Original Article

Impact of the Human Papillomavirus Status on the Development of High-Grade Cervical Intraepithelial Neoplasia in Women Negative for Intraepithelial Lesions or Malignancy at the Baseline: A 9-Year Swedish Nested Case-Control Follow-Up Study

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BACKGROUND: The causal relation between high-risk human papillomavirus (HPV) and cervical cancer and its precursor lesions has led to the use of sensitive HPV molecular tests for screening. This study examined the impact of the baseline HPV status on the future risk of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) among women with cytology negative for intraepithelial lesions or malignancy (NILM). **METHODS:** This was a nested case-control study including women with NILM baseline cytology participating in the Swedish cervical screening program in 2005-2007. Ninety-six cases of CIN2+ and 5 age-matched controls per case were identified through the National Cervical Screening Registry by follow-up through 2014. Baseline liquid-based cytology samples were tested for HPV. Conditional logistic regression analysis was used to calculate odds ratios (ORs) with confidence intervals (CIs). **RESULTS:** The risk of future high-grade cervical intraepithelial neoplasia (CIN) was strongly associated with the baseline HPV status. For women younger than 30 years, HPV-16/18 showed a significant association with future risk for CIN2+ (OR, 9.44; 95% CI, 3.37-26.4). Other HPV types were not significantly associated with future CIN2+ in these younger women. For women 30 years old or older, both HPV-16/18 and other HPV subtypes conferred a significant risk. **CONCLUSIONS:** The presence of HPV-16/18 among women with NILM cytology is associated with an elevated future risk of high-grade CIN. HPV types other than HPV-16/18 seem to have a greater impact on women 30 years old or older than younger women. Women with NILM cytology and HPV-16/18 need specific follow-up management within screening. ***Cancer* 2019;125:239-248**. © *2018 American Cancer Society.*

KEYWORDS: case-control studies, cervical intraepithelial neoplasia, genotype, papillomaviridae, uterine cervical neoplasms.

INTRODUCTION

Persistent high-risk human papillomavirus (HPV) infection has a key etiological role in cervical cancer development, with subtypes HPV-16 and HPV-18 most frequently found in invasive cervical cancers.[1] The causal relation between HPV infection and cervical cancer and its precursor lesions (cervical intraepithelial neoplasia grade 2 or worse [CIN2+]) has led to the introduction of sensitive molecular tests for HPV into clinical practice.[2] Screening based on HPV reportedly provides 60% to 70% greater protection against invasive cervical cancer than cytology screening.[3]

With the aim of avoiding unnecessary treatment and in light of the greater effectiveness of HPV primary screening in comparison with cytology, European guidelines now recommend HPV primary screening starting at the age of 30 years.[4] This age was chosen to avoid detecting transient HPV infections among younger women. Moreover, the better negative predictive value of HPV testing is thought to permit a relatively safe extension of the screening interval.[3,4] This approach can help us to avoid the potential harms of overtreatment. Adverse obstetric outcomes, including preterm birth, are among these harms, and they are linked, in particular, to excisional procedures.[5,6] Avoiding overtreatment would also lower costs, provide more efficient utilization of health care resources, and diminish anxiety and inconvenience for the patient.[7]

The European guidelines advise that cytology-based screening be begun before peak cervical cancer incidence: not earlier than the age of 20 years nor later than the age of 30 years. The American Cancer Society's cervical cancer screening

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DOI: 10.1002/cncr.31788, **Received:** April 22, 2018; **Revised:** August 9, 2018; **Accepted:** August 29, 2018, **Published online** December 10, 2018 in Wiley Online Library (wileyonlinelibrary.com)

recommendations are partially concordant with European guidelines.[8] Namely, cytology is recommended from the age of 21 years at 3-year intervals, with HPV and cytology cotesting from the ages of 30 to 65 years.

The genotyping of HPV subtypes HPV-16 and HPV-18 among women with an HPV infection has been suggested as a way of avoiding overdiagnosis and overtreatment of transient HPV infections and regressive cervical intraepithelial neoplasia (CIN).[3,9] In clinical trials in the United States, genotyping for HPV-16 and HPV-18 has been found to improve risk stratification for women with cytology negative for intraepithelial lesions or malignancy (NILM).[9,10] However, data supporting this strategy are limited outside the United States.

This observational study from the Swedish population–based screening program examines women with baseline NILM cytology who developed CIN2+ up to 9 years later. These women are compared with age-matched women with baseline NILM cytology who had no high-grade CIN detected during that follow-up period. The study question is as follows: What are the odds of developing high-grade CIN according to the baseline HPV status? We also aim to add knowledge about the impact of HPV genotyping for women younger than 30 years and for women 30 years old or older. These findings are viewed in light of how they might help to inform cervical cancer screening recommendations, especially because these recommendations are becoming increasingly reliant on HPV testing.

