

Contribution of Etiologic Cofactors to CIN3+ Risk Among Women With Human Papillomavirus–Positive Screening Test Results

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Objective: The US screening and management guidelines for cervical cancer are based on the absolute risk of precancer estimated from large clinical cohorts and trials. Given the widespread transition toward screening with human papillomavirus (HPV) testing, it is important to assess which additional factors to include in clinical risk assessment to optimize management of HPV-infected women.

Materials and Methods: We analyzed data from HPV-infected women, ages 30–65 years, in the National Cancer Institute–Kaiser Permanente Northern California Persistence and Progression study. We estimated the influence of HPV risk group, cytology result, and selected cofactors on immediate risk of cervical intraepithelial neoplasia grade 3 or higher (CIN 3+) among 16,094 HPV-positive women. Cofactors considered included, age, race/ethnicity, income, smoking, and hormonal contraceptive use.

Results: Human papillomavirus risk group and cytology test result were strongly correlated with CIN 3+ risk. After considering cytology and HPV risk group, other cofactors (age, race/ethnicity, income, smoking, and hormonal contraceptive use) had minimal impact on CIN 3+ risk and did not change recommended management based on accepted risk thresholds. We had insufficient data to assess the impact of long-duration heavy smoking, parity, history of sexually transmitted infection, or immunosuppression.

Conclusions: In our study at the Kaiser Permanente Northern California, the risk of CIN 3+ was determined mainly by HPV risk group and cytology results, with other cofactors having limited impact in adjusted analyses. This supports the use of HPV and cytology results in risk-based management guidelines.

Key Words: cervical cancer screening, risk estimation, guidelines, smoking, hormonal contraception

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Cervical cancer screening is shifting from cytology to the more sensitive approach of human papillomavirus (HPV) testing, either as HPV and cytology cotesting, or as HPV testing alone.^{1,2} Testing HPV negative permits safe extension of screening intervals. However, testing HPV positive alone does not necessarily require colposcopy referral and/or treatment; additional tests or predictive factors are needed to estimate precancer risk and determine the next step in clinical management. The 2019 ASCCP Risk-Based Management Consensus Guidelines assess an individual's risk of precancer using combinations of past and current screening results and indicate recommended management accordingly, with the goal of maximizing benefits (i.e., cervical cancer prevention) and minimizing harms (e.g., unnecessary referrals to colposcopy and treatment).¹ The clinical actions range from intensified surveillance for women at a slightly elevated 5-year risk of cervical intraepithelial neoplasia grade 3 or higher (CIN 3+), to colposcopic referral, to possible treatment, or even to preferred treatment for very high immediate risk.

Data from large observational studies and regulatory trials were used to generate precise precancer risk estimates for the many possible combinations of test results and cofactors. An essential step was to assess the importance of each risk predictor considered for risk estimation. Specifically, management guidelines for HPV-positive women needed to address which factors have sufficient impact on the estimated risk of precancer to warrant routine consideration in management for each clinical encounter.³ Human papillomavirus infection is the necessary cause of cervical cancer, and both HPV infection and abnormal cytology results are strong predictors of elevated immediate risk of precancer and cancer. Several factors have also been found to be associated with cervical cancer, including HPV genotype, genetic and immunologic host factors, and other factors such as smoking status, long-term contraceptive use, parity, and sexually transmitted infections. Some factors may elevate the risk of cancer up to approximately twofold.^{1,4–13} In the context of the 2019 guidelines, this analysis aimed to assess whether in the setting of known HPV infection and cytology results, some of the previously evaluated cofactors and potential risk modifiers for cervical precancer warrant routine consideration in clinical management of patients with HPV-positive screening test results.

METHODS

Study Design and Population

This was a retrospective cohort analysis using data from HPV cotesting of a large set of residual specimens after HPV testing

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The National Cancer Institute (including all NCI-affiliated authors) receives cervical screening results at reduced or no cost from commercial research partners (Qiagen, Roche, BD, MobileODT, Arbor Vita) for independent evaluations of screening methods and strategies. A.-B.M. is a Merck and GSK, Advisory Board member. P.E.C. has received human papillomavirus tests and assays at a reduced or no cost from Roche, Becton Dickinson, Arbor Vita Corporation, and Cepheid for research. A.H. has received reagents for free from Roche, Denmark, for an unrelated study. The other authors have declared they have no conflicts of interest.

