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Five-year risk of recurrence following treatment of CIN2, CIN3, or AIS: performance of HPV and Pap cotesting in post-treatment management

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Abstract

Objective—After excisional treatment, CIN2+ can recur. It is not clear how many negative post-treatment Pap or cotest results are needed to assure adequate safety against CIN2+, prior to return to extended retesting intervals.

Methods—We observed 5-year risks of CIN2+, and outcomes for 3 follow-up management strategies after treatment (Pap alone, HPV alone, and cotesting) for 3273 women aged 25 and older who were treated for CIN2, CIN3, or AIS between 2003–2010 at Kaiser Permanente Northern California.

Results—Five-year risks of recurrent CIN2+ after treatment varied both by antecedent screening test result and the histology of the treated lesion. The risk ranged from 5% for CIN2 preceded by HPV-positive/ASC-US or LSIL to 16% for CIN3/AIS preceded by AGC/ASC-H/HSIL+ ($p < 0.0001$). However, after post-treatment negative tests, risks were lowered and similar regardless of antecedent screening test and histology of treated disease. The 5-year recurrent CIN2+ risk associated with a negative post-treatment cotest (2.4%) was lower than that of an HPV-negative test alone (3.7%, $p = 0.3$) or Pap-negative result alone (4.2%, $p = 0.1$). Two negative

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Conflicts of Interest: Dr. Schiffman and Dr. Gage report working with Qiagen, Inc. on an independent evaluation 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 HPV testing for research at no cost 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.

post-treatment tests of each kind conferred slightly lower 5-year CIN2+ risk than one (Pap-negative: 2.7% vs. 4.2%, $p=0.2$; HPV-negative: 2.7% vs. 3.7%, $p=0.7$; HPV-negative/Pap-negative: 1.5% vs. 2.4%, $p=0.8$). The 5-year CIN2+ risk associated with 2 negative cotests of 1.5% (95%CI 0.3% to 7.2%) approached the 0.68% risk associated with a negative Pap test during routine screening.

Conclusions—Women with antecedent AGC/ASC-H/HSIL+ Pap results or those treated with CIN3/AIS had a substantial risk of developing CIN2+ after treatment. Based on the principle of “benchmarking to implicit risk thresholds”, after negative test results following treatment, no subgroup of women achieved risk sufficiently low risk to return to 5-year routine screening. However, negative cotests after treatment provided more reassurance against recurrent CIN2+ than either negative Pap tests or HPV tests alone.

Keywords

Human Papillomavirus (HPV); cancer prevention; Pap; cervical intraepithelialneoplasia (CIN); Hybrid Capture 2 (HC2); post-treatment; test of cure

Introduction

Virtually all cases of cervical cancer and its immediate precursor lesions are caused by persistently detectable infection with human papillomavirus (HPV) (1). As a corollary, in the absence of detectable HPV as measured by DNA or RNA tests, the short-term risk of subsequent CIN2, CIN3, AIS, or cancer (in the aggregate, “CIN2+”) is extremely low. Accordingly, new guidelines make use of the sensitivity and negative predictive value of HPV testing throughout the cervical cancer screening program and management of screening abnormalities, including the most “downstream” application, i.e., HPV testing can play a role in the management of women following treatment of CIN2+.

Women treated for CIN2 or CIN3 retain an elevated risk of recurrence or even invasive cancer for years following treatment (2, 3). Thus, heightened surveillance has been the rule, with uncertainty as to whether (and when) a return to normal screening intervals can be safely permitted. This uncertainty was less of an issue when annual cytology was standard for all women. With the adoption of 3-year cytology and 5-year cotesting intervals, the safety of routine screening after(?) the treatment(?)has become more uncertain. The question now arises whether the reassurance provided by a negative HPV and cytology cotest is sufficient to overcome the elevated concern regarding post-treatment recurrence. In particular, it is not clear how many subsequent negative cotest results should be recommended prior to return to extended retesting intervals.

The many observational studies suggesting that HPV testing or cotesting can provide a post-surgical “test of cure” have been modest in size and generally conducted as research efforts(4–22). We now have data from Kaiser Permanente Northern California (KPNC), a large integrated health system that has been using cotesting for cervical cancer screening, management of screening abnormalities, and management of women following colposcopy and treatment of CIN2+ since 2003. 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 KPNC guidelines, as a test of cure following treatment of CIN 2+, cotesting is recommended at 6 and 12–18 months, with repeat colposcopy for HPV-positive/Pap-negative or worse. As stated in the Guidelines, 2 consecutive negative cotests permit return to routine screening, with extension of screening intervals to 3 years.

