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Conservative management of women with cervical intraepithelial neoplasia grade 2 in Denmark: a cohort study

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Objective Assess the progression, persistence, and regression of cervical intraepithelial neoplasia grade 2 (CIN2) after new guidelines on conservative treatment, compared with previous practice.

Design Nationwide register-based cohort study.

Setting Denmark.

Population Women aged 18–44 years diagnosed with CIN2 on biopsy: 6721 in 2008–2011 and 6399 in 2014–2017.

Methods Register data were retrieved from before (2008–2011) and after (2014–2017) the introduction of new guidelines. Histology diagnoses at second visit were used to assess progression (CIN3+), persistence (CIN2), or regression (CIN1/normal).

Main outcome measures Proportion of CIN2 by type of management. Relative risk (RR) and corresponding 95% confidence intervals (95% CIs) for progression, persistence, and regression at second visit in 2014–2017, versus 2008–2011.

Results The proportion of CIN2 managed conservatively increased from 29.6% in 2008–2011 to 53.3% in 2014–2017 (RR 1.81, 95% CI 1.73–1.89). Time to second visit increased by 2 months. Regression increased from 23.5 to 30.2% (RR 1.29, 95% CI 1.22–1.36), whereas persistence and progression decreased, from 42.6 to 34.9% (RR 0.82, 95% CI 0.78–0.86) and from 28.0 to 22.8% (RR 0.81, 95% CI 0.77–0.86), respectively. In 2008–2011, women managed conservatively had a regression rate of 41.8%, persistence rate of 40.9%, and progression rate of 16.6%. In 2014–2017, these rates were 46.7, 35.5, and 17.1%, respectively.

Conclusion After implementation of the new guidelines, conservative management became more frequent, and is now used for more than half of women with CIN2. Lesion regression became more frequent, now experienced by 47% of women managed conservatively. Similar regression rates were seen in women younger and older than 30 years, suggesting that conservative management is justifiable for women of childbearing age.

Keywords Cervical dysplasia, CIN2, conservative management, histology diagnoses, regression potential.

Tweetable abstract In Denmark, more than half of women with CIN2 are managed conservatively, and half of these women experience lesion regression.

Linked article This article is commented on by AM Mills and LR Duska, p. 737 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16153.

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Introduction

In Denmark, women aged 23–49 years are invited to cervical screening with cytology every third year, and women aged 50–65 years are invited every fifth year. A human papillomavirus (HPV) DNA test is offered to women aged 60 years and above.[1] Since the beginning of screening, the incidence of cervical cancer has dropped from 44.4 per 100 000 women in 1966 to 8.9 per 100 000 women in 2016.[2] From the early 1990s, conisations were increasingly performed with a loop electrosurgical excision procedure (LEEP).[3] This treatment is less invasive than earlier treatment with cold-knife conisation and laser treatment,[4] although there is still a risk of side effects such as bleeding, infection, and obstetric adverse events, e.g. preterm birth.[5–8] With these possible side effects it is highly desirable to avoid conisation, especially for women who wish for a future pregnancy.

In Denmark, the first guideline on cervical intraepithelial neoplasia (CIN) treatment was issued in 2001 by the

Danish Society of Obstetrics and Gynaecology (DSOG).[3] Conisation was recommended for women with CIN2+, whereas the recommendation for CIN1 or normal histology was repeated cytology after 12 months. The guideline was updated in 2012.[9] For CIN2, conisation was still recommended for postmenopausal women and for women with no wish for a future pregnancy; however, for women with CIN2 who wish for a future pregnancy the recommendation was changed from immediate conisation to conservative management with a biopsy 6 months later, and this could be repeated every 6 months for up to 2 years.

