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Comparative risk of high-grade histopathology diagnosis following a CIN1 finding in endocervical curettage vs. cervical biopsy

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Abstract

Objective—No evidence-based clinical management recommendations exist for women with an endocervical curettage (ECC) cervical intraepithelial neoplasia (CIN) grade 1 (CIN1) result when the concurrent cervical biopsy is not high-grade. For women with these pathology findings, we assessed their short-term risk of high-grade histopathology diagnosis in the Calgary Health Region where ECC was routinely performed.

Materials and Methods—We analyzed pathology and colposcopy reports from 1902 referral colposcopies where both ECC and biopsies were normal or CIN1. We calculated the short-term risk of CIN2 or more severe (CIN2+) detected 12–24 months after colposcopy. Pearson chi-square tests or Fisher's exact tests were used to compare risks of a CIN2+ diagnosis between combinations of test results and strata of risk factors.

Results—The short-term risk of CIN2+ was the same following a CIN1 biopsy and CIN1 ECC (4.9% of 1389 vs. 5.0% of 359, respectively, P=.37). Compared to low-grade referral cytology, the risk of CIN2+ following high-grade cytology was elevated significantly for CIN1 ECC (13.3% vs. 3.3%, P<.01) and non-significantly for CIN1 biopsy (7.1% vs. 4.6%, P=.12).

Conclusions—Following low-grade cytology, the short-term risk of a high-grade histologic diagnosis in women with either CIN1 ECC or biopsy is equivalent, suggesting similar management. A CIN1 ECC may warrant different management in the context of high-grade referral cytology.

Keywords

cervical intraepithelial neoplasia; colposcopy; curettage; diagnosis; endocervical sampling

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Introduction

In a colposcopy examination, colposcopists take biopsies of visualized lesions and may perform endocervical curettage (ECC) to rule out the presence of cervical intraepithelial neoplasia hidden in the endocervical canal. The management implications of an ECC diagnosis of low-grade lesion (cervical intraepithelial neoplasia grade 1 [CIN1]) are uncertain if the concurrent cervical biopsy result shows no evidence of high-grade lesions (normal or CIN1). Depending on the referral cytology, the patient could be managed as either 1) having a low-grade cervical lesion with an anticipated high rate of spontaneous regression warranting conservative management for up to two years; or 2) having a lesion that possibly extends into the endocervical canal and therefore triggers a diagnostic excisional procedure (1), although limited data have informed this guideline.

The Calgary Health Region and the Alberta Cervical Cancer Screening Program in Alberta, Canada have an extensive data collection system that records histopathology, cytopathology and colposcopic and patient characteristics for all colposcopy exams conducted. Because ECC was routinely taken at essentially all colposcopy exams in Alberta's outpatient colposcopy clinics from 2003 until recently, we were able to examine the risks of high-grade histopathology diagnosis, cervical intraepithelial neoplasia grade 2 or more severe (CIN2+), associated with a CIN1 ECC and compare them with a CIN1 on biopsy, which is managed by follow-up rather than immediate treatment.

Materials and Methods

The Calgary Health Region provides services to a population of approximately 1.2 million. Colposcopy, cytopathology and histopathology are regionalized services with uniform practice guidelines and standards. Details of the data extraction procedures are provided elsewhere (2). Briefly, de-identified pathology reports were obtained for histological specimens collected at colposcopy exams read between January 1, 2003 and December 31, 2007 and linked to records from colposcopy examinations. Cytopathology records for specimens processed at Calgary Laboratory Services up to two years prior to the date of the reading of the histopathology specimen were retrieved and linked as well. The record review received human subjects research approval from the Conjoint Health Research Ethics Board Review, University of Calgary and Calgary Health Region and was considered exempt from review by the National Cancer Institute, National Institutes of Health.