To analyze the performance of cotesting in post-treatment management, we estimated the absolute risks of recurrent CIN2+ following treatment and 1 or 2 negative Pap results, HPV tests, or cotests in KPNC.

Methods

The design of our cohort study from KPNC has been described previously (23); in this report we enlarged the dataset to include all women age 25 and older screened from 2003 to 2010. 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.

For each woman in the cohort, we considered her baseline screen as the first cotest or Pap test from 2003 to 2010 (Figure 1). We included women with baseline test results that would lead to referral for colposcopy (HPV-positive/ASC-US, LSIL, AGC, ASC-H, HSIL+). We refer to the baseline screen immediately before colposcopic referral as the “antecedent screen” leading to the colposcopy. We defined our study population as women who had a definitive CIN2, CIN3 or AIS diagnosed by biopsy taken at the time of colposcopy and, had surgical (mainly LEEP) treatment for the lesion. We calculated post-treatment risk of recurrent CIN2+, stratified by the severity of the treated lesion (CIN2 versus CIN3/AIS) and the antecedent screen (HPV-positive/ASC-US and LSIL versus AGC, ASC-H, and HSIL+).

Of note, due to small numbers of outcomes, we focused on risk of recurrent CIN2+. CIN2+ is generally treated, and is a clinically important, although less certain, surrogate endpoint for cancer risk than CIN3+. To examine risk levels following post-treatment negative tests, we further restricted the analysis to women who had a negative test (Pap-alone, HPV-alone, or cotest) at their first post-treatment follow-up. Of note, when risk was calculated for a cytology result without regard to HPV testing, or vice versa, we refer to those risks as “Pap-alone” or “HPV-alone”.

Based on the first follow-up test result post-treatment, we divided women into 1 negative Pap test, 1 negative HPV test, or 1 negative cotest. Though the majority of women underwent cotesting post-treatment, we considered test results independently and then compared 3 management strategies to follow-up women post-treatment: Pap-alone, HPV-alone, and cotesting. Of note, a woman with a negative cotest following treatment fit into all 3 categories: she was HPV-negative/Pap-negative and also Pap-negative and HPV-negative for the purpose of these analyses. We calculated the cumulative risk of recurrent CIN2+ starting from the date of the first post-treatment follow-up test.

Women who returned for a second follow-up test and had consecutive negative test results are noted as having 2 negative Pap results, 2 negative HPV tests, or 2 negative cotests. Cumulative risks of recurrent CIN2+ were calculated starting from the date of the second negative follow-up test.

Pap tests were performed at KPNC regional and facility labs. HPV tests were performed only at the 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 Pap testing using BD SurePath (BD Diagnostics, Burlington, NC, USA). Conventional or liquid-based Pap tests are reported according to the 2001 Bethesda System(24). Hybrid Capture 2 (HC2; Qiagen, Germantown, MD, USA) was used to test for high-risk HPV types according to manufacturer’s instructions.

Cumulative risk of recurrent CIN2+ for each cotest result was calculated as the sum of risk at first (or second) follow-up test (plotted at time zero on each figure) and the incidence after the first (or second) follow-up test(23). When zero incident CIN2+ events occurred, no exact p-value or confidence interval can be calculated, so we calculated conservative confidence intervals by calculating the right-endpoint of the confidence interval with 1 CIN2+ event and inverting this interval to obtain p-values when needed.

Results

Table 1 shows the distribution, by antecedent Pap or cotest result, of the worst histologic findings through 2010, for all women after treatment for CIN2, CIN3, or AIS (this table includes women with subsequent positive and negative tests). Half of recurrent CIN2+ (111/205) and cancer (8/15) occurred in the 28% of the women (920/3273) having antecedent HSIL+ (includes HSIL and the few SCC and AIS Paps). Not shown in Table 1, there were 161 women with treated CIN2, CIN3, or AIS following an antecedent persistent HPV-positive/Pap-negative test result; the 5-year CIN2+ risks following negative screening tests were extremely unreliable due to small numbers (n=4 recurrent CIN2+) and therefore are not presented.

Figure 2 shows post-treatment CIN2+ stratified by antecedent screening test and by whether treated histology was CIN2 or CIN3/AIS. Among the antecedent screening tests, ASC-H was grouped with HSIL and AGC because of its high risk as diagnosed at KPNC. The 5-year risks of developing CIN2+ after treatment depended both on antecedent screening test and the histology of the treated lesion. The risk ranged from 5% for treated CIN2 preceded by HPV-positive/ASC-US or LSIL to 16% for treated CIN3/AIS preceded by AGC, ASC-H or HSIL+($p<0.0001$). We mention for completeness, although the data are not presented, that the pattern was similar for CIN3+ after treatment.

