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Rates of regression of cervical dysplasia between initial biopsy and excisional procedure in routine clinical practice

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Abstract

Purpose To determine rates and factors associated with regression of cervical intraepithelial neoplasia (CIN) 2 + between colposcopic biopsy and therapeutic excisional procedure in standard practice.

Methods A retrospective chart review was performed for women undergoing a cervical excisional procedure for CIN 2 + at clinics at three academic institutions over a 3-year period. Cytology, histology, patient age and time-to-excision were analyzed to determine factors influencing rates of regression.

Results Of 356 women undergoing excision for CIN 2 + on colposcopic biopsy, 91 (25.3%) of final pathology diagnoses displayed clinically significant regression. Age and time-to-excision were not associated with regression, but referral cytology and severity of initial biopsy histology were, with ASC-H (aOR 0.1, CI 0.03, 0.8) and CIN 3/AIS (aOR 0.4, CI 0.2, 0.7) being less likely to regress than less severe lesions.

Conclusions Disease severity by referral cytology or diagnostic biopsy, as opposed to age or length of time-to-excision, is likely the most relevant factor in determination of regression for cervical intraepithelial neoplasia in women undergoing excisional treatment for biopsy-confirmed CIN2 +.

Keywords Squamous intraepithelial lesions · Human papillomavirus · Spontaneous neoplasm regression · Colposcopy · Pap test

Introduction

Screening to identify and treat cervical intraepithelial neoplasia (CIN) has significantly decreased the incidence of and mortality from cervical cancer in the United States [1]. The progression from CIN to cervical cancer is typically slow and the lesions regress in as many as 28–44% of women [2–4]. Excisional treatment of these lesions is not without risk, so a positive screening result can lead to difficult decisions for clinicians and their patients. Women of childbearing age, in particular, must weigh the benefits of excision while considering the potential risk of adverse pregnancy outcomes including preterm birth, premature rupture of membranes, low birth weight, and increased perinatal mortality [5–8]. The risks associated with excisional treatment, combined with a reasonably high likelihood of regression without treatment, together support consideration of a more conservative treatment approach for reproductive age women, especially those with more equivocal diagnoses such as CIN grade 2.

This study was approved by the Institutional Review Boards of University of Maryland, Johns Hopkins University and George Washington University.

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Previous studies have shown that younger women may have a higher rate of regression, even when followed for a relatively short time period (e.g., 3–4 months) [2, 3, 9–12]. The delay between biopsy and treatment provides an opportunity to examine short-term regression rates in routine clinical practice. We sought to evaluate the likelihood of regression of biopsy-confirmed CIN grade 2 or more severe ($CIN2^+$) at the time of excision by age, CIN grade at biopsy, referral cytology result, smoking status, and time-to-treatment in three large academic institutions.

Methods

This study was approved by the Institutional Review Boards of George Washington University (GWU), Johns Hopkins Medical Institutions (JHU), and the University of Maryland Medical Center (UMD). Due to the retrospective design of the study, a waiver of consent was obtained. Data from Johns Hopkins were collected from one hospital, Johns Hopkins Bayview Medical Center (JHBMC), which functions as a community-based clinic with an ethnically diverse population.

Women at least 21 years of age with a histologic diagnosis of $CIN2^+$ from colposcopic biopsy who subsequently underwent cervical excision between July 2013 and December 2016 at one of the three institutions were identified via retrospective chart review for inclusion in this study. Demographic information, human papillomavirus (HPV) testing, cytology and subsequent pathology results, as well as the dates of each woman's biopsy and excision were collected. Data were then entered and stored in a REDCap electronic database hosted by GWU. Patients were excluded if they had incomplete pathology reports at biopsy or excision, had a diagnosis of HIV, or were pregnant at any time between colposcopy and excisional procedure. Regression was defined as a change from CIN 2, CIN 2/3, CIN 3, high-grade intraepithelial lesion (HSIL), or adenocarcinoma in situ (AIS) to a diagnosis that would not typically warrant treatment, specifically either CIN 1 or normal pathology. Time-to-regression was assessed initially as a continuous variable and then divided into three categories based on the distribution to determine significant differences. When examining final pathology diagnosis results, AIS was combined with CIN3, and HSIL with CIN2/3, due to a small number of observations and the synonymous nature of these diagnostic terms. HPV testing is differentially indicated based on age and cytology result, and was missing in a substantial proportion of women. On the basis of this clinical indication we did not further analyze this as a predictor of regression.

