Human Papillomavirus Type-Specific Prevalence

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Introduction

Genital Human Papillomavirus (HPV) infection appears to be the most common sexually transmitted virus and may be the most common sexually transmitted disease (STD) [1]. Prevalence of HPV infection in a population provides a measure of the percentage of individuals in that population that has new, persistent, or recurring HPV infection at a particular time and point. Prevalence represents an important measure of the disease burden within a population and can vary several-fold depending on the method of diagnosis and the demographic and behavioral determinants of the group under study [2]. For example, HPV prevalence in the United States appears to correlate with lower socioeconomic status [2, 3]. In longitudinal investigations, cumulative HPV prevalence has been shown to increase as the numbers of repeated test measurements increase [4–7]. This increase can be attributed to several factors including biological phenomena associated with transient and persistent HPV infections, sampling error, and overall assay characteristics. The reported prevalence of genital HPV infection suggests that age-specific prevalence rates parallel age-specific incidence rates. This would be expected if HPV infections are as a rule only transiently detectable. The prevalence of cervical HPV DNA peaks in early adulthood [8] and declines sharply with age [9, 10], increases with the number of different sexual partners, and in particular with the number of new sexual partners [11]. This observed age-related HPV prevalence may reflect a birth cohort effect or may suggest a role for immunological clearance with increasing age [12, 13].

The natural history of HPV infection remains incompletely understood. In general, HPV prevalence increases as cervical diagnoses increase from normal to high grade cervical intraepithelial neoplasia (CIN) and invasive cervical cancer [14] . Cross sectional [15–17] and prospective studies [18–20] have shown that specific HPV types predict the risk of progression to high grade CIN. Most genital HPV types are associated with CIN 1 and the types associated with CIN 2 and 3 are more frequently those classified as cancer-associated HPVs including HPVs 16, 18, 31, and 45 [21–22]. HPV 16 represents the most prevalent HPV type among cytologically normal women [3] as well as the most common cancer-associated type [23]. In a worldwide investigation of over 1000 invasive cervical cancers, HPV 16 represented approximately 50% of the infections and HPV-negative cervical cancers were relatively rare [23]. Recent studies have demonstrated that persistence of cancer-associated HPVs [24, 25] and in particular high levels of viral genomes are linked to persistent diagnosis of CIN when both are measured longitudinally [25].

The individual type-specific prevalences of HPVs associated with the anogenital tract remain somewhat unclear. In general, HPV type distribution appears similar among different age groups [26]. PCR-based detection suggests that mixed infections with multiple HPV types occur in 20% to 30% of infected women [11, 27, 28]. Infection with multiple HPV types has been associated with an increased risk of CIN [29, 30], however it is not known whether specific HPV types can promote or exclude infection with specific other HPV types.

The majority of reliable information concerning HPV prevalences in specific anogenital sites is predominantly limited to the uterine cervix. Few studies of cervical HPV infection have provided type-specific prevalence information except for HPV 6, 11, 16, 18, 31, and 33 [31]. Although more than 30 genital HPVs have been described for several years now, the consistent analysis of HPV types 6, 11, 16, 18, 31, 33 is one that remains historical. This group of HPVs comprised both “low” and “high” risk HPVs that delineated differences in disease risk between these groups of viruses. It was identified early on, and cloned genomes were made readily available to the HPV community for their detection. The implementation of polymerase-chain reaction (PCR)-based HPV analyses has subsequently facilitated the expanded detection and typing of additional HPVs (for a review see [32]) however, epidemiologic

investigations have continued to use hybridization-based procedures where expanded HPV type-specific information is not obtained. HPV type-specific characterizations of PCR products and especially of those generated by consensus and general primer methods has included oligonucleotide-based hybridization [33–35] and restriction fragment length polymorphism (RFLP) determinations [36].

The majority of the information presented below was provided in response to a written request for HPV type-specific data contributions. The purpose of this compendium effort was to provide available HPV type-specific prevalence data especially of less prevalent HPVs. These types of data are largely unavailable and seldom presented in published works. In addition to the historical reasons mentioned previously, less prevalent HPV types are often probed for in mixed probe cocktails; or if individual HPV types are distinguished, this information is often collapsed into groupings of HPVs for reasons of achieving statistical power. In addition to statistical issues, the high costs associated with individual HPV type determinations has precluded their distinction in most investigations. The current compilation is restricted to PCR-based cervical HPV data using general or consensus PCR methods. The data selected for presentation represents the studies most comparable from several geographic regions including North and South America, Europe and South East Asia. Data submitted to this project detailing HPV prevalence related to other anatomic sites were limited to single contributions and considered few HPV types in their analyses.