The field effort was a collaboration of the National Cancer Institute and the Kaiser Permanente Northern California and was supported in part by the intramural program of the NCI. The NCI has received HPV and cytology test results at no cost from Roche Molecular Systems, Qiagen, and BD Diagnostics for independent evaluations of these technologies.

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This study was approved by institutional review boards at the National Cancer Institute and Kaiser Permanente Northern California.

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conducted at the Kaiser Permanente Northern California (KPNC), with supplemental HPV typing directed by the National Cancer Institute. This study was approved by institutional review boards at the National Cancer Institute and KPNC. Written consent was obtained from participants. At the KPNC, women were tested by Hybrid Capture 2 (HC2) for the group of high-risk genotypes of HPV (as a pool without genotyping) as a cotest with cytology in women 30 years and older beginning in 2003.^{14,15} Women younger than 30 years, who had HC2 results mainly for ASC-US triage, were not comparable with women 30 years and older undergoing routine screening with HPV/cytology cotesting and were not considered for this analysis.

The HPV Persistence and Progression Cohort (PaP Cohort) was created by banking residual, discarded cervical specimens, collected into specimen transport medium (STM; Qiagen), from women tested by HC2. Women were contacted, and 92% agreed to specimen storage and research testing. The study collection from the enrollment phase of the PaP Cohort (January 2007–January 2011) consisted of a group of 45,000 HPV-positive residual specimens (approximately 80% of HC2-positive specimens from KPNC cotesting during that time). Women were followed prospectively

through 2017 or until they left the KPNC system. The core collection used for the present analysis was drawn from nearly 30,000 specimens from women 30 years or older who tested positive by HC2 during routine screening, with a small number of HC2-negative specimens included as negative controls. Given the interest in evaluating progression of type-specific infection to cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ, or cancers (CIN 3+), we restricted this analysis to women with a positive HPV test result by HC2 test at baseline and information on HPV typing. Specifically, this analysis used data from 16,094 women with positive screening HC2 results who were chosen by stratified random sampling in previously published investigations for masked HPV typing to distinguish the individual carcinogenic HPV risk group(s) present.^{14,15} Specimens were processed at BD Diagnostics (Sparks MD) by the Onclarity assay, or at Roche Molecular Systems (Pleasanton CA) by cobas and/or Linear Array (the latter intended for research and not Food and Drug Administration approved for clinical use). Fewer than 10% were HPV typed using research assays, either MY09-MY11 with dot-blot typing (R. Burk MY09-MY11 PCR) or Linear Array (F. Coutlee lab).

TABLE 1. Sociodemographic, Behavioral, and Clinical Characteristics of HPV-Infected (or HPV-Positive) Women in the Sample

		Total		CIN 3+	
		<i>n</i>	%	<i>n</i>	%
Age, y	30–44	10,390	64.7	1,440	9.0
	45–54	3,341	20.8	340	2.1
	55–65	2,318	14.4	206	8.9
Race/ethnicity	Non-Hispanic White	8,268	49.4	1,224	7.6
	Hispanic	3,590	21.5	468	0.3
	Non-Hispanic African American	1,638	9.8	144	0.1
	Non-Hispanic Asian/Pacific Islander	3,047	18.2	437	0.3
	Multiracial	189	1.1	15	0.0
Neighborhood income ^a	Low	1,969	11.3	258	0.2
	Middle	5,559	32.0	745	0.5
	High	9,858	56.7	1,313	8.2
Smoking	Never	12,408	74.0	1,593	9.9
	Former	2,356	14.1	322	0.2
	Current	2,000	11.9	321	0.2
Duration of OCP use, y ^b	0	9,864	55.9	1,268	7.9
	1–6	6,837	38.7	932	5.8
	7–10	697	3.9	117	4.3
	10+	260	1.5	40	0.0
Duration of DMPA use, y ^b	0	16,382	91.6	2,177	13.6
	1–6	1,466	8.2	202	1.3
	7+	40	0.2	4	0.0
Cytology	NILM	8,077	46.5	613	3.8
	ASC-US/LSIL	7,403	42.6	922	5.7
	ASC-H/AGC	992	5.7	329	2.0
	HSIL+	894	5.1	465	2.9
HPV risk group	35/39/51/56/59/66/68	5,269	34.2	226	1.4
	31/33/52/58	4,557	29.6	634	4.0
	18/45	1,732	11.3	227	1.4
	16	3,832	24.9	1,198	7.5

Note that CIN 3+ cases refer to cases diagnosed at baseline or during follow-up.

