to HPV exposure: the HLA tested group was younger, had a higher number of partners, a higher frequency of women with sexually transmitted diseases, including HPV-related abnormalities, had lower income, and more oral contraceptive use, relative to the non-tested group. Importantly, race – a factor that influences HLA distribution - was not different between these groups.

Table 1 displays the sociodemographic variables of the study sample by race. In general, the distributions of most characteristics were comparable between white and non-white women, such as educational level, number of pregnancies, oral contraceptive and condom use. However, non-white women had lower income, were more frequently current smokers, and reported higher number of sex partners and lower age at first intercourse than white women.

The distribution of *HLA-A*, *HLA-B*, HLA-*DQB1* and *HLA-DRB1* alleles by HPV status is presented in Tables S2–S5. Molecular characterization of HLA class I genes revealed 19 *HLA-A* and 29 *HLA-B* alleles. The most frequent *HLA-A* allele was *HLA-A**02, found in

30.3% and 31.6% of HPV negative and positive women, respectively. Concerning *HLA-B* alleles, B*07, B*14, B*15, B*35, B*44 and B*51 were the most common alleles found in more than 10% of the study population. Fourteen *HLA-DQB1* and 49 *HLA-DRB1* alleles were identified. *HLA-DQB1**02:01, *HLA-DQB1**03:01, *HLA-DQB1**05:01 and *HLA-DQB1**06:02; and *HLA-DRB1**07:01, *HLA-DRB1**03:01, *HLA-DRB1**11:01, *HLA-DRB1**13:01 and *HLA-DRB1**15:01 were the most frequent alleles of *HLA-DQB1* and *HLA-DRB1* genes, identified in at least 20% and 10% of the study population respectively.

Tables 2–5 show the age- and race-adjusted ORs and 95% CIs of the association between HPV infection and *HLA-A*, *HLA-B*, *HLA-DQB1*, and *HLA-DRB1* alleles, respectively. The outcomes investigated were positivity for HPV types from Subgenus 1 (n= 194), Subgenus 2 (n= 603), Subgenus 3 (n=251) or for any HPV type (n=714). Regarding HLA class I genes, no significant difference in allele distribution between HPV positive and negative women was found for any *HLA-A* alleles (Table 2). Concerning *HLA-B* locus (Table 3), *HLA-B**08 was significantly associated with any HPV positivity, both in unrestricted and restricted analyses and mainly for subgenera 1 and 2. Some associations found in the unrestricted analysis were attenuated after restriction, i.e., *HLA-B**35 and *HLA-B**44.

Concerning HLA class II loci, we observed negative associations between *HLA-DQB1**06:03 and subgenus 1 HPV positivity, which persisted in restricted analytical subsets (Table 4). The association between *HLA-DQB1**03:01 and subgenus 2 HPV positivity was not maintained in the restricted analyses (Table 4). Regarding *HLA-DRB1* (Table 5), allele *HLA-DRB1**08:07 was associated with overall HPV infections, mainly driven by subgenus 2 HPV positivity, but the risk estimates were imprecise upon additional restriction because no *HLA-DRB1**08:07 carriers were found in the reference group. On the other hand, we observed negative associations for *HLA-DRB1**15:01 and *DRB1**15:02 with cumulative risk of HPV infections, overall and by subgenus 2 positivity.

We attempted to further examine alleles whose associations persisted in restricted analyses, e.g., *HLA-B*08*, *HLA-DQB1**06:03, *HLA-DRB1**04:03, *HLA-DRB1**13:01, *HLA-DRB1**08:07, and *HLA-DRB1**15:01 in analyses in which the case group (i.e., women with a specific subgenus infection) was restricted to women with infections of no other subgenera. These analyses confirmed the findings for *HLA-B**08 (OR=0.19, 95% CI: 0.04–0.89) and for *DRB1**15:01 (OR=0.55, 95% CI: 0.28–1.09), with respect to subgenus 2. Due to the low number of women positive for HPV types from Subgenus 1 only (n=8), it was not possible to perform the same analysis for *HLA-DQB1*06:03* and *HLA-DRB1*13:01*.

We also performed a genotype analysis, but only *HLA-DRB1* 13:01* was present in a minimum of 5 homozygous women. Estimates for heterozygous (OR=0.88, 95% CI: 0.61–1.28) and homozygous (OR=0.67, 95% CI: 0.13–3.47) effects in unrestricted analysis of HPV positivity were statistically uninformative.

Concerning haplotype associations, *HLA-B**08-*DRB1*03:01-DQB1*02:01* was negatively associated with HPV positivity in unrestricted (OR=0.24, 95% CI 0.10–0.59), but not restricted analysis (OR=0.42, 95% CI 0.13–1.33). The *HLA-DRB1* 08:07-DQB1**04:02

haplotype was associated with HPV positivity (OR=5.63, 95% CI 1.28–24.76), but this haplotype was not found in the referent group in both HPV restricted or Subgenus 2 only analysis. *HLA-DRB1*15:01-DQB1*06:02* haplotype was negatively associated with HPV positivity in unrestricted analysis (OR=0.62, 95% CI 0.41–0.94), with the directions of the association confirmed in both restricted analyses (OR=0.62, 95% CI 0.37–1.04 and OR=0.54, 95% CI 0.26–1.11). No associations were observed for *HLA-DRB1*13:01-DQB1*06:03* or *HLA-DRB1**04:03-*DQB1**03:02 haplotypes.

DISCUSSION

We investigated if HLA polymorphisms could play a risk-mediating role in HPV infections among women enrolled in the Ludwig-McGill cohort study. Although many studies have investigated the HLA associations with cervical cancer, only a few focused on the possible influence of different HLA loci on HPV positivity.[6–9,22] We also examined associations at the HPV subgenus level,[21] which reflects genome sequence identity and expectedly similar antigenic epitopes to be presented by HLA molecules within each group. As the biological function of HLA molecules is antigen presentation to enable T lymphocyte recognition, HLA class II alleles were translated into groups of alleles with equal amino acid sequences.

