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Five-year risks of CIN2+ and CIN3+ for women with HPV-positive and HPV-negative LSIL Pap results

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Abstract

Objective—LSIL Pap results do not typically lead to HPV testing. HPV triage is not cost-effective because most cases are HPV-positive. However, under new national guidelines recommending cotesting for women ages 30–64, clinicians will increasingly receive the HPV test result for LSIL Pap results. Some authors have suggested that HPV triage might be effective at older ages, when the percentage of HPV positivity among women with LSIL declines.

Methods—We estimated 5-year risks of CIN2+ and CIN3+ for 9,033 women aged 30–64 who had both an HPV test and an LSIL Pap result.

Results—HPV-positivity of LSIL decreased only slightly with age (30–34: 88% vs. 60–64: 72%, $p < 0.0001$). The 5-year risks of CIN2+ and CIN3+ for women aged 30–64 testing HPV-positive/LSIL were larger than those for women testing HPV-negative/LSIL (CIN2+: 19% vs. 5.1%, $p < 0.0001$; CIN3+: 6.1% vs. 2.0%, $p < 0.0001$). The 5-year CIN3+ risk in HPV-negative/LSIL

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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 was similar to that for women with ASC-US Pap without knowledge of HPV test results (2.0% vs. 2.6%, $p=0.4$).

Conclusions—HPV-negative/LSIL posed lower risk than other Pap results that guidelines currently recommend for referral to immediate colposcopy. By the principle of “equal management of equal risks,” women with HPV-negative/LSIL might reasonably be managed similarly to those with ASC-US Pap results without knowledge of HPV testing, i.e., re-testing at 6–12 months, rather than immediate colposcopy. Although the HPV test result for LSIL Pap results provides actionable information to clinicians who screen with cotesting, the high HPV-positivity of LSIL at even the oldest ages suggests the lack of cost-effectiveness of HPV triage of LSIL for clinicians who do not use routine cotesting.

Keywords

Human Papillomavirus (HPV); cancer prevention; cytology; cervical intraepithelial neoplasia (CIN); Hybrid Capture 2 (HC2); LSIL

Introduction

In the Bethesda System of cervical cytology, low-grade squamous intraepithelial lesion (LSIL) is the classification that represents strong cytologic evidence of human papillomavirus (HPV) infection. At present, women with Pap results of LSIL are referred to colposcopy (1). The classification of cytology as LSIL is reproducible (2) but LSIL interpretations reliably capture only a minority of HPV infections detectable by more sensitive molecular HPV tests (3). Like molecularly detected HPV, the cytologic detection of HPV infection, LSIL, is very common among young women, but declines with age.

Conversely, because LSIL is effectively the insensitive but reliable cytologic sign of HPV infection, a very high percentage of LSIL cases test positive for HPV DNA/RNA, especially with carcinogenic HPV types (4). Two-thirds or more of LSIL cases have been found to be positive for carcinogenic types, and up to 90% are positive for any HPV when the broad range of non-carcinogenic HPV types are tested for (4). In fact, the percentage of LSIL that is HPV positive is often presumed to be so high among young women that it is not cost-effective to attempt to triage LSIL using HPV testing, prior to colposcopic referral (5).

The percentage of LSIL that is positive for carcinogenic HPV types might be lower in older women because (a) cytologic findings that mimic HPV infections are more prevalent; and, (b) to some extent, the proportion of sampled HPV infections attributable to non-carcinogenic HPV types is greater (6). Thus, carcinogenic HPV testing as a potentially cost-effective triage of LSIL in women above a certain age may warrant consideration.

Determining whether LSIL might be triaged by HPV testing requires a large population of adult women, with both cytology and HPV results, followed for sufficient years to determine absolute risks of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) as a marker of cancer risk. We were able to conduct such a prospective cohort study of age-stratified risk estimation at Kaiser Permanente Northern California, which instituted cotesting with conventional cytology and Hybrid Capture 2 (HC2) for women aged 30 and older in 2003. Importantly, this large population had enough women with HPV-negative/LSIL to calculate risks of CIN3+ or cancer, and enable us to assess the value of HPV triage of LSIL for clinicians who have not adopted cotesting.

