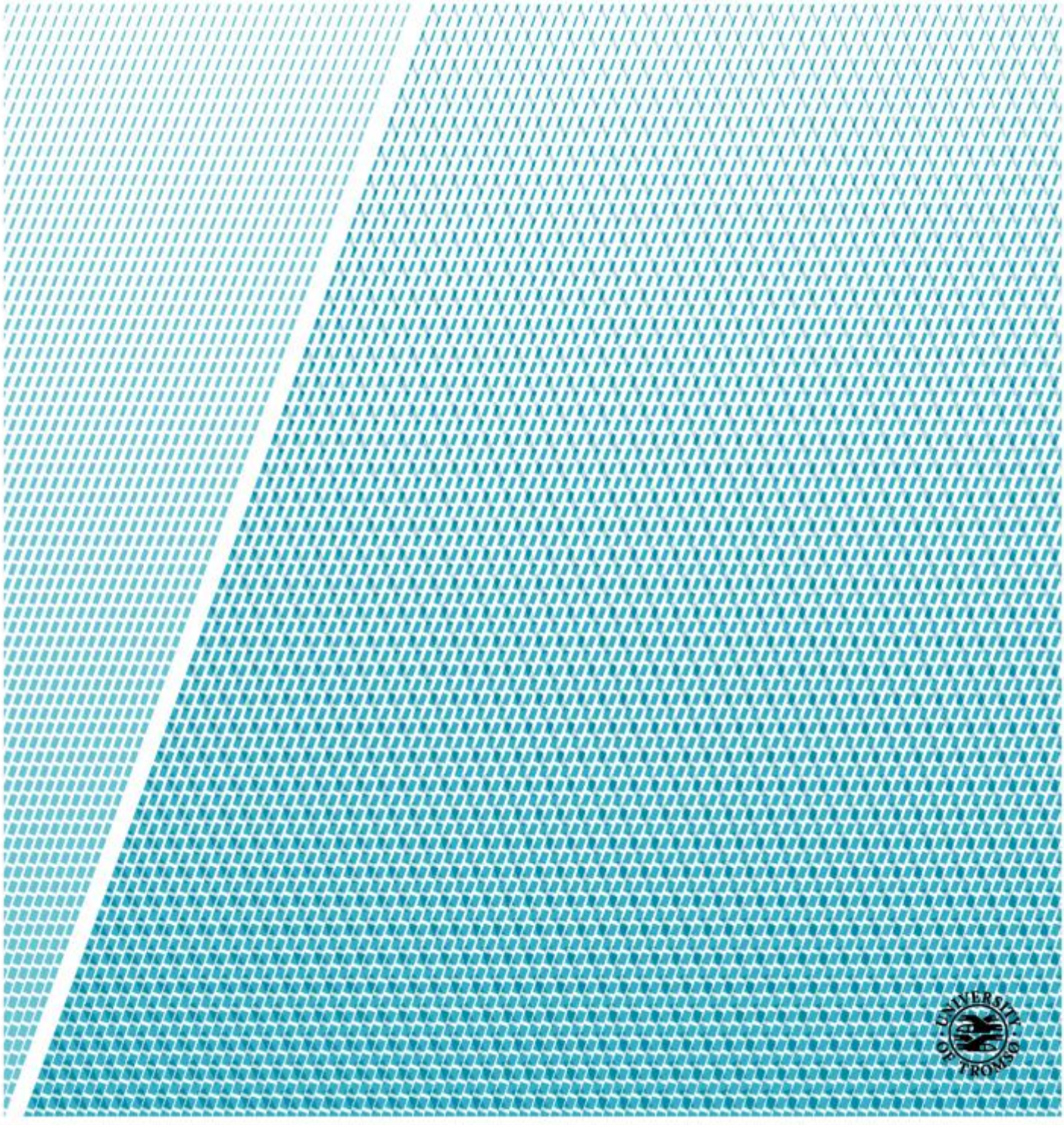
UiT
THE ARCTIC
UNIVERSITY
OF NORWAY

Faculty of Health Sciences

Risk for cervical intraepithelial neoplasia grade 2 or higher (CIN2+) among women with histologically confirmed CIN1 or less in cervical cancer screening

Liv Reidun Tverelv

Report: MED-3950 Master thesis/kull 2012
Tromsø: Profesjonsstudiet i medisin
UiT The Arctic University of Norway 2017



Preface

I would like to thank my supervisor Finn Egil Skjeldestad, The Department of Community Medicine (ISM), UiT The Arctic University of Norway, Tromsø, for his dedicated guidance and constructive feedback. I would also like to thank my co-supervisor Sveinung Wergeland Sørbye, The Department of Clinical Pathology, University Hospital of Northern Norway (UNN), Tromsø, for his knowledgeable and inspirational contributions. Thanks to my fellow students for all discussions and ideas.

Project origin

This project originated in spring 2015, when I searched for subjects to my MED-3950 master thesis. I wanted a subject within the field of pathology, and I contacted Skjeldestad for advice on how- and where to find relevant projects. He offered me to work on this project, supervised by him and co-supervised by Sørbye. The subject comprised follow-up of women having normal and low-grade histology diagnoses in the cervical cancer screening programme in Troms and Finnmark counties. The project was originally their idea, based on an article published by Katki et. al. (17) on risk stratification, and current application of risk stratification in the Norwegian Cancer Registry recommendations. We wanted to verify what Katki et. al. reported and compare that to Norwegian follow-up practice.

The writing process

The protocol was submitted by October 2015, and then I started the writing process. Both supervisors and I contributed to search for relevant literature. A few more students were supervised by Skjeldestad and Sørbye in related projects. We had regular meetings where we presented, evaluated and discussed the relevant literature, our project designs and plans for analyses. During fall 2016 and spring 2017, Skjeldestad and I had meetings to program the SPSS syntax used for the study population selection. The statistical analyses, their interpretation and discussions were done by the same manner.

June 6th, 2017
Liv Reidun Tverelv

Table of Contents

List of Tables

List of Figures

Abstract

Background/objective: Follow-up after histologically confirmed normal/CIN1 in cervical cancer screening is less studied. The current Norwegian follow-up guideline is combined cytology and HPV-testing after six months. The study objective is to examine compliance to guidelines and subsequent risk for CIN2+ in this subset of women.

