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Three-Year Risk of Cervical Precancer and Cancer After the Detection of Low-Risk Human Papillomavirus Genotypes Targeted by a Commercial Test

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Abstract

Objective—To investigate the risk of cervical precancer and cancer associated with detection of human papillomavirus (HPV) 6, 11, and 42.

Methods—We used data from the New Mexico HPV Pap Registry. A stratified sample of 59,644 residual cervical cytology specimens from a population of 379,000 underwent HPV genotyping. We measured the 3-year cumulative incidence of cervical intraepithelial neoplasia grade 2 or more severe (CIN2+) and grade 3 or more severe (CIN3+) after detection of single HPV6, 11, or 42 infections or single or multiple infections by of HPV6, 11, or 42 (“HPV6, 11, 42, or combinations”)(n=581).

Results—The overall prevalence of a single infection of HPV6, 11, or 42 was 0.8% (95% confidence interval [95%CI]: 0.7%, 0.9%). The 3-year risks of CIN2+ and CIN3+ after HPV6, 11, 42, or combinations infections (n = 581) were 0.4% (CI: 0.1%, 0.7%) for CIN2+ and 0.0% for CIN3+ (nota bene, no confidence interval was calculable because no events occurred), respectively. By comparison, the 3-year risks of CIN2+ and CIN3+ after a negative HPV result (n = 27,522) were 0.2% (95%CI: 0.1%, 0.2%) and 0.1% (95%CI: 0.0%, 0.1%), respectively.

Conclusion—Detection of HPV6, 11, 42, or combinations in the absence of high risk HPV types does not identify women at increased 3-year risk for cervical precancer. Testing for HPV6, 11, 42, or combinations of those types should be discontinued as it has no proven benefit to patients.

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Roche Molecular Systems, Inc. provided HPV Linear Array reagents and equipment to automate HPV genotyping assays.

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Introduction

High-risk human papillomavirus (HPV) DNA testing has been increasingly integrated into cervical cancer screening and management. Current screening guidelines recommends HPV co-testing every 5 years in women aged 30–65 as the preferred alternative to cytology every 3 years (4;5) and high-risk HPV (HR-HPV) DNA testing is recommended for the management of ASC-US cytology (“reflex” testing), for follow-up of women who have undergone colposcopy, and for surveillance after treatment of precancerous lesions (6;7).

Despite national guidelines for the use of high-risk HPV DNA testing and warnings against inappropriate use, there is evidence that clinicians are ordering HPV testing in excess of its recommended use (8;9). This includes ordering co-testing more frequently than recommended (9) for patients who already have cytologic evidence of serious abnormalities and should be referred to colposcopy regardless of the HPV test result (8), and testing for low-risk HPV types 6, 11, 42, 43, and 44 using Probe A (Qiagen, Gaithersburg, MD, USA) (8). The latter potentially adds cost and identifies more women as HPV positive while apparently offering little benefit since these types rarely or never cause cervical cancer.

However, it is theoretically possible that the detection of these types could identify women at higher risk of subsequently acquiring high-risk HPV genotypes that do cause cervical cancer since they are all transmitted identically through sexual contact (10). We therefore conducted a population-based analysis of the 3-year risks for women to develop either CIN2+ or CIN3+ associated with infection with HPV 6, 11 and 42. HPV 43 and 44 results were not available.

Materials and Methods

The New Mexico HPV Pap Registry is located at the University of New Mexico and acts as a designee of the New Mexico Department of Health. The New Mexico HPV Pap Registry operates under New Mexico Administrative Code 7.4.3.12, which specifies the list of Notifiable Diseases and Conditions for the state of New Mexico. In 2006, with the intention of monitoring the impact of HPV vaccination, New Mexico Administrative Code 7.4.3.12 specified that laboratories must report to the New Mexico HPV Pap Registry all cervical cytology, cervical pathology, and HPV tests performed on New Mexico residents. NMAC 7.4.3.12 was updated in 2009 to include vulvar and vaginal pathology (<http://nmhealth.org/ERD/healthdata/documents/NotifiableDiseasesConditions022912final.pdf>).