MATERIALS AND METHODS

Study Design

This is a nested case-control investigation including women with NILM cytology from our previous study within the Swedish cervical screening program.[11] From 2005 to 2007, 9464 women were screened with liquid-based cytology. For 9047 of these women, the baseline cytology was NILM. Follow-up data through 2014 on cervical cytology and histopathology were retrieved from the National Cervical Screening Registry with personal identification numbers. Figure 1 summarizes the process by which the 96 cases of histologically confirmed CIN2, CIN3, adenocarcinoma in situ (AIS), and cervical cancer were included in this study. Controls (n = 480) were matched by age (±365 days), baseline screening date (±180 days), and screening history before and after the baseline (0 vs 1 or more screening cytologies). Until 2014 (the end of the follow-up period), the controls had no cytological or histopathological diagnoses indicating CIN2+.

In planning for stratified analyses by age and HPV subtypes, with the power at approximately 90% for detecting a 1-sided α value of ~.05, we performed simulations to arrive at a ratio of 5 controls per case. The study was approved by the local ethics committee (2004-679/3, 2010/944-32, and 2013/763-32).

HPV Testing

Sample liquid-based cytology vials (ThinPrep and PreservCyt; Hologic, Bedford, Massachusetts) from the baseline screening for cases and controls were stored at Karolinska University Hospital until HPV testing in 2016. The liquid-based samples, collected at the inclusion visit, were stored in PreservCyt solution. The liquid-based cytology containers were vortexed for 15 to 20 seconds before a 2-mL aliquot was transferred into a test tube labeled with a unique identifier and transported to the Institute of Microbiology and Immunology of Ljubljana University (Ljubljana, Slovenia). The HPV DNA testing laboratory was blinded for clinical data, including the case-versus-control status. The presence of HPV was determined with the RealTime High-Risk HPV assay (Abbot, Wiesbaden, Germany) according to the manufacturer's instructions. The clinically validated, quantitative, multiplex real-time polymerase chain reaction test was used to detect 14 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and for concomitant partial genotyping for HPV-16 and HPV-18. Endogenous human β-globin was amplified and detected simultaneously to ensure sample adequacy (cellular internal control). If the sample had an invalid internal control (negative β-globin), the testing was repeated. If the internal control was again found to be invalid, the sample was excluded from further analysis. Fifty-nine samples showed some degree of HPV-specific positive amplification signal, but the cycle threshold values were above the manufacturer's cutoff. These samples were repeated as part of the laboratory's internal procedure. These samples were, therefore, run a second time. In this second run, 34 clearly tested as HPV-negative, 1 tested as HPV-positive, and in 24 samples, the HPV signal was again above the manufacturer's fixed assay cutoff. These last samples were considered to be HPV-negative because they twice tested as negative according to the assay cutoff cycle. This repeated testing procedure is the standard protocol used at the Institute of Microbiology and Immunology of Ljubljana University to determine whether or not a given liquid-based cytology sample is HPV-negative after it is repeatedly found that the HPV signal is above the manufacturer's fixed assay cutoff.

