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Heterogeneity of high grade cervical intraepithelial neoplasia related to HPV16: Implications for natural history and management

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Abstract

Factors associated with progression from cervical intraepithelial neoplasias (CIN) grade 2 and 3 to invasive cancer are not well understood; most CIN2 and CIN3 do not progress to cancer. Among carcinogenic HPV types, infections with HPV16 have the highest risk of progressing to cancer. We evaluated the heterogeneity of risk factors, lesion size, colposcopic impression, and colposcopic biopsy results in relation to HPV16 status among 627 women with CIN2 or CIN3 in women referred to colposcopy at the University of Oklahoma. Loop excision specimens were evaluated in 12 radial segments to estimate lesion size. The mean age at CIN3 was 27.7 years for HPV16-positive women (n=225) and 33.6 years for HPV16-negative women (n=104), respectively. The average lesion size did not differ by HPV16 status (p=0.83). Among HPV16-positive women with CIN3, lesions were significantly larger in women 30 years and older (p=0.03). Colposcopic impression was worse in women with HPV16 infections (p=0.009), but the detection of CIN3 at the preceding biopsy was not improved in HPV16-positive women. CIN3 is detected at the same lesion size, but at much younger age in women with HPV16 infections, suggesting faster growth. CIN2 lesion size in women without HPV16 peaks below 30 years and then decreases, suggesting frequent regression, while HPV16-related CIN2 is more likely to persist. Lesion size seems to be the most important determinant of colposcopy and biopsy performance. Genotyping for HPV16 in cervical cancer screening can improve risk stratification, but may pose challenges to finding small lesions in colposcopy.

Keywords

HPV16; CIN3; biopsy; colposcopy; screening

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Introduction

Virtually all cervical cancers are caused by persistent infections with carcinogenic human papillomaviruses (HPV). However, HPV infections are very common; only few infections progress to high grade CIN (including the cancer precursor CIN3 and the less certain, clinically important endpoint of CIN2); and even fewer will invade to cancer (1). It is estimated that about 30–50% of large CIN3s will progress to cancer over a period of 30 years (2), but the determinants of invasion are not well understood.

Data from large cohorts and from laboratory studies have demonstrated that there is a substantial heterogeneity in risk of developing cervical cancer within the group of carcinogenic HPV types. HPV16 is unique as the genotype with the highest carcinogenic potential in laboratory studies, with the highest risk for progression to CIN3 and cancer demonstrated in large cohort studies, and with the highest attribution for cervical cancers worldwide (3–6).

Currently, HPV genotyping information is not routinely used in clinical practice. There is limited data about how HPV genotype status is related to natural history and clinical presentation of CIN2 and CIN3 and how this may affect clinical management. Previous studies have reported a younger age at diagnosis for HPV16-related cancers and precancers, but the reasons for the age difference have not been fully explained (7;8). A previous study conducted as part of the ASCUS-LSIL Triage Study (ALTS) demonstrated that HPV16-positivity was associated with worse colposcopic appearance, suggesting that HPV16-related high grade CIN may be easier detectable at colposcopy (9). An evaluation of colposcopy performance in vaccine trial control arms suggested that HPV16 status improved agreement between preceding biopsy and LEEP outcome (10). Here, we evaluated how risk factors for cervical cancer, lesion size, colposcopic impression, and biopsy results are related to HPV16-positivity among women with CIN2 and CIN3 in a large referral population in Oklahoma.

Material and Methods

Study Population

The Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED) design and methodology, including the details on enrollment, questionnaire data, HPV DNA genotyping, histology, and cytology procedures, have been described previously in detail (11–13). In brief, between 2003 and 2007, women 18 years and older without prior cancer diagnosis and referred to colposcopy at the Oklahoma University Health Sciences Center (OUHSC) Dysplasia Clinic following an abnormal Pap smear result or a biopsy diagnosis of CIN were eligible for enrollment into SUCCEED. Additional accrual of women diagnosed with CIN3 and cancers continued until March 2010. Written informed consent was obtained from all women enrolled into the study and Institutional Review Board approval was provided by OUHSC and the US National Cancer Institute.