To help rule out chance associations due to multiple comparisons, we performed analytical restrictions to enhance construct validity by permitting contrasts to include only women with ample follow-up opportunities for HPV detection and those with a behavioral profile that would have placed them at high risk of HPV positivity. The downside of these restricted analyses was a penalty on the statistical precision of the estimates for allele-HPV associations. Yet, we were able to confirm some of the original findings and discovered additional alleles potentially influencing risk of HPV infection (or detectability) relative to our previous study.[9]

We found *HLA-B**08 to be negatively associated with HPV positivity, a finding that was replicated when we examined this allele in the haplotype *HLA-B**08-*DRB1**03:01-*DQB1**02:01. Although the allele *HLA-DQB1**0201 was found to be associated with a decreased risk for cervical cancer,[23] the *HLA-DRB1**0301-*DQB1**0201 haplotype was reported as positively[24] and negatively[25] associated with cervical cancer in different populations. It is possible that these associations with HPV positivity or HPV-related diseases may result from HLA-B8 presentation of an E7 peptide, which was able to induce HPV16 E7-specific and HLA class I-restricted T-cell responses in peripheral blood lymphocytes from healthy individuals.[26] This epitope is also recognized by tumor-infiltrating T cells or T cells from tumor-draining lymph nodes from patients with cervical cancer.[26] Biological relevance of *HLA-B* locus in HPV infection and cervical cancer can be supported by observation of *HLA-B* inactivating mutations in cervical lesions and carcinomas.[27,28]

We also found associations of *HLA-DRB1**08:07 allele and *HLA-DRB1**08:07-*DQB1**04:02 haplotype with HPV positivity. This allele and haplotype were associated with HPV16 positivity and persistence in our previous report.[9] *HLA-DRB1**08:07 is found mainly in South American populations, but association of cervical cancer with DR*08-

DQ*04 was observed previously in Swedish population.[24] In a recent report aiming to identify HLA influence in HPV type-specific clearance and redetection, *HLA-DRB1**08:07 was described as associated with HPV16 redetection.[22]

We found *HLA-DRB1**15:01 and *15:02 to be negatively associated with HPV infection, particularly with subgenus 2, and haplotype *HLA-DRB1**15:01-*DQB1**06:02 negatively associated with HPV positivity in unrestricted analysis, as well. Previously, Hildesheim et al[4] described a reduced risk of HPV16 high grade squamous intraepithelial lesion for *HLA-DRB1**15:01 and *HLA-DRB1**15:01-*DQB1**06:02 women in a cohort from United States. These findings support the hypothesis of an efficient immune response against HPV infection and consequently to cervical disease progression by *HLA-DRB1**15:01-*DQB1**06:02 carriers. In spite of that, Mahmud et al[6] found both *HLA*-DRB1*15:01 allele and its corresponding haplotype associated with cumulative risk of HPV16 infections. In that study the association of only 5 alleles (*HLA-B**07, *DQB1**03, *DQB1**06:02, *DRB1**13, and *DRB1**15:01) - previously associated with cervical cancer, with cumulative HPV positivity and HPV persistence were investigated in a cohort of 524 female university students in Montreal. Indeed, most of the studies reported positive associations between *HLA-DRB1**15 alleles or haplotypes with cervical disease,[4,17,29–33s] including GWAS studies.[34s–36s] Leo and cols[36s] demonstrated strong association of cervical neoplasia with risk, including *HLA-DRB1**15-*DQB1**0602-*DQA1**0102 that are determined by the amino acids carried at positions 13 and 71 in pocket 4 of HLA-DRB1. This divergence regarding *HLA-DRB1**15 may result from different alleles found in linkage disequilibrium within this haplotype in ethnically distinct populations.[4] It is also possible that other genital infections or HPV viral load may interfere with antigen availability and influence the natural immune response to HPV. We cannot exclude that non-HPV derived tumor antigens may influence the association of HLA polymorphism with cervical cancer.

Limitations of this study include the relatively small sample size and lack of sufficient power given the rarity of many HPV types and HLA alleles. In conclusion, our data suggest that HLA polymorphisms may influence the natural history of HPV infection. Larger studies are warranted to understand the complex interactions between host immune response and HPV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Baseline Characteristics of the study population by race, n=1226.

		White (N = 790)	Non-White (N = 436)	P value[a]
Age (years), Mean ± SD		31 ± 7.8	30 ± 7.0	0.0111
Age (years), n (%)				0.017
	18–22	123 (15.6)	68 (15.6)	
	22–29	219 (27.7)	141 (32.3)	
	30–39	341 (43.2)	193 (44.3)	
	≥ 40	107 (13.5)	34 (7.8)	
Education, n (%)				0.704
	< elementary	160 (20.2)	89 (20.4)	
	Completed elementary	465 (58.9)	268 (61.5)	
	Completed high School	141 (17.9)	70 (16.1)	
	Completed college/University	23 (2.9)	9 (2.1)	
	Missing	1 (0.1)	0 (0)	
No. of Pregnancies, Mean ± SD		3 ± 2.1	3 ± 2.1	0.1737
No. of Pregnancies, n (%)				0.583
	0–1	139 (17.6)	76 (17.4)	
	2–3	361 (45.7)	181 (41.5)	
	4–6	221 (28.0)	139 (31.9)	
	≥ 7	62 (7.9)	37 (8.5)	
	Missing	7 (0.9)	3 (0.7)	
Oral contraceptive use, n (%)				0.279
	Never	103 (13.0)	70 (16.1)	
	< 6 years	461 (58.3)	253 (58.0)	
	≥ 6 years	226 (28.6)	113 (15.9)	
Income (in US $, quartiles), n (%)				0.033
	Q1: 30–384	174 (22.0)	129 (29.6)	
	Q2: 387–740	186 (23.5)	87 (20.0)	
	Q3: 750–25,000	160 (20.2)	76 (17.4)	
	Q4: ≥ 30,000	252 (31.9)	138 (31.7)	
	Missing	18 (2.3)	6 (1.4)	
Number of lifetime sex partners, n (%)				0.009
	0–1	376 (47.6)	167 (38.3)	
	2–3	269 (34.1)	170 (39.0)	
	4	145 (18.3)	98 (22.5)	
	Missing	0 (0)	1 (0.2)	
Number of sex partners in the last 5 years, n (%)				0.088
	0–1	609 (77.1)	317 (72.7)	