During the 17-month period of December 2007 through April 2009 approximately 379,000 cervical cytology tests were reported to the New Mexico HPV Pap Registry by 9 in-state and 7 out-of-state clinical laboratories (11). All available liquid cervical cytology specimens were collected from 7 of the 9 in-state laboratories, which accounted for 79% of all cervical cytology tests done during this period. Specimens were randomly selected from each of these 7 labs for HPV genotyping within four strata defined by the age of the woman (≤ 30 years vs. > 30 years) and by the cytologic result on the laboratory report (negative vs. abnormal). Randomization was carried out by using a random number generator to select, without replacement, a target sampling proportion of all cytology samples within each stratum. Target sampling proportions varied by strata: 45% of negative specimens in women ≤ 30 years, 8% of negative specimens in women > 30 years, and 100% of abnormal specimens, regardless of the woman’s age. Ultimately, a total of 59,644 specimens on 54,848 women were retrieved and successfully genotyped for HPV. Prior to HPV genotyping, specimens were de-identified by the use of randomly assigned study-specific identifiers. The UNM Human Research Review Committee approved this study.

HPV genotyping was done as previously described (11–13). Briefly, DNA was purified from 500 μ L aliquots from vigorously mixed residual liquid cytologic specimens SurePath™ (Beckton, Dickinson and Company, New Jersey USA) or ThinPrep (Hologic, Inc., Massachusetts USA), using a Cobas X421 robot (Roche Molecular Systems (RMS), Inc., California USA). Fifty microliters (50 μ L) of purified DNA was transferred to a tube with 50 μ L of HPV Linear Array (HPV LA; Roche Diagnostics, Indianapolis, Indiana USA) mastermix, and the mixture was amplified by polymerase chain reaction (PCR) as specified by the manufacturer. Controls for contamination and assay sensitivity were included in each 96-well assay.

The HPV LA is based on PGMY 09/11 consensus PCR primers and a prototype Line Blot assay, which have been previously reported in detail (12–14). Using the Roche HPV LA detection kit, hybridizations were automated using Tecan ProfiBlot-48 robots (Tecan, Austria). The Roche HPV LA Genotyping Test detects 13 high-risk (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and 24 low-risk (6, 11, 26, 40, 42, 53–55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73, 81, 82, 82v, 83, 84, and 89) HPV types. The presence of HPV 52 is not determined directly by a type-specific probe but through inference as previously described (14). Two independent readers interpreted the presence of HPV genotypes using a reference template provided by the manufacturer. Any discrepancies were identified by a custom computer application applied to the data input and were adjudicated by a third review.

Cytologic results were classified according to the 2001 Bethesda System (TBS) (15): high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells cannot rule out HSIL (ASC-H), atypical glandular cells (AGC), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells of undetermined significance (ASC-US), and negative for intraepithelial lesion or malignancy. There were a few examples of use of non-TBS terminology, which were classified as follows (11): 1) LSIL cannot rule out HSIL (LSIL-H) as ASC-H; 2) cervical intraepithelial neoplasia (CIN) grade 1 as LSIL; CIN2, CIN3, carcinoma in situ (CIS), or possible carcinoma as HSIL; and 4) atypical squamous and glandular cells of undetermined significance as AGC. Cytologic results were generally dichotomized as normal (negative) and abnormal (ASC-US or more severe).

Data on cytologic interpretations and histologic diagnoses were collected from medical records. Both were based on local readings and no attempt was made to review them centrally or undertake quality assurance activities.

Diagnoses for cervical precancer (CIN2, CIN3) and cancer were based on the results of all cervical biopsies, including excisional biopsies (LEEP), and all endocervical curettages (ECC) from the date of the index cytology for a period of 3 years. An outcome of CIN2+ was defined as a result of CIN2, HSIL, CIN2–3, CIN3, CIS, AIS, or carcinoma. An outcome of CIN3+ was defined as a result of CIN2–3, CIN3, CIS, AIS, or carcinoma.

