Nationwide Rereview of Normal Cervical Cytologies before High-Grade Cervical Lesions or before Invasive Cervical Cancer

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Keywords

Rereview · Normal cytology · False negative · Cervical cancer

Abstract

Sweden has experienced an unexpected >30% increase in cervical cancer incidence among women with normal cytological screening results. We therefore performed a nationwide assessment of false-negative cytology before invasive cervical cancer. The Swedish national cervical screening registry identified 2,150 normal cytologies taken up to 10 years before 903 cases of invasive cervical cancer. The 27 cytological laboratories in Sweden were asked to rereview the slides, and all of them completed the rereview. One thousand nine hundred fifteen slides were retrieved and reviewed. Abnormalities were found in 30% of the slides, and the proportion of slides that had a changed diagnosis on rereview increased on average by 3.9% per sampling year during 2001–2016 ($p < 0.03$). We also asked for rereview of normal smears taken up to 42 months before a histopathologically diagnosed high-grade squamous intraepithelial lesion (HSIL) or adenocarcinoma in situ (AIS). 19/27 laboratories responded, and out of 6,101 normal smears taken before HSIL/AIS, 5,918

were retrieved and rereviewed. The diagnosis was changed in 25% of cases. In summary, we found an increasing time trend of false-negative smears taken before invasive cervical cancer. This indicates a decreased protection of normal cytology in the screening program supporting earlier findings that this is the main reason behind the recent Swedish increase in cervical cancer. We suggest that optimal cervical cancer control may be promoted by routine nationally coordinated rereview of negative smears before high-grade cervical lesions or invasive cervical cancer.

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Introduction

Cervical screening is a globally recommended cancer control policy. Implementation of organized cervical screening programs has resulted in dramatic declines of cervical cancer incidence and mortality. Since the implementation of a nationwide, organized cervical screening program in Sweden in 1967, a steady decrease in the number of invasive carcinomas from 24/100,000 in 1965 to 8/100,000 in 2011 was seen [1]. However, in 2014, there was a sudden, unexpected, and sustained increase in cer-

vical cancer incidence. Comparing 2014–2015 with the previous period 2002–2013, we found a 17% rise in cervical cancer incidence (adenocarcinoma: +31% and squamous cell carcinoma +12%), corresponding to a rise from 450 to 550 annual cases [2]. The increase was statistically significant in most age groups offered screening but not in women aged 50 years or older. The increase was confined to cancers in FIGO stage IA and IB, and there was no increase in mortality [2].

There were notable differences between different counties from decreasing incidences to increasing incidences, up to +82%. However, there was no increase in the incidence for women who had not participated in screening, and the most significant increase (+30%) was seen in women who had had a normal cytology in the preceding screening round [2]. This was even more pronounced (+60% increase) among women with cancer and a history of 2 consecutive normal cytologies [3]. We also investigated if HPV vaccinations or immigration had impacted the incidence, but that was not the case [3].

Liquid-based cytology (LBC) was introduced in Sweden in clinical practice from 2009 and onwards. When this study was done, all laboratories except one (Uppsala) used LBC in cervical cancer screening and follow-up. Indeed, the 2017 national screening guidelines state that LBC is mandatory for screening laboratories. There was however no obvious correlation between LBC and cervical cancer: the incidence was still low among several laboratories using LBC, and there was also an increase in cancer incidence in the single laboratory that did not use LBC [3].

Accreditation for cytology laboratories in Sweden started in the early 2000s and became mandatory in 2017. The importance of continuous quality assurance work is emphasized in the European guidelines of quality assurance work in cervical cancer screening [4]. This is also well reflected in the updated national screening guidelines in Sweden [5]. When this study was done, only 2 (out of 27) laboratories were not accredited. Annual reviewing of normal cytology samples taken up to 10 years before cancer and up to 36 months before high-grade squamous intraepithelial lesion (HSIL) and adenocarcinoma in situ (AIS) is mandatory for accredited laboratories. However, there has not been any nationally standardized coordination of the rereviews or publication of the results. A recent performance assessment of the cervical screening program in Sweden has further emphasized the need for improved quality assurance work in cytological laboratories [6].