The three tables that follow list the selected data contributed to the compendium by cervical diagnostic category. Overall population prevalences are not shown because data provided included mixed HPV infections that could not be distinguished in several of the contributions. The actual data presented was often calculated herein from raw data provided simply for purposes of general comparability. Deviations from standard diagnostic classifications were sometimes necessary because of the data available, but the deviations are subsequently defined. The details relating to corresponding specimen collection and laboratory methods, targeted populations, and contributing investigators follow the figures and are presented in brief as described by the principal contributors.

As a point of reference, comparable published information has been included in this report when less prevalent HPV types were distinguished. In future updates to the compendium, we can expand this information pertaining to cervical HPV infections and we can also include information pertaining to additional anatomic sites providing that investigators are interested and willing to submit data. For the sake of avoiding redundancy, submissions only including groupings of HPV types were omitted, as were published or in press data that was submitted but subsequently detailed and cited in a recent monograph compiled by the International Agency for Research on Cancer (IARC) [31]. This IARC monograph provides an exhaustive summary of information not included here concerning quantitative epidemiological data on HPV infections from multiple anatomic sites.

Investigators who provided contributions that are presented as well as those that responded but who were not included here are listed in the final acknowledgments.

Table I Type-Specific HPV Prevalence Determined by PCR—Normal Cervix

STUDY	A		B		C		D		E		F	
#Tested	467		260		518		1030		325		525	
HPV type	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
6/11	16	(3)	2	(0.8)	2	(0.4)	28	(2.7)	11	(3.4)	23	(4.4)
16	40	(9)	1	(0.4)	4	(0.8)	57	(5.9)	28	(8.6)	28	(5.3)
18	24	(5)	1	(0.4)	3	(0.6)	18	(1.8)	8	(2.5)	11	(2.1)
26	ND		0		0		NA		ND		0	
31	22	(5)	0		0		27	(2.7)	12	(3.7)	3	(0.6)
33	12	(3)	0		2	(0.4)	8	(0.8)	19	(5.9)	13	(2.5)
35	2	(1)	0		0		14	(1.4)	0		4	(0.8)
39	15	(3)	0		2	(0.4)	13	(1.3)	2	(0.6)	0	
40	ND		0		0		11	(1.1)	ND		0	
42	ND		0		0		6	(0.6)	ND		0	
45	5	(3)	0		0		16	(1.6)	6	(1.9)	3	(0.6)
51	13	(3)	1	(0.4)	2	(0.4)	31	(3.1)	2	(0.6)	0	
52	21	(5)	5	(1.9)	11	(2.1)	19	(1.9)	7	(2.2)	4	(0.8)
53	ND		3	(1.2)	4	(0.8)	35	(3.5)	11	(3.4)	5	(1)
54	ND		0		0		23	(2.3)	6	(1.9)	1	(0.2)
55	ND		1	(0.4)	4	(0.8)	10	(1)	ND		0	
56	ND		1	(0.4)	1	(0.2)	23	(2.3)	3	(0.9)	2	(0.4)
57	ND		5	(1.9)	9	(1.8)	0		ND		0	
58	11	(2)	4	(1.5)	7	(1.4)	20	(2.0)	7	(2.2)	7	(1.3)
59	ND		0		0		12	(1.2)	1	(0.3)	0	
66	22	(5)	ND		ND		8	(0.8)	3	(0.9)	7	(1.3)
68/ME180	ND		1	(0.4)	2	(0.4)	6	(0.6)	ND		1	(0.2)
MM4/W13B	ND		ND		ND		3	(0.3)	3	(0.9)	ND	
MM7/Pap291	ND		ND		ND		12	(1.2)	1	(0.3)	ND	
MM8/Pap155	17	(4)	ND		ND		13	(1.3)	ND		ND	
MM9/Pap238A	ND		ND		ND		13	(1.3)	ND		ND	
OTHER	61	(13)	9	(3.5)	23	(4.5)	21	(2.1)	12	(3.7)	21	(4.0)

A = Bauer et al.
B = Liaw et al.
C = Hsing et al.
D = Schiffman et al.
E = Becker et al.
F = Franco and Villa et al.