		White (N = 790)		Non-White (N = 436)		P value[a]
	≥ 2	181 (22.9)		119 (27.3)		
Number of sex partners in the last year, n (%)						0.777
	0–1	743 (94.1)		406 (93.1)		
	≥ 2	43 (5.4)		28 (6.4)		
	Missing	4 (0.5)		2 (0.5)		
Condom use, n (%)						0.261
	No	270 (34.2)		163 (37.4)		
	Yes	520 (65.8)		273 (62.6)		
Sexually Transmitted Diseases (STD), n (%)						0.096
	None	610 (77.2)		340 (78.0)		
	HPV-related STD	34 (4.3)		31 (7.1)		
	Other STD	143 (18.1)		64 (14.7)		
	Missing	3 (0.4)		1 (0.2)		
Age at Menarche, n (%)						0.329
	0–11	177 (22.4)		99 (22.7)		
	12–19	609 (77.1)		337 (77.3)		
	Missing	4 (0.5)		0 (0)		
Age at first Intercourse, n (%)						0.000
	20–50	203 (25.7)		79 (18.1)		
	18–19	171 (21.7)		89 (20.4)		
	16–17	219 (27.7)		113 (25.9)		
	≤ 15	197 (24.9)		155 (35.6)		
Smoking status, n (%)						0.005
	Never	412 (52.1)		189 (43.3)		
	Current	251 (31.8)		177 (40.6)		
	Former	127 (16.1)		70 (16.1)		
Highest Grade of Cytology,[b] n (%)						0.746
	NILM	603 (76.3)		325 (74.5)		
	ASC-US	75 (9.5)		49 (11.2)		
	LSIL	79 (10.0)		48 (11.0)		
	HSIL	31 (3.9)		13 (3.0)		
	Missing	2 (0.2)		1 (0.2)		
HPV infection,[b, c] n (%)						
	Negative in all visits	346 (43.8)		166 (38.1)		0.05
	Positive for subgenus 1 at any visit	113 (14.3)		81 (18.6)		0.05
	Positive for subgenus 2 at any visit	368 (46.6)		235 (53.9)		0.014
	Positive for subgenus 3 at any visit	161 (20.4)		90 (20.6)		0.913
Number of Visits,[b] Mean ± SD		12 ± 3.4		12 ± 3.1		0.1746

	White (N = 790)		Non-White (N = 436)		P value[a]
Follow-up time (months),[b] Mean ± SD	75.7 ± 24.8		78.1 ± 22.3		0.0972

[a]P-values from the appropriate test (Pearson chi-square and Wilcoxon signed-rank tests) were calculated treating missing values as a separate category.

[b]Variable relate to follow-up (three visits in the first year and every six months thereafter).

[c]Subgenus 1 includes HPV types 6, 11, 32, 40, 42, 44, and 54, from species α1, α8, α10, and α13. Subgenus 2 includes HPV types 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82, from species α5, α6, α7, α9, and α11. Subgenus 3 includes HPV types 57, 61, 62, 71, 72, 81, 83, 84 and 89, from species α3, α4, and α14.

Abbreviations: NILM, negative for intraepithelial lesion or malignancy; ASC-US: Atypical squamous cells of undetermined significance; LSIL: low squamous intraepithelial lesion; HSIL, high squamous intraepithelial lesion.

Table 2:

Age- and race- adjusted odds ratios and 95% confidence intervals for the association between HLA-A alleles and HPV infection

HLA-A allele	Subgenus 1[a]	Subgenus 2[a]	Subgenus 3[a]	Any HPV[b]
Overall study population, unrestricted analysis[c]				
A*01	0.55 (0.19–1.60)	1.00 (0.49–2.03)	0.98 (0.43–2.23)	0.85 (0.41–1.78)
A*02	1.32 (0.85–2.05)	1.19 (0.83–1.71)	1.07 (0.71–1.61)	1.12 (0.77–1.64)
A*11	0.54 (0.24–1.24)	0.61 (0.36–1.06)	0.79 (0.41–1.54)	0.61 (0.35–1.05)
A*23	0.90 (0.48–1.70)	1.41 (0.84–2.36)	0.72 (0.39–1.32)	1.13 (0.66–1.93)
A*24	1.16 (0.64–2.10)	0.99 (0.61–1.61)	0.98 (0.56–1.70)	0.89 (0.54–1.47)
A*31	**1.77 (1.02–3.07)**	1.21 (0.74–1.97)	1.62 (0.97–2.71)	1.63 (0.94–2.83)
A*68	0.91 (0.50–1.68)	1.22 (0.75–1.97)	0.77 (0.43–1.36)	1.07 (0.65–1.75)
First restricted analysis: referent group restricted to HPV negative with sufficient follow-up[d]				
A*01	0.60 (0.18–2.06)	0.95 (0.43–2.10)	1.04 (0.39–2.76)	1.02 (0.47–2.22)
A*02	1.53 (0.90–2.59)	1.29 (0.86–1.93)	1.29 (0.79–2.11)	1.23 (0.83–1.83)
A*11	0.44 (0.18–1.10)	0.58 (0.32–1.05)	0.59 (0.28–1.24)	0.60 (0.34–1.06)
A*23	1.10 (0.52–2.32)	1.20 (0.69–2.08)	0.89 (0.43–1.83)	1.14 (0.66–1.96)
A*24	0.96 (0.48–1.95)	0.86 (0.51–1.45)	0.85 (0.45–1.63)	0.83 (0.49–1.39)
A*31	1.90 (0.95–3.79)	1.35 (0.76–2.37)	1.81 (0.95–3.45)	1.44 (0.82–2.52)
A*68	0.96 (0.47–1.98)	1.15 (0.68–1.93)	0.85 (0.44–1.66)	1.08 (0.64–1.81)
Second restricted analysis: referent group further restricted to women with a high probability of HPV exposure[e]				
A*01	0.41 (0.12–1.41)	0.63 (0.28–1.44)	0.63 (0.23–1.72)	0.67 (0.29–1.54)
A*02	1.35 (0.76–2.40)	1.10 (0.69–1.76)	1.10 (0.63–1.91)	1.07 (0.66–1.72)
A*11	0.46 (0.17–1.23)	0.63 (0.31–1.26)	0.64 (0.28–1.48)	0.67 (0.33–1.36)
A*23	0.88 (0.40–1.96)	1.01 (0.54–1.88)	0.70 (0.32–1.53)	0.85 (0.45–1.60)
A*24	0.93 (0.44–2.01)	0.86 (0.46–1.60)	0.87 (0.42–1.79)	0.86 (0.46–1.60)
A*31	1.81 (0.83–3.91)	1.29 (0.66–2.53)	1.74 (0.83–3.66)	1.35 (0.69–2.67)
A*68	0.84 (0.39–1.80)	0.98 (0.54–1.78)	0.72 (0.35–1.49)	0.87 (0.47–1.61)

[a] Subgenus 1 includes HPV types 6, 11, 32, 40, 42, 44, and 54, from species α1, α8, α10, and α13. Subgenus 2 includes HPV types 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82, from species α5, α6, α7, α9, and α11. Subgenus 3 includes HPV types 57, 61, 62, 71, 72, 81, 83, 84 and 89, from species α3, α4, and α14.

[b] HPV positive women were compared to HPV negative women.

[c] Women with a specific subgenus group infection were compared against a floating referent group of all those who did not have that particular group infection.

[d] Women with a specific subgenus group infection were compared to a fixed referent group of HPV-negative women who had at least 4 follow-up visits.

[e] Women with a specific subgenus group infection were compared to a fixed referent group of HPV-negative women who had at least 4 follow-up visits and a high propensity score (i.e., probability of acquiring an HPV infection above the 35% percentile).

