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Low Risk of Cervical Cancer/Precancer Among Most Women Under Surveillance Postcolposcopy

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Objective: To inform impending postcolposcopy guidelines, this analysis examined the subsequent risk of CIN 3+ among women with a grade lower than CIN 2 (< CIN 2) colposcopy results, taking into account the referring results that brought them to colposcopy and cotest results postcolposcopy.

Methods: We analyzed 107,005 women from 25 to 65 years old, recommended for colposcopy at Kaiser Permanente Northern California. We estimated absolute risks of CIN 3+ among women: (1) recommended for colposcopy (precolposcopy), (2) following colposcopy and with histology results < CIN 2 (postcolposcopy), and (3) with cotest results 12 months after a < CIN 2 colposcopy (return cotest).

Results: After colposcopy showing < CIN 2 (n = 69,790; 87% of the women at colposcopy), the 1-year risk of CIN 3+ was 1.2%, compared with 6.3% at the time of colposcopy recommendation. Negative cotest results 1 year after colposcopy identified a large group (37.1%) of women whose risk of CIN 3+ (i.e., <0.2% at 3 years after postcolposcopy cotest) was comparable with women with normal cytology in the screening population. These risks are consistent with current guidelines recommending repeat cotesting 12 months after colposcopy < CIN 2 and a 3-year return for women with a negative postcolposcopy cotest.

Conclusions: Most women are at low risk of subsequent CIN 3+ after a colposcopy showing < CIN 2, especially those who are human papillomavirus–negative postcolposcopy, consistent with current management guidelines for repeat testing intervals. Before the finalizing the upcoming guidelines, we will consider additional rounds of postcolposcopy cotesting.

Key Words: postcolposcopy surveillance, management guidelines, risk, CIN 3+, colposcopy

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In preparation for the next round of American Society for Colposcopy and Cervical Pathology–sponsored risk-based cervical screening and management guidelines, we are considering all parts of the cervical screening program.[1] A series of articles is addressing risks of subsequent precancer/cancer after abnormal screening results, "surveillance" of women attending colposcopy when CIN 2+ is not found, follow-up posttreatment, the impact of previous screening history, and other topics. To inform guidelines for surveillance of the postcolposcopy population when CIN 2+ is not found, the goal of this analysis was to examine the subsequent risk of CIN 3+ among women after an initial colposcopic visit result of lower than CIN 2 (< CIN 2), taking into account the screening results that brought them to colposcopy and the results of the first postcolposcopy visit. We examined in particular whether the risk for women with negative results on cytology and human papillomavirus (HPV) testing at the first postcolposcopy visit 1 year after colposcopy was sufficiently low to support retesting at an extended interval (e.g., 3 years) as recommended in current guidelines.

Women being followed postcolposcopy are considered to be a population at elevated risk for eventual diagnosis of precancer (defined here as CIN 3 or adenocarcinoma in situ) and cancer, even when the initial colposcopy and biopsies show only low grade or no pathology. Most women referred to colposcopy have minor cytologic abnormalities suggestive of HPV infection. Even in the absence of cytologic abnormalities, a sizable subset of HPV-positive women is referred to colposcopy because their return testing at 1 year shows continued HPV positivity. Because most HPV infections, even those producing cytologic abnormalities, clear within months to a few years, it follows that most women referred to colposcopy are found not to have a precancer/cancer needing treatment.[2,3] Nonetheless, the number of women in postcolposcopy "surveillance"[1] is likely to increase with the expansion of HPV testing as part of cervical cancer screening, although only a small minority will be diagnosed with precancer.[3,4] It is important to determine which subsets of women might be returned to less intensive surveillance.

MATERIALS AND METHODS

Since 2001, women at Kaiser Permanente Northern California (KPNC) have been tested by Hybrid Capture 2 (HC2) to triage the equivocal cytologic result of atypical squamous cells of undetermined significance (ASC-US). Starting in 2003 through 2015, women aged 30 to 65 have been screened with HC2 and cytology combined (cotesting) every 3 years.[4,5]

Cytology was performed at KPNC regional and local laboratories. The HPV status was based on HC2 testing performed at the regional laboratory. Cytology results were reported based on the 2001 Bethesda System. Between 2003 and 2009, conventional Pap smears were first processed using the BD FocalPoint Slide Profiler (BD Diagnostics; Burlington, NC) primary screening and directed quality control system and then manually reviewed. In 2009, KPNC switched to liquid-based cytology (BD SurePath). Clinical

[1]For this discussion, "surveillance" refers to the follow-up of women referred to colposcopy, with histology results lower than CIN 2.

outcomes were obtained by matching to KPNC computerized cytology and histopathology records.