Chi-squared analysis and logistic regression were used to compare the probability of regression among and across institutions as well as among different demographic groups. A general linear model was used to determine whether differences in time-to-excision existed across institutions. STATA14.2 (Stata Statistical Software: Release 14. StataCorp LP. 2015. College Station, TX, USA) and SAS 9.4 (SAS. SAS Institute Inc. 2014. Cary, NC, USA) software were used to perform analyses.

Results

A total of 424 women were identified in the initial cohort across all three institutions. After excluding women who were: pregnant during the study time period ($n=11$), HIV positive ($n=39$), ineligible based on most severe diagnosis at biopsy ($n=7$), missing an excision date ($n=2$), missing cytology referral diagnosis ($n=8$) or a discrepancy in the excision and biopsy dates ($n=1$), 356 women remained and were included in the analysis. Their ages ranged from 21 to 76 years with a median age of 31.5 years old.

The overall proportion of biopsy-diagnosed CIN2 + with regression (< CIN2) at the time of excision was 25.3% (90/356) (Table 1). The overall median time from biopsy to excision across the three sites was 55.5 days (~ 8 weeks) with a range of 0–461 days. The mean times between biopsy and excision were 57.9, 86.0 and 61.8 days at GWU, JHBMC, and UMD, respectively. On average, women at JHBMC had a significantly longer time-to-excision compared to women at GWU and UMD ($p<0.0001$) (Table 2).

The probability of regression did not vary significantly among institutions ($p=0.17$), by age ($p=0.90$), by smoking status ($p=0.94$), or by length of time between biopsy and excision ($p=0.54$) (Table 2). Sensitivity analysis evaluating time-to-excision as a log-transformed continuous variable found no significant association between time-to-excision and probability of regression. Patients with atypical

Table 1 Initial biopsy results and final diagnosis after excision

Post biopsy diagnosis	Post excision diagnosis						
	Normal	CIN 1	CIN 2	CIN 3	CIN 2/3	SCA	Total
CIN 2	20, 16.8%	16, 13.5%	40, 33.6%	19, 16.0%	24, 20.2%	0 0.0%	119, 100%
CIN 2/3/HSIL	23, 18.9%	15, 12.3%	11, 9.0%	13, 10.7%	60, 49.2%	0 0.0%	125, 100%
CIN 3/AIS	9, 7.8%	7, 6.1%	13, 11.3%	59, 51.3%	25, 21.7%	2 1.7%	117, 100%
Total	52, 14.6%	38, 10.7%	64, 18.0%	91, 25.6%	109, 30.6%	2 0.6%	356, 100%

Table 2 Regression rates related to demographic factors, cytology, histology, and time-to-excision

Indicator	*N* (%)	Regression at time of treatment	OR (95% CI)	Adj OR (95% CI)
Total	356 (100)	90 (25.3)		
Institution				
GWU	103 (28.9)	24 (23.3)	1.0	
JHBMC	118 (33.2)	37 (31.4)	1.5 (0.8, 2.7)	
UMD	135 (37.9)	29 (21.5)	0.9 (0.5, 1.7)	
Age (years)				
21–29	132 (37.1)	33 (25.0)	1.0	
30–34	100 (28.1)	24 (24.0)	0.9 (0.5, 1.7)	
35+	124 (34.8)	33 (26.6)	1.1 (0.6, 1.9)	
Smoking*				
No	250 (70.8)	64 (25.6)	1.0	
Yes	103 (29.2)	26 (25.2)	1.0 (0.6, 1.7)	
Referral cytology				
NILM	24 (6.7)	9 (33.3)	1.0	1.0
ASCUS	86 (24.2)	25 (29.1)	0.8 (0.3, 2.2)	1.0 (0.4, 2.5)
LSIL	95 (26.7)	31 (32.6)	1.0 (0.4, 2.5)	1.0 (0.4, 2.7)
HSIL	123 (34.5)	24 (19.5)	0.5 (0.2, 1.3)	0.6 (0.2, 1.6)
ASC-H	28 (7.9)	2 (7.1)	0.2 (0.02, 0.8) p-trend = 0.006	0.1 (0.03, 0.8) p-trend = 0.009
Time-to-excision (days)				
0–41	112 (31.5)	25 (22.3)	1.0	
42–69	125 (35.1)	31 (24.8)	1.1 (0.6, 2.1)	
70–461	119 (33.4)	34 (28.6)	1.4 (0.8, 2.5) p-trend = 0.27	
Biopsy diagnosis				
CIN2	119 (33.4)	36 (30.1)	1.0	1.0
CIN2/3 or HSIL	122 (34.3)	38 (31.2)	1.04 (0.6, 1.8)	1.1 (0.6, 1.9)
CIN3/AIS	115 (32.3)	16 (13.9)	0.4 (0.2, 0.7) p-trend = 0.005	0.4 (0.2, 0.7) p-trend = 0.006