Methods

The design of our cohort study within KPNC has been described previously (7); in this report we expanded to later years in order to include substantially more data on women 30–64. Briefly, we assembled a cohort of 965,360 women aged 30–64. The baseline for women was their first screening test in this age range. Biopsy and cancer information was collected on all women through December 31, 2010. KPNC guidelines recommend cotesting for women aged 30+ (96% of LSIL had an HPV test result at baseline).

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 cytology using BD SurePath (BD Diagnostics, Burlington, NC, USA). Conventional or liquid-based Pap tests were categorized using the 2001 Bethesda System (8). Note that a meta-analysis (9) and 2 large randomized clinical trials (10, 11) have failed to show any clinical performance advantage of liquid-based cytology over conventional Pap smears for detection of CIN3+. Because biopsy information was only collected through 2010, we had too little data to separately estimate risks based on liquid-based cytology. 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) develops Clinical Practice Guidelines for cervical cancer screening and management of abnormal tests in partnership with the KP National Guideline Program, Care Management Institute, to support clinical decisions of their providers. According to guidelines, women with LSIL or worse Pap results should undergo colposcopy.

Cumulative risk of CIN2+, CIN3+ (which includes AIS), or cervical cancer for each cotest result was calculated as the sum of risk at the baseline test (plotted at time zero on each figure) and the risk after baseline. Risk at the baseline test was the risk of CIN2+, CIN3+, or cancer for Pap-alone or cotest results when women were sent for immediate colposcopy and was estimated separately for each Pap-alone or cotest result as a proportion or, for risks by age, using logistic regression on 5-year age groups, 30–34 up to 60–64. We used Weibull survival models (12) 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 (13), and naturally handle interval-censoring of disease outcomes between screening tests. Separate Weibull models were fit for each cotest result or cytology result, 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 HPV test results for LSIL cytology among women age 30–64, by worst histologic diagnoses. Approximately 1% of all Pap results were LSIL, and the percentage decreased with age (data not shown). The number of cancers following LSIL Pap tests was very low (n=10). Thus, we did not consider cancer outcomes further.

Figure 1 shows that for LSIL, in contrast to ASC-US which is shown for comparison, HPV positivity declined only modestly with age (30–34: 88% vs. 60–64: 72%, $p<0.0001$). Overall, of the 9033 women with LSIL and a known HPV result, 7334 (81%) tested HPV positive, while 1699 (19%) tested HPV negative (Table 1).

Figure 2 shows the 5-year cumulative risks of CIN2+ and CIN3+ for women aged 30–64. Risks of CIN2+ and CIN3+ for women testing HPV-positive/LSIL were greater than those for women testing HPV-negative/LSIL (CIN2+: 19% vs. 5.1%, $p<0.0001$; CIN3+: 6.1% vs.

2.0%, $p<0.0001$). As expected, risks related to LSIL overall were very close to those for HPV-positive/LSIL because 81% of women aged 30–64 with LSIL tested HPV-positive.

Figure 3 shows the 5-year risks of CIN2+ and CIN3+ by age from 30 to 64. Risks after HPV-positive/LSIL decreased with age, while risks after HPV-negative/LSIL did not show a clear trend with age. The difference in CIN3+ risk between HPV-positive vs. HPV-negative for each Pap result reveals the possible value of HPV testing to stratify risk for that Pap result. The difference between the risks of HPV-positive/LSIL and HPV-negative/LSIL varied by age but with no clear pattern (the difference in CIN3+ risk for women aged 35–39 was lowest due to a high spike in risk from HPV-negative/LSIL). Of note, for women aged 30–64, this risk difference between HPV-positive/LSIL and HPV-negative/LSIL was a little less than that from ASC-US (4.1% vs. 6.4%, $p<0.0001$).