Conservative management relies on the tendency of the lesion to regress. For women managed conservatively, a recent systematic review and meta-analysis found a CIN2 regression rate after 6 months of 52%, and a regression rate of 50% after 24 months. Regression was most frequent for women under the age of 30 years.[10] This suggested that conservative management is justifiable, allowing half of women with CIN2 to be spared conisation and the risk of overtreatment. Most of the 36 studies included in the review were small, however, with fewer than 100 women, and the heterogeneity was substantial for most of the outcomes assessed. The aim of this study was to investigate the regression, persistence, and progression of CIN2 in 13 000 women from Denmark, with half of them recruited when immediate conisation of CIN2 was recommended, and with half of them recruited after implementation of the new guideline that included the possibility for conservative management.

Methods

Study population

We conducted a population-based cohort study using national health register data. In Denmark, the general practitioner collects the routine screening sample. This liquid-based cytology sample is sent to the local pathology department for analysis. If the sample is severely or repeatedly abnormal, the woman is referred to the gynaecologist for colposcopy, biopsy, and cytology, and further follow-up and treatment if necessary. We refer to the Danish screening guidelines for further details.[1] In 2018, of the 795 039 Danish women eligible for screening, 573 027 (72%) women aged 23–44 years had a screening sample collected.[11]

The new guideline on the management of CIN2 was developed in 2012, and it was available for the gynaecologists from the beginning of 2013. We studied women diagnosed with CIN2 on biopsies in two time periods: 2008–2011 as a reference period, when the old guideline was used, and 2014–2017, which was at least 1 year after implementation of the new guideline.

The requisition date, i.e. the date the biopsy was taken by the gynaecologist, was used as the time of diagnosis. If there were more than one CIN2 diagnoses, we used the first one as the baseline. Within the same sample, the most severe diagnosis was used. All women had to be living in Denmark for the 3 years prior to their first CIN2 diagnosis, and we excluded women who had any histological diagnoses during these 3 years. We restricted the age to 18–44 years because women in this age group may have a wish to retain their fertility. Age was calculated from the date of birth and to the requisition date at first CIN2 diagnosis, and then stratified: ≤20, 21–25, 26–30, 31–35, 36–40, and 41–44 years. Addresses were used to divide women into the five Danish geographical regions. The women were followed up until their second visit within 10 months. This time period was chosen because we wanted to investigate the guideline recommendation of 6 months and allowed for some delay in the diagnostics. Whether the second visit was for a biopsy, a conisation, or cytology only, or if there was no second visit, was recorded. The diagnoses at the second visit were also recorded. Conisations were primarily performed with LEEP. Cryotherapy and thermal ablation have not been used as standard care in Denmark, at least not during the last three decades.

Data sources and outcomes

The project was approved by the Danish Data Inspective Agency (514-0038/18-3000), which provides ethical approval for register-based projects. Data on women were extracted from the Danish Pathology Register and Central Population Register.[12,13] This included vital status, emigration, addresses, date of birth, histology and cytology diagnoses, conisation, if performed, and the requisition date. All data were linked via the unique personal identification number given to all persons born or settled in Denmark.

In Denmark, coding with Systematized Nomenclature of Medicine is used for the classification of pathological specimens, and all specimens are assigned a T-code for topography and an M-code for morphology. In case of more than one M-code per sample, the worst diagnosis was chosen.[14] Histology diagnoses were classified into: cancer, adenocarcinoma in situ (AIS), CIN3, CIN2, CIN1, normal, unsatisfactory, and 'other'.[15] Progression was defined as CIN3+ (including cancer, AIS, and CIN3), persistence as CIN2, and regression as CIN1 or normal at the second visit. For women undergoing conisation shortly after the CIN2 diagnosis, it might not be reasonable to use the term 'progression to CIN3+' in a biological sense. In our study 'progression to CIN3+' therefore means only that the diagnosis changed from CIN2 at the index visit to CIN3+ at the second visit. This may include cases where the first biopsy had been insufficient to assess the true diagnosis, for instance. For cytology diagnoses, we distinguished between atypical squamous cells of undetermined

significance or worse (ASCUS+), normal, unsatisfactory, and 'other'. In both groups (histology and cytology diagnoses), 'other' refers to all M-codes non-classifiable according to the other categories of the group.