Cervical Specimen Collection, Colposcopy

The main analyses are based on the colposcopic impression, cytology results, and HPV genotyping results at the time of LEEP. For a subset of the cases biopsy results from the preceding visit were available and included in the analysis. Treatment decisions were based on the ASCCP guidelines (14). All lesions with biopsy-proven CIN2 or CIN3 were referred to loop electrosurgical excision procedure (LEEP) of the transformation zone. In addition, some women with persistent cytologic abnormalities (especially HSIL), women with unsatisfactory colposcopy and strong suspicion of a lesion, women with abnormal bleeding, women with positive ECC, and women with previous high grade disease and recurrent

cytological abnormalities were offered LEEP. The correlation between preceding biopsy and LEEP outcomes is summarized in Supplementary Table 1. Among 138 women referred to LEEP without a CIN2 or CIN3 found in the preceding biopsy, 27 (20%) had HSIL cytology and a high grade colposcopy impression, 17 (12%) had HSIL cytology alone, and 52 (38%) had a high grade colposcopy impression alone (30%). For the remaining 42 women, (30%), the reason for LEEP referral was not recorded in the study, but may have been related to persistent cytologic abnormalities <HSIL, a history of high grade disease, or abnormal bleeding. Treatment of CIN2 was delayed among very young women and women desiring future fertility. Prior to LEEP, colposcopic examination was performed and cervical cell samples were collected and rinsed directly into PreservCyt™ solution (Hologic, Boxborough, MA) as previously described (11). Colposcopic examination was conducted by an experienced gynecologic oncologist according to routine practice at OUHSC. Acetic acid was applied and cervical assessment was based on the Reid colposcopic index, including the colposcopic signs 'lesion margin', 'color', and 'vessels'. Based on these categories, the colposcopist documented the overall visual impression of the cervix as normal, CIN1, CIN2, CIN3, or cancer. When required, iodine was applied to identify transformation zone boundaries. Quality of colposcopy performance was continuously monitored by weekly meetings to review colposcopy drawings and impression, referral Pap result, and pathology results. HPV genotyping results were not revealed to the physicians and did not influence screening or clinical management at any point. The cytology specimen was used for ThinPrep™ (Hologic, Boxborough, MA) cytology and for HPV genotyping using the Linear Array (LA) HPV Gentoyping Test (Roche Molecular Diagnostics, Branchburg, NJ).

LEEP processing and lesion size measurement

Every LEEP specimen was divided into 12 radial segments for detailed histopathological mapping and lesion size determination and analyzed to generate individual histology results for each segment by o'clock position. The study pathologists at OUHSC, masked to HPV genotyping data, determined the histology using CIN terminology. One or more of the following diagnoses were noted for each o'clock segment of the cervix per individual: other, negative/normal, atypical metaplasia, CIN1, CIN2, CIN3. CIN3 and CIN2 segments were added for each LEEP to determine lesion size. Per common practice, the cases were categorized according to the worst diagnosis for each woman based on the diagnosis of the most abnormal LEEP segment.

Analytic Population

During the study period, 298 women were diagnosed with a CIN2 and 329 women were diagnosed with a CIN3 in their LEEP specimen (Figure 1). Among these 627 women, 301 had single carcinogenic infections. 327 of 627 women (139 with CIN2 and 188 with CIN3) with LEEP had a preceding biopsy in the study, allowing a comparison of biopsy outcome with LEEP results.

Statistical Analyses

All analyses were stratified by diagnostic result of the LEEP. Contingency tables and Pearson's chi square statistics were used to analyze risk factor distributions by HPV16 status and within LEEP outcomes (CIN2, CIN3). HPV16 status was defined as positive if HPV16 was detected by Linear Array in the cytology specimen at the time of LEEP. HPV16 status was defined as negative when any other HPV genotype except for HPV16 was present. We considered the following HPV types as carcinogenic: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. We evaluated lifetime number of sexual partners (categorized in four groups: 1–3, 4–5, 6–10, and >10), oral contraceptive use (Never, Ever), smoking status (Never, Former, Current), number of high risk HPV types (<2 and ≥2), and cytology result (<HSIL, HSIL and greater). Differences in mean age and mean sexual activity span

(calculated as age of diagnosis – age of sexual debut) as well as number of LEEP segments with CIN2, CIN3, and CIN2 and CIN3 combined in women with CIN3 were compared between groups using a two-sample t-test. Contingency tables and Pearson's chi-square statistics were used to analyze the distribution of colposcopic impression (normal, CIN1, CIN2 and greater) and biopsy results (<CIN2, CIN2+) by HPV16 status among women with CIN2 or greater in their LEEP. P-values <0.05 were considered significant. All analyses were performed using Stata 10 (StataCorp, College Station, TX) and SAS 9.1 (Cary, NC).

