Human Papillomavirus Genotype Distribution in Low-Grade Cervical Lesions: Comparison by Geographic Region and with Cervical Cancer

Gary M. Clifford,[1] Rashida K. Rana,[2] Silvia Franceschi,[1] Jennifer S. Smith,[3] Gerald Gough,[2] and Jeanne M. Pimenta[2]

[1]International Agency for Research on Cancer, Lyon, France; [2]GlaxoSmithKline R&D, Middlesex, United Kingdom; and [3]University of North Carolina, Chapel Hill, North Carolina

Abstract

Low-grade squamous intraepithelial lesions (LSIL) associated with certain human papillomavirus (HPV) genotypes may preferentially progress to cervical cancer. HPV genotyping may thus have the potential to improve the effectiveness of screening programs and to reduce overtreatment. LSIL cases (n = 8,308) from 55 published studies were included in a meta-analysis. HPV genotype distribution was assessed by geographic region and in comparison with published data on cervical squamous cell carcinoma (SCC). HPV detection in LSIL was 80% in North America but less than 70% in other regions, most likely reflecting regional differences in LSIL diagnosis. Among 5,910 HPV-positive LSILs, HPV16 was the most common genotype (26.3%) followed by HPV31 (11.5%), HPV51 (10.6%), and HPV53 (10.2%). HPV-positive LSILs from Africa were 2-fold less likely to be infected with HPV16 than those in Europe, and HPV-positive LSILs from North America were more likely to be infected with HPV18 than those from Europe or South/Central America. Interpretation for rarer genotypes was hampered by variation in HPV testing methodology. SCC/LSIL prevalence ratios indicated that HPV16 was 2-fold and HPV18 was 1.5-fold more common in SCC than in HPV-positive LSIL, thus appearing more likely to progress than other high-risk genotypes (SCC/LSIL prevalence ratios between 0.05 and 0.85). HPV53 and HPV66 showed SCC/LSIL ratios of 0.02 and 0.01, respectively. HPV genotype distribution in LSIL differs from that in cervical cancer, highlighting the importance of HPV genotype in the risk of progression from LSIL to malignancy. Some regional differences in the relative importance of HPV genotypes in LSIL were noted. (Cancer Epidemiol Biomarkers Prev 2005;14(5):1157–64)

Introduction

About 1.5 million women (2-3% of all those screened for cervical cancer) are diagnosed with low-grade squamous intraepithelial lesions (LSIL) each year in the United States (1). LSILs are most often managed by colposcopy to confirm underlying cervical intraepithelial neoplasia (CIN) 1 (2). CIN1 is then managed either by tissue destruction/ablation or by active follow-up depending on the setting. However, diagnosis and treatment of LSIL is associated with patient anxiety, morbidity, and cost (3). Furthermore, if left untreated, only a fraction of LSIL progress toward malignancy, with most regressing spontaneously, especially in young women (4).

A specific subset of human papillomavirus genotypes (HPV), called high-risk genotypes, has now been firmly established as the cause of invasive cervical cancer and its precursor lesions (5). Even high-risk genotypes, however, may differentially progress from LSIL to malignancy (6), so that HPV genotype may have potential use in separating HPV-positive women at greater risk of cancer from those who can be safely screened at longer intervals. In the era of widespread HPV-based primary screening (7) and HPV-based triage of screen-detected cervical abnormalities (8), this would improve performance and cost-effectiveness of programs while reducing patient anxiety and overtreatment.

Furthermore, as both current (HPV16/HPV18) and future vaccine candidates (9) are likely to be HPV genotype specific, understanding the HPV genotype distribution in screen-detected lesions also helps predict the effect of vaccination on the reduction of abnormal findings in cervical screening programs.

The aim of this study was to collate all published information on HPV genotype distribution among LSIL across different geographic regions and to estimate potential for progression of HPV genotype-specific LSIL to malignancy by comparing with the HPV genotype distribution among cervical squamous cell carcinoma (SCC).

Materials and Methods

Study Selection. Medline was employed to search for citations published from January 1989 to June 2004 using the MeSH terms ''papillomavirus,'' ''cervical intraepithelial neoplasia,'' ''cervical neoplasms,'' ''human,'' and ''female'' in combination with keywords ''polymerase chain reaction'' or ''PCR.'' Studies had to include at least 20 cases of LSIL. For the purpose of this analysis, LSIL refers both to lesions cytologically equivalent to LSIL according to the Bethesda system (10) and to lesions histologically confirmed as CIN1 (11). Included studies had to test for HPV using one of four validated PCR primer sets or refinements of them [MY09/11 (12), PGMY09/11 (13), GP5+/6+ (14), or SPF10 (15)] and report genotype-specific prevalence of at least one HPV genotype other than HPV6, HPV11, HPV16, or HPV18.

Data Abstraction. The following key variables were extracted by one investigator (R.K.R.): type of cervical specimen for HPV DNA testing (biopsies or exfoliated cells), cytologic or histologic LSIL diagnosis, PCR primers used to detect HPV, and overall and genotype-specific prevalence of

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Requests for reprints: Gary M. Clifford, IARC, 150 Cours Albert Thomas, F-69372 Lyon cedex 08, France. Phone: 33-4-72-73-84-25; Fax: 33-4-72-73-83-45. E-mail: clifford@iarc.fr

Table 1. Regional distribution and overall HPV prevalence among 8,308 LSILs

Region	Studies, *n*	Countries represented	LSIL cases, *n*	HPV positive, *n* (%)
Europe	21	Belgium, Croatia, Czech Republic, France, Germany, Greece, Holland, Italy, Portugal, Sweden, United Kingdom	4,051	2,746 (67.8)
North America	13	Canada, United States	2,425	1,943 (80.1)
South/Central America	13	Argentina, Brazil, Colombia, Costa Rica, Honduras, Jamaica, Mexico, Paraguay	1,279	874 (68.3)
Africa	4	Ivory Coast, Kenya, Nigeria, Senegal	301	178 (59.1)
Asia	4	China, Korea, Thailand	252	169 (67.1)
Total	55		8,308	5,910 (71.1)

HPV infection. Extracted data were independently verified (G.M.C.) and discrepancies were agreed upon. Each study was classified into one of five regions: Africa, Asia, Europe, North America, or South/Central America. If publications did not present the relevant data but study methods suggested that this information was available, data requests were made to authors (16-31). Detailed information on all included studies is presented in Appendix A.