Statistical analyses

We calculated the proportion of women with CIN2 and diagnosed with progression, persistence, or regression at the second visit. This calculation was made for all women with CIN2, and then separately for those undergoing immediate conisation and for those managed conservatively. Comparison between individual outcomes in the two populations (2014–1017 versus 2008–2011) was made by computing relative risks (RRs), risk differences, and corresponding 95% confidence intervals (95% CIs) with a multinomial logistic regression model.

Data processing and statistical analyses were performed using SAS 9.4 (TS1M5) and the macros NLMEANS 1.04 and NLESTIMATE 1.51. Plots were generated using R 3.5.1 and the GGPLOT 2 package.

Patient and public involvement

There was no patient involvement in the study design, in the development of outcome measures, or in the conduct of the study. No core outcome set has been used. There is no plan on disseminating the results directly to laypeople, but the results will be communicated to gynaecologists at annual meetings and in local departments.

Funding

The study was supported financially from the Danish Cancer Society (130-A8279-15-S38) and the Fund for Development of Evidence Based Medicine in Private Specialized Practices (15/869).

Results

Study population

In total, 6721 women aged 18–44 years at diagnosis were diagnosed for the first time with CIN2 in 2008–2011, with the number of diagnoses increasing slightly (8%) over the 4-year period (Table 1). At their second visit, 29.6% of these women had a biopsy, 65% were treated with a conisation, 2.9% had a cytology only, and 2.5% did not have a second visit. In total, 6399 women were diagnosed with CIN2 in 2014–2017, with the number of diagnoses decreasing in total by 21% over the 4-year period. At the second visit, 53.3% of these women had a biopsy, 35.4% were treated with a conisation, 3.1% had a cytology, and 7.9% did not have a second visit (Table 1). The mean age of all women with a CIN2 diagnosis was fairly equal in the two periods: 29.76 and 30.36 years, respectively. Women treated with conisation were older, with an average age of 31.08 years in 2008–2011 and 34.55 years in 2014–2017.

The mean time from diagnosis to second visit increased overall by almost 2 months (52.2 days) from 2008–2011 to 2014–2017, with the largest increase for women who had a biopsy (137.02 versus 173.43 days, respectively) and for cytology only at the second visit (146.96 versus 191.81, respectively) (Table 1).

In both periods about two-fifths of the women lived in the Capital Region, and about one-fifth of the women lived in the Central and Southern regions, respectively. The Central Region already had a frequent use of biopsies (60%) before the new guideline. Region Zealand had a very low percentage of biopsies before the new guideline, and even though the proportion of women with biopsy increased significantly, Region Zealand was the only region that continued to have a higher proportion of women treated with conisation than follow-up with biopsies after the new guideline (Table 1).

The proportion of women with a biopsy at second visit increased by 81% from before to after the implementation of the new guideline (RR 1.81, 95% CI 1.73–1.89; RD 24.0, 95% CI 22.3–25.6), and the proportion of women with a conisation was reduced by 45% (RR 0.55, 95% CI 0.52–0.57; RD −29.5, 95% CI −31.2 to − 27.9) (Table 2). A fairly similar proportion of women were followed up with cytology only, 2.9 versus 3.1%, but the proportion of women with no second visit increased from 2.9 to 7.9%. Together, the risk of not being followed up with histology and/or conisation in due time doubled (RR 2.02, 95% CI 1.77–2.26; (RD 5.6, 95% CI 4.6–6.5).