^aHigh income: ≥80% in Census Tract are >200% of poverty level. Low income: ≥20% households in Census Tract are below poverty level.

^bOral contraceptive pill packs and DMPA injections prescribed were categorized with their equivalent in number of years used (never users: 0 packs or injections, 1–6 years: 1–83 packs or 1–28 injections, 7–9 years: 83–120 packs or ≥ 28 injections, and 10+ years: ≥120 packs).

Variables

This analysis studied the immediate risk of CIN 3+ after the baseline screening visit to determine whether, after controlling for HPV risk group and cytology results, sociodemographic cofactors changed risk estimates sufficiently to merit different clinical actions. Infection with a specific HPV genotype was defined hierarchically to match currently available HPV DNA assays (HPV 16, else HPV 18, else 45, else 31/33/52/58, or 35/39/51/56/59/66/68). Patients were assigned to the HPV risk group associated with their first detected infection.

Cytology results included NILM (negative for intraepithelial lesions or malignancy), ASC-US (atypical squamous cells of undetermined significance), LSIL (low-grade squamous intraepithelial lesion), ASC-H (atypical squamous cells of undetermined significance—cannot exclude high-grade squamous intraepithelial lesion [HSIL]), AGC (atypical glandular cells), HSIL, adeno-

carcinoma in situ, and cancer. Cytology results were then grouped by precancer risk into 4 categories for analysis: (1) NILM, (2) ASC-US or LSIL, (3) ASC-H or AGC, and (4) HSIL, adenocarcinoma in situ, or cancer (HSIL+).^{14,15}

Potential sociodemographic and behavioral cofactors selected were based on the previous literature. Age was categorized in 5-year categories from 30 to 65 years. Race/ethnicity was categorized using medical record data as non-Hispanic White, Hispanic, non-Hispanic Black, non-Hispanic Asian/Pacific Islander, and multiracial/other. Neighborhood income was categorized based on census tract: high ($\geq 80\%$ in Census tract were $>200\%$ of poverty level) low ($\geq 20\%$ households in Census tract were below poverty level), and middle (incomes between high and low). Smoking was categorized as never, former, and current. Hormonal contraceptive use was determined by the total number of oral contraceptive pill (OCP) packs or depot medroxyprogesterone acetate (DMPA) injections dispensed in the years before and including enrollment

TABLE 2. Univariate Measures of Association (OR) for Prevalent CIN 3+ Between Sociodemographic and Clinical Characteristics

		Prevalent CIN 3+		
		OR	95% CI	
Age, y	30–34	1.0	—	—
	35–39	0.9	0.8	1.1
	40–44	1.0	0.8	1.1
	45–49	0.8	0.7	0.9
	50–54	0.6	0.5	0.7
	55–59	0.5	0.4	0.6
	60–65	0.7	0.6	0.8
Race/ethnicity	Non-Hispanic White	1.0	—	—
	Hispanic	0.9	0.8	1.0
	Non-Hispanic African American	0.6	0.5	0.7
	Non-Hispanic Asian/Pacific Islander	0.9	0.8	1.0
	Multiracial	0.6	0.4	0.8
Income ^a	High income	1.0	—	—
	Low income	1.0	0.9	1.1
	Middle income	1.0	0.9	1.1
Smoking	Never	1.0	—	—
	Former	1.0	0.9	1.1
	Current	1.4	1.3	1.6
Duration of OCP use, y ^b	0	1.0	—	—
	1–6	1.1	1.0	1.2
	7–10	1.1	0.9	1.3
	10+	1.3	0.9	1.6
Duration of DMPA use, y ^b	0	1.0	—	—
	1–6	1.2	1.0	1.3
	7+	1.0	0.2	1.9
Cytology	NILM	1.0	—	—
	ASC-US/LSIL	5.3	4.6	6.0
	ASC-H	20.5	16.7	24.2
	AGC	12.2	8.9	15.5
	HSIL+	67.6	54.6	80.7
HPV risk group	35/39/51/56/59/66/68	1.0	—	—
	31/33/52/58	3.0	2.7	3.4
	18/45	2.7	2.3	3.1
	16	8.2	7.3	9.0

^aHigh income: $\geq 80\%$ in Census Tract are $>200\%$ of poverty level. Low income: $\geq 20\%$ households in Census Tract are below poverty level.