For comparisons with SCC, genotype-specific HPV distribution among SCC was obtained from a meta-analysis carried out using a similar protocol to the present one (32).

Estimation of Genotype-Specific Prevalence. Genotype-specific prevalence is presented for the 15 most common LSIL-associated HPV genotypes as identified by this review. All studies provided information on HPV16 and HPV18. For other genotypes, prevalence was estimated only among those studies testing for the HPV genotype in question, so sample size varies between the analyses. PCR primers MY09/11, PGMY09/11, and SPF10 were considered to satisfactorily amplify all 15 HPV genotypes above and PCR primer GP5+/6+ to amplify all 15 genotypes, except HPV53 (33). Genotype-specific prevalence includes that in either single or multiple infections as many of the included studies did not test for a comprehensive range of HPV genotypes (so a large proportion of multiple infections would have been missed) and/or did not publish the genotype-specific breakdown for multiple infections.

Throughout the text, figures, and tables, genotype-specific HPV prevalence is expressed as a proportion of HPV-positive LSIL. In Appendix A, however, genotype-specific HPV prevalence is reported study by study as a proportion of all LSIL cases tested.

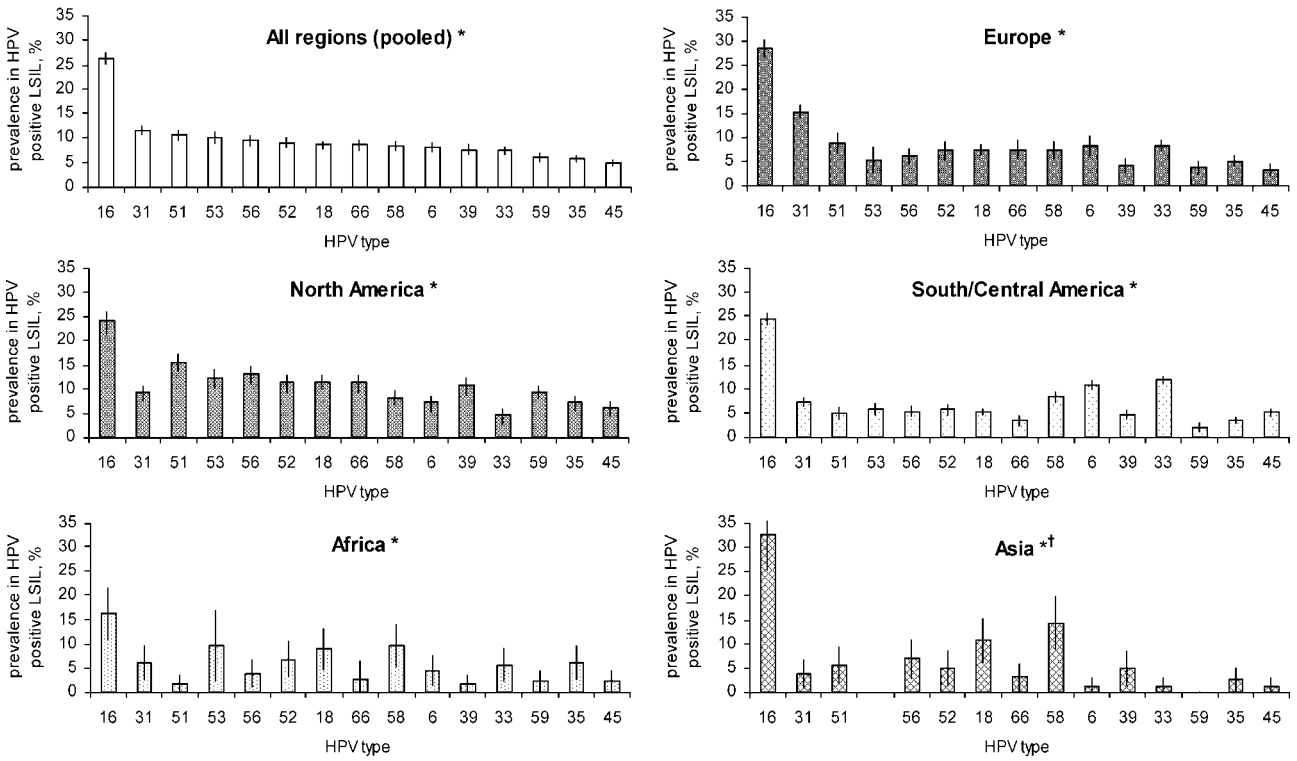

Figure 1. Prevalence of the 15 most common HPV genotypes in 5,910 HPV-positive LSILs by region. *, Denominators of HPV-positive LSIL vary by HPV type, from 2,516 to 5,910 for all regions, from 268 to 2,746 for Europe, from 1,640 to 1,943 for North America, from 466 to 874 for South/Central America, from 62 to 178 for Africa, and from 160 to 169 for Asia. †, In Asia, upper 95% CI for HPV16 is 39.6%, and HPV53 is not shown because the denominator was 33 cases only.

