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Clinical follow-up practices after cervical cancer screening by co-testing: A population-based study of adherence to U.S. guideline recommendations

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Abstract

Failure to follow-up women after abnormal cervical screening could lead to cervical cancers, yet little is known about adherence to recommended follow-up after abnormal co-testing [cytology and high-risk human papillomavirus (hrHPV) testing]. We documented clinical management following cervical screening by co-testing in a diverse population-based setting. A statewide surveillance program for cervical screening, diagnosis, and treatment was used to investigate all cytology, hrHPV and biopsy reports in the state of New Mexico from January 2015 through

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ypmed.2021.106770>.

August 2019. Guideline-adherent follow-up after co-testing required 1) biopsy within 6 months for low-grade cytology if positive for hrHPV, for high-grade cytology irrespective of hrHPV, and for HPV 16/18 positive results irrespective of cytology and; 2) repeat co-testing within 18 months if cytology was negative and hrHPV test was positive (excluding types 16/18).

Screening co-tests (2015–2017) for 164,522 women were analyzed using descriptive statistics, Kaplan Meier curves, and pairwise comparisons between groups. Guideline adherence was highest when both cytology and hrHPV tests were abnormal, ranging from 61.7% to 80.3%. Guideline-adherent follow-up was lower for discordant results. Women with high-grade cytology were less likely to receive a timely biopsy when hrHPV-testing was negative (48.1%) *versus* positive (83.3%) ($p < 0.001$). Only 47.9% of women received biopsies following detection of HPV16/18 with normal cytology, and 30.8% received no follow-up within 18-months. Among women with hrHPV-positive normal cytology without evidence of HPV 16/18 infection, 51% received no follow-up within 18 months. Provider education and creation of robust recall systems may help ensure appropriate follow-up of abnormal screening results.

Keywords

Cervical cancer screening; Clinical practice; Cotesting follow-up; Co-testing

1. Introduction

Co-testing with cervical cytology and high-risk human papillomavirus (hrHPV) testing was introduced for cervical cancer screening in 2002 (Saslow et al., 2002). Subsequently, co-testing was recommended nationally by consensus processes in 2012–2013 (Saslow et al., 2012; USPSTF, 2013), and reaffirmed in subsequent screening guidelines in 2018 (Preventive Services Task Force et al., 2018). Co-testing recommendations were based on long-term reassurance against cancer following a negative HPV test, thereby permitting safe extension of screening intervals to 5 years among women with negative results (Saslow et al., 2012; USPSTF, 2013). Co-testing recommendations were paired with strong public health messages to adopt longer screening intervals (ACOG, 2013), leading to increasing use of co-testing and declining screening prevalence over time (Watson et al., 2018). Managing abnormal co-test results requires more complex management algorithms incorporating both cytology and hrHPV results, including partial hrHPV genotyping (Massad et al., 2013; Perkins et al., 2020). Because women are seen less frequently for screening, the ability to ensure timely and appropriate follow-up after an abnormal result is essential (Huh et al., 2015). We evaluated compliance with clinical management guidelines after abnormal co-test results at the state-wide level across a diverse range of health systems, clinics and providers.

2. Methods

Data from the New Mexico HPV Pap Registry (NMHPVPR) (Cuzick et al., 2015; Cuzick et al., 2014) was used to measure compliance with clinical guideline recommendations following abnormal cervical cancer screening tests (Massad et al., 2013; Huh et al., 2015). All cytology, hrHPV test, and pathology reports in the NMHPVPR from January 2015 through August 2019 were identified. Data were restricted to women aged 30–64 years, for

whom co-testing is consistently recommended ($n = 291,913$) (Supplemental Fig. 1) (NCQA, 2020). Women with known prior hysterectomy and those under potential active surveillance due to prior abnormal results were excluded. Of the 249,155 cytology records remaining, 181,586 were co-tests. The final sample was restricted to the first co-test record per woman ($n = 164,522$). HPV screening results were grouped as HPV16/18 positive, HPV16/18 negative but positive for a pool of other hrHPVs (partial genotyping), hrHPV positive for a pool of hrHPVs including HPV16/18 (no genotyping), or hrHPV negative. Screening cytology results included normal, hereafter referred to as negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells cannot exclude HSIL (ASC-H), and atypical glandular cells (AGC), and cancer.