Materials and methods: Women aged 25-69 years in Troms and Finnmark counties attending the Norwegian Cervical Cancer Screening Programme were included in this registry-based cohort study. An exposed cohort with histologically confirmed normal/CIN1 after ASC-US/LSIL or ASC-H/HSIL cytologies (N=374) was compared to a control cohort having normal cytologies in primary screening (N=25,948). The exposed cohort was stratified by the first follow-up cytology being normal or abnormal. Both cohorts were followed up to the last time-point of observation of 78 months.

Results: 69.5% of the exposed cohort and 42.2% of the control cohort was compliant to guidelines. The 42-month cumulative incidence of CIN2+ was, in the exposed cohort 17.9% (abnormal follow-up) and 7.1% (normal follow-up), and 0.43% in the control cohort ($p < 0.01$). The 42-month cumulative incidence of CIN3+ was 2.5% (95% CI: 0.0-5.2) in the exposed cohort with normal follow-up. Age-adjusted HR for CIN2+ was 22.5 (abnormal follow-up) and 9.0 (normal follow-up) ($p < 0.01$). Women aged 25-39 years had higher CIN2+ risks compared to women aged 55-69 years (HR 6.1, $p < 0.01$).

Conclusion: Compliance to guidelines was better, and the cumulative incidence of CIN2+ was significantly higher among women attending follow-up after histologically confirmed normal/CIN1 compared to women having normal cytologies in primary screening. The CIN2+ risk was higher among younger women. The cumulative incidence of CIN3+ provided by a normal follow-up cytology after histologically confirmed normal/CIN1, was closely consistent to allow screening in three years. A negative co-test probably provides a risk consistent to safe return to screening within three years.

1 Introduction

1.1 The Norwegian Cervical Cancer Screening Programme

Cervical cancer develops over several years through a series of precancerous lesions. Since 1995, The Norwegian Cervical Cancer Screening Programme (NCCSP) has recommended primary screening by cervical cytology every third year for women between 25-69 years. The screening programme aims to reduce cervical cancer incidence and mortality by detecting and treating premalignant cervical lesions. Age-adjusted incidences of cervical cancer decreased by 25 % from 1990-94 to 2000-04, and age-adjusted disease specific mortality decreased by 34 % during the same period. (1) The organized screening program has shown to be cost effective, has increased the screening coverage and has reduced the cervical cancer incidence. (2)

1.2 Human Papillomavirus and cervical cancer

Over the past decades, Human papillomavirus (HPV) has been determined as the causal agent for cervical cancer. (3) Cervical HPV-infections cause detectable premalignant lesions in the cervical epithelium. Approximately 80 % of sexually active women acquires an infection during their lifetime. Most HPV-infections are terminated by the immune system, have a mean duration of 6-18 months and most premalignant lesion regress. (4, 5) The variety of clinical presentations depend on the oncogenic potential provided by the present HPV-type. Thus, there are low- and high-risk groups of HPVs, the former causing condylomas and non-malignant lesions and the latter causing high grade neoplasia and cancer. (4, 5) 96 % of cervical cancer cases are attributed to 13 high risk HPV-types (6) where HPV 16/18/31/33 and HPV 35/45/52/58 are associated with high and medium risks for high-grade cell dysplasia over time, respectively. (7) Presence of HPV in a cervical sample can be confirmed either by HPV DNA- or HPV mRNA-tests. HPV mRNA-tests detect HPV E6/E7 mRNA coding for oncoproteins that inhibit tumor suppressors and maintain the malignant transformation of cervical cancer cells. (5) Thus, HPV mRNA-tests indicate oncogenic viral activity and HPV DNA-tests presence of HPV-virus.

1.3 Cervical cytology and biopsy diagnoses

The sampling methods performed in most cervical cancer screening programs, including the NCCSP, are liquid based cervical cytology (LBC) and biopsies (histology). The methods are quite different regarding sampling, morphology and classification.

Liquid based cervical cytology is the most frequent sampling method used for screening. It is mostly the only test used in primary screening, but cytology is also used in combination with HPV-testing to manage different screening test outcomes. The sampling is performed by collecting cells from the ecto- and endocervix using specially designed spatulas and brushes. The specimen shows single cell morphologies and any cell abnormalities are classified either as atypical squamous cells of undetermined significance (ASC-US), low grade squamous intraepithelial lesion (LSIL), atypical squamous cells that cannot exclude high grade lesion (ASC-H) or high grade squamous intraepithelial lesion (HSIL). The cytological diagnose criteria are mainly based on nuclear morphology (size, number, shape, nuclear/cytoplasm ratio, distribution of chromatin, membrane shape etc.). The cytological diagnosis is determined by the extensiveness and combination of these criteria. (8, 9)

Only women with histologically confirmed high grade dysplasia are recommended treatment. Biopsies are tissue samples collected from the cervix during a colposcopic examination. The biopsies are performed either colposcopically guided at visible lesions or from each quadrant of the cervix. (9) The biopsies are processed to histological specimens and are evaluated by pathologists. Histological specimens show the total tissue composition and any abnormal findings are classified as cervical intraepithelial neoplasia (CIN). The CIN grade depends on dysplastic distribution within the epithelial layer, for instance differentiation, maturation, extent of mitoses and nuclear changes as earlier mentioned. Low grade dysplasia (CIN1) is characterized by undifferentiated cells restricted to the basal third of the epithelium. Moderate dysplasia (CIN2) show more distinctive nuclear abnormalities in the lower half or two thirds of the epithelium. Severe dysplasia (CIN3) is characterized by low differentiation, nuclear abnormalities, extensive and abnormal mitoses localized to the whole thickness of the epithelium. (10) A biopsy may also show invasive cancer, mostly squamous cell carcinoma (SCC) and adenocarcinomas (ACC). (5) High grade dysplasia (CIN2+) is defined as CIN2, CIN3 and cancer. According to Norwegian guidelines, women with CIN2+ are recommended treatment, usually by conization.