Results

Characteristics of Key Risk Factors and Screening Results by HPV16 status

Of 627 women with a LEEP-confirmed CIN2 or CIN3, 329 were diagnosed with CIN3 and 298 were diagnosed with CIN2. Among women with CIN3, 225 (68.3%) were positive for HPV16, while 136 (45.6%) of the women with CIN2 were positive for HPV16. We compared key risk factors and cervical cancer screening test results within each histological category by HPV16 status (Table 1). Within both CIN2 and CIN3, women with HPV16 were significantly younger and had a shorter sexual activity span: the mean age at CIN2 was 26.8 years for HPV16-positive women and 29.8 years for HPV16-negative women; the mean age at CIN3 was 27.7 years for HPV16-positive women and 33.6 years for HPV16-negative women, respectively; and the average time from first sexual activity until detection was 10.9 years for HPV16-positive CIN2, 13.3 years for HPV16-negative CIN2, 11.9 years for HPV16-positive CIN3 and 18.0 years for HPV16-negative CIN3. Despite a shorter period of sexual activity, women with HPV16 had similar or higher numbers of sexual partners than HPV16-negative women. Oral contraceptive use and smoking status were evenly distributed among women with and without HPV16. Women with HPV16 infections were found to have more concurrent carcinogenic HPV infections (p=0.002), a finding that persisted in age-stratified analyses (data not shown). We did not observe a differential distribution of HSIL cytology results by HPV16-positivity in the individual disease groups (CIN2 and CIN3).

Size of CIN2 and CIN3 lesions in relation to HPV16 status and age

We evaluated the number of LEEP segments with CIN2 and CIN3 as a surrogate for lesion size in women diagnosed with CIN2 and CIN3, stratified by age and HPV16 status. CIN2 lesions were larger in women with HPV16 infections compared to women with CIN2 related to other types (3.1 vs. 2.2 segments, p<0.001). In contrast, CIN3 lesion size did not differ by HPV16 status (2.9 vs. 2.8 segments, p=0.83). Similarly, when combining CIN2 and CIN3 segments in women with CIN3, lesion size did not differ by HPV16 status (4.4 vs. 4.4, p=0.95), indicating that CIN3 is detected at about the same size, independent of viral genotype. Stratifying by age (<30 years vs. 30 years and older) revealed different patterns related to HPV16 status: Although not statistically significant, we observed a slight decrease in CIN2 lesion size in women without HPV16 (2.0 vs. 2.4, p=0.08). In contrast, in women with CIN2 and HPV16 infections, lesion size was slightly, but insignificantly, larger in women 30 years and older, suggesting that CIN2 related to HPV16 is more likely to persist. Lesion size was larger for CIN3 in both strata in women 30 years and older, but there was a much stronger increase in lesion size in HPV16+ women (3.4 vs. 2.7 segments, p=0.03), supporting the notion that HPV16-related CIN3 grows faster compared to CIN3 caused by other carcinogenic types.

Colposcopic Impression and HPV16 Status

We evaluated colposcopic impression in 627 women who had a LEEP-confirmed CIN2 or CIN3 in SUCCEED (Table 3). Overall, 82.4% of women with CIN2 or CIN3 had a high grade colposcopic impression. Both in the CIN2 and CIN3 groups, women with HPV16 had

a significantly worse colposcopic appearance that was more pronounced for CIN3 (p=0.009). In contrast, the distribution of colposcopic impression within HPV16 strata was very similar in CIN2 and CIN3 (p=0.53 for HPV16−, p=0.40 for HPV16+). When restricting the population to the 301 women with single carcinogenic HPV infections, the effect persisted (Table 4): In women with single HPV16 infections, colposcopic impression was worse compared to women with single carcinogenic infections with other types than HPV16 both in women with CIN2 (p=0.031) and CIN3 (p=0.001).