^bOral contraceptive pill packs and DMPA injections prescribed were categorized with their equivalent in number of years used (never users: 0 packs or injections, 1–6 years: 1–83 packs or 1–28 injections, 7–9 years: 83–120 packs or ≥ 28 injections, and 10+ years: ≥ 120 packs).

date, categorized as a proxy for duration of use: never (0 packs or injections prescribed), 1–6 years (1–83 one-month packs or 1–28 three-month injections), 7–9 years (83–120 one-month packs or ≥ 28 three-month injections), and 10+ years (≥ 120 one-month packs; no DMPA users had >10 years of use recorded).

Statistical Analysis

We compiled descriptive statistics for the study population as a whole and for women with CIN 3+. Sample-weighted logistic-Cox models were used to combine risk of prevalent CIN 3+ estimated by odds ratios (ORs) with risk of incident CIN 3+ estimated by hazard ratios (HRs). To assess the impact of each factor independently, univariate cumulative risks combining OR at baseline and HR were shown for years 1, 3, and 5. Bivariate cumulative risks combined the main predictive variables of HPV genotype and cytology. To consider the clinical utility of additional predictor variables, mul-

tivariate analyses considered as third variables those cofactors found to be significant in univariate models. Cofactors were dichotomized by clinical relevance for inclusion in the final model. We chose immediate risk among HPV-positive women for the focus of this analysis as the primary outcome of interest was whether sociodemographic variables would change indications for colposcopic referrals. We report 95% CIs when informative. Multiple comparisons corrections were not used in the variable selection because the analysis is explorative rather than confirmative.

RESULTS

As shown in Table 1, the women studied in this subset of HPV-positive KPNC members had a median age of 37 years. Nearly half (49.4%) were non-Hispanic White, 21.5% were Hispanic, 18.2% were Asian, and 9.8% were non-Hispanic Black. Most (88.7%) lived

TABLE 3. Univariate Cumulative Risk of CIN 3+ Among HPV-Positive Women by Sociodemographic and Clinical Characteristics

		Cumulative Risk									
		1 y		95% CI		3 y		95% CI		5 y	
Age	30–34	10.9	10.2	11.6	13	12.2	13.8	13.8	12.9	14.7	
	35–39	10.4	9.6	11.3	12	11	12.9	12.8	11.8	13.9	
	40–44	10.4	9.4	11.3	12.3	11.2	13.4	13.2	12	14.5	
	45–49	8.7	7.8	9.7	10.1	9	11.2	10.9	9.7	12.2	
	50–54	6.7	5.7	7.6	7.9	6.8	9	9	7.8	10.3	
	55–59	5.7	4.7	6.6	6.8	5.7	8	7.9	6.6	9.3	
	60–65	7.4	6.1	8.6	8.4	6.9	9.9	9.3	7.7	10.9	
Race/ethnicity	Non-Hispanic White	10.3	9.8	10.8	12.2	11.6	12.9	13.6	12.8	14.4	
	Hispanic	9.3	8.6	10.1	10.6	9.8	11.5	11.5	10.5	12.4	
	Non-Hispanic African American	6.1	5.2	7	6.7	5.7	7.6	7.3	6.3	8.4	
	Non-Hispanic Asian/Pacific Islander	9.9	9	10.7	12.1	11	13.1	13.1	11.9	14.2	
	Multiracial	6.8	4.1	9.5	7.2	4.3	10.1	7.2	4.3	10.1	
Income ^a	Low income	9.5	8.4	10.5	10.8	9.6	12	11.6	10.3	12.9	
	Middle income	9.5	8.9	10.1	10.9	10.2	11.7	11.8	11	12.6	
	High income	9.5	9	9.9	11.2	10.7	11.8	12.6	11.9	13.3	
Smoking	Never	9.2	8.8	9.6	10.7	10.2	11.1	12.1	11.5	12.7	
	Former	9.1	8.1	10	11	9.8	12.1	12.1	10.8	13.4	
	Current	12.1	11	13.3	13.8	12.4	15.1	14.5	13.1	15.9	
Duration of OCP use, y ^b	0	9.6	9.1	10.1	11.1	10.6	11.7	12.3	11.7	13	
	1–6	9.2	8.6	9.8	10.8	10.2	11.5	12	11.2	12.8	
	7–10	9.6	7.8	11.3	12.4	10.2	14.7	13.4	11	15.8	
	10+	11.2	8	14.4	13.1	9.4	16.8	13.5	9.7	17.4	
Duration of DMPA use, y ^b	0	9.5	9.1	9.8	11.0	10.6	11.4	12.4	11.9	13.0	
	1–6	10.0	8.1	11.8	12.2	9.9	14.4	13.4	10.9	15.9	
	7+	9.3	7.6	11.0	10.5	8.6	12.5	11.6	9.5	13.7	
Cytology	NILM	2.9	2.6	3.2	4.7	4.3	5.1	6.0	5.4	6.6	
	ASC-US/LSIL	11.0	10.4	11.6	12.5	11.9	13.2	13.4	12.6	14.2	
	ASC-H/AGC	27.6	24.9	30.3	30.6	27.5	33.7	31.3	28.2	34.4	
	HSIL+	64.3	60.4	68.1	65.2	61.3	69.0	66.0	62.2	69.9	
HPV risk group	35/39/51/56/59/66/68	4.2	3.7	4.9	4.2	5.0	4.4	5.2	4.6	6.0	
	31/33/52/58	7.2	6.4	8.1	7.2	9.0	8.1	9.4	8.5	10.4	
	45	5.3	3.7	7.6	5.3	6.9	5.3	7.3	5.6	9.5	
	18	9.2	7.6	11.1	9.2	10.7	9.0	11.5	9.6	13.6	
	16	16.9	15.5	18.5	16.9	20.8	19.2	21.6	19.9	23.4	