Risk of recurrent CIN2+ was lower for women following a single negative post-treatment follow-up test. Also, risk no longer significantly differed by antecedent screening test and histology of the treated lesion. While the overall 5-year CIN2+ risk after treatment for CIN3/AIS preceded by AGC/ASC-H/HSIL+ was significantly higher than for CIN2 preceded by HPV-positive/ASC-US or LSIL (16% versus 5.0%, $p<0.001$ as shown above), following negative follow-up tests the magnitudes of the risks were much reduced and no longer significantly different (after Pap-negative: 5.8% vs. 3.5%, $p=0.1$; HPV-negative: 5.0% vs. 1.7%, $p=0.2$; HPV-negative/Pap-negative: 2.8% vs. 1.4%, $p=0.4$).

Figure 3 shows recurrent CIN2+ risks for women following 1 or 2 negative tests after treatment. For statistical power and because the risks did not differ that much, after a negative follow-up test, we combined all antecedent screening tests and also combined treated CIN2 and CIN3/AIS. Based on these combined data, the more negative follow-up tests, the (non-significantly) lower was the subsequent 5-year CIN2+ risk (1 negative Pap result vs. 2 negative Pap results: 4.2% vs. 2.7% ($p=0.2$); one negative HPV test vs. 2 negative HPV tests: 3.7% vs. 2.7% ($p=0.7$); one negative cotest vs. 2 negative cotests: 2.4% vs. 1.5% ($p=0.8$)). Although there was considerable uncertainty around these estimates due to small numbers, 2 negative cotests were associated with lower 5-year risk of CIN2+ (1.5%; 95% CI: 0.3% to 7.2%) than 2 negative HPV tests (1.5% vs. 2.7%, $p=0.6$) or 2 negative Pap tests (1.5% vs. 2.7%, $p=0.7$).

Table 2 benchmarks 5-year recurrent CIN2+ risk for negative screening tests after treatment for CIN2, CIN3, or AIS to the established implicit risk thresholds for management of Pap test results alone (23). All Pap-negative or HPV-negative risks were similar to those that, in the context of screening, currently entail a 6–12 month return, such as ASC-US (6.9%), or

were intermediate, falling between 6.9% and a risk low enough to permit a 3-year return, such as a negative Pap result (0.68%) (25). The risk associated with one negative cotest was intermediate, falling between risk thresholds for a 6–12 month and 3-year return. After 2 negative cotests, the 1.5% (95%CI 0.3% to 7.2%) risk approached the threshold for a 3-year return (0.68% for a negative Pap test). No negative test result following treatment ever came close to that associated with an HPV-negative/Pap-negative screening test, i.e., the ultra-low risk threshold of 0.27% 5-year CIN2+ risk enabling a 5-year return.

Discussion

Negative cotesting appeared to provide more reassurance than Pap alone when following women after treatment. One negative cotest had equivalent risk to 2 consecutive negative Pap tests. After surgical treatment of CIN2, CIN3, or AIS, 2 sequential negative cotests, at approximately 6–12 months and 18–24 months following treatment, conferred reassurance against recurrent CIN2+. It appears that the residual risk is low enough to warrant a 3-year return, but we could not be certain, because our risk estimates were imprecise due to small numbers of events. The fact that there were an inadequate number of events for precise estimates despite 8-year follow-up of a population in excess of a million women vividly demonstrates the difficulty in obtaining sufficient information from which to craft clinical practice guidelines, and suggests a role for expert opinion in the guidelines process for the foreseeable future.

Even 2 negative cotest results were insufficient to reduce risk for CIN2+ to a level required for 5-year routine screening. With additional of years follow-up we may be able to ascertain whether any repeated sequence of negative tests, e.g., 3 or more sequential negative cotests, make it safe to return to 5-year screening intervals after treatment.

We also observed that overall, regardless of post-treatment positive/negative screens, the antecedent screen that referred to colposcopy/treatment and the severity of the treated histology (CIN2 versus CIN3/AIS) affected post-treatment risk substantially. Most women who experienced recurrences had antecedent HSIL Pap results. The highest 5-year risk of recurrent CIN2+ (16%) was observed when the antecedent Pap result was HSIL and the treated histology was CIN3/AIS. The lowest 5-year risk (5.0%) was observed when the antecedent Pap result was HPV-positive ASC-US, or LSIL, and the treated histology was CIN2. Moreover, a single negative cotest was associated with a much lower risk of 1.4%. In this context, it remains to be seen whether the recent histology classification guidelines that remove the distinction between CIN3 and (p16-positive) CIN2(26), will eliminate a distinction of clinical value.