Colposcopic Biopsy and HPV16 Status

We analyzed the distribution of biopsy results by HPV16-positivity in women who had a colposcopic biopsy taken during the study before the LEEP procedure. We analyzed the distribution stratified by LEEP result among 314 women (139 with CIN2, and 175 with CIN3) (Table 5). In women with a LEEP result of CIN2 or CIN3, the distribution of biopsy results was not significantly different by HPV16 status (p=0.44 and 0.32, respectively); there was even a suggestion of fewer prior CIN3 biopsy results among HPV16-positive women with CIN3 in LEEP specimens (50.4% vs. 62.7%, p=0.12).

Discussion

HPV16 is the major carcinogenic HPV type that causes about 57% of cervical cancers worldwide (15). Long-term prospective studies have shown that women with HPV16 infections have a substantially higher risk of developing CIN3 and cancer than women infected with other carcinogenic types (4;5). The factors that confer this apparent risk difference between HPV16 and other known carcinogenic types are not well understood. Here, we report on the relationship between HPV16-positivity with cervical cancer risk factors, lesion size, and cervical cancer screening test results examined in a large US-based referral population with LEEP-confirmed CIN2 and CIN3.

We confirmed that women with HPV16 had a younger age at diagnosis of CIN3 (7). In our study, we observed this effect for both CIN2 and CIN3 separately. In accordance, we also demonstrated that the span of sexual activity was shorter among women with disease related to HPV16 compared to other carcinogenic types. Despite the shorter span of sexual activity, women with HPV16-positive CIN2 and CIN3 had a similar or higher number of sexual partners and they had more concurrent carcinogenic HPV infections. Other cervical cancer risk factors did not show a different distribution by HPV16 status. The sexual activity span marks the upper boundary of the estimated progression time from initial HPV infection to CIN3. Thus, despite the lack of prospective data, HPV16-related CIN2 and CIN3 appear to grow faster than those related to other types, with a progression time that is on average a third (5 years) shorter for HPV16-related CIN3.

Remarkably, we observed that CIN3 lesion size did not differ between women with HPV16 and without. Age at diagnosis, however, was significantly different. This indicates that CIN3 is detected at the same size irrespective of genotype, but that CIN3 related to HPV16 reaches the size of detection much faster than CIN3 related to other types, further suggesting faster growth of HPV16-related CIN3. Furthermore, we also observed a greater increase of HPV16 lesion size among women older than 30 years compared to CIN3 related to other types.

Our findings suggest different behavior of high grade CIN, related to lesion grade and HPV genotype. CIN2 lesion size related to types other than HPV16 peaks in women younger than 30 years and decreases in women 30 years and older, supporting a previous observation in ALTS that many CIN2 lesions regress spontaneously (16). In contrast, lesion size increases in CIN2 related to HPV16 at older age, suggesting that HPV16-related CIN2 is more likely

to persist. CIN3 size increases with older age irrespective of HPV genotype, but the increase in CIN3 size is much more pronounced for cases related to HPV16.

We showed that within diagnostic categories based on the LEEP outcome, women with HPV16 had a worse colposcopic impression compared to those with other carcinogenic types; however, the worse appearance of the cervical surface did not translate to a better agreement between biopsy result and LEEP outcome for HPV16-positive women. In contrast to our findings, Stoler et al. showed that HPV16 positivity was associated with better agreement between preceding biopsy and LEEP outcome in an analysis of colposcopy performance among women enrolled in vaccine trial control arms (10). Importantly, women enrolled in the vaccine trial control arms were very young and intensely screened at short screening intervals. Furthermore, multiple biopsies were routinely taken, while in SUCCEED, a single biopsy protocol was used. Thus, the worse appearance in women infected with HPV16 could have led to taking more biopsies and improving the detection of HPV16-related lesions.

HPV16 was associated with worse colposcopic impression overall, and when restricting to women with single carcinogenic infections, supporting that the worse colposcopic impression was directly related to HPV16. Similarly, ALTS analyses showed a worse colposcopic impression for HPV16, but not for coincident infections with multiple genotypes (9).