Table II Type-Specific HPV Prevalence Determined by PCR—Low Grade Cervical Diagnoses

STUDY	G		H		I		J		K	
# Tested	37		49		426		55		971/235*	
HPV type	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
6/11	3	(8.1)	3	(6.1)	26	(6.1)	7	(12.7)	24	(2.4)
16	2	(5.4)	5	(10.3)	101	(23.7)	20	(36.4)	240	(24.7)
18	2	(5.4)	4	(8.2)	38	(8.9)	5	(9.1)	52	(5.3)
26	0		0		ND		ND		ND	
31	2	(5.4)	2	(4.1)	37	(8.7)	8	(14.6)	67	(6.9)
33	1	(2.7)	1	(2.0)	19	(4.5)	9	(16.4)	37	(3.8)
35	0		0		27	(6.3)	3	(5.5)	6	(2.6)
39	1	(2.7)	1	(2.0)	30	(7.0)	2	(3.6)	1	(0.4)
40	0		0		4	(0.9)	ND		1	(0.4)
42	0		0		7	(1.6)	ND		3	(1.3)
43	ND		ND		ND		ND		4	(1.7)
45	0		0		20	(4.7)	2	(3.6)	8	(3.4)
51	1	(2.7)	1	(2.0)	24	(5.6)	3	(5.5)	11	(4.7)
52	4	(10.8)	5	(10.2)	25	(5.9)	5	(9.1)	16	(6.8)
53	0		1	(2.0)	20	(4.7)	2	(3.6)	0	
54	1	(2.7)	1	(2.0)	11	(2.6)	0		3	(1.3)
55	1	(2.7)	1	(2.0)	5	(1.2)	ND		1	(0.4)
56	1	(2.7)	1	(2.0)	49	(11.5)	7	(12.7)	2	(0.08)
57	0		0		0		ND		0	
58	1	(2.7)	1	(2.0)	13	(3.1)	4	(7.3)	19	(8.0)
59	0		0		13	(3.1)	2	(3.6)	3	(1.3)
61	ND		ND		ND		ND		2	(0.08)
66	ND		ND		33	(7.8)	4	(7.3)	10	(4.3)
68/ME180	1	(2.7)	1	(2.0)	12	(2.8)	ND		ND	
MM4/W13B	ND		ND		10	(2.4)	1	(1.8)	ND	
MM7/Pap291	ND		ND		22	(5.2)	0		ND	
MM8/Pap155	ND		ND		17	(4.0)	ND		ND	
MM9/Pap238A	ND		ND		7	(1.6)	ND		ND	
OTHER	5	(13.5)	9	(18.9)	34	(8.0)	4	(7.2)	119	(12.3)

G = Liaw et al.
H = Hsing et al.
I = Shiffman et al.
J = Becker et al.
K = Roda Husman et al. (* includes mild and moderate dysplasia, also see description below)

Table III Type-Specific HPV Prevalence Determined by PCR—High Grade Cervical Diagnoses

STUDY	L		M		N		O		P		Q	
# Tested	48		95		50		187		402/54*		932	
HPV type	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
6/11	2	(4.2)	2	(2.1)	1	(2)	10	(5.4)	5	(1.2)	2	(0.2)
16	21	(43.8)	38	(40)	26	(52)	98	(52.4)	202	(50)	465	(49.9)
18	3	(6.2)	4	(4.2)	6	(12)	18	(9.6)	36	(9)	128	(13.7)
26	0		0		ND		ND		ND		4	(0.4)
31	0		6	(6.3)	3	(6)	23	(12.3)	32	(8)	49	(5.3)
33	0		1	(1.0)	4	(8)	27	(14.4)	15	(3.7)	26	(2.8)
35	0		1	(1.0)	2	(4)	3	(1.6)	1	(1.9)	16	(1.7)
39	0		1	(1.0)	1	(2)	4	(2.1)	0		14	(1.5)
40	0		0		0		ND		0		0	
42	0		0		0		ND		0		0	
43	ND		ND		ND		ND		0		ND	
45	0		2	(2.1)	2	(4)	9	(4.8)	5	(9.3)	78	(8.4)
51	1	(2.1)	1	(1.0)	3	(6)	3	(1.6)	3	(5.6)	7	(0.8)
52	9	(18.8)	13	(13.7)	3	(6)	6	(3.2)	5	(9.3)	25	(2.7)
53	3	(6.2)	5	(5.3)	0		3	(1.6)	0		0	
54	0		0		2	(4)	1	(0.5)	2	(3.7)	0	
55	0		0		0		ND		0		2	(0.2)
56	0		0		3	(6)	9	(4.8)	0		16	(1.7)
57	0		0		0		ND		0		0	
58	9	(18.8)	13	(13.7)	2	(4)	13	(7)	3	(5.6)	19	(2.0)
59	0		0		0		4	(2.1)	4	(7.4)	15	(1.6)
61	ND		ND		ND		ND		1	(1.9)	ND	
66	ND		ND		0		4	(2.1)	ND		0	
68/ME180	1	(2.1)	1	(1.0)	0		ND		ND		11	(1.2)
MM4/W13B	ND		ND		0		5	(2.7)	ND		6	(0.6)
MM7/Pap291	ND		ND		1	(2)	3	(1.6)	ND		1	(0.1)
MM8/Pap155	ND		ND		0		ND		ND		0	
MM9/Pap238A	ND		ND		1	(2)	ND		ND		6	(0.6)
OTHER	2	(4.2)	7	(9.6)	3	(6)	10	(5.3)	27	(6.7)	12	(1.3)