In order to investigate the possible role of false-negative cytology in the rising cancer incidence, the National Cervical Screening Registry (NKCx) sent lists on all normal screening samples taken before histologically confirmed cancer and before high-grade intraepithelial squamous lesions (HSIL/CIN3/CIN2) (including AIS) to all cytology laboratories in Sweden, asking for participation in a nationally coordinated rereview.

The research questions in this study are as follows:

- Is the proportion of normal smears before cancer that have changed diagnosis on rereview increasing over time?
- Can an increased proportion of normal smears that have changed diagnosis on rereview before HSIL and AIS be used as an early indicator of decreasing sensitivity?
- Are there differences between laboratories?
- Does detection of false-negative samples increase after introduction of LBC?
- Can we suggest strategies to improve the quality assurance work in cervical cytology to ensure the highest possible cancer protection of the screening program?

Materials and Methods

The Swedish cervical screening registry (NKCx) collects data on all cervical screening tests taken in Sweden. For the present study, all cases of invasive cervical cancer diagnosed in Sweden during 2008–2016 were linked to NKCx to identify smears with normal cytology taken before the diagnosis of cervical cancer. Among women having had only normal cytology in the past 0.5–3.5 years, we identified normal smears taken up to 5 years before histologically confirmed invasive carcinomas from 2008 until 2010 and up to 10 years before carcinomas diagnosed from 2011 until 2016. Cytology samples taken <6 months before invasive carcinoma were considered to possibly have led to the cancer diagnosis and were not included when identifying cases with only normal cytology in the past screening interval. However, these samples were included in the rereview.

Cytologically normal samples taken up to 42 months before histologically confirmed high-grade lesion (HSIL or AIS) diagnoses between 2012 and 2017 were also identified in NKCx among women having had only normal cytology in the past screening interval. Cytology samples taken <6 months before HSIL or AIS were not included when identifying cases with only normal cytology. Only smears taken from women 50 years or younger were included, as the largest increase in cervical cancer was seen before 50 years of age and since the screening intervals are longer after age 50 in Sweden.

Records identifying the slides to rescreen were sent from NKCx to all 24 active screening laboratories in Sweden, asking for retrieval and rereview. One thousand nine hundred fifteen of the 2,150 slides identified by the registry as taken before cancer could be located and retrieved. All retrieved slides were rereviewed. The

registry identified 9,472 slides with normal cytology taken before histopathological HSIL or AIS. Only 19 out of 27 laboratories participated in this study. In these 19 laboratories, the registry had identified 6,101 slides, and 5,918 of these slides could be located, retrieved, and rereviewed (62% of the 9,472 cases identified for all laboratories in the whole country). At the time of the study, 3 of 27 laboratories that had been analyzing screening smears during the period had been closed, and the files were sent to the remaining 24 labs. The archives of the 3 discontinued labs had been sent to the central laboratory for Southern Sweden in Lund, and this lab therefore received the request for rereview also for the 3 discontinued labs.

Review was performed at the local hospitals according to each laboratory's own guidelines and only on in-house cases (except in Lund). All cases were rescreened between September 1, 2018, and January 31, 2019, with 1 exception where rescreening was completed during autumn 2019. We collected data on the rereviewed diagnoses and if the slide was LBC or conventional. Results were collected and analyzed by the Swedish quality assurance and standardization group in exfoliative cytology (KVASt-group, Swedish acronym) in collaboration with NKCx [7].

We used Poisson regression models to estimate the average yearly change of proportion of slides rediagnosed as abnormal in the rereview, adjusted for lag year between the slides and invasive cervical cancer or HSIL/AIS diagnoses. A similar model was also used to assess the difference in proportion of abnormal slides in the rereview between conventional cytology and LBC, adjusted for lag year.

