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Risk of Cervical Intraepithelial Neoplasia 2 or Worse by Cytology, Human Papillomavirus 16/18, and Colposcopy Impression: A Systematic Review and Meta-analysis

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Abstract

Objective—To calculate pooled risk estimates for combinations of cytology result, human papillomavirus (HPV) 16/18 genotype, and colposcopy impression to provide a basis for risk-stratified colposcopy and biopsy practice.

Data source—A PubMed search was conducted on June 1, 2016, and a ClinicalTrials.gov search was conducted on June 9, 2018, using key words such as “uterine cervical neoplasms,” “cervical cancer,” “mass screening,” “early detection of cancer” and “colposcopy.”

Methods of Study Selection—Eligible studies must have included colposcopic impression and either cytology results or HPV16/18 partial genotype results as well as a histologic biopsy

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diagnosis from adult women. Manuscripts were reviewed for the following: cytology, HPV status, and colposcopy impression, as well as age, number of women, and number of CIN2, CIN3, and cancer cases. Strata were defined by the various combinations of cytology, genotype, and colposcopic impression.

Tabulation, Integration, and Results—Of 340 abstracts identified, 9 were eligible for inclusion. Data were also obtained from three unpublished studies, two of which have since been published. We calculated the risk of CIN2+ and CIN3+ based on cytology, colposcopy, and HPV16/18 test results. We found similar risk patterns across studies in the lowest risk groups such that risk estimates were similar despite different referral populations and study designs. Women with a normal colposcopy impression (no acetowhitening), <HSIL cytology, and HPV16/18 negative were at low risk of prevalent precancer. Women with at least two of the following: HSIL cytology, HPV16 or HPV18 positive, high-grade colposcopic impression were at highest risk of prevalent precancer.

Conclusions—Our results support a risk-based approach to colposcopy and biopsy with modifications of practice at the lowest and highest risk levels.

Introduction

Effective cervical cancer screening programs have greatly reduced the incidence of cervical cancer in the United States ¹. A key component is identifying and appropriately managing women with abnormal screening results following cytology or HPV tests. Frequently, this involves referral to colposcopy where the cervix is visualized under magnification and biopsies are collected for histologic diagnosis, enabling identification of high-risk women in need of treatment and lower risk women in need of follow-up.

Although all women referred for colposcopy have had an abnormal screening result, their underlying risk of cervical cancer varies greatly depending on the type of test(s) and corresponding result(s) leading to their referral. Risk also varies according to colposcopic findings. Combined, these factors can be used to estimate a woman's risk of precancer, and in turn guide colposcopy practice and appropriate next steps, including whether to treat immediately or take biopsies, and the appropriate number of biopsies to take.

Despite its key role in cervical cancer screening, colposcopy is subjective and imprecise ². In light of this, the American Society for Colposcopy & Cervical Pathology (ASCCP) established several working groups to review current colposcopy practices in the US and develop consensus recommendations to standardize colposcopy practices and ensure a complete exam^{3–7}. This entailed establishing risk estimates to guide management recommendations at the time of colposcopy. To do so, a literature review and meta-analysis was conducted evaluating risk strata based on combinations of cytology, HPV 16/18 genotyping, and colposcopy impression that may impact colposcopy and biopsy practice.

Sources

An extensive literature review was conducted and data were pooled from published and unpublished studies for a systematic review and meta-analysis evaluating the risk of

precancer in various strata based on cytology, HPV testing, and colposcopy impression. The following search terms were used in PubMed on June 1, 2016: (((“uterine cervical neoplasms”[MeSH Terms] OR (“uterine”[All Fields] AND “cervical”[All Fields] AND “neoplasms”[All Fields]) OR “uterine cervical neoplasms”[All Fields] OR (“cervical”[All Fields] AND “cancer”[All Fields]) OR “cervical cancer”[All Fields]) AND (“diagnosis”[Subheading] OR “diagnosis”[All Fields] OR “screening”[All Fields] OR “mass screening”[MeSH Terms] OR (“mass”[All Fields] AND “screening”[All Fields]) OR “mass screening”[All Fields] OR “screening”[All Fields] OR “early detection of cancer”[MeSH Terms] OR (“early”[All Fields] AND “detection”[All Fields] AND “cancer”[All Fields]) OR “early detection of cancer”[All Fields])) AND “female”[MeSH Terms] AND “adult”[MeSH Terms]) AND ((“Colposcopy/methods”⁸ OR “Colposcopy/statistics and numerical data”⁸ OR “Colposcopy/utilization”⁸) AND “female”[MeSH Terms] AND “adult”[MeSH Terms]) AND (“female”[MeSH Terms] AND “adult”[MeSH Terms]). The following search terms were used in ClinicalTrials.gov on June 9, 2018: ((“uterine” AND “cervical” AND “neoplasms”) OR (“cervical” AND “cancer”))AND (“diagnosis” OR “screening” OR (“early” AND “detection” AND “cancer”)) AND “female” AND “adult” AND “colposcopy”.

