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a population-based cohort study

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Clinical course of cervical intraepithelial neoplasia grade 2: a population-based cohort study

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BACKGROUND: Cervical intraepithelial neoplasia grade 2 has historically been the threshold for surgical excision, but because of high regression rates, many countries are transitioning to active surveillance. However, estimates for regression rates are based on small studies with heterogeneous definitions of regression and progression.

OBJECTIVE: This study aimed to describe regression and progression rates of cervical intraepithelial neoplasia grade 2 using nationwide healthcare registry data.

STUDY DESIGN: This was a nationwide population-based cohort study on women aged 18 to 40 years who had undergone active surveillance for cervical intraepithelial neoplasia grade 2 in Denmark from 1998 to 2020. This study excluded women with a previous record of cervical intraepithelial neoplasia grade 2 or worse or surgical excision. Cumulative incidence functions were used to estimate the rates of regression and progression at 6, 12, 18, and 24 months after diagnosis. In addition, a modified Poisson regression was used to estimate the crude and adjusted relative risks of progression within 24 months stratified by index cytology and age.

RESULTS: During the study period, 11,056 women underwent active surveillance, 6767 of whom regressed and 3580 of whom progressed within 24 months. This corresponded to regression rates of 62.9% (95% confidence interval, 61.9—63.8) and progression rates of 33.3% (95% confidence interval, 32.4—34.2) at 24 months of follow-up. Most women regressed (90%) or progressed (90%) within the first 12 months. Women with high-grade index cytology had a higher risk of progression than women with normal index cytology (adjusted relative, 1.58; 95% confidence interval, 1.43—1.76), whereas there was no difference in the risk of progression between women aged 30 and 40 years and women aged 23 to 29 years (adjusted relative risk, 0.98; 95% confidence interval, 0.88—1.10).

CONCLUSION: The observed high regression rates of cervical intraepithelial neoplasia grade 2 supported the transition in clinical management from surgical excision to active surveillance, particularly among women with low-grade or normal index cytology.

Key words: cervical intraepithelial neoplasia grade 2, loop electrosurgical excision procedure, progression, regression

Introduction

Cervical cancer screening allows for the detection and subsequent treatment of precursor lesions, that is, cervical intraepithelial neoplasia (CIN), thereby preventing progression to cervical cancer. Historically, CIN has been categorized on the basis of lesion severity into CIN1 (cervical intraepithelial neoplasia 1; mild), CIN2 (cervical intraepithelial neoplasia 2; moderate), and CIN3 (cervical intraepithelial neoplasia 3; severe).[1,2] CIN1 represents an active and transient human papillomavirus infection (HPV) with a low risk of progression and is managed with repeated testing after 1 year.[3,4] CIN2 and CIN3 have a higher risk of progression to cancer and are classified as high-grade lesions. Accordingly, women diagnosed with CIN2 or worse have been recommended immediate loop electrosurgical excision procedure (LEEP).[3,4]

The management of CIN2 with immediate LEEP has been debated within the past years as studies have shown high spontaneous regression rates of CIN2.[2,5] Of note, 2 systematic reviews have demonstrated regression rates of CIN2 of 50% to 57% within 2 years.[2,5] The high regression rate indicates that immediate LEEP of CIN2 will likely result in overtreatment, which carries an increased risk of preterm delivery in subsequent pregnancies.[6] Consequently, countries have transitioned from immediate LEEP to active surveillance.[7] However, most studies in the systematic reviews include <100 women. Furthermore, the outcome definition is heterogeneous, resulting in a high risk of bias. In this context, nationwide registry data are worthy of exploration as this allows for a larger study population. In Denmark, recommendations for active surveillance were implemented nationally in 2013, but the Central Denmark Region (composed of 20% of the Danish population) began active surveillance in 1995.[8,9] Hence, the Danish individual-level registries are composed of data that enable estimation of regression and progression in a large nationwide setting. Therefore, this study aimed to describe the rates of regression and progression in women undergoing active surveillance for CIN2 in Denmark.

Materials and Methods

Study population

In this nationwide population-based cohort study, we included women aged 18 to 40 years with a first-time diagnosis of CIN2 on cervical biopsies from January 1, 1998, to December 31, 2020. Women with a previous record of CIN2+, LEEP, vulvar, or vaginal cancer were excluded. We restricted the analyses to women who underwent active surveillance, which we defined as having a subsequent record of a cervical biopsy

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AJOG at a Glance

Why was this study conducted?

Cervical intraepithelial neoplasia grade 2 (CIN2) has been the threshold for loop electrosurgical excision procedure (LEEP), but because of regression rates of 50% to 57% within 24 months, and the association of LEEP and preterm birth, many countries have implemented active surveillance for CIN2. However, most previous studies are limited by sample size.

Key findings

This study provided results on the largest cohort of women undergoing active surveillance for CIN2 (N=11,056); 63% regressed and 33% progressed within 24 months. Although the woman's age had limited effect on the risk of progression, a high-grade index cytology was associated with a 58% increased risk.

What does this add to what is known?

Our results support active surveillance for CIN2 in women planning for future pregnancy, particularly in women with normal or low-grade index cytology.

within 10 months after their CIN2 diagnosis (Supplemental Figure 1). As we did not have access to medical journals, we had to classify women as undergoing active surveillance based on their subsequent record in the Danish Pathology Registry. We chose a window of 10 months as this allowed for diagnostic delay from the CIN2 diagnosis until the first record of a cervical biopsy.[8] We excluded women who were followed up solely with cytology or underwent immediate LEEP. In addition, we excluded women with no record of cervical biopsy within 10 months as they were considered noncompliant.