1.4 Risk stratification in screening

Designing suitable follow-up algorithms are challenging for any screening diagnose. The purpose of any screening programme is to identify individuals with high risk for severe disease. Risk stratification is used to manage the test result follow-up. Castle et. al. (11) consider CIN3+ as the best risk indicator for precancer/cancer, because the CIN2 diagnosis is poorly reproducible and often indicates an acute HPV-infection. A cumulative incidence of CIN3+ (CIN3 and worse) lower than 2.0% is considered as an acceptable threshold to serve as basis for the 3-year screening interval recommendation. For CIN3+ risks between 2% and 10%, the suggested follow-up threshold is within one year. Women having more than 10% risk for CIN3+, are recommended immediate referral for colposcopy and biopsy. (11) Application of the term "equal management of equal risks" is used to evaluate which management that is suitable for cases with similar risk profiles. (12)

1.5 Primary screening test outcome

According to the NCCSP guidelines, women having normal primary screening results should return to screening within three years. Women having high-grade cytology results (ASC-H/HSIL) are referred to a gynecologist for colposcopy and biopsy. Unsatisfactory test results were followed up by new cytology within 6-12 months between 2005-2008 and within 1-3 months from 2009. (13)

Women with minor cervical lesions (ASC-US/LSIL) are, on the other hand, managed differently due to increased risk of CIN3+, though not high enough to recommend immediate referral to colposcopy and biopsy. (11, 14) In 2005, HPV-tests were introduced in the screening programme, and women with ASC-US/LSIL cytologies in primary screening were triaged with HPV and cytology co-testing within 6-12 months (delayed triage). (14)

1.6 ASC-US/LSIL cytology triage

The NCCSP 2005 guidelines for triage (Figure 1) (15) was valid during the inclusion period of this study, and was therefore used as basis to select the study population (see materials and methods). Women with triage results of HPV-negative and normal/inadequate/ASC-US/LSIL returned to screening. Women with triage results of HPV-positive and ASC-US/LSIL, or ASC-H/HSIL regardless of HPV-status, were recommended further examination with

colposcopy and biopsy. (14, 15) Women triaged to colposcopy, needed further follow-up or treatment, if the biopsy had a histological CIN-diagnosis.

1.7 Histology follow-up

The current Norwegian follow-up practice of histologically confirmed normal/CIN1 is combined cytology and HPV testing after six months. Histologically confirmed CIN2+ is normally treated with conization of the cervix. (9)

1.8 Challenges regarding follow-up of histologically confirmed normal/CIN1

The distribution of histological diagnoses has changed since introduction of HPV-testing and ASC-US/LSIL triage in several screening programs, and is possibly explained by additional low-risk women being eligible for colposcopy and biopsy. (16, 17) In Norway, the mean CIN1 fraction of all histology diagnoses has showed an increasing trend; 6.7% (2009), 7.14% (2012) and 9.0% (2014). (18-20) The sensitivity for detecting CIN2+ lesions at colposcopy has been reported as 39% (21) and 66.2% (22), suggesting that suspected high-grade lesions cannot be ruled out even if a woman is diagnosed with a histologically confirmed low-grade lesion. (22) There are significant interpretive variations among pathologists for histopathological cervical specimens (23), and there are few definitive methods yet, that help identify cases in high risk for progression. p16 immunostaining is a frequently used biomarker for this purpose, suggestively indicated to evaluate uncertain dysplasia present on conventional hematoxylin-eosin (HE)-stains, or for negative HE-stains together with positive HPV-tests or antecedent high-grade cytology results. (24) The HPV test-type used has been reported to influence the colposcopy referral rate, being 57 % higher for HPV DNA-tests compared to HPV mRNA-tests. (25)

Studies have shown that 50-70% of CIN1 lesions spontaneously regress within 12 months and only 4% and 7% progress to CIN2+ within six and 12 months, respectively. (26, 27) According to Castle et al. (28) the CIN1 diagnosis itself is not a significant risk factor for CIN3 above the risk attributed to the genotype specific HPV-infection. Sørbye et al (29) described similar risk for CIN2+ in follow-up regardless of normal or CIN1 histology.

Several factors challenge the normal/CIN1 histology management. A complex follow-up algorithm may lead to decreased compliance and psychological distress. By conservative follow-up, 9-16 % develop CIN2-3, suggesting similar management as for an ASC-US/LSIL cytology. (30) A triage test with high specificity may reduce the number of unnecessary referrals. (25, 31)

1.9 Relevant literature on CIN2+ risks after histologically confirmed normal/CIN1

The CIN2+ risk among women having histologically confirmed normal/CIN1, has shown to be influenced by their antecedent cytology and/or HPV-test result. Katki et. al. (17) reported that women who had an antecedent ASC-US/LSIL cytology and who were HPV-positive, had a lower 5-year risk for CIN2+ (10%) than for antecedent ASC-H (16%) or HSIL (24%). They examined the CIN2+ risks in follow-up by different combinations of negative HPV-tests and negative cytology results (co-test negative, HPV-negative or cytology negative). In this subset of women, the lowest 5-year CIN2+ risk of 1.1% and 2.2% was provided by one negative co-test for antecedent HPV-positive/ASC-US/LSIL and antecedent ASC-H/HSIL, respectively. The negative co-test among antecedent ASC-US/LSIL and HPV-positive women, provided a CIN2+ risk consistent to follow-up within three years.

Guido et. al. (32) compared follow-up of women having CIN1 or less on immediate colposcopy and biopsy after HPV-positive ASC-US or LSIL, in the ASC-US LSIL Triage Study (ALTS). They reported the CIN2/3 risk to be 9.8% and 11.3%, respectively.

Mittal et. al. (33) assessed the CIN2+ risk and associated risk factors in follow-up of high-risk HPV (HR-HPV) positive women having histologically confirmed normal/CIN1, in a public screening demonstration project in rural areas in India. In this subset of women, 6.3% progressed to CIN2+, and the only significant factor was HPV-persistence.

1.10 Study objective

There are few studies investigating the histologically confirmed normal/CIN1 follow-up in a screening scenario. The objective of this study is to examine guideline compliance and CIN2+ risks among women with histologically confirmed normal/CIN1, compared to a control

cohort. Which cytology and HPV-test outcomes, alone or in combination, provides the lowest risk applicable for safe and well-organized management in a continuously increasing patient group?

2 Materials and methods

2.1 Study design and data

This study is a prospectively designed registry-based cohort study of an exposed cohort compared to a non-exposed control cohort. The data is obtained from a database containing cervical cancer screening data from the Department of Clinical Pathology, University Hospital of Northern Norway (UNN).

2.2 Defining the exposed cohort, control cohort and index sample

The exposed cohort (study population) is defined as women having histologically confirmed normal/CIN1 (exposed cohort index). The non-exposed cohort (control cohort) is defined as women having a normal inclusion cytology (control cohort index).