The Bethesda classification for cervical cytology was made mandatory in Sweden from 2017 [5] and onwards, and the rereviews were done using the Bethesda classification and terminology [8]. Before 2017, cytology samples from the cervix were mainly classified according to the CIN terminology [9]. Most samples in this study had originally been diagnosed according to the CIN system.

The rereviewed samples had all been part of cytology-based screening or follow-up only. HPV-based screening or follow-up had not been introduced in Sweden by then [5].

Results

Normal Cytology before Cancer

Results were reported for all 27 laboratories. A total of 1,915 slides were rescreened (Table 1). The number of rescreened slides varied between 13 and 197 per laboratory (Table 1). Diagnosis was changed, from normal to any atypia (including unsatisfactory for evaluation), in 566 cases (30%). Of these, 161 (8%) were reported as ASCUS, 47 (2%) as LSIL, 85 (4%) as HSIL, 60 (3%) as ASC-H, 103 (5%) as glandular atypia, and 52 (3%) as severe atypia NOS (severe atypia in cells of uncertain origin). Findings consistent with or suspicious for malignancy were seen in 35 cases (2%). Twenty-three (1%) slides were regarded as unsatisfactory for evaluation.

Fig. 1. All laboratories. Proportion of tests with changed cytology by year of smear before 903 cases of invasive cancer.

The percentage of changed diagnoses varied between 9 and 72% between different laboratories. The number of changed diagnoses for each laboratory is displayed in Table 1.

Between 2001 and 2006, the percentage of changed diagnoses was 10–20% on a national level. From 2007/2008, there was an increase in the percentage of changed diagnoses (Fig. 1). Figure 1 also shows the proportion of slides with changed diagnosis by calendar time, when stratified to a fixed lag time (3 years) before cancer. There was a strong correlation with risk of false-negative smears if there had been a negative cytology shortly before the diagnosis of cancer. In a multivariate analysis that also included calendar time, the risk for a false-negative smear increased with 12% for each year of shorter lag time between the normal smear and the cancer ($p < 0.001$). The increasing trend for false-negative cytologies over time was +4% for each calendar year and was statistically significant also in the multivariate model that included lag time before cancer ($p < 0.03$) (Table 2). For the country as a whole, there was no significant correlation between the introduction of LBC and the proportion of false-negative cytologies (not shown).

Normal Cytology before HSIL and AIS

Results were reported by 19 out of 27 laboratories, with 5,918 cases (62% of the 9,472 cases identified for all labo-

Table 1. Rereview of normal cytology (2001–2016) before invasive cervical carcinoma (2008–2016) and number of changed diagnoses – individual laboratories

Lab	M09010 unsatis- factory	M69710 ASCUS	M69719 ASC-H	M69720 atypical glandular cells	M80770 LSIL	M80772 HSIL	M80701 squamous cell carcinoma	M81401 AIS/ adeno- carcinoma	M80001 other malignancy	M69700 severe atypia	Changed diagnoses, N	Reviewed cases, n	Changed diagnoses, %
1. Eskilstuna	1	0	1	3	0	2	0	0	0	0	7	41	17
2. Sundsvall	0	2	1	6	0	1	0	1	0	1	12	43	28
3. Västerås	1	4	2	4	0	3	0	1	0	1	16	69	23
4. Sunderyn	0	6	3	2	3	2	0	0	0	3	19	63	30
5. Malmö	0	2	3	9	0	0	0	2	0	3	19	51	37
6. Lund	0	14	2	1	0	2	0	0	0	5	24	47	51
7. Skövde	0	5	1	1	1	4	0	0	0	2	14	57	25
8. Linköping	0	14	3	2	6	4	0	2	0	0	31	116	27
9. Kristianstad	0	12	1	3	1	5	0	0	0	5	27	53	51
10. Gävle	0	10	1	1	3	6	0	0	0	0	21	58	36
11. Falun	2	0	3	5	1	3	6	0	0	0	20	92	22
12. St. Göran	0	1	0	0	0	0	0	0	0	2	3	13	23
13. Helsingborg	0	2	0	3	0	3	0	1	0	3	12	59	20
14. Huddinge	0	11	0	11	14	1	1	7	1	1	47	173	27
15. Karlstad	0	2	6	6	5	2	0	1	0	1	23	96	24
16. Kalmar	0	0	1	1	0	0	0	0	0	2	4	46	9
17. Halmstad	3	5	3	13	0	2	0	0	0	0	26	91	29
18. Medilab	7	13	11	7	1	21	2	1	0	16	79	197	40
19. Karlskrona	0	4	3	8	1	6	1	2	0	1	26	36	72
20. Örebro	0	0	0	4	4	0	0	0	0	1	9	70	13
21. Borås	0	2	1	2	0	0	0	0	0	0	5	45	11
22. Växjö	0	1	0	2	0	0	0	0	1	2	6	25	24
23. Umeå	0	0	3	2	0	6	0	2	0	1	14	36	39
24. Uppsala	0	0	0	0	4	4	1	0	0	0	9	79	11
25. Jönköping	0	5	2	1	0	0	0	0	0	0	8	60	13
26. Trollhättan	0	7	0	1	1	7	1	0	0	1	18	35	51
27. Sahlgrenska	9	39	9	5	2	1	0	0	2	0	67	164	41
All labs	23	161	60	103	47	85	12	20	3	52	566	1,915	30
Changed diagnoses of all labs, %	1	8	3	5	2	4	1	1	0	3	30		

