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Five-year risk of CIN3+ and cervical cancer for women with HPV-positive and HPV-negative high-grade Pap results

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Abstract

Objective—High-grade Pap results (e.g., AGC, ASC-H, and HSIL) predict high cancer risks, resulting in referral to colposcopy without HPV triage. However, new guidelines recommending cotesting for women 30 and older imply that clinicians will often receive the HPV test result concurrently for high-grade Pap results. We examined whether HPV testing provides useful risk stratification in this context.

Methods—From a cohort of 965,360 women age 30–64 undergoing cotesting at Kaiser Permanente Northern California, we estimated 5-year risks of cervical cancer and CIN3+ for AGC (2,074 women), ASC-H (1,647 women), and HSIL (2,019 women) according to HPV test results.

Results—HPV positivity of AGC Pap results was 25% and decreased with age (30–34: 44% vs. 60–64: 17%, $p<0.0001$), while HPV-positivity of ASC-H and HSIL were much higher (71% and 94% respectively) and decreased less with age. Even for these high-grade Pap results, 5-year CIN3+ risks differed substantially between HPV-positive and HPV-negative women (AGC: 33% vs. 0.93%, $p<0.0001$; ASC-H: 25% vs. 3.5%, $p<0.0001$; HSIL: 49% vs. 30%, $p=0.006$). However, except for AGC, cervical cancer risks differed less between HPV-positive and HPV-negative

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Conflicts of Interest: Dr. Schiffman and Dr. Gage report working with Qiagen, Inc. on independent evaluations of non-commercial uses of CareHPV (a low-cost HPV test for low-resource regions) for which they have received research reagents and technical aid from Qiagen at no cost. They have received free testing of specimens for research from Roche. Dr. Castle has received compensation for serving as a member of a Data and Safety Monitoring Board for HPV vaccines for Merck. Dr. Castle has received HPV tests and testing for research at a reduced or no cost from Qiagen, Roche, MTM, and Norchip. Dr. Castle is a paid consultant for BD, GE Healthcare, and Cepheid, and has received a speaker honorarium from Roche. No other authors report any conflicts of interest.

women (AGC: 9.0% vs. 0.37%, $p<0.0001$; ASC-H: 2.5% vs. 2.1%, $p=0.8$; HSIL: 6.6% vs. 6.8%, $p=0.7$).

Conclusions—The risks of CIN3+ for HPV-negative high-grade Pap results were lower than for HPV-positive high-grade Pap results, especially for AGC. However, by the principle of “equal management of equal risks”, all HPV-negative high-grade Pap results had cancer risks high enough to warrant colposcopy, confirming that there is no current role for HPV triage of high-grade Pap results.

Keywords

Human Papillomavirus (HPV); cancer prevention; baseline; cervical intraepithelial neoplasia (CIN); Hybrid Capture 2 (HC2); screening guidelines; HSIL; AGC; ASC-H

Introduction

The great majority of cervical Pap abnormalities are minor. Only a few elicit the most clinical concern and suggest the possibility of cancer or its immediate precursors. These high grade results include the squamous cell epithelial cell abnormalities: atypical squamous cells, cannot rule out HSIL (ASC-H), high-grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SCC); and the glandular cell epithelial cell abnormalities: atypical glandular cells (AGC), adenocarcinoma *in situ* (AIS), and adenocarcinoma. ASC-H, HGSIL, SCC, AGC, AIS, and adenocarcinoma each individually accounts for 0.5% of Pap results in the US (1).

Virtually all women with cytologic HSIL, SCC, AIS, and adenocarcinoma test positive for human papillomavirus (HPV); thus, HPV testing has had no role in their management. In fact, immediate treatment is sometimes considered for women with HSIL Pap results. However, a substantial fraction of women with ASC-H and AGC are not HPV-positive. Furthermore, new guidelines recommending cotesting for women 30 and older imply that clinicians will often receive the HPV test result concurrently for high-grade Pap results. We investigate whether knowing HPV status could be clinically useful in those settings.

Because high-grade results are so uncommon, a very large clinical database is required to study their prevalences and attendant risks. Moreover, to analyze the possible role of HPV testing requires a clinical setting in which HPV testing is performed concurrent with baseline (cotesting), because reflex testing is not currently recommended for high-grade abnormalities.

Kaiser Permanente Northern California (KPNC) is a large integrated health system that has routinely performed cotesting since 2003. We evaluate CIN3+ and cancer risks following high-grade results, with consideration of cotesting, based on data from the KPNC population.

