

Low recurrence rate of high-grade cervical intraepithelial neoplasia after successful excision and routine colposcopy during follow-up

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Abstract

The aim of the present cohort study was to assess the long-term (follow-up period up to 22 years) recurrence rate of preinvasive disease and the newly detected invasive disease rate in a cohort of women treated with excisional methods for high-grade cervical intraepithelial neoplasia (CIN).

Women treated with large loop excision of the transformation zone (LLETZ) and cold knife conization (CKC) for histologically proven high-grade CIN were followed up for up to 22 years. Surgical specimens underwent histological examination and the status of endocervical as well as ectocervical margins was recorded. Follow-up protocol included conventional Pap test, colposcopy and pelvic examination at 3, 6, and 12 months after the initial treatment, and every 12 months thereafter, provided that the results were normal. In case of high-grade cytological findings and/or atypical colposcopic impression, multiple punch biopsies were taken in order to verify or exclude recurrent disease.

In total, 804 women were followed for a mean time of 77.1 months (range: 6–266). LLETZ was used in 569 (70.7%) and CKC in 235 cases (29.2%). No woman developed invasive cervical cancer. Recurrent high-grade disease, developed in 9 women (1.1%, 95% confidence interval 0.5–2.2). Median treatment-to-recurrence time was 46.5 months (range: 6–235.3). One woman treated for squamous CIN2 on clear margins developed adenocarcinoma in situ 59.2 months post-treatment.

Women having undergone excisional treatment for high-grade CIN indicate a very low risk for recurrent disease and potentially negligible risk for invasive cancer, provided that a strict and vigorous follow-up is offered after treatment.

Abbreviations: AGUS = atypical glandular cells of undetermined significance, ASC-H = atypical squamous cells—cannot exclude high-grade SIL, ASCUS = atypical squamous cells of undetermined significance, CI = confidence interval, CIN = cervical intraepithelial neoplasia, CKC = cold knife conization, HPV DNA = human papillomavirus deoxyribonucleic acid, LEEP = loop electrosurgical excision procedures, LLETZ = large loop excision of the transformation zone, LSIL = low-grade squamous intraepithelial lesion, OR = odds ratio, RR = risk ratio, SIR = standardized incidence ratio.

Keywords: cervical conization, cervical intraepithelial neoplasia, CIN2-3, CKC, colposcopy, LLETZ

1. Introduction

Organized cervical cancer screening has greatly reduced mortality from the disease by allowing detection and treatment of premalignant lesions.^[1] Still, studies demonstrated that women who received appropriate cervical intraepithelial neoplasia (CIN) treatment require close follow-up as they remain at higher risk for

subsequently developing invasive cervical cancer when compared to the general population.^[2–10]

This concept was largely developed after a UK multicenter study by Soutter et al,^[2] who found that 2116 women, treated for CIN2/3 had a cumulative risk of invasion 0.58% during the 8 years following treatment (85 per 100,000 woman-years), which was about 5 times higher compared to the general population. Kalliala et al^[3] in their retrospective cohort study based on 7564 women treated for CIN and followed-up through the Finnish cancer registry up to 29 years showed also an elevated (2.8 times) risk for invasive cancer during the first 20 years after treatment. A larger study of 37,000 women from Canada showed also that the long-term risk of invasive cancer remained higher among women treated for CIN, and highlighted for the first time the association of cryotherapy and advanced age with recurrence risk.^[4] Other studies, too, have noted an increased risk for invasive disease post-treatment.^[5–8,10,11]

In contrast to these findings, Reich et al,^[12] after 30 years of follow-up post CIN3 treatment reported not a single case of invasive disease among 4417 women treated with cold knife conization (CKC) with clear margins, whereas the recurrence rate for CIN2/3 was only 0.35%.^[12] On the other hand, the same group reported only 1 woman with a stage Ib cervical carcinoma detected 8 years after treatment and 5 women with microinvasive carcinoma among 390 cases with involved margins.^[13] Similar

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results (i.e., no invasive disease postconization) were presented by a French study with 460 patients and mean follow-up 5 years (range: 1–13 years).^[14] Finally, in 3 smaller studies from Greece, Norway, and Thailand, no invasive disease after CIN2+ treatment with excisional methods had been detected, follow-up time being from 2 to 8.5 years, 19 to 23 years, and 11 to 16 years, respectively.^[15–17]

It is obvious that many factors and confounders could play significant roles in the risk of recurrence after treatment for CIN, especially regarding the long-term risk of invasive cervical cancer. Age, mode of treatment, status of the excised cone, follow-up protocol, and other parameters should be taken into consideration, in order to assess the risk of disease recurrence after treatment for CIN2/3 and especially in order to approach the real magnitude of the risk of invasive cancer after such a treatment.