Diagnoses at second visit

Compared with women diagnosed with CIN2 in 2008–2011, women with CIN2 in 2014–2017 had lesions that were less likely to persist or progress and were more likely to regress. The proportion of women diagnosed with CIN3+ and CIN2 at the second visit decreased from 28.0 and 42.6%, respectively, in the early period to 22.8 and 34.9%, respectively, in the late period. Progression was reduced by 19% (RR 0.81, 95% CI 0.77–0.86; RD −5.2, 95% CI −6.7 to –3.7) and persistence was reduced by 18% (RR 0.82, 95% CI 0.78–0.86; RD −7.7, 95% CI −9.3 to − 6.0). The number of cervical cancers showed a non-significant decrease from 14 cases (0.21%) in the early period to eight cases (0.13%) in the late period (RR 0.60, 95% CI 0.25–1.43). In both time periods, cancers occurred primarily in the conisation group, but the division could not be reported because of the small numbers. Meanwhile, the proportion of women diagnosed with CIN1 or normal histology increased from 23.5 to 30.3% (RR 1.29, 95% CI 1.22–1.36; RD 6.8, 95% CI 5.3–8.3) (Table 2).

In women with biopsy at the second visit, the proportion of women progressing was similar for the two time periods (16.6 versus 17.1%), but the proportion of persistence was higher in 2008–2011 (40.9 versus 35.5%) and the

Table 1. Number of women diagnosed with cervical intraepithelial neoplasia grade 2 (CIN2) in 2008–2011 and 2014–2017 by second-visit procedure (within 10 months), year of recruitment, age at diagnosis, days to second visit by age, region, and days to second visit by region