To guide possible management strategies among women aged 30–64, we benchmarked the risk of HPV-positive/LSIL and HPV-negative/LSIL to Pap-alone results, for which management is already established (Table 2). Risk of CIN3+ for HPV-positive/LSIL was slightly higher than the risk of CIN3+ for LSIL Pap results overall; the latter leads to colposcopy. Risk of CIN3+ for HPV-negative/LSIL was less than the risk for LSIL Pap results, and comparable to ASC-US Pap results (2.0% vs. 2.6%, $p=0.4$) that do not lead immediately to colposcopy (e.g., 6–12 month return).

Discussion

In the consensus screening guidelines, women with LSIL are referred to colposcopy without HPV triage. We wished to observe whether HPV testing could be of some use in the management of women with LSIL (1). In contrast to the clear value of HPV testing of ASC-US cytology to stratify risk and guide management (14, 15), we observed less utility for HPV testing of LSIL cytology, regardless of a woman's age. In the KPNC population, LSIL truly reflects the cytologic signs of HPV infection, mainly with carcinogenic types. As a result, for HPV-positive LSIL, risks of CIN2+ and CIN3+ were not that much higher than for LSIL without consideration of HPV.

On the other hand, the 5-year risks of CIN2+ and CIN3+ in HPV-negative/LSIL women aged 30–64 of 5.1% and 2.0% respectively were lower, although not nearly as low enough as a negative Pap (0.68% and 0.26% respectively) (16). Therefore, the risks in HPV-negative/LSIL women were intermediate between those for a negative Pap alone and those for an LSIL Pap alone or HPV-positive/ASC-US cotest referred for immediate colposcopy (approximate 5-year risks of 10% for CIN2+ and 5% for CIN3+). Based on the principle of “equal management for equal risk,” management of HPV-negative/LSIL could be considered as intermediate between that of negative Pap-alone (3-year return) and immediate colposcopy, e.g., a 1-year return for HPV-negative/LSIL.

However, management guidelines have to balance individualizing care against simplicity and practical usability. For LSIL, even though the 5-year risks of CIN2+ and CIN3+ were higher for HPV-positive than for HPV-negative cases, the magnitude of the risk difference was not as large as that observed when ASC-US subjects were stratified by HPV result and, more importantly, HPV-positivity did not vary sufficiently (i.e., around 80%) to permit clearly useful triage based on HPV testing. Thus, the group of women with HPV-negative/LSIL, which was only 0.18% of all women screened, is relatively small. A cost-benefit analysis that considers all costs including discomfort related to colposcopy and costs imposed by more complex guidelines would provide useful insight. This judgment ultimately belongs to the health community, which needs to decide how much extra

complexity in guidelines can be permitted for a small group, although other sites may have lower HPV-positivity that we see in KPNC.

As a major goal of this analysis, we examined the possible modification of LSIL management by age. As expected, the percentage of cytology read as LSIL declined with age. In women 30 to 64, for whom HPV test results are almost always available, we observed the expected decline with age in the proportion of LSIL readings and in HPV positivity of the LSIL cases that did occur; nonetheless, the lowest HPV prevalences of LSIL at the oldest ages were still near 70%. This suggests that only a minority of LSIL results at older ages are either due to HPV types not detected by the HC2 assay (which targets 13 types but cross-reacts with several others as well (17)), or represent “look-alike” lesions. However, if all the HPV-negative/LSIL results were the result of cytology “look-alikes” unrelated to CIN2+ and CIN3+ risk, we would have expected the risks to be similar to risks after a normal cytologic result. Instead, although the risk(s) was indeed low, the risk was higher than for normal cytology or HPV-negative ASC-US, without a strong age trend in risk. The lack of very strong risk discrimination for CIN3+ by HPV result, even at older ages, coupled with the sustained high HPV positivity, did not support using HPV testing selectively in the older age group to modify management of LSIL cytology.