Setting

In Denmark, the healthcare system is tax funded and includes free and equal access to cervical cancer screening. Screening began in the 1960s for women aged 23 to 59 years, and in 2007, screening was extended to women aged 60 to 64 years.[9,10] In case of abnormal screening, the woman may be referred for colposcopy. At colposcopy, abnormal areas are identified, and targeted biopsies are collected. Since 2013, it has been recommended to take 4 biopsies, regardless of the colposcopic findings.[9] The result of biopsies and associated cytology determines the recommendation for further management.[9]

Women with CIN2 in Denmark are offered active surveillance if they are planning for future pregnancy.[8,9] Thus, active surveillance is offered regardless of age, but often to women below the age of 40 years.[8] In addition, it is irrespective of cytology and lesion size. Active surveillance consists of semiannual follow-up visits for up to 2 years. In the case of regression to CIN1 or normal, cervical cytology is repeated after 1 year (Supplemental Figure 2). LEEP is recommended in the case of progression to CIN3 or persistent disease after 2 years. Of note, LEEP is standard care in Denmark, whereas cryotherapy and thermal ablation have not been routinely performed within the past 3 decades.

Data sources

All residents in Denmark are assigned a unique civil registration number (CPR number) at birth or immigration, which allows for individual-level linkage of all national registries.[11] The CPR number is registered in the Civil Registration System, which is updated daily, has a virtually complete follow-up, and stores information on the date of birth, address, emigration, and death.[11]

Here, we linked data from the Civil Registration System, the Danish National Pathology Registry, the Danish Cancer Registry, and the Danish Patient Registry.

The Danish National Pathology Registry holds information on all pathology specimens, composed of all cytologic and histologic samples from the uterine cervix, including cytology, cervical biopsies, endocervical curettage, LEEP, and hysterectomies.[12] This registry is considered highly complete since 1998. All samples are assigned a topographic and morphologic code according to the Systematized Nomenclature of Medicine.[12] Histologic samples are classified according to the CIN classification, whereas cytologic samples are classified according to the Bethesda classification system.[13] We obtained information on all women diagnosed with CIN2 on cervical biopsies and all their subsequent cervical cytologic and histologic samples. Furthermore, we collected information on index cytology, defined as the most recent cytology within 6 months before or 7 days after CIN2 diagnosis. Results of the index cytology were classified as normal, low grade, high grade, other, and missing.

We identified cases of cervical cancer through the Danish National Pathology Registry and the Danish Cancer Registry (International Classification of Diseases, Tenth Revision, DC53*).[14]

Lastly, we obtained information on the date of hysterectomy from the Danish Patient Registry. The Danish Patient Registry was established in 1977. It holds information on date and type of procedure performed in all public and private hospitals.[15]

Outcome

To estimate the rates of regression and progression, we used the diagnosis on all subsequent cervical histologic samples. In case a sample had more than 1 morphologic code, we used the worst diagnosis. Histologic diagnoses were categorized as normal, CIN1, CIN2, CIN3 (including carcinoma in situ, adenocarcinoma in situ, and ungradable CIN), or malignancy. We defined regression as histologic CIN1 or normal and progression as histologic CIN3+. Our secondary outcome was LEEP, which was obtained from the Danish National Pathology Registry.

In addition, we performed 2 sensitivity analyses in which we estimated (1) regression to histologic CIN1 and normal separately and (2) regression to histologic CIN1 or normal combined with normal or low-grade cytology.

Statistical analyses

We used the cumulative incidence function to estimate the rates of regression and progression at 6, 12, 18, and 24 months after CIN2 diagnosis and considered regression and progression as competing events. Women were followed from CIN2 diagnosis until date of regression, progression, hysterectomy, emigration, death, or latest histologic sample within 24 months, whichever occurred first.

We used modified Poisson regression with robust variances to estimate the crude relative risk (RR) and adjusted RR (aRR) of CIN3+ and LEEP within 24 months.[16] We stratified the estimates by age group, index cytology, and calendar year. For the age group estimates, we used women aged 23 to 29 years as reference as screening begins at the age of 23 years in Denmark. We adjusted for age, index cytology, and calendar year.

We performed data management in SAS (version 9.4; SAS Institute Inc, Cary, NC) and statistical analyses in Stata (version 17.0; StataCorp, College Station, TX).

Ethics approval

According to Danish legislation, approval from the ethics committee is not required for registry-based research. The study was reported to the Danish Data Protection Agency through registration at Aarhus University (2016-051-000001; sequential number 1648), the Central Region Denmark (1-16-02-367-21), and the Danish Health Data Authority (FSEID-00005496).

Results

We identified 11,056 women with incident CIN2 who had undergone active surveillance from 1998 to 2020 (Table 1). Most women were aged <30 years (71%) and had abnormal index cytology (82%), with high-grade cytology being predominant. Because of the nationwide recommendation of active surveillance in 2013, half of the women in our study population were diagnosed after 2013 (53%).

Regarding regression, 3070 women had histologic regression within 6 months, corresponding to 27.9% (Table 2 and Figure). Regression rates were doubled after 12 months of follow-up (55.4%). At 24 months of follow-up, 6767 had regressed to normal or CIN1, corresponding to 62.9%. Approximately 90.0% of the women who experienced regression regressed within the first 12 months. Of the women who regressed, 3647 (54.0%) regressed to normal, whereas 3120 (46.0%) regressed to CIN1 (Supplemental Table 1 and Supplemental Figure 3). When defining regression as histologic CIN1 or normal and normal or low-grade cytology, regression rates at 24 months decreased to 48.7% (Supplemental Tables 2 and 3 and Supplemental Figure 4).