For women with more than one cytology specimen, only the chronologically earliest was considered. In addition, only specimens from screening tests were used, which was defined as a cervical cytology test with no previous cytology collected within 300 days ($n=47,541$). Estimation of the 3-year risk of CIN2+ and CIN3+ was restricted to the 27,522 HPV negative specimens, and specimens positive for a single infection by HPV6 ($n=235$), by HPV11 ($n=29$), or by HPV42 ($n=307$) (i.e., 571 single HPV genotype infections by either 6, 11, or 42) and specimens positive and specimens positive for one ($n=571$) or more ($n=10$) of HPV6, 11, or 42 and no other HPV type (“HPV6, 11, 42, or combinations”)($n=581$). Additional analyses considered the risk of CIN2+ and CIN3+ for women positive for one or more HR-HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) with or

without HPV6, 11, 42, or combinations. All confidence intervals and p-values are exact except for those reported for “All ages”, “All cytology”, and All, which were computed using sample survey techniques appropriate for a stratified random sample with unequal sampling fractions. SAS (v 9.3) procedures FREQ and SURVEYFREQ were used to compute exact and weighted proportions and tests of significance, respectively. Sample weights were computed as the inverse of the sampling fraction and variances were computed by the Taylor series linearization method. Weighted confidence intervals were based on normal approximations.

Results

Overall, 2.7% of women tested positive for an infection by HPV6, 11, 42, or combinations (95%CI: 2.6%-2.9%). The majority of these infections were concurrent with infections of other HPV types and single HPV genotype infections by HPV6, 11, or 42 were found in only 0.8% (95%CI: 0.7%-0.9%) of women. This analysis focused on the sub-group of women infected with HPV6, 11, 42, or combinations of these types to estimate the excess risk of cervical precancer and cancer attributable to HPV6, 11, or 42 infections above testing HPV negative.

The prevalence of single infections of HPV6, 11, or 42 was <2% in all sampling subgroups defined by cytologic status (negative vs. abnormal) and age (≤ 30 vs. >30 years) (Table 1). The prevalence was significantly lower in women aged > 30 years with negative cytology compared to all other subgroups ($p < 0.001$). The prevalence among those with abnormal cytology in either age group was only slightly greater than the prevalence among those aged ≤ 30 years with negative cytology.

Table 2 shows the distribution of cytologic results concurrent with infections by HPV6, 11, 42, or combinations versus those with no HPV detected. HPV6, 11 42 positives were associated with significantly more abnormal squamous-cell cytology ($p < 0.001$), specifically ASC-US and LSIL.

The 3-year risks of CIN2+ and CIN3+ after single HPV6, 11, or 42 infections and HPV6, 11, 42, or combinations infection versus HPV negatives are shown in Table 3. No women with single HPV6, 11, or 42 infections and negative cytology were diagnosed with CIN2+ or CIN3+ and very few were after a negative HPV result. A small number of women with HPV6, 11, 42, or combinations and an abnormal negative cytology were diagnosed with CIN2+ but none were diagnosed with CIN3+. Accounting for sampling fractions, the overall 3-year risks after HPV6, 11, 42, or combinations infections ($n = 581$) were 0.4% (95%CI: 0.1, 0.7) for CIN2+ and 0.0% for CIN3+ (note below, no confidence interval was calculable because no events occurred). By comparison, the 3-year risks after a negative HPV result ($n = 27,522$) were 0.2% (95%CI: 0.1, 0.2) for CIN2+ and 0.1% (95%CI: 0.0, 0.1) for CIN3+. Overall, the difference in risk of CIN2+ between HPV-negative and women positive for HPV6, 11, 42, or combinations-- was small but statistically significant ($p=0.02$). Among women with abnormal cytology, the risk for CIN2+ but not CIN3+ was greater for HPV6, 11, or 42-positive women than HPV-negative women (3.1% vs. 0.6%, respectively, $p < 0.0001$), most notably in women older than 30 years of age (4.5% vs. 0.4%, respectively, $p < 0.0001$).

As an ancillary analysis, we examined whether detection of HPV6, 11, 42, or combinations increased the risk of CIN2+ and CIN3+ among those with a concurrent HR-HPV infection (Table 4). In most strata, testing positive for these low-risk HPV types did not increase risk of CIN2+ or CIN3+. Among women with abnormal cytology, detection of HPV6, 11, 42, or combinations was associated with a significant decrease in risk of CIN2+ and CIN3+.