^aHigh income: $\geq 80\%$ in Census Tract are $>200\%$ of poverty level. Low income: $\geq 20\%$ households in Census Tract are below poverty level.

^bOral contraceptive pill packs and DMPA injections prescribed were categorized with their equivalent in number of years used (never users: 0 packs or injections, 1–6 years: 1–83 packs or 1–28 injections, 7–9 years: 83–120 packs or ≥ 28 injections, and 10+ years: ≥ 120 packs).

in middle- or high-income neighborhoods, and 88.9% were non-smokers. Most women (55.9%) had no documented prescriptions for oral contraceptive pills, and 91.6% had no documented prescriptions for depo-medroxyprogesterone acetate. Most (53.5%) of this sample of HPV-positive women had concurrently abnormal cytology; approximately 80% of cytology abnormalities were low grade (ASC-US or LSIL) and 20% were high grade (ASC-H, AGC, HSIL or higher).

Table 2 describes univariate measures of association for prevalent CIN 3+. In this well-screened population, ages 50–65 years were associated with lower CIN 3+ prevalences than age 30–34 years (ORs = 0.5–0.7, 95% CI = 0.5–0.8). Non-Hispanic Black and multiracial women had slightly lower CIN 3+ prevalence than non-Hispanic White women (non-Hispanic Black OR = 0.6, 95% CI = 0.5–0.7; multiracial OR = 0.4, 95% CI = 0.4–0.8). Income, smoking status, and use of hormonal contraception were not associated with prevalent CIN 3+ in univariate analyses. Cytology results and HPV risk group were most strongly associated with CIN 3+, with a current HSIL cytology having a 67.6-fold increased risk of prevalent CIN 3+ compared with a normal cytology (95% CI = 54.6–80.7), and HPV 16 having an 8.2-fold increased risk of prevalent CIN 3+ compared with the lowest risk subtypes (95% CI = 9.7–17.2). Table 3 illustrates the cumulative risk of developing CIN 3+ over 5 years by different characteristics. Most CIN 3+ was diagnosed within the first year, indicating prevalent disease. For most factors, cumulative absolute CIN 3+ risks increased by approximately 2%–4% between years 1 and 5. The greatest increase in cumulative CIN 3+ risk was seen for HPV 16 infections, increasing from 16.9% at year 1 to 21.6% at year 5.

Table 4 describes the immediate risk of CIN 3+ by combinations of HPV risk group and cytology. For the lowest risk types (35/39/51/56/59/66/68), immediate risk ranged from 1.1% for NILM cytology to 31% for HSIL+ cytology. For the second risk group (31/33/52/58), immediate risk ranged from 2.5% for NILM cytology to 41.0% for HSIL+ cytology. For HPV 18 and 45, immediate risks ranged from less than 3% for NILM cytology to approximately 40% for HSIL+ cytology. Again, HPV 16 was

associated with the highest risks: 6% for NILM cytology and 62% for HSIL+ cytology.