L = Liaw et al.
M = Hsing et al.
N = Schiffman et al.
O = Becker et al.
P = Roda Husman et al.(see description below)
Q = Bosch et al.

HPV Study Information for Tables I–III

Study A - Bauer et al. [3]

Population: A cross sectional population (obtained during August through October 1989) at the University Health Service at the University of California, Berkeley. U.S.A. Invited participation exceeded 95%, 467 women were enrolled, most were white, (72%), and the mean age was 22.9 years.

Specimens: Dacron swabs were used to collect both vulvar and cervical samples. Swabs were placed in separate ViraPap collection tubes containing 1 ml of medium. Aliquots of this medium were ethanol precipitated and resuspended in Tris buffer containing EDTA for subsequent amplification.

PCR method: Amplification utilized the MY09/11 consensus PCR system and generic and HPV type-specific determinations were conducted as described [3]. The cervical cell samples were tested for the presence of HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 58 designated as Pap 251 at the time of this study, and clinical types for which an HPV type designation had not been assigned at the time of the testing. These clinical types included Pap88 (now designated as HPV 66), Pap155, Pap238A, and W13B. HPV types not considered in the type-specific hybridization analyses are designated as not done (ND). Two and five percent of the original swab sample were evaluated. A beta-globin gene fragment was used as a co-amplified internal control for evaluation of sample integrity. Approximately 3% of specimens were inadequate or unavailable for analysis. Specimens negative by type-specific hybridization and positive for the generic probe only are listed under HPV Other.

Specific Comments: Data presented in Table 1 applies to combined HPV prevalence from both vulvar and cervical sites sampled.

Study B - Liaw et al. [37]

Population: During 1991 through June, 1992, a community-based cervical neoplasia screening study was conducted among women aged 30–64 in four rural townships in Taiwan with high cancer mortality rates. Women who had never been married or who had a history of cervical neoplasia or a hysterectomy were ineligible for the study. The mean age of this group of women was 43 years. A total of 5,286 Chinese women were recruited into the screening cohort. From each township, about 50% of the eligible female population participated in the study. A nested prevalent case-control study was conducted and these data represent the 260 controls with normal cytology.

Specimens: Cervical cells were collected using dacron swabs that were then placed in ViraPap collection tubes containing 1 ml of Digene standard transport media (STM). Aliquots of cervical samples were processed essentially as described in Hildesheim et al. and Gravitt et al.

PCR method: Amplification was conducted with the modified MY09/11 consensus PCR system and generic and type-specific HPV determinations were conducted as described [24, 33, 34]. The cervical cell samples were tested for the presence of HPV types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, ME180 (an HPV 68 subtype), and a cocktail of clinical types for which an HPV type designation had not been assigned at the time of the testing. These clinical types included Pap88 (now designated as HPV 66), Pap155, Pap238A, Pap291, and W13B. HPV types not considered in the type-specific hybridization analyses are designated as not done (ND). Approximately 0.3% of the samples were insufficient. A beta-globin gene fragment was used as a co-amplified internal control for evaluation of sample integrity. Specimens negative by type-specific hybridization and positive for the generic probe only are listed under HPV Other.

