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# HPV Test as Test of Cure After Conization for CIN2+: A Nationwide Register-Based Cohort Study

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**Objective:** The purpose of this study was to assess if cytology can be omitted in the follow-up after treatment for cervical intraepithelial neoplasia grade 2 or worse (CIN2+) and if human papillomavirus (HPV) test can be used alone as test of cure (TOC) after stratifying for resection margins.

**Material and Methods:** In this retrospective register-based study, women who had a conization performed in Denmark between January 1 and December 31, 2013, were included. Histology, cytology, and HPV test results were obtained from The Danish Pathology Data Bank for a 3-year follow-up.

**Results:** A total of 5,174 women were included, of whom 6.1% (318/5,174) had histological residual/recurrent disease in the follow-up period. In the group with free margins, 2.6% (73/2,780) had residual/recurrent disease in contrast to 10.2% (245/2,394) in the group with involved margins. In the group with free resection margins and negative HPV test results, residual/recurrent disease was found in 0.5% (13/2,780) compared with 0.3% (9/2,780) in the group with negative HPV test results and normal cytology at 6 months' follow-up. Based on margin status and HPV test result as follow-up, the sensitivity, specificity, and positive and negative predictive values were 95.9%, 43.2%, 10.0%, and 99.4% respectively, and for combined testing (margin status, HPV, and cytology), 97.2%, 41.2%, 9.8%, and 99.6%, respectively.

**Conclusions:** Using the HPV test at the first post-treatment control as TOC for cervical intraepithelial neoplasia grade 2 or worse after stratifying for resection margins in cone resections yields an equally high sensitivity and negative predictive value as cotesting with cytology. We suggest that women with free resection margins return to the routine screening program after negative HPV test result as TOC at 6 months.

**Key Words:** cervical intraepithelial neoplasia, conization, follow-up, cytology, human papillomavirus test

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Women treated with cervical conization for cervical intraepithelial neoplasia grade 2 or worse (CIN2+) continue to be at risk for persistence or recurrence of CIN2+ and developing invasive carcinoma.<sup>1,2</sup> Most recurrent lesions are seen within 2 years after treatment, but the risk remains in the following years.<sup>3,4</sup> Adequate follow-up is therefore crucial. Several factors are

thought to predict the risk of recurrence, and follow-up programs have traditionally involved cervical smears and/or colposcopy. It is well known that women with involved resection margins have a higher risk of residual/recurrent CIN2+ than women with free margins.<sup>5,6</sup> Recognition of high-risk human papillomavirus (HPV) as a causal factor for CIN and invasive cervical cancer has led to the addition of HPV testing to cytology in many follow-up programs. However, only a few studies on HPV testing alone have been published,<sup>7–11</sup> and until today, there is still no international consensus on post-treatment surveillance strategies.

In Denmark, the postconization follow-up is described in national clinical guidelines under The Danish Health Authority.<sup>12,13</sup> At the 1st follow-up visit 6 months after conization, a cotest with cytology and HPV test as test of cure (TOC) is performed. Depending on the resection margins and the result of the TOC, the women are allocated into 1 of 3 categories. Women with free resection margins and 1) normal cytology and negative HPV test results are returned to the national screening program; 2) atypical squamous cells of undetermined significance (ASCUS)/low-grade squamous intraepithelial lesion (LSIL) and/or positive HPV test results are recommended a repeated TOC after 6 months; and 3) high-grade squamous intraepithelial lesion (HSIL)/atypical squamous cells—cannot exclude HSIL/atypical glandular cells/adenocarcinoma in situ (AIS) and/or positive HPV test results are referred to colposcopy with biopsy. Women with involved or unclarified resection margins and 1) negative HPV test result and cytology normal/ASCUS/LSIL are recommended a repeated TOC after 6 months; 2) positive HPV test results and normal cytology are recommended a repeated TOC after 6 months; and 3) ASCUS/LSIL, and positive HPV, or atypical squamous cells—cannot exclude HSIL/HSIL/atypical glandular cells/AIS with any HPV result are referred to colposcopy with biopsy.<sup>12</sup>

The aim of our study was to assess if cytology can be omitted in the follow-up after treatment for CIN2+ and if HPV test can be used alone as TOC after stratifying for resection margin status.