Table 5 describes the multivariate analysis of the cumulative risk of CIN 3+ by HPV risk group, cytology, and selected sociodemographic cofactors, considering one additional sociodemographic cofactor at a time. The goal of the analysis was to determine whether these factors, when considered in the context of HPV and cytology results, would change management recommendations as defined by clinical action thresholds.¹ The 2019 ASCCP Risk-Based Management Consensus Guidelines defined clinical action thresholds that determined management recommendations. Specifically, an immediate CIN 3+ risk of 4%–24% leads to a recommendation of colposcopy, a risk of 25%–59% leads to a recommendation of colposcopy or treatment, and a risk of 60% or higher leads to a recommendation of treatment. After accounting for HPV risk group and cytology status, sociodemographic variables did not substantially impact risk estimates. In no case did age, race, smoking status, or oral contraceptive use lead to a different clinical recommendation than would be recommended by HPV type and cytology result alone.

DISCUSSION

As previously shown, the risk of prevalent or incident CIN 3+ was mainly determined by HPV typing and cytology results. In addition, as previously observed, age, race/ethnicity, long-term oral contraceptive use, and current smoking were significant albeit much weaker stratifiers of risk. The 2019 Risk-Based Management Consensus Guidelines describe 6 possible clinical actions (return in 5 years, return in 3 years, return in 1 year, colposcopy recommended, expedited treatment or colposcopy acceptable, or expedited treatment preferred) with defined risk thresholds determined by a national consensus.¹ These data demonstrate that HPV risk group and cytology results were clinically important risk factors. High-grade cytology increased the immediate risk of CIN 3+ by up to tenfold, and high-risk HPV types increased the immediate risk of CIN 3+ up to fivefold. However, after considering cytology

TABLE 4. Bivariate Cumulative Risk of CIN 3+ by Combinations of HPV Risk Group and Cytology

HPV risk group (hierarchical)	Cytology	<i>n</i>	%	Immediate CIN 3+ risk	95% CI	
35/39/51/56/59/66/68	NILM	5,343	17	1.1	0.66	1.5
	ASC-US/LSIL	4,175	13	3.1	2.5	3.6
	ASC-H/AGC	322	1	11	7.1	14
	HSIL+	259	0.82	31	25	37
31/33/52/58	NILM	5,307	17	2.5	1.9	3.1
	ASC-US/LSIL	4,015	13	5	4.3	5.8
	ASC-H/AGC	509	1.6	16	13	20
	HSIL+	449	1.4	41	36	46
45	NILM	1,163	3.7	0	0	0.002
	ASC-US/LSIL	621	2	3.6	2	5.2
	ASC-H/AGC	124	0.39	17	10	25
	HSIL+	86	0.27	42	29	54
18	NILM	1,309	4.1	3.8	2.4	5.2
	ASC-US/LSIL	954	3	5	3.5	6.6
	ASC-H/AGC	202	0.64	23	17	30
	HSIL+	125	0.39	37	27	47
16	NILM	3,149	9.9	6	4.9	7.2
	ASC-US/LSIL	2,675	8.4	11	9.7	12
	ASC-H/AGC	462	1.5	30	25	35
	HSIL+	476	1.5	62	57	67

TABLE 5. Multivariate Immediate Risk of CIN 3+ by HPV Risk Group, Cytology, and Selected Cofactors

