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Treatability by Cryotherapy in a Screen-and-Treat Strategy

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Abstract

Objectives—We estimated the percentage of women infected with human papillomavirus (HPV +) who cannot be immediately treated with cryotherapy.

Materials and Methods—In a 10,000-woman Costa Rican cohort, we analyzed the 559 HPV+ women aged 25-55, and estimated the proportion for whom immediate cryotherapy was not indicated (i.e., invasive cancer, large precancerous lesions, or benign abnormalities that risk failure such as large ectopy, squamocolumnar junction not visualized, polyps, ulcers, or distorted or atrophied cervix). To determine whether cryotherapy at time of baseline HPV screening would effectively treat HPV+ women, two expert gynecologists independently judged entire clinical histories (5-7 years of cytology, histology, and HPV tests) and a full longitudinal series of digitized cervical images..

Results—Reviewers judged 144 (25.8%) of 559 HPV+ women as not treatable by immediate cryotherapy. Among 72 women with cervical intraepithelial neoplasia grade 3 (CIN3) who would benefit most from a screening program, 35 (48.6%) were not treatable. In particular, 29 women (40.3%) were determined not treatable for reasons most likely associated with cryotherapy's inadequacy (lesion was large, suspected cancerous or in the endocervical canal or fornix).

Conclusions—“Screen-and-treat” programs in low-resource settings will soon use a rapid HPV test to screen older women once or twice in their lifetime, identifying women at higher risk for precancer. Our findings suggest cryotherapy might not effectively treat many precancers and other safe, low-technology treatment options could be required, in a scenario where all HPV+ women in this targeted group would receive cryotherapy at the same visit.

Keywords

cervical intraepithelial neoplasia; cryotherapy; mass screening; human papillomavirus; low-resource settings

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Precis (25 words) One-half of HPV-positive women, diagnosed subsequently to have persistent HPV or CIN2+, are not immediately treatable by cryotherapy suggesting other low-technology treatment might be needed.

INTRODUCTION

World-wide, approximately 250,000 women die from cervical cancer annually, with 80% of the cancer burden in low-resource regions¹. The incidence and mortality in more developed countries is half that of less developed countries, due primarily to aggressive, lifelong screening programs based on frequent cervical cytology (Pap tests)²⁻³. However, frequent screening and follow-up visits for abnormal results are often not feasible in low-resource settings. A preferred “screen-and-treat” strategy would administer a screening test once or twice in a lifetime and treat women in the same visit without the complexity and expense of diagnostic confirmation by colposcopically-directed biopsy⁴.

A rapid low-cost screening test for carcinogenic genotypes of human papillomavirus (HPV) has been developed for cervical cancer screening in poor countries⁵. Persistently detectable infections with carcinogenic HPV genotypes have been identified as a necessary, but not sufficient, cause of cervical cancer⁶⁻⁷. Persistence infections occur in the small minority (<<10%) of infections. Epidemiologic studies suggest that screen-and-treat strategies using an HPV test might be suitable, targeted after the peak age of new and typically self-limited infections, i.e., approximately 10-15 years after the average societal age of initiating sexual activity⁸⁻¹⁰. HPV detection would be used as the basis for treatment of the cervix to destroy detectable and inapparent cervical intraepithelial neoplasia (CIN), in order to prevent cervical cancer. In such a program all HPV+ women would receive immediate treatment even if a lesion was not visualized, with the understanding that some underlying small precancerous lesions would accordingly be treated while some women would be subjected to unnecessary treatment. A randomized trial in South Africa showed that such a screen-and-treat strategy using HPV testing performed better than visual inspection with acetic acid (VIA), another screening method used in low resource settings¹¹.

When treatment is broadly applied without certain knowledge of need for treatment, the safety of the intervention is of heightened importance. One safe low-technology method for treatment is cryotherapy. A freezing probe destroys HPV-infected and precancerous cervical tissue to a fixed depth. A problem is the inability of cryotherapy to treat all women (e.g. invasive cancer, large pre-cancerous lesions, and benign conditions that risk failure).

Faced with these issues in planning a new public health strategy, we approximated how many HPV+ women would not be immediately treatable with cryotherapy in a community with a high age-adjusted incidence rate of cervical cancer, averaging 33 cases per 100,000 women¹².