Study Selection

The PubMed search was performed on June 1, 2016 and yielded 340 manuscripts. An additional search of ClinicalTrials.gov on June 9, 2018 did not yield any additional results. The search results were divided among eight co-authors and abstracts were reviewed and screened for relevance. One hundred ninety-six references were divided among eight co-authors and read in their entirety to determine eligibility and the availability of relevant data for analysis. Twenty-five percent of articles had a second review to ensure consistency. In order to calculate absolute risk estimates in the various risk strata, an abstraction sheet was developed to capture information on the following: Cytology (<HSIL vs HSIL+), HPV status with partial genotyping (HPV16 or HPV18 positive vs HPV16 and HPV18 negative), and colposcopy impression (normal, metaplasia/acetowhitening not suspicious for intraepithelial lesion, low-grade, or high-grade), as well as age, number of women in different risk strata, and number of CIN2, CIN3, and cancer. A normal colposcopic impression was defined as no acetowhitening or other abnormalities. Metaplasia/acetowhitening not suspicious for intraepithelial lesion (hereafter referred to as acetowhitening) is denoted as a separate category, since normal squamous metaplasia can have a mild acetowhite appearance, which is considered by many colposcopists to be benign. Study identification of CIN2+ and CIN3+ endpoints included both targeted and random biopsies as well as excisional procedures (LEEP/conization). Biopsy procedures varied by study—no specified number of biopsies was required.

References were excluded if they did not contain colposcopic impression along with either cytology or HPV16/18 partial genotyping. Nine references met the criteria for inclusion and risk information was abstracted from the full manuscript^{9–17}. Bias was assessed in these studies using an adapted QUADAS tool¹⁸. All studies were found to have a low to uncertain risk of bias, so all were included in the analysis. In addition, unpublished primary data were obtained from three studies (ASCUS-LSIL Triage Study¹⁹, The Biopsy Study²⁰, and the

BD Onclarity trial) and included in the meta-analysis. Two of these studies have since been published^{21,22}. Details about included studies can be found in Table 1.

The proportion of women in each of the risk strata were calculated using the three studies with complete data across all 32 risk strata (BD, Biopsy, ALTS). Pooled risks of CIN2 and CIN3 using all 12 studies were calculated using available data for each strata using *metaprop_one*²³ in Stata 14.2 (College Station, TX, USA). *Metaprop* was designed as an addition to the *metan* command specifically for binomial data. The Freeman-Tukey double arc-sine transformation was used to stabilize the variance and account for studies with zero events to ensure confidence intervals remained within plausible bounds (0–1)²³. I^2 was used as a measure of heterogeneity, and random effects models were used to account for the variability in the studies. This paper will present the meta-analysis results for CIN2+ risk estimates as more data were available for this outcome; however, the meta-analysis results for CIN3+ risk estimates are included in Appendix 1–3, **available online at** <http://links.lww.com/xxx>.

Results

We considered risk estimates based on all combinations of the results a woman could have at the time of colposcopy that included colposcopic impression and could affect management: 8 strata of colposcopy impression and cytology results; 8 strata of colposcopy impression and HPV16/18 status; 16 strata of colposcopy impression, cytology result, and HPV16/18 status. The specifics of these risk strata are detailed in Box 1. A minimum of three studies per strata were required for the meta-analysis, and all but one stratum (normal colposcopy, HSIL+ and HPV16/18+) met this criterion.