OR odds ratio, *ADJ OR* adjusted odds ratio, *NILM* negative for intraepithelial lesions or malignancy, *ASCUS* atypical squamous cells of undetermined significance, *LSIL* low-grade squamous intraepithelial lesion, *HSIL* high-grade intraepithelial lesion, *ASC-H* atypical squamous cells/cannot exclude HSIL, *CIN2* cervical epithelial neoplasia grade 2, *CIN2/3* cervical intraepithelial neoplasia grade 2/3, *CIN3/AIS* cervical intraepithelial neoplasia grade 3/adenocarcinoma in situ. Eight participants with missing cytology referral data were excluded from all analyses

*Three women with missing smoking status were excluded

squamous cells/cannot exclude high-grade lesion (ASC-H) referral cytology had a lower probability of regression (OR 0.2, 95% CI 0.02, 0.8) when compared to patients with atypical squamous cells of undetermined significance referral cytology (ASCUS) (Table 2). Pap test results that were negative for intraepithelial lesions or malignancy (NILM), low-grade squamous intraepithelial lesions (LSIL), and HSIL did not have a significantly different probability of regression as compared to ASCUS. The severity of biopsy diagnosis was associated with regression, with CIN3/AIS being less likely to regress (OR 0.4, CI 0.2, 0.7) than CIN 2. CIN 2/3 or HSIL had similar probabilities of regression to CIN 2 (OR 1.0, CI 0.6, 1.8).

The trend toward low-risk regression associated with biopsy diagnosis and referral cytology remained in the multivariable analysis, indicating that mutual adjustment of these variables did not measurably change the independent associations of higher grade lesions and CIN 3/AIS biopsy diagnosis.

Rates of p16 testing were reported in 98 (26.9%) biopsies, but meaningful analysis was unable to be performed as only 1 of the 98 biopsies with results available was reported as p16-negative.

Discussion

In this multi-center study of regression between colposcopic biopsy diagnosis and final excisional pathology, one in four women had no evidence of CIN2 + at the time of cervical excision. No difference was found in pathology discordance by age. Although time-to-excision varied among institutions, it was not associated with regression between biopsy and excisional diagnosis.

Biopsies found to have CIN2 were more likely than CIN3 + to show disease regression between biopsy and final excision. It is possible that this reflects a higher proportion of false positive pathological diagnoses for CIN2 versus CIN3 + rather than true lesion regression. It has previously been shown that CIN2 has a higher inter-observer discrepancy among pathologists [13–16]. Alternatively, given that colposcopic biopsies are targeted toward the most abnormal appearing areas, it is also possible that the biopsy may have excised the entire lesion or the highest grade lesion, particularly in women with small lesions. Lastly, it is possible that these discrepancies represent true regression of disease either naturally or as a result of inflammatory/healing response from the biopsies [2, 9]. The probability of regression with conservative management has been reported to be as high as 40% [2, 9, 17, 18], but our study indicates that this may happen in a shorter period of time than previously thought. Future studies delineating the cause of this discrepancy would prove beneficial to determining which patients truly need excisions.

We found no evidence to support our a priori hypothesis of higher regression among younger (< 30 years) than older (≧ 30 years) women. This is in contrast to a recent meta-analysis showing increased rates of regression in women under 30 [3]. This difference may be explained by study design and patient selection. Because we used administrative data reflecting routine clinical practice, the median follow-up from biopsy diagnosis to excision was shorter than most studies in the meta-analysis, many of which were observational studies with standardized follow-up times. Similarly, our study design required a record of histologic diagnosis from both biopsy and excisional tissue, and thus excluded women who may have regressed during conservative, observational management. Indeed, the ASCCP guidelines allow for conservative management in young women, based on data that showed extremely low probability of invasive cancer in young women [11, 19] as well as the fact that HPV infections are often transient in young women [10]. Based on this recommendation, it is possible that our data underestimate the probability of regression in young women due to the selection bias which excluded those managed by observational follow-up. More studies which carefully track women undergoing conservative, observational management are needed to adequately estimate the age-specific probability of regression. The PRINCess trial, a multi-center, prospective study evaluating long-term outcomes of young women diagnosed with CIN 2 is currently ongoing and may provide further information [20].