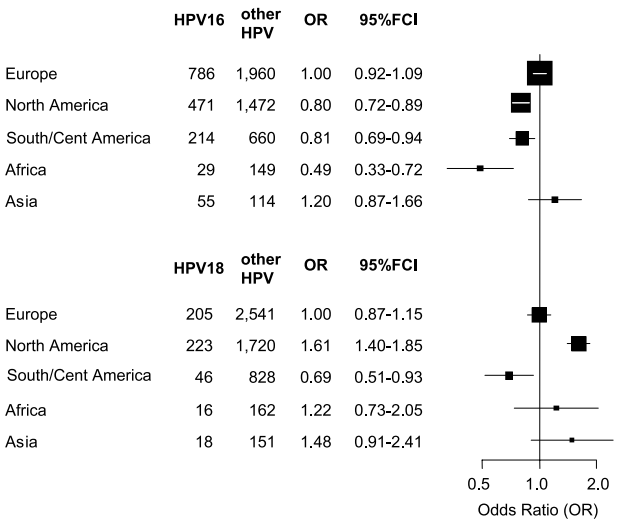

Figure 2. ORs and corresponding 95% FCIs for infection with HPV16 and HPV18 in HPV-positive LSILs by region.

Statistical Analyses. Genotype-specific HPV prevalence was compared between LSIL and SCC by prevalence ratios, with corresponding 95% confidence intervals (95% CI; ref. 34).

Odds ratios (OR) for infection with HPV16 and HPV18 among HPV-positive LSIL were estimated by unconditional logistic regression using Stata 8.0 (Stata Corp., College Station, TX). Corresponding 95% floating CIs (95% FCI) are calculated using the method of Plummer (35). This approach, which avoids an arbitrary reference group by attributing all categories their own variance, does not alter the point estimate of the ORs but slightly reduces the variances attributed to those ORs that are not defined as 1.0 (36). Graphically, ORs are represented as black squares, with areas inversely proportional to the variance of the log of the OR, indicating the amount of statistical information available for that particular estimate. The corresponding 95% FCI is drawn as a horizontal line.

Results

HPV Genotype Distribution among HPV-Positive LSIL. A total of 8,308 LSILs [5,341 (64%) diagnosed cytologically and 2,967 (36%) histologically as CIN1] from 55 studies were included in this meta-analysis (Table 1). Most cases came from studies in Europe (49%), North America (29%), and South/Central America (15%). Africa (3.6%) and Asia (3.0%) contributed few cases.

A total of 5,910 (71.1%) LSILs tested positive for HPV DNA (Table 1). Overall, HPV prevalence ranged from only 67.1% to 68.3% for Europe, South/Central America, and Asia but was especially high in North America (80.2%) and low in Africa (59.1%). Due to geographic variation in overall HPV prevalence, HPV genotype distribution by region was compared among HPV-positive LSIL only.

HPV genotype distribution in the 5,910 HPV-positive LSILs is shown overall and by region in Fig. 1, in order of decreasing prevalence, for the 15 most frequently identified HPV genotypes. The most commonly identified HPV genotype was HPV16, present in 26.3% of all HPV-positive LSILs (Fig. 1). After HPV16, the most common genotypes overall were, in order of decreasing prevalence, HPV31 (11.5%), HPV51 (10.6%), HPV53 (10.2%), HPV56 (9.5%), HPV52 (9.0%), HPV18 (8.6%), HPV66 (8.6%), HPV58 (8.4%), HPV6 (8.0%), HPV39 (7.6%), HPV33 (7.4%), HPV59 (6.1%), HPV35 (5.7%), and HPV45 (4.9%; Fig. 1). All other HPV genotypes were detected in <5.0% of HPV-positive LSIL. HPV6 or HPV11 were detected in 12.1% of HPV positive LSIL (9.4% of all LSIL tested) (data not shown).

HPV16 was the most common genotype in all regions ranging from 16.3% of HPV in Africa to 32.6% in Asia. HPV18 varied from 5.0% of HPV-positive LSIL in South/Central America to 11.5% in North America. The relative importance of HPV genotypes other than HPV16 and HPV18 also appeared to vary somewhat by region. In particular, HPV31 prevalence appeared high in Europe (15.3%), HPV33 high in South/Central America (11.8%), and HPV58 high in Asia (14.4%). Furthermore, several HPV genotypes (HPV39, HPV51, HPV53, HPV56, HPV59, and HPV66) appeared more prevalent in North America compared with other regions.

ORs for infection with HPV16 and HPV18 among HPV-positive LSIL are compared by region in Fig. 2, with Europe as the reference category based on sample size. HPV-positive LSILs in Africa were 2-fold and significantly less likely to be infected with HPV16 (OR, 0.49; 95% FCI, 0.33-0.72) than those in Europe (OR, 1.00; 95% FCI, 0.92-1.09). HPV-positive LSILs in North America and South/Central America showed ORs for HPV16 infection in between those for Africa and those for Europe.

HPV-positive LSILs in North America were significantly more likely to be infected with HPV18 (OR, 1.61; 95% FCI, 1.40-1.85) than those in Europe (OR, 1.00; 95% FCI, 0.87-1.15) or South/Central America (OR, 0.69; 95% FCI, 0.51-0.93).