Methods

The design of our cohort study from KPNC has been described previously (2); in this report we enlarged the dataset to include all women age 30 and older entering cotesting from 2006–2010. As a result of the data expansion, we were able to analyze data from 965,360 women aged 30–64 undergoing routine screening from 2003 to 2010. For each woman, we considered as the baseline cotest the first available cotest in the age range and in the study interval. Histologic outcome information was collected on all women through December 31, 2010. The Kaiser Permanente Northern California Institutional Review Board (IRB)

approved use of the data, and the National Institutes of Health Office of Human Subjects Research deemed this study exempt from IRB review.

Pap tests were performed at KPNC regional and facility labs. HPV testing was performed at the single regional lab. Conventional Pap slides were manually reviewed following processing by the BD FocalPoint Slide Profiler (BD Diagnostics, Burlington, NC, USA) primary screening and directed quality control system, in accordance with FDA-approved protocols. Starting in 2009, KPNC transitioned to liquid-based baseline using BD SurePath (BD Diagnostics, Burlington, NC, USA). Conventional or liquid-based Pap tests are reported according to the 2001 Bethesda System (3). AIS baseline was extremely rare and the few (n=15) cases were combined with HSIL. We refer to HSIL and AIS as HSIL+ and refer to HSIL+, ASC-H, and AGC in aggregate as “high-grade Pap results”. For benchmarking, we excluded the extremely rare cases of cytologic SCC and adenocarcinoma because they imply extraordinarily high (histologic) cancer risk (4). For example, only 3 women had HPV-negative/SCC; thus, we could not examine possible HPV triage of cytologic SCC, which overall has extremely high cancer risk of 68% (4). Hybrid Capture 2 (HC2; Qiagen, Germantown, MD, USA) was used to test for high-risk HPV types according to manufacturer’s instructions.

The Permanente Medical Group (TPMG), which is the physician component of KPNC, develops Clinical Practice Guidelines for cervical cancer screening and management of abnormal tests in KPNC in partnership with the KP National Guideline Program, Care Management Institute, to support the clinical decisions of their providers. According to guidelines, women with high-grade Pap abnormalities should undergo colposcopy.

Cumulative risk of histologic CIN2+, CIN3+ (which includes AIS), or cervical cancer for each cotest result was calculated as the sum of risk at baseline test (plotted at time zero on each figure) and the incidence after baseline (4). Risk at the baseline test was the risk of CIN2+, CIN3+, or cancer for baseline or cotest results where women were referred, without further screening, to colposcopy and was estimated using logistic regression on 5-year age groups from 25–29 to 60–64, separately for each co-test result or Pap-alone result. We used Weibull survival models (5) to estimate risks over time strictly after the baseline test, among women for whom CIN2+ was not found at the baseline test. Weibull models can make smoother and more accurate risk estimates than non-parametric methods analogous to Kaplan-Meier (6) and naturally handle interval-censoring of disease outcomes between screening tests. Separate Weibull models were fit for each cotest result at baseline, with age group as a covariate. When risk was calculated for a cytology result without regard to HPV testing, we refer to those risks as “Pap-alone”.

Results

Table 1 shows the distribution of worst cervical histology diagnoses observed from 2003–2010 for high-grade Pap results for women age 30–64. Of the 3 categories of high-grade Pap results, AGC was the one most likely to lead to histologic adenocarcinoma (AGC: 1.5% (31/2074); ASC-H: 0.2% (p=0.008 vs. AGC); HSIL: 0.6% (p<0.0001 vs. AGC)). However, comparable percentages of women with each of the 3 high-grade Pap results developed AIS histology (AGC: 1.8%; ASC-H: 1.1% (p=0.1); HSIL: 1.5% (p=0.5)). AGC had by far the lowest HPV positivity of the 3 high-grade results (AGC: 25%; ASC-H: 71% (p<0.0001); HSIL: 94% (p<0.0001)).

Figure 1 shows that HPV positivity in AGC declined strongly with age (30–34: 44% vs. 60–64: 17%, p<0.0001). HPV positivity in ASC-H declined somewhat with age (30–34: 84%

vs. 60–64: 67%, $p=0.0002$), but HPV positivity in HSIL hardly varied with age (30–34: 96% vs. 60–64: 94%, $p=0.7$).

Figure 2 shows 5-year risks of CIN2+, CIN3+ and cancer for women aged 30–64. Despite the high-grade Pap abnormalities, 5-year CIN3+ risks differed between HPV-positive and HPV-negative results (AGC: 33% vs. 0.93%, $p<0.0001$; ASC-H: 25% vs. 3.5%, $p<0.0001$; HSIL: 49% vs. 30%, $p=0.006$). Five-year cancer risks also differed between women with HPV-positive and HPV-negative results for AGC (9.0% vs. 0.37%, $p<0.0001$) but not for ASC-H or HSIL (ASC-H: 2.5% vs. 2.1%, $p=0.8$; HSIL: 6.6% vs. 6.8%, $p=0.7$).