To study the risk of CIN 3+ postcolposcopy, we first restricted to 107,005 women who warranted colposcopy based on cytology and/or HPV results. In addition to women with any cytologic abnormalities, we included those women with HPV-positive, cytology-negative results who had repeat HPV positivity at the 1-year retest. In arriving at the study population, we excluded only women with any past history (before the cotesting visit warranting colposcopy referral) of CIN 2+, cytologic high-grade squamous intraepithelial lesion or worse (HSIL+), or hysterectomy. Women with a previous history of CIN 2+ or HSIL+ will be the subject of a future analysis. We analyzed cumulative risks of CIN 3+, using logistic-Weibull models stratified by the reason for colposcopy referral,[6] by the result of colposcopy/biopsy, and by the postcolposcopy cotest result.

As previously mentioned, women referred to colposcopy can be divided conceptually into those with "signs of HPV infection" versus those with cytologic evidence suggesting heightened risk of precancer (CIN 2, CIN 3, adenocarcinoma in situ) or cancer. Women referred to colposcopy for "signs of HPV infection" had low-grade squamous intraepithelial lesion (LSIL), HPV-positive ASC-US, or HPV-positive Negative for Intraepithelial Lesion or Malignancy (NILM) followed by either continued HPV positivity or ASC-US cytology 1 year later. Patients with results leading to heightened concern regarding precancer had initial cytology results of HSIL+, atypical squamous cells cannot exclude HSIL (ASC-H), or atypical glandular cells (AGC).[7,8]

Throughout this article, we distinguish 2 populations: precolposcopy and postcolposcopy. "Precolposcopy" applies to the population referred to colposcopy, regardless of whether they attended colposcopy or not, and regardless of their histology results. To define the postcolposcopy group, we restricted to women who actually attended colposcopy, had biopsies taken, and had histology of < CIN 2 at enrollment. Women found at colposcopy to have CIN 2 or worse (and then treated or untreated) are addressed in other manuscripts in preparation. In addition, women at KPNC were often followed annually after a negative cotest after a < CIN 2 colposcopy, rather than at 3 years as recommended by current American Society for Colposcopy and Cervical Pathology guidelines. The colposcopy protocol at KPNC evolved during the study period, but was designed to maximize CIN 2+ detection, and suggested multiple biopsies for all patients.

We first estimated how much a colposcopy visit with biopsy showing histology results < CIN 2 (CIN 1 or less) reduced risk. To do so, we contrasted the risk of subsequent CIN 3+ (and secondarily CIN 2 in ancillary analyses) in the postcolposcopy group, compared with the original precolposcopy population.

To estimate the additional reassurance of a negative result at the first postcolposcopy visit, we estimated the immediate and 3-year risks of CIN 3+ associated with the first visit postcolposcopy cotest result to examine whether some women had risks low enough to consider return to 3-year screening, as recommended in current guidelines. In our interpretations, we assessed whether any group of women had low enough risks to return to longer interval visits by comparison with established "benchmarks" from the 2012 consensus guidelines. Specifically, we reasoned by the principle of "equal management of equal risk" that a 3-year risk equivalent to that of a woman with NILM cytology in a screening setting could justify return to 3-year screening, as recommended for women with NILM.

RESULTS

Table 1 compares risks among the precolposcopy and the postcolposcopy groups, stratified by reason for colposcopy referral. The table gives frequencies and distributions for each cytology and HPV test category leading to colposcopy referral. The left side of the table (labeled "total number of women at colposcopy with biopsy") provides information on the precolposcopy group, that is, people referred to colposcopy, regardless of whether they attended colposcopy or not and regardless of the diagnosis from the colposcopy visit. The middle column (labeled "biopsy at colposcopy") indicates the high percentage of women referred for colposcopy who did, in fact, attend a colposcopy visit and had a biopsy taken. This group was further subdivided in 2 groups: women with CIN 2+ biopsy at colposcopy and women with histology results of lower than CIN 2. Women with CIN 2+ received recommended treatment or intensive follow-up and were not part of the subsequent analyses (n.b., they are considered in an upcoming article on follow-up after treatment). Women with histology results < CIN 2 (CIN 1 or less) are labeled as the "postcolposcopy" group placed under surveillance.

Overall, we can document biopsy results for 76.2% of women referred to colposcopy. Most of the women referred to colposcopy had cytologic (LSIL or ASC-US) and/or virologic (HPV test positive) evidence of HPV infection without evidence of precancer. Human papillomavirus–positive women with higher-grade cytology were the most likely to have a documented colposcopy visit with biopsy results (AGC, 89.4%; ASC-H, 87.8%; HSIL +, 88.0%). Note that colposcopy without biopsy would not be detected, and the denominators are not controlled for membership duration after screening nor postscreening hysterectomy.