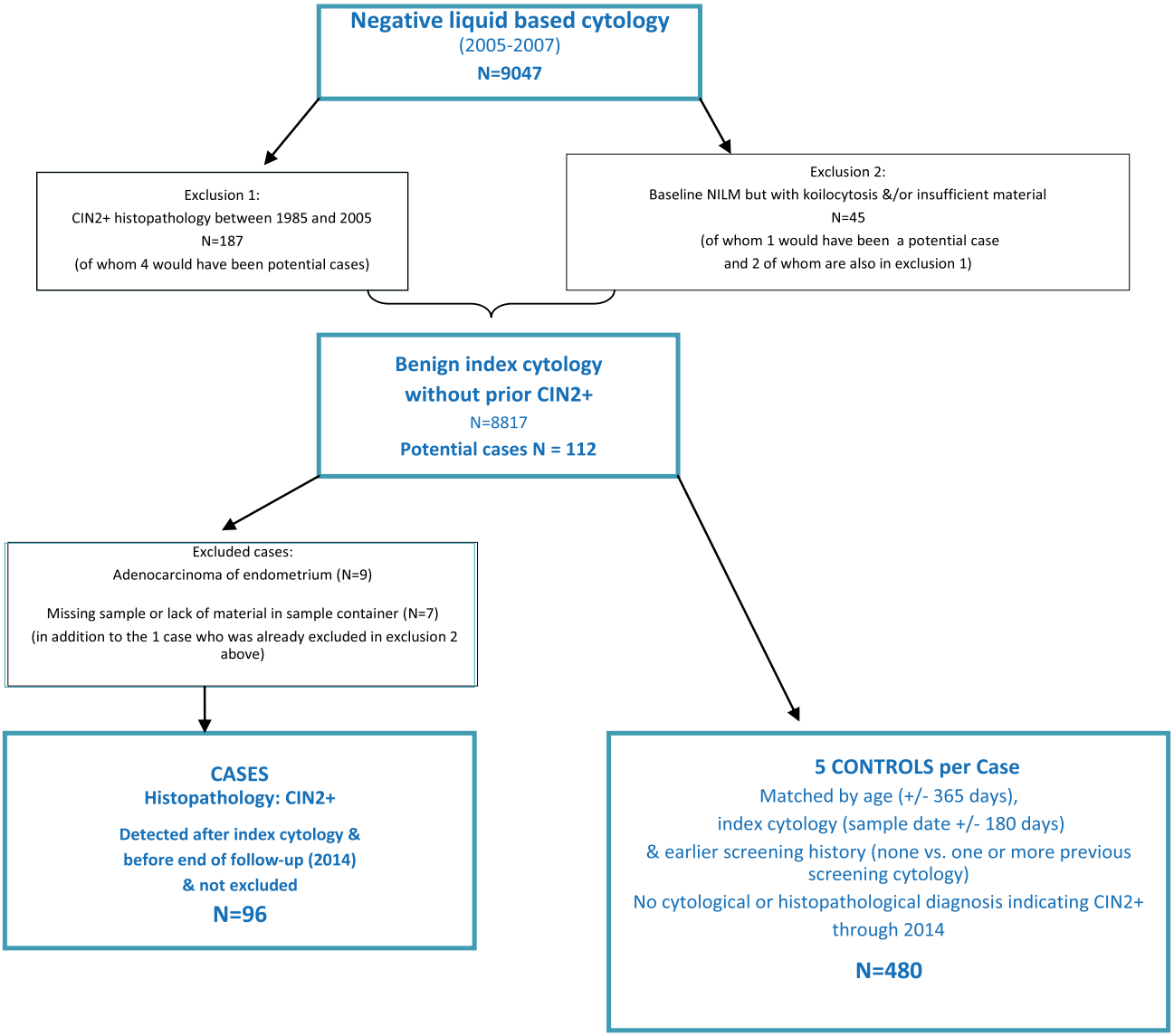

Figure 1. Flow chart of the data retrieval process for identifying cases and controls with the Swedish National Cervical Screening Registry. CIN2+ indicates cervical intraepithelial neoplasia grade 2 or worse; NILM, negative for intraepithelial lesions or malignancy.

Statistical Analysis

Pearson chi-square tests were used to assess associations between categorical variables. Conditional logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for 2 outcomes: CIN2+ and CIN3+. The independent variable was the HPV status, which was defined first as an infection with any HPV and subsequently as an infection with HPV-16/18 and with other HPV types only. No HPV infection was used as a reference. Stratified analyses with matched controls were performed for cases with CIN2+ and CIN3+ and for age groups younger than 30 years and 30 years old or older.

RESULTS

Table 1 displays the baseline prevalence of HPV among the 96 patients with CIN2+ at follow-up and among the 480 controls. The findings of any HPV, HPV-16/18, and only other HPV types were all observed significantly more often among the cases. The HPV data were missing for 3 cases and 11 controls because of negative results for

TABLE 1. Baseline HPV Status Among Women Who at the 9-Year Follow-Up Had Cervical Intraepithelial Neoplasia Grade 2 or Worse and Controls

	Cases			Controls	
HPV Result	No.	%	*P*	No.	%
No HPV detected	44	45.8		402	83.8
Any HPV detected	49	51.0	<.001	67	14.0
HPV-16/18	30	31.3	<.001	30	6.3
Other HPV only	19	19.8	<.001	37	7.7
Negative for β-globin	3	3.1		11	2.3
Total	96			480	

Abbreviation: HPV, human papillomavirus.
A 2-sided Pearson chi-square analysis was performed.

β-globin. Forty-four cases (45.8%) were diagnosed with CIN2. Fifty-two cases (54.2%) developed CIN3 or more severe pathology; they included 7 women with AIS, 3 women with squamous cell carcinoma, and 1 woman with adenocarcinoma. The finding of any HPV did not differ significantly between the patients with CIN2 and the patients with more severe findings. However, HPV-16/18 was more often found among patients with CIN3 or worse histopathology in comparison with cases with CIN2 (Pearson χ^2, 6.12; $P < .02$ [2-sided]).

In Table 2, the prevalence of any HPV and HPV-16/18 is presented by 5-year age groups among cases and controls. There was no significant difference in any HPV at the baseline or HPV-16/18 when we compared cases younger than 30 years and cases 30 years old or older. However, HPV was found among significantly more controls younger than 30 years in comparison with controls 30 years old or older. The prevalence of baseline HPV-16/18 did not differ between the 2 age groups for cases or controls.