METHODS

We estimated treatability by cryotherapy at the time of baseline HPV screening of women aged 25-55 who were found to be HPV+ at enrollment into a population-based cohort study of HPV and cervical neoplasia in Guanacaste, Costa Rica. We evaluated whether a screen-and-treat strategy would have worked at enrollment. To determine the underlying disease status of each woman, we evaluated her multi-year clinical follow-up within the cohort, including all cytologic results, repeated HPV tests, longitudinal series of digitized cervical images, and colposcopic biopsies if any. We used the entire clinical histories to estimate how many women would not have been treatable by cryotherapy at enrollment, at the time when baseline HPV screening was performed, instead requiring referral for specialized health care.

Detailed methods of recruitment, screening and follow-up of the Proyecto Epidemiológico Guanacaste (PEG) have been previously published¹²⁻¹³. PEG is a longitudinal, natural history

study of HPV and cervical precancer/cancer that enrolled over 10,000 women in 1993-1994 with the approval of the National Cancer Institute (NCI) and Costa Rican institutional review boards. Of the 11,742 potentially eligible subjects, 10,049 (93.4%) women were eligible and provided written informed consent.

In this analysis, women were excluded if they had a hysterectomy, did not have a pelvic exam, were virgins, or were missing an enrollment HPV test (by PCR testing¹⁴) or cervigram (paired high resolution cervical photograph taken after application of acetic acid). We further restricted this analysis to women meeting the following criteria: a) aged 25 to 55, b) infection at enrollment with at least one of 14 carcinogenic HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68), and c) five or more years of follow-up (or censoring treatment) to permit estimation of need for and treatability by cryotherapy. We selected women infected with one or more of the 14 carcinogenic HPV genotypes included in the new rapid HPV test to identify approximately which women would have screened positive at enrollment, had the new test been used. The level of analytical sensitivity of the new test⁵ appears to be slightly less than that of HC2 (Qiagen, Gaithersburg, MD) which, in turn, performs similarly to consensus primer PCR methods¹⁵.

The age range of this analysis was selected to encompass the optimal target range of a screen-and-treat program in Guanacaste. Specifically, the lower bound was set approximately a decade after the median age for first sexual intercourse in Guanacaste (17 years) and the upper bound was extended beyond the peak of precancerous lesions in Guanacaste, to age 55. We restricted the upper limit based upon previous research showing visual assessment of cervical images works best for identification of precancerous lesions in women under 55 years due to age- and menopause-related changes in the transformation zone where most precancerous lesions arise¹⁶.

Two reviewers, gynecologists experienced in cervical cancer screening and management in low-resource settings, used an evaluation tool recently designed collaboratively by the National Library of Medicine and the National Cancer Institute to evaluate the highly-magnified, high-resolution cervigrams taken during PEG visits¹⁷. The software provided zooming capacities to view images collected during follow-up visits. Because not all disease was necessarily visible in the cervigrams taken at enrollment, reviewers had access to the women's entire clinical histories throughout their multiple visits in PEG including: enrollment and follow-up cervigrams, results from longitudinal cytology and HPV tests, and histological diagnoses from biopsies and excisional treatment. Women diagnosed with precancerous lesions in PEG were not treated with cryotherapy but with loop electrical excision of the transformation zone (LEEP) or cold-knife cone excision, providing histopathology to assess lesion severity.

For each woman that was HPV+ at enrollment, reviewers were asked to judge whether she was treatable by cryotherapy at enrollment. Most women whose chart review revealed an invasive cancer diagnosis were considered to be untreatable by cryotherapy at enrollment, even for the few cases of cancer diagnosed during follow-up. [These were considered missed diagnoses given that average length of time between enrollment and diagnosis, and the severity of many of the lesions.] When chart review indicated a precancerous lesion (CIN2 or CIN3) diagnosed either at enrollment or during follow-up, the reviewers judged whether cryotherapy at enrollment would have provided the needed treatment (e.g., whether histology indicated a deep lesion).

