Published OnlineFirst February 5, 2018; DOI: 10.1158/1940-6207.CAPR-17-0293

Research Article

Cancer Prevention Research

Clinical Outcomes after Conservative Management of Cervical Intraepithelial Neoplasia Grade 2 (CIN2) in Women Ages 21–39 Years

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Abstract

Cervical intraepithelial neoplasia grade 2 (CIN2) frequently regresses, is typically slow-growing, and rarely progresses to cancer. Some women forgo immediate treatment, opting for conservative management (heightened surveillance with cytology and colposcopy), to minimize overtreatment and increased risk of obstetric complications; however, there are limited data examining clinical outcomes in these women. We performed a retrospective cohort analysis of younger women diagnosed with initially untreated CIN1/2, CIN2 and CIN2/3 lesions at Kaiser Permanente Northern California between 2003 and 2015. Clinical outcomes were categorized into five mutually exclusive hierarchical groups: cancer, treated, returned to routine screening, persistent high-grade lesion, or persistent low-grade lesion. Median follow-up for the 2,417 women was 48 months. Six women were diagnosed with cancer (0.2%), all with history of high-grade cytology, and none after a negative cotest. Thirty percent of women were treated, and only 20% returned to routine screening; 50% remained in continued intensive follow-up, of which 86% had either low-grade cytology/histology or high-risk human papillomavirus (HPV) positivity, but not necessarily persistence of a single HPV type. No cancers were detected after a single negative cotest in follow-up. Almost half of initially untreated women did not undergo treatment, but remained by protocol in colposcopy clinic for 2 or more years in the absence of persisting CIN2$^+$. Their incomplete return to total negativity was possibly due to sequential new and unrelated low-grade abnormalities. The prolonged colposcopic surveillance currently required to return to routine screening in the absence of persisting CIN2$^+$ might not be necessary after a negative cotest.

Significance: Many younger women under conservative management following an initial CIN2 result remain in a clinical protocol of prolonged intensified surveillance without a subsequent diagnosis of CIN2 or more severe diagnoses. More research is needed to determine whether such prolonged management might be unnecessary following a negative cotest for those women with an initial CIN2 but otherwise only low-grade findings. *Cancer Prev Res; 11(3); 165–70. ©2018 AACR.*

Introduction

Cervical cancer incidence rates have declined dramatically where screening programs have been successfully implemented, as precancerous high-grade cervical lesions are detected before the onset of cervical cancer and treated (1–3). There is evidence that about one third of large lesions graded cervical intraepithelial neoplasia grade 3 (CIN3), among older women, will eventually invade (4, 5). On the other hand, lesions graded CIN grade 2 (CIN2), a less reproducible diagnosis, are more biologically heterogeneous, ranging from benign human papillomavirus (HPV) infection to evolving CIN3 (6–8); CIN2 is more likely to regress than CIN3 (8, 9). Although exact figures are lacking, several hundred thousand cases of CIN2 are diagnosed in the United States per year.

Accordingly, the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines specify that observation is preferred for young women with a diagnosis of CIN2, acceptable for young women with CIN2/3, and not

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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doi: 10.1158/1940-6207.CAPR-17-0293

Published OnlineFirst February 5, 2018; DOI: 10.1158/1940-6207.CAPR-17-0293

recommended for young women with unambiguous CIN3 (3, 10). Such conservative management (intensified surveillance with cytology and colposcopy instead of immediate treatment) is sometimes preferred among women still desiring childbearing because of the increased risk of future obstetric complications associated with excisional treatment (11, 12).

Only small studies have evaluated the clinical outcomes for women diagnosed with CIN2 or CIN2/3 and followed with conservative management (13–19), none in routine practice, and few studies included women over age 21 years (16, 17, 19) or more than 50 women (17). We determined clinical outcomes among 2,417 initially untreated women between the ages of 21 and 39 years in the Kaiser Permanente Northern California (KPNC) Cohort Study of over 1.5 million women undergoing cervical cancer screening from 2003 to 2015.

