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ORIGINAL RESEARCH ARTICLE

Management and treatment of cervical intraepithelial neoplasia in the Netherlands after referral for colposcopy

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Abstract

Introduction: The aim of this study was to describe trends in the diagnosis and treatment of women referred from the national screening program with cervical intraepithelial neoplasia (CIN) in the Netherlands, and to compare these trends with national guidelines and identify potential areas for improvement for the new primary high-risk HPV screening program.

Material and methods: We conducted a population-based cohort study using data from the Dutch pathology archive. Women aged 29-63 years who took part in the Dutch cervical screening program between 1 January 2005 and 31 December 2014 were selected. Three referral groups were identified: direct referrals and those referred after either one (first indirect referrals) or two (second indirect referrals) repeat cytology tests, totaling 85 239 referrals for colposcopy. The most invasive management technique and the most severe diagnosis of each screening episode was identified. Rates of management techniques were calculated separately by referral type, highest CIN diagnosis and age group.

Abbreviations: AGC, atypical glandular cells; AIS, adenocarcinoma in situ; ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; hrHPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LLETZ, large loop excision of the transformation zone; LSIL, low-grade squamous intraepithelial lesion; PALGA, nationwide network of cyto- and histo-pathology in the Netherlands.

Results: In all, 85.1% of CIN 3 lesions were treated with excision (either large excision or hysterectomy) and 26.4% of CIN 1 lesions were treated with large excision. Rates of overtreatment (CIN 1 or less) in see-and-treat management were higher for indirect referrals than for direct referrals and increased with age. Large excision rates increased with CIN diagnosis severity.

Conclusions: Despite guideline recommendations not to treat, CIN 1 lesions were treated in just over 25% of cases and approximately 15% of CIN 3 lesions were possibly undertreated. Given the expected increase in CIN detection in the new primary high-risk HPV screening program, reduction in CIN 1 treatment and CIN 2 treatment in younger women is needed to avoid an increase in potential harm.

KEYWORDS

cervical cancer screening, cervical intraepithelial neoplasia, cohort study, treatment guidelines, treatment of cervical dysplasia

1 | INTRODUCTION

In the Netherlands, cervical intraepithelial neoplasia (CIN) detection rates have increased over the last decade, largely independent of the socioeconomic and demographic factors.[1] The replacement of conventional cytology by high-risk human papillomavirus (hrHPV) DNA testing as primary screening test in the Dutch Cervical Cancer Screening Program in 2017 will likely further increase CIN detection, given the higher sensitivity of hrHPV testing for CIN 2+ lesions.[2] Recent Dutch modeling estimated that the number of detected CIN lesions would increase by 196% for CIN 1 and 54% for CIN 2 over the lifetime of women entering the program in 2017 due to primary hrHPV screening.[3]

As more CIN lesions are detected, there is concern about overtreatment, which could result in increased harm associated with screening.[4] Evidence suggests that there is an association between excisional treatments for CIN and adverse obstetric outcomes including preterm birth and low birthweight.[5,6] Increasing excision volume has been associated with increased risk.[6,7] Additionally, a robust randomized controlled trial concluded that immediate side-effects of excisional treatments such as discharge and pain occur more frequently, more severely and for longer in women treated with large loop excision of the transformation zone (LLETZ) compared with both colposcopy-only and biopsy-diagnosed women.[8]

The Dutch Association of Obstetrics and Gynecology has published consensus-based guidelines for CIN treatment and management which detail the recommended treatment practices, including recommending no treatment of CIN 1 and excisional treatment of CIN 2+.[9] However, compliance with these guidelines has never been evaluated. The lack of evaluation of CIN management in the Dutch setting has been recognized by others[4] as a knowledge gap in an otherwise closely monitored program. Our study intends to objectify current clinical management of CIN to understand discrepancies between guideline recommendations and observed interventions. By doing so, we aim to identify potential areas for improvement for the new primary hrHPV screening program.

Key message

Both over- and undertreatment of cervical intraepithelial neoplasia occurs after referral from organized cervical cancer screening, despite treatment guidelines being available.

2 | MATERIAL AND METHODS

National organized cervical cancer screening has taken place in the Netherlands since the 1980s. Women are invited for cytology screening every 5 years from the ages 30 to 60. Screening takes place within primary care. Women are referred to a gynecologist when colposcopy is required. Details of clinical guidelines for management of CIN are given in Table 1. Since 1998, the recommendations for management of abnormal cytology have been fairly stable, allowing for more reliable measurement of procedural parameters after colposcopy. In 2017, hrHPV testing replaced cytology as the primary screening test within the program.[10]

Our study is a population-based cohort study. Women aged 29-63 years who participated in the national screening program and received referral advice between 1 January 2005 and 31 December 2014 were included. Possible referral pathways within the Dutch screening program can be found in Figure 1. Three groups of referrals were identified:

TABLE 1 Summary of Dutch CIN treatment guidelines

	2004 Guidelines[9]	2015 Guidelines[21]
Histological diagnosis at colposcopy	Targeted biopsies are required only with an atypical transformation zone	Biopsy can be omitted if there is slight cytological dysplasia and no visible colposcopic abnormalities, in situations when the whole transformation zone can be seen. At least two random biopsies should be taken where there are severe cytological abnormalities with no colposcopic abnormalities. In the case of severe cytological and colposcopic abnormalities, either two targeted biopsies can be taken or "see-and-treat" management can be used.
CIN 1	Generally not treated	In principle, should not be treated. In the case of persistent low-grade cytology outside of reproductive age, treatment options may be discussed with the patient.
CIN 2	Should be treated, preferably by LLETZ[a]	Individual assessment is required, particularly in younger women, weighing up the risks and benefit of treatment. If treatment is decided on, LLETZ[a] is recommended.
CIN 3	Should be treated, preferably by LLETZ[a]	Should always be treated. Women with high-grade cytology (moderate dyskaryosis/dysplasia or worse) and colposcopy are eligible for see-and-treat management. LLETZ[a] recommended.
Glandular disease	Conization is preferred if there is suspicion of AIS	It should be discussed with the patient whether she wants an excisional treatment or hysterectomy, provided that invasive carcinoma is excluded as far as possible. Conization is preferred for AIS as it allows for better assessibility of the endocervical area and margins. If LLETZ is chosen, the pathologist must be notified for a better assessment of the margins.

CIN, cervical intraepithelial neoplasia; LLETZ, large loop excision of the transformation zone; AIS, adenocarcinoma in situ.
[a]Large loop excision of the transformation zone.

- Direct referrals: Women who received referral advice after primary cytology of high-grade squamous intraepithelial lesion (HSIL)/adenocarcinoma in situ (AIS)/atypical endometrial glandular cells (AGC)AGC favoring neoplasia/cancer. The classification ASC-H (atypical squamous cells cannot exclude HSIL) is not utilized in the Netherlands.
- First indirect referrals: Women who received referral advice for repeat testing 6 months after primary cytology of atypical squamous cells of undetermined significance (ASC-US)/low-grade squamous intraepithelial lesion (LSIL) or endocervical AGC.
- Second indirect referrals: Women who received referral advice after two triage cytology tests (at 6 and 18 months), with the first repeat cytology being negative, hrHPV-negative with endocervical ASC-US/LSIL/AGC or hrHPV positive with negative cytology, and second triage cytology being ASC-US or higher.

We excluded women with primary smears taken by a gynecologist, as women under the care of a gynecologist in the Netherlands are usually already receiving specialist care. Indirect referrals must have been referred within 4 years of primary screening to be included, in line with the definitions used in the monitoring of the national screening program. Repeat cytology testing at 6 months could be performed either with or without hrHPV triage. As hrHPV triage was not a standard practice in all pathology labs during the study period, we did not include hrHPV status information in our study.

There is no national registry of gynecological treatments in the Netherlands. Therefore, we used an extract of all cervical cytology and histology records from the nationwide network and registry of histo- and cyto-pathology in the Netherlands (PALGA). PALGA has a nationwide coverage of all pathology labs.[11] Women are identified by the first eight letters of their surname (maiden name is used for married women) and date of birth. Information about primary screening as well as up to five follow-up cytology and/or histology samples were selected. Follow up of primary smears was included until the end of the database—31 March 2016. We defined "episode of screening" as the period starting with the primary screening test, possibly followed by follow-up tests and/or treatment and ending with the next primary cytology in the database. We only analyzed information recorded during this window (see Appendix S1). As PALGA is not a registry of treatments, we validated our results with two expert groups and with clinical data from one gynecology clinic (see Appendix S2).

Our primary outcome measure was the proportion of the most invasive diagnostic tests and therapeutic treatments by the most severe CIN diagnosis within a screening episode. Our secondary outcome measure was the proportion of overtreatment in see-and-treat management. The most severe diagnosis within the screening episode was identified from all diagnostic codes recorded after referral advice as follows: most to least severe—cancer, CIN 3; CIN 2, CIN 1, benign/reactive, cytology only, no diagnosis recorded.

Diagnostic tests and therapeutic treatments are pre-coded by PALGA. The most aggressive test/treatment of the episode after referral was ranked as follows: most to least aggressive--hysterectomy, large excision (including cone biopsy, LLETZ, other excisional treatments), polypectomy, endometrial curettage, endocervical curettage, punch biopsy (excluding cone biopsy), cytology only, other techniques. This ranking was verified by gynecologists and pathologists.