Table 3:

Age- and race- adjusted odds ratios and 95% confidence intervals for the association between HLA-B alleles and HPV infection by analysis set

HLA-B allele		Subgenus 1[a]	Subgenus 2[a]	Subgenus 3[a]	Any HPV[b]
Overall study population, unrestricted analysis[c]					
	B*07	1.52 (0.78–2.97)	0.84 (0.48–1.47)	0.65 (0.32–1.33)	0.78 (0.44–1.40)
	B*08	0.32 (0.09–1.07)	**0.33 (0.16–0.65)**	0.78 (0.34–1.75)	**0.29 (0.15–0.56)**
	B*14	1.48 (0.73–3.00)	1.01 (0.56–1.82)	1.35 (0.71–2.57)	1.23 (0.66–2.31)
	B*15	0.86 (0.47–1.59)	1.03 (0.64–1.65)	1.11 (0.64–1.91)	0.96 (0.58–1.57)
	B*18	1.75 (0.77–4.02)	1.14 (0.55–2.34)	1.19 (0.54–2.66)	1.24 (0.57–2.70)
	B*35	0.90 (0.49–1.66)	1.37 (0.86–2.19)	**1.83 (1.11–3.01)**	1.38 (0.84–2.28)
	B*39	2.14 (0.97–4.76)	0.69 (0.33–1.45)	0.92 (0.38–2.21)	1.25 (0.56–2.80)
	B*40	0.54 (0.20–1.45)	1.42 (0.72–2.79)	0.95 (0.43–2.07)	1.50 (0.72–3.12)
	B*42	1.32 (0.49–3.51)	0.85 (0.37–1.96)	1.06 (0.41–2.77)	1.00 (0.41–2.41)
	B*44	0.88 (0.47–1.64)	**1.86 (1.14–3.04)**	0.66 (0.36–1.19)	1.52 (0.91–2.55)
	B*45	0.31 (0.07–1.35)	1.00 (0.44–2.24)	1.52 (0.64–3.60)	1.11 (0.47–2.63)
	B*49	1.50 (0.60–3.76)	0.64 (0.29–1.41)	1.47 (0.62–3.50)	1.15 (0.49–2.74)
	B*51	0.85 (0.41–1.78)	1.43 (0.82–2.50)	0.75 (0.38–1.47)	0.94 (0.53–1.65)
	B*53	1.20 (0.51–2.81)	0.70 (0.34–1.42)	1.60 (0.75–3.43)	0.78 (0.38–1.63)
	B*57	1.02 (0.44–2.38)	1.10 (0.54–2.23)	0.80 (0.34–1.90)	0.92 (0.44–1.91)
	B*58	0.67 (0.25–1.81)	0.54 (0.27–1.11)	0.40 (0.14–1.17)	0.52 (0.25–1.06)
First restricted analysis: referent group restricted to HPV negative with sufficient follow-up[d]					
	B*07	1.29 (0.60–2.79)	0.83 (0.45–1.53)	0.64 (.028–1.43)	0.81 (0.45–1.48)
	B*08	**0.20 (0.06–0.72)**	**0.28 (0.13–0.58)**	0.43 (0.18–1.02)	**0.29 (0.14–0.58)**
	B*14	1.46 (0.64–3.36)	1.07 (0.56–2.06)	1.33 (0.55–1.94)	1.13 (0.60–2.14)
	B*15	0.87 (0.43–1.75)	0.94 (0.56–1.57)	1.03 (0.55–1.94)	0.89 (0.53–1.49)
	B*18	1.45 (0.53–3.92)	1.14 (0.51–2.54)	1.24 (0.48–3.23)	1.11 (0.51–2.44)
	B*35	1.03 (0.50–2.10)	1.39 (0.82–2.34)	**1.94 (1.06–3.55)**	1.31 (0.79–2.19)
	B*39	2.12 (0.79–5.72)	0.97 (0.40–2.38)	1.16 (0.40–3.34)	1.32 (0.56–3.07)
	B*40	0.70 (0.22–2.25)	1.46 (0.68–3.09)	1.17 (0.46–2.99)	1.41 (0.67–2.96)
	B*42	1.22 (0.38–3.90)	1.00 (0.38–2.60)	1.12 (0.36–3.46)	1.15 (0.46–2.90)
	B*44	1.37 (0.65–2.89)	**1.79 (1.04–3.08)**	1.03 (0.50–2.10)	1.61 (0.94–2.75)
	B*45	0.35 (0.07–1.82)	1.18 (0.46–2.99)	1.51 (0.53–4.36)	1.23 (0.50–3.05)
	B*49	1.85 (0.58–5.92)	0.99 (0.38–2.59)	1.67 (0.58–4.84)	1.32 (0.53–3.26)
	B*51	0.91 (0.40–2.11)	1.16 (0.64–2.08)	0.79 (0.37–1.70)	0.98 (0.55–1.77)
	B*53	0.95 (0.37–2.46)	0.67 (0.31–1.45)	1.11 (0.47–2.60)	0.75 (0.36–1.57)
	B*57	1.18 (0.44–3.18)	1.04 (0.49–2.24)	0.83 (0.31–2.24)	1.01 (0.48–2.15)
	B*58	0.52 (0.18–1.54)	0.54 (0.25–1.17)	0.34 (0.11–1.08)	0.56 (0.26–1.18)

HLA-B allele		Subgenus 1[a]	Subgenus 2[a]	Subgenus 3[a]	Any HPV[b]
Second restricted analysis: referent group further restricted to women with a high probability of HPV exposure[e]					
	B*07	1.86 (0.74–4.70)	1.18 (0.54–2.61)	0.87 (0.34–2.28)	1.13 (0.51–2.52)
	B*08	**0.25 (0.07–0.94)**	**0.36 (0.15–0.86)**	0.60 (0.23–1.58)	**0.38 (0.16–0.89)**
	B*14	2.75 (0.92–8.22)	2.17 (0.81–5.82)	2.76 (0.95–8.00)	2.17 (0.81–5.82)
	B*15	0.94 (0.43–2.03)	1.07 (0.58–1.97)	1.19 (0.57–2.45)	1.00 (0.54–1.87)
	B*18	1.28 (0.44–3.75)	0.93 (0.38–2.31)	1.05 (0.36–3.03)	0.77 (0.30–1.96)
	B*35	1.01 (0.47–2.19)	1.29 (0.70–2.39)	1.73 (0.87–3.45)	1.29 (0.69–2.41)
	B*39	2.24 (0.74–6.81)	1.12 (0.39–3.21)	1.18 (0.35–3.91)	1.49 (0.54–4.12)
	B*40	0.60 (0.18–1.97)	1.13 (0.49–2.63)	0.97 (0.35–2.68)	1.03 (0.43–2.44)
	B*42	1.44 (0.39–5.38)	1.19 (0.37–3.78)	1.21 (0.34–4.50)	1.38 (0.44–4.33)
	B*44	1.22 (0.54–2.75)	1.62 (0.85–3.08)	0.85 (0.38–1.91)	1.46 (0.76–2.81)
	B*45	0.29 (0.06–1.53)	0.83 (0.31–2.23)	1.18 (0.39–3.59)	0.80 (0.30–2.18)
	B*49	2.25 (0.55–9.19)	1.47 (0.40–5.37)	2.56 (0.65–10.12)	1.97 (0.56–6.99)
	B*51	0.76 (0.30–1.90)	0.99 (0.50–1.97)	0.69 (0.29–1.62)	0.94 (0.47–1.89)
	B*53	0.82 (0.30–2.24)	0.60 (0.26–1.39)	0.94 (0.38–2.35)	0.64 (0.28–1.49)
	B*57	1.21 (0.41–3.56)	1.08 (0.44–2.64)	0.85 (0.28–2.53)	1.07 (0.43–2.63)
	B*58	0.46 (0.15–1.43)	0.49 (0.21–1.15)	0.32 (0.09–1.07)	0.46 (0.20–1.10)