An important clinical consequence of our results is that lesion size seems to be the most important determinant of colposcopy and biopsy performance. HPV16/18 genotyping has been proposed as a triage tool for women with ASC-US cytology results or for women who are found to be HPV-positive and cytology-negative in co-testing (17). Our findings support the notion that HPV16-positive CIN2 and CIN3 develop faster, which warrants earlier follow-up of HPV16/18-positive women. However, our findings indicate that colposcopy might be challenged by increased referral of HPV16/18-positive women without cytological abnormalities, since colposcopy demonstrates limited performance in detecting small CIN2 and CIN3 irrespective of HPV genotype. The proportion of HSIL in women with CIN3 was similar between women with HPV16 infection and women without HPV16, further suggesting that HPV16 status, adjusted for lesion size, was not more likely to be associated with high grade cytology.

The main strengths of our study are the large number of high grade disease endpoints drawn from a large population covering two thirds of the state of Oklahoma, the availability of high quality HPV genotyping, and a very unique and thorough histological workup of biopsy and LEEP specimens that provided lesion size estimates for all 627 included high grade CIN. While examination of the 12 LEEP segments allowed us to study lesion size in unprecedented detail in a large series of LEEPs, a detailed morphometric approach may further improve the accuracy of lesion size measurement. Limitations of our analysis are inherent to all cross-sectional studies of cervical carcinogenesis and include the lack of longitudinal HPV genotyping data to determine the actual time from a specific HPV infection to detection of CIN2 and CIN3. Further, we made inferences from cross-sectional data of lesion size to lesion growth, but it is not possible to observe lesion size prospectively in any study design- even if it was possible to follow biopsy-confirmed CIN2 and CIN3, it is not possible to estimate lesion size without measuring specimens from excisional procedures. The low sensitivity of cytological testing and the limitations of disease ascertainment during colposcopy may particularly have led to an underrepresentation of small CIN2 and CIN3. However, since HPV genotyping was not revealed during diagnostic workup and treatment and no differential management related to HPV type was performed, the comparison between HPV16+ and HPV16− CIN2 and CIN3 is likely to be unbiased. In

our analysis, we used the community histology diagnosis rather than adjudicated histology results. We previously demonstrated in our studies of disease ascertainment and HPV genotype attribution in this population (11–13) that histology categories reported in SUCCEED are comparable to general US practice. Thus, we do not expect that adjudication of the histology endpoints would substantially change our findings.

In summary, our findings suggest that CIN3s related to HPV16 grow faster than those related to other carcinogenic types, but are detected at the same lesion size. HPV16-associated CIN2 and CIN3 have a worse colposcopic appearance, suggesting that HPV16 infections result in more evident infections. However, the worse appearance did not improve detection of the worst lesion on the cervix in our study. Thus, when using HPV16/18 genotyping as triage option for HPV-positive women, downstream management of positive test results has to be considered. The limited performance of colposcopy in detecting early lesions irrespective of HPV type may limit the benefits from detecting HPV16-related lesions early with molecular tests. To improve our understanding of the topographical development of CIN3 related to HPV16 and other carcinogenic types, we are now moving to more detailed mapping of the cervical surface, including multiple-biopsy sampling, documentation of colposcopic impression by digital imaging, and lesion-based genotyping.