There were important limitations to this analysis. First, although this treated cohort was an order of magnitude larger than other studies of HPV testing after treatment of CIN2, CIN3, and AIS, we still observed relatively small numbers of recurrences. We did not have enough information to consider whether age affected risk of recurrence; therefore we combined all women aged 25–64. Also, we had no information on ectocervical margin status (although KPNC guidelines do not differentiate management by margin status in the case of squamous lesions). Importantly, this was an observational study of women followed using different post-treatment strategies chosen by their providers, mainly cotesting, with estimations of the safety afforded by different follow-up strategies, rather than a clinical trial with randomization to different strategies, which would guard against unexpected biases in patient characteristics or physician preferences.

The major innovative aspect of this analysis was our benchmarking post-treatment risks to those established for abnormal screening Pap test results. The underlying logic behind this

strategy is that equal risks should be managed equally, regardless of whether the context is screening, post-colposcopic management, or post-treatment. Using this approach, we could clearly see that it is difficult to justify return to routine, long-interval (i.e., 5-year) screening for a woman after she has been treated for CIN2. It will require longer follow-up of women with 3 or more repeated negative cotests to document whether and how soon their risk returns to “normal.”

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Figure 1.

Diagram of women treated for treatment for CIN2, CIN3, or AIS

Figure 2.

Cumulative risk of CIN2+ after treatment for CIN2, CIN3, or AIS among women aged 25 and older given antecedent screening test that preceded colposcopy was HPV-positive/ASC-US or LSIL (Left Panel) or HSIL+, ASC-H, AGC (Right Panel).

Figure 3.

Cumulative risk of CIN2+ following subsequent negative follow-up tests after treatment for CIN2, CIN3, or AIS, for women age 25 and older. The negative Pap test curves are for all Pap results alone regardless of HPV test results and the HPV negative test curves are for all HPV results alone regardless of Pap test results. A “negative cotest” means testing both HPV-negative and Pap-negative.

Table 1

Distribution of worst histologic diagnosis over 2003–2010 after treatment for CIN2, CIN3, or AIS among women aged 25 and older for each antecedent Pap or cotest result that preceded colposcopy.

Antecedent Pap and HPV test result that preceded treatment	Total	Worst histologic diagnosis during follow-up after treatment for CIN2, CIN3, or AIS								
	n	<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	3,273	3,026	42	85	99	6	105	13	1	15
HPV-positive/ASC-US	1,115	1,064	17	21	11	0	11	2	0	2
LSIL	697	655	6	14	19	0	19	3	0	3
AGC	121	108	2	3	4	3	7	1	0	1
ASC-H	420	402	5	6	5	1	6	1	0	1
HSIL+	920	797	12	41	60	2	62	6	1	8

Note: Total cancers includes not only squamous cell carcinoma and adenocarcinoma but also adenosquamous carcinoma, and cervical cancer of unknown histology or histology unrelated to HPV infection. "HSIL+" includes HSIL and the few women with SCC and AIS Pap results.

Benchmarking CIN2+ risks for negative follow-up tests following treatment for CIN2, CIN3 or AIS among women aged 25 and older, to CIN2+ risk thresholds implicitly used to determine clinical management options based on screening Pap tests.

Table 2

Current recommended management strategy based on Pap-alone screening	Women treated for CIN2, CIN3, or AIS aged 25 and older					
	Follow-up with Pap-alone ^d		Follow-up with HPV testing-alone ^b		Follow-up with cotesting	
	Pap result(s)	5-year CIN2+ risk after last test	HPV test result(s)	5-year CIN2+ risk after last test	HPV/Pap result(s)	5-year CIN2+ risk after last test
Immediate colposcopy						
		LSIL: 16%				
6-12 month return	1 negative Pap	4.2%	1 negative HPV test	3.7%		
Intermediate	2 negative Paps	2.7%	2 negative HPV tests	2.7%	1 negative cotest	2.4%
3-year return		Pap-: 0.68%			2 negative cotests	1.5%

^aFollow-up Pap result(s) alone (regardless of HPV test result)

^bFollow-up HPV test result(s) alone (regardless of Pap result)

^dData 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.