The aim of the present study was to analyze the long-term rate of recurrence of preinvasive disease and that of newly detected invasive disease in a cohort of women who were treated with excisional methods for high-grade CIN and were followed up prospectively up to 22 years postoperatively with an intensive and strict protocol followed by the same operator.

2. Patients and methods

This is a retrospective clinical study reporting on the long-term (range: 6–266 months) follow-up of a cohort of women, who consecutively received excisional treatment for histologically proven high-grade CIN (CIN2 and/or CIN3, i.e., CIN2/3). Treatment modalities included large loop excision of the transformation zone (LLETZ) and CKC. The specimens underwent histological examination and the status of the excisional endocervical as well as ectocervical margins was recorded. The study has been approved by the Ethical Committee of the Department of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, which also waived the requirement of obtaining informed consent specifically for this study, since data were used retrospectively after de-identification and each patient had already given informed consent at the time of treatment.

The follow-up protocol included conventional Pap test, colposcopy, and pelvic examination by a single operator at 3, 6, and 12 months after the initial treatment, and every 12 months thereafter, provided that the results were normal. In case of high-grade cytological findings and/or suspicious or atypical colposcopic impression, multiple punch biopsies were taken in order to verify or exclude recurrent disease; particularly in small lesions, this procedure often resulted in removal of most of the aberrant epithelium. In case of low-grade cytological and colposcopic

findings, women were followed-up with shorter follow-up intervals, either by biopsy taking or (mostly) conservatively, and only during the last years of the follow-up with addition of human papillomavirus deoxyribonucleic acid (HPV DNA) testing.

Cases with recurrent CIN2/3 were re-treated with LLETZ or CKC, and 1 case (aged 29 years at initial treatment, and diagnosis of CIN2 46.5 months post-treatment) was followed-up closely without further surgical intervention.

The outcome of the study was the recurrent disease (CIN2/3) or invasive disease per treatment modality and margin status. Residual disease, defined as detection of CIN2/3 during the first 6 months of follow-up, was excluded from the analysis. Recurrence was defined as detection of high-grade CIN (CIN2/3) thereafter.

The prevalence of each outcome was calculated, together with its 95% confidence intervals (95% CIs). Comparisons were made using proportion differences, together with their 95% CIs. Statistical analyses were performed using SPSS Statistics 17.0 (SPSS Statistics for Windows, version 17.0, Chicago, IL).

3. Results

In total 804 women were followed for a mean time of 77.1 months (range: 6–266 months) after excisional treatment for high-grade CIN. The treatment method used was LLETZ in 569 (70.7%) and CKC in 235 cases (29.2%). The latter was the method preferred during the earlier years and in cases with dysplasia of the glandular epithelium.

None of the women of this cohort developed invasive cervical cancer. Recurrent high-grade disease, developed in 9 women (1.1%, 95% CI 0.5–2.2) (Table 1). The median treatment-to-recurrence time was 46.5 months (range: 6–235.3 months). Interestingly, in 1 woman treated for squamous CIN2 on clear margins, an adenocarcinoma in situ was diagnosed 59.2 months post-treatment.

Twelve women (1.5% [95% CI 0.8–2.7]) developed histologically proven low-grade CIN (CIN1) at a median time of 10.5 months (range: 3.2–80.7 months), which regressed without treatment. In addition, 29 women (3.6%) presented, during follow-up, low-grade cytological findings (koilocytic atypia [n = 4], atypical squamous cells of undetermined significance [ASCUS] [n = 5], atypical glandular cells of undetermined significance [AGUS] [n = 2], atypical squamous cells—cannot exclude high-grade SIL [ASC-H] [n = 1], low-grade squamous intraepithelial lesion [LSIL] [n = 17]). Based on a colposcopic impression which had been negative or indicative of low-grade lesion, no biopsies were taken and women were followed-up conservatively, until no

Table 1
Characteristics of the patients with recurrent cervical disease.