A total of 83 of the 93 cases with HPV data had 5 valid controls. Nine cases had 4 valid controls, and 1 case had 3 valid controls. Thus, the total number of matched controls was 454.

In Table 3, the ORs and 95% CIs for future high-grade CIN are presented for detecting any HPV, HPV-16/18, and other HPV types at the baseline among cases versus matched controls. Altogether, 49 of the 93 cases with CIN2+ and 67 of the 454 controls tested positive for any HPV (OR, 6.78; 95% CI, 4.01-11.5). Testing positive for HPV-16/18 yielded a somewhat higher OR for having CIN2+, but the CIs were wider. Testing positive for other HPV revealed a somewhat lower OR for having CIN2+.

Table 3 also displays age-stratified analyses for women younger than 30 years and for women 30 years old or older. The ORs for having CIN2+ were significant for HPV and for HPV-16/18 in both age groups. However, having other HPV subtypes only was significant for the case status solely among women 30 years old or older.

TABLE 2. Age-Stratified Prevalence of HPV and HPV-16/18 at the Baseline

Age Group	HPV+, No. (%)	HPV-16/18+, No. (%)	Total No.[a]
Cases[b]			
20-24 y	10 (76.9)	8 (61.5)	13
25-29 y	10 (47.6)	7 (33.3)	21
30-34 y	12 (60.0)	7 (35.0)	20
35-39 y	11 (57.9)	7 (36.8)	19
40-44 y	3 (30.0)	0	10
45-49 y	2 (28.6)	1 (14.3)	7
50-54 y	1 (50.0)	0	2
55-59 y	0	0	1
20-59 y	49 (52.7)	30 (32.3)	93
Controls			
20-24 y	15 (21.7)	8 (11.6)	69
25-29 y	21 (20.0)	7 (6.7)	105
30-34 y	16 (16.0)[c]	8 (8.0)	100
35-39 y	7 (7.5)	3 (3.2)	93
40-44 y	5 (8.9)	2 (3.6)	56
45-49 y	3 (8.3)	2 (5.6)	36
50-54 y	0	0	5
55-59 y	0	0	5
20-59 y	67 (14.3)	30 (6.4)	469

Abbreviations: CIN2+, cervical intraepithelial neoplasia grade 2 or worse; HPV, human papillomavirus.
[a]Three cases and 11 controls with negative results for β-globin were excluded (missing data).
[b]CIN2+ at follow-up.
[c]Pearson χ^2, 9.26; $P < .01$ (2-sided).

Among the 51 cases with CIN3+, 31 tested positive for any HPV, as also shown in Table 3. Altogether, 253 controls were matched to these 51 cases, 38 of whom tested positive for HPV at the baseline. Thus, testing positive for any HPV showed an OR of 9.1 for having CIN3+. Testing positive for HPV-16/18 yielded an OR of 19.2 with very wide CIs for having CIN3+. For other HPV subtypes only, the OR for having CIN3+ showed a lower level of statistical significance. The age-stratified results for the future development of CIN3+ were similar to those for CIN2+. Namely, the ORs for having CIN3+ were significant for HPV and for HPV-16/18 in both age groups. However, having other HPV subtypes only was significant for the case status solely among women 30 years old or older.

Three of the cases were older than 50 years, and all of these cases had CIN3+. Two of these patients tested negative for HPV, and the remaining patient tested positive only for other HPV subtypes.

Figure 2 shows a sharp rise in CIN2+ and CIN3+ 3 years after the baseline NILM result (corresponding to

TABLE 3. Detection of HPV and Subtypes at the Baseline Among Cases and Matched Controls