Second-visit procedure	2008–2011					2014–2017				
	Biopsy	Conisation	Cytology	No 2nd visit	Total	Biopsy	Conisation	Cytology	No 2nd visit	Total
Total number of women, *n* (%)	1989 (29.6)	4365 (65.0)	196 (2.9)	171 (2.5)	6721 (100)	3427 (53.6)	2266 (35.4)	199 (3.1)	507 (7.9)	6399 (100)
Number of women, *n* (%)										
2008/2014	373 (23.7)	1116 (70.8)	54 (3.4)	34 (2.2)	1577 (23.5)	964 (53.5)	645 (35.8)	57 (3.2)	136 (7.6)	1802 (28.2)
2009/2015	503 (27.5)	1234 (67.5)	49 (2.7)	42 (2.3)	1828 (27.2)	831 (51.7)	591 (36.8)	47 (2.9)	137 (8.5)	1606 (25.1)
2010/2016	513 (31.7)	1023 (63.2)	41 (2.5)	41 (2.5)	1618 (24.1)	848 (53.7)	565 (35.9)	46 (2.9)	117 (7.4)	1573 (24.6)
2011/2017	600 (35.3)	992 (58.4)	52 (3.1)	54 (3.2)	1698 (25.3)	787 (55.5)	465 (32.8)	49 (3.5)	117 (8.3)	1418 (22.2)
Mean age at diagnosis, years (SD)	27.2 (5.4)	31.1 (6.6)	27.1 (5.8)	28.9 (6.5)	29.8 (6.5)	27.9 (5.5)	34.6 (6.3)	28.8 (6.1)	28.7 (5.3)	30.4 (6.6)
Age at diagnosis, *n* (%)										
≤20	95 (42.2)	107 (47.6)	15 (6.7)	8 (3.6)	225 (3.4)	83 (81.4)	7 (6.7)	7 (6.7)	5 (4.9)	102 (1.6)
21–25	822 (43.0)	953 (49.8)	81 (4.2)	56 (2.9)	1912 (28.5)	1316 (74.5)	228 (12.9)	64 (3.6)	158 (9.0)	1766 (27.6)
26–30	609 (32.6)	1154 (61.8)	53 (2.8)	51 (2.7)	1867 (27.8)	1093 (61.5)	427 (24.0)	61 (3.4)	196 (11.0)	1777 (27.8)
31–35	275 (21.9)	929 (74.0)	26 (2.1)	25 (2.0)	1255 (18.7)	524 (46.5)	481 (42.7)	36 (3.2)	85 (7.6)	1126 (17.6)
36–40	130 (14.4)	745 (82.3)	14 (1.6)	16 (1.8)	905 (13.5)	278 (28.5)	628 (64.4)	20 (2.1)	49 (5.0)	975 (15.2)
41–44	58 (10.4)	477 (85.6)	7 (1.3)	15 (2.7)	557 (8.3)	133 (20.4)	495 (75.8)	11 (1.7)	14 (2.1)	653 (10.2)
Mean time to 2nd visit, days (SD)										
≤20	140.1 (44.1)	43.7 (27.0)	146.8 (75.7)	–	–	181.9 (56.1)	37.3 (13.4)	154.4 (43.0)	–	–
21–25	143.3 (48.8)	39.1 (26.5)	154.2 (76.0)	–	–	175.8 (46.7)	42.9 (37.3)	186.9 (52.0)	–	–
26–30	136.6 (51.5)	37.7 (25.3)	151.6 (76.1)	–	–	174.0 (48.0)	41.8 (29.9)	198.4 (64.8)	–	–
31–35	134.4 (51.5)	38.2 (26.1)	116.4 (75.0)	–	–	172.6 (48.7)	44.0 (32.4)	195.4 (70.2)	–	–
36–40	118.7 (53.3)	42.2 (28.7)	134.5 (68.9)	–	–	167.9 (57.0)	45.2 (31.6)	206.2 (51.7)	–	–
41–44	100.7 (60.1)	38.4 (23.6)	166.6 (84.7)	–	–	154.6 (60.1)	45.0 (34.0)	169.5 (56.4)	–	–
All	137.0 (51.2)	39.1 (26.2)	147.0 (75.9)	–	72.1 (60.0)	173.4 (49.3)	44.0 (32.6)	191.8 (60.0)	–	124.3 (77.3)
Region of residence, *n* (%)										
Northern Region	123 (20.9)	431 (73.1)	22 (3.7)	14 (2.4)	590 (8.8)	458 (60.4)	208 (27.4)	39 (5.2)	53 (7.0)	758 (11.9)
Central Region	1030 (62.1)	500 (30.1)	70 (4.2)	60 (3.6)	1660 (24.7)	851 (67.4)	272 (21.5)	33 (2.6)	107 (8.5)	1263 (19.7)
Southern Region	286 (24.3)	788 (66.8)	59 (5.0)	46 (3.9)	1179 (17.5)	585 (48.9)	479 (40.1)	41 (3.4)	91 (7.6)	1196 (18.7)
Zealand	66 (11.4)	492 (85.1)	8 (1.4)	12 (2.1)	578 (8.6)	234 (30.6)	450 (58.9)	29 (3.8)	51 (6.7)	764 (11.9)
Capital	484 (17.8)	2154 (79.4)	37 (1.4)	39 (1.4)	2714 (40.4)	1299 (53.7)	857 (35.4)	57 (2.4)	205 (8.5)	2418 (37.8)
Mean time to 2nd visit, days (SD)										
Northern Region	150.3 (58.4)	44.7 (26.8)	20.1 (71.9)	–	–	180.1 (46.8)	69.5 (46.9)	166.0 (63.4)	–	–
Central Region	139.6 (37.1)	50.8 (34.0)	139.6 (37.1)	–	–	185.2 (41.1)	50.8 (34.0)	192.8 (49.1)	–	–
Southern	149.9 (59.0)	44.6 (24.6)	171.6 (78.5)	–	–	176.0 (45.3)	49.2 (32.0)	194.3 (50.4)	–	–
Region Zealand	124.7 (74.1)	41.9 (26.1)	172.6 (70.8)	–	–	164.2 (57.1)	40.1 (28.5)	188.5 (57.4)	–	–
Capital	122.3 (61.5)	32.7 (23.0)	131.9 (54.3)	–	–	163.9 (53.1)	34.8 (25.1)	208.8 (66.3)	–	–

Table 2. Diagnoses at second visit by second-visit procedure. Relative risk (2014–2017 versus 2008–2011) with 95% CIs