Age at initial treatment, years	Grade at initial treatment	Treatment modality	Endocervical margin status	Months to recurrence	Grade at recurrence
33	CIN2	Cold knife	Negative	5.3	CIN2
29	CIN2	LLETZ	Negative	46.5	CIN2
20	CIN2	LLETZ	Positive	95.8	CIN2
39	CIN3	LLETZ	Positive	25.9	CIN3
48	CIN2	LLETZ	Negative	67.3	CIN3
41	CIN3	LLETZ	Positive	8.5	CIN3
42	CIN2	LLETZ	Negative	4.6	CIN3
40	CIN2	LLETZ	Negative	59.2	AIS
32	CIN2	LLETZ	Negative	235.3	CIN2

AIS = adenocarcinoma in situ, CIN = cervical intraepithelial neoplasia, LLETZ = large loop excision of the transformation zone.

abnormal findings were identified in terms of cytology and colposcopy.

In 575/804 (71.5%) of the patients (95% CI 68.2–74.6), the lesion was excised on clear endocervical as well as ectocervical margins while endocervical margins, regardless of the ectocervical margin status, had been positive in 62 women (7.7%). The rate of recurrence in women with negative endocervical margins was 0.8% (6/742) (95% CI 0.3–1.8) versus 4.8% (3/62) (95% CI 0.6–5.0) in women with positive margins ($P=.03$). Conversely, the rate of positive endocervical margins was 33.3% (3/9) in the women who later developed CIN2+ recurrence versus 7.4% (59/795) in those who did not (risk ratio [RR] of 4.5 [95% CI 1.7–11.7]). The recurrence rate was 1/235 (0.4%), (95% CI 0.1–2.8) for CKC and 8/569 (1.4%), (95% CI 0.7–2.9) for LLETZ, a difference not statistically significant ($P=.3$).

4. Discussion

Our results indicate that excisional (LLETZ or CKC) treatment for high-grade CIN combined with an intensive and strict follow-up protocol (cytology plus colposcopy plus pelvic examination at 3, 6, and 12 months after the initial treatment, and every 12 months thereafter) is associated with a very low rate of recurrent disease (1.1%) with practically no long-term risk for invasive cervical cancer development.

A determinant reason for the low recurrence rate could be the strict definitions applied for recurrence, that is, the need for histological confirmation of high-grade or invasive disease. If cases with CIN1 (N=12) as well as cases with low-grade cytological findings not confirmed on histology (N=29) were also included, then the recurrence rate would become 2.6% or 6.2%, respectively. This would still be at the very lower end of follow-up studies, despite the inclusion of inadequately ascertained and largely transient conditions (low-grade Pap results and CIN1, respectively).

As mentioned, the age of the patient, mode of treatment, status of the excised cone, and protocol of follow-up examinations are the major parameters playing crucial role in the rate of recurrence after treatment for CIN and especially in the detection rate of invasive cancer after such a treatment.

Age of the patient was significantly linked to invasive cervical cancer occurrence in the study of Rapiti et al,^[11] with no cases among women below the age of 25 years, whereas the highest risk was noted in women >50 years of age. Age of ≥ 50 years, together with incomplete excision of the lesion, had been also associated with an increased risk of recurrence in the study of Flannelly et al.^[6] Strander et al^[9] first reported a 2.5-fold increased risk of cervical and vaginal cancer among women with a previous diagnosis of CIN3, which was higher for women aged >50 years at treatment; recently, the same group of authors in a multivariable regression model reported a 5 times increase in risk for treatment at age 60 to 69 years, compared with treatment at age 30 to 39 years, and this risk accelerated with further aging.^[10] In our study, the small number of women with recurrent disease prevented a multivariate analysis including age as potential factor linked with recurrence.

Regarding *mode of treatment*, most of the studies revealed increased rates of recurrence after destructive methods of CIN treatment, in contrast to excisional ones. Soutter et al^[2] in their initial study found a 5-fold increase of invasive cancer after CIN treatment, based, however, on excisional as well as on destructive methods of CIN treatment. The same authors in their review of 24 studies reported a 2.8-fold higher risk for post-treatment