2.3 Defining the inclusion cytology

The inclusion cytology is restricted to women who had at least one cytology analyzed at the Department of Clinical Pathology, UNN, for the exposed cohort within January 1, 2006 through December 31, 2011 and for the control cohort within January 1, 2006 through December 31, 2007. The inclusion cytology result determined cohort allocation. The exposed cohort comprised women having ASC-US/LSIL (eligible for triage) or ASC-H/HSIL (eligible for immediate biopsy) inclusion cytologies. The control cohort comprised women with a normal inclusion cytology (eligible for screening after three years).

2.4 Exclusion criteria

After identifying all women eligible for study participation, we excluded non-residents of the Troms and Finnmark counties, women outside screening age (≤ 24 years and ≥ 70 years) and women who had a history of high grade cervical cytology (≥ HSIL) and/or high-grade histology (≥ CIN1).

Further exclusion was restricted to women in the exposed cohort, who either underwent ASC-US/LSIL triage (Figure 1) or had immediate colposcopy and biopsy (inclusion ASC-H/HSIL). We excluded women missing follow-up, women returning to screening (HPV negative ASC-US/LSIL or normal cytology), women having incomplete follow-up (not according to management guidelines or case unsolved) and women having high-grade cervical lesions or cancer (CIN2+).

2.5 Follow-up and endpoint

Both cohorts were followed up from the time of their respective index samples, through December 31, 2014 (study end). Histologically confirmed CIN2+ was considered as endpoint of disease. Risk calculations were in the exposed cohort stratified by the first follow-up cytology being normal or abnormal (inadequate, ASC-US+). Cervical cancer was classified according to The International Federation of Gynecology and Obstetrics (FIGO) classification system. (9)

2.6 Compliance to follow-up and first screening round

Women in the exposed cohort were recommended follow-up within 6-12 months. Compliance to follow-up was considered as within interval if < 12 months and as late if > 13 months. Women in the control cohort were recommended screening in three years. Compliance to follow-up was considered as early if < 23 months, within interval between 23-42 months and late if > 42 months. Women meeting within interval were considered compliant. Women not attending follow-up were classified as non-attenders. Women meeting too early, too late or not attending were considered non-compliant.

In both cohorts, 42 months (3.5 years) of follow-up after index were set as threshold for determination of most severe outcome in the first follow-up round (first screening round). 42

months to 78 months of follow-up (6.5 years from index) was considered the second screening round.

2.7 Statistics

All statistical analyses were done using IBM SPSS Statistics, version 24.0 and included chi-square, survival analysis and Cox-regression. Due to small numbers of study participants beyond 81 months of observation, we stopped survival analyses at 81 months, making 78 months the last time-point for observation. P-values < 0.05 were considered statistically significant.

2.8 Ethics

The Regional Committee for Medical and Health Research Ethics, North Norway, has evaluated the protocol as a quality assurance study fulfilling the requirements for data protection procedures within the department (2011/2605/REK Nord). Norwegian regulations exempt quality assurance studies from written informed consent from the patients. The Patient Ombudsman, University Hospital of Northern Norway, has approved the start of the study.

3 Results

3.1 Inclusion, exclusion and cohort characteristics

3,089 women had an ASC-US/LSIL inclusion cytology and 850 women an ASC-H/HSIL inclusion cytology. Table 1 illustrates the exposed cohort and control cohort selection according to the inclusion- and exclusion criteria. In total, 2,864 ASC-US/LSIL women and 701 ASC-H/HSIL women were excluded, leaving an exposed cohort of 374 women having histologically confirmed normal (59.1%) and CIN1 (40.9%) ($p < 0.01$). 31,335 women had a normal inclusion cytology, and 5,387 women were excluded, leaving a control cohort of 25,948 women.

Table 2 illustrates the exposed cohort and control cohort characteristics. The age was evenly distributed within the control cohort. Women in the exposed cohort were significantly younger, where 55.1% were aged 25-39 years. More women in the exposed cohort had no screening history (15.2%) or had an ASC-US/LSIL cytology (7.2%) before inclusion compared to the control cohort (6.9% and 1.6%, respectively).

3.2 Compliance to first follow-up after index

There were significant differences between cohorts regarding compliance to first follow-up after index (Table 3). Most women in the exposed cohort (69.5%) were compliant compared to 42.2% in the control cohort. 5.3% of women in the exposed cohort and 14.4% of women in the control cohort did not attend further follow-up. There were no obvious differences in compliance by age groups.

3.3 First and second screening round

The worst histological diagnose at 42 and 78 months by cohort is illustrated in Table 4. The CIN2+ fractions in the exposed cohort at 42 and 78 months were almost ten-fold compared to the control cohort.

By 42 months, the proportions of women that returned to screening were 69.0% in the exposed cohort and 46.1% in the control cohort. 17.6% of women in the exposed cohort and

38.8% of women in the control cohort had an incomplete follow-up (cytological abnormalities in follow-up, but not yet solved). By 78 months, the proportions of women that returned to screening were 56.7% in the exposed cohort and 42.4% in the control cohort. In the same order, 27.3% and 42.3% had an incomplete follow-up.

3.4 Cervical cancer

At 42 months, 8 cases of cervical cancer (3 squamous cell carcinomas and 5 adenocarcinomas) occurred in the control cohort only. At 78 months, 1 woman (0.3%) in the exposed cohort and additionally 11 women in the control cohort had developed cervical cancer, of which 8 cases (including the case among exposed cohorts) were squamous cell carcinomas and 4 cases were adenocarcinomas. (Table 4) The median time to diagnosis among women developing cervical cancer was 53.5 months (range 3-76). Five cases were classified as FIGO-stage Ia, 6 were Ib and one was stage IV.

The exposed woman that developed squamous cell carcinoma had an inclusion cytology of ASC-H/HSIL. She was compliant and was followed-up according to guidelines at scheduled intervals with subsequent normal cytologies and had a histological examination after three subsequent ASC-US/LSIL cytologies. The cancer diagnose was set 76 months of follow-up after index and was FIGO-staged Ia.

3.5 HPV-status before index

Table 5 shows the HPV-status before index by screening status at 78 months in the exposed cohort. 197 of 374 women (52.7%) had no HPV-result. Of women with an HPV-test, 149 of 177 (84.2%) were HPV-positive, of which 21 (of 40 in total) women had CIN2+ at 78 months. 28 of 177 (15.8%) were HPV-negative, of which 2 women had CIN2+ at 78 months. The only case of squamous cell carcinoma in the exposed cohort had no HPV-result before index.