Concerning progression, 1658 women had histologically verified progression within 6 months after CIN2 diagnosis (15.1%). Within 24 months, 3580 women (33.3%) had progressed. Most women (n=2804 [90.0%]), who progressed during the surveillance period, progressed within the first 12 months (Table 2 and Figure). Overall, 33 women were diagnosed with cervical cancer within 24 months, corresponding to 0.3%. Of these, 22 cases (67%) were among women aged 30 to 40 years. Information of the International

TABLE 1
Baseline characteristics of women undergoing active surveillance for CIN2

Baseline characteristics	n	%
Total	11,056	100.0
Age group (y)		
18–22	1161	10.5
23–29	6723	60.8
30–40	3172	28.7
Index cytology		
Normal	1258	11.4
Low grade[a]	3932	35.6
High grade[b]	5125	46.4
Other	137	1.2
Missing	604	5.5
Year of diagnosis		
1998–2006	1849	16.7
2007–2012	3290	29.8
2013–2020	5917	53.5
Region, residence		
Capital Region	3142	28.4
Central Region	4503	40.7
Northern Region	1081	9.8
Zealand Region	604	5.5
Southern Region	1726	15.6

CIN2, cervical intraepithelial neoplasia grade 2.

[a] Includes atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions; [b] Includes atypical squamous cells, atypical glandular cells, high-grade squamous intraepithelial lesions, adenocarcinoma in situ, and carcinoma.

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TABLE 2
Regression and progression rates of CIN2

		Regression		Progression	
Months since CIN2 diagnosis	At risk	Events	CIF, % (95% CI)	Events	CIF, % (95% CI)
6 mo	11,056	3070	27.9 (27.0–28.7)	1658	15.1 (14.4–15.7)
12 mo	6269	2994	55.4 (54.5–56.3)	1546	29.3 (28.4–30.1)
18 mo	1617	558	60.9 (60.0–61.9)	281	32.1 (31.2–33.0)
24 mo	614	145	62.9 (61.9–63.8)	95	33.3 (32.4–34.2)

CI, confidence interval; *CIF*, cumulative incidence function; *CIN2*, cervical intraepithelial neoplasia grade 2.
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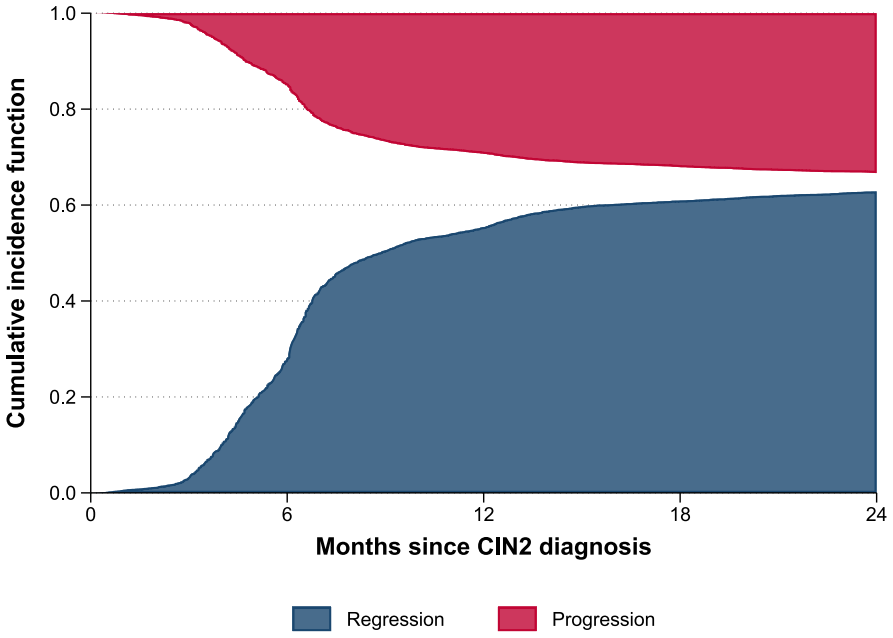
Federation of Gynaecology and Obstetrics stage was available in 21 cases (64%). None of these cases were worse than stage 2, and nearly 60% of cases were stage 1a (12 of 21).

The risk of progression within 24 months was similar in women aged 30 to 40 years compared with women aged 23 to 29 years (aRR, 0.98; 95% confidence interval [CI], 0.88–1.10), whereas women aged 18 to 22 years had a lower risk of progression than women aged 23 to 29 years (aRR, 0.80; 95% CI, 0.71–0.90) (Table 3 and Supplemental Table 4). In contrast, women with abnormal index cytology had a higher risk of progression than women with normal cytology, with the highest risks in women with high-grade index cytology (aRR, 1.58; 95% CI, 1.43–1.76) (Table 3 and Supplemental Table 5). See Supplemental Table 6 for estimates stratified by calendar year.

Regarding the risk of LEEP within 24 months of follow-up, 4109 women (37.6%) underwent LEEP (Table 4). Most women had the procedure performed within the first year where 3132 LEEPs (75.0%) were performed. Women aged 18 to 22 years at CIN2 diagnosis had 11% lower risk of LEEP than women aged 23 to 29 years (aRR, 0.89; 95% CI, 0.80–0.99). In general, women with an abnormal index cytology had an increased risk of LEEP compared with women with normal cytology, and the risk was the highest in women with a high-grade index cytology (aRR, 1.48; 95% CI, 1.35–1.63).