[a]Subgenus 1 includes HPV types 6, 11, 32, 40, 42, 44, and 54, from species α1, α8, α10, and α13. Subgenus 2 includes HPV types 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82, from species α5, α6, α7, α9, and α11. Subgenus 3 includes HPV types 57, 61, 62, 71, 72, 81, 83, 84 and 89, from species α3, α4, and α14.

[b]HPV positive women were compared to HPV negative women.

[c]Women with a specific subgenus group infection were compared against a floating referent group of all those who did not have that particular group infection.

[d]Women with a specific subgenus group infection were compared to a fixed referent group of HPV-negative women who had at least 4 follow-up visits.

[e]Women with a specific subgenus group infection were compared to a fixed referent group of HPV-negative women who had at least 4 follow-up visits and a high propensity score (i.e., probability of acquiring an HPV infection above the 35% percentile).

Table 4:

Age- and race- adjusted odds ratios and 95% confidence intervals for the association between HLA-DQB1 alleles and HPV infection by analysis set.

HLA-DQB1 alleles		Subgenus 1[a]	Subgenus 2 [a]	Subgenus 3 [a]	Any HPV[b]
Overall study population, unrestricted analysis[c]					
	*02:01	1.04 (0.74–1.45)	0.90 (0.70–1.15)	0.89 (0.65–1.21)	0.93 (0.72–1.20)
	*03	0.92 (0.66–1.28)	0.81 (0.63–1.04)	1.13 (0.83–1.53)	0.84 (0.65–1.08)
	*03:01	0.94 (0.65–1.35)	**0.75 (0.57–0.98)**	1.02 (0.73–1.41)	0.85 (0.65–1.12)
	*03:02	1.26 (0.80–2.00)	0.91 (0.63–1.30)	1.24 (0.81–1.89)	0.97 (0.67–1.39)
	*03:03	1.19 (0.63–2.24)	1.28 (0.77–2.11)	1.19 (0.66–2.14)	1.16 (0.69–1.95)
	*04:02	1.13(0.72–1.77)	1.19 (0.84–1.70)	1.45 (0.97–2.16)	1.37 (0.95–1.98)
	*05	1.07 (0.76–1.51)	1.02 (0.79–1.32)	1.13 (0.82–1.54)	0.97 (0.75–1.26)
	*05:01	0.99 (0.68–1.44)	1.07 (0.80–1.41)	1.01 (0.71–1.43)	1.04 (0.78–1.39)
	*05:02	1.10 (0.54–2.23)	0.88 (0.51–1.51)	1.73 (0.96–3.12)	0.93 (0.54–1.61)
	*05:03	1.28 (0.58–2.83)	0.78 (0.42–1.48)	1.09 (0.51–2.32)	0.64 (0.34–1.20)
	*06	0.81 (0.57–1.14)	0.95 (0.74–1.23)	**0.71 (0.52–0.97)**	0.83 (0.64–1.07)
	*06:02	0.94 (0.63–1.39)	0.91 (0.68–1.23)	0.80 (0.55–1.16)	0.85 (0.63–1.14)
	*06:03	**0.47 (0.24–0.93)**	1.08 (0.72–1.61)	1.04 (0.63–1.69)	0.86 (0.57–1.28)
	*06:04	0.97 (0.48–1.97)	1.39 (0.81–2.38)	0.49 (0.22–1.10)	1.49 (0.84–2.65)
	*06:05	1.19 (0.39–3.64)	1.11 (0.45–2.74)	0.42 (0.10–1.85)	0.97 (0.39–2.43)
First restricted analysis: referent group restricted to HPV negative with sufficient follow-up[d]					
	*02:01	1.00 (0.69–1.45)	0.91 (0.70–1.19)	0.88 (0.62–1.24)	0.95 (0.73–1.24)
	*03	0.85 (0.59–1.23)	0.80 (0.61–1.05)	0.98 (0.70–1.37)	0.81 (0.63–1.06)
	*03:01	0.88 (0.59–1.32)	0.78 (0.59–1.04)	0.91 (0.63–1.31)	0.83 (0.63–1.10)
	*03:02	1.09 (0.65–1.83)	0.92 (0.63–1.36)	1.14 (0.71–1.82)	0.92 (0.63–1.34)
	*03:03	1.47 (0.70–3.07)	1.29 (0.74–2.24)	1.33 (0.68–2.61)	1.27 (0.74–2.19)
	*04:02	1.37 (0.81–2.31)	1.34 (0.91–1.99)	**1.74 (1.09–2.80)**	1.38 (0.94–2.03)
	*05	1.00 (0.68–1.47)	1.01 (0.77–1.33)	1.09 (0.77–1.54)	1.00 (0.76–1.31)
	*05:01	0.99 (0.65–1.52)	1.08 (0.80–1.47)	1.07 (0.73–1.57)	1.12 (0.83–1.50)
	*05:02	0.96 (0.43–2.11)	0.90 (0.50–1.62)	1.40 (0.72–2.72)	0.88 (0.50–1.57)
	*05:03	1.00 (0.42–2.37)	0.71 (0.37–1.37)	0.84 (0.37–1.91)	0.64 (0.33–1.24)
	*06	0.75 (0.51–1.09)	0.86 (0.65–1.12)	**0.67 (0.47–0.95)**	0.84 (0.64–1.09)
	*06:02	0.92 (0.59–1.42)	0.88 (0.64–1.21)	0.78 (0.52–1.18)	0.86 (0.63–1.17)
	*06:03	**0.42 (0.20–0.87)**	0.88 (0.58–1.34)	0.87 (0.51–1.48)	0.83 (0.55–1.26)
	*06:04	1.26 (0.54–2.92)	1.52 (0.82–2.82)	0.66 (0.26–1.67)	1.54 (0.84–2.83)
	*06:05	1.04 (0.30–3.63)	0.98 (0.39–2.49)	0.44 (0.09–2.11)	0.97 (0.39–2.43)
Second restricted analysis: referent group further restricted to women with a high probability of HPV exposure[e]					
	*02:01	1.08 (0.73–1.60)	0.98 (0.73–1.33)	0.95 (0.65–1.38)	1.04 (0.77–1.42)