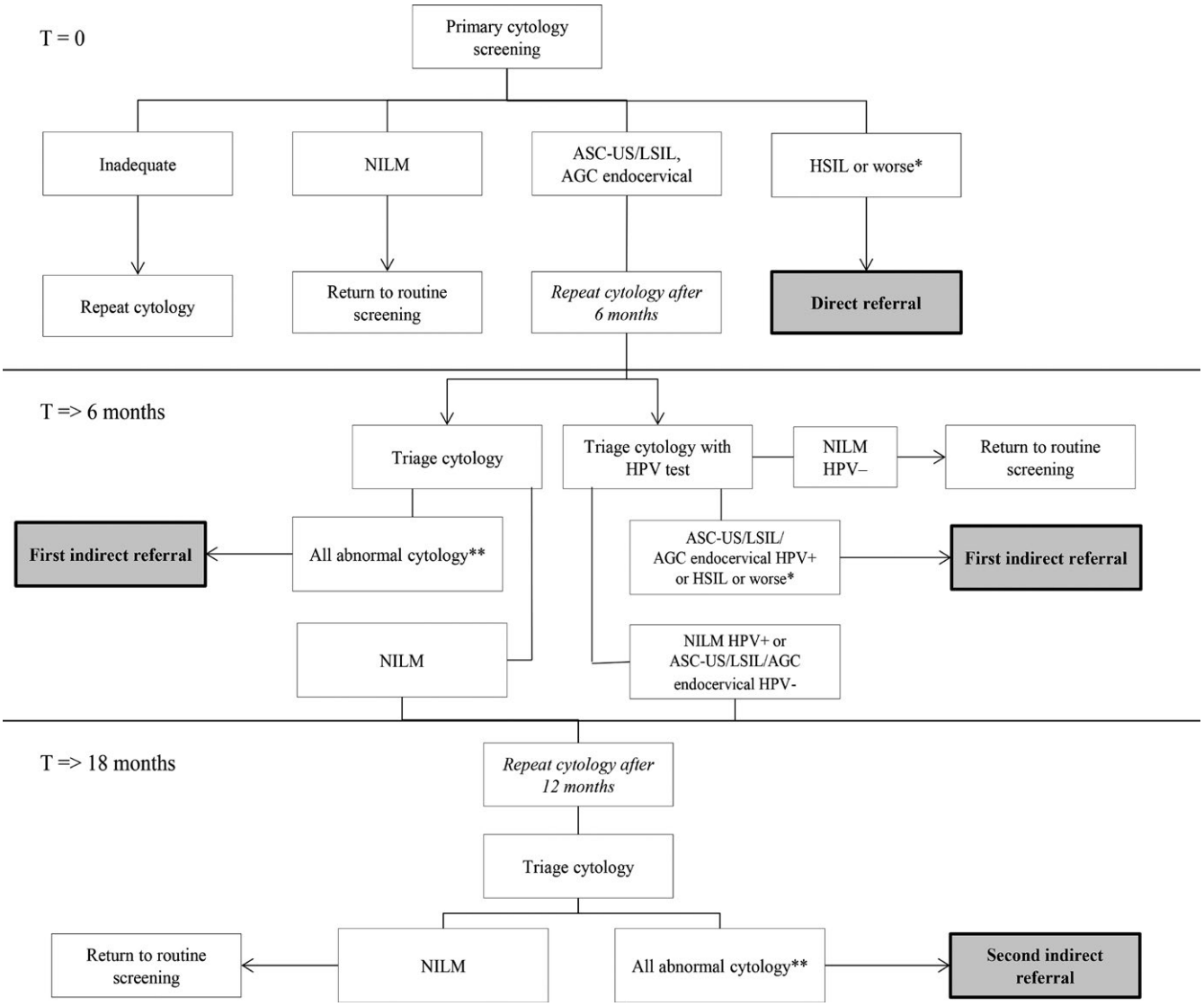

FIGURE 1 Pathways to referral within the Dutch Cervical Cancer Screening Program, adapted from Bekkers et al[31] and Rozemeijer.[32] *Includes HSIL, AGC endometrial, AGC favoring neoplasia, adenocarcinoma in situ and cancer irrespective of hrHPV status. **Includes ASC-US, LSIL, AGC endometrial and HSIL or worse* cytology results. ASC-US/LSIL, atypical squamous cells of undetermined significance/ low-grade squamous intraepithelial lesion; AGC, atypical glandular cells; HSIL, high-grade squamous intraepithelial lesion

See-and-treat management involves combining colposcopy and treatment in the same outpatient visit.[12] A large excision in the next record after referral was considered indicative of see-and-treat management. We estimated possible overtreatment in see-and-treat management as the proportion of women with CIN 1 or lower histological diagnosis as the highest diagnosis of the episode who were treated by large excision at the first contact with a gynecologist, divided by all women who were treated by large excision at the first contact with a gynecologist (definition from Ebisch et al[12]). Age at primary screening was grouped into 5-year age-groups.

2.1 | Statistical analyses

Chi-square tests were performed to compare differences between proportions. Analysis of variance was used to compare mean ages across referral types. For one-way tables, a chi-square goodness of fit test was applied. Confidence intervals for proportions were calculated using a binomial distribution. All analyses were performed using SAS Base v9.4 (SAS Institute Inc., Cary, NC, USA).