Box 1

List of Risk Strata

Colposcopy & Cytology
High-grade colpo and HSIL+
High-grade colpo and <HSIL
Low-grade colpo and <HSIL
Low-grade colpo and HSIL+
Metaplasia/Acetowhite colpo and HSIL+
Metaplasia/Acetowhite colpo and <HSIL
Normal colpo and <HSIL
Normal colpo and HSIL+

Colposcopy & HPV16/18
High-grade colpo and HPV16/18+
High-grade colpo and HPV16/18–
Low-grade colpo and HPV16/18+

Colposcopy & HPV16/18
Low-grade colpo and HPV16/18–
Metaplasia/Acetowhite colpo and 16/18+
Metaplasia/Acetowhite colpo and 16/18–
Normal colpo and HPV16/18+
Normal colpo and HPV16/18–

Colposcopy & Cytology & HPV16/18+
High-grade colpo and HSIL+ and HPV16/18+
High-grade colpo and HSIL+ and HPV16/18–
High-grade colpo and <HSIL and HPV16/18+
High-grade colpo and <HSIL and HPV16/18–
Low-grade colpo and HSIL+ and HPV16/18+
Low-grade colpo and HSIL+ and HPV16/18–
Low-grade colpo and <HSIL and HPV16/18+
Low-grade colpo and <HSIL and HPV16/18–
Metaplasia/Acetowhite colpo and HSIL+ and 16/18+
Metaplasia/Acetowhite colpo and HSIL+ and 16/18–
Metaplasia/Acetowhite colpo and <HSIL and 16/18+
Metaplasia/Acetowhite colpo and <HSIL and 16/18–
Normal colpo and HSIL+ and HPV16/18+
Normal colpo and HSIL+ and HPV16/18–
Normal colpo and <HSIL and HPV16/18+
Normal colpo and <HSIL and HPV16/18–

Complete data for all possible combinations of risk strata were available from three of the twelve included studies^{19,20,24}), and were used to estimate the proportion of women expected to fall within each stratum. These distributions are summarized in Figure 1. The pattern was more similar between ALTS and the Biopsy study (cytology-referral populations) than between either of those studies and the BD Study (HPV-referral population), although the three studies were largely in agreement on the largest and smallest strata. Based on colposcopy and cytology results, between 40–60% of the women seen in colposcopy clinic could be expected to have a low-grade colposcopy impression and <HSIL cytology, while 1% or less will have high-grade cytology and a normal colposcopy impression. Similarly, when colposcopic impression and HPV16/18 status are known, 30–50% could be expected to have low-grade colposcopy and HPV16/18 negative results, while 6% or less would have normal colposcopies, but be HPV16/18 positive. For clinics using cytology and HPV16/18 genotyping along with colposcopy impression, the largest proportion of women (35–65%) would be expected to have normal or low-grade colposcopic impression, <HSIL cytology and HPV16/18 negative. In contrast, <2% of women with HSIL+ had a normal or acetowhite colposcopy. Exact numeric estimates for the three studies can be found in Table 2.

CIN2+ pooled risk estimates were first calculated for a positive result on each of the three tests and then for all possible combinations of colposcopy impression, cytology, and HPV16/18 genotyping results (Figure 2). High-grade colposcopy impression and high-grade cytology results yielded similar risk estimates (0.73 (95% CI: 0.53–0.89) and 0.75 (95% CI: 0.64–0.85), respectively). The CIN2+ risk associated with a positive HPV16/18 result alone was 0.43 (95% CI: 0.24–0.63).

All twelve included data sources providing data for at least one of the risk strata using colposcopy impression and cytology result as risk markers for CIN2+. In this set of data, there was a range of risk estimates from 0.83 (95% CI: 0.74–0.91) at the high end for high-grade colposcopy with HSIL+ to 0.02 (95% CI: 0.01–0.02) at the low end for normal colposcopy and <HSIL (Figure 3).

The CIN2+ risk estimates using colposcopy and HPV16/18 status, ranged from 0.76 (95% CI: 0.66–0.85) for high-grade colposcopy impression and HPV16/18+ to 0.01 (95% CI: 0.01–0.02) for normal colposcopy impression and HPV16/18– (Figure 4).