This analysis was conducted at the patient level and we included women for whom the first visit was a referral (that is, their cytopathology result was within 270 days of the examination and the result was unsatisfactory or abnormal) and the diagnoses for ECC and biopsy specimens were either CIN1 or normal. In addition, they had to have had at least one subsequent cervical biopsy, ECC, loop electrosurgical excision procedure (LEEP), or endometrial biopsy 12 to 24 months after the first visit. The standard and widely-practiced management for CIN1 biopsy and CIN1 ECC established in the Calgary Health Region in 2003 was repeat colposcopy at 6 and 12 months with return to annual cytology if no CIN2+ was identified after 18 months of repeat colposcopy. For women with normal biopsy after an ASC-US or LSIL referral cytology, a repeat colposcopy was recommended at 6 months with discharge to annual cytology if subsequent colposcopy was still normal.

We compared the risk of a precancerous diagnosis among combinations of normal and CIN1 biopsy and ECC results. We defined precancer as a histologic diagnosis of CIN2+, detected in cervical biopsy, ECC, loop electrosurgical excision procedure (LEEP), or endometrial biopsy 12 to 24 months after the initial pathology reading. We also used CIN3 as a more

scientifically rigorous precancerous endpoint and a better surrogate of cervical cancer risk (3, 4).

Findings were stratified by the woman's age at the examination, referral cytology, satisfactory colposcopy exam, and colposcopy impression when available. We also considered the difference in outcome given length of follow-up. Pearson chi-square tests or Fisher's exact tests were used to compare risks of high-grade histopathology diagnosis between combinations of test results and strata of risk factors. All analyses were conducted using Stata 11.0 analytic software (StataCorp LP, College Station, TX).

Results

Overall, 1,902 women were identified as having either a normal or CIN1 diagnosis on biopsy and ECC (Table 1). Women with a CIN1 biopsy result were younger and more likely to have a low-grade colposcopic impression than women with a normal biopsy result. Women with a CIN1 ECC result were similarly older than women with a normal ECC result. Overall, the risk of CIN2+ 12–24 months after the colposcopy exam was almost identical for a CIN1 biopsy result compared to a CIN1 ECC result (4.9% for biopsy vs. 5.0% for ECC, P=.37); the risk of CIN3 or worse was also similar (2.0% for biopsy and 2.8% for ECC, P=.93) (Table 2). When the biopsy was normal, an (albeit infrequent) ECC result of CIN1 conferred no greater risk of high-grade histopathology compared to an ECC result of normal (7.4% vs. 6.1% risk of CIN2+, P=.76 and 3.7% vs. 2.4% risk of CIN3 or worse, P=.64). Similarly, when the biopsy was CIN1, a CIN1 ECC result was associated with similar minimal risk of high-grade histopathology and 2.6% vs. 1.8% risk of CIN3 or worse, P=.39). Finally, across all four combinations of biopsy and ECC results (normal/normal, normal/CIN1, CIN1/normal, and CIN1/CIN1), the risks of CIN2+ were similar (6.1%, 7.4%, 5.0%, and 4.6%, respectively, P=.59).

However, when stratifying by referral cytology, the risks of CIN2+ differed (Table 3). Following an ECC result of CIN1, the risk of CIN2+ was elevated when the referral cytology was high-grade squamous intraepithelial lesion (HSIL) or worse compared to a referral cytology of atypical squamous cells of undetermined significance (ASC-US) or low grade squamous intraepithelial lesion (LSIL) (13.3% vs. 3.3%, respectively, P<.01). Following a biopsy result of CIN1, the risk of CIN2+ was also higher when the referral cytology was HSIL or worse compared to a referral cytology of ASC-US or LSIL, although the association did not reach statistical significance (7.1% vs. 4.6%, respectively, P=.12).

Among women over 45 years old, none of the 116 women with a CIN1 ECC result were diagnosed with CIN2+ and only 4 of the 316 (1.3%) women age 45 or older with a CIN1 biopsy result were subsequently diagnosed with CIN2+. Women under 30 years old were at 7.3% risk for CIN2+, regardless if either their biopsy or ECC was CIN1. A colposcopic impression of high-grade or worse was associated with a two to three times higher risk of CIN2+ compared to a normal or low grade impression among women with a CIN1 result on either biopsy or ECC (P=.01 for ECC and P<.01 for biopsy).

No other factors appeared to be statistically significant determinants of the risk of CIN2 or worse following CIN1 biopsy or ECC, although we noted a qualitative difference in the risk of CIN2 or worse following CIN1 ECC compared to a CIN1 biopsy among those with a unsatisfactory colposcopy (1.9% vs. 5.3%, respectively, P=.45).