2.2 | Ethical approval

We used a retrospective, anonymized dataset from PALGA, which is exempt from ethical approval by a Medical Ethics Testing Committee. We obtained anonymized clinical data (only women referred from the national screening program) for validation as part of the evaluation of the national cervical cancer screening program (evaluation of national screening programs is legislated in the Population Screening Act in the Netherlands). We received

written approval from the Medical Director of the specialist outpatient clinic to use their clinical data for research purposes.

3 | RESULTS

From the 5 450 148 primary cytology smears taken within the screening program from women aged 29-63 years between 2005 and 2014, 98.9% were taken by a non-gynecologist and were eligible for inclusion (n = 5 389 342). Of these smears, 44 209 (0.8%) resulted in a direct referral to a gynecologist, 34 282 (0.6%) resulted in a first indirect referral and 6748 (0.1%) resulted in a second indirect referral (Table 2). The majority of referrals were within reproductive age range (29-43 years: 65.5%). The number of referrals was higher in 2010-2014 than in 2005-2009 for all referral types (Table 2).

Of all women directly referred, 81.1% were diagnosed with a CIN lesion (that is CIN 1, 2 or 3) within the episode of screening (Table 2). The proportion of indirectly referred women diagnosed with a CIN lesion was lower, 64.9% for first indirect referrals and 39.9% for second indirect referrals (Table 2). When restricted to referrals that resulted in a histological diagnosis (i.e. excluding episodes with no recorded diagnosis or no histology taken), there were still differences in the proportion of episodes diagnosed with a CIN lesion between the referral groups (direct: 88.7%; first indirect: 78.1%; second indirect: 67.0%) and the difference were statistically significant (χ^2 [2, n = 72 902] = 2161.98, $P < 0.001$) (figures not presented). Among direct referrals, there was a higher proportion of women with a CIN 3 diagnosis (53.5%) than among indirect referrals (first indirect: 17.5%; second indirect: 8.8%) (Table 2).

The highest proportion of CIN lesions were diagnosed in women aged 29-33 years; 79.8% of all the referrals in this age group were diagnosed with a CIN lesion (Figure 2). The proportion of episodes with no recorded diagnosis or no histology increased

TABLE 2 Demographic characteristics of women referred for colposcopy following participation in the Dutch cervical cancer screening program, all referral types, 2005–2014, rounded percentages

Variable	Direct referrals		First indirect referrals		Second indirect referrals		*P*
	N	%	*N*	%	*N*	%	
Total referrals	44 209		34 282		6 748		
Total unique woman ID[a]	43 827		34 081		6 725		
Age							
Mean age	39.16	*SD*: 8.58	39.54	*SD*: 8.49	41.35	*SD*: 8.74	< 0.001
29–33	12 452	28.2%	9 086	26.5%	1 352	20.0%	< 0.001
34–38	9 373	21.2%	6 661	19.4%	1 117	16.6%	
39–43	8 151	18.4%	6 351	18.5%	1 250	18.5%	
44–48	6 027	13.6%	5 448	15.9%	1 196	17.7%	
49–53	3 944	8.9%	3 567	10.4%	1 005	14.9%	
54–58	2 527	5.7%	2 022	5.9%	513	7.6%	
59–63	1 735	3.9%	1 147	3.4%	315	4.7%	
Period							
2005–2009	20 630	46.7%	14 400	42.0%	2 803	41.5%	< 0.001
2010–2014	23 579	53.3%	19 882	58.0%	3 945	58.5%	
Highest diagnosis of the episode after referral							
No recorded diagnosis	1 770	4.0%	1 275	3.7%	835	12.4%	< 0.001
Cytology only	2 023	4.6%	4 540	13.2%	1 894	28.1%	
Benign/Other[b]	3 019	6.8%	6 072	17.7%	1 306	19.4%	
CIN 1	4 039	9.1%	9 024	26.3%	1 411	20.9%	
CIN 2	8 152	18.4%	7 219	21.1%	688	10.2%	
CIN 3	23 649	53.5%	5 996	17.5%	594	8.8%	
Cancer[c]	1 557	3.5%	156	0.5%	20	0.3%	

See Figure 1 for description of referral types.

SD: Standard deviation; CIN: Cervical intraepithelial neoplasia.

[a]Some IDs have more than one referral within the same referral type. The number of unique IDs represents the number of individual women referred within the referral type.

[b]Benign/Other includes histological results that are lower grade than CIN 1.

[c]Includes micro-invasive and invasive disease.