For the CIN2+ risk estimates including all 3 results, the range was 0.85 (95% CI: 0.78–0.90) for those with a high-grade colposcopy impression, HSIL+, and HPV16/18 positive to 0.015 (95% CI: 0.007–0.026) for those with a normal colposcopy impression, <HSIL cytology, and HPV16/18 negative (Figure 5). Four strata had pooled risk estimates above 60%: high-grade colposcopy impression, HSIL+, and HPV16/18 positive; high-grade colposcopy impression, HSIL+, and HPV16/18 negative; high-grade colposcopy impression, <HSIL, and HPV16/18 positive, and low-grade colposcopy impression, HSIL+, and HPV16/18 positive.

Pooled risk estimates for CIN3+ can be found in Appendixes 1–3 (<http://links.lww.com/xxx>), and demonstrate a reduction in heterogeneity of risk estimates for this higher-grade outcome compared to CIN2+, both across and within risk strata. Pooled risk estimates for CIN3+ exhibited similar patterns to CIN2+, but lower absolute risks were seen for all strata. CIN3+ risk estimates for colposcopy/cytology risk strata can be found in Appendix 1 (<http://links.lww.com/xxx>), for colposcopy/HPV16/18 risk strata in Appendix 2 (<http://links.lww.com/xxx>), and for colposcopy, cytology and HPV16/18 in Appendix 3 (<http://links.lww.com/xxx>).

Comment

Colposcopy, biopsy and subsequent management following abnormal Pap smears have played a critical role in our ability to prevent cervical cancer by identifying and treating precancers. Yet, as screening shifts to Pap/HPV cotesting or primary HPV testing and the vaccinated population ages into screening, the volume and underlying risk of women referred to colposcopy will change dramatically. To prevent overburdening the health system and over-treating women at low-risk, a risk-based approach to triage and management is needed that accounts for varying levels of risk among a colposcopy referral population. We calculated pooled risk estimates for combinations of cytology, HPV, and colposcopy

impression of all currently available data to support recommendations for risk-based colposcopy and biopsy practice.

Importantly, we found a similarity in risk patterns across studies in the lowest risk groups such that risk estimates were similar within a stratum despite different referral populations and study designs. Greater heterogeneity was seen at the highest risk groups, though all estimates in those categories would still be considered high-risk. With fine risk stratification, differences between populations can be addressed to a certain point. Our results also demonstrated the rarity of extreme combinations such as normal or acetowhite colposcopies with HPV16/18+ or HSIL+, regardless of the referral strategy, though these data come from trained colposcopists in trial settings, and may not be generalizable to the national population of providers performing colposcopy.

We focused primarily on results for CIN2+ due to the limited number of studies presenting data for CIN3+. However even with the small sample size, the pooled risk estimates for CIN3+ were much less heterogeneous than the CIN2+ results, likely reflecting the known variability and lack of reproducibility of CIN2 diagnoses²⁵²⁶, and suggesting the need for separation of CIN2 from CIN3+ when presenting clinical outcomes of cervical cancer screening, triage, and management. The reduced homogeneity and consistency of risk estimates for these true precancer outcomes supports the use of a risk-based approach to cervical cancer screening and management.

The ASCCP recently issued new colposcopy standards and risk-based management guidelines for the lowest and highest risk groups of women based on available test results (cytology, HPV, and colposcopy impression). Our results support the recommendation against non-targeted (random) biopsies for women with a normal colposcopy impression (no acetowhitening), <HSIL cytology, and HPV16/18 negative, due to their low risk of prevalent precancer, estimated to be under 2% for CIN2+ and under 0.5% for CIN3+. This modification in protocols can eliminate unnecessary biopsies for anywhere between 6 and 33% of women undergoing colposcopy depending on the measures used for initial referral to colposcopy.

The new ASCCP recommendations also suggest immediate excisional treatment for the highest risk women (at least two of the following: HSIL cytology, HPV16 or HPV18 positive, high-grade colposcopic impression) as an alternative to colposcopic biopsy⁷, as is currently allowed for HSIL cytology alone²⁷. Again, our calculations support this, showing risks of prevalent CIN2+ ranging from 60% to 85% and CIN3+ risks of 29% to 57% for most women with at least 2 high-grade results. We estimate this new guideline could allow immediate treatment for 2–25% of women (depending on the measures used for referral), reducing cost and emotional distress for the patient as well as the need for an additional visit and potential loss to follow-up.