	2008–2011 *n* = 6721 (%)	2014–2017 *n* = 6399 (%)	RR (95% CI)
Second visit procedure			
Biopsy	1989 (29.6)	3427 (53.6)	1.81 (1.73–1.89)
Conisation	4365 (65.0)	2266 (35.4)	0.55 (0.52–0.57)
Cytology/no second visit	367 (5.5)	706 (11.0)	2.02 (1.77–2.26)
Histological diagnosis			
Cervical intraepithelial neoplasia grade 1+2+3 (CIN1 + CIN2 + CIN3)	5606 (83.4)	4572 (71.4)	
Normal	716 (10.7)	1056 (16.5)	
Other/unsatisfactory	32 (0.5)	65 (1.0)	
Total	6354 (94.5)	5693 (89.0)	
Cytological (if no histology)			
High-grade squamous intraepithelial lesion (HSIL)	42 (0.6)	30 (0.5)	
Atypical squamous cells of undetermined significance or worse (ASCUS)/low-grade squamous intraepithelial lesion (LSIL)	63 (0.9)	57 (0.9)	
Normal	79 (1.2)	105 (1.6)	
Other/unsatisfactory	12 (0.2)	7 (0.1)	
Total	196 (2.9)	199 (3.1)	
No second visit	171 (2.5)	507 (7.9)	
Overall			
Progression (=CIN3+)	1881 (28.0)	1457 (22.8)	0.81 (0.77–0.86)
Persistence (=CIN2)	2862 (42.6)	2233 (34.9)	0.82 (0.78–0.86)
Regression (=CIN1 + normal)	1579 (23.5)	1938 (30.3)	1.29 (1.22–1.36)
Undefined*	228 (3.4)	264 (4.1)	1.22 (1.00–1.43)
No second visit	171 (2.5)	507 (7.9)	3.11 (2.58–3.64)
Conisation			
Progression	1550 (35.5)	872 (38.5)	
Persistence	2049 (46.9)	1018 (44.9)	
Regression	747 (17.1)	339 (15.0)	
Undefined*	19 (0.4)	37 (1.6)	
Total	4365 (100)	2266 (100)	
Biopsy			
Progression	331 (16.6)	585 (17.1)	
Persistence	813 (40.9)	1215 (35.5)	
Regression	832 (41.8)	1599 (46.7)	
Undefined*	13 (0.7)	28 (0.8)	
Total	1989 (100)	3427 (100)	

*Other/unsatisfactory or cytology at second visit.

proportion of regression was higher in 2014–2017 (41.8 versus 46.7%) (Table 2). Women managed conservatively after the implementation of the new guideline had a regression rate of 46.7%, a persistence rate of 35.5%, and a progression rate of 17.1% (Table 2).

In both time periods, about three-quarters of the women with a biopsy at the second visit were ≤30 years of age (Table 3). The distribution of diagnoses was similar for women younger and older than 30 years of age. In particular, statistically significant differences were not observed in the regression rates between the two age groups. Namely, in 2008–2011 the CIN2 lesions regressed in 42.1% of women aged ≤30 years and in 40.8% of women aged >30 years (RR 0.97, 95% CI 0.84–1.08), whereas in 2014–2017 these proportions were 47.1 and 45.5%, respectively (RR 0.96, 95% CI 0.89–1.04).

Discussion

Main findings

In the present register-based study from Denmark, we investigated the impact of a new national guideline for the conservative management of CIN2 on the management and follow-up diagnoses of women with CIN2.

First, we observed that the proportion of all women with CIN2 with a biopsy only at their second visit to the gynaecologist almost doubled (29.6 versus 53.6%; Table 1). Second, the average time from diagnosis to second visit

Table 3. Progression, persistence, and regression of cervical intraepithelial neoplasia grade 2 (CIN2) by age and second-visit procedure