cervical cancer, however the mode of treatment among these studies was destructive (cryotherapy, diathermy ablation, and laser vaporization) in 8, excisional (CKC, LLETZ, and laser conization) in 7, hysterectomy in 4, and various in 5, showing lower recurrence rate of invasive cancer after excisional compared to destructive methods.^[7] In the Canadian cohort study, cryotherapy, compared with other treatments (CKC, LLETZ, laser excision, or ablation), was also associated with the highest rate of subsequent invasive disease (odds ratio [OR] 2.98, 95% CI 2.09–4.60).^[4] In the Italian study by Cecchini et al,^[5] the incidence rate of invasive cancer showed not clear statistically significant difference concerning modes of treatment, however the highest difference was associated with local destructive treatments (diathermy or laser vaporization) (OR 5.5, 95% CI 0.46–66.5). Rapiti et al^[11] in their Swiss study found a 7.5 increased risk of cervical cancer up to 9 years after diagnosis, which was much higher among women treated with cryotherapy (standardized incidence ratio [SIR] 16.8, 95% CI 2.0–60.5), or with other destructive methods (SIR 24.1, 95% CI 0.7–134.0), whereas women with excisional treatment had the lowest and nonsignificantly elevated risk (SIR 2.4, 95% CI 1.0–4.9) and they concluded that omission of excisional therapy is associated with an increased risk of invasive cervical cancer after CIN3. Kalliala et al^[3] first showed an increased risk for invasive cervical cancer (SIR 2.8, 95% CI 1.7–4.2) in the first 20 years post CIN treatment, based on women treated by excisional (knife or laser conization, LLETZ) or by destructive methods (laser vaporization, cold coagulation); in a subsequent study on the same cohort of women, the authors calculated an almost double hazard ratio of cryotherapy compared to LLETZ or laser as treatment techniques.^[18] Surprisingly, this is the only study, where CKC seemed to be the least favorable in terms of further risk for invasive cancer.

On the contrary, using only CKC for treatment of 4417 women with CIN3, the group from Graz reported no case of invasive cancer after follow-up of 30 years when the margins were clear,^[12] and only 1 case with stage Ib and 5 cases with microinvasive carcinomas when the margins were involved.^[13] Equally, using LLETZ as the treatment method, Hulman et al^[19] reported no case of invasive cancer among 669 women followed post-treatment up to 3.5 years, and Zaitoun et al^[20] reported only 1 case among 1600 women with CIN, which has been diagnosed with invasive cervical cancer 44 months after incomplete excision of the lesion.^[20] Finally, Stasinou et al^[21] using also LLETZ for conservative treatment of 3861 patients, in whom the histological evaluation of the initially excised specimen showed not only CIN (n=3348) but also microinvasive (n=94, 2.4%) and invasive diseases (n=206, 5.3%)—without giving further details about staging—found only 3 cases of microinvasive disease in a follow-up period up to 22 years. As already mentioned, in our cohort of 804 women with CIN2+ treated with excisional methods only and followed-up up to 22 years, we found no case with invasive disease post-treatment.

Numerous studies have highlighted the association of *excisional margins* with recurrence risk after treatment for CIN. In the vast majority of the cases—however, not in all^[22]—the definition of clear or not clear margins includes the endocervix as well as the ectocervix. The importance of clear margins of the excised specimen, meaning theoretically the complete excision of the lesion, has also been shown to be crucial regarding the recurrence rate of preinvasive but also of invasive disease at least by the aforementioned studies.^[6,12,13,19,20] Positive margins especially after loop electrosurgical excision

procedures (LEEP) was one of the significant factors affecting recurrent disease in some studies,^[14,17] however, the relation between free margins and relapse was not always statistically significant.^[16,23,24] In the extensive meta-analysis by Ghaem-Maghani et al^[22] (66 studies, 35,109 women), women with involved margins had 18% chance for high-grade post-treatment disease versus 3% for women with complete excision (RR 6.09, 95% CI 3.87–9.60). The risk was greater if the deep (endocervical) margins of the biopsy were involved by CIN and greater still if CIN extended to the deep and the superficial (ectocervical) margins. Reich et al^[12] reported a 0.35% recurrence rate after CKC with clear margins, which however increased to 22% when the margins were involved.^[13] In our study, the rate of margin involvement (28.5%) was very close to the pooled rate of the aforementioned meta-analysis.^[22] The rate of recurrence was significantly higher in women with positive endocervical margins (4.8% vs 0.8%, $P=.03$) and the RR for recurrence in these women was 4.4, close to that (RR 3.1) of LEEP in the meta-analysis.^[22] The recurrence rate was 0.4% for CKC versus 1.4% for LLETZ, a statistically nonsignificant difference. Concerning the reported increased rate of adverse pregnancy outcome after CIN treatment, our data on subsequent pregnancy outcome are not sufficient to draw any conclusion.