A limitation of this analysis worth noting is the variability in how colposcopy impression is defined and identified by individual providers. This may lead to some added heterogeneity or misclassification in colposcopy impression across studies. Widespread implementation of the newly established colposcopy standards can aid in reducing the variability of colposcopy.

These guidelines create a set of standardized terminology and standardized procedures for conducting and documenting colposcopy and also developed quality improvement recommendations. A second limitation is that as HPV-vaccinated women mature into screening, we expect risk estimates for colposcopic impression and cytology to decline, so the estimates generated here may require updating in the future. Differences in referral populations may influence risk estimates, particularly in an HPV screened population, where women may be referred for colposcopy for two consecutive HPV positive NILM Pap smears, who wouldn't be found in a cytology referral population. These women likely will have smaller lesions, which are harder to detect by colposcopy.

While colposcopy procedures will change for women at the highest and lowest risks of cervical precancer and cancer, the majority of women referred to colposcopy (60–80%) will present with intermediate risk levels (at least one risk factor: high-grade colposcopy, HSIL cytology, or HPV16/18 positive), and these women should continue to be managed according to standard protocol including at least two and up to four biopsies of acetowhite lesions to determine appropriate next steps⁷²⁷. It is among this group of intermediate-risk results where identification of additional biomarkers for cervical cancer will be most beneficial, allowing increased precision for risk estimation and tailored management recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Population distribution of risk strata combinations. Colposcopy and cytology (A), colposcopy and HPV16/18 (B), and colposcopy, cytology, and HPV16/18. HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesions; BD, Becton Dickinson; ALTS, ASCUS/LSIL Triage Study.

Figure 2.

Pooled risk estimates by test result. Rank ordered pooled risk estimate of CIN2+ by strata of test results. HPV, human papillomavirus. HSIL, high-grade squamous intraepithelial lesions; CIN, cervical intraepithelial neoplasia.

Figure 3.

Risk estimates for CIN2+ based on colposcopy impression and cytology result. I^2 only calculated when number of studies is greater than 3. ES, estimated risk of CIN2+; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesions; BD, Becton Dickinson; ALTS, ASCUS/LSIL Triage Study.

Figure 4.

Risk estimates for CIN2+ based on colposcopy impression and HPV16/18 status. I^2 only calculated when number of studies is greater than 3. ES, estimated risk of CIN2+; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; ALTS, ASCUS/LSIL Triage Study; BD, Becton Dickinson.

Figure 5.

Risk estimates for CIN2+ based on colposcopy impression, cytology result, and HPV16/18 status. I^2 only calculated when number of studies is greater than 3. **B** is a continuation of **A**. ES, estimated risk of CIN2+; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesions; HPV, human papillomavirus; BD, Becton Dickinson; ALTS, ASCUS/LSIL Triage Study.

Table 1

Summary data from included studies by strata

Strata	Manuscript first author	Year	Age Group	N	CIN2+	CIN3+	Proportion CIN2+	Proportion CIN3+
High-grade colpo and HSIL+	Sadan	2007	NS	79	56		0.7089	
	Aue-aungkul	2011	25+	110	102		0.9273	
	Bosgraaf	2013	17+	1543	1473		0.9546	
	Errington	2006	NS	448	372		0.8304	
	Szurkus	2003	NS	34	24		0.7059	
	Vanseviciute	2003	23+	33	30		0.9091	
	ALTS	2017	18+	155	122	92	0.7871	0.5935
	BD	2017	25+	17	13	10	0.7647	0.5882
	Biopsy	2017	18+	108	81	28	0.7500	0.2593
	Aue-aungkul	2011	25+	40	23		0.5750	
High-grade colpo and <HSIL	Bosgraaf	2013	17+	256	181		0.7070	
	ALTS	2017	18+	206	75	39	0.3641	0.1893
	BD	2017	25+	150	24	10	0.1600	0.0667
	Biopsy	2017	18+	99	48	14	0.4848	0.1414
	Errington	2006	NS	117	59		0.5043	
	Szurkus	2003	NS	58	34		0.5862	
	Aue-aungkul	2011	25+	23	17		0.7391	
	Bosgraaf	2013	17+	238	170		0.7143	
	Hedge	2011	20+	11	8	6	0.7273	0.5455
	Vanseviciute	2003	23+	15	4		0.2667	
Low-grade colpo and HSIL+	ALTS	2017	18+	229	121	75	0.5284	0.3275
	BD	2017	25+	67	41	19	0.6119	0.2836
	Biopsy	2017	18+	80	42	10	0.5250	0.1250
	Bosgraaf	2013	17+	297	79		0.2660	
	Aue-aungkul	2011	25+	19	6		0.3158	
	Hedge	2011	20+	25	1	1	0.0400	0.0400
	ALTS	2017	18+	1259	173	65	0.1374	0.0516
	BD	2017	25+	1830	200	80	0.1093	0.0437