3.6 Cumulative incidence of CIN2+ and CIN3+

At the first follow-up visit, 227 women had a normal cytology or histology and 147 women had an abnormal cytology (inadequate or ASC-US+). Table 6 shows the cumulative

incidences of CIN2+ and CIN3+ with 95% confidence intervals for the exposed cohort stratified by the first follow-up cytology, and the control cohort.

Figure 2 shows the cumulative incidence of CIN2+ plotted by follow-up in months after index. The cumulative incidence of CIN2+ at 42 and 78 months was significantly higher among exposed cohort women having an abnormal follow-up cytology (17.9% and 22.0%) compared to exposed cohort women having a normal follow-up cytology (7.1% and 11.9%). In the exposed cohort, both follow-up outcomes had significantly higher cumulative incidences of CIN2+ compared to the control cohort (0.43% and 1.4%).

Figure 3 shows the cumulative incidence of CIN3+ plotted by follow-up in months after index. The cumulative incidence of CIN3+ at 42 and 78 months was significantly higher among exposed cohort women having an abnormal follow-up cytology (8.5% and 9.8%) compared to exposed cohort women having a normal follow-up cytology (2.5% and 5.2%). In the exposed cohort, both follow-up outcomes had significantly higher cumulative incidences of CIN3+ compared to the control cohort (0.24% and 0.73%).

Cumulative incidences by most recent cytology or normal histology results before inclusion were not statistically significant for any outcome.

3.7 Age-stratified cumulative incidence of CIN2+ and CIN3+

The age-stratified (women aged ≥ 40 or < 40 years) cumulative incidences of CIN2+ are illustrated in figure 4. All age-specific exposed cohorts had significantly higher cumulative incidences of CIN2+ compared to the age-specific control cohorts. The cumulative incidence of CIN2+ was significantly higher for younger women in the control cohort compared to older women. The cumulative incidence of CIN2+ was significantly higher for younger women in the exposed cohort with an abnormal follow-up compared to younger women in the exposed cohort with a normal follow-up. Within exposed cohort follow-up results, the cumulative incidence of CIN2+ was independent of age.

The age-stratified (women aged ≥ 40 or < 40 years) cumulative incidences of CIN3+ are illustrated in figure 5. The cumulative incidence of CIN3+ was significantly higher for the

younger women in the control cohort compared to older women. Within exposed cohort follow-up results, the cumulative incidence of CIN3+ was independent of age.

3.8 Hazard ratio

Table 7 shows the age-adjusted hazard ratio (HR) for CIN2+ and CIN3+ with 95% confidence intervals. The risk for developing CIN2+ was significantly higher for exposed cohort women having an abnormal first follow-up cytology (HR 22.5) than exposed cohort women having a normal first follow-up cytology (HR 9.0) using the control cohort as reference. The increased risk for developing CIN2+ was highly significant among women aged 25-39 years (HR 6.1) compared to women aged 55-69 years. The age-adjusted HR for CIN3+ showed the same trend, where women in the exposed cohort with an abnormal follow-up had significantly higher risk (HR 17.1) than women in the exposed cohort with a normal follow-up (HR 6.8) using the control cohort as reference. Women aged 25-39 years also had significantly higher risk for CIN3+ (HR 9.0) compared to women aged 55-69 years.

4 Discussion

4.1 Important findings

Compliance to follow-up was better among women in the exposed cohort than women in the control cohort. The fact that few exposed women were lost to follow-up and about 70% were compliant, is possibly explained by different follow-up practices between groups. The exposed women were probably provided information by their physician or gynecologist and were aware of their increased cancer risk, compared to women in the control cohort that should rescreen in three years.

The cumulative incidences of CIN2+ and CIN3+ were significantly higher among women in the exposed cohort having their first follow-up cytology being abnormal compared to normal. The risks for CIN2+ in both follow-up outcomes were significantly higher compared to the control cohort. Age-stratified cumulative incidences of CIN2+ and CIN3+ showed no significant differences within the exposed cohort follow-up outcomes, but younger women had significantly higher cumulative incidences of both CIN2+ and CIN3+ within the control cohort. Age-adjusted hazard ratios showed significantly higher risks for both CIN2+ and CIN3+ among women in the exposed cohort, using the control cohort as reference. Women aged 25-39 years had significantly higher risk for CIN2+ and CIN3+ compared to women aged 55-69 years.

Within the exposed cohort, the 95% confidence intervals for cumulative incidences overlapped, both between screening rounds and age-stratified, meaning there was no significant differences in risk increase between screening rounds or by age. However, the results showed an increasing trend between screening rounds. The 95% confidence intervals for age-adjusted HR's also overlapped, meaning the HR between abnormal and normal follow-up cytologies were not significantly different. The 95 % confidence intervals of HR's on CIN2+ and CIN3+ between age groups were narrow and not overlapping, and thus the differences were significant.

We initially wanted to assess CIN2+ risks in follow-up of women having histologically confirmed normal/CIN1 by cytology and HPV-testing alone or in combination, and by that apply the concept of risk stratification to our study population. Of all 53,220 women screened

in our background population between 2006 to 2011, the control cohort only resembled 0.7%. Because small numbers of exposed women and no uniform HPV-testing in follow-up, the risk calculations by multiple follow-up test results were not possible. However, we were able to calculate cumulative incidences in the exposed cohort stratified by the first follow-up cytology being normal or abnormal.

The cumulative incidence of CIN2+ at 42 months was significantly higher for exposed women having an abnormal follow-up (17.9%, 95% CI: 11.6-24.2) compared to women having a normal follow-up (7.1%, 95% CI: 2.7-11.5). The cumulative incidence of CIN3+ was, in the same order, 8.5% (95% CI: 3.8-13.2) and 2.5% (95% CI: 0.0-5.2). Using the concept of risk stratification on CIN3+ risks presented by Castle et. al. (11), women having a normal cytology at the first follow-up after normal/CIN1 are close to the 3-year screening threshold of 2%. Having an abnormal cytology, the cumulative incidence of CIN3+ is consistent to follow-up within one year. The highly statistical uncertainty of our results, provides no basis for direct recommendations, but suggests that by adding HPV-testing to the first follow-up, a negative co-test could provide lower CIN3+ risks consistent to a safe return to screening within three years.