Nomenclature used to report colposcopic and excisional biopsy pathology varied in this study. Some reported low- or high-grade squamous intraepithelial lesions (LSIL and HSIL), others reported cervical intraepithelial neoplasia (CIN) grades 1, 2, and 3, and still others reported a combination of both. The LAST project recommended using SIL naming conventions for consistency purposes, but allowed for further categorization with CIN grade due to the different guidelines for CIN 2 versus 3 in young women [21, 22]. Our results suggest that consistency is needed in reporting to allow for analysis of outcomes and to help further inform clinical guidelines.

A major goal of conservative management of dysplasia in young women is to avoid excisional procedures that may have negative effects on reproductive outcomes such as preterm birth in future pregnancies [5–7]. However, the average maternal age at birth of her first child is 26.3 years and has been steadily increasing over the past decade [23], with over 30% of women age 30 years or older at the time of first birth [23]. Given the overall trend toward older maternal age, conservative management of dysplasia in women over 25 is also of great interest. In fact, many practitioners report that they are applying conservative management guidelines to all reproductive age women who still desire childbearing despite the lack of formal recommendations allowing for this approach [24]. If, as our findings suggest, regression is more likely to be related to disease severity than to age, then conservative management may merit consideration for women who are considering future childbearing regardless of age.

Given that there was a 10% loss to follow-up in Tainio's cohort studying conservative management [3], it is prudent to advise that a woman's willingness and ability to comply with follow-up recommendations be considered when deciding the appropriateness of observation. As most women with CIN3 do not have regression and the rates of clinically significant dysplasia are high in women of all ages with the high grade cytology and visible lesions [25], see-and-treat methodology may be considered in women who are noncompliant, have barriers to accessing care or who do not desire future fertility.

There are some notable limitations of this study. The retrospective nature did not allow for collection of all variables such as initial lesion size, use of oral contraceptive pills, previous treatment for dysplasia, sexual practices and medication use that may contribute to regression or persistence [2, 26, 27]. Previous studies have shown HPV type and certain HLA alleles to be related to persistence [2], but over a quarter of the women included in this study did not have any HPV testing performed and very few had typing available. The patients included in the study were those for whom excisional procedures were recommended, which represents a selected group whose probability of persistent dysplasia is likely higher. Additionally, likely due to the ASCCP recommendations for conservative management in young women, our cohort had a small number of women undergoing excision who were under 25. Due to this, we analyzed all women 29 years of age and younger in our young women cohort,

which may have underestimated the probability of regression in younger women.

However, the study also has some notable strengths. We evaluated the probability of discrepancy and possible regression of cervical dysplasia between biopsy and cervical excision in actual practice, which is important for appropriate comparison of monitoring and evaluation of practice outcomes relative to published observational studies. The inclusion of hospitals in three major hospital systems over an extended timeframe increases the applicability of these results. In addition, though our time intervals between biopsy and excision were shorter (~ 10 weeks) and more variable, they are strikingly similar to those of Trimble et al. who followed 100 women prospectively for 15 weeks after the time of biopsy and found a 28% probability of regression by the time of final excision [2]. The relative agreement between the prospective and retrospective study designs supports the potential for expanded use of biopsy/excisional diagnostic concordance in electronic medical record (EMR) data for future pragmatic trials to evaluate biomarkers of regression as putative triage markers in screening.

Conclusion

In summary, our data suggest that disease severity, as opposed to age or length of time-to-excision, is likely the most relevant factor in determination of persistence or regression for cervical intraepithelial neoplasia in women undergoing excisional treatment for biopsy-confirmed CIN2 + . These data further emphasize diagnostic uncertainties of histologic grading of CIN and the urgent need for better molecular triage markers to reduce unnecessary harms associated with cervical cancer screening, especially in reproductive age women.