Table 2. Prevalence of 15 most common HPV genotypes in HPV-positive LSILs and comparison with that in SCC

HPV genotype	HPV-positive LSIL*		SCC†,‡		SCC/LSIL
	Tested, *n*	HPV positive, %	Tested, *n*	HPV positive, %	Prevalence ratio (95% CI)
HPV16	5,910	26.6	8,594	54.3	2.06 (2.02-2.11)
HPV18	5,910	8.6	8,502	12.6	1.47 (1.39-1.54)
HPV45	3,545	4.9	5,174	4.2	0.85 (0.77-0.94)
HPV33	5,744	7.6	8,449	4.3	0.58 (0.54-0.62)
HPV31	5,801	11.7	7,204	4.2	0.36 (0.34-0.39)
HPV58	3,380	8.5	5,646	3.0	0.36 (0.32-0.39)
HPV52	3,262	8.8	5,304	2.5	0.28 (0.25-0.31)
HPV35	4,754	5.9	6,223	1.0	0.17 (0.15-0.20)
HPV59	3,232	6.0	4,488	0.8	0.13 (0.11-0.16)
HPV6	3,638	8.1	6,569	0.6	0.08 (0.06-0.09)
HPV56	3,348	9.7	4,493	0.7	0.07 (0.06-0.09)
HPV51	3,566	10.9	4,580	0.6	0.06 (0.05-0.07)
HPV39	3,251	7.8	3,899	0.4	0.05 (0.04-0.07)
HPV66	3,132	8.5	4,799	0.2	0.02 (0.02-0.04)
HPV53	2,516	10.1	3,053	0.1	0.01 (0.01-0.02)

*Regional distribution of included cases: Europe 46.5%, North America 32.9%, South/Central America 14.8%, Africa 3.0%, and Asia 2.9%.
† Data from Clifford et al. (32).
‡ Regional distribution of included cases: Europe 32.0%, North America 13.0%, South/Central America 16.5%, Africa 6.9%, and Asia 31.7%.

ORs for infection with HPV16 and HPV18 by region were additionally calculated with adjustment for (*a*) method of LSIL diagnosis (cytology or histology) and (*b*) PCR primers (MY09/11 only, GP5+/6+ only, or other/combination). In the multivariate model, ORs for infection with HPV16 and HPV18 were higher for HPV-positive LSIL confirmed histologically compared with those diagnosed cytologically only (HPV16: OR, 1.17; 95% CI, 1.01-1.37; $P = 0.040$; HPV18: OR, 1.38; 95% CI, 1.09-1.75; $P = 0.009$) and were higher for studies using GP5+/6+ PCR primers only compared with those using MY09/11 only (HPV16: OR, 1.08; 95% CI, 0.89-1.31; $P = 0.449$; HPV18: OR, 1.53; 95% CI, 1.13-2.08; $P = 0.006$). Nevertheless, these covariates had little material effect on ORs by region (adjusted ORs for Europe, North America, South/Central America, Africa, and Asia were 1.00, 0.89, 0.86, 0.55, and 1.16 for HPV16 and 1.00, 1.92, 0.79, 1.46, and 1.26 for HPV18, respectively). Furthermore, significant findings by region were robust on restriction to studies testing with MY09/11 PCR primers only (data not shown).

Comparison of HPV-Positive LSIL with SCC. HPV genotype-specific prevalence among HPV-positive LSIL is compared with similar published data for SCC in Table 2. HPV16 was 2-fold and HPV18 1.5-fold more common in SCC relative to HPV-positive LSIL. Other high-risk HPV genotypes were less common in SCC compared with HPV-positive LSIL, with SCC/LSIL ratios of 0.28 to 0.85 for high-risk HPV31, HPV33, HPV45, HPV52, and HPV58, SCC/LSIL ratios of 0.05 to 0.17 for high-risk HPV35, HPV39, HPV51, HPV56, and HPV59, and SCC/LSIL ratios of <0.05 for HPV53 (0.01) and HPV66 (0.02).

SCC/LSIL prevalence ratios were additionally calculated within studies from Europe, North America, and South/Central America separately to check for consistency of findings across regions. There were no material differences in SCC/LSIL ratios for HPV16 (2.16, 2.58, and 2.11, respectively), HPV33 (0.62, 0.83, and 0.35, respectively), or HPV18 (1.75, 1.25, and 1.97, respectively). However, the SCC/LSIL ratio for HPV31 in South/Central America (1.00; 95% CI, 0.85-1.17) was notably high compared with that in Europe (0.28; 95% CI, 0.25-0.31) and North America (0.56; 95% CI, 0.47-0.65). Sample sizes were not sufficient for robust subanalyses of other HPV genotypes or among Africa and Asia.

Discussion

HPV Genotype Distribution in LSIL. HPV16 was clearly the most prevalent HPV genotype in LSIL from all regions. However, the proportion of HPV-positive LSIL attributable to HPV16 varied significantly. In particular, HPV-positive LSILs from Africa were significantly less likely to be infected with HPV16 than LSIL from Europe, with LSIL from North America and South/Central America showing intermediate risk. This pattern was consistent with that seen in similarly designed meta-analyses of high-grade squamous intraepithelial lesions (HSIL) and SCC: 32%, 37%, 46%, and 53% of HSIL from Africa, South/Central America, North America, and Europe, respectively, were HPV16 positive (37), as were 50%, 52%, 63%, and 62% of SCC (32). The consistency of this pattern points toward a true phenomenon, whereby the prevalence of HPV16 varies by region, being highest in Europe and lowest in Africa.

HPV-positive LSILs from North America, and possibly Asia, were significantly more likely to be infected with HPV18 than those from Europe or South/Central America. This pattern was again consistent with that seen among both HSIL and SCC: 10%, 6.5%, and 7.1% of HSILs from North America, Europe, and South/Central America, respectively, were HPV18 positive (37), as were 15%, 13%, and 10% of SCC (32).