## MATERIAL AND METHODS

### Ethical Approval

The project was approved by the institutional review board (IRB) and the national Data Protection Agency. The requirement for written informed consent was waived by the IRB because the study was register-based.

### Participants

This population-based and register-based study included women who had a cervical conization performed in Danish hospitals between January 1 and December 31, 2013. The women were identified in The Danish Pathology Data Bank, a national online health care registry in Denmark containing information on all histological and cytological specimens handled by pathology departments in Denmark since the 1990s. The Danish Pathology Data Bank uses Systematized Nomenclature of Medicine, which has separate codes for topography, morphology, etiology, function, disease, and procedure. The topography code T83701 for cone was used to identify the study population. All Danish citizens have a unique, personal 10-digit identifier by which histology, cytology, and HPV test results for each woman were obtained for a 3-year

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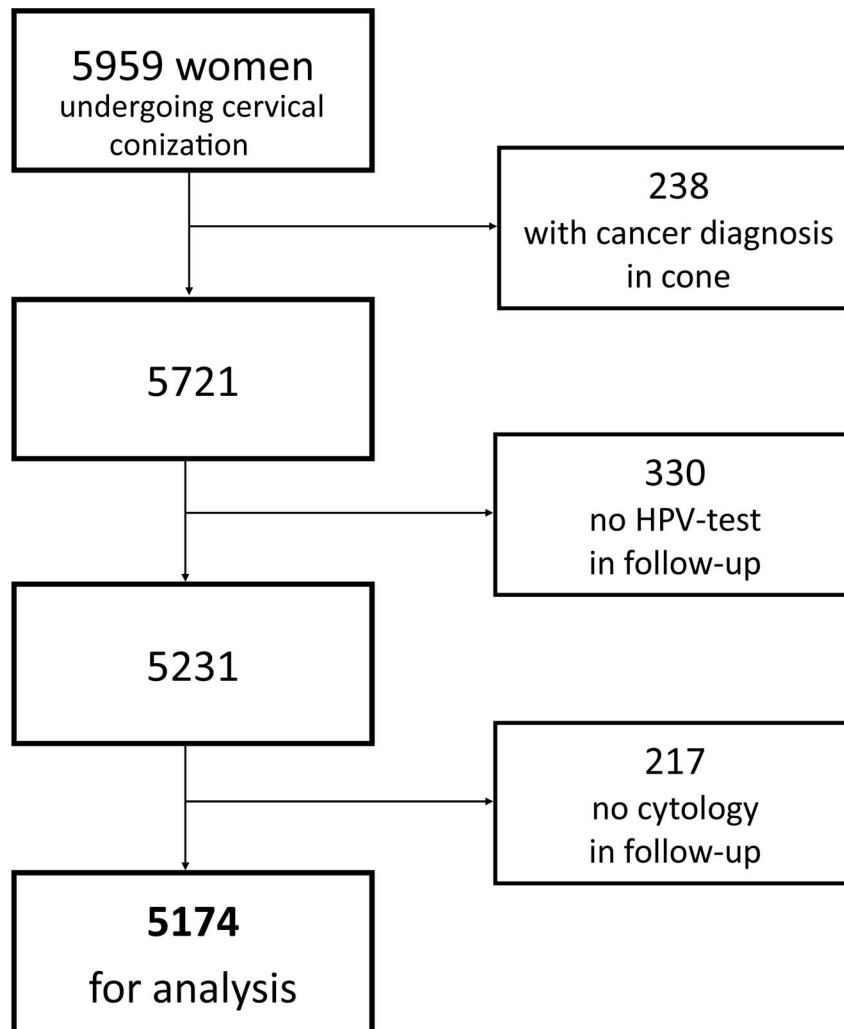


FIGURE 1. Study population.

follow-up period. Data from January 1 to December 31, 2012, were also obtained to validate a potential preconization biopsy for the women who had surgery in early 2013.

Women who had a cervical conization performed in Denmark between January 1 and December 31, 2013, were included. Women diagnosed with cancer in the cone or absent cytology and/or HPV test results postconization were excluded (Figure 1).