Discussion

Although CIN2 is the threshold for excisional treatment, the increased risk associated with HPV6, 11, 42, or combinations is minor on an absolute risk scale and is not actionable i.e. a risk that is sufficiently greater to take more aggressive clinical action such as referring women positive for any of these HPV types to colposcopy (17). In addition, it is well known that CIN2 is an equivocal, regressive high-grade diagnosis and is a diagnosis that sometimes can be caused by non-carcinogenic HPV genotypes with no risk of progression to cancer (18–21). These additional cases of CIN2 possibly attributable to HPV6, 11, 42, or combinations infections may not represent real cancer risk but would be treated by an excisional procedure in routine clinical practice. Notably, these cases were found without the use of low-risk HPV testing. The introduction of p16^{INK4A} immunohistochemistry to clarify which CIN2 are truly precancer should reduce the treatment of CIN2 caused by low-risk HPV types like HPV6, 11, and 42 (as well as HPV43 and 44) that is not destined to become cancer (22).

Another limitation is that there was only 3 years of follow-up for this cohort, and small sampling fractions of the Pap-negative population, which likely resulted in a small number of measurable events occurring in these low-risk populations, leading to imprecise estimates of risk. Moreover, since an abnormal Pap was required for referral to colposcopy and biopsy, and women positive for these HPV types were more likely to have an abnormal Pap than the HPV-negative women, there is potentially a bias in the disease ascertainment that would lead to higher risk estimates in the HPV6, 11, 42-positive women. However, the percentage of women with at least one follow-up cytology, cervical biopsy, or ECC in the 3-year period was not significantly different between those who were HPV negative and those who tested positive for a single infection of HPV6, 11, or 42 (70.7% vs. 72.3%, $p = 0.6$). Nevertheless, longer-term follow-up will address both these limitations.

Because little disease occurs in HPV-negative women, where the necessary cause of cervical cancer and its immediate precursors are absent (28), and because HPV6, 11, 42, or combinations contribute very little to the risk of CIN2 and not at all to that of CIN3, we had insufficient power to detect small risk differences between the two groups. A *post-hoc* power calculation found that there was 80% power to detect a risk difference between HPV6, 11, 42, or combinations positives and HPV negatives of 1.7, 4.4, 2.1, and 2.6 cases of CIN2+ per 100 women in the 30 and negative cytology, 30 and abnegative cytology, >30 and negative cytology, and >30 and abnegative cytology groups, respectively. Thus, smaller but clinically unimportant differences would likely have been missed.

The risks were likely underestimated since some women in this cohort moved out of state during follow-up and then developed cervical disease. Although we have no way of knowing the out-migration specifically for women in this cohort, the estimates of out-migration from the state of New Mexico decreased with increasing age and varied by observational year of the cohort but was never greater than 8% for a given year and age group (data not shown). In an analysis comparing all women with HPV6, 11, 42, or combinations infections to those with adequate follow-up (i.e. Adequate follow-up was defined for high-grade Pap samples as cervical biopsy or ECC, for LSIL or high-risk HPV positive ASC-US Pap samples as biopsy or ECC or repeat negative cytology that is negative for high-risk HPV, and for all other Pap samples as biopsy or ECC or repeat negative cytology.) (Appendix 2, available online at <http://links.lww.com/xxx>), there was no meaningful difference in the risk estimates. Since HPV infection is asymptomatic, we do not anticipate a differential bias in our estimates of risk due to out-migration and therefore our conclusions regarding similar risk between HPV-negative and HPV6, 11, or 42-positive populations are likely correct.

We conclude that risk of cervical precancer within 3 years of detection of HPV6, 11, 42, or combinations is low and not appreciably different than for HPV negative women, and therefore testing for these types should not be included in cervical cancer prevention programs. Testing for HPV6, 11, or 42 or combinations of these types may result in some women being labeled as HPV positive, which can have a psychosocial impact such as stigmatization from testing positive for a sexually transmitted infection or anxiety from being “screen positive”. Importantly, testing for HPV 6, 11, or 42 could lead to the interpretation of a positive “screening” result that might result in referral to colposcopy and a diagnosis of CIN2, which is the threshold of treatment in the U.S. (29). It is now recognized that excisional treatment, currently the predominant method for treating CIN2 and CIN3, may increase the risk of negative reproductive outcomes, including preterm delivery and perinatal mortality (30). Importantly, HPV prevalence is greatest in young reproductive-age women, those who might experience the greatest harms of low-risk HPV testing. Therefore, testing for low-risk HPV6, 11, 42, or combinations of these types (or related types such as HPV43 and 44) should be strongly discouraged to reduce the potential harms due to unnecessary testing and to conserve healthcare resources needed for other services that do benefit to patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesions
LSIL	low-grade squamous intraepithelial lesions
US	United States
NMHPVPR	New Mexico HPV Pap Registry
HPV LA	HPV LINEAR ARRAY
PCR	polymerase chain reaction
TBS	the 2001 Bethesda System
ASC-H	atypical squamous cells cannot rule out HSIL
AGC	atypical glandular cells
ASC-US	atypical squamous cells of undetermined significance
LSIL-H	LSIL cannot rule out HSIL
CIN	cervical intraepithelial neoplasia
CIN1	cervical intraepithelial neoplasia grade 1
CIN2	cervical intraepithelial neoplasia grade 2