Strata	Manuscript first author	Year	Age Group	N	CIN2+	CIN3+	Proportion CIN2+	Proportion CIN3+
Acetowhite/Metaplasia colpo and HSIL+	Biopsy	2017	18+	248	74	12	0.2984	0.0484
	ALTS	2017	18+	15	5	1	0.3333	0.0667
	BD	2017	25+	15	3	1	0.2000	0.0667
	Biopsy	2017	18+	17	5	2	0.2941	0.1176
Acetowhite/Metaplasia colpo and <HSIL	ALTS	2017	18+	182	24	8	0.1319	0.0440
	BD	2017	25+	943	45	21	0.0477	0.0223
	Biopsy	2017	18+	56	4	0	0.0714	0.0000
	Huh	2014		2106	42	17	0.0199	0.0081
Normal colpo and <HSIL	ALTS	2017	18+	503	5	3	0.0099	0.0060
	BD	2017	25+	1766	37	17	0.0210	0.0096
	Biopsy	2017	18+	42	3	0	0.0714	0.0000
	ALTS	2017	18+	21	1	1	0.0476	0.0476
Normal colpo and HSIL+	BD	2017	25+	34	8	4	0.2353	0.1176
	Biopsy	2017	18+	2	0	0	0.0000	0.0000
	Zaal	2012		18	17	14	0.9444	0.7778
	ALTS	2017	18+	182	133	103	0.7308	0.5659
High-grade colpo and HPV16/18+	BD	2017	25+	31	19	13	0.6129	0.4194
	Biopsy	2017	18+	83	65	29	0.7831	0.3494
	ALTS	2017	18+	182	63	28	0.3462	0.1538
	BD	2017	25+	136	18	7	0.1324	0.0515
High-grade colpo and HPV16/18-	Biopsy	2017	18+	131	69	17	0.5267	0.1298
	ALTS	2017	18+	463	180	107	0.3888	0.2311
	BD	2017	25+	287	98	58	0.3415	0.2021
	Biopsy	2017	18+	85	51	16	0.6000	0.1882
Low-grade colpo and HPV16/18+	ALTS	2017	18+	1040	119	36	0.1144	0.0346
	BD	2017	25+	1610	153	41	0.0950	0.0255
	Biopsy	2017	18+	250	69	7	0.2760	0.0280
	ALTS	2017	18+	48	11	5	0.2292	0.1042
Acetowhite/metaplasia colpo and 16/18+	BD	2017	25+	137	15	11	0.1095	0.0803
	Biopsy	2017	18+	15	3	1	0.2000	0.0667
	ALTS	2017	18+	150	18	4	0.1200	0.0267