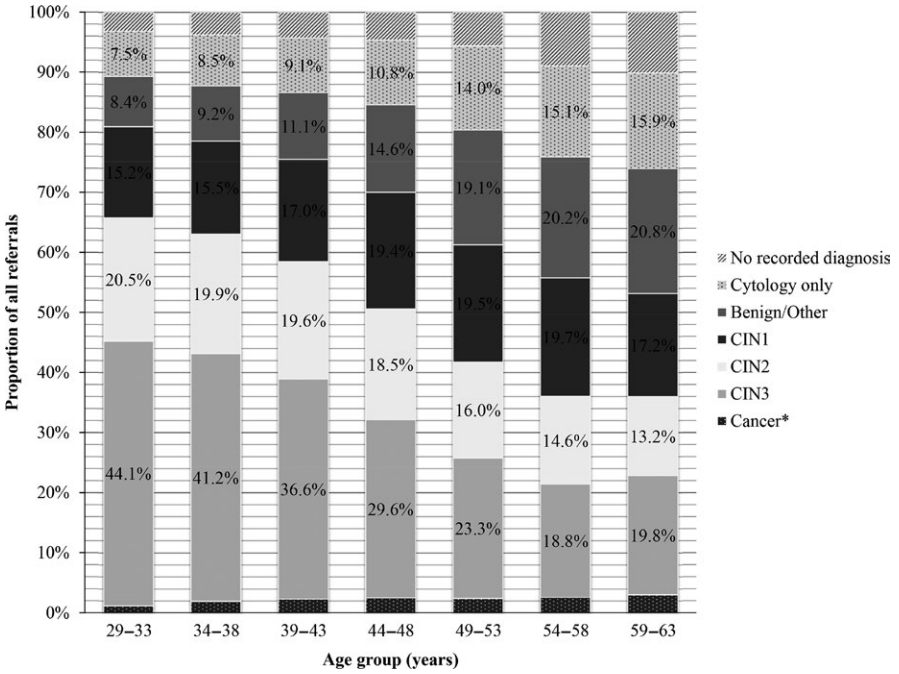

FIGURE 2 Highest diagnosis of the screening episode within age groups, all women referred, rounded percentages. * Includes micro-invasive and invasive disease. CIN, cervical intraepithelial neoplasia

TABLE 3 Most invasive management technique of the screening episode by most severe CIN diagnosis of the screening episode, rounded percentages

	CIN I (%)	CIN 2 (%)	CIN3 (%)	*P*
Direct referrals				
Hysterectomy	1.2	1.8	3.4	<0.001
Large excision[a]	34.4	69.4	82.0	
Biopsy[b]	62.5	28.2	14.3	
Other techniques[c]	1.9	0.6	0.3	
First indirect referrals				
Hysterectomy	0.9	1.7	2.9	<0.001
Large excision[a]	23.9	66.9	81.3	
Biopsy[b]	73.2	30.8	15.4	
Other techniques[c]	1.9	0.6	0.4	
Second indirect referral				
Hysterectomy	0.6	2.2	1.9	<0.001
Large excision[a]	19.7	61.8	80.3	
Biopsy[b]	77.5	35.3	17.3	
Other techniques[c]	2.2	0.7	0.5	
All referrals				
Hysterectomy	1.0	1.8	3.3	<0.001
Large excision[a]	26.4	68.0	81.8	
Biopsy[b]	70.7	29.7	14.6	
Other techniques[c]	1.9	0.6	0.3	

See Figure 1 for description of referral types.
[a]Large excision includes cone biopsy, LLETZ and other excisional therapies.
[b]Includes all types of biopsies (excluding cone biopsy).
[c]Includes polypectomy, endometrial and endocervical curettage, and histology not otherwise specified.

with age (Figure 2). In women aged 44 years and older, 61.3% of the no recorded diagnosis and 55.3% of the no histology group had no further primary screening episodes after referral. The remainder had further cytology and/or histology tests taken in the next primary episode, which were excluded from analysis (figures not presented).

The more severe the CIN diagnosis, the higher the proportion of women treated with a large excision (Table 3). Women who were directly referred and diagnosed with CIN 1 had higher rates of large excision treatment compared with women who were indirectly referred: 34.4% vs 23.9% (first indirect) and 19.7% (second indirect); χ^2 (2, n = 14 474) = 193.1, $P < 0.001$). No age-dependency was seen in the percentage with large excision treatment of CIN 3 (figures not shown). For CIN 1 lesions, the proportion of treatment with large excision increased with age. Rates of treatment with large excision differed significantly between referral types across all age groups for CIN 1 lesions (from 13.1% to 50.4%) and for the four youngest age groups for CIN 2+ lesions (Figure 3).

See-and-treat management was observed more often in direct referrals than indirect referrals and was performed mostly in women with severe CIN lesions (Figure 4). Treatment of CIN 1 or lower, in see-and-treat management increased with age across all referral types and were higher for indirect referrals in all age groups (Figure 5).