CIN3	cervical intraepithelial neoplasia grade 3
CIS	carcinoma <i>in situ</i>
AIS	adenocarcinoma <i>in situ</i>

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Prevalence of HPV6, 11, and 42 Infections Among the Sampled Subgroups Defined by Cytologic Status (Normal vs. Abnormal [Atypical Squamous Cells of Undetermined Significance or More Severe]) and by Age (30 Years or Younger and Older Than 30)

Table 1

	Negative Cytology			Abnegative Cytology		
	30 years (n = 23,030)	> 30 years (n=10,539)		30 years (n=7,312)	> 30 years (n=6,660)	
	%	(95% CI)	%	(95% CI)	%	(95% CI)
Any infections with HPV6, 11, or 42						
HPV6	2.1	(1.9, 2.3)	0.4	(0.3, 0.6)	6.7	(6.1, 7.3)
HPV11	0.3	(0.2, 0.4)	0.1	(0.0, 0.1)	0.9	(0.7, 1.2)
HPV42	2.6	(2.4, 2.8)	0.6	(0.4, 0.7)	8.4	(7.7, 9.0)
HPV 6, 11, 42, or combinations	4.8	(4.5, 5.0)	1.0	(0.9, 1.3)	14.9	(14.1, 15.7)
Only infections with HPV6, 11, or 42						
HPV6	0.6	(0.5, 0.7)	0.2	(0.1, 0.3)	0.7	(0.5, 0.9)
HPV11	0.1	(0.0, 0.1)	0.0	(0.0, 0.1)	0.1	(0.0, 0.1)
HPV42	0.6	(0.5, 0.7)	0.3	(0.2, 0.4)	0.8	(0.6, 1.0)
HPV 6, 11, 42, or combinations	1.3	(1.2, 1.5)	0.5	(0.4, 0.7)	1.5	(1.3, 1.9)

CI, confidence interval; HPV, human papillomavirus.

All confidence intervals are exact.

Table 2

Distribution of Cytologic Results for Human Papillomavirus (HPV)-Negative Pap Smears and for Pap Smears Positive for HPV 6,11, 42, or Combinations

Cytologic Result	HPV Negative (n=27,522)			HPV 6,11, 42, or Combinations (n=581)		
	n	%	(95% CI)	n	%	(95% CI)
Negative	23,062	97.0	(97.0, 97.1)	357	86.5	(84.3, 88.7)
ASC-US	3,746	2.5	(2.4, 2.5)	141	8.5	(6.8, 10.1)
LSIL	195	0.1	(0.1, 0.1)	73	4.4	(3.3, 5.5)
ASC-H	145	0.1	(0.1, 0.1)	5	0.3	(0.0, 0.6)
HSIL	13	0.0	(0.0, 0.0)	1	0.1	(0.0, 0.2)
AGC	350	0.2	(0.2, 0.3)	4	0.2	(0.0, 0.5)
Adenocarcinoma	10	0.0	(0.0, 0.0)	0	0.0	---
Suspicious for carcinoma	1	0.0	(0.0, 0.0)	0	0.0	---

Frequency (n) is un-weighted. Percent and confidence interval were computed using sample weights. The difference in distribution of cytologic results was statistically significant ($p < 0.001$, Rao-Scott chi-square).

CI, confidence interval; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions; ASC-H, atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesions; AGC, atypical glandular cells.