Strata	Manuscript first author	Year	Age Group	N	CIN2+	CIN3+	Proportion CIN2+	Proportion CIN3+
Normal colpo and HPV16/18+	BD	2017	25+	821	33	11	0.0402	0.0134
	Biopsy	2017	18+	62	6	1	0.0968	0.0161
	Huh	2014		221	19	9	0.0860	0.0407
	ALTS	2017	18+	110	2	2	0.0182	0.0182
	BD	2017	25+	203	17	9	0.0837	0.0443
	Biopsy	2017	18+	5	0	0	0.0000	0.0000
Normal colpo and HPV16/18-	Huh	2014		1885	23	8	0.0122	0.0042
	ALTS	2017	18+	423	4	2	0.0095	0.0047
	BD	2017	25+	1597	28	12	0.0175	0.0075
	Biopsy	2017	18+	45	3	0	0.0667	0.0000
	ALTS	2017	18+	105	90	75	0.8571	0.7143
	BD	2017	25+	9	8	6	0.8889	0.6667
High-grade colpo and HSIL+ and HPV16/18+	Biopsy	2017	18+	57	45	19	0.7895	0.3333
	ALTS	2017	18+	49	31	17	0.6327	0.3469
High-grade colpo and HSIL+ and HPV16/18-	BD	2017	25+	8	5	4	0.6250	0.5000
	Biopsy	2017	18+	50	35	9	0.7000	0.1800
High-grade colpo and <HSIL and HPV+	ALTS	2017	18+	75	43	28	0.5733	0.3733
	BD	2017	25+	22	11	7	0.5000	0.3182
High-grade colpo and <HSIL and HPV-	Biopsy	2017	18+	24	18	9	0.2400	0.3750
	ALTS	2017	18+	131	32	11	0.2443	0.0840
Low-grade colpo and HSIL+ and HPV+	BD	2017	25+	128	13	3	0.1016	0.0234
	Biopsy	2017	18+	75	30	5	0.4000	0.0667
Low-grade colpo and HSIL+ and HPV-	ALTS	2017	18+	116	78	57	0.6724	0.4914
	BD	2017	25+	22	17	10	0.7727	0.4545
Low-grade colpo and HSIL- and HPV+	Biopsy	2017	18+	27	19	9	0.7037	0.3333
	ALTS	2017	18+	112	42	18	0.3750	0.1607
Low-grade colpo and HSIL- and HPV-	BD	2017	25+	45	24	9	0.5333	0.2000
	Biopsy	2017	18+	53	23	1	0.4340	0.0189
Low-grade colpo and <HSIL and HPV+	ALTS	2017	18+	340	98	48	0.2882	0.1412
	BD	2017	25+	265	81	48	0.3057	0.1811
Low-grade colpo and <HSIL and HPV-	Biopsy	2017	18+	58	32	7	0.5517	0.1207

Strata	Manuscript first author	Year	Age Group	N	CIN2+	CIN3+	Proportion CIN2+	Proportion CIN3+
Low-grade colpo and <HSIL and HPV-	ALTS	2017	18+	915	75	17	0.0820	0.0186
	BD	2017	25+	1565	119	32	0.0760	0.0204
	Biopsy	2017	18+	188	42	5	0.2234	0.0266
	ALTS	2017	18+	9	3	1	0.3333	0.1111
Acetowhite/metaplasia colpo and HSIL+ and HPV+	BD	2017	25+	6	1	1	0.1667	0.1667
	Biopsy	2017	18+	6	2	1	0.3333	0.1667
	ALTS	2017	18+	6	2	0	0.3333	0.0000
	BD	2017	25+	9	2	0	0.2222	0.0000
Acetowhite/metaplasia colpo and HSIL+ and HPV-	Biopsy	2017	18+	11	3	1	0.2727	0.0909
	ALTS	2017	18+	39	8	4	0.2051	0.1026
	BD	2017	25+	131	14	10	0.1069	0.0763
	Biopsy	2017	18+	8	1	0	0.1250	0.0000
Acetowhite/metaplasia colpo and <HSIL and HPV+	ALTS	2017	18+	141	16	4	0.1135	0.0284
	BD	2017	25+	812	31	11	0.0382	0.0135
	Biopsy	2017	18+	48	3	0	0.0625	0.0000
	ALTS	2017	18+	7	1	1	0.0000	0.0000
Normal colpo and HSIL+ and HPV+	BD			9	5	3	0.5556	0.3333
	Biopsy			--	--	--		
	ALTS	2017	18+	14	0	0	0.0000	0.0000
	BD	2017	25+	25	3	1	0.1200	0.0400
Normal colpo and HSIL+ and HPV-	Biopsy	2017	18+	2	0	0	0.0000	0.0000
	Huh	2014		221	19	9	0.0860	0.0407
	ALTS	2017	18+	100	1	1	0.0100	0.0100
	BD	2017	25+	194	12	5	0.0619	0.0258
Normal colpo and <HSIL and HPV+	Biopsy	2017	18+	4	0	0	0.0000	0.0000
	Huh	2014		660	15	6	0.0227	0.0091
	ALTS	2017	18+	402	4	2	0.0100	0.0050
	BD	2017	25+	1572	25	11	0.0159	0.0070
Normal colpo and <HSIL and HPV-	Biopsy	2017	18+	38	3	0	0.0789	0.0000