Table 2. Mean change per calendar year from the multivariate model controlling for lag time between diagnosis of cervical cancer/HSIL/AIS and normal cytology

Parameter	Estimated annual increase of proportion of changed diagnoses among normal smears	<i>p</i> value
Smears before invasive cervical cancer		
Calendar year	0.0391	0.0269
Lag time, years	−0.1188	<0.001
Smears before HSIL/AIS		
Calendar year	0.0148	0.3428
Lag time, years	0.0303	0.2784

HSIL, high-grade squamous intraepithelial lesion; AIS, adenocarcinoma in situ.

ratories in the whole country) having been rescreened. The number of smears rereviewed varied between 124 and 595 by lab. Diagnosis was changed, from normal to any atypia (including unsatisfactory for evaluation), in 1,506 cases (25.4%). Of these, 599 (10%) were reported as ASCUS, 256 (4%) as LSIL, 276 (5%) as HSIL, 214 (4%) as ASC-H, 64 (1%) as atypical glandular cells, and 48 (1%) as severe atypia NOS. Findings suspicious for or consistent with malignancy were seen in 11 cases (0.2%). Thirty-eight (1%) slides were regarded as unsatisfactory for evaluation (Table 3). The percentage of changed diagnoses varied between 10 and 45% between different laboratories.

The number of changed diagnoses for each laboratory is seen in Table 3. There was a notable variation in the reported percentage of low- or high-grade SIL from 3% up to 29%. Findings consistent with or suspicious for squamous cell carcinoma were not seen in any case. Only 10 cases were reported as suspicious for AIS. Less than 1% were regarded as not satisfactory for evaluation.

False-negative slides over time were analyzed with the same multivariate model as described above. Over 2012–2017, there was a mild tendency that the proportion of false-negative smears increased (1.5% increase for each calendar year), but it was not statistically significant (Table 2). A sensitivity analysis showed that the proportion of tests with changed cytology before cancer by year of smear tended to be lower among nonresponding laboratories (2.2% per year, *p* value 0.55) than among the 19 responding laboratories (4.4% per year, *p* value 0.028).

Discussion

Our study showed that the proportion of normal cytologies before cancer that had a changed diagnosis on rereview has increased over time between 2001 and 2016. The increase of false-negative cytology was evident from 2007/2008 and onwards. For the whole period and all laboratories included, diagnosis was changed in 28% of re-screened cytologies. There were notable differences between laboratories. The proportion of false-negative cytologies before cancer differed between 9 and 72% with a reported variation in low- and high-grade SIL between 0 and 23%.

For the whole country, there was no significant correlation between the introduction of LBC and the proportion of false-negative cytologies. However, it cannot be excluded that for some laboratories, the introduction of LBC has contributed to the increase in false-negative samples.