Among all women who went to colposcopy and had one or more biopsies, 13.0% had CIN 2+. Except for women referred for HPV+ HSIL, the minority, ranging from 1.8% to 37.2%, of women in each referral category had histology results CIN 2+. Because the vast majority (84.8%) of women were referred with evidence of HPV infection (LSIL or lower cytology), most (61.0%) of the CIN 2+ were diagnosed among this group, although on an individual basis, the absolute risk was low.

Table 2 shows 1- and 3-year cumulative risk of CIN 3+ among precolposcopy and postcolposcopy patients. The effectiveness of colposcopy in finding and removing precancer, as practiced at KPNC, was evident; the 1-year risk of CIN 3+ in the precolposcopy group (6.5%) was greatly reduced in the postcolposcopy group found not to have CIN 2+ at colposcopy (1.2%). In the precolposcopy group, risk of CIN 3+ varied widely by cytology and HPV status, with 1-year estimates ranging from 0.91% among HPV-negative women with cytologic AGC to 44.4% in HPV-positive women with HSIL+. Most HPV-negative categories (except HPV-negative HSIL+) had precolposcopy 1-year risks less than 3%. Postcolposcopy, among women who had colposcopy results of < CIN 2, the risk of subsequent CIN 3+ was low for those referred with minor changes (LSIL or lower cytology): 1.3% or lower at 1 year and 2.2% or lower at 3 years.

Table 3 summarizes the absolute and relative risk reduction when comparing precolposcopy and postcolposcopy risks. Overall, the 1-year risk of CIN 3+ lowered from 6.3% precolposcopy to 1.2% postcolposcopy, representing a 5.1% absolute risk reduction. Risk reductions were maintained through the 3-year follow-up (5.4%). Absolute risk reduction was heterogeneous (1-year risk reductions of 0.5% for HPV-negative LSIL to 36.7% for HPV-positive HSIL+), with greater risk reduction in higher-grade cytology groups.

Table 4 shows the risk of CIN 3+ stratified by first cotest results postcolposcopy. The HPV results were the main determinant of risk subsequent to the postcolposcopy visit, although cytology result did influence risk among HPV-positive women (and rare HSIL+ suggested high risk even among HPV-negative women.) The magnitude of the overall contribution of cytology to the return cotest sensitivity was 25/965; this percentage (2.6%) of the CIN

TABLE 1. Frequency of Reasons for Colposcopy Referral and Follow-up Time for Women in the Precolposcopy and Postcolposcopy Groups

Reason for colposcopy referral		Precolposcopy[b]		Women at colposcopy visit with biopsy							
				Total no. women at colposcopy with biopsy		CIN 2+ biopsy at colposcopy			<CIN 2 biopsy at colposcopy (postcolposcopy[c])		
HPV status[a]	Cytology	n	%	n	% women within each reason for colpo referral category who had colpo with biopsy [d]	n	% of women at colposcopy with biopsy, with CIN 2+	% reason for referral for women with CIN 2+ biopsy at colposcopy	n	% of women at colposcopy with biopsy, with <CIN 2	% reason for referral for women with <CIN 2 biopsy at colposcopy
HPV+	HSIL+	3,788	3.9	3,334	88.0	2,218	66.5	18.8	1,116	33.5	1.6
	ASC-H	4,092	4.2	3,591	87.8	1,336	37.2	11.3	2,255	62.8	3.2
	AGC	1,112	1.1	994	89.4	296	29.8	2.5	698	70.2	1.0
	LSIL	25,309	26.0	21,656	85.6	2,310	10.7	19.6	19,346	89.3	27.7
	HPV+ ASC-US	39,125	40.1	33,932	86.7	3,465	10.2	29.4	30,467	89.8	43.7
	HPV+ NILM[e]	13,376	13.7	9,392	70.2	523	5.6	5.0	8,869	94.4	12.7
HPV-	HSIL+	272	0.3	231	84.9	86	37.2	0.7	145	62.8	0.2
	ASC-H	1,662	1.7	1,355	81.5	82	6.1	0.7	1,273	93.9	1.8
	AGC	3,860	4.0	2,975	77.1	53	1.8	0.4	2,922	98.2	4.2
	LSIL	4,931	5.1	2,769	56.2	70	2.5	0.6	2,699	97.5	3.9
Total		**97,527**		**80,229**	**82.3**	**10,439**	**13.0**		**6,9790**	**87.0**	

[a]HPV status based on HC2 results at baseline.