		Cases		Controls		
Outcome/Age Group	Baseline HPV Status	No.	%	No.	%	OR (95% CI)
CIN2+/23-59 y		93		454		
	HPV-negative	44	47.3	387	85.2	
	HPV-positive	49	52.7	67	14.8	6.78 (4.01-11.5)
	HPV-16/18[a]	30	32.2	30	6.6	8.93 (4.53-17.6)
	Other HPV only[b]	19	20.4	37	8.1	5.31 (2.58-10.9)
CIN2+/<30 y		34		169		
	HPV-negative	14	41.2	133	78.7	
	HPV-positive	20	58.8	36	21.3	4.95 (2.20-11.1)
	HPV-16/18[a]	15	44.0	15	8.9	9.44 (3.37-26.4)
	Other HPV only[b]	5	14.7	21	12.4	2.24 (0.69-7.19)
CIN2+/≥30 y		59		285		
	HPV-negative	30	50.8	254	89.1	
	HPV-positive	29	49.2	31	10.9	8.01 (4.02-16.0)
	HPV-16/18[a]	15	25.4	15	5.3	8.16 (3.28-20.3)
	Other HPV only[b]	14	23.7	16	5.6	9.04 (3.42-23.9)
CIN3+/23-59 y		51		253		
	HPV-negative	20	39.2	215	85.0	
	HPV-positive	31	60.8	38	15.0	9.10 (4.39-18.9)
	HPV-16/18[a]	22	43.1	18	7.1	19.2 (6.56-56.4)
	Other HPV only[b]	9	17.7	20	7.9	4.69 (1.71-12.8)
CIN3+/<30 y		20		104		
	HPV-negative	6	30.0	82	78.9	
	HPV-positive	14	70.0	22	21.1	8.14 (2.61-25.4)
	HPV-16/18[a]	12	60.0	11	10.6	19.2 (4.22-87.3)
	Other HPV only[b]	2	10.0	11	10.6	1.88 (0.30-11.7)
CIN3+/≥30 y		28		149		
	HPV-negative	12	42.9	133	89.3	
	HPV-positive	16	57.1	16	10.7	9.35 (3.61-24.2)
	HPV-16/18[a]	10	35.7	7	4.7	17.8 (3.84-82.9)
	Other HPV only[b]	6	21.4	9	6.0	7.12 (2.05-24.8)

Abbreviations: CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; OR, odds ratio.
[a]HPV-16 and/or HPV-18 with or without other HPV types.
[b]Only types other than HPV-16/18.

the recommended screening interval after NILM), which continued to increase throughout the follow-up period. Among the 15 patients younger than 30 years who developed CIN2+ and had a positive result for HPV-16/18 at the baseline, the number of detected cases rose steadily until the 8th year of follow-up. In contrast, all 5 of these younger patients with other HPV subtypes only were detected by the 6th year of follow-up (Fig. 3 upper panel). For patients 30 years old or older, the number of cases detected rose quite steadily both for those with HPV-16/18 and for those with other HPV subtypes only until approximately 6.5 years after the baseline (Fig. 3 lower panel).

DISCUSSION

Among women with NILM baseline cytology, the future risk of high-grade CIN was strongly associated with HPV detection. Age-stratified results were most informative because for women younger than 30 years, HPV-16/18 was significantly associated with the future risk of CIN2+. This significant association was not found for the other HPV subtypes alone among these younger women. Moreover, baseline HPV was detected in the control group in a significantly larger percentage of the women younger than 30 years in comparison with those 30 years old or older. On the other hand, for women 30 years old or older, not only HPV-16/18 but also other HPV subtypes conferred significant risk. Our results indicate that the cumulative incidence of CIN2+ continued to rise throughout the follow-up period for younger women who were positive for HPV-16/18 at the baseline.

Results have recently been reported for 15 women with baseline NILM findings who developed CIN2+ among 2383 women in Japan followed for 6 years, with very high loss to follow-up (46.3%).[12] Concordantly with our findings, HPV positivity was significantly increased among cases versus controls and for women younger than 30 years. However, no stratified analyses were reported for HPV subtypes.

In a Dutch nested case-control investigation of women with baseline NILM findings, 77 patients were identified with CIN3+ during the 12-year follow-up.[13] Baseline HPV was classified as in our study, with results