Rescreened normal cytology before HSIL/AIS showed similar results with an average of changed diagnosis of 25.4% for all laboratories and individual laboratories showing between 10 and 45% false negatives. Among those, the proportion that was changed to low- or high-grade SIL varied between 3 and 29%.

Rescreening results of normal cytology before HSIL and AIS were reported only by 19 out of 27 laboratories. This is still a 62% response rate and corresponds to 5,918 cases, with results from different settings: university laboratories, community hospitals, and private laboratories. Reporting laboratories represented counties with high, low, or no increase in cervical cancer in 2014–2015 [2]. We regard this as a very good response with a high number of cases and being representative of different types of laboratories in Sweden. There was no statistically significant trend over time in false-negative smears before HSIL. The nonresponse for some labs is not an explanation of the lack of time trend as the nonresponders rather tended to have a lower trend over time with regard to false-negative smears before cancer, that is, we had no reason to believe that the nonresponders represented laboratories with a higher rate of changed diagnoses than the responders. The nonresponders all represented accredited laboratories. Therefore, quality assurance systems and rescreening procedures were not likely to be worse than among participants. Workload, lack of time, and understaffing were the most probable explanations for not taking part in the study.

The purpose for rescreening of normal smears taken before histopathological HSIL was to identify a quality

Table 3. Rereview of normal cytology (2009–2017) before HSIL and AIS (2012–2017) and number of changed diagnosis – individual laboratories

Individual laboratories	M09010 unsatis- factory	M69710 ASCUS	M69719 ASC-H	M69720 glandular atypia	M80770 LSIL	M80772 HSIL	M80701 squamous cell carcinoma	M81401 AIS/ adeno- carcinoma	M80001 other malignancy	M69700 severe atypia NOS	Changed diagnoses, N	Reviewed cases, n	Changed diagnoses, %
1. Eskilstuna	2	18	7	0	2	9	0	0	0	0	38	252	15
2. Sundsvall	3	7	3	5	0	5	0	1	0	0	24	147	16
3. Västerås	2	19	7	2	15	5	0	1	0	0	51	320	16
4. Sunderbyn	0	32	19	3	14	20	0	0	0	0	91	313	29
5. Malmö	4	39	15	5	26	4	0	0	0	6	99	408	24
6. Lund	3	42	13	5	14	7	0	1	0	6	91	274	33
7. Skövde	6	39	7	1	10	10	0	0	0	1	74	332	22
8. Linköping	0	95	17	6	37	18	0	2	0	0	175	561	31
9. Kristianstad	6	25	11	4	7	8	0	1	0	0	62	175	35
10. Gävle	0	40	0	2	29	8	0	0	0	0	79	370	21
11. Falun	5	9	22	1	28	55	0	1	0	0	121	285	42
12. St. Göran	0	15	7	2	1	0	0	0	0	0	25	124	20
13. Helsingborg	3	30	8	6	7	4	0	0	0	8	66	290	23
14. Huddinge	0	27	0	4	14	11	0	2	1	0	59	207	29
15. Karlstad	3	25	18	2	26	64	0	0	0	0	138	482	29
16. Kalmar	0	0	15	0	5	2	0	0	0	4	26	251	10
17. Halmstad	0	35	20	5	3	10	0	0	0	3	77	348	22
18. Medilab	0	67	14	7	5	19	0	0	0	19	128	595	22
19. Karlskrona	1	35	11	4	13	17	0	1	0	1	83	184	45
All labs	38	599	214	64	256	276	0	10	1	48	1,506	5,918	25
Changed diagnoses of all labs, %	1	10	4	1	4	5	0	0	0	1	25		
HSIL, high-grade squamous intraepithelial lesion; AIS, adenocarcinoma in situ.													

indicator that would rapidly indicate if problems in sensitivity occur. Rescreening of normal smears taken before cancer is of course the most medically relevant quality indicator, but this indicator develops only slowly, and it is also desirable with an indicator that will detect possible problems long before anyone develops invasive cancer.