Geographic differences in the relative prevalence of HPV genotypes may be related to the complex interplay between different HPV genotypes and/or variants with host immunogenetic factors (e.g., HLA polymorphisms; reviewed in ref. 38). Alternatively, a recent study showed that HPV16 appears less influenced by immune status than other HPV genotypes (39). This fact, coupled with impairment in cellular immunity (e.g., through chronic cervical inflammation, parasitic infection, malnutrition, and/or more recently HIV), may be somehow contributing to the penetrance of HPV genotypes other than HPV16 in some populations.

Care was taken not to overinterpret apparent geographic differences in HPV genotypes other than HPV16 and HPV18, as they were tested for in only a subset of included studies and tended to be rarer. Thus, estimated prevalences were more sensitive to the potential sources of variation discussed below under study limitations. Nevertheless, high prevalence of HPV58 in Asia and HPV31 in Europe is also consistent with findings from both HSIL (37) and SCC (32).

The demonstration of regional variation in the proportion of screen-detected lesions positive for HPV16 and HPV18 suggests that the effect of HPV16/HPV18 vaccines on cytologic abnormalities detected by cervical screening programs will, at least to some degree, vary by region. However, regional differences appear to become less pronounced with increasing severity of lesions, as HPV16 becomes increasingly dominant.

Progression of HPV Genotype-Specific LSIL to Cancer. Findings from this study suggest that LSILs positive for HPV18, and most notably HPV16, are more likely to progress to cervical cancer than LSIL containing other HPV genotypes. This conclusion is based on the fact that these HPV genotypes are more common in SCC compared with HPV-positive LSIL. Together, HPV16 and HPV18 account for ~35% of HPV-positive LSILs but nearly 70% of worldwide cervical cancers (32, 40). Supportive evidence comes from prospective studies showing that HPV16 is more persistent (26, 41, 42), as well as more likely to progress to CIN3 (43), than other high-risk HPV genotypes. Thus, in the setting of HPV-based cervical screening programs, genotyping may have diagnostic utility in separating LSIL cases positive for HPV16 (and perhaps HPV18), who require the closest surveillance, from LSIL cases infected with other high-risk genotypes.

All HPV genotypes, other than HPV16 and HPV18, were found to be underrepresented in cervical cancer compared with LSIL. However, the degree of underrepresentation varied greatly by genotype, and there were no clear-cut points between SCC/LSIL ratios for different groups of HPV genotypes other than HPV16 and HPV18. HPV31, HPV33, HPV45, HPV52, and HPV58 (the next most commonly identified genotypes in SCC worldwide) were each associated with SCC/LSIL ratios between 0.28 and 0.85, highlighting an intermediate, but considerable, potential for progression to cancer. About 40% of HPV-positive LSILs were positive for these five genotypes, which are responsible for ~15% of cervical cancer worldwide (32).

Other high-risk genotypes HPV35, HPV39, HPV51, HPV56, and HPV59 were each associated with SCC/LSIL ratios between 0.05 and 0.2, suggesting a lower potential for progression compared with other high-risk genotypes. These five genotypes are found in up to 40% of HPV-positive LSILs but are responsible for only 3% of cervical cancer worldwide (32). In settings where resources are limited, some of these genotypes, although oncogenic, may be chosen for exclusion from HPV screening tests, with the aim to concentrate resources on women most at risk.

HPV66 and HPV53, which have been classified as ''probable high-risk'' genotypes, were found relatively commonly in LSIL but are rarely detected in cancer and actually showed SCC/LSIL ratios lower than for low-risk HPV6. Thus, HPV-based screening, including HPV66 and HPV53, would likely result in the identification of a large number of LSILs with very low risk for progression to cancer.

Study Strengths and Limitations. This meta-analysis combined genotype-specific HPV data from a large number of studies, each performing HPV testing using well-validated PCR primers known to amplify a broad spectrum of HPV genotypes. However, even this well-validated set of primers do not amplify all genotypes with exactly the same sensitivity (33) and such differences remain a potential source of variation in the detection of genotypes between studies, particularly for genotypes other than HPV16 and HPV18. Furthermore, other specific conditions of PCR are known to affect HPV sensitivity. For example, the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (27) was one of the few studies reporting to have used AmpliTaq Gold DNA polymerase, which is associated with higher detection of HPV (44). This may partly account for the high prevalence of some HPV genotypes observed for North America.

Substantial variation in overall HPV positivity across included studies may reflect additional study-specific variations in the (*a*) quality of cytologic/histologic assessment, (*b*) local definitions of LSIL, and/or (*c*) the frequency of cervical cancer screening. Unfortunately, most included studies did not publish the necessary data to take these differences into account. Restricting comparisons of HPV genotype distribution to HPV-positive LSIL, however, was expected to reduce heterogeneity in the clinical relevance of included lesions.

Up to 50% of LSIL are shown to contain multiple HPV infections using the best detection methods (27). However, as many of the included studies tested for only a subset of HPV genotypes, this analysis was unable to estimate how often each HPV infection was found alone or in the presence of another genotype. Thus, estimates for the total proportion of LSIL attributable to a combination of genotypes must be interpreted with caution, as the prevalence reported for each individual HPV genotype include those in multiple infections. Among HPV-positive women from studies reporting data on multiple infections (n = 3268), 1.8% were infected with both HPV16 and HPV18.