For all women, including those who did not have a precancerous lesion but would still have been treated in this screen-and-treat scenario because of a positive HPV status, the reviewers considered whether there was a benign condition for which cryotherapy was contraindicated. Specifically, women were considered not eligible for immediate treatment with cryotherapy

if: the entire squamocolumnar junction was not visualized, 2. the lesion was too large for the cryotherapy probe to cover in one application, 3. large ectopy would not allow the transformation zone to be covered by two applications, 4. the lesion extended into the endocervical canal, 5. presence of cervical atrophy, 6. presence of severe anatomical changes in the cervix (distorted), 7. the vaginal wall was close to cervix and not a result of poor speculum placement.

Reviewers were instructed to assume that at enrollment they could have manipulated the exam to remove blood or mucus, repositioned the speculum, or used a swab to improve visibility of the cervix and endocervical canal. Their decision was to be based on their comprehensive review of all images and clinical data throughout PEG follow-up. It was acknowledged that for some cases, neither the enrollment nor subsequent pictures were sufficient to determine whether the woman was treatable. For cases where the reviewers disagreed, they discussed and resolved these discrepancies by consensus. During this process, reviewers decided that a) patients could be treated for cervicitis so that neither mucopurulent discharge nor severe cervicitis excluded women, b) women with an intrauterine device (IUD) could still have cryotherapy, c) cryotherapy would be practiced in only one application except for women with no visible lesions but a large transformation zone (ectopy) requiring two applications.

We identified women with characteristics associated with not being treatable by cryotherapy using standard contingency table analysis with Chi-square statistics and multiple regression modeling. Analyses were performed using Stata/SE 9.0 analytic software (StataCorp LP, College Station, TX).

RESULTS

Of 10,049 study participants who provided written informed consent, 1,632 were excluded because they had a hysterectomy, did not have a pelvic exam or were virgins, or were missing a PCR or cervigram at enrollment. Of the remainder, 577 HPV+ women aged 25-55 were identified but reviewers agreed that 18 could not be evaluated due to poor enrollment image quality, resulting in a total sample of 559 women.

Independent of this evaluation, PEG clinical history showed that 123 (22.0%) of the 559 women evaluated had CIN2+ (80 were diagnosed at enrollment and 43 were diagnosed during follow-up (3.3 years average)) and 28 other women (5.0%) had a type-specific HPV infection that was persistent at study exit (6.7 years average follow-up). Based on disease status at study exit, 408 (73.0%) of women cleared HPV infection by study end (6.7 years average follow-up) and therefore did not require treatment because they were not at appreciable risk of cancer (although they would receive immediate cryotherapy in this screen-and-treat scenario).

After an initial review of 559 HPV+ women and before consensus, overall agreement on treatability by cryotherapy was 75.5% (Kappa=0.30): 363 (64.9%) were determined treatable by both reviewers, 59 (10.6%) not treatable by both, and 137 (24.5%) not treatable by one or the other. Each reader called a similar percent not treatable (23.8% and 21.8%). Most disagreements could be settled by thoroughly reviewing all clinical information.

By consensus of the reviewers, 144 (25.8%) of 559 HPV+ women were determined not treatable by cryotherapy and instead required referral to colposcopically-guided biopsy. The percent determined not treatable by cryotherapy varied significantly by age from 14.3% among women 25-29 years to 55.0% among women 50-55 years (p for trend <.01) (Table 1). Women's need for treatment was strongly and inversely associated with treatability even after adjusting for age (p for trend <.01). Among women with definite precancerous lesions most targeted in a screening program (CIN3), 48.6% were determined not treatable by cryotherapy. An only slightly smaller proportion of women with CIN2 (39.5%) or a persistent carcinogenic type-

specific HPV infection lasting to exit >5 years from enrollment (42.9%) were not treatable by cryotherapy. Conversely, women who cleared their type-specific HPV infection by study exit and did not need treatment were the most likely to be treatable by immediate cryotherapy (82.6% of 408 women). Other factors were also strongly associated with treatability by cryotherapy, even after adjusting for the confounding affects of age. Women were more likely to be determined not treatable by cryotherapy if they were more parous (p for trend=.01), had large ectopy (p for trend =.02), or were post-menopausal (p =.01).