Novelty and impact statement

We demonstrate that HPV16-related CIN2 and CIN3 are diagnosed at younger age and have worse colposcopic appearance than lesions caused by other carcinogenic types. CIN3 have the same lesion size at detection irrespective of HPV type, suggesting that HPV16-related CIN3s grow faster and reach the size of detectability earlier. Our findings support earlier follow-up of women with HPV16 infections, but indicate that colposcopy may be challenged to find early precancers independent of HPV genotype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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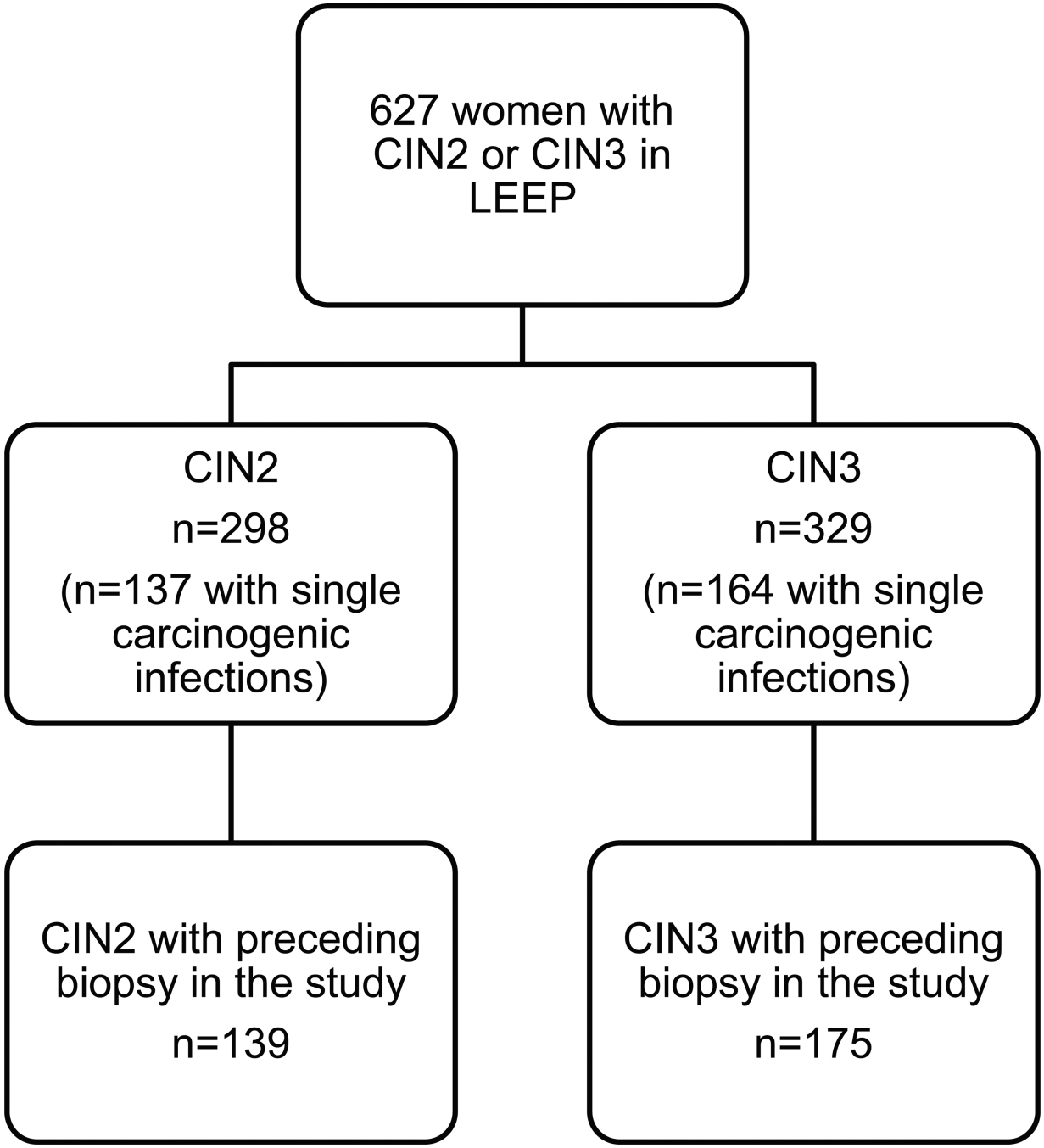

Figure 1.

Table 1

Characteristics of women with CIN2 and CIN3 on LEEP

	CIN2 (n=298)		CIN3 (n=329)	
	HPV16−	HPV16+	HPV16−	HPV16+
Determinants	**n=162**	**n=136**	**n=104**	**n=225**
Age at LEEP				
Mean years (SD)	29.8 (8.8)	26.8 (6.9)	33.6 (11.1)	27.7 (7.1)
p-value	0.002		<0.001	
Sexual activity span				
Mean years (SD)	13.3 (8.9)	10.9 (7.0)	18.0 (12.0)	11.9 (6.9)
p-value	0.017		<0.001	
Lifetime number of sexual partners				
1–3	45 (32.4%)	21 (17.4%)	17 (20.7%)	39 (18.6%)
4–5	24 (17.3%)	37 (30.6%)	21 (25.6%)	59 (28.1%)
6–10	43 (30.9%)	37 (30.6%)	32 (39.0%)	67 (31.9%)
>10	27 (19.4%)	26 (21.5%)	12 (14.6%)	45 (21.4%)
p-value	0.013		0.466	
Oral contraceptive use				
Never	21 (15.8%)	13 (10.6%)	6 (7.6%)	28 (13.7%)
Ever	112 (84.2%)	110 (89.4%)	73 (92.4%)	177 (86.3%)
p-value	0.219		0.158	
Smoking status				
Never	53 (38.4%)	44 (34.1%)	22 (26.8%)	54 (25.2%)
Former	20 (14.5%)	14 (10.9%)	16 (19.5%)	26 (12.2%)
Current	65 (47.1%)	71 (55.0%)	44 (53.7%)	134 (62.6%)
p-value	0.395		0.211	
Number of HR-HPV types				
<2	108 (66.7%)	56 (41.2%)	72 (69.2 %)	112 (49.8 %)
≥2	54 (33.3%)	80 (58.8%)	32 (30.8%)	113 (50.2%)
p-value	<0.001		0.001	
Cytology				
<HSIL	77 (49.0%)	53 (40.4%)	20 (19.8%)	46 (20.7%)
HSIL+	80 (51.0%)	78 (59.5%)	81 (80.2%)	176 (79.3%)
p-value	0.145		0.849	