HPV risk group (hierarchical)	Cytology	Age		Race/ethnicity		Smoking		OCP, y	
		Age group	CIN 3+ immediate Risk	Race/ethnicity group	CIN 3+ immediate risk	Smoking status	Immediate CIN 3+ risk	OCP, y	CIN 3+ immediate risk
35/39/51/56/ 59/66/68	NILM	30-44	11	1.3 (0.73, 1.8)	White/Hispanic/Asian/other	16	1.1 (0.67, 1.6)	0-6	16
		45-65	6.4	0.76 (0.39, 1.1)	Black ^b	1.5	0.84 (0.28, 1.4)	7+	0.97
	ASC-US/LSIL	30-44	8.9	3.5 (2.8, 4.3)	White/Hispanic/Asian/other	12	3.1 (2.5, 3.7)	0-6	12
		45-65	4.3	2.1 (1.5, 2.8)	Black	0.97	2.3 (1.1, 3.6)	7+	0.77
	ASC-H/AGC	30-44	0.6	12 (7.6, 17)	White/Hispanic/Asian/other	0.95	10 (6.6, 14)	0-6	0.89
		45-65	0.4	7.6 (4.3, 11)	Black	0.04	7.9 (3, 13)	7+	0.1
	HSIL+	30-44	0.55	34 (26, 41)	White/Hispanic/Asian/other	0.71	31 (24, 38)	0-6	0.81
		45-65	0.28	23 (16, 30)	Black	0.12	25 (14, 36)	7+	0.02
	NILM	30-44	11	2.7 (2, 3.5)	White/Hispanic/Asian/other	15	2.4 (1.7, 3.1)	0-6	16
		45-65	5.9	2 (1.4, 2.5)	Black	1.8	1.9 (1.1, 2.6)	7+	1
31/33/52/58	ASC-US/LSIL	30-44	9	5.5 (4.6, 6.4)	White/Hispanic/Asian/other	12	5.1 (4.4, 5.9)	0-6	12
		45-65	3.5	4 (3, 4.9)	Black	1	4 (2.4, 5.6)	7+	0.79
	ASC-H/AGC	30-44	1.1	18 (14, 22)	White/Hispanic/Asian/other	1.5	17 (13, 21)	0-6	1.6
		45-65	0.53	13 (9.6, 17)	Black	0.14	13 (7.7, 19)	7+	0.07
	HSIL+	30-44	0.98	42 (36, 48)	White/Hispanic/Asian/other	1.3	41 (35, 46)	0-6	1.4
		45-65	0.42	34 (28, 41)	Black	0.15	34 (25, 44)	7+	0.05
	NILM	30-44	2.4	0.26 (0, 1.5)	White/Hispanic/Asian/other	3.3	0 (0, 0.01)	0-6	3.5
		45-65	1.2	0.22 (0, 1.3)	Black	0.38	0 (0, 0.01)	7+	0.17
	ASC-US/LSIL	30-44	1.3	3.8 (1.9, 5.7)	White/Hispanic/Asian/other	1.8	3.7 (2, 5.4)	0-6	1.9
		45-65	0.6	3.2 (1.1, 5.4)	Black	0.16	4 (0, 8.1)	7+	0.07
45	ASC-H/AGC	30-44	0.21	18 (8.2, 28)	White/Hispanic/Asian/other	0.34	17 (8.4, 25)	0-6	0.35
		45-65	0.16	15 (6.8, 24)	African	0.04	18 (3, 33)	7+	0.03
	HSIL+	30-44	0.22	41 (27, 55)	White/Hispanic/Asian/other	0.25	40 (26, 54)	0-6	0.28
		45-65	0.07	37 (19, 55)	Black	0.04	42 (17, 67)	7+	0
	NILM	30-44	2.7	4.1 (2.1, 6.1)	White/Hispanic/Asian/other	3.7	4.1 (2.5, 5.6)	0-6	3.9
		45-65	1.4	2.8 (1.5, 4.1)	Black	0.41	2.3 (0.18, 4.5)	7+	0.2
	ASC-US/LSIL	30-44	2.1	5.3 (3.5, 7.1)	White/Hispanic/Asian/other	2.7	5 (3.4, 6.6)	0-6	2.8
		45-65	0.84	3.6 (1.9, 5.3)	Black	0.25	2.9 (0.25, 5.5)	7+	0.14
	ASC-H/AGC	30-44	0.4	25 (17, 34)	White/Hispanic/Asian/other	0.6	23 (16, 31)	0-6	0.58
		45-65	0.21	18 (10, 27)	Black	0.01	15 (1.9, 27)	7+	0.03
18	HSIL+	30-44	0.23	41 (29, 54)	White/Hispanic/Asian/other	0.34	40 (28, 51)	0-6	0.37
		45-65	0.15	32 (20, 44)	Black	0.04	27 (8.5, 46)	7+	0.01