HLA-DQB1 alleles		Subgenus 1[a]	Subgenus 2 [a]	Subgenus 3 [a]	Any HPV[b]
	*03	0.78 (0.52–1.15)	0.75 (0.56–1.02)	0.90 (0.62–1.30)	0.76 (0.56–1.03)
	*03:01	0.83 (0.54–1.27)	0.75 (0.54–1.04)	0.86 (0.58–1.28)	0.84 (0.61–1.16)
	*03:02	1.16 (0.67–2.01)	0.96 (0.62–1.50)	1.19 (0.71–2.00)	0.90 (0.57–1.41)
	*03:03	1.30 (0.60–2.86)	1.24 (0.66–2.31)	1.26 (0.60–2.63)	1.14 (0.60–2.15)
	*04:02	1.28 (0.74–2.22)	1.24 (0.80–1.91)	1.59 (0.95–2.64)	1.20 (0.78–1.87)
	*05	0.97 (0.64–1.44)	0.94 (0.69–1.28)	1.02 (0.70–1.48)	0.93 (0.68–1.27)
	*05:01	1.01 (0.64–1.58)	1.08 (0.77–1.53)	1.06 (0.70–1.62)	1.05 (0.74–1.48)
	*05:02	0.93 (0.40–2.15)	0.83 (0.43–1.59)	1.34 (0.65–2.78)	0.96 (0.50–1.84)
	*05:03	0.86 (0.35–2.13)	0.61 (0.30–1.25)	0.73 (0.31–1.73)	0.56 (0.26–1.19)
	*06	0.77 (0.52–1.16)	0.89 (0.66–1.21)	0.69 (0.47–1.01)	0.87 (0.64–1.19)
	*06:02	0.92 (0.58–1.46)	0.90 (0.63–1.29)	0.78 (0.50–1.22)	0.89 (0.62–1.28)
	*06:03	**0.41 (0.19–0.86)**	0.82 (0.51–1.31)	0.84 (0.47–1.49)	0.69 (0.42–1.12)
	*06:04	1.24 (0.51–3.02)	1.48 (0.73–2.98)	0.65 (0.24–1.74)	1.61 (0.80–3.24)
	*06:05	1.52 (0.36–6.37)	1.51 (0.47–4.84)	0.73 (0.13–4.14)	1.65 (0.52–5.21)

[a]Subgenus 1 includes HPV types 6, 11, 32, 40, 42, 44, and 54, from species α1, α8, α10, and α13. Subgenus 2 includes HPV types 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82, from species α5, α6, α7, α9, and αll. Subgenus 3 includes HPV types 57, 61, 62, 71, 72, 81, 83, 84 and 89, from species α3, α4, and α14.

[b]HPV positive women were compared to HPV negative women.

[c]Women with a specific subgenus group infection were compared against a floating referent group of all those who did not have that particular group infection.

[d]Women with a specific subgenus group infection were compared to a fixed referent group of HPV-negative women who had at least 4 follow-up visits (N = 472).

[e]Women with a specific subgenus group infection were compared to a fixed referent group of HPV-negative women who had at least 4 follow-up visits and a high propensity score (i.e., probability of acquiring an HPV infection above the 35% percentile) (N = 306).

Table 5:

Age- and race- adjusted odds ratios and 95% confidence intervals for the association between HLA-DRB1 alleles and HPV infection by analysis set.

HLA-DRB1 alleles		Subgenus 1[a]	Subgenus 2 [a]	Subgenus 3 [a]	Any HPV[b]
Overall study population, unrestricted analysis[c]					
	*01	0.97 (0.64–1.45)	1.17 (0.87–1.57)	1.10 (0.77–1.56)	1.09 (0.81–1.47)
	*01:01	0.95 (0.53–1.70)	1.20 (0.80–1.81)	1.20 (0.75–1.94)	1.11 (0.73–1.68)
	*01:02	1.11 (0.64–1.90)	1.15 (0.76–1.73)	0.92 (0.56–1.53)	1.21 (0.79–1.85)
	*03	0.93 (0.62–1.39)	0.94 (0.70–1.26)	0.92 (0.65–1.32)	0.83 (0.62–1.12)
	*03:01	0.81 (0.51–1.30)	0.83 (0.60–1.16)	0.70 (0.46–1.08)	0.73 (0.52–1.01)
	*03:02	1.51 (0.80–2.86)	1.49 (0.87–2.57)	**1.72 (0.97–3.05)**	1.48 (0.83–2.63)
	*04	1.02 (0.68–1.52)	0.82 (0.61–1.10)	1.03 (0.72–1.46)	0.76 (0.57–1.02)
	*04:01	0.79 (0.27–2.31)	0.71 (0.35–1.45)	0.84 (0.34–2.07)	0.69 (0.34–1.38)
	*04:03	**2.67 (1.05–6.82)**	0.57 (0.23–1.38)	2.12 (0.87–5.15)	1.20 (0.49–2.94)
	*04:05	0.58 (0.20–1.68)	1.02 (0.54–1.92)	1.37 (0.67–2.79)	0.82 (0.44–1.55)
	*04:07	0.98 (0.28–3.45)	0.88 (0.36–2.16)	0.95 (0.31–2.88)	0.90 (0.36–2.21)
	*07:01	1.32 (0.92–1.90)	1.01 (0.77–1.33)	0.87 (0.62–1.22)	1.02 (0.78–1.35)
	*08	1.13 (0.71–1.80)	1.08 (0.76–1.54)	0.90 (0.59–1.40)	1.33 (0.92–1.92)
	*08:01	0.82 (0.31–2.16)	1.03 (0.54–1.98)	0.82 (0.36–1.89)	1.34 (0.68–2.62)
	*08:04	1.53 (0.71–3.30)	0.88 (0.46–1.67)	1.39 (0.68–2.83)	1.25 (0.64–2.43)
	*08:07	1.06 (0.30–3.72)	**4.12 (1.35–12.59)**	0.69 (0.20–2.39)	**6.28 (1.44–27.49)**
	*09:01	1.90 (0.98–3.68)	1.18 (0.66–2.11)	1.31 (0.68–2.51)	1.34 (0.73–2.46)
	*10:01	0.81 (0.36–1.84)	1.23 (0.70–2.16)	0.97 (0.49–1.91)	1.25 (0.70–2.23)
	*11	0.97 (0.66–1.43)	0.88 (0.66–1.16)	1.01 (0.72–1.42)	0.97 (0.73–1.30)
	*11:01	0.85 (0.52–1.38)	1.17(0.83–1.65)	0.83 (0.54–1.28)	1.11 (0.78–1.58)
	*11:02	0.68 (0.28–1.63)	0.57 (0.32–1.02)	0.78 (0.37–1.62)	0.63 (0.36–1.11)
	*12	0.60 (0.21–1.71)	1.28 (0.67–2.43)	1.09 (0.51–2.32)	1.50 (0.76–2.96)
	*13	0.66 (0.44–1.00)	1.07 (0.81–1.41)	0.82 (0.58–1.16)	1.00 (0.76–1.33)
	*13:01	0.57 (0.32–1.00)	1.09 (0.76–1.55)	0.91 (0.59–1.41)	0.89 (0.62–1.27)
	*13:02	0.87 (0.48–1.58)	1.21 (0.80–1.84)	0.91 (0.54–1.52)	1.38 (0.89–2.14)
	*14	**2.00 (1.08–3.69)**	0.85 (0.50–1.43)	0.81 (0.42–1.59)	0.79 (0.47–1.33)
	*15	0.99 (0.66–1.49)	0.84 (0.63–1.13)	0.80 (0.55–1.16)	0.75 (0.56–1.01)
	*15:01	0.58 (0.31–1.09)	**0.57 (0.39–0.85)**	0.83 (0.52–1.35)	**0.59 (0.40–0.86)**
	*15:02	1 (empty)	0.16 (0.02–1.32)	0.55 (0.07–4.53)	**0.11 (0.01–0.88)**
	*15:03	**1.69 (1.01–2.80)**	1.53 (0.99–2.36)	0.91 (0.54–1.53)	1.29 (0.82–2.01)
	*16	0.90 (0.45–1.81)	0.72 (0.44–1.19)	**1.95 (1.15–3.29)**	0.95 (0.58–1.57)
	*16:01	0.68 (0.20–2.28)	0.79 (0.37–1.71)	1.82 (0.81–4.09)	1.12 (0.51–2.43)
First restricted analysis: referent group restricted to HPV negative with sufficient follow-up[d]					
	*01	1.00 (0.64–1.58)	1.15 (0.84–1.58)	1.15 (0.78–1.71)	1.15 (0.84–1.57)