We chose to ask the laboratories to perform the rescreening on their own in-house cases rather than having a centralized rescreening process. This made the rescreening procedure more similar to the real-life setting. Collecting slides from all laboratories in Sweden for centralized rescreening was not considered a realistic approach for real-life quality assurance. Apart from logistic problems, national rescreening would have required an overwhelming amount of work. Furthermore, involving all different laboratories in the study as a part of a nationwide quality assurance project gave the laboratories valuable insights in their own strengths and areas possibly requiring improvements. When results of the rescreening were collected and reported, it became obvious that the reviewing process itself differs between laboratories, and that the documentation of annual mandatory quality assurance reviewing is not standardized and is performed differently in different laboratories.

Most of the rereviewed smears had originally been diagnosed using the CIN classification and terminology [9]. The Bethesda system [8] was used in the rereview, but since the original diagnosis was normal cytology in all rereviewed slides, there were no translation problems between the terminologies of the 2 systems.

Comparison with Others

In this study, the average level of false-negative slides before high-grade lesions and cancer is not high compared with other studies. A Dutch study reported that 61% of normal screening samples taken before histological HSIL (CIN2 or 3) were upgraded at review from normal to ASCUS or more (144 cases) [10]. When evaluating the Finnish screening program, Lönnberg et al. [11] found that 53% of slides taken before CIN3 or cancer (345 cases) were upgraded from normal to ASCUS, and in the English audit of invasive cervical cancer, 40% of normal slides were upgraded to borderline or more before 2012 (2,080 cases) and 36% to borderline or more from 2012 and onwards (273 cases) [12]. Lönnberg et al. [11] also found that the proportion of upgraded diagnoses increased when the slides also were rescreened outside the primary screening laboratory [11].

Strengths and Limitations

A limitation of this study is that reviewing was done on unblinded in-house cases, and the strengths of this study include that it is nationally comprehensive, has a national identification of the smears for review, and has a large number of rescreened cases representing normal cytology before cancer from >15 years. Furthermore, all laboratories took part in reviewing normal cytology before cancer, and a majority of laboratories also rescreened normal cytology before HSIL/AIS.

There was no centralized rescreening. This means that results from 1 laboratory cannot be directly compared with results from others. Rescreening unblinded in-house cases when the final outcome is known is difficult. Strict cytologic criteria must be applied when rereviewing. At least 2 experienced cytotechnologists and cytopathologists should be involved in the changing of diagnoses. This could prevent reporting very subtle and nonsignificant findings as atypias leading to an overestimation of the number of changed diagnoses. On the other hand, if important findings are disregarded or interpreted as too small a change, for example, a very small number of cells representing HSIL, underestimation is likely to result.

Conclusions

This study revealed an increase of false-negative samples taken before cervical cancer in Sweden, particularly obvious from 2007/2008 onwards. This supports our earlier epidemiological findings that the increase in cervical cancer in Sweden is mainly attributable to a lower protection of normal cytology [2] indicating an increased occurrence of false-negative smears over time. We suggest that accreditation requirements should include a nationwide annual reporting of mandatory routine rescreening of normal cytology before cancer and high-grade lesions.

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Statement of Ethics

The rereview of cervical smears taken before cancer was classified as quality assurance. The registry linkages and statistical analyses to investigate possibly preventable program deficits causing cancer were approved by the Regional Ethical Review Board of Stockholm (Decision No. 2016/2136).

Conflict of Interest Statement

None of the authors have any conflicts of interest to declare.

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Author Contributions

The study was designed by H.E., P.S., B.S., B.A., and J.D. and was coordinated by H.E. with assistance from J.W., P.S., B.S., and J.D. Statistical analyses were done by J.W. and P.S. Sourcing of data was done by H.E., and H.E. is also a guarantor of data integrity. Drafting of the manuscript was done by H.E. and J.D. All authors contributed to revision of the manuscript for important intellectual content and approved of the final version. B.S. and J.D. were responsible for acquisition of funding.

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