[b]Precolposcopy: women eligible for colposcopy based on referrals using cytology or HPV results, regardless of whether they went to colposcopy or not and, for those who went, regardless of histology results at baseline.

[c]Postcolposcopy: women who went to colposcopy and had histology results of lower than CIN 2 at baseline.

[d]No. women at colposcopy with biopsy divided by total number of women "precolposcopy" in each category of "reason for colposcopy referral".

[e]HPV+ NILM includes women with 2 consecutive HPV+ NILM results or with HPV+ NILM and a consecutive HPV- ASC-US result.

TABLE 2. Risk of CIN 3+ by Reason for Colposcopy Referral and HPV Status for Women in the Precolposcopy and Postcolposcopy Groups

		1 year risk of CIN 3+		3 years risk of CIN 3+	
		Precolposcopy[c]	Postcolposcopy[d]	Precolposcopy[b]	Postcolposcopy[d]
Reason for colposcopy referral[a,b]		Risk[e]	Risk[e]	Risk[e]	Risk[e]
HPV+	HSIL+	44.4 (42.6, 46.2)	7.69 (0.29, 15.0)	45.4 (43.6, 47.3)	9.3 (0.27, 18.3)
	ASC-H	22.2 (20.8, 23.6)	4.7 (1.7, 7.7)	23.9 (22.4, 25.4)	6.5 (2.2, 10.8)
	AGC	23.6 (21.0, 26.4)	5.6 (1.3, 9.9)	26.0 (23.3, 28.9)	8.0 (1.5, 14.5)
	LSIL	3.9 (3.6, 4.2)	1.1 (0.71, 1.5)	4.6 (4.3, 5.0)	1.8 (1.1, 2.6)
	HPV+ ASC-US	4.3 (4.1, 4.5)	1.3 (1.0, 1.6)	5.2 (4.9, 5.4)	2.2 (1.6, 2.8)
	HPV+ NILM[f]	3.4 (3.1,3.8)	1.1 (0.73, 1.6)	4.5 (4.1, 4.9)	2.1 (1.2, 3.0)
HPV-	HSIL+	18.8 (14.3, 24.5)	1.9 (0, 9.7)	19.4 (14.8, 25.2)	2.6 (0, 14.2)
	ASC-H	2.1 (1.5, 3.0)	0.59 (0, 5.2)	2.4 (1.8, 3.3)	0.67 (0, 5.9)
	AGC	0.91 (0.64, 1.3)	0.13 (0, 0.76)	0.98 (0.70, 1.4)	0.19 (0, 1.2)
	LSIL	0.96 (0.70, 1.3)	0.49 (0, 2.0)	1.22 (0.92, 1.61)	0.68 (0, 2.8)
Total		**6.3 (5.7, 6.9)**	**1.2 (0.97, 1.4)**	**7.2 (6.6, 7.8)**	**1.8 (1.4, 2.1)**

[a]HPV status based on HC2 results at baseline.

[b]Frequencies for each category shown in table 1.

[c]Precolposcopy: women eligible for colposcopy based on referrals using cytology or HPV results, regardless of whether they went to colposcopy or not and, for those who went, regardless of histology results at baseline.

[d]Postcolposcopy: women who went to colposcopy and had histology results of lower than CIN 2 at baseline.

[e]Absolute risks calculated using logistic-Weibull models.

[f]HPV+ NILM includes women with 2 consecutive HPV+ NILM results or with HPV+ NILM and a consecutive HPV- ASC-US result.

3+ detected occurred among women with HPV-negative results but abnormal cytology. After considering the postcolposcopy cotest results, among women found to have < CIN 2 at colposcopy, the original reason for colposcopy referral could be grouped based on similar risks into higher than LSIL (suggestive of precancer, with 3-year risks higher than 10% among HPV+ women) versus LSIL or lower (suggestive of HPV infection, with 3-year risks around 5% among HPV+ women). The specifics of the < CIN 2 colposcopic biopsy diagnosis (CIN 1, atypia, normal, no biopsy taken) did not affect subsequent risk (data not shown).