Follow-up categories included: cervical biopsy within 6 months, cervical biopsy within >6–18 months, repeat testing (co-test, cytology-alone or hrHPV-alone) within 18 months without prior biopsy, or no follow-up within 18 months. Although clinical guidelines recommended follow-up in 12 months, we allowed a 6-month grace period to be considered adherent. Kaplan Meier curves were used to show the time to biopsy for different combinations of cytology and hrHPV results, and pairwise comparisons between the groups were performed at 6 months to compute differences.

Management guidelines during the study period recommended colposcopy (with biopsy of visible lesions with or without endocervical curettage as indicated) following cytology results of ASC-US or LSIL if hrHPV-positive, cytology results of ASC-H, AGC, HSIL regardless of hrHPV test results, and following HPV 16/18-positive results with NILM cytology (Massad et al., 2013; Huh et al., 2015). Repeat co-testing in 12 months was recommended when NILM results were associated with hrHPV-positive co-tests *i.e.*, positive for a hrHPV pool (no genotyping) or negative for HPV16/18 but positive for a pool of other hrHPV (partial genotyping) and also for hrHPV-negative LSIL results. Although not evaluated in this report, repeat testing in 3 years was recommended following hrHPV-negative ASC-US, and repeat testing in 5 years following hrHPV-negative NILM cytology (Massad et al., 2013).

2.1. Role of the funder

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2.2. IRB approval

The University of New Mexico, Human Research Review Committee determined that analyses of routine screening data from public health reporting to the New Mexico HPV Pap Registry is exempt.

3. Results

Table 1 shows follow-up by cytology and hrHPV groupings among 164,522 women meeting final eligibility criteria across the period of 2015–2017 with follow-up through August 2019. A total of 141,799 women had hrHPV-negative NILM cytology co-test results. Among 22,723 abnormal co-test results, 9960 (43.8%) were hrHPV-positive NILM cytology. Approximately half (47.9%) of women with HPV16/18-positive NILM cytology received biopsy within 6 months (guideline-adherent), and 30.8% had no follow-up within 18 months. Only 29.0% of women with hrHPV-positive NILM cytology who were HPV 16/18 negative (partial genotyping) and 30.1% of women with HPV 16/18 unknown but positive for hrHPV (no genotyping) received repeat testing within 18 months (guideline-adherent); 51.4% and 51.2% respectively had no follow-up in 18 months. Rates of biopsy within 6 months after hrHPV positive ASC-US and LSIL were 61.7% and 70.6%, respectively. Following HSIL cytology, 83.3% of women with hrHPV-positive results received biopsy follow-up within 6 months compared with 48.1% of women with hrHPV-negative results ($p < 0.001$). Most HSIL and ASC-H cytology results were hrHPV-positive: 94.1% (436/463) and 78.7% (573/728) respectively.

Fig. 1 depicts the time to biopsy by co-test results, divided into low-grade cytology (ASCUS, LSIL) and high-grade cytology (ASC-H, AGC, HSIL). At-risk women at time 0, 6, 12 18 and 24 months are shown for each group in Supplemental Table 1. Further, pairwise comparisons between the various cytology and hrHPV groups shown in Fig. 1 were determined at 6 months to estimate differences (Supplemental Table 2). Most women who ever received biopsies did so within 6 months. Among women with hrHPV-positive NILM cytology, a second rise in biopsies was observed at 12 months, consistent with guideline-adherent follow-up of re-testing at 12 months and performing colposcopy for persistently abnormal results. The rank order of biopsy follow-up at 6 months was hrHPV-positive high-grade cytology (77–78%) > hrHPV-positive low-grade cytology (63–70%) > hrHPV-negative high-grade cytology (62%) > HPV16/18-positive NILM cytology (48%) (Fig. 1; Supplemental Table 2).

4. Discussion

These data demonstrate a lack of guideline-adherent clinical management of women with abnormal co-testing results. While more than two-thirds of women received guideline-adherent management when both cytology and hrHPV tests were abnormal, fewer than half were managed appropriately when cytology and hrHPV tests were discordant (*e.g.*, abnormal cytology with negative hrHPV results or NILM cytology with positive hrHPV results). A minority of women with hrHPV-positive NILM cytology received appropriate re-testing follow-up, and nearly half had no follow-up within 18 months. HPV16 and 18 together cause over 70% of invasive cervical cancers (Bosch et al., 2008), yet nearly one third of women with these infections had no follow-up within 18 months, consistent with other studies (Saraiya et al., 2020). Among the highest risk cytology results, hrHPV test results were also managed inappropriately. While guideline-adherent colposcopic biopsy exceeded 80% for hrHPV-positive HSIL, only 48.1% of women with hrHPV-negative HSIL received biopsy within 6 months.