Data included the women's age at time of surgery, histological diagnosis on potential preconization biopsy, and the cone resection, along with information about the resection margins of the cone. The postconization data were HPV test result, cytology, and/or biopsies.

The assay used for HPV testing was cobas 4800 System (Roche Diagnostics, Basel, Switzerland) in 4 of 5 regions in Denmark and digene HC2 High-Risk HPV DNA test (Qiagen, Hilden, Germany) in 1 region.<sup>14</sup>

Residual/recurrent disease was defined as histologically confirmed CIN2+ in the follow-up period. Cervical intraepithelial neoplasia grade 2 or worse includes CIN2, CIN3, AIS, adenocarcinoma (AC), and squamous cell carcinoma (SCC).

Resection margins were defined as involved when CIN2+ occurred. If the resection margins were unclear or not evaluated, they were defined as involved margins as per the recommendations of the Danish National Board of Health. Human papillomavirus

types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were defined as HPV positive. The finding of ASCUS or worse (ASCUS+) was defined as cytology positive.

On January 1, 2013, the recommendations from the Danish National Board of Health for follow-up after treatment of precursor lesions was implemented, by which a combination of cytology and HPV-DNA testing stratified by resection margin status was performed. When the result was negative HPV test and normal cytology after free resection margins at follow-up 6 months after conization, the women were recommended to return to the national screening program. Should any of the 3 parameters be abnormal, the recommendation was to continue the follow-up program with control at a gynecologist every 6 to 12 months depending on the results.<sup>13</sup>

### Statistical Analyses

Characteristics of the population were summarized using descriptive statistics. Pearson  $\chi^2$  tests were performed to test for statistically significant (level 0.05) differences between the women with and without residual/recurrent disease. To investigate the agreement between single testing and cotesting predicting recurrent disease after conization, we estimated the sensitivity (SN), specificity (SP), positive predictive value (PPV), and negative

predictive value (NPV) with exact binomial 95% CI for HPV, margins, and cytology, a combination where at least 1 test was positive. All statistical analyses were performed in Stata, version 15.0 (StataCorp, College Station, TX).

## RESULTS

The study identified 5,174 women who had a cervical conization performed at a Danish hospital in 2013 and followed up with HPV test and cytology at first control visit (Figure 1). Characteristics of the study population are listed in Table 1. The median age of the 5,174 women was 33.8 years (interquartile range [IQR] = 27.5–41.5).

In 83.5% (4,322/5,174) of the total study population, CIN2+ was detected in the cone, whereas 16.5% (852/5,174) had normal histology, unclassified CIN, and CIN1. A total of 53.7% (2,780/5,174) of the women had free resections margins. Margins were categorized as involved in 46.3% (2,394/5,174) as per recommendation of the Danish National Board of Health (Table 2). Of these, 1,415 were histologically verified as involved, and in 979, the margins were unclear or not evaluated. Residual/recurrent disease was most frequently seen in the cases with histologically involved margins (13.6%) compared with unclear/not evaluated (5.2%) margins.

Most of the population (93.9%, 4,856/5,174) had no residual/recurrent disease during the 3-year follow-up period in the study, but histologically confirmed CIN2+ (residual/recurrent disease) was observed in 6.1% (318/5,174) of the women. The women with recurrent disease were slightly older (median 37.4 years [IQR = 30.3–45.7]) than the women without recurrent disease (median 33.5 years [IQR = 27.5–41.3]). Of the women with residual/recurrent disease, the margins were involved in 77.0% (245/318) compared with 44.2% (2,149/4,856) in the group without residual/recurrent disease. A positive HPV test was found in 83.7% (266/318) and 24.7% (1,197/4,856) of the 2 groups respectively, and 66.7% (212/318) versus 11.0% (536/4,856) had ASCUS+.

The distribution of residual/recurrent disease related to margin status and follow-up results are shown in Figure 2. In the group with

margins+/HPV+/cytology+, 43.8% (152/347) had residual/recurrent disease (39 CIN2, 101 CIN3, 6 AIS, 1 AC, and 5 SCC). By comparison, in the group with margins–/HPV–/cytology–, only 0.4% (9/2,008) had residual/recurrent disease (5 CIN2 and 4 CIN3). The follow-up results of the group with margins– shows that 13 of 2,780 (0.5%) with HPV– had residual/recurrent disease and 9 of 2,780 (0.3%) when cytology– was added, and there were no cancers in this group. On the other hand, in the margin+/HPV– group, 1.6% (39/2,394) had residual/recurrent disease and 0.9% (22/2,394) when cytology– was added, and there were 2 SCC.