As far as the *follow-up protocol* after treatment for CIN is concerned, it is interesting that the majority of the large aforementioned studies^[2–6,8–11] as well as the review by Soutter et al^[7] and the meta-analysis by Ghaem-Maghani et al^[22] dealing with the detection of preinvasive and especially invasive disease long term after treatment refer to follow-up examinations performed basically via conventional or liquid-based cytology at different time intervals between 1 and 5 years. Thus, according to national or regional guidelines in the UK,^[2,7] Sweden,^[9,10] Finland,^[3] The Netherlands,^[8] British Columbia/Canada,^[4] Tuscany/Italy,^[5] and Geneva/Switzerland,^[11] which were valid for the previous 20 to 30 years, that is, the time period to which the studies are referred to (and before the introduction of HPV testing for the prediction of residual/recurrent disease) the follow-up protocol after treatment for CIN—irrespective of the treatment method—included cytological testing at 6 and 12 months after treatment without additional colposcopy or with only a single colposcopy appointment^[2,3,7–11]—with the exception of the Canadian study, where the recommendation had been follow-up cytology with colposcopy at 3, 7, and 13 months post-treatment.^[4] After the first year, treated women were accordingly screened either yearly until 5 or 10 or even 25 years,^[2,3,7,10,11,19] or after 3 consecutive negative smears, they returned to population-based cytological screening every 3 or 5 years.^[25] The vast majority of these studies showed cases of invasive disease detected in a very long period of time (till 30 years) after the initial treatment, and substantiated the opinion that women treated for CIN2/3 have a higher risk of developing cervical cancer than the general population.

In contrast to that, there are other smaller studies reporting follow-up protocols with a combination of pelvic examination, cytology, and colposcopy at (3), 6, (9) 12 (18), and 24 months after excisional therapy, and every 12 months thereafter, until 5 to 20 years post initial treatment.^[12–17,22] A quite similar protocol was also followed in our study. Stasinou et al^[21] also reported biennial cytological and colposcopic examinations over a follow-up period up to 22 years and showed a 1.25% rate of microinvasive disease; this rate can however not be taken into account, as they had initially treated 4.12% early invasive cancers. It is interesting that in the vast majority of the studies

using cytology plus colposcopy in follow-up of women treated for CIN, including our study, no invasive disease was detected post-treatment in a follow-up period of ≥ 20 years.

The use of routine colposcopy in addition to cytology in the follow-up after CIN treatment has been investigated by many authors, with contradictory results. In the UK, according to Soutter et al,^[26] although the National Guidelines advise for use of cytology alone, because of lack of evidence for the additional use of colposcopy and in order to reduce the workload, many colposcopy clinics do use colposcopy, at least once after treatment. According to the authors, in cases with uncertain status of the margins or involved margins, the sensitivity of colposcopy reaches 97%, with the specificity 93.4%. As a result, they propose the addition of at least 1 colposcopic examination during the follow-up visits, and >1 in high-risk women.^[26] Initial colposcopy (at 6 months after treatment) is also found to increase life-expectancy and quality-adjusted life-expectancy and is highly valued in terms of cost-utility analysis in a modeling study by Melnikow et al^[44] representing clinical practice strategies in the USA. In favor for the inclusion of colposcopy are also Flannelly et al^[27] and Paraskevaidis et al,^[28] emphasizing the low-sensitivity rates for cytology (63% and 82%, respectively) for the detection of post-treatment disease. Recently, in order to facilitate implementation of common standards across Canada, Bentley analyzed all the systematic reviews, randomized control trials/controlled clinical trials, and observational studies dealing with colposcopic management of abnormal cervical cytology and histology and recommended the use of excisional procedures for the treatment of CIN3 as well as the use of colposcopy in women who have positive margins.^[29]

Numerous trials during the last decade showed that testing for high-risk HPV DNA in order to detect post-treatment disease in women treated for CIN has presented higher sensitivity and almost equal specificity compared to follow-up cytology alone or histological assessment of the margins of the excised specimen.^[30,31] It is obvious that in the near future screening for cervical cancer, triage algorithms for screen-positive women, as well as follow-up after treatment for cervical precancer will shift from cytology to full molecular screening based on HPV-related biomarkers.^[32] However, for now, the scientific data concerning the long-term detection rate of precancer and especially invasive cervical cancer are based not on molecular but on morphological, that is, cytological and colposcopic data.