These data have important implications for patients, providers, clinics and healthcare systems. The United States does not have an organized healthcare system with centralized patient reminders or recall systems. Each provider and clinic is responsible for determining management and tracking their own patients, which presents challenges as patients may move or change insurance carriers, limiting their ability to continue care in the same location. The lack of appropriate care demonstrated in this study may result from breakdowns at the provider, patient, and/or system levels. Lower levels of appropriate colposcopy follow-up based on hrHPV test results *versus* cytology results highlights a need for provider education, given that colposcopy referral is generally provider-driven, and patients often have limited understanding of the implications of hrHPV test results (Kim and Han, 2019; Tiro et al., 2019; Barlow et al., 2019). In contrast, loss to follow-up in the longer term may reflect failure of healthcare systems to appropriately flag, recall, and inform patients about the need for re-testing at intervals of 12 months or longer (Baron et al., 2010). Providers are not currently incentivized to follow guidelines for managing abnormal cervical screening results. Quality measures should be developed to promote guideline-adherent management of abnormal screening results and this is likely a broadly generalizable need.

This study has limitations. Follow-up may have occurred outside of New Mexico, although the NMHPVPR surveillance data are highly complete and receive reports from neighboring states and from regional and national laboratories (Cuzick et al., 2015; Cuzick et al., 2014). We do not have information on colposcopies in which biopsies were not performed, although biopsies are routinely recommended (Wentzensen et al., 2017). Our ability to assess overtreatment is limited as information on symptoms that might prompt biopsy independent of cytology/hrHPV results is not available. Also, we are not able to document a direct relationship between lack of follow-up and development of invasive cancer. In addition, we were not able to assess the relative contributions of systems factors (lack of reminder/recall systems), provider factors (lack of knowledge on current guidelines for managing results), and patient factors (lack of knowledge, healthcare access, insurance coverage, or other factors leading to non-adherence with follow-up). Additional research to understand the relative contributions of systems, provider, and patient factors to non-adherence is crucial to solve the problem of inadequate follow-up.

5. Conclusions

Women undergoing co-testing were more likely to receive guideline-adherent follow-up when both cytology and hrHPV tests were abnormal than when results were discordant. Both hrHPV-positive tests with normal cytology and hrHPV-negative tests with high-grade cytology received less follow-up than recommended. Improved education of healthcare providers and patients, as well as the development of robust recall systems and quality measures are important to ensure appropriate follow-up of abnormal screening test results and avoid preventable cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

HPV	Human Papillomavirus
hrHPV	high risk Human Papillomavirus
NILM	Negative for Intraepithelial Lesion and Malignancy
ASC-US	Atypical Squamous Cells of Undetermined Significance
LSIL	Low-grade Squamous Intraepithelial Lesion
ASC-H:	Atypical Squamous Cells cannot exclude HSIL
AGC	Atypical Glandular Cells
HSIL+	High-grade Squamous Intraepithelial Lesion (HSIL) and cancer (HSIL+)
hrHPV	high-risk HPV
m	months