Specific Comments: Because pooled hybridizations were conducted for the listed clinical HPV isolates, individual prevalences of these HPV types are designated as ND.

Study C - Hsing et al.

Population: This study conducted in Chinese women residing in Taiwan represents and expansion of the case-control study reported by Liaw et al (Study B [37]). A total of 11,000 women were recruited into the screening cohort from seven rural townships in Taiwan. Of these, about 400 were screened

positive either by a Pap smear or a cervicography. A nested prevalent case-control study was conducted and data from 518 control women with normal cytology are presented. Women who had never been married or who had a history of cervical neoplasia or a hysterectomy were ineligible for the study. From each township, about 50% of the eligible female population participated in the study.

Specimens: Cervical cells were collected using dacron swabs that were then placed in ViraPap collection tubes containing 1 ml of Digene standard transport media (STM). Aliquots of cervical samples were processed essentially as described in Hildesheim et al. and Gravitt et al.

PCR method: Amplification was conducted with the modified MY09/11 consensus PCR system and generic and type-specific HPV determinations were conducted as described [24, 33, 34]. The cervical cell samples were tested for the presence of HPV types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, ME180 (an HPV 68 subtype), and a cocktail of clinical types for which an HPV type designation had not been assigned at the time of the testing. These clinical types included Pap88 (now designated as HPV 66), Pap155, Pap238A, Pap291, and W13B. HPV types not considered in the type-specific hybridization analyses are designated as not done (ND). A beta-globin gene fragment was used as a co-amplified internal control for evaluation of sample integrity. Specimens negative by type-specific hybridization and positive for the generic probe only are listed under HPV Other.

Specific comments: Because pooled hybridizations were conducted for the listed clinical HPV isolates, individual prevalences for these HPV types are designated as ND. These subjects specifically include the Liaw study controls presented in Study B, additional controls from an expanded case-control study, and additional normal subjects from the same screening cohort.

Contributors: In addition to the authors included in [37], Dr. Robert Burk contributed substantially to this study.

Study D - Schiffman et al. [22]

Population: These women represent a cross-sectional sample of 1030 women from a U.S.A, Portland, Oregon cohort. This cohort study conducted by the U.S. National Cancer Institute represents a total population of 17,654 women [22]. The cohort established between April 1989 and November 1990 was chosen to be representative of all women presenting for routine cervical cytologic screening at Kaiser Permanente, which serves about one fourth of the population of Portland. Subjects that were cytologically normal and who reported no past history of CIN are represented. Women were predominantly white and the median age was 35.

Specimens: 10 ml cervicovaginal saline lavage specimens were collected from all women. A 1ml lavage aliquot was processed for PCR.

PCR method: Duplicate amplification reactions utilizing 0.05% of the original 10 ml lavage were tested using the MY09/11 consensus primer PCR method [24, 33, 34]. A beta-globin gene fragment was used as a co-amplified internal control for evaluation of sample integrity. Approximately 4% of samples were inadequate. PCR products were tested for the presence of HPV types using a generic probe and type-specific probes for HPVs 6/11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58 (Pap251), 59, 66 (Pap88), ME180 (HPV68 subtype). HPV types designated Pap155, Pap238A, Pap291, and W13B were also evaluated. HPV types not considered in the type-specific hybridization analyses are designated as not done (ND). Specimens negative by type-specific hybridization and positive for the generic probe only are listed under HPV Other.

Specific Comments: Data for HPV 26 type-specific hybridizations was not available (NA).

Study E - Becker et al. [29]

Population: These women represent 325 control women enrolled in a case-control investigation conducted at the University of New Mexico Women's Health Care and Maternal and Infant care clinics, Albuquerque, New Mexico, U.S.A. Subjects with normal cytological diagnoses and no past history of an abnormal Pap smear, who were Hispanic or non-Hispanic white (by self-report), aged 18–40 years

and not pregnant were eligible. The median age of the case-control subjects was 26 years and 98.5% of invited/eligible controls were enrolled.

Specimens: Cervical cells were collected using dacron swabs that were then placed in ViraPap collection tubes containing 1 ml of Digene standard transport media (STM). Aliquots of cervical samples were processed essentially as described in Hildesheim et al. and Gravitt et al.