The results were the same when we examined risks for CIN2+ and for CIN3+, the more definite surrogate endpoint of cancer risk, as the clinical thresholds for treatment. We did not present the unstable and unreliable findings for invasive cancer because very few cases were observed. It is interesting that LSIL is not a frequent preceding cytology for overtly invasive disease.

In summary, the largest study yet performed confirms that ordering an HPV test to triage LSIL is unlikely to be clinically useful (5, 18–24). In the context of cotesting of women 30–64, when HPV testing of LSIL cytology is available as a matter of course, the HPV result modified the risk of CIN2+ or CIN3+ enough to warrant consideration of repeat testing of women with HPV-negative/LSIL, e.g., at 1 year, rather than recommending immediate colposcopy, the current standard of care. However, the affected group is relatively small and, if simpler guidelines are preferred, immediate colposcopy of all women with LSIL might be attractive. We found little support for less aggressive management of LSIL among older women. A more specific biological marker of carcinogenic risk is truly needed in this setting, as clinicians currently devote a great deal of time and energy, and the health care system incurs substantial costs, doing colposcopy on women with LSIL who have very low risk of cancer.

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Figure 1.
HPV positivity by age group among women with ASC-US or LSIL Pap results at baseline.

Figure 2. Cumulative risk of CIN2+ (Left Panel) and CIN3+ (Right Panel) among women aged 30–64 by baseline Pap and HPV test result. The ASC-US and LSIL curves are for all results alone regardless of HPV test results. Note that the y-axes have different scales for different panels.

Figure 3. 5-year cumulative risk of CIN2+ (Left Panel), CIN3+ (Right Panel) given age group by baseline Pap and HPV test results. The LSIL curves are for all LSIL results alone regardless of HPV test results. 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 LSIL Pap at baseline.

Baseline Pap and HPV test result	Total n	Worst histologic diagnosis during follow-up								
		<CIN1, n	CIN1, n	CIN2, n	CIN3, n	AIS, n	Total CIN3 or AIS, n	Squamous carcinoma, n	Adeno- carcinoma, n	Total cancers, n
Total	965,360	942,657	15,357	4,235	2,480	228	2,723	198	114	388
LSIL ^a	9,374	4,845	3414	780	315	8	325	6	2	10
HPV-positive/LSIL	7,334	3,455	2860	718	288	7	296	4	1	5
HPV-negative/LSIL	1,699	1,168	466	42	20	1	21	1	1	2
HPV-unknown/LSIL	341	222	88	20	7	0	8	1	0	3

Total cancers include not only squamous cell carcinoma and adenocarcinoma but also adenosquamous carcinoma, and cervical cancer of unknown histology or histology unrelated to HPV infection. The category “Total CIN3 or AIS” also includes women with diagnoses that did not differentiate between CIN3 and AIS. “<CIN1” is included for completeness, and includes normal or metaplastic biopsy findings, no biopsy taken, and no record of colposcopy found.

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

Benchmarking CIN3+ risks for HPV-positive/LSIL and HPV-negative/LSIL cotest results to risk thresholds implicitly used to determine clinical management options based on screening Pap tests.

Table 2

Current recommended management strategy based on Pap-alone	Implicit risk threshold: 5-year CIN3+ risk by baseline Pap result alone (regardless of HPV test result) [/]		5-year CIN3+ risk by baseline cotest result	
	Management defining result	Frequency in women aged 30–64	CIN3+ risk	HPV/Pap result
Immediate Colposcopy	LSIL	0.97%	5.2%	HPV+/ASC-US HPV+/LSIL
6–12 month return	ASC-US	2.8%	2.6%	HPV–/LSIL
3-year return	Pap-Neg	95.6%	0.26%	HPV–/ASC-US
				1.8%
				0.43%

[/] 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.