Materials and Methods

Study population

We conducted a retrospective cohort analysis nested within the larger KPNC study of women receiving cervical cancer screening with HPV and cytology cotesting between 2003 and 2015 (20). Eligibility criteria are summarized in Fig. 1. We initially identified 24,515 women with a first biopsy diagnosis of equivocal high-grade lesion or greater [CIN1/2, CIN2, CIN2/3, or CIN3 or more severe diagnosis (CIN3+)]. We restricted this population to younger women, defined here as ages 21 to 39 years, as they are the target for conservative management guidelines due to the potential for obstetric complications of treatment, leading to the exclusion of 7,871 women aged <21 or >39 years. We further restricted our analysis to lesions that would be considered eligible for conservative management (CIN1/2, CIN2, and CIN2/3), excluding 6,015 women with CIN3+. We then excluded women treated within 4 months of their biopsy diagnosis ($N = 376$) or >4 months after their biopsy diagnosis but without an intervening biopsy, HPV, or cytology test ($N = 6{,}660$), as these women received immediate treatment rather than conservative management. There were 3 cancers diagnosed among these excluded women. Finally, women were required to have at least 22 months of follow-up after biopsy diagnosis [the practical minimum time that would permit return to routine screening (i.e., at least 4 months until first follow-up cytology/colposcopy, then 6 months to the second, followed by a cotest 12 months later)], resulting in another 1,176 women being excluded (there were 89 high-grade lesions and no cancers among the 1,176 women excluded for insufficient follow-up time; the rest persisted with low-grade lesions). This resulted in a final cohort of 2,417 women conservatively managed with intensified surveillance (cytology and colposcopy) instead of immediate treatment for equivocal high-grade lesions (CIN1/2, CIN2, or CIN2/3).

Study procedures

Women were categorized into one of five mutually exclusive hierarchical groups according to their clinical outcomes as described in Table 1. Women were categorized as developing cancer if any future biopsy or treatment histology resulted in a cancer diagnosis. If a woman did not have cancer but underwent treatment including loop electrosurgical excision procedure, cold knife cone (cone biopsy), cryotherapy, and/or hysterectomy, they were considered treated. A woman was classified as "exited from colposcopy surveillance" and returned to routine KPNC screening with a cotest every 3 years if she met the KPNC criteria of two or more sequential negative cytologies and colposcopies at least 6 months apart, followed by a negative cotest 12 months later, and did

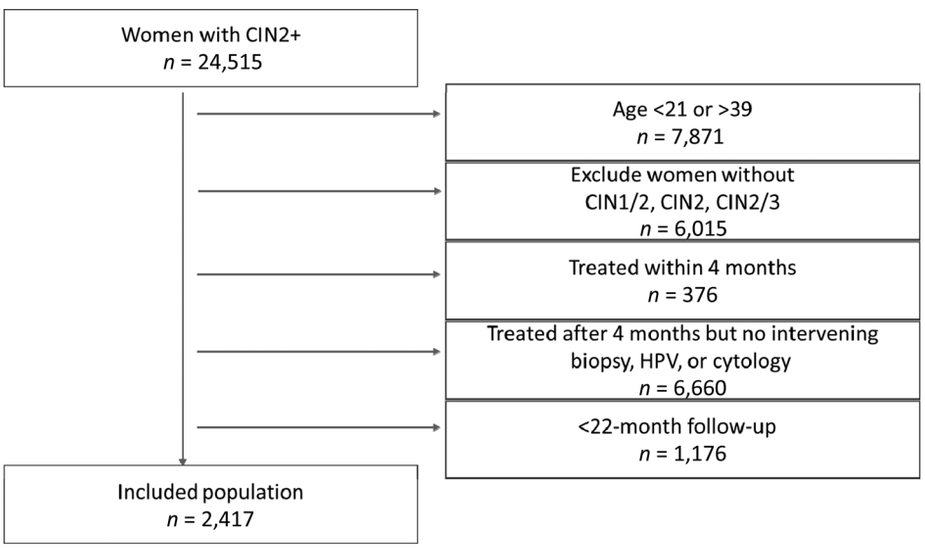

Figure 1.
Flow chart of study eligibility.