Half (49%) of women in surveillance after a diagnosis of < CIN 2 at colposcopy were HPV negative at postcolposcopy cotesting and had very low (0.5% or less) 1-year risk of CIN 3+. In fact, those referred to colposcopy for LSIL cytology or less and with HPV-negative NILM cotesting results postcolposcopy

TABLE 3. Postcolposcopy[c] Absolute Risk Reduction of Risk of CIN 3+, by Reason for Colposcopy Referral and HPV Status

		1 year			3 years		
Reason for colposcopy referral[a]		Precolpo[b] risk	Postcolpo[c] risk[d]	Absolute risk reduction	Precolpo[b] 3-yr risk[d]	Postcolpo[c] 3-yr risk[d]	Absolute risk reduction
HPV+	HSIL+	44.4	7.7	36.7	45.4	9.3	36.1
	ASC-H	22.2	4.7	17.5	23.9	6.5	17.4
	AGC	23.6	5.6	18	26	8	18
	LSIL	3.9	1.1	2.8	4.6	1.8	2.8
	HPV+ ASC-US	4.3	1.3	3	5.2	2.2	3
	HPV+ NILM[e]	3.4	1.1	2.3	4.5	2.1	2.4
HPV-	HSIL+	18.8	1.9	17	19.4	2.6	16.8
	ASC-H	2.1	0.59	1.6	2.4	0.67	1.8
	AGC	0.91	0.13	0.8	0.98	0.19	0.8
	LSIL	0.96	0.49	0.5	1.2	0.68	0.5
Total		**6.3**	**1.2**	**5.1**	**7.2**	**1.8**	**5.4**

[a]HPV status based on HC2 results at baseline.

[b]Precolposcopy: women eligible for colposcopy based on referrals using cytology or HPV results, regardless of whether they went to colposcopy or not and, for those who went, regardless of histology results at baseline.

[c]Postcolposcopy: women who went to colposcopy and had histology results of less than CIN 2 at baseline.

[d]Absolute risks calculated using logistic-Weibull models.

[e]HPV+ NILM includes women with 2 consecutive HPV+ NILM results or with HPV+ NILM and a consecutive HPV- ASC-US result.

TABLE 4. Risk of CIN 3+ by Return Cotest Results Postcolposcopy[a]