In total, 8 women developed carcinoma during the 3-year follow-up. Most (6/8) were identified in the margin+/HPV+/cytology+ group and 2 women in the margin+/HPV–/cytology– group. The median age for the 8 women with carcinoma was 49.6 years (IQR = 34.3–57.3) compared with the study population's median age of 33.8 (IQR = 27.5–41.3).

Table 3 shows the rate and distribution of residual/recurrent disease according to time for first follow-up, where HPV test and cytology were done for the entire study population. The guidelines recommend first control at 6 months. A total of 70.9% (3,667/5,174) had first control within 6 months after conization (defined as <7 mo), and 19.6% (1,014/5,174) had first control at ≥7 and <12 months. The remaining 9.5% (493/5,174) had first control ≥12 months after conization with a median of 16.5 months (IQR = 13.7–21.7).

The SN, SP, PPV, and NPV for different TOC strategies to predicting recurrent disease after conization are listed in Table 4. Using HPV test as standalone TOC after stratifying for margins status, the SN, SP, PPV, and NPV were 95.9%, 43.2%, 10.0%, and 99.4%, respectively, and for combined testing (margin status, HPV, and cytology) 97.2%, 41.2%, 9.8%, and 99.6%, respectively.

## DISCUSSION

In this register-based study, we find that TOC with HPV test at the first post-treatment follow-up visit after stratifying for resection

**TABLE 1.** Characteristics of the Study Population

	Total (n = 5,174)	No Residual/Recurrent Disease (n = 4,856)	Residual/Recurrent Disease (n = 318)	<i>p</i>
Age (median ± IQR)	33.8 (27.5–41.5)	33.5 (27.5–41.3)	37.4 (30.3–45.7)	<.001
Pathology at conization				<.001
Normal	365 (7.1)	341 (7.0)	24 (7.6)	
CIN NOS	139 (2.7)	136 (2.8)	3 (0.9)	
CIN1	337 (6.5)	331 (6.8)	6 (1.9)	
CIN2	957 (18.5)	921 (19.0)	36 (11.3)	
CIN3	3,168 (61.2)	2,938 (60.5)	230 (72.3)	
AIS	197 (3.8)	180 (3.7)	17 (5.4)	
Other/NA	11 (0.2)	9 (0.2)	2 (0.6)	
Margins				<.001
Free	2,780 (53.7)	2,707 (55.8)	73 (23.0)	
Involved	2,394 (46.3)	2,149 (44.2)	245 (77.0)	
High risk HPV (follow-up)				<.001
Negative	3,711 (71.7)	3,659 (75.3)	52 (16.3)	
Positive	1,463 (28.3)	1,197 (24.7)	266 (83.7)	
Cytology (follow-up)				<.001
Normal	4,426 (85.5)	4,320 (89.0)	106 (33.3)	
ASCUS+	748 (14.5)	536 (11.0)	212 (66.7)	

IQR indicates interquartile range; NA, not available; NOS, not otherwise specified.

**TABLE 2.** Characteristics of the 5,174 Women According to Resection Margins

	Free Resection Margins (n = 2,780)	Involved Resection Margins (n = 2,394)
Age (median ± IQR)	33.8 (27.5–41.7)	33.7 (27.6–41.2)
Biopsy		
Normal	122 (4.4)	48 (2.0)
CIN NOS	133 (4.8)	101 (4.2)
CIN1	123 (4.4)	80 (3.3)
CIN2	643 (23.1)	504 (21.0)
CIN3	1,584 (57.0)	1,479 (61.8)
AIS	81 (2.9)	96 (4.0)
AC	1 (0.1)	1 (0.1)
SSC	3 (0.1)	2 (0.1)
Other/NA	90 (3.2)	83 (3.5)
Pathology at conization		
Normal	365 (13.1)	—
CIN NOS	60 (2.2)	79 (3.3)
CIN1	201 (7.2)	136 (5.6)
CIN2	552 (19.9)	405 (16.9)
CIN3	1,524 (54.8)	1,644 (68.7)
AIS	78 (2.8)	119 (5.0)
Other/NA	—	11 (0.5)
Combined testing		
HPV+/Cyt+	168 (6.0)	347 (14.5)
HPV+/Cyt−	502 (18.1)	446 (18.6)
HPV−/Cyt+	102 (3.7)	131 (5.5)
HPV−/Cyt−	2,008 (72.2)	1,470 (61.4)
Disease in follow-up	73 (2.6)	245 (10.2)
CIN2	37	63
CIN3	33	159
AIS	3	15
AC	—	1
SSC	—	7