4 | DISCUSSION

Despite recommendations not to treat CIN 1 lesions, we found that 26.4% of the diagnosed CIN1 lesions underwent an excisional procedure, ranging from 13.2% to 50.4% depending on age and referral type. Compared with the European guidelines for clinical management of abnormal cervical cytology,[13] the Dutch CIN 1 advice in the 2004 Guidelines was quite conservative. Despite this, the proportion of CIN 1 treated by large excision is slightly higher than previously reported figures from Italian colposcopy audits[14,15] with the latest reporting that 16% of CIN 1 lesions were treated and that there was an increase in the proportion of CIN 1 that was not treated between audit periods. However, compared with the European Federation for Colposcopy guidelines[16] that state that 85% of the excisional treatments should have a definitive histology of CIN 2+, our data show that the Dutch program exceeds this benchmark, at 87%. To our knowledge, no other European countries have published CIN treatment rates by diagnosis in peer-reviewed journals, though Danish researchers have recommended monitoring of CIN treatment trends in light of the increasing CIN treatment rates in Denmark.[17]

Monitoring of treatment rates can have a positive effect on compliance with guidelines by making practitioners cognizant of recommendations. A study from one US hospital found that active monitoring of excisional treatments led to an increase in guideline compliance and a decrease in inappropriate excisional treatments.[18] Regular monitoring should be implemented given the expected rise in CIN 1 diagnoses, due to the new, more sensitive hrHPV primary test. Modeling estimated that CIN 1 diagnoses will approximately double in the new screening program.[3] In the old cytology screening program, if the CIN 1 treatment rate was 5% during the period of our study, rather than 26.4%, this would have resulted in approximately 300 fewer CIN 1 lesions treated by large excision per year. Under the new hrHPV screening program, the impact of reduced CIN 1 treatment rates could be even larger.

It is unrealistic to expect no CIN 1 treatment, as there will always be women with persistent or recurring low-grade abnormalities for whom treatment may be favorable or reassuring.[19] Guidelines are only one factor in clinical decision making for CIN; gynecologists consider information about colposcopy, cytology, hrHPV status, family planning, age, women's preferences and other factors when advising about treatment. Communication between pathologists and gynecologists also influences treatment decisions.[18] There may be situations where CIN 1 would have been preceded by HSIL cytology, hrHPV positivity and CIN 2+ colposcopic impression or biopsies. Additionally, in women with transformation zone type 3, diagnostic LLETZ after high-grade cytology is indicated in IARC

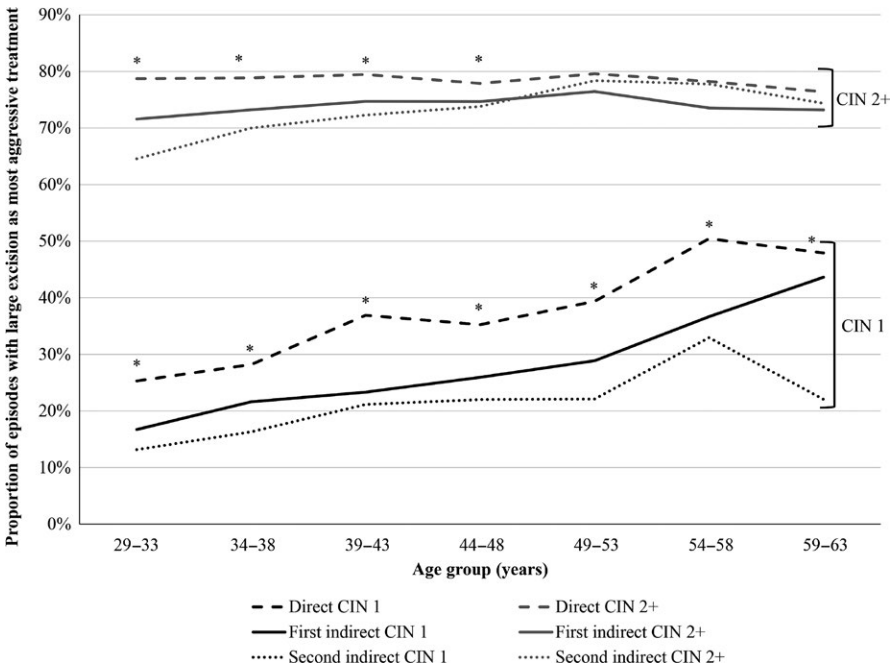

FIGURE 3 Proportion of episodes with large excision as most aggressive treatment for CIN 1 and CIN 2+ (denominator: total episodes within each age group with the same highest diagnosis), by age group and referral type. *Pearson's chi-square test significantly different between referral types. See Figure 1 for description of referral types. CIN, cervical intraepithelial neoplasia