				At return cotest		3 years after return cotest	
Reason for referral	**Cotest results[b]**	**n[c]**	**Percent [d]**	**n[e]**	**Risk**	**n[f]**	**Risk**
HSIL+[g]	HPV+ overall	397	0.6	53	17.7 (13.9, 22.5)	62	19.5 (15.4, 24.5)
	HPV+/>LSIL	145	0.2	38	24.1 (17.1, 31.1)	40	-
	HPV+/ASCUS or LSIL	174	0.2	11	11.4 (7.0, 18.5)	17	12.8 (8.0, 20.1)
	HPV+/NILM	78	0.1	4	7.7 (3.2, 18.0)	5	11.3 (5.4, 22.8)
	HPV- overall	630	0.9	1	0.3 (0.1, 1.6)	2	0.6 (0.2, 2.0)
	HPV-/>LSIL[h]	22	0.0	1	4.5 (−4.1, 13.2)	1	4.5 (−4.1, 13.2)
	HPV-/ASC-US or LSIL	88	0.1	0	0.0	0	0.0
	HPV-/NILM	514	0.7	0	0.0	0	0.0
ASC-H	HPV+ overall	353	0.5	25	8.8 (6.2, 12.6)	31	10.5 (7.6, 14.6)
	HPV+/>LSIL	69	0.1	15	23.5 (14.8, 36.1)	16	26.1 (16.4, 40.1)
	HPV+/ASCUS or LSIL[h]	118	0.2	6	4.2 (0.6, 7.9)	6	4.2 (0.6, 7.9)
	HPV+/NILM	160	0.2	4	5.0 (2.4, 10.2)	9	7.3 (3.9, 13.2)
	HPV- overall [h]	2,662	3.8	7	0.2 (0.0, 0.4)	10	-
	HPV-/>LSIL[h]	58	0.1	6	8.6 (1.4, 15.8)	6	8.6 (1.4, 15.8)
	HPV-/ASC-US or LSIL	147	0.2	0	0.0	0	0.0
	HPV-/NILM	2,420	3.5	1	-	4	-
AGC	HPV+ overall	781	1.1	63	10.7 (6.7, 16.8)	79	12.6 (8.3, 19.0)
	HPV+/>LSIL	163	0.2	39	28.6 (21.7, 37.3)	42	30.2 (22.9, 39.3)
	HPV+/ASCUS or LSIL	370	0.5	17	6.7 (4.3, 10.3)	24	8.7 (5.7, 12.9)
	HPV+/NILM	244	0.3	6	4.8 (2.6, 9.0)	12	6.9 (4.0, 11.7)
	HPV- overall	1,840	2.6	5	0.5 (0.2, 1.1)	8	0.7 (0.4, 1.4)
	HPV-/>LSIL[h]	39	0.1	2	5.1 (−1.7, 12.0)	2	5.1 (−1.7, 12.0)
	HPV-/ASC-US or LSIL	227	0.3	2	1.4 (0.4, 4.4)	3	2.0 (0.8, 5.4)
	HPV-/NILM [h]	1,565	2.2	1	0.2 (0, 1.0)	3	-
LSIL	HPV+ overall	7,280	10.4	176	3.6 (2.8, 4.7)	240	4.7 (3.8, 5.8)
	HPV+/>LSIL	467	0.7	86	20.8 (16.9, 25.3)	90	21.7 (17.8, 26.4)
	HPV+/ASCUS or LSIL	4,625	6.6	77	2.9 (2.4, 3.5)	118	4.0 (3.4, 4.8)
	HPV+/NILM	2,118	3.0	12	1.3 (0.9, 2.0)	30	2.4 (1.7, 3.3)
	HPV- overall	1,1472	16.4	8	0.1 (0.1, 0.2)	12	0.3 (0.2, 0.4)
	HPV-/>LSIL	60	0.1	2	4.1 (1.2, 13.8)	3	5.5 (1.7, 16.7)
	HPV-/ASC-US or LSIL [h]	1,622	2.3	4	0.2 (−0.0, 0.4)	6	-
	HPV-/NILM	9,678	13.9	2	0.1 (0.0, 0.2)	3	0.2 (0.1, 0.3)
HPV+ ASC-US	HPV+ overall	8,636	12.4	229	4.4 (3.5, 5.4)	339	5.6 (4.7, 6.6)
	HPV+/>LSIL	542	0.8	91	21.5 (17.8, 25.9)	102	23.4 (19.5, 28.0)
	HPV+/ASCUS or LSIL	4,603	6.6	113	4.0 (3.4, 4.7)	163	5.0 (4.3, 5.7)
	HPV+/NILM	3,413	4.9	25	2.2 (1.6, 2.8)	74	3.5 (2.9, 4.3)
	HPV- overall	12,111	17.4	2	0.1 (0.0, 0.2)	10	0.3 (0.2, 0.4)
	HPV-/>LSIL	60	0.1	0	0.0	0	0.0
	HPV-/ASC-US or LSIL	990	1.4	1	0.3 (0.1, 1.2)	3	0.7 (0.3, 1.7)
	HPV-/NILM	10,966	15.7	1	0.1 (0.0, 0.2)	7	0.2 (0.1, 0.4)
HPV+ NILM	HPV+ overall	4,237	6.1	107	4.0 (3.4, 4.7)	168	5.3 (4.6, 6.1)
	HPV+/>LSIL	221	0.3	49	27.5 (21.5, 34.6)	54	28.3 (22.3, 35.6)
	HPV+/ASCUS or LSIL	1,519	2.2	38	3.6 (2.7, 4.8)	56	4.9 (3.8, 6.2)
	HPV+/NILM	2,470	3.5	19	2.2 (1.7, 3.0)	57	3.5 (2.8, 4.4)
	HPV- overall	5,470	7.8	1	0.1 (0.0, 0.2)	4	0.2 (0.1, 0.5)
	HPV-/>LSIL [h]	15	0.0	1	6.7 (−5.9, 19.2)	1	6.7 (−5.9, 19.2)
	HPV-/ASC-US or LSIL	196	0.3	0	0.0	0	0.0
	HPV-/NILM [i]	5,220	7.5	0	0.1 (0, 0.2)	3	-

[a]Postcolposcopy: women who went to colposcopy and had histology results of less than CIN 2 at baseline.
[b]Cotest results for HPV+ or HPV- overall include cytology categories shown and missing cytology (not shown in table).
[c]No. CIN 3+ by the end of follow-up.
[d]Percent of surveillance population (69,790 women with lower than CIN 2 histology at first colposcopy).
[e]No. CIN 3+ at return cotest.
[f]No. CIN 3+ 3-years after return cotest.
[g]Includes AIS and cancer.
[h]Estimate based on prevalent risk at return cotest. Inadequate data preclude risk estimate at 3 years.
[i]Nonzero risk estimate with "0" cases because of Weibull assumptions.