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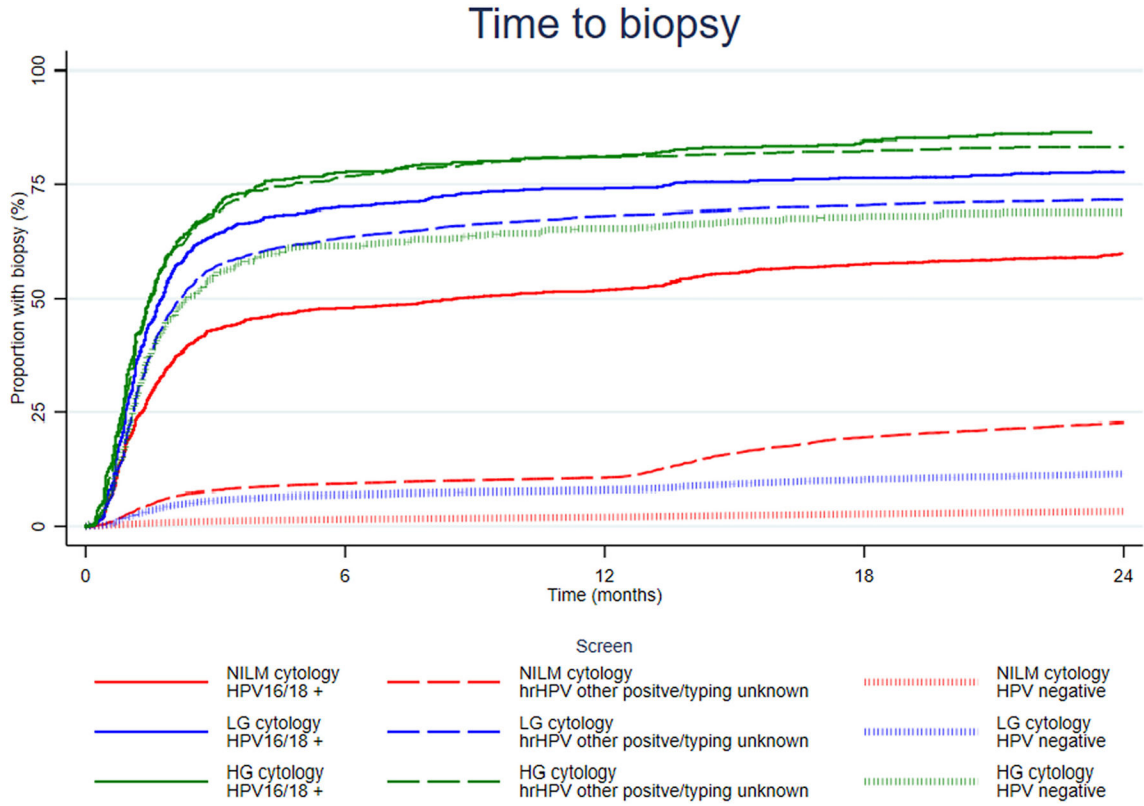


Fig. 1. Time to biopsy for different screening co-test results.

Figure describes time to biopsy estimated by Kaplan Meier method for a) NILM cytology co-test b) low-grade (LG) cytology co-test c) high-grade (HG) cytology co-test, by HPV status (HPV16/18 positive, HPV16/18 negative other hrHPV positive or typing unknown, or HPV negative) following the first *co-test* per woman, for women attending routine screening in 2015–2017 aged 30–64 years. Total number of at-risk women included in Figure is 8478. NILM: Negative for Intraepithelial Lesion and Malignancy, HPV: Human Papillomavirus. Low-grade (LG) includes both atypical squamous cells of unknown significance (ASC-US) and low-grade squamous intraepithelial lesion (LSIL). High-grade (HG) includes atypical cells of unknown significance favor high-grade (ASC–H), atypical glandular cells (AGC) and high-grade squamous intraepithelial lesions (HSIL) and worse (HSIL+). Other high-risk (hr) HPV positive includes no genotyping and partial genotyping groups.

Table 1

Tabulation of first biopsy and any repeat test following the first co-test per woman, by cytology and HPV test result. Women aged 30–64 years attending routine screening in 2015–2017 ($n = 164,522$). Each woman only contributes to one follow-up category. (%) represents column percentages for each co-test outcome (HPV test result and cytology category).