	2008-2011		2014-2017	
	≤30 years	>30 years	≤30 years	>30 years
CIN2 with biopsy at second visit (%)	1989 (29.6)		3427 (53.6)	
	1526 (76.7)	463 (23.3)	2492 (72.7)	935 (27.3)
Histology diagnoses (%)				
CIN1	353 (23.1)	86 (18.6)	494 (19.8)	182 (19.5)
Normal	290 (19.0)	103 (22.3)	680 (27.3)	243 (26.0)
Progression (=CIN3+)	243 (15.9)	88 (19.0)	438 (17.6)	147 (15.7)
Persistence (=CIN2)	635 (41.6)	178 (38.4)	865 (34.7)	350 (37.4)
Regression (=CIN1 + normal)	643 (42.1)	189 (40.8)	1174 (47.1)	425 (45.5)
Undefined*	5 (0.3)	8 (1.7)	15 (0.6)	13 (1.4)
CIN2 with conisation at second visit (%)	4365 (65.0)		2266 (35.4)	
	2214 (50.7)	2151 (49.3)	662 (29.2)	1604 (70.8)
Histology diagnoses (%)				
CIN1	230 (10.4)	194 (9.0)	51 (7.7)	155 (9.7)
Normal	151 (6.8)	172 (8.0)	35 (5.3)	98 (6.1)
Progression (=CIN3+)	761 (34.4)	789 (36.7)	278 (42.0)	594 (37.0)
Persistence (=CIN2)	1060 (47.9)	989 (46.0)	291 (44.0)	727 (45.3)
Regression (=CIN1 + normal)	381 (17.2)	366 (17.0)	86 (13.0)	253 (15.8)
Undefined*	12 (0.5)	7 (0.3)	7 (1.1)	30 (1.9)

*Other/unsatisfactory at second visit.

increased by almost 2 months (from 72 to 124 days; Table 1), probably reflecting less concern among the gynaecologists about the waiting time after the implementation of the new guidelines. Third, under the new guideline almost one-third (30.2%) of women with CIN2 had CIN1 or normal histology at their second visit, compared with one-quarter (23.5%) in the previous time period.

Strengths and limitations

Our study took advantage of a new guideline for the management of CIN2. Using register data we ensured that all Danish women with CIN2 were included in the study, and that follow-up data for the second visit were complete. To the best of our knowledge, to date this is the largest study investigating the outcome of conservatively managed women with CIN2.

We used two cohorts recruited at different points in time, which could lead to confounding if the background risks of cervical dysplasia had changed. In Denmark, the first HPV-vaccinated cohort was invited to screening in 2016. In these women high-grade squamous intraepithelial lesions diagnosed by cytology decreased by 40%,[16] probably reflecting an overall decrease in dysplasia. Taking into account the birth cohort distribution in our population, the vaccination coverage was estimated to be 4.8% in women aged 18–44 years in 2008–2011 and 17.3% in 2014–2017,[17] which may explain the lower number of CIN2 in 2014–2017, but this is not expected to affect choice of treatment. We did not have data on smoking and HPV prevalence, with both factors associated with dysplasia progression.[18,19] Also, we lacked data on HIV status and potential anti-viral medication. There might be more HIV-infected women with CIN2 than in the general population, but HIV infection is rare overall in Denmark.

The reasons for choice of treatment and deviations from the new guideline are unknown. Tradition may also have played a role: for example, a low proportion of women were managed conservatively in Region Zealand in 2008–2011, and to some extent this pattern continued in 2014–2017. Furthermore, a woman could have requested a conisation even though she was eligible for follow-up with a biopsy, and a gynaecologist could decide on conisation based on clinical assessment, e.g. bleeding.

We did not have an opportunity to review samples. Misclassification in grading could potentially affect the recording of regression and progression, but it would not change compliance with the guideline, because the gynaecologist must act on the CIN2 diagnosis given by the pathology department.

Interpretation

The proportion of women followed-up with cytology only remained low and stable, but the proportion of women

without a second visit increased from 2.5 to 7.9% (Table 1). Our follow-up period included 10 months after CIN2 diagnosis, and the proportion of women with a second visit might have increased with a longer period, but we would then include women not managed according to the guideline time interval. The risk of loss or improper follow-up must be considered a disadvantage of conservative management, and it must be taken into account by the gynaecologists when selecting women for conservative management. Repeated examinations at the gynaecologist might affect a woman's well-being, but a questionnaire-based study found no difference in quality of life, anxiety, or sexual functioning between women managed conservatively and women treated with immediate conisation.[20] This suggests that conservative management is justifiable from the patient's point of view.