Published OnlineFirst February 5, 2018; DOI: 10.1158/1940-6207.CAPR-17-0293

Table 1. Defined clinical outcomes among women with conservative management of equivocal high-grade cervical lesions[a]

Outcome category	Definition	Example[b]
1. Progressed to cancer	Cancer histology from biopsy or treatment	Initial CIN2 diagnosis followed by a cone biopsy or other procedure, which identified a squamous cell carcinoma
2. Treated	Cryotherapy LEEP Cone biopsy Hysterectomy	Initial CIN2 diagnosis followed by HPV$^+$/HSIL leading to a LEEP or other treatment (with a histology result other than cancer)
3. Return to routine screening (exit colposcopy)	2+ sequential negative cytologies and colposcopies 6 months apart followed by a negative cotest 12 months later	Initial CIN2 diagnosis followed by 2 normal Pap smears and colposcopies at 6 and 12 months and a negative cotest at 24 months
4. High-grade lesion	CIN2/3/AIS detected at biopsy without subsequent regression	Initial CIN2 followed by persistent CIN2 or CIN3 or AIS, no regression and no treatment
5. Low-grade lesion	Remaining women who did not fit into 4 groups above. All had at least 1 abnormal biopsy, HPV or Pap test, and at least 22 months of follow-up	Initial CIN2 followed by persistent HPV positivity, LSIL, or CIN1 (without progression, regression, or treatment)

[a](i) Women were categorized as developing cancer if any future biopsy or treatment histology resulted in a cancer diagnosis. (ii) Women were considered treated if they underwent a loop electrosurgical excision procedure (LEEP), cold knife cone (cone biopsy), cryotherapy, and/or hysterectomy. (iii) A woman was classified as "exited from colposcopy surveillance" and returned to routine 3-year cotesting if she did not have cancer, a high-grade lesion or receive treatment, and met the KPNC criteria of two or more sequential negative cytologies and colposcopies at least 6 months apart, followed by a negative cotest 12 months later. (iv) Untreated women with at least one subsequent biopsy or treatment finding of CIN2, CIN2/3, CIN3, or AIS that did not regress were categorized as having continued "high-grade lesions." (v) Finally, a woman was categorized as having a "low-grade lesion" if she did not fall into the other 4 categories, but had a CIN1 or low-grade squamous intraepithelial lesion result in either biopsy or cytology or tested HPV-positive.
[b]An example of screening patterns that would lead to each outcome category. These are illustrative examples, not exhaustive lists.

not have cancer, a high-grade lesion, or receive treatment. Untreated women with at least one subsequent biopsy finding of CIN2, CIN2/3, CIN3, or adenocarcinoma *in situ* (AIS) that did not regress were categorized as having a "persisting high-grade lesion." Finally, a woman was categorized as having a "low-grade lesion" if she did not fall into the other 4 categories, but had a CIN1 or low-grade squamous intraepithelial lesion result from

Table 2. Outcome by reason for colposcopy referral[a] and baseline histology among women with conservatively managed CIN1/2, CIN2, and CIN2/3 biopsy results

		Total		CIN1-2		CIN2		CIN2-3	
Reason for referral	Outcome	*N*	Col	*n*	Col	*n*	Col	*n*	Col
TOTAL		2,189	100	387	100	1,534	100	268	100
	Cancer	6	0.3	1	0.3	3	0.2	2	0.7
	Treated	654	29.9	90	23.3	464	30.2	100	37.3
	Exit colposcopy[b]	403	18.4	78	20.2	265	17.3	60	22.4
	High-grade lesion	166	7.6	33	8.5	115	7.5	18	6.7
	Low-grade lesion	960	43.9	185	47.8	687	44.8	88	32.8
Repeat HC2$^+$		63	100	12	100	44	100	7	100
	Cancer	0	0.0	0	0.0	0	0.0	0	0.0
	Treated	18	28.6	4	33.3	13	29.5	1	14.3
	Exit colposcopy	15	23.8	4	33.3	10	22.7	1	14.3
	High-grade lesion	5	7.9	0	0.0	5	11.4	0	0.0
	Low-grade lesion	25	39.7	4	33.3	16	36.4	5	71.4
ASC-US/HC2$^+$		758	100	154	100	518	100	86	100
	Cancer	2	0.3	0	0.0	1	0.2	1	1.2
	Treated	206	27.2	38	24.7	149	28.8	19	22.1
	Exit colposcopy	156	20.6	29	18.8	101	19.5	26	30.2
	High-grade lesion	49	6.5	11	7.1	30	5.8	8	9.3
	Low-grade lesion	345	45.5	76	49.4	237	45.8	32	37.2
LSIL		824	100	164	100	597	100	63	100
	Cancer	0	0.0	0	0.0	0	0.0	0	0.0
	Treated	228	27.7	33	20.1	171	28.6	24	38.1
	Exit colposcopy	134	16.3	34	20.7	92	15.4	8	12.7
	High-grade lesion	68	8.3	17	10.4	47	7.9	4	6.3
	Low-grade lesion	394	47.8	80	48.8	287	48.1	27	42.9
High-grade cytology[c]		544	100	57	100	375	100	112	100
	Cancer	4	0.7	1	1.8	2	0.5	1	0.9
	Treated	202	37.1	15	26.3	131	34.9	56	50.0
	Exit colposcopy	98	18.0	11	19.3	62	16.5	25	22.3
	High-grade lesion	44	8.1	5	8.8	33	8.8	6	5.4
	Low-grade lesion	196	36.0	25	43.9	147	39.2	24	21.4