FIGURE
Regression and progression of CIN2 within 24 months



CIN2, cervical intraepithelial neoplasia grade 2.
Lycke. Regression and progression of cervical intraepithelial neoplasia grade 2. Am J Obstet Gynecol 2023.

Comment

Principal findings

To the best of our knowledge, this is the largest study on women undergoing active surveillance for CIN2. Within 24 months, we observed regression and progression rates of 63% and 33%. Of note, 90% of cases with regression or progression occurred within the first 12 months. In addition, our results showed that high-grade index cytology was associated with an increased risk of progression, whereas age had limited effect.

Results in the context of what is known

We found a regression rate of 63% at 24 months of follow-up, which is higher than the previously reported regression rates in the systematic reviews, that is, 50% to 57%.[2,5] However, some of the included studies used a stricter definition of regression, that is, histologic CIN1 or normal combined with cytology of normal or low grade. Thus, we did a sensitivity analysis where we used this stricter definition. This resulted in a reduction of the regression rates to 48.7% (95% CI, 47.7–49.6) within 24 months (Supplemental Figure 4 and

TABLE 3
Risk of CIN3+ within 24 months in women undergoing active surveillance for CIN2

Risk of CIN3+	Total	CIN3+ within 24 mo, n (%)	CIF, % (95% CI)	Crude RR(95% CI)	Adjusted RR (95% CI)[a]
Total	11,056	3583 (32.4)	—	—	—
Age at CIN2 diagnosis (y)					
18–22	1161	285 (24.6)	25.1 (22.6–27.6)	0.74 (0.67–0.83)	0.80 (0.71–0.90)
23–29	6723	2224 (33.1)	33.9 (32.8–35.1)	1.0 (ref)	1.0 (ref)
30–40	3172	1074 (33.9)	35.2 (33.4–36.9)	1.02 (0.96–1.09)	0.98 (0.88–1.10)
Index cytology					
Normal	1258	304 (24.2)	24.9 (22.5–27.3)	1.0 (ref)	1.0 (ref)
Low–grade[b]	3932	1086 (27.6)	28.4 (27.0–29.8)	1.14 (1.02–1.28)	1.13 (1.01–1.26)
High grade[c]	5125	1990 (38.8)	39.9 (38.6–41.3)	1.61 (1.45–1.78)	1.58 (1.43–1.76)
Missing or other	741	203 (27.4)	28.3 (25.1–31.7)	1.13 (0.97–1.32)	1.11 (0.95–1.29)

CI, confidence interval; *CIF*, cumulative incidence function; *CIN2*, cervical intraepithelial neoplasia grade 2; *CIN3+*, cervical intraepithelial neoplasia grade 3 or worse; *ref*, reference; *RR*, relative risk.

[a] Adjusted for age (continuous), index cytology (normal, low grade, high grade, and missing or other), and calendar year (1998–2006, 2007–2012, and 2013–2020); [b] Includes atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions; [c] Includes atypical squamous cells, atypical glandular cells, high-grade squamous intraepithelial lesions, adenocarcinoma in situ, and carcinoma.

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Supplemental Table 3). Hence, the higher regression rates in our main analyses may be explained by differences in outcome definition. Moreover, our regression rates are higher than those reported in previous Danish registry-based studies. However, their study results were based on the histologic results at the first follow-up visit within 10 months.[8] Finally, our definition of regression may also explain the low rate of persistent CIN2 (4%) in our primary analysis; however, when we used the strict definition, the persistence rate (18%) was comparable with the meta-analyses.[2,5] We found the highest regression rates in women aged 18 to 22 years (70%), whereas women aged 23 to 29 and 30 to 40 years had comparable regression rates, that is, 62% and 61% (Table 3 and Supplemental Table 4). Combining the results for women aged 18 to 22 and 23 to 29 years resulted in slightly higher regression rates for women <30 years (63.5%; 95% CI, 62.4–64.6) than women aged 30 to 40 years (61.3%; 95% CI, 59.5–63.0), as reported in other studies.[5,17–20]

TABLE 4
Risk of LEEP within 24 months in women undergoing active surveillance for CIN2

Risk of LEEP	Total	LEEP within 24 mo, n (%)	CIF, % (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)[a]
Total	11,056	4109 (37.2)	37.6 (36.6–38.5)	—	—
Age at CIN2 diagnosis (y)					
18–22	1161	317 (27.3)	27.6 (25.0–30.2)	0.75 (0.68–0.83)	0.89 (0.80–0.99)
23–29	6723	2455 (36.5)	37.0 (35.8–38.1)	1.0 (ref)	1.0 (ref)
30–40	3172	1337 (42.2)	42.5 (40.7–44.2)	1.23 (1.17–1.30)	0.95 (0.86–1.04)
Index cytology					
Normal	1258	360 (28.6)	28.9 (26.4–31.5)	1.0 (ref)	1.0 (ref)
Low grade[b]	3932	1267 (32.2)	32.5 (31.1–34.0)	1.13 (1.03–1.25)	1.11 (1.00–1.22)
High grade[c]	5125	2238 (43.7)	44.1 (42.8–45.5)	1.55 (1.41–1.70)	1.48 (1.35–1.63)
Missing or other	741	244 (32.9)	33.3 (29.9–36.8)	1.19 (1.04–1.36)	1.12 (0.98–1.28)

CI, confidence interval; *CIF*, cumulative incidence function; *CIN2*, cervical intraepithelial neoplasia grade 2; *IQR*, interquartile range; *LEEP*, loop electrosurgical excision procedure; *ref*, reference; *RR*, relative risk.