Table 2 benchmarks the risks from HPV-positive and HPV-negative high-grade Pap results to “implicit risk thresholds” that have already been established for clinical management of common screening results, as described in the Introduction to this Monograph (4). The lowest cancer risk from high-grade Pap results was HPV-negative/AGC, but this risk of 0.37% was similar to the risk for HPV-positive/ASC-US (0.41%) and greater than the LSIL cancer risk of 0.16% ($p=0.2$), each of which implies referral to colposcopy. Except for HPV-negative/AGC, all the other high-grade Pap results had significantly higher cancer risk than non-high-grade results.

Discussion

Our results from the large KPNC database confirm the substantial risk of CIN3 and cervical cancer following a Pap result of AGC, ASC-H, or HSIL. Even when the accompanying HPV test is negative, the risks remain high enough to warrant referral of high-grade Pap results to colposcopy.

Colposcopic triage aside, with routine baseline cotesting, HPV results will commonly be available even when the Pap result is high-grade. We made several interesting observations regarding the meaning of HPV testing in this context.

AGC is an uncommon glandular finding that is linked to a substantial risk of cervical adenocarcinoma and AIS, when HPV testing is positive. When HPV testing is negative, at older ages, AGC can indicate substantial risk of endometrial cancer (7). Thus, even if triage to colposcopy is not possible, HPV testing of AGC provides some risk stratification and suggests the anatomical site at risk. For cervical neoplasia, the 5-year risk *differences* between HPV-positive and HPV-negative/AGC (CIN2+: 42%; CIN3+: 32%; Cancer: 8.7%) are larger than for any other Pap result. Apart from rare SCC Pap results, HPV-positive/AGC had the highest cervical cancer risk of any cotest result but HPV-negative/AGC had far lower cervical cancer risk. These risk differences are larger than the 5-year risk differences between HPV-positive and HPV-negative/ASCUS, which motivate HPV triage of ASCUS (CIN2+: 17%; CIN3+: 6.4%; Cancer: 0.35%) (8). Nonetheless, the risk of cancer in HPV-negative/AGC, while far lower than that of HPV-positive/AGC, was comparable to that for HPV-positive/ASCUS and somewhat higher than that for LSIL Pap results alone (without consideration of HPV test results); women with either are currently referred to colposcopy. Thus, the salient difference between managements of AGC and ASC-US is the following: even when HPV testing is negative for AGC, the risk remains too large to defer colposcopy.

ASC-H is an equivocal Pap interpretation, in which the differential diagnosis is between a negative Pap and HSIL. The HPV positivity rate is higher than for ASC-US or AGC, but lower than for HSIL. The 5-year risk differences between HPV-positive and HPV-negative/ASC-H are again larger than those for ASC-US (CIN2+: 34%; CIN3+: 21%) except for Cancer (0.40%). Nonetheless, despite the strong risk stratification, the 5-year risk following HPV-negative/ASC-H is too high to defer colposcopy.

HSIL is almost always HPV-positive; thus, HPV-negative/HSIL is a discordant cotest result. While the HPV test can sometimes indicate that the HSIL is a false positive, or caused by an HPV type of low cancer potential, it is also possible that the HPV test is in error, as indicated by the high risks of CIN2+, CIN3+, and cancer following a HPV-negative/HSIL. Thus, HPV triage has virtually no clinical value for HSIL.

The current analysis focused on the risks following HPV-negative/high-grade Pap test baseline cotest results. But these data also highlight that the risks of CIN3+ and cancer for HSIL, and possibly for HPV-positive/AGC and HPV-positive/ASC-H, are sufficiently great that they merit serious concern. Separate articles address the issue of the treatment of high-grade Pap abnormalities, when histology confirms CIN2+ (9) or does not (10).

In passing, we noted that AGC Pap results, particularly HPV-positive/AGC, predicts an especially elevated risk of histologic adenocarcinoma but is relatively less predictive of histologic AIS. In the KPNC data, the AIS:adenocarcinoma ratio following HPV-positive/AGC was only about 1:1, lower than the ratio for other high-grade Pap results (ASC-H: 5:1; HSIL: 2.5:1), and much lower than the corresponding CIN3:squamous cancer ratios. This might be an indication that histologic AIS is difficult to find, even when baseline data suggest that there is a glandular lesion, i.e., the glandular vs. squamous distinction in Pap tests did not lead to more identification of histologic AIS. The precursors to histologic adenocarcinoma remain less well established than for SCC.