HLA-DRB1 alleles		Subgenus 1[a]	Subgenus 2 [a]	Subgenus 3 [a]	Any HPV[b]
	*01:01	0.99 (0.52–1.89)	1.18 (0.75–1.84)	1.25 (0.73–2.16)	1.18 (0.77–1.83)
	*01:02	1.20 (0.65–2.23)	1.17 (0.74–1.82)	1.03 (0.58–1.82)	1.20 (0.78–1.85)
	*03	0.84 (0.54–1.31)	0.86 (0.63–1.18)	0.83 (0.55–1.23)	0.81 (0.60–1.11)
	*03:01	0.68 (0.41–1.14)	0.75 (0.53–1.06)	0.59 (0.37–0.95)	0.70 (0.50–0.99)
	*03:02	1.87 (0.86–4.05)	1.56 (0.84–2.88)	2.13 (1.06–4.30)	1.53 (0.83–2.81)
	*04	0.85 (0.55–1.32)	0.78 (0.57–1.07)	0.88 (0.60–1.30)	0.77 (0.56–1.04)
	*04:01	0.69 (0.22–2.16)	0.65 (0.31–1.38)	0.69 (0.26–1.79)	0.67 (0.32–1.36)
	*04:03	3.23 (0.95–10.96)	1.29 (0.41–4.05)	2.81 (0.89–8.85)	1.90 (0.67–5.39)
	*04:05	0.49 (0.15–1.56)	0.96 (0.49–1.90)	1.14 (0.51–2.53)	0.85 (0.43–1.68)
	*04:07	0.90 (0.23–3.52)	0.81 (0.31–2.08)	0.85 (0.26–2.84)	0.89 (0.36–2.18)
	*07:01	1.29 (0.86–1.94)	0.99 (0.74–1.33)	0.90 (0.62–1.31)	1.02 (0.77–1.36)
	*08	1.33 (0.78–2.26)	1.23 (0.83–1.82)	1.11 (0.68–1.82)	1.31 (0.89–1.92)
	*08:01	1.21 (0.42–3.50)	1.20 (0.58–2.48)	1.05 (0.41–2.69)	1.22 (0.60–2.50)
	*08:04	1.53 (0.63–3.71)	0.95 (0.46–1.94)	1.33 (0.59–3.01)	1.19 (0.61–2.34)
	*08:07	7.38 (0.72–75.23)	**12.18 (1.59–93.17)**	5.72 (0.59–55.87)	**11.30 (1.48–86.21)**
	*09:01	2.10 (0.96–4.58)	1.31 (0.69–2.49)	1.58 (0.74–3.38)	1.34 (0.72–2.50)
	*10:01	0.82 (0.33–2.04)	1.14 (0.63–2.08)	1.03 (0.48–2.22)	1.06 (0.58–1.93)
	*11	1.02 (0.66–1.57)	0.96 (0.71–1.31)	1.02 (0.70–1.50)	0.99 (0.73–1.33)
	*11:01	1.01 (0.58–1.74)	1.21 (0.83–1.75)	0.95 (0.58–1.56)	1.15 (0.79–1.66)
	*11:02	0.55 (0.22–1.39)	0.54 (0.29–1.01)	0.60 (0.27–1.30)	0.59 (0.33–1.05)
	*12	0.89 (0.28–2.86)	1.45 (0.70–2.98)	1.43 (0.59–3.49)	1.56 (0.78–3.15)
	*13	0.69 (0.44–1.09)	1.02 (0.76–1.38)	0.87 (0.59–1.27)	1.03 (0.77–1.38)
	*13:01	0.55 (0.30–1.01)	0.93 (0.64–1.36)	0.86 (0.53–1.39)	0.90 (0.62–1.29)
	*13:02	1.02 (0.52–2.00)	1.26 (0.80–1.99)	1.07 (0.60–1.93)	1.34 (0.86–2.10)
	*14	1.76 (0.88–3.51)	0.89 (0.50–1.56)	0.81 (0.39–1.69)	0.87 (0.50–1.52)
	*15	0.89 (0.57–1.39)	0.78 (0.57–1.07)	0.70 (0.47–1.06)	0.75 (0.55–1.02)
	*15:01	0.53 (0.27–1.03)	**0.58 (0.38–0.88)**	0.67 (0.40–1.13)	**0.57 (0.38–0.86)**
	*15:02	1 (empty)	**0.12 (0.01–0.98)**	0.27 (0.03–2.21)	**0.10 (0.01–0.86)**
	*15:03	1.72 (0.95–3.12)	1.36 (0.86–2.16)	1.01 (0.55–1.84)	1.30 (0.82–2.05)
	*16	0.74 (0.34–1.61)	0.76 (0.44–1.30)	1.39 (0.77–2.50)	0.87 (0.52–1.45)
	*16:01	0.66 (0.18–2.47)	0.82 (0.36–1.91)	1.42 (0.57–3.51)	0.89 (0.40–2.00)
Second restricted analysis: referent group further restricted to women with a high probability of HPV exposure[e]					
	01	1.22(0.74–2.01)	1.39 (0.95–2.02)	1.39 (0.89–2.16)	1.33 (0.911.95)
	01:01	1.27 (0.62–2.61)	1.48 (0.85–2.55)	1.57 (0.84–2.94)	1.39 (0.80–2.42)
	01:02	1.48 (0.75–2.94)	1.50 (0.87–2.59)	1.31 (0.68–2.50)	1.51 (0.87–2.61)
	03	1.00 (0.62–1.61)	1.02 (0.71–1.46)	1.01 (0.65–1.57)	0.97 (0.67–1.40)
	03:01	0.84 (0.48–1.45)	0.92 (0.61–1.38)	0.75 (0.45–1.25)	0.88 (0.58–1.33)
	03:02	2.00 (0.86–4.62)	1.60 (0.80–3.23)	**2.25 (1.03–4.90)**	1.53 (0.76–3.10)
	04	0.79 (0.50–1.25)	**0.73 (0.51–1.03)**	0.81 (0.54–1.23)	0.68 (0.48–0.97)