[a] Adjusted for age (continuous), associated cytology (normal, low grade, high grade, and missing or other), and calendar year (1998–2006, 2007–2012, and 2013–2020); [b] Includes atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions; [c] Includes atypical squamous cells, atypical glandular cells, high-grade squamous intraepithelial lesions, and carcinoma.

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Compared with the systematic reviews, our estimates of progression within 24 months are higher (33% vs 18%−22%). This may be due to stricter inclusion criteria in the included studies. As opposed to our study, many previous studies are restricted to women aged <25 or 30 years, small lesions (<50% of the cervix), or fully visualizable transformation zone, that is, transformation zone type 1 or 2.[17−21]

Clinical implications

The observed high spontaneous regression rate (63%) of CIN2 supports the use of active surveillance for up to 24 months.[7] However, as 90% of regression and progression occurred within the first year, it may be worth considering reducing the active surveillance period to 12 months. Importantly, women should be informed about this finding at CIN2 diagnosis, as it may be used for shared decision-making. Although the risk of cervical cancer within 24 months was low in our study (0.3%), women should be informed about this risk at the time of CIN2 diagnosis and may suggest a need to include risk markers in clinical counseling. One such marker could be cytology as we find that women with high-grade index cytology have a 60% higher risk of progression and a 50% higher risk of LEEP within 24 months than women with normal index cytology (Table 3). Thus, our findings support restricting active surveillance to women with less than high-grade cytology at CIN2 diagnosis.[7]

In addition, most countries restrict active surveillance to women aged <25 or <30 years.[7] Comparatively, we found similar regression rates between women aged 23 to 29 years and women aged 30 to 40 years. However, it is important to consider that the prevalence of transformation zone type 3 (TZ3) is higher in women aged >30 years. In women with TZ3, the transformation zone is retracted into the cervical canal, resulting in an increased risk of missing prevalent disease. Of note, nearly 70% of the cervical cancer cases in our study were among women aged 30 to 40 years.

Another perspective on risk stratification and shared decision-making is HPV genotyping, but currently only the Swedish and Norwegian guidelines consider HPV genotype; women with HPV type 16 (HPV16) are ineligible for active surveillance.[22,23] The importance of HPV genotyping for risk stratification is evident as studies have demonstrated that HPV16 and HPV type 18 are associated with increased risk of progression of CIN2.[5,19,21] In this context, and given that an increasing proportion will receive the HPV vaccine, it would be interesting to explore whether HPV vaccination status at CIN2 diagnosis may be used for risk stratification moving forward.[24,25] Here, HPV-vaccinated women entered screening in 2016. Hence, the even higher regression rates in the latter study period, 2013−2020, may be due to an effect of the HPV vaccination (Supplemental Table 3). Unfortunately, we had no information on HPV genotype and HPV vaccination status.

In summary, findings from our study and previous studies indicate that information on index cytology, visibility of the transformation zone, HPV genotype, and HPV vaccination may be used to risk stratify women, hereby strengthening shared decision-making.

Research implications

Our study and previous studies demonstrate high regression rates of CIN2 within 24 months, but not much is known about the long-term risk of cervical cancer in women undergoing active surveillance for CIN2. Several studies have demonstrated that women who have had a LEEP performed because of CIN3 have a long-lasting increased risk of cervical cancer compared with women without cervical precursor lesions.[26,27] Given that women undergoing a LEEP have the lesion and the underlying HPV infection removed surgically, and because several studies have demonstrated that HPV may establish latency, future studies should explore whether women undergoing active surveillance have an increased risk of cervical cancer in the longer term, even despite initial regression. This information will be important in the clinical counseling of women diagnosed with CIN2 moving forward.

Strengths and limitations

One of the main strengths of this large study is the use of nationwide individual-level data from high-quality Danish healthcare registries.[11,12,14,15] This allowed for the inclusion of all women undergoing active surveillance for CIN2 in Denmark. Hence, our study population was not selected on the basis of age or cytology as opposed to most of the previous studies on CIN2, wherefore we expected a limited selection bias.[2,5] However, we cannot completely rule out selection bias as women undergoing active surveillance may have smaller lesions than women with CIN2 treated with immediate LEEP.

In addition, this study has limitations. First, the CIN2 diagnosis is equivocal and has high intra- and interobserver variations,[28] wherefore regression and progression may reflect histologic misclassification rather than the natural course. Notwithstanding, our results are clinically relevant as we used diagnostic information available for CIN2 management decisions in a real-world clinical setting. Second, our definition of active surveillance may have introduced selection bias as we had to rely on records in the Danish Pathology Registry. Thus, some women in the noncompliant group may have had a follow-up visit with colposcopy without collection of biopsies. However, as the collection of random biopsies was implemented nationwide in 2013, we expected a limited effect, particularly for women included in the most recent study period (2013−2020).[9,29] Third, we cannot rule out residual confounding as we had no information on colposcopic findings, number of biopsies, HPV genotype, HPV vaccination status, or lifestyle factors, such as smoking. Fourth, we expect some verification bias as women who progress undergo LEEP, whereas women with persistent CIN2 or regression are offered repeated colposcopy with biopsies or cytology, respectively. Moreover, we expect this bias to be limited in the most recent study period because of the recommendation of 4 biopsies.