Lastly, the authors recognize that inferences on LSIL progression based on simple cross-sectional data should be interpreted with caution. The diagnostic utility of using genotyping to separate screen-detected LSIL clearly needs to be established in a sequence of appropriately designed prospective studies. Indeed, the triage of LSIL into high-risk HPV positive or high-risk HPV negative has been shown to have only limited potential diagnostic utility (1). Nevertheless, differences in the distribution of HPV in LSIL and cancer, as well as supporting evidence on genotype-specific risk from prospective studies in women with normal cytology, suggest that the distinction of high-risk HPV genotypes has the potential to improve the management of LSIL in clinical practice.

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Appendix A: Study methods and prevalence of HPV by study and region

First author	Reference	Country	HPV DNA source	PCR primers	Cases *n*	LSIL/CIN1
Africa						
de Vuyst H	Sex Transm Dis (2002)	Kenya	Cells	SPF10	30	0/30
La Ruche G	Int J Cancer (1998)	Ivory Coast	Cells	MY09/11	151	151/0
Thomas JO	Br J Cancer (2003)	Nigeria	Cells	GP5+/6+	34	34/0
Xi LF	Int J Cancer (2003)	Senegal	Cells	MY09/11	86	86/0
Africa subtotal					*301*	*271/30*
Asia						
Bhattarakosol P	J Med Assoc Thai (2002)	Thailand	Biopsies	MY09/11	27	0/27
Chan PKS	J Med Virol (1999)	China	Cells	MY09/11	51	0/51
Chan PKS	J Med Virol (1999)	China	Cells	MY09/11	51	0/51
Cho NH	Am J Obstet Gynecol (2003)	Korea	Cells	GP5+/6+	150	150/0
Hwang TS	Gynecol Oncol (2003)	Korea	Cells	GP5+/6+	24	0/24
Asia subtotal					*252*	*150/102*
Europe						
Astori G	Virus Res (1997)	Italy	Cells	MY09/11	111	111/0
Baay MFD	Eur J Gynaecol Oncol (2001)	Belgium	Biopsies	GP5+/6+	58	0/58
Cuschieri KS	J Clin Pathol (2004)	United Kingdom	Cells	GP5+/6+	243	243/0
Cuzick J	Br J Cancer (1999)	United Kingdom	Cells	MY09/11	50	0/50
Giannoudis A	Int J Cancer (1999)	United Kingdom	Biopsies	GP5+/6+	118	118/0
Grce M	Eur J Epidemiol (1997)	Croatia	Cells	MY09/11	183	183/0
Grce M	Anticancer Res (2001)	Croatia	Cells	MY09/11	1,028	1,028/0
Humbey O	Eur J Obstet Gynecol Reprod Biol (2002)	France	Cells	MY09/11	40	40/0
Kalantari M	Hum Pathol (1997)	Sweden	Cells	MY09/11	141	0/141
Labropoulou V	Sex Transm Dis (1997)	Greece	Biopsies/cells	MY09/11	51	0/51
Laconi S	Pathologica (2000)	Italy	Biopsies	GP5+/6+	20	0/20
Medeiros R	Int Meet Gynecol Oncol (1997)	Portugal	Biopsies	MY09/11	31	0/31
Meyer T	Int J Gynecol Cancer (2001)	Germany	Biopsies/cells	MY09/11	130	130/0
Nindl I	J Clin Pathol (1999)	Germany	Cells	GP5+/6+	49	0/49
Reesink-Peters N	Eur J Obstet Gynecol Reprod Biol (2001)	Netherlands	Cells	SPF10	35	0/35
Southern S	Hum Pathol (2001)	United Kingdom	Biopsies	GP5+/6+	49	0/49
Tachezy R	J Med Virol (1999)	Czech Republic	Cells	MY09/11	87	87/0
Venturoli S	J Clin Virol (2002)	Italy	Cells	MY09/11	40	40/0
Voglino G	Pathologica (2000)	Italy	Biopsies	MY09/11	1,499	0/1,499
Zehbe I	Virchows Arch (1996)	Sweden	Biopsies	GP5+/6+	45	0/45
Zerbini M	J Clin Pathol (2001)	Italy	Cells	MY09/11	43	43/0
Europe subtotal					*4,051*	*2,023/2,028*
North America						
Adam E	Am J Obstet Gynecol (2000)	United States	Cells	MY09/11	161	0/161
ASCUS-LSIL Triage Study Group	Am J Obstet Gynecol (2003)	United States	Cells	PGMY09/11	1,242	1,242/0
Brown DR	Sex Transm Dis (2002)	United States	Cells	MY09/11	25	25/0
Evans MF	Mod Pathol (2002)	United States	Biopsies	GP5+/6+	26	0/28
Jarboe EA	Hum Pathol (2004)	United States	Cells	PGMY09/11	95	0/95
Kulasingam S	JAMA (2002)	United States	Cells	MY09/11	166	166/0
Liaw K	J Natl Cancer Inst (1999)	United States	Cells	MY09/11	173	173/0
Richardson H	Cancer Epidemiol Biomarkers Prev (2003)	Canada	Cells	MY09/11	44	44/0
Schiff M	Am J Epidemiol (2000)	United States	Cells	MY09/11	190	0/190
Sellors JW	CMAJ (2000)	Canada	Cells	MY09/11	22	22/0
Sellors JW	CMAJ (2000)	Canada	Cells	MY09/11	24	24/0
Tortolero-Luna	Cad Saude Publica (1998)	United States	Cells	MY09/11	175	175/0
Tran-Thanh D	Am J Obstet Gynecol (2003)	Canada	Biopsies	MY09/11	80	0/80
North America subtotal					*2,425*	*1,872/554*
South/Central America						
Abba MC	Rev Argent Microbiol (2003)	Argentina	Cells	MY09/11	279	279/0
Ferrera A	Int J Cancer (1999)	Honduras	Cells	MY09/11	44	0/44
Franco E	Pan Am J Public Health (1999)	Brazil	Cells	MY09/11	27	27/0
Giuliano A	Cancer Epidemiol Biomarkers Prev (2001)	Mexico (some United States)	Cells	PGMY09/11	40	40/0
Gonzalez-Losa MdR	J Clin Virol (2004)	Mexico	Biopsies	MY09/11	104	104/0
Herrero R	J Natl Cancer Inst (2000)	Costa Rica	Cells	MY09/11	181	181/0
Illades-Aguiar B	Int Papillomarivus Conf Proc (2001)	Mexico	Biopsies	MY09/11	148	0/148
Lorenzato F	Int J Gynecol Cancer (2000)	Brazil	Cells	MY09/11	62	0/62
Molano J	Br J Cancer (2002)	Colombia	Cells	GP5+/6+	70	70/0
Rattray C	J Infect Dis (1996)	Jamaica	Cells	MY09/11	62	62/0
Strickler H	J Med Virol (1999)	Jamaica	Cells	MY09/11	186	186/0
Tonon SA	Infect Dis Obstet Gynecol (1999)	Argentina/Paraguay	Cells	GP5+/6+	55	55/0
Torroella-Kouri M	Gynecol Oncol (1998)	Mexico	Biopsies/cells	MY09/11	21	21/0
South/Central America subtotal					*1,279*	*1,025/254*
Total					**8,308**	**5,341/2,967**