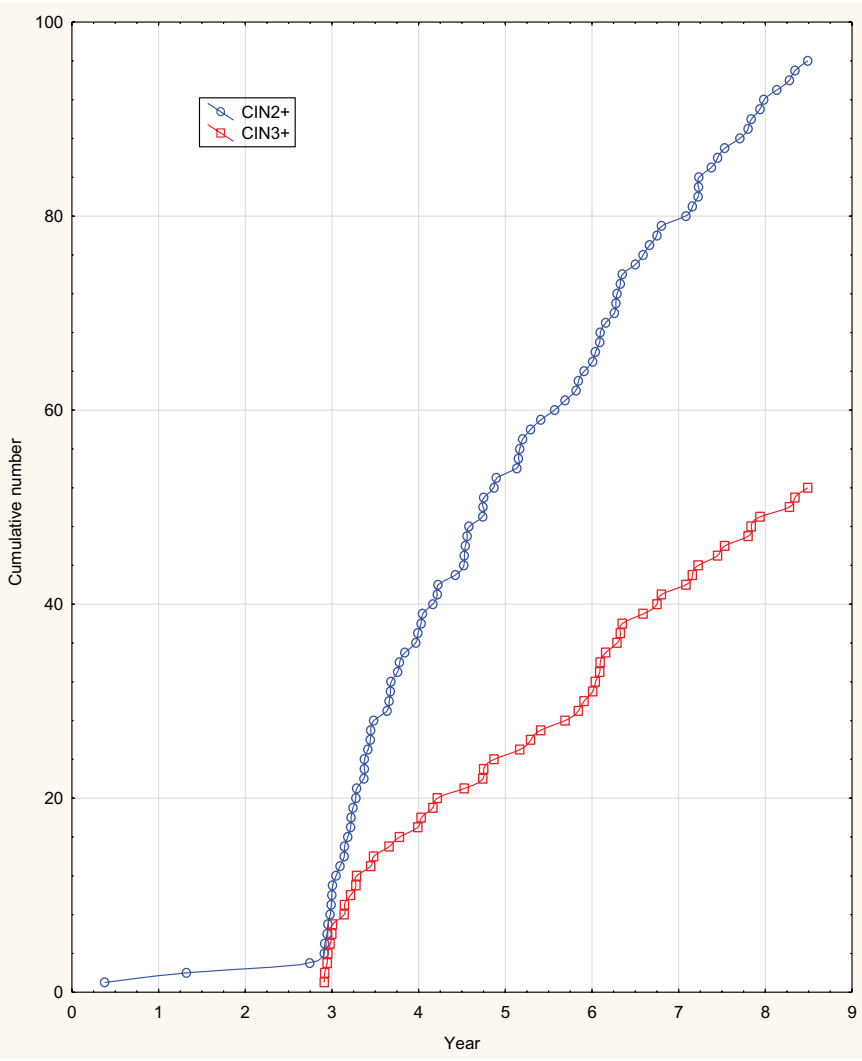

Figure 2. Cumulative number of patients with CIN2+ and CIN3+ after negative baseline cytological screening. CIN2+ indicates cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse.

also reported separately for HPV-16, HPV-18, HPV-31, and HPV-33. Overall, HPV DNA was found in 71% of baseline Papanicolaou smears from the 77 cases and in 11% of smears from the 270 controls. The OR reported for CIN3+ with respect to HPV was higher (24) than that in our study, but the CI was wider (34). Some follow-up HPV data were available; an HPV analysis of a second smear was performed for 49 of the 77 cases after an average of 3 years. A third smear was available for 17 cases. Notably, among the 38 patients with HPV-positive findings at the baseline, only 1 patient subsequently had a negative HPV finding. Conversely, for 11 patients with negative baseline smears, 6 were positive for HPV-16 or other HPV at follow-up. Thus, their results are concordant with our study, with some additional, complementary analyses. However, unlike our study, no age-stratified analyses were reported, nor were patients with CIN2 included.

The importance of identifying HPV-16/18 subtypes has been underscored: CIN3 developed sooner after HPV-16 detection than after the detection of other HPV types.[14] Notably, HPV-18 has shown a strong association with the risk of AIS and adenocarcinoma, diagnoses that are often missed on cytology.[14] Swedish prospective data similarly indicate that infection with HPV-18 and also HPV-16 is strongly associated with the future risk of AIS as well as invasive adenocarcinoma.[15]

In an earlier Swedish nested case-control investigation of women participating in cytologic screening, archival