The progression rate of 17% in women treated conservatively after implementation of the new guideline is in line with the 10–18% reported previously. The regression rate of 47% is, however, slightly lower than the 50–76% reported elsewhere.[10,18,21–24] In most studies the follow-up period investigated was longer than in our study, however, and we might have found a higher regression rate if our follow-up period had been of equal length.

It was expected that the approximately 30% of women managed conservatively under the old guideline was a selected low-risk group. On this basis, it was noteworthy that the regression rate of conservatively managed women increased from 42% under the old guideline to 47% under the new guideline, despite the fact that the proportion of conservatively managed women had then increased to 54%. This strongly indicates that the prolonged time from the CIN2 diagnosis to the second visit diagnosis allowed for more lesions to regress.

Rather surprisingly, in our study similar regression rates were found for women younger and older than 30 years having a biopsy at their second visit, with an RR of 0.97 (95% CI 0.84–1.08) in 2008–2011 and an RR of 0.96 (95% CI 0.89–1.04) in 2014–2017 (Table 3). This is in contrast with a recent meta-analysis where the regression rate was higher in women aged <30 years than in women aged >30 years: 60 versus 44%.[10] Most other studies included only women younger than 25 or 30 years, however. Furthermore, a re-examination of the cones in one study found that the lesions were more likely to be CIN1 or no dysplasia in women aged <25 years than in women aged >25 years.[25]

It is worth noting that the proportion of women aged ≤30 years treated with conisation changed from 59.2% in 2008–2011 to 20.9% in 2014–2017 (RR 0.35), whereas for women aged >30 years the proportions were 82.3% and 63.2% (RR 0.77), respectively (Table 3). This indicates that the major change was a reduction in the conisations performed for young women.

Our study did not investigate recurrence for women whose CIN2 lesion regressed. One study found that spontaneously regressed CIN2 behaves like a low-grade lesion, although the recurrence risk is higher for women treated conservatively than for women treated with conisation.[26] The current Danish guideline recommends follow-up after 12 months with a cytology sample also for women with normal diagnosis at the second visit. This ensures that women with recurrence will be diagnosed and treated accordingly.

The results presented here allowed for an estimate of overtreatment. In 2008–2011, out of 6354 women with CIN2 who had a histological examination at their second visit, 1989 (31.3%) had a biopsy only and 4365 (68.7%) had a conisation. In 2014–2017, these numbers were 5693, 3427 (60.2%), and 2266 (39.8%), respectively. If we assume that the distribution in 2008–2011 was the same as that in 2014–2017, then there would have been 3825 women with a biopsy and 2529 women with a conisation in 2008–2011, corresponding to 4365 – 2529 = 1836 fewer conisations than actually occurred. Of these, 0.467 * 1836 = 857 would have possibly experienced a regression of the CIN2. Therefore, of the 4365 CIN2 lesions treated with conisation in 2008–2011, 857/4365 = 19.6% would have regressed spontaneously. This means that every fifth women undergoing conisation in 2008–2011 might have been overtreated.

Conclusion

As a result of the Danish guideline change in 2012, more women with CIN2 are now managed conservatively instead of undergoing immediate conisation. This has led to more women with spontaneously regressed lesions and to fewer women with progressed and/or persistent lesions. In 2014–2017, the regression rate in women followed-up with biopsy was 47%. This suggests that conservative management is safe for women of childbearing age diagnosed with moderate dysplasia.

Disclosure of interests

MS, JS and GN have no interests to declare. EL received HPV test kits from Roche for a randomised controlled trial. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

MS, JS and EL contributed to the project design and collection of register data. MS and GN cleaned the data and GN performed the statistical analyses. MS drafted the article. All authors interpreted the data and approved the final version for publication.

Details of ethics approval
Not required.

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