The cumulative incidence of CIN3+ was in the control cohort 0.24% and 0.73% at 42 and 78 months, respectively. The 95% confidence intervals were narrow, did not overlap and provided high statistical power. The cumulative incidence of CIN3+ was under 2%, still at 78 months, consistent to rescreening in three years, as already practiced.

The age-stratified cumulative incidence of CIN2+ and CIN3+ was significantly higher for women aged < 40 years in the control cohort compared to women aged ≥ 40 years, suggesting that most CIN2+ occur among younger women. By first follow-up cytology, in the age-span < 40 years, exposed women having an abnormal cytology had a significantly higher cumulative incidence of CIN2+ than exposed women having a normal cytology. As there were no differences in cumulative incidences among women having abnormal or normal cytologies at first follow-up by age, the slope of the curves may indicate that abnormal cytologies were expressions of persistent HPV-infections.

Women aged 25-39 years had significantly higher risks for progression to both CIN2+ and

CIN3+ compared to women aged 55-69 years, suggesting that younger women should be followed up more closely that older women.

The proportion of women who had an incomplete follow-up at both 42 and 78 months were higher in the control cohort, but also increased during follow-up of the exposed cohort, suggesting that high numbers of women underwent follow-up for unsolved cytologies over long time.

55.1% of women in the exposed cohort were aged 25-39 years. The prevalence of HPV-infections has been reported as higher in younger age groups (34), suggesting that most low-grade and undetermined cytological abnormalities occur among younger women. This probably explain the higher proportion of exposed women with no previous screening data that participate in screening for the first time.

4.2 Results compared to relevant literature

There are few studies examining CIN2+ risks in follow-up of histologically confirmed normal/CIN1 in a screening scenario. Most studies are performed as case-series on normal histology, CIN1 and/or normal colposcopy without biopsy as part of larger and organized cohort studies (e.g. the ALTS) with objectives deviating from ours.

The cumulative incidences of CIN2+ provided by our study were much higher compared to Katki. et. al. (17) that reported 5-year CIN2+ risks of 2% and lower. The risks were provided by negative co-tests in follow-up of women having HPV-positive ASC-US and ASC-H/HSIL and subsequent histologically confirmed normal/CIN1 or normal colposcopy without biopsy. The study was performed on the Kaiser Permanente Northern California (KPNC) population, a well-screened American population with historically below-average cancer risks. (12) The inclusion- and exclusion criteria were relatively the same compared to our study, but they did not exclude women having histories of high-grade cervical lesions and women over 70 years. They also included women not having histologically confirmed results. The study population of 20,319 women was much larger than ours, making calculations on specific follow-up managements possible. Their follow-up guidelines after histologically normal/CIN1 included co-testing, but they did not specify at which intervals. They only followed up women with negative co-tests compared to our study where women were stratified by only one follow-up

cytology of normal or abnormal. The 5-year CIN2+ risks were benchmarked to implicit risk thresholds for management, based- and developed on research on the KPNC population (12).

The 2-year CIN2/3 risk, presented by Guido et. al. (32) of 9.8% (HPV-positive ASC-US) and 11.3% (LSIL) was not stratified by any follow-up result. This study was part of a larger study designed to evaluate management (triage, conservative management, immediate colposcopy) of ASC-US and LSIL cytologies in primary screening (not HSIL). Since this subset of women was derived from the ALTS immediate colposcopy arm, the time to further examination and resolution probably was shorter and increased the risk of detection bias. Additionally, the post-histology follow-up was at 6, 12, 18 and 24 months with cytology, HPV-test and cervigram, and was much more thorough and organized compared to our population. All ASC-US were HPV-positive at inclusion, which probably increased the probability to find CIN2+ compared to our study population that was only included by cytology results.

Mittal et. al. (33) assessed the CIN2+ risk in follow-up of high-risk HPV (HR-HPV) positive women having histologically confirmed normal/CIN1 in a public screening demonstration project in rural areas in India. 6.3% of study participants progressed to CIN2+ and the highest fraction progressing were aged 50-60 years, which is opposite of our findings. All women were HR-HPV-positive, being the only inclusion criteria, which is not comparable to ours that comprised cytology results in primary screening, only. As of our study, they excluded women having history of any CIN. They found HPV-persistence to be the only significant factor for progression. This study was performed as a demonstration project in a rural population not previously screened which may explain the high fraction of older women progressing to CIN2+. The follow-up was organized yearly, by HR-HPV-testing, colposcopy and biopsy. Only 48.8% had at least one follow-up visit, despite actively reminding and even look up non-attending study participants.

Thus, our results cannot directly compare to other studies hence to differences in study objective, populations, study design and follow-up.

4.3 The natural course of an HPV-infection

The HPV-infection natural course is of relevance to our exposed cohort. The inclusion cytology of ASC-US/LSIL or ASC-H/HSIL indicated an HPV-infection. Our exposed cohort

comprised women having normal or low-grade histology results that most likely resembled an HPV-infection cleared or in regress, regardless if the lesion was true or missed during colposcopy and biopsy. The mean HPV-infection duration of 6-18 months (5) equaled time from primary screening to completed triage, enabling the infection to regress.

HPV-test coverage in the exposed cohort was low (47.3%). 149 of 177 (84.2%) women with a valid HPV-result, were HPV-positive. Considering our exposed cohort comprising women both having ASC-US/LSIL (eligible for triage with HPV-test and cytology) and ASC-H/HSIL (eligible for immediate colposcopy/biopsy) inclusion cytologies, the result was expected since ASC-H/HSIL women were not recommended an HPV-test. If excluding ASC-H/HSIL women, the HPV-test coverage was close to adequate (74.7%) during ASC-US/LSIL triage. Among women having ASC-US/LSIL inclusion, 63.1% were HPV-positive, which was expected since the HPV-positive triage test qualified for colposcopy and biopsy.

More exposed women (7.2%) had an antecedent ASC-US/LSIL cytology prior to inclusion compared to women in the control cohort (1.6%), indicating that the HPV-infection started before inclusion, and the inclusion cytology simultaneously was part of a follow-up. At some point of follow-up after histologically confirmed normal/CIN1, the HPV-infection or histological lesion should be suspected as persistent or providing high risk for progressing to CIN2+. As previously mentioned, large proportions of women in our study had incomplete follow-up without any histologically confirmed diagnose at 78 months, leaving the actual proportion of women progressing or having persistent infections unknown. Incomplete follow-up is little discussed in previous publications.