HPV test result	Follow-up	Cytology						Total
		NILM	ASC-US	LSIL	ASC-H	AGC	HSIL+	
hrHPV positive	Total	9960	3462	1577	573	162	436	16,170
	Biopsy 6 m	1441 (14.5)	2137 (61.7)	1113 (70.6)	406 (70.9)	133 (82.1)	363 (83.3)	5593 (34.6)
	Biopsy >6 – 18 m	988 (9.9)	240 (6.9)	100 (6.3)	44 (7.7)	6 (3.7)	21 (4.8)	1399 (8.7)
	Any repeat test in 18 m ^a	2691 (27.0)	398 (11.5)	130 (8.2)	27 (4.7)	7 (4.3)	12 (2.8)	3265 (20.2)
	No follow-up in 18 m	4840 (48.6)	687 (19.8)	234 (14.8)	96 (16.8)	16 (9.9)	40 (9.2)	5913 (36.6)
HPV16/18 + (partial genotyping)	Total	1336	576	249	185	58	186	2590
	Biopsy 6 m	640 (47.9)	387 (67.2)	191 (76.7)	129 (69.7)	51 (87.9)	153 (82.3)	1551 (59.9)
	Biopsy >6 – 18 m	125 (9.4)	31 (5.4)	21 (8.4)	15 (8.1)	2 (3.4)	12 (6.5)	206 (8.0)
	Any repeat test in 18 m ^a	160 (12.0)	53 (9.2)	12 (4.8)	7 (3.8)	1 (1.7)	5 (2.7)	238 (9.2)
	No follow-up in 18 m	411 (30.8)	105 (18.2)	25 (10.0)	34 (18.4)	4 (6.9)	16 (8.6)	595 (23.0)
HPV16/18 negative, positive other hrHPV types (partial genotyping)	Total	5852	1841	817	226	68	119	8923
	Biopsy 6 m	537 (9.2)	1148 (62.4)	596 (72.9)	171 (75.7)	56 (82.4)	100 (84.0)	2608 (29.2)
	Biopsy >6 – 18 m	608 (10.4)	137 (7.4)	53 (6.5)	13 (5.8)	4 (5.9)	6 (5.0)	821 (9.2)
	Any repeat test in 18 m ^a	1697 (29.0)	212 (11.5)	61 (7.5)	9 (4.0)	2 (2.9)	3 (2.5)	1984 (22.2)
	No follow-up in 18 m	3010 (51.4)	344 (18.7)	107 (13.1)	33 (14.6)	6 (8.8)	10 (8.4)	3510 (39.3)
hrHPV+, no genotyping	Total	2772	1045	511	162	36	131	4657
	Biopsy 6 m	264 (9.5)	602 (57.6)	326 (63.8)	106 (65.4)	26 (72.2)	110 (84.0)	1434 (30.8)
	Biopsy >6 – 18 m	255 (9.2)	72 (6.9)	26 (5.1)	16 (9.9)	0 (0.0)	3 (2.3)	372 (8.0)
	Any repeat test in 18 m ^a	834 (30.1)	133 (12.7)	57 (11.2)	11 (6.8)	4 (11.1)	4 (3.1)	1043 (22.4)
	No follow-up in 18 m	1419 (51.2)	238 (22.8)	102 (20.0)	29 (17.9)	6 (16.7)	14 (10.7)	1808 (38.8)
hrHPV negative	Total	1,41,799	5641	447	155	283	27	1,48,352
	Biopsy 6 m	2180 (1.5)	228 (4.0)	191 (42.7)	89 (57.4)	184 (65.0)	13 (48.1)	2885 (1.9)
	Biopsy >6 – 18 m	1663 (1.2)	171 (3.0)	25 (5.6)	15 (9.7)	9 (3.2)	6 (22.2)	1889 (1.3)

HPV test result	Follow-up		Cytology						Total
	18 m ^a	18 m	NILM	ASC-US	LSIL	ASC-H	AGC	HSIL+	
Total (irrespective of HPV status)	Any repeat test in 18 m ^a		15,247 (10.8)	1736 (30.8)	110 (24.6)	17 (11.0)	27 (9.5)	4 (14.8)	17,141 (11.6)
	No follow-up in 18 m		122,709 (86.5)	3506 (62.2)	121 (27.1)	34 (21.9)	63 (22.3)	4 (14.8)	126,437 (85.2)
	Total		1,51,759	9103	2024	728	445	463	1,64,522
	Biopsy 6 m		3621 (2.4)	2365 (26.0)	1304 (64.4)	495 (68.0)	317 (71.2)	376 (81.2)	8478 (5.2)
	Biopsy >6 – 18 m		2651 (1.8)	411 (4.5)	125 (6.2)	59 (8.1)	15 (3.4)	27 (5.8)	3288 (2.0)
Any repeat test in 18m ^a			17,938 (11.8)	2134 (23.4)	240 (11.9)	44 (6.0)	34 (7.6)	16 (3.5)	20,406 (12.4)
	No follow-up in 18 m		127,549 (84.1)	4193 (46.1)	355 (17.5)	130 (17.9)	79 (17.8)	44 (9.5)	132,350 (80.5)

227 (1.9%) of biopsies had insufficient results; 2256 women underwent hysterectomy, which was included in the “biopsy” count.

HPV: Human Papillomavirus, NILM: Negative for Intraepithelial Lesion and Malignancy, ASC-US: Atypical Squamous Cells of Undetermined Significance, LSIL: Low-grade Squamous Intraepithelial Lesion, ASC-H: Atypical Squamous Cells cannot exclude HSIL, AGC: Atypical Glandular Cells, HSIL+, AGC: High-grade Squamous Intraepithelial Lesion (HSIL) and cancer (HSIL+), hrHPV: high-risk HPV, m:months.

^aIncludes repeat co-test, cytology-only or HPV-only, if no biopsy in 18 months (18 m).