Most (79.9%) of the 144 women determined not treatable were categorized as such due to one reason only. The most common reason was the inability to visualize the squamocolumnar junction (14.0%), a condition more prevalent in women aged 35-55 (p for trend <.01) (Table 2). Of note, some reasons for being untreatable by cryotherapy might be especially important indicators of cryotherapy inadequacy: We found that 29 (40.3%) of 72 women with CIN3 were determined not treatable by cryotherapy for occult or suspicious cancer, a lesion in the endocervical canal, a large lesion or a lesion in the fornix. These women would require instead a subsequent colposcopy exam and possibly further treatment rather than immediate cryotherapy.

We were interested in characterizing the age range for screening to identify an optimal number of HPV+ women for whom cryotherapy would be useful, and a minimal number of women for whom it would not (Table 3). Extending the age limit from 45 to 50 would identify 8 more women with CIN3 (11% of the total identified), of whom 6 (76%) would not be treatable by cryotherapy. Also, an additional 33 women who eventually cleared their HPV infection would be treated by cryotherapy. Starting screening at age 30 as opposed to age 25 missed 16 women with CIN3, of whom 4 were not immediately treatable by cryotherapy. Yet, starting screening at 30 rather than 25 would lead to treating 132 fewer women who had cleared their HPV infection.

DISCUSSION

It is now possible to identify sensitively women who are at an elevated risk of cervical cancer using a rapid and low-cost HPV test. However, for a screen-and-treat program to work, an effective treatment method must be available. We estimated the effectiveness of cryotherapy.

We acknowledge an immediate limitation of our study, in that we could not determine with optimal accuracy whether cryotherapy would be effective. Despite access to years of clinical records for each woman, on initial assessment, agreement between reviewers on treatability by cryotherapy of HPV-positive women was sub-optimal. Such limited reproducibility is not surprising given the limited reliability of colposcopic assessment²⁰. Some of the poor reproducibility resulted from conflicting assumptions among reviewers regarding freezing techniques. In addition, reviewers had differing opinions as to whether some disease, if untreated, would preclude a woman from cryotherapy. During the consensus review process these conflicts were identified and resolved.

Among women of the age that might merit inclusion in a screen-and-treat program (e.g. 25-55) who would test HPV-positive and receive treatment in the same visit, 25.8% were not candidates for immediate cryotherapy. Yet, even among women aged 30-39 with definite precancerous lesions (CIN3), by expert review of images and clinical history still 40.3% were definitively not treatable by cryotherapy for reasons most associated with its failure (lesion was large, suspected cancerous or extended into the endocervical canal or fornix).

At first glance, the proportion of HPV+ women determined not treatable by cryotherapy (25.8%) does not appear to be comparable to that found in a recent randomized trial in South Africa¹¹. In that study, only 6.4% of all women aged 25-65 years enrolled for primary screening

were judged not treatable by cryotherapy before enrollment and therefore not included in the randomized trial. Yet, the proportion of HPV+ women who were not treatable could have been around 25% given that approximately 21.4% of women were HPV+ (estimated from the proportion found to be HPV+ among women randomized to the HPV screening arm) and the high probability that most women judged not treatable by cryotherapy were also HPV+.

Among women aged 25-45 (an age range sometimes proposed for VIA screen-and-treat strategies), 21.0% were not treatable by cryotherapy. This percent is relatively higher than those reported in screen-and-treat programs that have used cryotherapy, albeit based on screening by visual inspection with acetic acid (VIA) instead of HPV testing. A program targeting 25-45 years old women in Ghana found only 2.5% of VIA positive women (median age 34 years) were not treatable¹⁸. Another intervention in Thailand screened women 30-45 years (mean age 37 years) with VIA and reported 7.5% of VIA positive women, respectively, not receiving cryotherapy¹⁹. Apart from differences in reviewers' judgments, the reasons for these discrepancies are not clear. Women who were VIA+ and HPV- were not included in this analysis; thus we can not estimate their proportion untreatable. An intervention in Zambia showed results more similar to ours and referred 16.7% of VIA positive women to a physician because they were deemed not immediately treatable by cryotherapy²⁰. It is noted that at least 41.5% of these women were HIV seropositive, a characteristic much different than

Women were most likely to be determined not treatable due to an inability to visualize the squamocolumnar junction and having a lesion that extended into the endocervical canal. One primary limitation of this evaluation was that the reviewers were unable to manipulate the cervix. It is very possible that in many cases the squamocolumnar junction appeared to be in the canal when, in a live examination, the colposcopist could have visualized the limits of the junction close to the os. In Ghana, only 4% of 3,665 women aged 25-35 years had a squamocolumnar junction that was not easily visualized by a VIA exam¹⁸. The discrepancy with our results (18.0%, data not shown) could be due in part, therefore, to measurement error resulting from the use of static images as opposed to a live exam.