*HPV prevalence represents that at study enrollment and not at LSIL diagnosis.

Appendix A: Study methods and prevalence of HPV by study and region (Cont'd)

HPV prevalence (% of all LSILs tested)															
Any	16	31	51	53	56	52	66	58	6	18	39	33	59	35	45
60.0	13.3	3.3	3.3	10.0	3.3	13.3	3.3	6.7	0.0	6.7	0.0	0.0	0.0	23.3	3.3
68.2	10.6	5.3	0.0	—	2.6	2.6	—	3.3	3.3	6.0	2.0	5.3	1.3	1.3	2.0
38.2	5.9	2.9	2.9	—	2.9	2.9	0.0	5.9	2.9	2.9	0.0	0.0	0.0	0.0	0.0
51.2	8.1	1.2	1.2	3.5	1.2	3.5	1.2	9.3	2.3	4.7	0.0	2.3	2.3	2.3	0.0
59.1	*9.6*	*3.6*	*1.0*	*5.2*	*2.3*	*4.0*	*1.3*	*5.6*	*2.7*	*5.3*	*1.0*	*3.3*	*1.3*	*3.7*	*1.3*
33.3	0.0		—	—	—	—	—	—	0.0	3.7	—	0.0	—	—	—
64.7	21.6	7.8	0.0	0.0	2.0	5.9	0.0	15.7	2.0	9.8	0.0	2.0	0.0	0.0	0.0
64.7	21.6	7.8	0.0	0.0	2.0	5.9	0.0	15.7	2.0	9.8	0.0	2.0	0.0	0.0	0.0
73.3	26.7	1.3	5.3	—	6.0	2.7	0.7	10.0	0.7	7.3	4.0	0.7	0.0	2.0	1.3
70.8	16.7	0.0	4.2	—	4.2	4.2	4.2	0.0	0.0	16.7	8.4	0.0	0.0	4.2	0.0
67.1	*21.8*	*2.7*	*4.0*	*0.0*	*4.9*	*3.6*	*2.2*	*10.2*	*0.8*	*7.1*	*3.6*	*0.8*	*0.0*	*1.8*	*0.9*
77.5	24.3	5.4	0.0	7.2	0.9	0.0	0.0	7.2	10.8	5.4	0.9	0.0	0.9	1.8	0.0
69.0	24.1	1.7	3.4	—	5.2	1.7	1.7	0.0	0.0	19.0	0.0	0.0	0.0	0.0	5.2
90.9	28.0	12.8	17.3	—	9.9	12.3	11.9	5.0	0.0	9.5	9.1	7.4	8.6	2.1	5.3
42.0	12.0	0.0	2.0	—	4.0	12.0	—	2.0	—	10.0	—	2.0	—	0.0	—
100.0	12.7	5.1	7.6	—	5.9	—	11.9	7.6	15.3	7.6	0.8	0.8	2.5	14.4	2.5
35.5	6.0	8.7	—	—	—	—	—	—	—	2.2	—	1.6	—	—	—
54.5	11.6	5.8	—	—	—	—	—	—	—	2.9	—	3.1	—	—	—
60.0	30.0	—	5.0	—	—	5.0	—	7.5	2.5	10.0	—	7.5	—	2.5	2.5
70.9	17.7	5.7	—	—	—	—	—	—	—	12.1	—	5.0	—	—	—
90.2	11.8	9.8	0.0	2.0	—	—	2.0	—	11.8	11.8	—	9.8	—	—	—
95.0	30.0	0.0	20.0	—	0.0	0.0	—	0.0	10.0	0.0	0.0	0.0	—	0.0	—
74.2	35.5	—	—	—	—	—	—	—	—	3.2	—	0.0	—	—	—
69.2	13.1	13.1	3.1	2.3	0.8	3.1	3.8	5.4	3.1	2.3	1.5	5.4	0.0	3.1	0.8
53.1	12.2	2.0	4.1	—	4.1	0.0	2.0	8.2	—	0.0	2.0	6.1	0.0	0.0	4.1
97.1	28.6	31.4	—	—	11.4	—	—	—	—	31.4	—	17.1	—	—	—
100.0	10.2	2.0	4.1	—	2.0	6.1	6.1	10.2	24.5	8.2	4.1	2.0	0.0	0.0	0.0
52.9	34.5	2.3	1.1	2.3	0.0	1.1	0.0	5.7	—	4.6	0.0	2.3	0.0	2.3	1.1
47.5	7.5	10.0	—	—	—	—	—	—	5.0	2.5	—	2.5	—	—	0.0
73.0	24.7	15.9	—	—	—	—	—	—	—	4.2	—	8.9	—	4.3	—
93.3	40.0	11.1	—	—	6.7	2.2	—	6.7	6.7	6.7	—	2.2	—	2.2	0.0