Author contributions KM: project development, data collection, manuscript writing. AF: project development, data collection, manuscript editing. HH: project development, data analysis. ML-A: project development, manuscript editing. AB: data collection, manuscript editing. JE: data collection. OS: data collection. PG: project development, data analysis, manuscript writing.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

References

1. National Cancer Institute (2018) SEER cancer stat facts: cervical cancer. https://seer.cancer.gov/statfacts/html/cervix.html. Accessed Mar 7 2018
2. Trimble CL, Piantadosi S, Gravitt P, Ronnett B, Pizer E, Elko A, Wilqus B, Yutzy W, Daniel R, Shah K, Peng S, Hung C, Roden R, Wu TC, Pardoll D (2005) Sponataneous regression of high-grade cervical dysplasia: effects of human papillomavirus type and HLA phenotype. Clin Cancer Res 11:4717–4723. https://doi.org/10.1158/1078-0432.CCR-04-2599
3. Tainio K, Athanasiou A, Tikkinen K, Aaltonen R, Cardenas J, Hernandes Glazer-Livson S, Jakobsson M, Joronen K, Kiviharju M, Louvanto K, Oksjoki S, Tahtinen R, Virtanen S, Nieminen P, Kyrfiou M, Kalliala I (2018) Clincial course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. BMJ 27(360):k499. https://doi.org/10.1136/bmj.k499
4. Melnikow J, Nuovo J, Willan A, Chan B, Howell L (1998) Natural history of cervical squamous intraepithelial lesions: a meta-analysis. Obstet Gynecol 92:727–735 (**PMID:9764690**)
5. Bjorge T, Skare GB, Bjorge L, Trope A, Lonnberg S (2016) Adverse pregnancy outcomes after treatment for cervical intraepithelial neoplasia. Obstet Gynecol 128:1265–1273. https://doi.org/10.1097/AOG.0000000000001777
6. Sadler L, Saftlas A, Wang W, Exeter M, Whittaker J, McCowan L (2004) Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. JAMA 291:2100–2106. https://doi.org/10.1001/jama.291.17.2100
7. Samson SL, Bentley JR, Fahey TJ, McKay DJ, Gill GH (2005) The effect of loop electrosurgical excision procedure on future pregnancy outcome. Obstet Gynecol 105:325–332. https://doi.org/10.1097/01.AOG.0000151991.09124.bb
8. Kyrgiou M, Athanasiou A, Paraskevaidi M, Mitra A, Kalliala I, Martin-Hirsch P, Arbyn M, Bennett P, Paraskevaidis E (2016) Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. BMJ 28(354):i3633. https://doi.org/10.1136/bmj.i3633
9. Nasiell K, Nasiell M, Vaclavinkova V (1983) Behavior of moderate cervical dysplasia during long-term follow up. Obstet Gynecol 61:609–614 (**PMID:6835614**)
10. Ho G, Bierman R, Beardsley L, Chang C, Burk R (1998) Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med 338:423–428. https://doi.org/10.1056/NEJM199802123380703
11. Katki H, Schiffman M, Castle P, Fetterman B, Poitras N, Lorey T, Cheung L, Raine-Bennett T, Gage J, Kinney W (2013) Estimating 5-year risk of CIN 3 + to guide the management of women aged 21–24. J Low Genit Tract Dis 17:S64–S68. https://doi.org/10.1097/LGT.0b013e3182854399
12. Holowaty P, Miller A, Rohan T, To T (1999) Natural history of dysplasia of the uterine cervix. J Nat Can Inst 91(3):252–258 (**PMID:10037103**)
13. Dalla Palma P, Giorgi Rossi P, Collina G, Buccoliero AM, Ghiringhello B, Gilioli E, Onnis GL, Aldovini D, Galanti G, Casadei G, Aldi M, Gomes VV, Giubilato P, Ronco G, NTCC Pathology Group (2009) The reproducibility of CIN diagnoses among different pathologists: data from histology reviews from a multicenter randomized study. Am J Clin Pathol 132(1):125–132. https://doi.org/10.1309/ajcpbrk7d1yiuwfp
14. Ismail S, Colclough A, Dinnen J, Eakins D, Evans DM, Gradwell E, O'Sullivan JP, SUmmerell JM, Newcombe RG (1989) Observer variation in histopathological diagnosis and grading cervical intraepithelial neoplasia. BMJ 298:707–710 (**PMID:2496816**)
15. Castle P, Stoler M, Solomon D, Schiffman M (2007) The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report. Am J Clin Pathol 127:805–815. https://doi.org/10.1309/PT3PNC1QL2F4D2VL