TABLE 5. Cancer Frequencies and Time to Diagnosis

Reason for colposcopy referral[a]		Precolposcopy							Postcolposcopy (<CIN 2 biopsy at colposcopy)				
				Diagnosis time		Cancer type					Cancer type		
		Category frequency	No. cancers	At first colpo visit	Not found at first colpo visit	Adeno	SCC	Others	Category frequency	No. cancers	Adeno	SCC	Others
HPV+	HSIL+	3,788	184	180	4	32	135	17	1,116				
	ASC-H	4,092	34	29	5	7	24	3	2,255	5	3	2	
	AGC	1,112	49	43	6	37	7	5	698	7	5	1	1
	LSIL	25,309	11	9	2	3	8		19,346	1	1		
	HPV+ ASC-US	39,125	53	34	19	22	26	5	30,467	14	5	7	2
	HPV+ NILM[d]	13,376	29	9	20	19	4	6	8,869	6	4	1	1
HPV-	HSIL+	272	11	9	2	1	9	1	145				
	ASC-H	1,662	6	6	0	1	5		1,273	1		1	
	AGC	3,860	6	3	3	4	1	1	2,922				
	LSIL	4,931	5	2	3	1	4		2,699	3	1	2	
Total		**97,527**	**388**	**324**	**64**	**127**	**233**	**38**	**69,790**	**37**	**19**	**14**	**4**

[a]HPV status based on HC2 results at baseline.

[b]Precolposcopy: women eligible for colposcopy based on referrals using cytology or HPV results, regardless of whether they went to colposcopy or not and, for those who went, regardless of histology results at baseline.

[c]Postcolposcopy: women who went to colposcopy and had histology results of less than CIN 2 at baseline.

[d]HPV+ NILM includes women with two consecutive HPV+ NILM results or with HPV+ NILM and a consecutive HPV- ASC-US result.

(37.1% of total population in postcolposcopy surveillance) were at nearly the same 3-year risk (0.2%) as those with NILM cytology in the KPNC screening population.

Table 5 shows the frequencies and time to diagnosis of cancer cases. Of the 388 cancers diagnosed in the entire follow-up, 83.5% were detected through CIN 2+ histology at the initial colposcopy; 64 were not. Thirty-seven were detected through postcolposcopy surveillance after a biopsy of < CIN 2. Most (89.9%) of the cancers in the postcolposcopy population were HPV+ at the initial colposcopy referral visit. We were unable to further stratify our analyses by cotest results postcolposcopy because of the low number of cases.

DISCUSSION

Our results confirm and extend previous observations, and support the return of most women with < CIN 2 colposcopy results to the currently recommended 3-year interval after a single negative cotest, using the risk of CIN 3+ at 3 years after a negative cytology as the level of acceptable risk. Our results clarify the level of reassurance associated with a single < CIN 2 colposcopy, and the combination of a single < CIN 2 colposcopy and a negative cotest. In fact, a single negative cotest after a < CIN 2 colposcopy may provide sufficient protection even for women with higher-grade screening results preceding their < CIN 2 biopsies to resume screening at approximately 3-year intervals. This conclusion presumes sensitive colposcopic biopsy protocols, that is, including multiple biopsies.

All colposcopy results, like all screening test results, can be considered as measurements of risk.[9] Risk is rarely zero, as may be appreciated in Tables 2 to 4. Any set of management recommendations and the conduct of clinical practice therefore unavoidably flow from implicit judgments about what constitutes "acceptable risk". Failure to make the discussion of what constitutes "acceptable risk" explicit will hamper the evolution of screening recommendations as the incidence of invasive cancer in the United States continues to fall, changing the balance of risk and benefit associated with screening and management recommendations.

Among HPV-positive women with lower than HSIL cytology, colposcopy results of normal and CIN 1 signify viral carriage without precancer, predict very similar risks of CIN 3+, and therefore should be clinically managed as a single group (data not shown). Combining the report of Moscicki et al concerning the follow-up of untreated CIN 2 (equivocal precancer) and the "unfortunate experiment" in New Zealand with the follow-up of untreated CIN 3 (precancer), it is now possible to appreciate that there are 4 distinct colposcopic outcome categories with dramatically different risks, which should therefore be identified and managed differently: normal/CIN 1 (representing HPV infection), CIN 2 (equivocal precancer), CIN 3 (more definite precancer), and cancer.[10,11] States implying an HPV infection that resolves do not confer long-term elevations in cancer risk in contrast to CIN 2/3, which confers a higher progression risk over a longer period. Thus, distinguishing transient HPV infections from true and equivocal precancers is important.

Most women constituting colposcopic practice in the past 2 decades in the United States have been referred for minor screening abnormalities. In this report, LSIL, HPV+ ASC-US, 2 consecutive HPV+ NILM, or HPV+ NILM followed by HPV− ASC-US results comprised approximately 85% of women undergoing colposcopy and biopsy, and yielded 61.0% of the CIN 2+ cases (Table 1). Most (82.5%–97.5%) of women undergoing colposcopy for these minor abnormalities harbor < CIN 2 at colposcopy and are recommended to undergo repeat cotesting in 1 year. In other words, most (87%) CIN 2+ is diagnosed after low-grade cytologic abnormalities but most low-grade cytologies do not represent high-grade histology. Although 52.6% of these women will have a negative (HPV-NILM) cotest at their rescreening, 41.0% will be HPV+ (Table 4), and 15.7% will be diagnosed with CIN 2+ in the subsequent 3 years.