Table 2

Population distribution of risk strata combinations

Colposcopy & Cytology	ALTS		Biopsy		BD	
	N	%	N	%	N	%
High-grade colpo and HSIL+	155	7.1%	108	16.6%	17	0.4%
Low-grade colpo and HSIL+	229	10.5%	80	12.3%	67	1.4%
High-grade colpo and <HSIL	206	9.5%	99	15.2%	150	3.1%
Metaplasia/Acetowhite colpo and HSIL+	15	0.7%	17	2.6%	15	0.3%
Low-grade colpo and <HSIL	1259	58.0%	248	38.0%	1830	38.0%
Normal colpo and HSIL+	21	1.0%	2	0.3%	34	0.7%
Metaplasia/Acetowhite colpo and <HSIL	182	8.4%	56	8.6%	943	19.6%
Normal colpo and <HSIL	503	23.2%	42	6.4%	1766	36.6%
Total Population	2570		652		4822	

Colposcopy & HPV16/18	ALTS		Biopsy		BD	
	N	%	N	%	N	%
High-grade colpo and HPV16/18+	182	9.0%	83	12.3%	31	0.6%
Low-grade colpo and HPV16/18+	463	22.9%	85	12.6%	287	6.0%
High-grade colpo and HPV16/18–	182	9.0%	131	19.4%	136	2.8%
Metaplasia/Acetowhite colpo and 16/18+	48	2.4%	15	2.2%	137	2.8%
Low-grade colpo and HPV16/18–	1040	51.4%	250	37.0%	1610	33.4%
Metaplasia/Acetowhite colpo and 16/18–	150	7.4%	62	9.2%	821	17.0%
Normal colpo and HPV16/18+	110	5.4%	5	0.7%	203	4.2%
Normal colpo and HPV16/18–	423	20.9%	45	6.7%	1597	33.1%
Total Population	2598		676		4822	

Colposcopy & Cytology & HPV16/18+									
	ALTS		Biopsy		BD				
	N	%	N	%	N	%			
High-grade colpo and HSIL+ and HPV16/18+	105	5.3%	57	8.8%	9	0.2%			
Low-grade colpo and HSIL+ and HPV16/18+	116	5.8%	27	4.2%	22	0.5%			
High-grade colpo and HSIL+ and HPV16/18–	49	2.5%	50	7.7%	8	0.2%			
High-grade colpo and <HSIL and HPV16/18+	75	3.8%	24	3.7%	22	0.5%			
Low-grade colpo and HSIL+ and HPV16/18–	112	5.6%	53	8.2%	45	0.9%			
Low-grade colpo and <HSIL and HPV16/18+	340	17.0%	58	8.9%	265	5.5%			
Metaplasia/Acetowhite colpo and HSIL+ and 16/18+	9	0.5%	6	0.9%	6	0.1%			
Metaplasia/Acetowhite colpo and HSIL+ and 16/18–	6	0.3%	11	1.7%	9	0.2%			
High-grade colpo and <HSIL and HPV16/18–	131	6.6%	75	11.6%	128	2.7%			
Metaplasia/Acetowhite colpo and <HSIL and 16/18+	39	2.0%	8	1.2%	131	2.7%			
Low-grade colpo and <HSIL and HPV16/18–	915	45.8%	188	29.0%	1565	32.5%			
Metaplasia/Acetowhite colpo and <HSIL and 16/18–	141	7.1%	48	7.4%	812	16.8%			
Normal colpo and HSIL+ and HPV16/18+	7	0.4%	0	0.0%	9	0.2%			
Normal colpo and <HSIL and HPV16/18+	100	5.0%	4	0.6%	194	4.0%			
Normal colpo and HSIL+ and HPV16/18–	14	0.7%	2	0.3%	25	0.5%			
Normal colpo and <HSIL and HPV16/18–	402	20.1%	38	5.9%	1572	32.6%			
Total Population	2561		649		4822				