[a]$n = 228$ missing reason for colposcopy.
[b]Exit colposcopy means exit intensive surveillance with cytology and colposcopy and return to routine screening (cotesting at 3-year intervals).
[c]High-grade squamous intraepithelial lesion (HSIL), atypical squamous cells, cannot rule out HSIL (ASC-H), atypical glandular cells (AGC), or adenocarcinoma *in situ*.

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Table 3. Worst diagnosis at time of treatment by baseline histology[a]

	Baseline histology							
	CIN1-2		CIN2		CIN2-3		Total[a]	
Worst diagnosis at treatment	***n***	**Col**	***n***	**Col**	***n***	**Col**	***N***	**Col**
Normal	13	13.1	76	15.6	19	16.2	108	15.3
CIN1/LSIL	10	10.1	68	13.9	13	11.1	91	12.9
CIN2/HSIL	53	53.5	185	37.9	48	41.0	286	40.6
CIN3	19	19.2	153	31.4	34	29.1	206	29.3
AIS	3	3.0	4	0.8	1	0.9	8	1.1
Microinvasive	0	0.0	1	0.2	0	0.0	1	0.1
SCC	1	1.0	1	0.2	2	1.7	4	0.6

[a]Worst diagnosis available for 704/717 treated women; missing treatment record for 1 SCC case.

either biopsy or cytology or tested HPV positive. HPV and cytology cotesting were done as described previously (20). Women were referred to colposcopy following local KPNC guidelines, which were largely in accordance with national standards (3).

The KPNC Institutional Review Board (IRB) approved use of the data. The Albert Einstein College of Medicine IRB and National Institutes of Health Office of Human Subjects Research deemed this study exempt from IRB review because there was no protected health information exchanged. The study was conducted in accordance with recognized ethical guidelines (e.g., Declaration of Helsinki, CIOMS, Belmont Report, U.S. Common Rule).

Results

Of the 2,417 women included in this cohort, 428 (17.7%), 1,670 (69.1%), and 319 (13.2%) had an index diagnosis of CIN1/2, CIN2, and CIN2/3, respectively. We included all 3 diagnoses as CIN2. Overall, women had a median follow-up of 48 months [interquartile range (IQR), 31–71 months) from their initial CIN2 histology result. Table 2 shows the reason for the initial colposcopy referral, available for 2,189 of the 2,417 women (90.6%), leading to the index diagnosis. Most were referred (72.3%) due to HPV-positive ASC-US or LSIL cytology, whereas approximately 25% were referred because of a high-grade cytology result (ASC-H, HSIL, AIS, AGC), and <3% were referred for repeat HPV positivity. Women referred to colposcopy for high-grade cytology were most likely to receive treatment during their follow-up, regardless of their baseline histology. Conversely, fewer women referred for ASCUS/HPV$^+$ or LSIL results had treatment, and approximately 45% of these women referred for less than high-grade cytology continued to have low-grade lesions diagnosed during follow-up.

We identified 6 (0.2%; 95% confidence interval, 0.1–0.5) cancer cases, all of which were among women with persistent high-grade lesions and/or HR HPV. Their clinical histories are described in Supplementary Table S1. Furthermore, half of these cases also occurred after a 2- to 3-year gap in follow-up, deviating from the recommended management protocols. All cases had a recent history of a high-grade cytology prior to the cancer diagnosis. Importantly, none of the cases occurred after a negative cotest in follow-up of the index CIN2 diagnosis.

Through the duration of follow-up, almost a third of women eventually received some form of treatment (Table 2), with a median time to treatment of 12 months (IQR, 7–20 months). At the time of the treatment, almost 30% had a worst biopsy of <CIN2/HSIL histology, 41% had CIN2/HSIL histology, and 31% had CIN3+ (Table 3). This pattern was similar across all baseline histology diagnoses, although women with baseline CIN1/2 had a slightly higher proportion of CIN2/HSIL histologies and slightly lower proportion of CIN3 during follow-up compared with those with higher grade baseline lesions.