Table 3

Three-Year Risk of Cervical Intraepithelial Neoplasia Grade 2 or More Severe (CIN2+) and Grade 3 or More Severe (CIN3+) for Single Infections, or Single or Multiple Infections, by Human Papillomavirus (HPV) 6, 11, or 42 Infections (6, 11, 42, or Combinations) Compared With HPV Negative

A. After negative cytology result	Age	HPV Types	n	CIN2+			CIN3+		
				n+	%	(95% CI)	n+	%	(95% CI)
30 years	6		140	0	0.0	(0.0, 2.6)	0	0.0	(0.0, 2.6)
	11		18	0	0.0	(0.0, 18.5)	0	0.0	(0.0, 18.5)
	42		142	0	0.0	(0.0, 2.6)	0	0.0	(0.0, 2.6)
	6, 11, 42, or combinations		303	0	0.0	(0.0, 1.2)	0	0.0	(0.0, 1.2)
	Negative		14,483	53	0.4	(0.3, 0.5)	13	0.1	(0.0, 0.2)
	6		20	0	0.0	(0.0, 16.8)	0	0.0	(0.0, 16.8)
	11		2	0	0.0	(0.0, 84.2)	0	0.0	(0.0, 84.2)
	42		31	0	0.0	(0.0, 11.2)	0	0.0	(0.0, 11.2)
	6, 11, 42, or combinations		54	0	0.0	(0.0, 6.6)	0	0.0	(0.0, 6.6)
	Negative		8,579	7	0.1	(0.0, 0.2)	3	0.0	(0.0, 0.1)
All ages	06		160	0	0.0	---	0	0.0	---
	11		20	0	0.0	---	0	0.0	---
	42		173	0	0.0	---	0	0.0	---
	6, 11, 42, or combinations		357	0	0.0	---	0	0.0	---
	Negative		23,062	60	0.2	(0.1, 0.2)	16	0.0	(0.0, 0.1)
	6		49	1	2.0	(0.1, 10.9)	0	0.0	(0.0, 7.3)
	11		4	0	0.0	(0.0, 60.2)	0	0.0	(0.0, 60.2)
	42		56	1	1.8	(0.0, 9.6)	0	0.0	(0.0, 6.4)
	6, 11, 42, or combinations		113	2	1.8	(0.2, 6.2)	0	0.0	(0.0, 3.2)
>30 years	Negative		1,114	15	1.3	(0.8, 2.2)	2	0.2	(0.0, 0.6)
	6*		26	2	7.7	(0.9, 25.1)	0	0.0	(0.0, 13.2)

A. After negative cytology result	HPV Types	n	CIN2+			CIN3+		
			n+	%	(95% CI)	n+	%	(95% CI)
Age	11 [†]	5	2	40.0	(5.3, 85.3)	0	0.0	(0.0, 52.2)
	42	78	1	1.3	(0.0, 6.9)	0	0.0	(0.0, 4.6)
	6, 11, 42, or combinations [†]	111	5	4.5	(1.5, 10.2)	0	0.0	(0.0, 3.3)
	Negative	3,346	12	0.4	(0.2, 0.6)	9	0.3	(0.1, 0.5)
All ages	6 [†]	75	3	3.9	(0.0, 8.2)	0	0.0	---
	11 [†]	9	2	21.4	(0.0, 47.9)	0	0.0	---
	42	134	2	1.5	(0.0, 3.6)	0	0.0	---
	6, 11, 42, or combinations [†]	224	7	3.1	(0.8, 5.3)	0	0.0	---
	Negative	4,460	27	0.6	(0.4, 0.9)	11	0.2	(0.1, 0.4)
C. After any cytology result								
30 years	6	189	1	0.3	(0.0, 0.8)	0	0.0	---
	11	22	0	0.0	---	0	0.0	---
	42	198	1	0.3	(0.0, 0.7)	0	0.0	---
	6, 11, 42, or combinations	416	2	0.2	(0.0, 0.6)	0	0.0	---
	Negative	15597	68	0.4	(0.3, 0.5)	15	0.1	(0.0, 0.1)
>30 years	6 [†]	46	2	0.7	(0.0, 1.7)	0	0.0	---
	11 [†]	7	2	6.4	(0.0, 17.7)	0	0.0	---
	42	109	1	0.2	(0.0, 0.6)	0	0.0	---
	6, 11, 42, or combinations [†]	165	5	0.6	(0.1, 1.2)	0	0.0	---
	Negative	11,925	19	0.1	(0.0, 0.1)	12	0.0	(0.0, 0.1)
All ages	6	235	3	0.4	(0.0, 0.9)	0	0.0	---
	11 [†]	29	2	2.4	(0.0, 5.9)	0	0.0	---
	42	307	2	0.2	(0.0, 0.5)	0	0.0	---
	6, 11, 42, or combinations [†]	581	7	0.4	(0.1, 0.7)	0	0.0	---

A. After negative cytology result				CIN2+			CIN3+		
Age	HPV Types combinations [‡]	n	n+	%	(95% CI)		n+	%	(95% CI)
	Negative	27,522	87	0.2	(0.1, 0.2)		27	0.1	(0.0, 0.1)

CI, confidence interval.