HPV-persistence (33) and type-specific HPV-infections (28) are associated with progression to CIN2+/CIN3 and taking into account that few CIN1 progress within the first year after detection (27, 28), a follow-up test with high specificity could be favorable. We did not have enough data to look upon HPV- or histology persistence in our exposed cohort, but other studies have examined both test characteristics in normal/CIN1 follow-up (29) and treatment of persistent CIN1 (35).

Sørbye et. al. (29) compared test characteristics of cytology and HPV E6/E7 mRNA-testing in follow-up after histologically confirmed normal/CIN1 in the same background population as ours. The HPV mRNA-test compared to cytology with cutoff ASC-US+ was as sensitive

(89.1% and 84.1%, respectively), but more specific (92.5% and 76.4%, respectively) for CIN2+. The HPV mRNA test also had higher positive predictive value (PPV) than cytology with cutoff ASC-US+ (78.8% and 52.8%, respectively). The results show that a negative HPV E6/E7 mRNA-test would identify most cases having low risk for progression to CIN2+ in follow-up of women having histologically confirmed normal/CIN1. Compared to our study, the background population is the same, but Sørbye et. al. did not exclude women having a history of high-grade cytological- and histological cervical lesions. However, despite some differences in study design, the results are probably applicable to our study population.

Spinillo et. al. (35) assessed the cumulative CIN2+ risks in an Italian screening population having persistent CIN1 (>2 years), treated with Loop Electrosurgical Excision Procedure (LEEP). The cumulative incidence of CIN2+ was, after 2 and 3 years of follow-up with cytology, colposcopy and molecular diagnostics after six months, 1 year and thereafter every year, 2.3% and 5.5%, respectively. Persisting- and HR-HPV-infection in follow-up were associated with higher rate of CIN persistence/progression and all cases of CIN2+ had cytological abnormalities during follow-up. (35) The CIN3+ risks in this publication were not calculated, but considering the CIN3+ risks usually being lower than CIN2+ risks, the post-treatment risks were probably closely consistent to a prolonged screening interval.

4.4 Strengths of the study

This study is population-based in a country having had a well-organized screening programme for over 20 years. When selecting the study population, we excluded women having history of high-grade cytology and/or CIN that represented persistent HPV-infections, leaving a subset of low-risk women being exposed- or not exposed to a probable incident HPV-infection.

We tried to avoid selection bias by defining the inclusion cytology as the first cytology within the inclusion period. E.g. to avoid extracting cases from the control cohort, making it seem healthier. If a woman had an HSIL cytology after a normal cytology within the inclusion period, the normal cytology had priority in cohort allocation. We tried to avoid observation bias by comparing follow-up outcomes within consistent intervals.

4.5 Limitations and weaknesses of the study

Detection bias is a consequence of our study design. The historical and register-based data provides limited information. We don't know how assessments were made, how the clinicians interpreted results and what reasons that determined further management (could explain not-indicated CIN2+ and high number of follow-up visits before being solved). The exposed cohort and the control cohort represent women having different recommendations of follow-up. Therefore, high- and low-grade lesions will be over-detected in the exposed cohort. Differences in compliance also contributes to detection bias among the exposed and non-exposed cohort.

The low number of women in our exposed cohort provided low statistical power and wide, overlapping confidence intervals.

4.6 Implication of findings

The background characteristics and CIN2+ risks probably vary between populations. Katki et. al. (12) suggested the concept of benchmarking to be generalizable to other populations, only requiring the risks for equal management to be the same within the population to which they are being applied. A study with this objective, calculating CIN3+ risks on cytology or other follow-up practices on our population would be advantageous for benchmarking co-test outcomes for different subsets of women.

Future clinical trials with organized co-testing after histologically confirmed normal/CIN1 would be favorable because of limitations to the registry-based study design. Introduction HPV-testing in primary screening, knowing the HPV-status both before and after the normal/CIN1 histology, the HPV-infection course would classify as either persistent or regressed, making future studies easier to perform as registry-based.

Younger women are, both after histologically confirmed normal/CIN1 and primary screening, under increased risks for developing both CIN2+ and CIN3+, and should be followed up closer than older women. Women having histologically confirmed normal/CIN1 resemble a small part of the total screening population, suggesting that closer follow-up would not require excessive use of resources.

A high proportion of women undergo unsolved follow-up over long time. It is a challenge for the health care system that almost 30% of women in the exposed cohort and nearly 40% of women in the control cohort were still unsolved after 78 months. This suggest that high proportions of women undergo unnecessary follow-up, probably inducing psychological distress and decreased trust to the screening programme. Early intervention with vaporization or diagnostic conization are suggestions to avoid unnecessary follow-up. Using follow-up tests with high specificity may reduce the number of unnecessary colposcopies.

5 Conclusion

Compliance to guidelines was better among women attending follow-up after histologically confirmed normal/CIN1 compared to women having normal cytologies in primary screening.

Women in follow-up after histologically confirmed normal/CIN1 were under higher CIN2+ risks compared to women having normal cytologies in primary screening. By the first follow-up cytology after normal/CIN1, the cumulative incidence of CIN2+ was significantly higher for women having an abnormal cytology compared to a normal cytology Women aged 25-39 years were under higher risks for CIN2+ than older women, and should be followed up closely.

For women that had a normal cytology at the first follow-up after histologically confirmed normal/CIN1, the cumulative incidence of CIN3+ was closely consistent to screening in three years. A negative co-test at the first follow-up after histologically confirmed normal/CIN1 probably provides a risk consistent to safe return to screening within a three-year interval.

Improving the assessment of HPV-persistence by future HPV-testing in primary screening, would make future studies easier to perform as registry-based.

6 References

1. Haldorsen T, Skare GB, Steen R, Thoresen SO. Cervical cancer after 10 years of nationally coordinated screening. Tidsskr Nor Laegeforen. 2008;128(6):682-5.

2. Nygard JF, Skare GB, Thoresen SO. The cervical cancer screening programme in Norway, 1992-2000: changes in Pap smear coverage and incidence of cervical cancer. J Med Screen. 2002;9(2):86-91.

3. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol. 2002;55(4):244-65.

4. Tommasino M. The human papillomavirus family and its role in carcinogenesis. Semin Cancer Biol. 2014;26:13-21.

5. zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer. 2002;2(5):342-50.