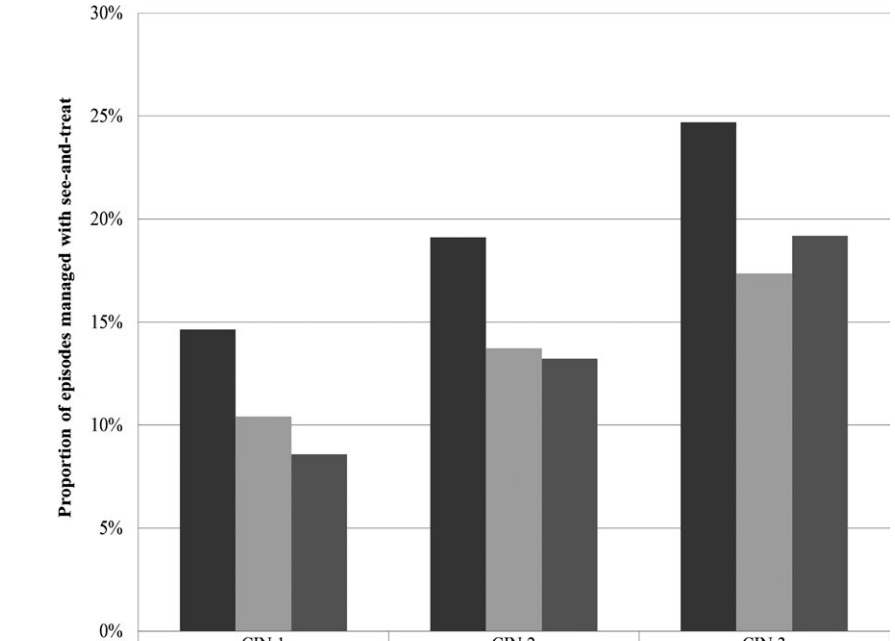

FIGURE 4 Proportion of episodes managed with see-and-treat* within each CIN diagnosis group and referral type, 2005-2014. *See-and-treat management is defined as episodes where the first treatment after referral advice is large excision. See Figure 1 for description of referral types

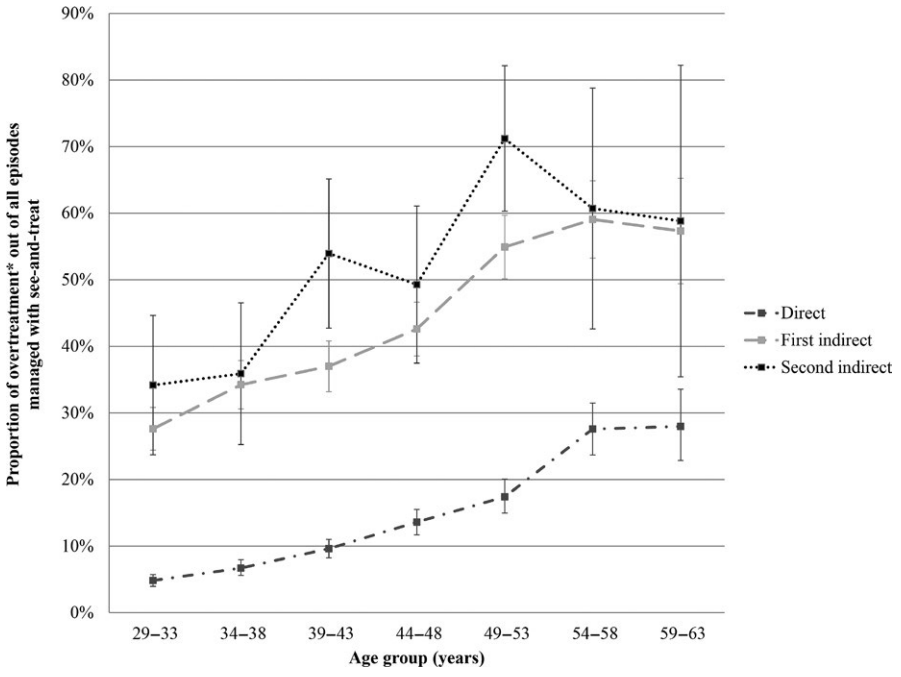

FIGURE 5 Proportion of overtreatment* in see-and treat management by age group and referral type. *Overtreatment in see-and-treat management is defined as the proportion of women with a CIN 1 or lower histological diagnosis who were treated with large excision at the first contact with a gynecologist, divided by all women who were treated with large excision at the first contact with a gynecologist. See Figure 1 for description of referral types. CIN, cervical intraepithelial neoplasia

guidelines.[20] In such situations, performing LLETZ may be a justifiable, appropriate treatment. Clarification of a reasonable rate of treatment for CIN 1 should be given in future guideline revisions, preferably accompanied by intuitive nomograms to assist in decision making, for example, that hrHPV negative biopsies can be observed rather than treated.