* p = 0.005 for risk of CIN2+

[†] p < 0.001 for risk of CIN2+

[‡] p = 0.02 for risk of CIN2+

All confidence intervals and *P*-values are exact except for those reported for “all ages,” “all cytology,” or “all ages,” which are computed using the sample weights. Tests of significance are Pearson chi-square with exact *P*-value (exact results) or Rao-Scott chi-square with approximate *P*-value (weighted results). Confidence intervals for weighted results are not computed when there are no events. There was no statistical significance in the 2-year risk of CIN2+ or CIN3+ between HPV6-positive, HPV11-positive, or HPV42-positive specimens and HPV-negative specimens except where denoted.

Three-Year Risk of Cervical Intraepithelial Neoplasia (CIN)2+ and CIN3+ for Pap Samples That Test Positive for One or More Carcinogenic Human Papillomavirus (HPV) Types with and without HPV6, 11, 42, or Combinations

Table 4

CIN2+											CIN3+	
Carcinogenic HPV With or Without HPV6, 11, 42, or Combinations												
Cytology result	Age		n	n+	%	(95% CI)	n+	%	(95% CI)	n+	%	(95% CI)
Normal	30 years	With	546	14	2.6	(1.4, 4.3)	4	0.7	(0.2, 1.9)			
		Without	4672	127	2.7	(2.3, 3.2)	61	1.3	(1.0, 1.7)			
					p=0.9				p=0.3			
Normal	>30 years	With	31	0	0.0	(0.0, 11.2)	0	0.0	(0.0, 11.2)			
		Without	818	6	0.7	(0.3, 1.6)	3	0.4	(0.1, 1.1)			
					p=1				p=1			
Normal	All ages	With	577	14	2.0	(1.0, 3.0)	4	0.6	(0.0, 1.1)			
		Without	5490	133	1.8	(1.4, 2.2)	64	0.9	(0.6, 1.1)			
					p=0.7				p=0.4			
Abnormal	30 years	With	801	89	11.1	(9.0, 13.5)	35	4.4	(3.1, 6.0)			
		Without	4281	740	17.3	(16.2, 18.5)	323	7.5	(6.8, 8.4)			
					p<0.0001				p=0.002			
Abnormal	>30 years	With	171	17	9.9	(5.9, 15.4)	9	5.3	(2.4, 9.8)			
		Without	1988	391	19.7	(17.9, 21.5)	228	11.5	(10.1, 13.0)			
					p=0.002				p=0.01			
Abnormal	All ages	With	972	106	10.9	(9.0, 12.9)	44	4.5	(3.2, 5.8)			
		Without	6269	1131	18.0	(17.0, 19.0)	551	8.7	(8.0, 9.4)			
					p<0.0001				p<0.0001			
All cytology	30 years	With	1347	103	5.8	(4.6, 7.0)	39	2.1	(1.4, 2.8)			
		Without	8953	867	6.7	(6.3, 7.2)	384	3.0	(2.7, 3.3)			
					p=0.2				p=0.04			
All cytology	>30 years	With	202	17	3.0	(1.4, 4.5)	9	1.6	(0.5, 2.6)			
		Without	2806	397	3.7	(3.1, 4.3)	231	2.1	(1.7, 2.5)			
					p=0.4				p=0.4			
All cytology	All ages	With	1549	120	5.2	(4.2, 6.2)	48	2.0	(1.4, 2.6)			

		CIN2+				CIN3+			
Cytology result	Age	Carcinogenic HPV With or Without HPV6, 11, 42, or Combinations							
		n	n+	%	(95% CI)	n+	%	(95% CI)	
Without		11759	1264	5.4	(5.1, 5.8)	615	2.6	(2.4, 2.9)	
		p=0.7				p=0.09			

p=0.09

p=0.7

CI, confidence interval.