Conclusions

Our results on 11,056 women undergoing active surveillance for CIN2 showed that 63% of women spontaneously regressed

within 24 months and that 33% of women progressed to CIN3+. Progression was associated with high-grade index cytology, whereas age had limited effect. Our results support the use of active surveillance for CIN2 for women who are planning for future pregnancy, but information on the long-term consequences of active surveillance is needed to better inform women about the pros and cons of active surveillance. ■

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This study was performed on the remote servers of the Danish Health Data Authority. Because of the Danish legislation, individual-level data cannot be shared by the authors, and cell counts of <5 cannot be reported. Data can be accessed after application to the Danish Health Data Authority.

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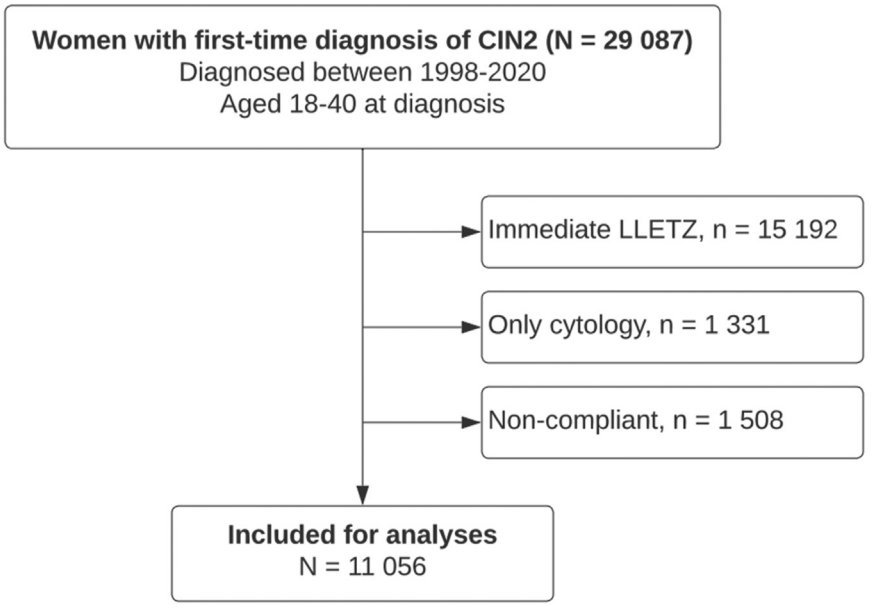
SUPPLEMENTAL FIGURE 1
Flowchart of the study population



CIN2, cervical intraepithelial neoplasia grade 2; *LLETZ*, large loop excision of the transformation zone.

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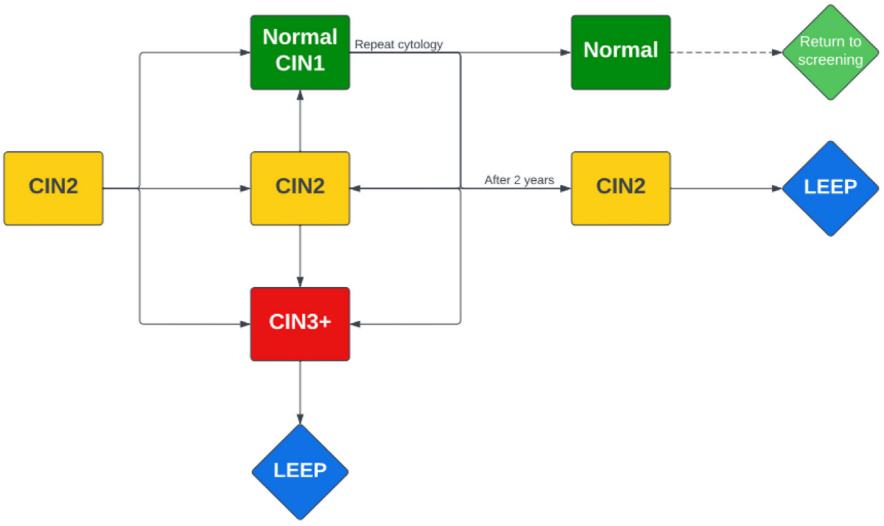
SUPPLEMENTAL FIGURE 2
Active surveillance of CIN2 in Denmark



CIN1-3+, cervical intraepithelial neoplasia grades 1, 2, and 3 or worse; *LEEP*, loop electrosurgical excision procedure.

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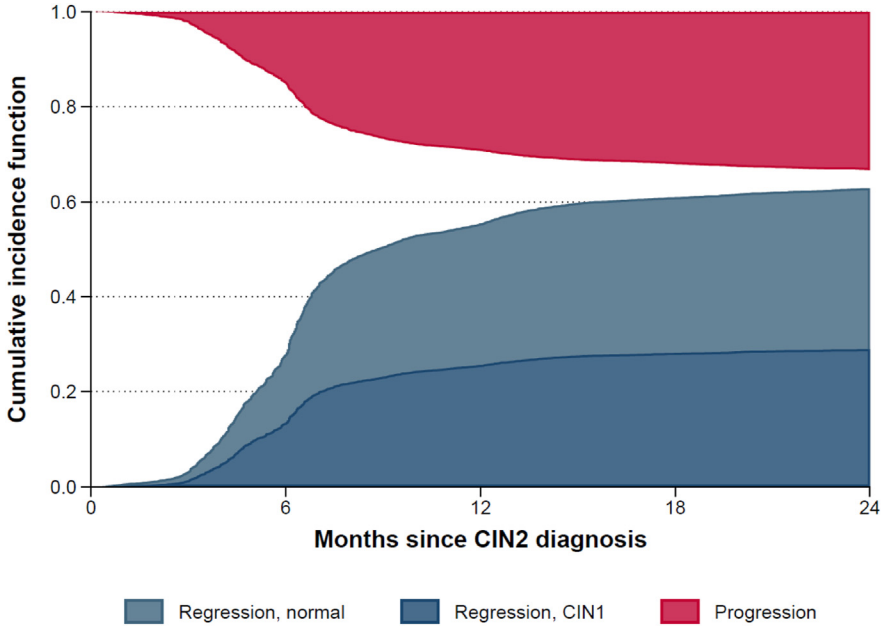
SUPPLEMENTAL FIGURE 3
Regression of CIN2 divided into regression to normal or CIN1



CIN1-2, cervical intraepithelial neoplasia grades 1 and 2.