The treatment guidelines were revised in 2015[21] and now advise see-and-treat for a subcategory of women. Although this approach has advantages (reduced loss to follow up, convenience for women, lower costs),[22] overtreatment is a risk.[23] See-and-treat needs careful implementation to reduce overtreatment risks. We found that treatment of women diagnosed with CIN 1 or lower was more frequent in indirect referrals than direct referrals, and increased with age. These findings are similar to those of other Dutch studies.[24] Given the higher number of CIN 1 and lower diagnoses in the two indirect referral groups, this finding is unsurprising. Our results are consistent

with Ebisch and colleagues[12], who found that women with low-grade cytology had higher overtreatment rates compared with women with high-grade cytology.[12]Restricting see-and-treat to women with concordant high-grade cytology and colposcopy could minimize overtreatment, as could the use of a grading system, such as the Swede score, which has shown to have high specificity for CIN 2+ lesions.[25]

It is not surprising that the rates of treatment with large excision for CIN 2+ lesions vary little by age within referral types. Up until 2015, treatment guidelines for CIN 2 were not age-specific. However, the 2015 Guidelines[21] state that women with CIN 2 lesions should be individually assessed as to whether the benefits of treatment outweigh the risks, largely related to future childbearing. Active surveillance of young women allows time for CIN 2 lesions to regress, which is likely to occur in most CIN 2 cases.[26] However, active surveillance also comes with the risk of loss to follow up or progression to a higher grade lesion. Going forward, we expect that CIN 2 treatment will vary by age, as more young women are conservatively managed. As such, both treatment and outcomes for women with CIN 2 lesions should be monitored to ensure that clinical practice reflects guidelines.

As expected, women diagnosed with CIN 3 had the highest rates of treatment with excisional techniques. This is consistent across referral types with no differences by age (figures not shown). On the other hand, between 14.6% and 17.8% of the women diagnosed with CIN 3 were not managed with an excisional treatment (large excision or hysterectomy). This apparent undertreatment may be the result of several factors. Although uncommon in the Netherlands, these women may have been treated non-invasively using electrocoagulation, cryotherapy or imiquimod prescription, and these procedures are not recorded in PALGA. Undertreatment may be overestimated due to data issues, such as records belonging to one woman not being properly linked. Finally, a clinician can decide to use an expectant management strategy if diagnostic biopsy removed most of the lesion. Regardless, guidelines state that CIN 3 should always be treated given the risks of progression; long-term follow up of women in an unethical study in which treatment was delayed or withheld from women with high-grade lesions showed that the cumulative incidence of cervical or vaginal vault cancer was 31.3% at 30 years, with a higher cumulative incidence (50.3%) among women with persistent high-grade lesions.[27] Timely and effective treatment of CIN 3 is therefore necessary to avoid the risk of disease progression. Communication of these results directly to gynecologists is essential, emphasizing that the benefits of treatment for these women greatly outweigh the risks.

Our study is the first to use a national database to investigate CIN treatment practices in the Netherlands. Analysis in this study was split by referral type, allowing us to investigate women with different risk profiles separately, as the severity of the initial cytology influences follow up. Reflective of this, we found that women who are directly referred have a much higher proportion of CIN 3 diagnoses.

Our study has some limitations. We did not include information about hrHPV status in our analysis, as the practice of hrHPV testing was not universally conducted during the study period. However, knowledge of hrHPV status may have resulted in more aggressive treatment for women who were hrHPV positive. We were also unable to evaluate conization and large loop excisions separately, or analyze by depth of excision or lesion size. This is not coded in PALGA. This information would be useful for stratification of results, as depth of excision can have implications for both the risk of adverse obstetric outcomes[5,6,28] and the risk of recurrent or progressive disease.[29] Furthermore, we do not have information about the results of colposcopy. If a woman is referred to a gynecologist and examined with colposcopy, but has no accompanying test or treatment, no information is reported to PALGA.

Validation of our results with clinical data found that PALGA may slightly overestimate CIN 1 treatments (Appendix S2), although these clinical data came from a highly specialized clinic with physicians who almost exclusively treat cervical dysplasia. As such, treatment of CIN 1 with excision at this clinic is likely to occur less often than the average. One Dutch study compared the impact of different CIN management strategies (more-or-less aggressive) in two hospital facilities in the same city and found that 68% fewer CIN 1 lesions were found with the less aggressive strategy.[30] As PALGA has national coverage, the treatment rates we observed were not influenced by the policies or practices of any single clinic.

PALGA does not have a unique identification code to track women's screening history; women are identified by the first eight letters of their surname and date of birth. It is possible that tests of multiple women are attributed to a single identification code. In such cases, it is possible that follow up was censored early for some women, leading to a misclassification of the highest diagnosis or the most invasive treatment of the episode.

5 | CONCLUSION

Our study shows that both under- and overtreatment take place, despite guidelines being available. Regular monitoring of national trends and reviews of treatment rates should be implemented at each clinic that treats women for CIN, to make both gynecologists and pathologists aware of the guidelines and their own performance in relation to them. This may lead to greater compliance with the guidelines, reducing potential harm to women referred from screening.

CONFLICT OF INTEREST

C.A., E.J. and I.d.K. work on the Evaluation of Dutch National Cervical Cancer Screening Program project funded by the Dutch National Institute for Public Health and the Environment. R.B. has received speaker's fees from Roche Diagnostics and grants for contract research from SP-MSD.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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