53.5	14.0	4.7	—	—	—	—	—	—	9.3	0.0	—	9.3	—	—	2.3
67.8	*19.4*	*10.4*	*6.9*	*3.7*	*4.8*	*5.4*	*6.0*	*5.7*	*6.8*	*5.1*	*3.4*	*5.7*	*3.0*	*3.8*	*2.5*
72.7	45.3	3.1	—	—	—	—	—	—	—	23.6	—	6.2	—	17.4	—
92.4	21.5	9.0	16.1	11.1	12.8	11.7	10.9	7.6	6.8	10.5	11.0	4.4	10.0	7.0	6.0
88.0	40.0	12.0	4.0	4.0	20.0	12.0	24.0	4.0	4.0	0.0	8.0	4.0	8.0	12.0	0.0
100.0	7.1	7.1	10.7	0.0	3.6	7.1	10.7	0.0	7.1	3.6	10.7	3.6	10.7	3.6	3.6
55.8	7.4	3.2	4.2	8.4	3.2	9.5	5.3	2.1	2.1	3.2	1.1	0.0	10.5	2.1	5.3
79.0	15.7	3.6	15.0	11.4	7.2	8.4	9.0	5.4	10.2	3.6	7.8	3.0	3.6	4.2	2.4
42.2	7.5	4.0	6.4	4.6	4.6	1.7	1.2	3.5	—	1.7	2.9	1.7	0.0	1.7	1.2
88.6	18.2	2.3	18.2	18.2	20.5	4.5	9.1	6.8	0.0	9.1	6.8	0.0	2.3	2.3	0.0
58.4	5.8	8.9	4.2	10.5	7.4	4.7	6.8	10.5	4.2	4.7	7.4	4.2	6.3	1.1	4.7
90.9	50.0	4.5	0.0	0.0	4.5	0.0	—	0.0	4.5	4.5	4.5	0.0	0.0	0.0	0.0
95.8	37.5	12.5	0.0	0.0	0.0	0.0	—	4.2	4.2	25.0	0.0	4.2	0.0	0.0	0.0
64.6	12.6	6.9	—	—	—	—	—	—	—	8.0	—	—	—	4.0	9.1
83.8	15.0	8.8	3.8	8.8	15.0	8.0	8.8	6.3	6.3	8.8	7.5	5.0	3.8	0.0	1.3
80.2	*19.4*	*7.4*	*12.6*	*10.1*	*10.7*	*9.3*	*9.3*	*6.8*	*6.3*	*9.2*	*8.8*	*3.9*	*7.6*	*5.8*	*5.0*
80.3	26.5	2.5	0.7	—	—	—	—	—	22.9	2.5	—	5.4	—	—	—
47.7	11.4	11.4	0.0	4.5	0.0	0.0	0.0	2.3	0.0	6.8	0.0	0.0	0.0	0.0	2.3
81.5	26.0	11.0	14.8	14.8	3.7	11.1	0.0	11.1	0.0	0.0	3.7	3.7	3.7	3.7	0.0
62.5	15.0	0.0	7.5	2.5	5.0	7.5	5.0	5.0	2.5	2.5	10.0	0.0	7.5	2.5	2.5
28.8	5.8	2.9	1.9	2.9	1.0	1.9	1.9	6.7	3.8	3.8	1.0	1.0	1.9	0.0	1.0
73.0	12.2	7.2	9.9	6.1	8.8	7.2	4.4	8.8	6.1	4.4	6.6	1.1	1.7	2.2	3.9
86.5	12.8	2.0	0.0	0.7	0.0	0.7	0.0	3.4	2.0	0.7	0.0	36.5	0.0	0.7	4.1
67.7	19.4	22.6	—	—	—	0.0	—	6.5	0.0	3.2	—	11.3	—	4.8	0.0
55.7	10.0	4.3	4.3	—	4.3	7.1	1.4	5.7	2.9	7.1	4.3	8.6	0.0	2.9	4.3
80.6	9.7	8.1	—	—	—	—	—	—	4.8	4.8	—	12.9	—	8.1	16.1
54.3	4.3	1.6	1.6	2.7	1.6	2.7	2.2	2.2	2.2	2.7	1.6	1.6	0.5	2.2	0.5
96.4	74.5	—	—	—	—	—	—	—	5.5	12.7	—	—	—	—	—
33.3	4.8	0.0	4.8	0.0	4.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.8
68.3	*16.7*	*4.8*	*3.3*	*3.6*	*3.3*	*3.6*	*2.1*	*5.2*	*7.4*	*3.6*	*2.9*	*7.9*	*1.2*	*2.2*	*3.3*
71.2	**18.7**	**8.2**	**8.0**	**7.6**	**7.2**	**6.7**	**6.5**	**6.3**	**6.2**	**6.1**	**5.8**	**5.3**	**4.6**	**4.3**	**3.7**

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