Only 20% of women met the criteria to exit colposcopic follow-up and return to routine screening. Thus, half of the population remained in the surveillance/colposcopy protocol due to persistent "abnormal" results. Of these, only 7% of women had high-grade lesions identified on colposcopy in follow-up; the other 1,048 women (43%) had low-grade histology or HC2 positivity that neither progressed nor cleared during the period of observation, preventing them from returning to routine screening. With each increasing age group, we saw an increase in the proportion of women who were either treated or exited colposcopy and a decrease in those with both persistent high- and low-grade lesions (Supplementary Table S2). When further stratified by initial histology result, similar patterns by age group remained for those initially called CIN2 or CIN2/3 versus CIN1/2.

Discussion

CIN2 is common, its natural history uncertain, and some women chose not to be treated immediately. Over an average of 4 years of follow-up of 2,417 women with an index CIN2 diagnosis, only 6 cancers were diagnosed. In comparison, approximately 30% were eventually treated and 20% met the criteria to exit surveillance and return to routine screening at 3-year intervals. Forty-three percent of women with an initially untreated CIN2 never received treatment during our follow-up period but remained by protocol in colposcopy clinic follow-up for 2 or more years in the absence of persisting CIN2 or more severe diagnoses (CIN2+). This may be due to persistence without disease or the acquisition of new HPV infections causing low-grade

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abnormal results that are common in younger sexually active women and unrelated to the initial CIN2. Longer follow-up is required to determine whether these women would eventually progress, return to normal, or continue to persist with low-grade abnormalities.

It is important to note that this is a retrospective analysis based on medical record data. As a result, we lack information on factors related to the decision for conservative management versus immediate treatment, such as whether this was a decision guided by other risk factors, provider recommendation, patient preference, or other unknowns. The initial CIN2 lesion was also not tested for p16 by IHC, so we are unable to assess whether that triage marker would have assisted in predicting the outcome.

Previous case series containing 40 to 385 women (mostly age <25 years) with CIN2 found regression rates ranging from 39% to 88% (13, 17, 18, 21) with wide variability in study design and definition of outcomes like "regression" and "persistence." In our slightly older population, we found less evidence of complete return to normalcy, instead finding a large proportion of women with persistent but nonprogressing low-grade lesions. This failure to "clear" or return to routine screening in the absence of progression resulted in a long-term cycle of continued frequent follow-up visits, many including repeat colposcopies and/or biopsy procedures. This cycle comes at a considerable cost to the patient in terms of time, finances, and emotional distress or anxiety.

These findings warrant a reconsideration of the current guidelines requiring a return to complete normalcy to exit increased surveillance in colposcopy clinic and return to routine screening. Further research is needed to determine whether there is a way to identify which women with an initial CIN2 who are under increased surveillance can be safely returned to routine screening after fewer follow-ups without inordinately increasing their cancer risk. Perhaps HPV genotyping, a negative cotest, and/or lack of high-grade cytology could serve as further means to distinguish which women are at higher cancer risk and need continued follow-up and which are lower cancer risk and could be released safely from such intensive surveillance back to routine screening. Circumstances in which younger women with an untreated, transient CIN2 diagnosis but persisting low-grade abnormalities can return safely to less intensive screening deserve further study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M.I. Silver, J.C. Gage, M. Schiffman, T. Lorey, W.K. Kinney, P.E. Castle

Development of methodology: J.C. Gage, M. Schiffman, L.C. Cheung

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Schiffman, B. Fetterman, T. Lorey, A. Locke, W.K. Kinney, P.E. Castle

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.I. Silver, J.C. Gage, M. Schiffman, N.E. Poitras, L.C. Cheung, P.E. Castle

Writing, review, and/or revision of the manuscript: M.I. Silver, J.C. Gage, M. Schiffman, T. Lorey, L.C. Cheung, H.A. Katki, W.K. Kinney, P.E. Castle

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B. Fetterman, N.E. Poitras, L.C. Cheung, A. Locke

Study supervision: M. Schiffman, P.E. Castle

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Received September 14, 2017; revised December 7, 2017; accepted January 25, 2018; published OnlineFirst February 5, 2018.

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