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16	NILM	30–44	7.1	6.4 (5.1, 7.7)	White/Hispanic/Asian/other	9.3	6.3 (5.1, 7.6)	Never/former	9	5.9 (4.7, 7.1)	0–6	9.4	6.1 (4.9, 7.3)
		45–65	2.9	5.6 (4.3, 6.9)	Black	0.72	4.2 (2.3, 6.1)	Current	0.94	7.5 (5.2, 9.8)	7+	0.6	7 (4, 10)
	ASC-US/LSIL	30–44	6.5	11 (9.7, 13)	White/Hispanic/Asian/other	7.9	11 (9.7, 13)	Never/former	7.3	11 (9.2, 12)	0–6	7.8	11 (9.4, 12)
		45–65	1.8	9.9 (7.9, 12)	Black	0.45	7.6 (4.4, 11)	Current	1.2	13 (10, 17)	7+	0.52	12 (8, 17)
	ASC-H/AGC	30–44	1	31 (25, 36)	White/Hispanic/Asian/other	1.3	31 (25, 36)	Never/former	1.2	29 (24, 34)	0–6	1.3	30 (25, 35)
		45–65	0.39	28 (22, 34)	Black	0.1	22 (14, 31)	Current	0.26	35 (27, 42)	7+	0.09	33 (23, 43)
	HSIL+	30–44	1.2	61 (55, 67)	White/Hispanic/Asian/other	1.4	61 (55, 67)	Never/former	1.1	60 (54, 66)	0–6	1.5	60 (54, 66)
		45–65	0.34	58 (50, 65)	Black	0.14	50 (39, 62)	Current	0.36	66 (59, 74)	7+	0.05	64 (53, 74)

^aDistribution refers to the % of column total that is represented in each cell.

^bNon-Hispanic Black.

result and HPV risk group, the additional sociodemographic factors considered in this study did not raise risk sufficiently to exceed any of these risk thresholds and lead to a change in management. These findings support the inclusion of current and past HPV and cytology test results, and the exclusion of sociodemographic factors in existing risk estimates used in the 2019 Risk-Based Management Consensus Guidelines.^{1,16}

As with the ASCCP 2019 Risk-Based Management Consensus Guidelines, we chose CIN 3+ as the surrogate endpoint for screening.^{1,17,18} Analyses used in the 2019 ASCCP Risk-Based Management Consensus Guidelines showed that using CIN 2+ yielded similar conclusions related to the limited clinical significance of sociodemographic factors on risk estimates.^{16,19} Specifically, ancillary analyses using the same methods to estimate risk of CIN 2+ suggest that the choice of the surrogate endpoint may change the magnitude of the effects and the hierarchy of HPV risk groups but not the direction of the associations of cofactors studied in this article (data not shown).

This study has several limitations. The study population consisted of women receiving care at the KPNC and typically has high rates of screening and follow-up of abnormal results. Previous literature showed that screened populations in other settings have similar patterns of risk stratification when considering cytology and HPV test results; unscreened populations have higher risks.²⁰ History of abnormal screening is important as noted in the guidelines and as further analyzed in separate articles focused on previous screening and history of high-grade results.²¹ Human papillomavirus vaccination is also relevant in lowering the risk of CIN 3+ and will need to be considered in triage strategies as individuals vaccinated before the onset of sexual activity age into cervical cancer screening.²² In addition, age of first sexual intercourse and number of partners have also been associated with cervical cancer. These were not assessed because they often are not reliably elicited or documented during medical care. We acknowledge that this analysis included few women with a history of smoking, long-term hormonal contraceptive use (>10 years), high parity (>4 births), and sexually transmitted infections, which limits our ability to draw meaningful conclusions related to these factors.^{8–10,13,22–25} Because smoking is associated not only with cervical cancer but with a variety of other negative health consequences, assessing for smoking and encouraging smoking cessation are warranted. Variables related to medications (OCP and DMPA) were based on prescriptions issued at the KPNC, regardless of whether or when women took them, and do not include prescriptions obtained in other health systems. We also did not assess body mass index as a cofactor in this analysis, as a previous large study within the full KPNC population indicated a lower risk of precancer, but higher risk of cancer among overweight and obese women compared with those with normal body mass index, likely due to underdiagnosis of precancer.²⁶ Of note, HPV typing in the 2019 guidelines is limited to HPV 16 and 18. These results indicate that further risk stratification by HPV risk group may be helpful, and the inclusion of additional types will be addressed in future guideline revision.

The 2019 ASCCP Risk-Based Management Consensus Guidelines currently use risk estimation that include current HPV and cytology test results, as well as past history.¹ This study aimed to assess whether certain sociodemographic cofactors, including age, race/ethnicity, smoking status, and oral contraceptive use meaningfully changed risk estimates that would affect clinical management based on the clinical action thresholds of the 2019 ASCCP Risk-Based Management Consensus Guidelines. Our results suggest that including these variables would add complexity without additional risk discrimination. Therefore, these results support continued use of the current risk estimates based on screening history.¹⁶

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