To account for this possible measurement error we can assume that all of the women who did not have a fully visualized squamocolumnar junction could have been visualized with manipulation. If so, we estimate that 32 of the 72 (44.4%) women with CIN3 based upon PEG clinical history would still not be treatable for other reasons. Moreover, if *all lesions* extending into the endocervical canal could have been visualized at the enrollment examination and therefore had been determined treatable, 16 women still would have been determined not treatable by cryotherapy. Accordingly, if direct manipulation at the time of examination is assumed to solve all issues related to visualization, 16 remaining women (22.2% of 72 CIN3 cases) would not have been treatable mainly due to a large lesion (9), suspicious cervical carcinoma (3), distorted appearance of the cervix (2), and severe atrophy (2).

This study suggests that screen-and-treat programs using cryotherapy could potentially be ineffective at treating a substantial fraction of cervical precancer. Before such a screen-and-treat program can be implemented, these findings should be tested in a truly prospective effectiveness study. It is possible that given inadequate referral options for advanced treatment in low-resource areas, other safe, low-technology treatment alternatives are required. A safe and easy treatment that is effective for larger lesions and those extending partially into the endocervical canal would permit widest application of HPV-based prevention strategies to those most at need.

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Table 1

Reviewers' consensus evaluation of non-treatability by cryotherapy among HPV+ women at enrollment: unadjusted and age-adjusted odds of *not* being treatable* given individual characteristics

	Total n, column %	Consensus evaluation not treatable n, row %	Odds of being judged not treatable by cryotherapy		
			OR	Adjusted for age OR	95% CI
Total	559	144	25.8%		
Age in years (mean 35.2, standard deviation 8.1):					
25-29	168	24	14.3%	1.0	
30-34	143	33	23.1%	1.80	
35-39	100	29	29.0%	2.45	
40-44	55	12	21.8%	1.67	
45-49	53	24	45.3%	4.97	
50-55	40	22	55.0%	7.33	
<i>p</i> -value for trend				<.01	
Oral contraceptive use:					
Never	118	40	33.9%	1.0	
Former user	272	74	27.2%	0.73	0.55 - 1.46
Current user	169	30	17.8%	0.42	0.38 - 1.24
<i>p</i> -value for trend				<.01	.21
Number of live births:					
None	24	4	16.7%	1.0	
1-2	184	30	13.3%	0.97	0.27 - 2.70
3-4	213	54	25.4%	1.70	0.40 - 3.90
5+	138	56	40.6%	3.41	0.58 - 5.99
<i>p</i> -value for trend				<.01	.01
Women reached menopause:					
No	511	114	22.3%	1.0	
Yes	48	30	62.5%	5.80	1.14 - 5.51
<i>p</i> -value				<.01	.02
Number of sexual partners:					
1-2	351	79	22.5%	1.0	

	Total <i>n</i> , <i>column</i> %	Consensus evaluation not treatable <i>n</i> , <i>row</i> %	Odds of being judged not treatable by cryotherapy		
			OR	Adjusted for age OR	95% CI
3-4	107	19.1%	1.82	1.78	1.09-2.90
5+	101	18.1%	1.32	1.14	0.68 - 1.92
<i>p</i> -value for trend			.10	.29	
Enrollment cytology:					
Normal	323	57.8%	1.0	1.0	
ASCUS/atypia	92	16.5%	1.37	1.39	0.80 - 2.45
LSIL	73	13.1%	0.84	1.00	0.51 - 1.96
HSIL or Cancer	71	12.7%	5.32	6.18	3.48 - 10.95
<i>p</i> -value for trend			<.01	<.01	
Disease status at exit:^α					
HPV negative ^β	408	73.0%	1.0	1.0	
Persistent HPV infection at exit ^γ	28	5.0%	3.56	2.74	1.19 - 6.30
CIN2	38	6.8%	3.10	3.80	1.84 - 7.85
CIN3	72	12.9%	4.49	4.48	2.58 - 7.78
Cancer	13	2.3%	26.11	27.7	5.81 - 131.92
<i>p</i> -value for trend			<.01	<.01	
Extent of ectopy:^δ					
Normal	520	93.0%	1.0	1.0	
Large	39	7.0%	1.48	2.33	1.12 - 4.84
<i>p</i> -value			.27	.02	