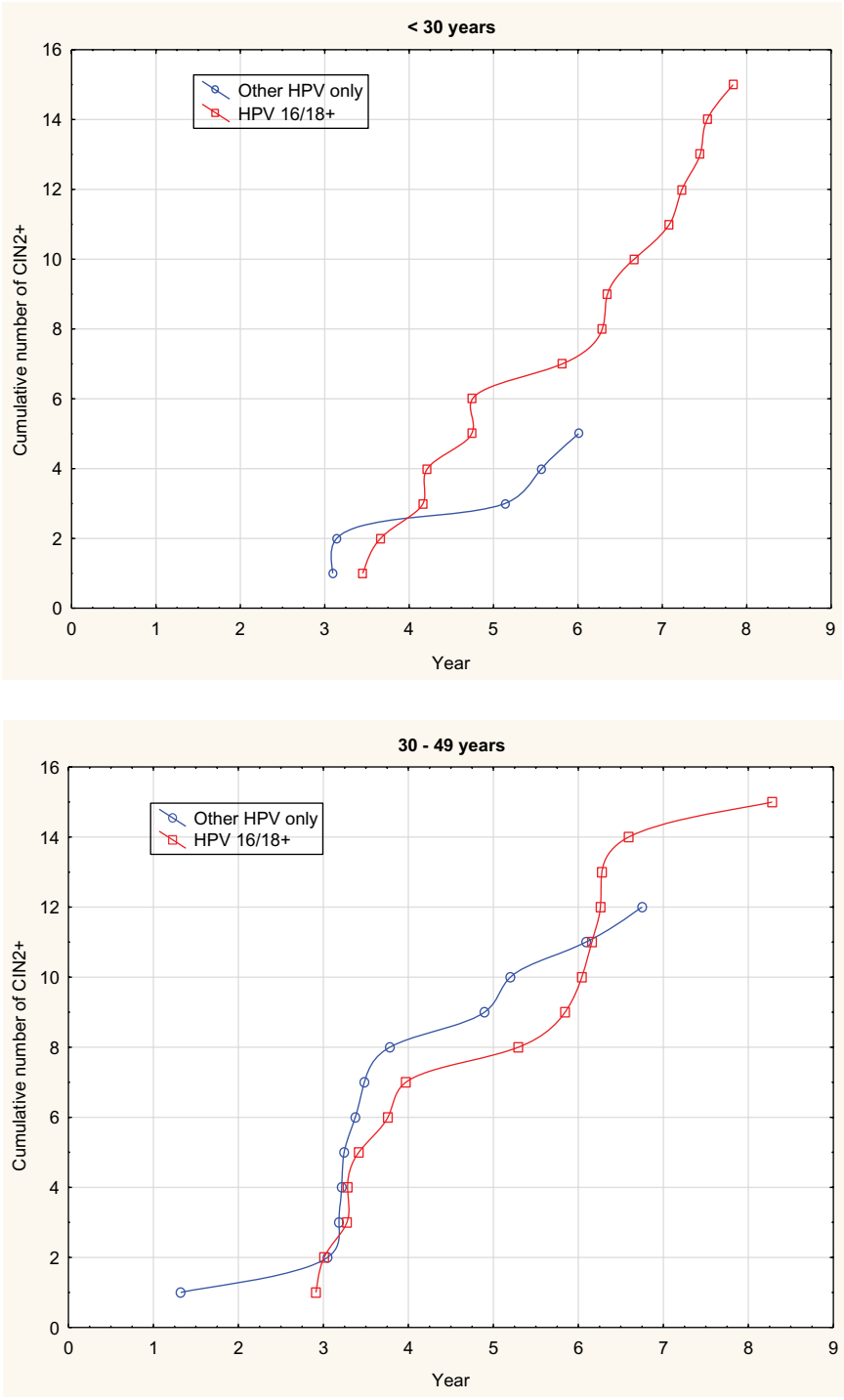

Figure 3. Cumulative number of patients with baseline NILM findings who subsequently developed CIN2+: (Upper panel) patients younger than 30 years and (lower panel) patients 30 years old or older. Those who were positive for HPV-16/18 at the baseline are compared with those who were positive only for other HPV subtypes. CIN2+ indicates cervical intraepithelial neoplasia grade 2 or worse; HPV, human papillomavirus; NILM, negative for intraepithelial lesions or malignancy.

smears were analyzed from 515 women with in situ carcinoma, 315 with invasive squamous cell carcinoma, and matched controls.[16] The median follow-up was 5 to 7 years. As in our study, which also used archival samples for HPV analysis, a substantial portion of the samples were negative for HPV. Moreover, finding HPV-16/18 in the baseline sample test was associated with a risk ratio of 8.5 (95% CI, 5.3-13.7) for carcinoma in situ and with a risk ratio of 18.6 (95% CI, 9.0-38.9) for invasive carcinoma in comparison with women negative for HPV. Similar risk ratios were reported for persistent HPV-16/18 infections. Infections with other HPV types also showed a significantly increased risk for in situ and invasive carcinoma. Thus, concordantly with our study, HPV-16/18 and other HPV types were associated with an elevated cervical cancer risk.

Our results are also somewhat in agreement with the findings of the large 14-year randomized Dutch trial.[17] Therein, the long-term incidence of CIN3+ was low among women with HPV-negative findings from samples taken and analyzed at the baseline. The authors concluded that cervical screening intervals could be safely extended beyond 5 years for women 40 years old or older with negative HPV findings. However, there was approximately 25% nonattendance in the third screening round among the study participants.[17]

In our study, we included patients with CIN2. This is concordant with a 2-tiered system in which CIN2+ histopathologic findings are classified as high-grade squamous intraepithelial lesions.[6] There were 44 patients with CIN2 in our study, nearly half of the patient cohort; 14 were younger than 30 years. Among patients younger than 25 years, conservative management of CIN2 is recommended on the basis of a 4-year retrospective review of 319 such patients treated immediately versus conservatively.[18] Although there was progression to CIN3 in 35 women, no invasive cancer occurred. In more than 70% of the women, the lesions regressed. Still, to ensure safety, conservative management requires full adherence with follow-up recommendations.[18] Our study suggests that positive findings for HPV-16/18 may further aid risk stratification for these younger women with CIN2.