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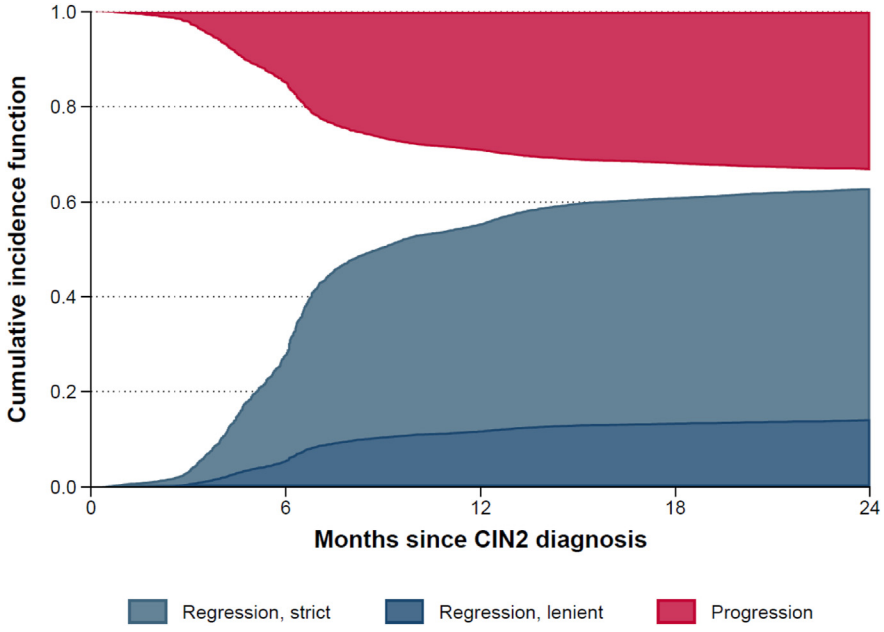
SUPPLEMENTAL FIGURE 4
Regression of CIN2 divided into strict or lenient regression



CIN2, cervical intraepithelial neoplasia grade 2.

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SUPPLEMENTAL TABLE 1
Risk of regression to normal (histologic) or CIN1 (histologic)

Months since CIN2 diagnosis	At risk	Regression to histologic normal		Regression to histologic CIN1	
		Events	CIF, % (95% CI)	Events	CIF, % (95% CI)
6 mo	11,056	1589	14.4 (13.8–15.1)	1481	13.4 (12.8–14.1)
12 mo	6269	1671	29.8 (28.9–30.7)	1323	25.6 (24.8–26.4)
18 mo	1617	302	32.8 (31.9–33.7)	256	28.2 (27.3–29.0)
24 mo	614	85	33.9 (33.0–34.8)	60	28.9 (28.1–29.8)

CI, confidence interval; *CIF*, cumulative incidence function; CIN1-2, cervical intraepithelial neoplasia grades 1 and 2.

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SUPPLEMENTAL TABLE 2
The associated cytology at date of regression (±7 days from regression date)

Associated cytology	n (%)
Total	6767 (100)
HSIL or AIS	169 (2.5)
AGC or ASC-H	83 (1.2)
LSIL	382 (5.6)
ASCUS	362 (5.3)
Normal	4511 (66.7)
Other	130 (1.9)
Missing	1130 (16.7)

AGC, atypical glandular cell; *AIS*, adenocarcinoma in situ; *ASC-H*, atypical squamous cell; *ASCUS*, atypical squamous cell of undetermined significance; *HSIL*, high-grade squamous intraepithelial lesion; *LSIL*, low-grade squamous intraepithelial lesion.

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SUPPLEMENTAL TABLE 3
Risk of regression according to strict[a] or lenient[b] criteria

		Strict, regression[a]		Lenient, regression[b]	
Variable	At risk	Events	CIF, % (95% CI)	Events	CIF, % (95% CI)
6 mo	11,056	2460	22.3 (21.6–23.1)	610	5.5 (5.1–6.0)
12 mo	6269	2309	43.6 (42.6–44.5)	685	11.8 (11.2–12.5)
18 mo	1617	395	47.5 (46.5–48.4)	163	13.5 (12.8–14.1)
24 mo	614	91	48.7 (47.7–49.6)	54	14.2 (13.5–14.9)

CI, confidence interval; *CIF*, cumulative incidence function; *CIN1*, cervical intraepithelial neoplasia grade 1.

[a] Histologic CIN1 or normal and associated cytology of less than or equal to low grade (low-grade squamous intraepithelial lesions or atypical squamous cells of undetermined significance or normal); [b] Histologic CIN1 or normal and other associated cytology (high-grade squamous intraepithelial lesions or adenocarcinoma in situ, atypical glandular cells or atypical squamous cells, other, or missing).