16. Carreon J, Sherman M, Guillen D, Solomon D, Herrero R, Jeronimo J, Wacholder S, Rodriguez AC, Morales J, Hutchinson M, Burk RD, Schiffman M (2007) CIN2 is a much less reproducible and less valid diagnosis than CIN3: results from a histological review of population based cervical samples. Int J Gynecol Pathol 26:441–446. https://doi.org/10.1097/pgp.0b013e31805152ab
17. Grimm C, Polterauer S, Natter C, Rahhal J, Hefler L, Tempfer CB, Heinze G, Stary G, Reinthaller A, Speiser P (2012) Treatment of cervical intraepithelial neoplasia with topical imiquomid: a randomized controlled trial. Obstet Gynecol 120:152–159. https://doi.org/10.1097/AOG.0b013e31825bc6e8
18. Rader JS, Sill MW, Beume JH, Lankes HA, Benbrook DM, Garcia F, Trinble C, Tate Thigpen J, Lieberman R, Zuna RE, Leath CA, Spirtos NM, Byron J, Thaker PH, Lele S, Alberts D (2017) A stratified randomized double-blind phase II trial of celecoxib for treating patients with cervical intraepithelial neoplasia: the potential predictive value of VEGF serum levels: an NRG oncology/gynecologic oncology group study. Gynecol Oncol 145(2):291–297. https://doi.org/10.1016/j.ygyno.2017.02.040
19. Massad L, Einstein M, Huh W, Katki H, Kinney W, Schiffman M, Solomon D, Wentzensen N, Lawson H, for the 2012 ASCCP consensus guidelines conference (2012) 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tact Dis 17:S1–S27. https://doi.org/10.1097/LGT.0b013e318287d329
20. Sykes P, Innes C, Harker D, Whitehead M, van der Griend R, Lawton B, Hibma M, Fitzergald P, Dudley N, Petrich S, Faherty J, Bergzoll C, Eva L, Parker C, Sadler L, Simcock B (2016) Observational management of CIN 2 in young women: a prospective multicenter trial. J Low Genit Tract Dis 20(4):343–347. https://doi.org/10.1097/LGT.0000000000000244
21. Waxman A, Chelmow D, Darragh T, Herschel L, Moscicki A (2012) Revised terminology for cervical histopathology and its implications for management of high-grade squamous intraepithelial lesions of the cervix. Obstet Gynecol 120:1465–1471. https://doi.org/10.1097/AOG.0b013e31827001d5
22. Darragh T, Colgan T, Cox J, Heller D, Henry M, Luff R, McCalmont T, Nayar R, Palefsky JM, Stoler MH, Wilkinson EJ, Zaino RJ, Wilbur DC, Members of the LAST Project Work Groups (2012) The lower anogenital squamous terminology standardization project for HPV-associated pathologists and the american society for colposcopy and cervical pathology. J Low Genit Tract Dis 16:205–242. https://doi.org/10.1097/lgt.0b013e31825c31dd
23. Matthews T, Hamilton B (2016). Mean age of mothers on the rise: United States 2000–2014, centers for disease control and prevention, national center for health statistics. https://www.cdc.gov/nchs/products/databriefs/db232.htm. Accessed Feb 25 2018
24. Macdonald M, Smith JHF, Tidy JA, Palmer JE (2018) Conservative management of CIN2: national audit of British society for colposcopy and cervical pathology members' opinion. J Obstet Gynaecol 6:1–7. https://doi.org/10.1080/01443615.2017.1316973
25. Smith HJ, Leath CA, Erickson BK (2016) See-and-treat for high grade cytology: do young women have different rates of high grade histology? J Low Genit Tract Dis 20:243–246. https://doi.org/10.1097/LGT.0000000000000229
26. Stensen S, Sk Kjaer, Jensen SM, Frederiksen K, Junge J, Iftner T, Munk C (2016) Factors associated with type-specific persistence of high-risk human papillomavirus infection: a population-based study. Int J Cancer 138:361–368. https://doi.org/10.1002/ijc.29719
27. Goodman MT, Shvetsov YB, McDuffie K, Wilkens LR, Zhu X, Thompson PJ, Ning L, Kileen J, Kamemoto L, Hernandez BY (2008) Prevalence, acquisition and clearance of cervical human papillomavirus infection among women with normal cytology: hawaii human papillomavirus cohort study. Cancer Res 68:8813–8824. https://doi.org/10.1158/0008-5472