HLA-DRB1 alleles		Subgenus 1[a]	Subgenus 2 [a]	Subgenus 3 [a]	Any HPV[b]
	04:01	0.48 (0.15–1.50)	0.47 (0.22–1.03)	0.50 (0.19–1.33)	0.47 (0.21–1.04)
	04:03	3.33 (0.82–13.46)	1.35 (0.35–5.17)	2.30 (0.75–11.19)	1.82 (0.50–6.67)
	04:05	0.55 (0.16–1.83)	1.05 (0.48–2.30)	1.29 (0.53–3.11)	1.00 (0.46–2.20)
	04:07	0.86 (0.21–3.55)	0.77 (0.27–2.21)	0.83 (0.23–3.00)	0.71 (0.24–2.09)
	07:01	1.20 (0.78–1.85)	0.94 (0.67–1.31)	0.84 (0.56–1.26)	0.98 (0.70–1.37)
	08	1.31 (0.74–2.31)	1.18 (0.76–1.83)	1.04 (0.61–1.78)	1.21 (0.78–1.89)
	08:01	0.98 (0.32–2.94)	0.97 (0.44–2.12)	0.86 (0.32–2.31)	0.98 (0.44–2.19)
	08:04	1.65 (0.63–4.32)	1.03 (0.46–2.33)	1.37 (0.55–3.39)	1.18 (0.53–2.62)
	08:07	1 (empty)	1 (empty)	1 (empty)	1 (empty)
	09:01	**2.45 (1.01–5.95)**	1.52 (0.70–3.29)	1.82 (0.76–4.36)	1.57 (0.72–3.40)
	10:01	0.71 (0.28–1.80)	0.94 (0.49–1.80)	0.87 (0.39–1.94)	0.82 (0.42–1.60)
	11	1.12 (0.71–1.79)	1.10 (0.77–1.58)	1.15 (0.75–1.76)	1.20 (0.84–1.72)
	11:01	1.07 (0.59–1.93)	1.34 (0.86–2.08)	1.02 (0.59–1.77)	1.34 (0.86–2.09)
	11:02	0.62 (0.23–1.66)	0.63 (0.31–1.27)	0.69 (0.30–1.62)	0.67 (0.34–1.34)
	12	0.70 (0.22–2.30)	1.12 (0.52–2.41)	1.02 (0.40–2.58)	1.28 (0.60–2.72)
	13	**0.59 (0.37–0.95)**	0.86 (0.62–1.20)	0.72 (0.48–1.09)	0.87 (0.62–1.21)
	13:01	**0.51 (0.27–0.97)**	0.86 (0.56–1.31)	0.78 (0.46–1.30)	0.78 (0.51–1.19)
	13:02	0.91 (0.45–1.82)	1.13 (0.68–1.88)	0.97 (0.51–1.81)	1.32 (0.80–2.18)
	14	1.57 (0.75–3.27)	0.81 (0.43–1.51)	0.73 (0.33–1.61)	0.84 (0.44–1.58)
	15	0.87 (0.55–1.40)	0.78 (0.55–1.11)	0.71 (0.46–1.10)	0.75 (0.52–1.07)
	15:01	0.51 (0.25–1.03)	**0.57 (0.35–0.91)**	0.66 (0.37–1.16)	**0.60 (0.37–0.97)**
	15:02	1 (empty)	**0.07 (0.01–0.61)**	0.17 (0.02–1.37)	**0.08 (0.01–0.65)**
	15:03	1.78 (0.94–3.36)	1.42 (0.84–2.40)	1.13 (0.59–2.16)	1.25 (0.74–2.13)
	16	0.76 (0.34–1.73)	0.76 (0.41–1.41)	1.46 (0.76–2.80)	0.93 (0.51–1.69)
	16:01	0.72 (0.17–2.99)	0.90 (0.33–2.46)	1.63 (0.57–4.69)	1.01 (0.37–2.75)

[a] Subgenus 1 includes HPV types 6, 11, 32, 40, 42, 44, and 54, from species α1, α8, α10, and α13. Subgenus 2 includes HPV types 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82, from species α5, α6, α7, α9, and α11. Subgenus 3 includes HPV types 57, 61, 62, 71, 72, 81, 83, 84 and 89, from species α3, α4, and α14.

[b] HPV positive women were compared to HPV negative women.

[c] Women with a specific subgenus group infection were compared against a floating referent group of all those who did not have that particular group infection.

[d] Women with a specific subgenus group infection were compared to a fixed referent group of HPV-negative women who had at least 4 follow-up visits (N = 472).

[e] Women with a specific subgenus group infection were compared to a fixed referent group of HPV-negative women who had at least 4 follow-up visits and a high propensity score (i.e., probability of acquiring an HPV infection above the 35% percentile) (N = 306).