* Because we considered the key possible problem in a screen-and-treat strategy to be women who are not treatable by cryotherapy, the proportion determined not treatable and odds of not being treatable are presented.

^α Based on worst histology or HPV testing in PEG clinical history. Note: disease status was determined independent of reviewer's consensus evaluation.

^β At study exit, women negative for the same HPV type(s) detected at enrollment

^γ At study exit, women positive for the same HPV type(s) detected at enrollment

^δ Determination made by reviewers during evaluation of enrollment cervigrams

Reviewers' consensus decision of reason(s) why women were not treatable by cryotherapy, by age at enrollment

Table 2

Reason not treatable*	Total (n=559)		Age at enrollment				Chi-square test for trend between 25-34 and 35-55 years				
	#	col%	25-29 (n=168)	30-34 (n=143)	35-39 (n=100)	40-55 (n=148)					
	#	col%	#	col%	#	col%	#	col%			
Cannot visualize the entire squamocolumnar junction	78	14.0%	7	4.2%	13	9.1%	17	17.0%	41	27.7%	<.01
Lesion in the canal	36	6.4%	4	2.4%	12	8.4%	7	7.0%	13	8.8%	.16
Large lesion	18	3.2%	6	3.6%	7	4.9%	3	3.0%	2	1.4%	.15
Suspicious cancer	13	2.3%	2	1.2%	2	1.4%	3	3.0%	6	4.1%	.07
Large ectopy	11	2.0%	5	3.0%	5	3.5%	0	0	1	0.7%	α
Distorted cervix	9	1.6%	4	2.4%	0	0	3	3.0%	2	1.4%	α
Severe atrophy	7	1.3%	0	0	1	0.7%	0	0	6	4.1%	α
Polyp	2	0.4%	0	0	0	0	0	0	2	1.4%	α
Lesion in the fornix	3	0.5%	0	0	2	1.4%	1	1.0%	0	0	α
Occult cancer	1	0.2%	0	0	0	0	1	1.0%	0	0	α
Vaginal wall close to the cervix	1	0.2%	1	0.6%	0	0	0	0	0	0	α

* With the exception of suspicious and occult cancer, women could have more than one reason

α Not calculated due to small sample size

Table 3
Number and percentage of women determined not treatable by cryotherapy, by age group* and disease status at exit^a

Age Group*	DISEASE STATUS AT EXIT ^a						HPV positive ^β		HPV negative ^γ	
	CIN3		CIN2		Determined not treatable by reviewer consensus		Determined not treatable by reviewer consensus		Determined not treatable by reviewer consensus	
	N	#	%	N	#	%	N	#	N	%
Starting at age 25										
25-40	53	25	47.2	34	12	35.3	14	3	309	21.4
25-45	59	28	47.5	36	13	36.1	21	7	353	33.3
25-50	67	34	50.8	37	14	37.8	23	8	386	34.8
25-55	72	35	48.6	38	15	39.5	28	12	408	42.9
Starting at age 30										
30-40	37	21	56.8	22	7	31.8	10	2	177	20.0
30-45	43	24	55.8	24	8	33.3	17	6	221	35.3
30-50	51	30	58.8	25	9	36.0	19	7	254	36.8
30-55	56	31	55.4	26	10	38.5	24	11	276	45.8

* Age groups are overlapping and not exclusive

^a Based on worst histology or HPV testing in PEG clinical history. Note: disease status was determined independent of reviewer's consensus evaluation.

^β At study exit, women positive for the same HPV type(s) detected at enrollment

^γ At study exit, women negative for the same HPV type(s) detected at enrollment