Definitive assessment of the role of cytology in the follow-up of women with < CIN 2 colposcopy is not possible, even starting with greater than 90,000 colposcopies, for 2 reasons. First, the occurrence of CIN 2+ in women after a < CIN 2 colposcopy and a subsequent negative HPV test is so vanishingly rare that risk

estimates associated with specific reasons for referral and postcolposcopy cotest results are imprecise (Table 4). Second, we need as a cervical cancer prevention community to be able to have an explicit conversation about "acceptable risk" and whether the additional reassurance provided by cytology is warranted.

In our study, a single colposcopy with < CIN 2 histology greatly reduced the risk of CIN 2+ over the subsequent 3 years. For example, among women with HSIL+ who were HPV positive at referral, CIN 3+ risk after 3 years was reduced from 45% precolposcopy to 9.3% after a colposcopy showing < CIN 2. This level of reassurance was not achieved by simply looking at the cervix with the colposcope. Starting in November of 2008, KPNC providers were given instructions about the conduct of colposcopy that mandated (at minimum) biopsy of all abnormal appearing tissue for every colposcopy, and an endocervical curettage for every colposcopy in the absence of pregnancy.[12,13] The 4-quadrant plus endocervical curettage biopsy recommendations of Pretorius and Belinson were "encouraged" if the requisite 2 mm punches were available.[14] To account for these changes in KPNC colposcopy protocols, we conducted ancillary analyses stratifying by colposcopy date in 3 groups: earlier than 2008, 2008 to 2010, and 2011 or later. Although the magnitude of the risks differed slightly, the reduction in risk postcolposcopy was observed in all strata, regardless of the year when colposcopy was performed.

The addition of a single negative cotest in follow-up of a colposcopy with < CIN 2 histology is very powerful for the exclusion of subsequent CIN 3+, regardless of the initial indication for colposcopy. The generally low risk levels that we observed are concordant with the 2012 management guidelines for minimally abnormal screening results, which recommended 3-year cotesting after a single negative cotest 1-year postcolposcopy.[7] Of note, KPNC procedures may differ from US standard of care and may limit the generalizability of our results. Additional datasets are needed to assess generalizability in different settings.

A new insight contained in the reported experience is that this combination of a single < CIN 2 colposcopy and subsequent HPV-negative NILM cotest confers risk levels low enough to permit consideration of a recommendation for a 3-year return interval after major screening abnormalities as well (Table 4).

It should be noted that of the 37 cancers in women after a < CIN 2 colposcopy, 3 were cotest negative and one was preceded by an HPV negative LSIL cotest. An explicit discussion of acceptable risks is required.

To our knowledge, this is the largest reported study of postcolposcopy risk of CIN 3+, with a final sample of 107,005 women referred to colposcopy. The main limitation is the lack of availability of HPV typing information for further risk stratification. The average follow-up time for women in this study was approximately 3 years, permitting reasonably precise longitudinal estimates of risk given the extremely large sample size. The postcolposcopy 3-year risk of CIN 3+ of women referred to colposcopy for HSIL+, HPV-positive ASC-H, or HPV-positive AGC was somewhat higher than the risk in women referred for other reasons (although greatly reduced from precolposcopy levels because of detection of the most overt cases at colposcopy). These are preliminary estimates leading to the risk matrix that will eventually be put on the next set of management guidelines. In future analyses, given the now-expanded KPNC experience, we will examine residual risk for this fortunately small group using different combinations and additional rounds of follow-up cotests.

Women referred to colposcopy based on initially HPV-positive NILM cotesting are a sizable population (20% of colposcopy referrals) and their 3-year risk of CIN 3+ is similar to the risk for HPV-positive ASC-US and HPV-positive LSIL referrals (Table 2). We need to continue to study this group of referrals to explore its heterogeneity. Specifically, future analyses should further stratify the risk within this referral category, evaluating HPV typing and detailed results from repeated cotest after 1 year to identify whether abnormal cytology (including ASC-US) at follow-up or persistence of HPV infection is triggering the colposcopy referral. For example, we would predict that women with persistent HPV positivity would be at higher risk than those whose second test was HPV-negative ASC-US.

The ultimate goal of coming analyses will be to divide women postcolposcopy into meaningful risk strata, permitting matching of management to risk. The ideal will be the quickest and safest return of most women, as appropriate, to extended-interval cervical cancer screening.

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