margins has an equally high sensitivity and NPV as combined testing with cytology and HPV. In the group with free resection margins, very few patients had residual/recurrent disease if HPV was negative or both HPV and cytology were negative (0.5% vs 0.3%).

A total of 6.1% had residual/recurrent disease in the 3-year follow-up period. This is in line with other studies showing recurrence rates between 3.6% and 6.6%.<sup>6,10,15–18</sup>

In a population-based study with 10-year follow-up, 2.5% of HPV− women had recurrent disease,<sup>9</sup> and a prospective 5-year study found no women with recurrence in the HPV− group and 12.3% in the HPV+ group.<sup>11</sup> Our finding of 1.4% (52/3,711) of HPV− women with residual/recurrent disease and 18.2% (266/1,463) of HPV+ women with residual/recurrent disease are equivalent to this.

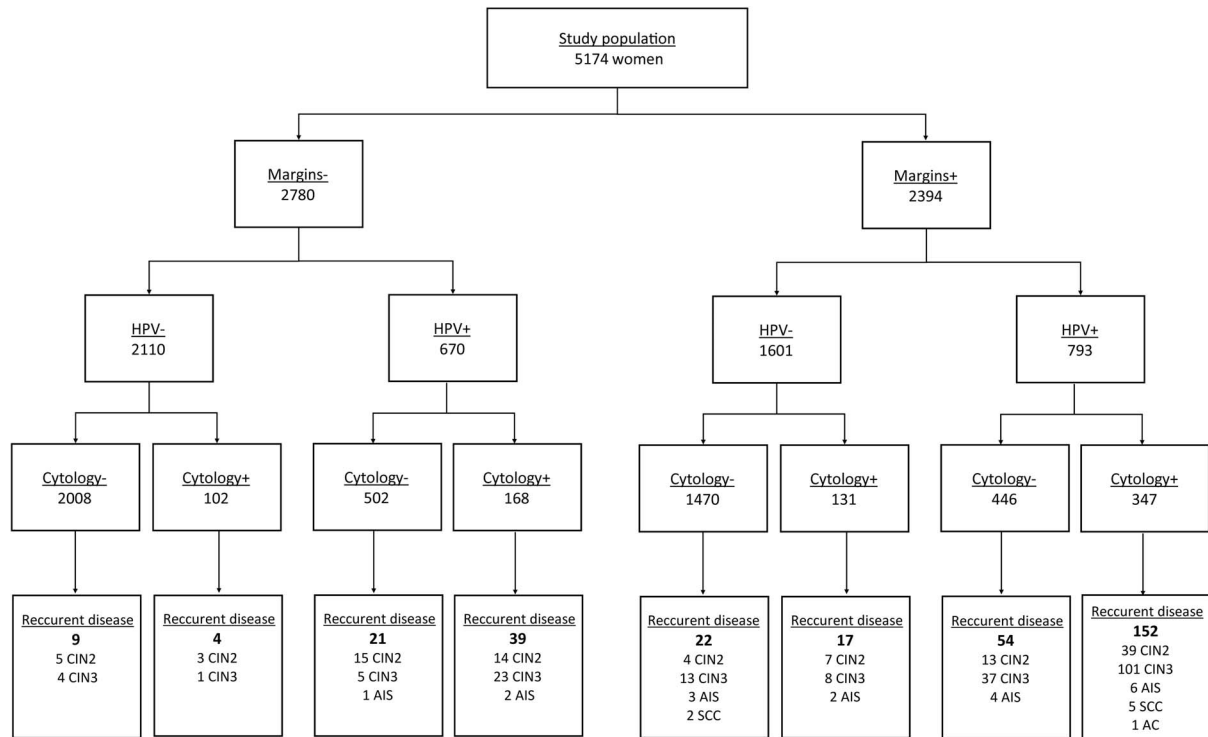
Combined testing has been implemented in many follow-up programs during the last decade, and the question whether HPV test can be used as a standalone TOC is still being discussed. Some studies provide data showing that the diagnostic accuracy of HPV test alone is similar to cotesting with cytology and HPV.<sup>19–21</sup> A recent systematic review and metaanalysis demonstrated that cotesting with HPV/cytology only provides a small reduction in risk of CIN2+ compared with HPV test alone at the cost of a higher test positivity.<sup>22</sup> A Japanese study, with pooled data from