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SUPPLEMENTAL TABLE 4
Risk of regression and progression of CIN2 stratified by age group

		Regression		Progression	
Months since CIN2 diagnosis	At risk	Events	CIF, % (95% CI)	Events	CIF, % (95% CI)
Age group					
18–22 y					
6 mo	1161	369	31.9 (29.2–34.6)	157	13.6 (11.7–15.6)
12 mo	630	349	62.4 (59.5–65.1)	99	22.2 (19.9–24.7)
18 mo	169	66	68.7 (65.9–71.3)	23	24.4 (22.0–27.0)
24 mo	67	11	69.7 (66.9–72.3)	6	25.1 (22.6–27.6)
23–29 y					
6 mo	6723	1828	27.3 (26.2–28.3)	965	14.4 (13.6–15.2)
12 mo	3905	1784	54.2 (53.0–55.4)	993	29.4 (28.3–30.5)
18 mo	1066	378	60.2 (59.0–61.4)	194	32.5 (31.4–33.6)
24 mo	408	106	62.4 (61.2–63.6)	69	33.9 (32.7–35.0)
30–40 y					
6 mo	3172	873	27.7 (26.2–29.3)	536	17.0 (15.7–18.3)
12 mo	1734	861	55.5 (53.7–57.2)	454	31.7 (30.1–33.3)
18 mo	382	114	59.6 (57.8–61.3)	64	34.0 (32.4–35.7)
24 mo	139	30	61.3 (59.5–63.0)	20	35.2 (33.4–36.9)

CI, confidence interval; *CIF*, cumulative incidence function; *CIN2*, cervical intraepithelial neoplasia grade 2.

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SUPPLEMENTAL TABLE 5

Risk of regression and progression of CIN2 stratified by index cytology

Months since CIN2 diagnosis	At risk	Regression		Progression	
		Events	CIF, % (95% CI)	Events	CIF, % (95% CI)
Index cytology					
Normal					
6 mo	1258	373	29.7 (27.2–32.3)	118	9.4 (7.9–11.1)
12 mo	763	426	64.0 (61.3–66.6)	149	21.4 (19.2–23.7)
18 mo	176	76	70.5 (67.9–73.0)	28	23.9 (21.5–26.3)
24 mo	57	15	72.1 (69.5–74.6)	9	24.9 (22.5–27.3)
Low grade[a]					
6 mo	3932	1162	29.6 (28.2–31.1)	493	12.6 (11.6–13.6)
12 mo	2257	1147	59.2 (57.7–60.8)	482	25.0 (23.7–26.4)
18 mo	593	232	65.7 (64.2–67.2)	84	27.4 (26.0–28.8)
24 mo	211	46	67.5 (65.9–68.9)	27	28.4 (27.0–29.8)
High grade[b]					
6 mo	5125	1245	24.4 (23.2–25.6)	930	18.2 (17.2–19.3)
12 mo	2923	1250	49.2 (47.9–50.6)	851	35.1 (33.8–36.4)
18 mo	764	227	54.1 (52.7–55.5)	153	38.4 (37.1–39.8)
24 mo	310	76	56.3 (54.9–57.7)	53	39.9 (38.6–41.3)
Other or missing					
6 mo	741	290	39.4 (35.9–43.0)	117	15.9 (13.4–18.6)
12 mo	326	171	63.2 (59.6–66.6)	64	24.8 (21.7–28.0)
18 mo	84	23	66.7 (63.1–70.0)	16	27.2 (24.0–30.5)
24 mo	36	8	68.2 (64.6–71.5)	6	28.3 (25.1–31.7)

CI, confidence interval; *CIF*, cumulative incidence function; *CIN2*, cervical intraepithelial neoplasia grade 2.

[a] Includes atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions; [b] Includes atypical squamous cells, atypical glandular cells, high-grade squamous intraepithelial lesions, and carcinoma.

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SUPPLEMENTAL TABLE 6

Risk of regression and progression of CIN2 stratified by calendar year

		Regression		Progression	
Months since CIN2 diagnosis	At risk	Events	CIF, % (95% CI)	Events	CIF, % (95% CI)
Calendar year					
1998–2006					
6 mo	1849	686	37.3 (35.1–39.6)	460	25.0 (23.1–27.0)
12 mo	687	298	53.8 (51.5–56.0)	197	35.9 (33.7–38.1)
18 mo	184	42	56.3 (54.0–58.5)	20	37.1 (34.9–39.3)
24 mo	91	8	57.0 (54.7–59.3)	9	37.9 (35.6–40.1)
2007–2012					
6 mo	3290	1182	36.1 (34.4–37.7)	635	19.4 (18.1–20.8)
12 mo	1452	655	56.4 (54.7–58.1)	336	29.8 (28.3–31.4)
18 mo	431	143	61.2 (59.5–62.9)	75	32.3 (30.7–34.0)
24 mo	180	44	62.8 (61.1–64.5)	26	33.4 (31.8–35.1)
2013–2020					
6 mo	5917	1202	20.4 (19.3–21.4)	563	9.5 (8.8–10.3)
12 mo	4130	2041	55.3 (54.1–56.6)	1 013	26.9 (25.8–28.0)
18 mo	1002	373	62.3 (61.0–63.5)	186	30.4 (29.2–31.6)
24 mo	343	97	64.6 (63.4–65.9)	62	31.8 (30.6–33.0)

CI, confidence interval; *CIF*, cumulative incidence function; *CIN2*, cervical intraepithelial neoplasia grade 2.

Lycke. Regression and progression of cervical intraepithelial neoplasia grade 2. Am J Obstet Gynecol 2023.