Our very large dataset permitted a careful look at high-grade Pap and HPV cotesting. However, we were limited by the age range of the routinely cotested population (ages 30–64). The median ages of HSIL, CIN2, and CIN3 in well-screened populations like KPNC is only slightly over 30. Our analysis, therefore, does not comprehensively cover the entire peak of high-grade Pap and histologic lesions, although the earlier high-grade lesions typically take a number of years to become invasive. For unclear reasons, some younger women with high-grade results were HPV tested; HPV testing of high-grade abnormalities in women aged 25–29 showed HPV-positive and HPV-negative risks very similar to those among women aged 30–34 (data not shown).

In conclusion, when HPV test results are available for women with high-grade Pap results, as occurs in routine cotesting, the HPV data do stratify risk, especially for AGC. However, the risks of CIN3+ and cancer for HPV-negative women are too high to affect management, i.e., to defer colposcopy. On the other extreme, the risks among women with HSIL and HPV-positive AGC are high enough to warrant serious immediate clinical concern.

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Figure 1.
HPV positivity by age among women with high-grade Pap results at baseline. HSIL+ includes HSIL and rare AIS.

Figure 2. Risk of CIN2+ (Left Panel), CIN3+ (Middle Panel), and cancer (Right Panel) among women aged 30–64 with AGC, ASC-H, or HSIL at baseline, stratified by HPV-positive (HPV+) and HPV-negative (HPV–). Note that the y-axes have different scales for different panels.

Table 1

Distribution of worst histologic diagnosis over 2003–2010 among women aged 30–64 with high-grade Pap results at baseline

Total		Worst histologic diagnosis during follow-up								
Baseline Pap and HPV test result	n	<CIN1, n	CIN1, n	CIN2, n	CIN3, n	AIS, n	Total CIN3 or AIS, n	Squamous carcinoma, n	Adenocarcinoma, n	Total cancers, n
AGC ^a	2,074	1,599	256	74	60	37	98	7	31	47
HPV-negative/AGC	1,491	1,315	150	15	3	3	6	1	1	5
HPV-positive/AGC	495	223	100	54	56	30	87	5	22	31
HPV-unknown/AGC	88	61	6	5	1	4	5	1	8	11
ASC-H ^a	1,647	828	333	249	188	18	209	18	3	28
HPV-negative/ASC-H	467	329	96	30	6	0	6	4	1	6
HPV-positive/ASC-H	1,136	471	232	214	178	18	199	14	2	20
HPV-unknown/ASC-H	44	28	5	5	4	0	4	0	0	2
HSIL ^a	2,019	551	201	489	627	30	659	88	12	119
HPV-negative/HSIL	119	45	24	24	20	1	22	4	0	4
HPV-positive/HSIL	1,830	490	174	445	592	27	620	74	11	101
HPV-unknown/HSIL	70	16	3	20	15	2	17	10	1	14

Note: Total cancers includes not only squamous cell carcinoma and adenocarcinoma but also adenosquamous carcinoma, and cervical cancer of unknown histology or cervical histology unrelated to HPV infection. The category "total CIN3 or AIS" also includes women for whom the diagnosis did not differentiate between CIN3 and AIS. <CIN1 shown for completeness; includes negative histology, no biopsy at colposcopy, and no colposcopy

^aBaseline Pap result alone (regardless of HPV test result)

Table 2

Benchmarking cancer risks for cotest results involving high-grade Pap findings to overall cancer risk thresholds implicitly used to determine clinical management options based on screening Pap tests.

Current recommended management strategy based on Pap-alone	Implicit risk threshold: 5-year cancer risk by baseline Pap result alone (regardless of HPV result) ^f			5-year cancer risks		
	Management-defining result	Frequency in women aged 30–64	Cancer risk	HPV/Pap result	Frequency in women aged 30–64	Cancer risk
Immediate colposcopy (high-grade Pap abnormalities)	SCC	0.005%	68%	HPV+/AGC	0.05%	9.0%
	HSIL	0.21%	7.3%	HPV–/HSIL	0.01%	6.8%
	AGC	0.21%	2.7%	HPV+/HSIL	0.20%	6.6%
				HPV+/ASC-H	0.12%	2.5%
	ASC-H	0.17%	2.6%	HPV–/ASC-H	0.05%	2.1%
Immediate Colposcopy	LSIL	0.97%	0.16%	HPV–/AGC	0.16%	0.37%
				HPV+/ASC-US	1.1%	0.41%
				HPV+/LSIL	0.81%	0.09%

[/] Data presented in: Katki HA, Schiffman M, Castle PE, Fetterman B, Poitras NE, Lorey T, et al. Benchmarking CIN3+ risk as the basis for incorporating HPV and Pap cotesting into cervical screening and management guidelines *J Low Genit Tract Dis* In press.