Discussion

We report the comparative risks of ECC and biopsy diagnoses of CIN1 and normal in "real-life" colposcopy practices where physicians with a variety of training levels routinely

conduct ECC at all colposcopy exams. In general, the short-term risk of CIN2+ following a CIN1 or normal diagnosis from an ECC or biopsy were the same. Therefore, we suggest that all these mildly abnormal histologic diagnoses or normal histology following a mildly abnormal cytology be managed identically.

The risk of high-grade histopathology varied by referral cytology. Women with referral cytology of ASC-US or LSIL and a CIN1 diagnosis on either cervical biopsy or ECC are at very low risk for precancer. Because the risks are so low, especially for CIN3 (our best proxy for cancer risk), surveillance with cytology or HPV DNA testing rather than treatment seems appropriate.

For women with a CIN1 biopsy preceded by an HSIL referral cytology, the current guidelines allow for either 1) diagnostic excisional treatment or 2) surveillance with repeat colposcopy and cytology at 6 month intervals for one year only if the ECC findings are negative (presumably the endocervical sampling does not contain CIN of any grade)(1). In this study the elevated risk of CIN1 in ECC was confirmed because, 8 of 60 (13.3%) women with an ECC result of CIN1 subsequent to an HSIL or worse referral cytology developed a high-grade lesion within 12–24 months. We suggest that the management of CIN1 on an ECC, like for a CIN1 biopsy, following HSIL referral cytology warrants different follow-up compared to CIN1 following mild cytologic abnormalities. Depending on the risk for noncompliance, continued observation would likely suffice as opposed to excisional treatment, which is indicated for higher risk groups (5).

Our findings are not informative to all management guidelines regarding CIN1 in ECC. Current management guidelines recommend that a diagnostic excisional procedure be performed for women with a CIN1 lesion that persists more than 2 years and positive endocervical sampling (CIN of any grade)(1). Our analysis includes women for whom the colposcopy visit was a referral subsequent to an unsatisfactory or abnormal referral cytology smear within 270 days. Therefore, we cannot definitively estimate the risk of high-grade lesions among women with a persistent CIN1 lesion on ECC. But, these data support that an ECC result of CIN1 subsequent to a low-grade cytologic finding requires no additional excisional management than that recommended for a biopsy result of CIN1.

This analysis was limited to a short-term follow-up period of 12–24 months after the initial biopsy and ECC diagnoses. It is possible that additional high-grade precancer (CIN3) and cancer were missed during this period and would be detected in subsequent years.

In conclusion, we found that ECC provided little information for risk stratification. The ECC was rarely called CIN1 when biopsy was called normal and the associated short-term risk of the CIN1 ECC was not appreciably different than the risk following a normal ECC, with the exception of women with high-grade referral cytology. As practiced now, ECC provides limited diagnostic utility and benefit to most patients, and its use should perhaps be limited to select populations (2). Further evidence of its limited utility lies in the finding that is subject to false positive results (6) and diagnoses in ECC are not necessarily reproducible (7).

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Table 1

Patient characteristics given biopsy and endocervical curettage (ECC) result

	Biopsy result						ECC result			
	Total		Normal		CIN1		Normal		CIN1	
	N	Col %	N	Col %	N	Col %	N	Col %	N	Col %
Total	**1902**	**100**	**513**	**100**	**1389**	**100**	**1543**	**100**	**359**	**100**
Referral Cytology										
ASC-US/LSIL	1613	84.8	420	81.9	1193	85.9	1314	85.2	299	83.3
HSIL or worse	289	15.2	93	18.1	196	14.1	229	14.8	60	16.7
p-value						.03				.37
Age (years)										
19–29	626	32.9	148	28.8	478	34.4	530	34.3	96	26.7
30–44	805	42.3	209	40.7	596	42.9	658	42.6	147	40.9
45 or older	471	24.8	156	30.4	315	22.7	355	23.0	116	32.3
p-value						<.01				<.01
Colposcopic Impression										
Normal	310	16.3	112	21.8	198	14.3	244	15.8	66	18.4
Low grade	1155	60.7	291	56.7	864	62.2	947	61.4	208	57.9
High grade or worse	37	7.2	149	10.7	149	9.7	149	9.7	37	10.3
Missing	251	13.2	73	14.2	178	12.8	203	13.2	48	13.4
p-value *						<.01				.39
Satisfactory Colposcopy										
Yes	1342	70.6	342	66.7	1000	72.0	1102	71.4	240	66.9
No	217	11.4	74	14.4	143	10.3	164	10.6	53	14.8
Missing	343	18.0	97	18.9	246	17.7	277	35.4	66	5.9
p-value						.03				.07
Time of Follow-up (days)										
365–553	950	49.9	253	49.3	697	50.2	749	48.5	201	56.0
554–730	952	50.1	260	50.7	692	49.8	794	51.5	158	44.0
p-value						.74				.01