The finding of HPV is clearly vital in identifying women with NILM who are more likely to develop high-grade CIN. Nevertheless, there is a proportion of women with NILM findings and negative tests for HPV who develop high-grade CIN. In a modeling simulation of the likely impact of primary HPV testing on cervical cancer incidence in England, an estimated 1% of HPV tests would come too late, whereas cervical cancer would still occur in 7.6% of women with NILM findings and a negative HPV test; approximately 4.3% of the current incident cervical cancer cases prevented by cytology-based screening are associated with false-negative HPV findings.[19]

Strengths and Limitations of This Study

A major strength of this study is the nested case-control design, with a ratio of nearly 1 to 5 between cases and controls. These 2 groups were matched almost identically for age and baseline screening date, and they were matched for cervical screening history. This was possible through the Swedish registry system, in which these data are kept for the entire country. A further advantage of our study is the long follow-up period. The relatively high participation rate (73% as of 2010) in the Swedish invitational, population-based cervical cancer screening program contributes further to the study's strength.[20] The generalizability (external validity) of the findings is enhanced thereby.

The samples in our study were stored for long periods at room temperature. This may have caused DNA degradation with nondetection of HPV. The storage time ranged from a couple of years up to 9 to 11 years. Although DNA is a relatively stable molecule, the long time since collection could have led to HPV DNA degradation. False-negative HPV findings with the RealTime High-Risk HPV assay may, therefore, have occurred.

Follow-up data on HPV are lacking, and this also probably reduced the associations found in our study. The women who developed CIN during the 9 years of follow-up may have acquired HPV during that time.

All the diagnoses of CIN2+ among the cases were made via histologic examination (the gold standard). Among the controls, however, the absence of high-grade CIN was inferred from all available registry data, which were based mainly on screening cytology.

Another limitation is the small number of cases older than 50 years. This group warrants attention because women treated for CIN3 are at increased risk of developing and dying of cervical or vaginal cancer, with the risk rising after the age of 60 years.[21]

Conclusions/Policy Implications/Future Perspectives

With today's introduction of HPV primary screening into several organized screening programs and with many triage algorithms available, further research is needed to ensure safe follow-up management and prevent the

unnecessary treatment of transient positive HPV findings associated with regressive high-grade CIN.

When we view our results together with the results of other such studies, we conclude that the finding of HPV among women with NILM findings at the baseline is associated with a significantly elevated future risk of high-grade CIN. The accumulated evidence indicates that a positive HPV finding is the strongest risk indicator for future CIN among women 30 years old or older. On the other hand, HPV was detected in a substantial percentage of the control group younger than 30 years with baseline NILM findings. As for subtypes, only HPV-16 and HPV-18 were significantly associated with the risk of future CIN2+ or CIN3+ among younger women. These latter findings suggest that genotyping for HPV-16/18 might be useful for risk stratification among younger women. Further prospective study on this topic is warranted.

Evidence-based guidelines would be further enhanced by studies with systematically repeated HPV measures. In this way, transient positive HPV findings with a minimal future risk of high-grade CIN could be more confidently identified. This would be especially helpful for preventing the harms of overscreening and overtreatment, particularly among younger women. As self-collected specimens for HPV testing become increasingly accurate,[22] repeated HPV testing would be a feasible option.

Educational initiatives, together with "a well-organized program with good compliance with screening and triage policies,"[2,23] are vital for the success of cervical cancer prevention efforts. Accurate knowledge of HPV, CIN, and cervical cancer is indispensable, especially among women at increased cervical cancer risk[24] and as cervical cancer screening becomes increasingly reliant on HPV testing.

FUNDING SUPPORT

This study was supported by the Swedish Cancer Foundation (110544, CAN2011/471), the Karolinska Institute (Cancer Strategic Grants), the Swedish Research Council (521-2008-2899), the Stockholm County Council (20130097 and 20160155), and the Gustaf V Jubilee Fund (154022 and 151202). Maria Fröberg was supported by the Stockholm County Council (combined clinical residency and post-doctoral appointment). The funders had no role in the study design or data collection and analysis.

CONFLICT OF INTEREST DISCLOSURES

Marc Arbyn reports grants from the 7th Framework Programme of DG Research and Innovation (European Commission) and from VALGENT during the conduct of the study.

AUTHOR CONTRIBUTIONS

Maria Fröberg: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, visualization, writing–original draft, and writing–review and editing. **Ellinor Östensson:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, visualization, writing–original draft, and writing–review and editing. **Karen Belkić:** Validation, visualization, writing–original draft, and writing–review and editing. **Anja Oštrbenk:** Investigation, methodology, validation, visualization, and writing–review and editing. **Mario Poljak:** Investigation, methodology, validation, visualization, and writing–review and editing. **Miriam Mint:** Funding acquisition, validation, visualization, and writing–review and editing. **Marc Arbyn:** Formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Sonia Andersson:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, validation, visualization, and writing–review and editing.

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