33 published articles including a total of 5,319 women, finds equal sensitivity and NPV for HPV test alone and cotesting (92% vs 93% and 99% vs 99%, respectively).<sup>21</sup> Other studies argue that HPV could be used as a standalone TOC after conization. A Danish study of 477 women found that adding cytology to a negative HPV test at the first post-treatment control did not improve the detection of residual/recurrent CIN2+ in long-term follow-up.<sup>9</sup> A large Canadian study of 2,340 women concluded that women with a negative HPV test 12 months post-treatment can safely return to annual routine screening.<sup>10</sup> In an Italian study, the authors concluded that HPV DNA testing at 6 months after treatment for CIN2+ effectively identifies women who are disease-free with an NPV of 100% at 5-year follow-up and suggested that the women can return to annual cytological testing after just a single follow-up 18 months post-treatment.<sup>11</sup>

There is no consensus on whether resection margins status should be included in follow-up. The Japanese study<sup>21</sup> found that women with margin+/HPV+ had a 67.5% risk of post-treatment CIN2+ versus only 1.3% risk in women with margin+/HPV− and 0.9% risk in women with margin−/HPV− and concluded that HPV testing may be used for identifying populations with different risks, especially in women with involved margins. The most recent metaanalysis including more than 40,000 women found that even though the risk of residual or recurrent CIN2+ is higher when resection margins are involved, a post-treatment HPV test predicts treatment failure more accurately than margin status.<sup>6</sup> However, a recent large prospective Swedish study including almost a thousand women found that women with margins+/HPV+ have a greater than 2.5-fold risk of recurrent disease compared with women with margins−/HPV+ and concluded that margin status combined with HPV test increase the accuracy for predicting treatment failure.<sup>5</sup> The importance of and benefits from looking at both the margin status and HPV in follow-up are becoming evident.<sup>16</sup> Our findings support that HPV test as TOC after stratifying for margins status is effective and sufficient to identify the woman at risk for residual/recurrent disease.

In our study, 0.15% (8/5,174) developed carcinoma during follow-up; 6 women had FIGO stage IA1 and 2 had FIGO stage IB1 disease, indicating that the follow-up program fulfilled its purpose and only few severe recurrences were seen. In each of the 8 cases, the margins were involved, and 6 were in the margin +/HPV+/cytology+ group, whereas 2 were in the margin+/HPV−/cytology− group. The 2 women who had negative HPV test results were slightly older than the median study population (aged 50 and 54 years). Sampling error because of the gradual retraction of the transformation zone from exocervix to endocervix with age<sup>23</sup> could be a possible explanation for the negative HPV test result and negative cytology. A concern for false negatives, as also raised in a smaller retrospective study,<sup>19</sup> is reasonable because this could result in a woman with residual/recurrent disease terminating the follow-up too early. However, the risk should be seen in the light of what subsequences the follow-up. In most countries, the women return to a routine screening program after follow-up. The screening programs differ in screening intervals, screening methods used, and age groups included. This should be taken in consideration when evaluating at what point it is safe to return to routine screening after completing a follow-up program after treatment for CIN2+.