* Excludes missing values

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Table 2

Absolute risk of precancer 12–24 months after initial colposcopy exam given biopsy and endocervical curettage. Abbreviations: Cervical intraepithelial neoplasia Grade 1 (CIN1), Grade 2 (CIN2) and Grade 3 (CIN3)

		Total		CIN2 or worse			CIN3 or worse		
Biopsy Result	**ECC Result**	**N**	**Col %**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**
Normal	*	513	27.0	32	6.2	4.3%–8.7%	13	2.5	1.4%–4.3%
CIN1	*	1389	73.0	68	4.9	3.8%–6.2%	28	2.0	1.3%–2.9%
*	Normal	1543	81.1	82	5.3	4.2%–6.6%	31	2.0	1.4%–2.8%
*	CIN1	359	18.9	18	5.0	3.0%–7.8%	10	2.8	1.3%–5.1%
Normal	Normal	459	26.3	28	6.1	4.1%–8.7%	11	2.4	1.2%–4.2%
Normal	CIN1	54	3.1	4	7.4	2.1%–17.9%	2	3.7	0.5%–12.7%
CIN1	Normal	1084	62.0	54	5.0	3.8%–6.5%	20	1.8	1.1%–2.8%
CIN1	CIN1	305	17.4	14	4.6	2.5%–7.6%	8	2.6	1.2%–5.1%
TOTAL		1902	100.0	100	5.3	4.3%–6.4%	41	2.2	1.6%–2.9%

* Either normal or CIN1 result

Table 3

Absolute risk of cervical precancer diagnosis 12–24 months after initial colposcopy exam given patient and exam characteristics. Cervical intraepithelial neoplasia Grade 1 (CIN1), Grade 2 (CIN2) and Grade 3 (CIN3), atypical squamous cells of undetermined significance (ASC-US), low grade intraepithelial lesion (LSIL), and high grade intraepithelial lesion (HSIL)

	ECC=CIN1				Biopsy=CIN1			
	N	**CIN2+**	**%**	***P***	**N**	**CIN2+**	**%**	***P***
Referral Cytology								
ASC-US/LSIL	299	10	3.3%		1193	54	4.6%	
HSIL or worse	60	8	13.3%	.001	196	14	7.1%	.123
Age (years)								
19–29	96	7	7.3%		478	35	7.3%	
30–44	147	10	6.8%		596	29	4.9%	
45 or older	116	0	0.0%	.004	316	4	1.3%	<.001
Colposcopic Impression								
Normal	66	2	3.0%		198	7	3.5%	
Low grade	208	9	4.3%		864	39	4.5%	
High grade or worse	37	5	13.5%	.014[a]	149	17	11.4%	<.001[a]
Missing	48	2	4.2%		178	5	2.8%	
Satisfactory Colposcopy								
Yes	240	14	5.8%		1000	50	5.0%	
No	53	1	1.9%	.3[b]	143	8	5.6%	.76[b]
Missing	66	3	4.5%		246	2	0.8%	
Time of Follow-up (days)								
365–553	201	9	4.5%		697	36	5.2%	
554–730	158	9	5.7%	.6	692	32	4.6%	.7

[a] Chi-square test calculated for high grade or worse vs. low grade and normal combined.

[b] Chi-square or Fisher's exact test calculated for not satisfactory vs. satisfactory.