There are 2 possibilities for the pathogenesis of invasive cervical cancer after treatment for CIN: either it develops from a small residual lesion not removed or destroyed during treatment, or it develops *de novo* in various periods of time after treatment. In the first case it seems likely that the residual lesions have characteristics that make them difficult to detect;^[26] in respect to that, the most successful treatment modality has to be chosen in order to diminish, as much as possible, the risk of even the smallest lesion being left behind. According to most studies, excisional treatment seems to be superior to destructive methods in this regard. In the second case, considering that the follow-up period in the abovementioned studies is very long (>20 years), one could expect that the rate of *de novo* development of cervical cancer in women treated successfully for CIN would be the same with the average population, unless one assumes that these women are characterized by a high-risk genetic profile, prone to interact badly with HPV infection. Although there are studies investigating a genetic predisposition for the development of cervical precancer and cancer, there is no evidence to date to clearly support this idea. In their extensive meta-analysis of 66

studies, Ghaem-Maghani et al,^[22] who found a significant association between the frequency of post-treatment disease and frequency of incomplete excision ($P < .001$), stated at the end that the data do not show definitely whether post-treatment disease is due to recurrence of the original disease or to the development of new disease, but the association with insufficient excision suggests that recurrence of the original disease is the more likely reason.

However, in both cases, the fact remains that long-term post-treatment follow-up of these patients based on cytology only has failed to reduce the persistently higher rate of cervical cancer detection compared to the general population. The fact that in some of these studies,^[4,7,15,21,26] colposcopy has been usually performed initially or at 6 and/or 12 (or 18) months post-treatment possibly explains the falling rates of detection of intraepithelial lesions during the first 2 years after the treatment. Soutter et al^[7] also hypothesized that lesions not fully removed during treatment might take time to regrow before reaching a detectable size, especially if the residual lesion is very small. During this longer period of time invasive cancer might develop, either from small residual lesion as a result of incomplete treatment, or *de novo*, without going through a premalignant stage. In either case, colposcopy seems to improve substantially the sensitivity of cytology alone for the detection of invasive disease.

The statement of Soutter et al^[7] that during long period of surveillance after the initial treatment, an increasing rate of default to follow-up could be an important parameter playing role in the persistently increased rate of invasive cervical cancer post-treatment is true. However, taking under consideration the close surveillance of women by the well-organized Swedish and Finnish National Screening Programs, and the fact that the increased rate of invasive disease has been confirmed earlier by Finnish^[3,18] and Swedish studies^[9,33] and very recently by a study based on Cancer and Death Registries covering the whole female Swedish population for 50 years,^[10,11] makes the assumption that diminishing compliance with follow-up could be the main cause for the increasing cancer rates, unlikely.

Our study has some limitations. First, the very small number of women with recurrent disease prevented a univariate or multivariate analysis including potential factors possibly interfering with these results, for example, age, mode of treatment, or marginal status. However, according to the mentioned studies, it seems that increased age of the patient, performance of cytology-only long-term follow-up, use of nonexcisional treatment methods, or incomplete excision of CIN are the main factors leading to the increasing rates of recurrence, particularly of invasive cervical cancer, after treatment for CIN. Consequently, women with CIN treated successfully with an excisional method and followed-up closely and intensively by a strict follow-up protocol including cytology and colposcopy (and probably in the near future HPV testing) might not be at increased risk for invasive cervical cancer in relation to general population.

Second, the majority of women in our cohort were not tested for HPV DNA, which currently plays a significant role in post-treatment follow-up for CIN, since this marker has not been available or significant throughout the cohort study period which started >20 years ago. Therefore, we could not examine the added value of this marker to the follow-up effectiveness. Lastly, for the same reason, women were not tested for other sexually transmitted diseases, a factor which also might play a role in the natural history of CIN and therefore in the post-treatment follow-up workout.

In conclusion, our data from the long-term follow-up of women having undergone excisional treatment for high-grade CIN indicate a very low risk for recurrent disease and potentially negligible risk for invasive cancer, provided that a strict and vigorous follow-up is offered after treatment.

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