The main goal of a follow-up program should be to identify not only women who have residual/recurrent disease but also women who are not at risk. One could argue that a high sensitivity and NPV is more important than specificity and PPV if adherence to routine screening after follow-up is expected. The current study shows that the diagnostic performance of HPV testing alone was good with high sensitivity and NPV. Especially in the group with



**FIGURE 2.** Distribution of recurrent disease in the study population. Margins+ defined as involved margins (CIN2+, also including unclear or not evaluated). HPV+ defined as high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and/or 68. Cytology+ defined as atypical squamous cells of unknown significance or worse.

free resection margins, where only 0.5% had residual/recurrent disease, HPV test as TOC is useful. Moreover, in the group with involved margins, the risk of recurring CIN2+ was low (1.6%) when using HPV test as TOC. However, because 2 women developed carcinoma in this group and CIN2+ is found in the group with HPV-/cytology+, we recommend to still follow the current Danish recommendation with repeated TOC with cotest (HPV and cytology) at 6 and 12 months for women with involved margins. This implicates using different testing strategies depending on margin status: HPV test alone as TOC when margins are free and still using cotest (HPV and cytology) when margins are involved.

The large sample size is a major strength in our study. Furthermore, the study is a national population-based and register-based study using valid and robust data from The Danish Pathology Data

Bank.<sup>24</sup> Even though the recommendations on follow-up were implemented just 1 year before the study, the adherence was high because more than 90% of the women who had a conization performed in 2013 had both cytology and HPV test at first post-treatment control and 70.9% of the women attending the first postconization control <7 months.

A 3-year follow-up could be considered a limitation to the study. We, however, chose this because it is known that the risk for recurrent/residual disease lowers through the years, and we wished to test the effect of the follow-up program. Had the period been longer, there would have been a risk for de novo disease.

The proportion of women with margins defined as involved might seem high compared with previous studies.<sup>6</sup> This is because of the fact that unclear or not evaluated margins is defined as involved as per the recommendations of the Danish National Board of Health, with the purpose of offering these women a second follow-up visit at 12 months for safety reasons.

Data on excision type used, size of excision, and test platform used for HPV testing were not reported systematically in The Danish Pathology Data Bank and could therefore not be analyzed in this study.

Overall, the study is, however, a representative picture of the current setting in Denmark, and the results can be extrapolated to similar populations and comparable screening programs.

### CONCLUSIONS

In conclusion, we suggest it might be safe to use HPV test alone as TOC for CIN2+ after stratifying for resection margin status. This strategy yields a comparably high SN and NPV as cotesting with cytology and HPV test. In the group with free resection margins, 1 TOC with HPV test alone at 6 months is sufficient, but in

**TABLE 3.** Residual/Recurrent Disease According to Time for First Follow-Up Visit, Where HPV Test and Cytology Were Done

Residual/Recurrent disease	Time for First Follow-Up Visit (n = 5,174)		
	<7 mo	≥7 & <12 mo	≥12 mo
No	3,429	954	473
Yes	238	60	20
CIN2	79	13	8
CIN3	145	41	8
AIS	10	5	3
AC	0	0	1
SCC	6	1	0

**TABLE 4.** Sensitivity, Specificity, PPV, and NPV for Different Testing Strategies for CIN2+ in Follow-Up for 5,174 Women

	No. Tested Positive	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value % (95% CI)	Negative Predictive Value % (95% CI)
Margins/HPV/cytology	3,401	97.2 (94.7–98.7)	41.2 (39.8–42.6)	9.8 (8.8–10.9)	99.6 (99.2–99.8)
Margins/HPV	3,313	95.9 (93.1–97.8)	43.2 (41.8–44.6)	10.0 (8.9–11.1)	99.4 (98.9–99.7)
HPV	1,463	83.7 (79.2–87.6)	75.4 (74.1–76.6)	18.3 (16.3–20.3)	98.6 (98.2–99.0)
Cytology	748	66.8 (61.3–71.9)	89.0 (88.1–89.8)	28.5 (25.3–31.9)	97.6 (97.1–98.0)

Threshold for positivity:

Margins+: margins involved, unclear or not evaluated (as per the recommendations of the Danish National Board of Health). HPV+: HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Cytology +: ASCUS or worse (ASCUS+). Residual/recurrent disease: histologically confirmed CIN2+ (CIN2, CIN3, AIS, AC, and SCC).

the group with involved margins, TOC as cotest with HPV and cytology are recommend.

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