PCR method: Amplification was conducted with the modified MY09/11 consensus PCR system and generic and type-specific HPV determinations were conducted as described method [24, 33, 34]. The cervical cell samples were tested for the presence of HPV types 6,/11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 54, 56, 58, 59, Pap88 (now designated as HPV 66), Pap238A, and W13B. HPV types not considered in the type-specific hybridization analyses are designated as not done (ND). A beta-globin gene fragment was used as a co-amplified internal control for evaluation of sample integrity. Specimens negative by type-specific hybridization and positive for the generic probe only are listed under HPV Other.

Study F - Franco and Villa et al. [38]

Population: These women represent a cross-sectional study of a random sample of women participants in a city-wide cervical cancer screening program conducted in Joao Pessoa, the capital of the state of Paraiba in northeastern Brazil. Women were somewhat predominantly white, mulatto, black, with a mean age of 41 years. Twenty-three of these women had abnormal Pap smears:15 (2.9%) with low-grade and 8 (1.5%) with high-grade lesions.

Specimens: Endo- and ecto cervical specimens were collected with a cytobrush which was used to make the study Pap smear. The remaining cells were resuspended in sterile buffered saline.

PCR method: Amplification was conducted with the modified MY09/11 consensus PCR system and generic and type-specific HPV determinations were conducted as described [24, 33, 34]. The cervical cell samples were tested for the presence of HPV types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59 66, and 68. HPV types not considered in the type-specific hybridization analyses are designated as not done (ND). A beta-globin gene fragment was used as a co-amplified internal control for evaluation of sample integrity. Of 718 subjects screened, the cervical specimens from 156 women (21.7%) were not evaluable because of problems in transport or storage. An additional set of 37 specimens (5.2%) failed to be amplified for beta-globin. Specimens negative by type-specific hybridization and positive for the generic probe only are listed under HPV Other.

Study G - Liaw et al.

Population: Same as study B. A nested prevalent case-control study was conducted and these data represent the 37 study subjects with low-grade cytology (CINI).

Specimens: Same as study B.

PCR method: Same as study B.

Specific Comments: Same as study B.

Study H - Hsing et al.

Population: Same as study C. An expanded nested prevalent case-control study was conducted and these data represent the 49 study subjects with low-grade cytology (CINI).

Specimens: Same as study C.

PCR method: Same as study C.

Specific comments: Because pooled hybridizations were conducted for the listed clinical HPV isolates (i.e. those designated PapXXX or MM), individual prevalences for these HPV types are designated as ND. These subjects specifically include the Liaw study cases with low-grade cervical abnormalites presented in Study G and additional cases from an expanded case-control study.

Contributors: Same as study C.

Study I - Schiffman et al.

Population: These women represent a cross-sectional sample of 426 women from a U.S.A, Portland, Oregon cohort described in Study D. Subjects that were cytologically abnormal (low grade squamous intraepithelial lesions LSIL) at the time of sampling are represented.

Specimens: Same as study D.

PCR method: Same as study D.

Specific Comments: Same as study D.

Study J - Becker et al.

Population: Same as study E except that these women represent 55 subjects diagnosed with a low-grade cervical abnormality (CINI).

Specimens: Same as study E.

PCR method: Same as study E.

Study K - Roda Husman et al. [39]

Population: Cervical scrapes used in this study were derived from the outpatient clinics of the Free University Hospital and the OLVG Hospital, situated in Amsterdam, The Netherlands. The subjects represented in this table were classified as Pap IIIa which includes both mild and moderate dysplasia diagnostic categories. The purpose of this investigation was to determine the HPV type-specific distribution in cytomorphologically abnormal cervical scrapes.

Specimens: Two cervical scrapes were taken with a brush. A routine smear was prepared from the first brush and the remaining cervical cells were combined with a second brush scrape and placed into phosphate buffered saline containing 0.05% Merthiolate. Cell pellets were resuspended in 1.0 ml of Tris buffer and 10ul aliquots were boiled prior to amplification.

PCR methods: The quality of the target DNA from cervical scrapes were pre-screened by PCR using beta-globin specific primers. Adequate specimens were subjected to general primer-PCR using GP5 and GP6 primers as described [39]. Resultant amplimers were used to identify HPV positive samples using a generic cocktail probe specific for HPV 6, 11, 16, 18, 31, and 33 under low stringency conditions. HPV type-specific PCR amplification reactions were performed for HPVs 6, 11, 16, 18, 31 and 33. Only specimens that were generic probe positive and negative for the HPV 6, 11, 16, 18, 31, and 33 type-specific amplification reactions were subjected to type-specific hybridization for HPV types 13, 30, 32, 35, 39, 40, 42, 43, 44, 45, 51, 53, 54, 55, 56, 57, 58, 59, 61 and 66.