Table 2

Size of CIN2 and CIN3 lesions stratified by HPV16 status and age

Age		CIN2 (n=298)		CIN3 (n=329)		CIN3 (including CIN2 segments) (n=329)	
		HPV16−	HPV16+	HPV16−	HPV16+	HPV16−	HPV16+
		n=162 (90 <30 years)	n=136 (99 <30 years)	n=104 (46 <30 years)	n=225 (162 <30 years)	n=104 (46 <30 years)	n=225 (162 <30 years)
All	**Mean number of segments** (SD)	2.2 (1.6)	3.1 (2.1)	2.8 (2.0)	2.9 (2.1)	4.4 (2.6)	4.4 (2.4)
	p-value (HPV16− vs. HPV16+)	<0.001		0.832		0.952	
<30	**Mean number of segments** (SD)	2.4 (1.8)	3.1 (1.9)	2.6 (1.7)	2.7 (1.9)	4.5 (2.3)	4.3 (2.4)
	p-value (HPV16− vs. HPV16+)	0.02		0.798		0.653	
30+	**Mean number of segments** (SD)	2.0 (1.3)	3.3 (2.6)	3.0 (2.3)	3.4 (2.4)	4.3 (2.8)	4.6 (2.6)
	p-value (HPV16− vs. HPV16+)	<0.001		0.394		0.508	
	p-value (<30 years vs. 30+ years)	0.08	0.54	0.34	0.03	0.70	0.40

Table 3

Colposcopic impression at time of LEEP in 627 women with CIN2 or CIN3 stratified by HPV16 status

	LEEP outcome			
Colpo impression	**CIN2 n=298**		**CIN3 n=329**	
	HPV16−	**HPV16+**	**HPV16−**	**HPV16+**
Normal	15	4	11	7
	9.3%	2.9%	10.6%	3.1%
Low grade	23	14	10	14
	14.2%	10.3%	9.6%	6.2%
High grade	124	118	83	204
	76.5%	86.8%	79.8%	90.7%
Total	162	136	104	225
Pearson chi-square	p=0.039		p=0.009	

Table 4

Colposcopic impression at time of LEEP in 301 women with CIN2 or CIN3 and single carcinogenic infections stratified by HPV16 status

	LEEP outcome			
Colpo impression	**CIN2 n=137**		**CIN3 n=164**	
	HPV16−	**HPV16+**	**HPV16−**	**HPV16+**
Normal	9	0	7	1
	11.1%	0%	13.5%	0.9%
Low grade	10	6	7	9
	12.4%	10.7%	13.5%	8.0%
High grade	62	50	38	102
	76.5%	89.3%	73.1%	91.1%
Total	81	56	52	112
Pearson chi-square	p=0.031		p=0.001	

Table 5

Result of colposcopic biopsy obtained before LEEP in 314 women with CIN2 or CIN3 stratified by HPV16 status

	LEEP outcome			
Biopsy result	**CIN2 n=139**		**CIN3 n=175**	
	HPV16−	**HPV16+**	**HPV16−**	**HPV16+**
<CIN2	24	16	6	16
	32.4%	24.6%	10.7%	13.5%
CIN2	40	36	15	43
	54.1%	55.4%	26.8%	36.1%
CIN3+	10	13	35	60
	13.5%	20.0%	62.5%	50.4%
Total	74	65	56	119
Pearson chi-square	p=0.444		p=0.324	