Specific comments: Because only generic HPV positive specimens failing to amplify with HPV type-specific primers (HPVs 6, 11, 16, 18, 31, and 33) were further analyzed by hybridization-based methods, it is likely that the prevalence of additional HPV types is underestimated. These additional HPVs most likely could be observed as mixed infections with these HPVs originally screened for by type-specific amplification. HPV prevalence was determined in 971 cases for HPV types 6, 11, 16, 18, 31, 33 and type other. Only 235 cases were considered in the prevalence determined for the specific additional HPV types listed above under PCR methods, as these were the only cases subjected to hybridization. The cervical diagnostic category of these cases includes both mild and moderate dysplastic diagnoses that overlap with the low end of high grade cervical abnormalities under the Bethesda classification system [40], therefore HPV type distributions may be somewhat misrepresented when compared to other studies in Table II that are restricted to the CIN I diagnostic category.

Study L - Liaw et al.

Population: Same as study B and G. A nested prevalent case-control study was conducted and these data represent the 48 study subjects with high-grade cytological diagnoses (CINII and CINIII).

Specimens: Same as study B and G.

PCR method: Same as study B and G.

Specific Comments: Same as study B and G.

Study M - Hsing et al.

Population: Same as study C and H. An expanded nested prevalent case-control study was conducted and these data represent the 95 study subjects with high-grade cytological diagnoses (CINII and CINIII).

Specimens: Same as study C and H.

PCR method: Same as study C and H.

Specific comments: Because pooled hybridizations were conducted for the listed clincial HPV isolates (i.e. those designated PapXXX or MM), individual prevalences of these HPV types are designated as ND. These subjects specifically include the Liaw study cases with high-grade cervical abnormalites presented in Study L and additional cases from an expanded case-control study.

Contributors: Same as study C and H.

Study N - Schiffman et al.

Population: These women represent a cross-sectional sample of 50 women from a U.S.A, Portland, Oregon cohort described in Study D. Subjects that were cytologically abnormal (high grade squamous intraepithelial lesions HSIL) at the time of sampling are represented.

Specimens: Same as study D and I.

PCR method: Same as study D and I.

Specific Comments: Same as study D and I.

Study O - Becker et al.

Population: Same as study E and J except that these women represent 187 subjects diagnosed with a high-grade cervical abnormality (CINII and CINIII).

Specimens: Same as study E and J.

PCR method: Same as study E and J.

Study P - Roda Husman et al.

Population:. Same as study K. The subjects represented in table III were classified as either Pap IIIb (severe dysplasia) or Pap IV (carcinoma in situ).

Specimens: Same as in study K.

PCR methods: Same as study K.

Specific comments: Because only specimens failing to amplify with HPV type-specific primers (HPVs 6, 11, 16, 18, 31, and 33) were further analyzed by hybridization-based methods, it is likely that the prevalence of additional HPV types is underestimated. These additional HPVs most likely could be observed as mixed infections with these HPVs originally screened for by type-specific amplification. HPV prevalence was determined in 402 cases for HPV types 6, 11, 16, 18, 31, 33 and type other. Only 54 cases were considered in the prevalence determined for the specific additional HPV types detailed in Study K as these were the only cases subjected to hybridization.

Study Q - Bosch et al. [23]

Population: This field study was conducted in 32 hospitals from 22 countries between June 1989 and June 1992. Sequential cases with invasive cervical cancer were included.

Specimens: Biopsy specimens were obtained and frozen without additives. Crude DNA samples were prepared and subjected to PCR.

PCR method: Specimens were amplified using the modified MY09/11 consensus primer PCR method. A beta-globin gene fragment was used as a co-amplified internal control for evaluation of

sample integrity. PCR products were tested for the presence of HPV types using a generic probe and type-specific probes for HPVs 6/11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 66 (Pap88), ME180 (HPV68 subtype). HPV types designated Pap155, Pap238A, Pap291, and W13B were also evaluated. HPV types not considered in the type-specific hybridization analyses are designated as not done (ND). Specimens negative by type-specific hybridization and positive for the generic probe only are listed under HPV Other.

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