6. Arbyn M, Tommasino M, Depuydt C, Dillner J. Are 20 human papillomavirus types causing cervical cancer? J Pathol. 2014;234(4):431-5.

7. Smelov V, Elfstrom KM, Johansson AL, Eklund C, Naucler P, Arnheim-Dahlstrom L, et al. Long-term HPV type-specific risks of high-grade cervical intraepithelial lesions: a 14-year follow-up of a randomized primary HPV screening trial. Int J Cancer. 2015;136(5):1171-80.

8. Nayar R, Wilbur D, Solomon D. The Bethesda System for Reporting Cervical Cytology. In: Bibbo M, editor. Comprehensive cytopathology. 3 ed. London: Elsevier; 2008.

9. Steen R, Fiane B, Hagen B, Tropé A, Bergland J. Veileder i gynekologisk onkologi 2009. Trondheim/Bergen/Oslo: Norsk gynekologisk forening; 2009. http://legeforeningen.no/Fagmed/Norsk-gynekologisk-forening/Veiledere/veileder-i-gynekologisk-onkologi-2009/. (cited 2015 09.13)

10. IARC. An Introduction to Cervical Intraepithelial Neoplasia (CIN). Lyon;2005. http://screening.iarc.fr/colpochap.php?chap=2. (cited 2015 10.09)

11. Castle PE, Sideri M, Jeronimo J, Solomon D, Schiffman M. Risk assessment to guide the prevention of cervical cancer. Am J Obstet Gynecol. 2007;197(4):356.e1-6.

12. Katki HA, Schiffman M, Castle PE, Fetterman B, Poitras NE, Lorey T, et al. Benchmarking CIN 3+ risk as the basis for incorporating HPV and Pap cotesting into cervical screening and management guidelines. J Low Genit Tract Dis. 2013;17(5 Suppl 1):S28-35.

13. Kreftregisteret. Flytskjema for oppfølging av cervix-cytologiske screeningprøver. https://www.kreftregisteret.no/globalassets/masseundersokelsen-mot-livmorhalskreft/flytdiagram/flytskjema.pdf. (cited 2017 06.02)

14. Haldorsen T, Baadstrand S, Bjørge T. Sekundærscreening med HPV-tester i masseundersøkelsen mo livmorhalskreft. Oslo: Kreftregisteret; 2011.

15. Kreftregisteret. Flytdiagram for utredning av ASC-US/LSIL og bruk av HPV-test i sekundærscreening i Masseundersøkelsen mot livmorhalskreft. 2009.

16. Deen S, Vreynhoef S, Gandhi N, Juliana A, Nunns D, O'Neill D. The day we started HPV triage. J Clin Pathol. 2016;69(9):822-5.

17. Katki HA, Gage JC, Schiffman M, Castle PE, Fetterman B, Poitras NE, et al. Follow-up testing after colposcopy: five-year risk of CIN 2+ after a colposcopic diagnosis of CIN 1 or less. J Low Genit Tract Dis. 2013;17(5 Suppl 1):S69-77.

18. Skare GB, Lönnberg S. Masseundersøkelsen mot livmorhalskreft. Årsrapport 2009-2011. Oslo; 2013.

19. Skare GB, Lönnberg S. Masseundersøkelsen mot livmorhalskreft. Årsrapport 2012. Oslo; 2014.

20. Skare GB, Lönnberg S. Masseundersøkelsen mot livmorhalskreft. Årsrapport 2014. Oslo; 2015.

21. Massad LS, Jeronimo J, Katki HA, Schiffman M. The accuracy of colposcopic grading for detection of high-grade cervical intraepithelial neoplasia. J Low Genit Tract Dis. 2009;13(3):137-44.

22. Zuchna C, Hager M, Tringler B, Georgoulopoulos A, Ciresa-Koenig A, Volgger B, et al. Diagnostic accuracy of guided cervical biopsies: a prospective multicenter study comparing the histopathology of simultaneous biopsy and cone specimen. Am J Obstet Gynecol. 2010;203(4):321.e1-6.

23. Stoler MH, Schiffman M. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. JAMA. 2001;285(11):1500-5.

24. del Pino M, Garcia S, Fuste V, Alonso I, Fuste P, Torne A, et al. Value of p16(INK4a) as a marker of progression/regression in cervical intraepithelial neoplasia grade 1. Am J Obstet Gynecol. 2009;201(5):488.e1-7.

25. Westre B, Giske A, Guttormsen H, Sorbye SW, Skjeldestad FE. 5-type HPV mRNA versus 14-type HPV DNA test: test performance, over-diagnosis and overtreatment in triage of women with minor cervical lesions. BMC Clin Pathol. 2016;16:9.

26. Ho GY, Einstein MH, Romney SL, Kadish AS, Abadi M, Mikhail M, et al. Risk factors for persistent cervical intraepithelial neoplasia grades 1 and 2: managed by watchful waiting. J Low Genit Tract Dis. 2011;15(4):268-75.

27. Bansal N, Wright JD, Cohen CJ, Herzog TJ. Natural history of established low grade cervical intraepithelial (CIN 1) lesions. Anticancer Res. 2008;28(3b):1763-6.

28. Castle PE, Gage JC, Wheeler CM, Schiffman M. The clinical meaning of a cervical intraepithelial neoplasia grade 1 biopsy. Obstet Gynecol. 2011;118(6):1222-9.

29. Sorbye SW, Arbyn M, Fismen S, Gutteberg TJ, Mortensen ES. HPV E6/E7 mRNA testing is more specific than cytology in post-colposcopy follow-up of women with negative cervical biopsy. PLoS One. 2011;6(10):e26022.

30. Wright TC, Jr., Cox JT, Massad LS, Carlson J, Twiggs LB, Wilkinson EJ. 2001 consensus guidelines for the management of women with cervical intraepithelial neoplasia. Am J Obstet Gynecol. 2003;189(1):295-304.

31. Sorbye SW, Fismen S, Gutteberg TJ, Mortensen ES, Skjeldestad FE. HPV mRNA is more specific than HPV DNA in triage of women with minor cervical lesions. PLoS One. 2014;9(11):e112934.

32. Guido R, Schiffman M, Solomon D, Burke L. Postcolposcopy management strategies for women referred with low-grade squamous intraepithelial lesions or human papillomavirus DNA-positive atypical squamous cells of undetermined significance: a two-year prospective study. Am J Obstet Gynecol. 2003;188(6):1401-5.

33. Mittal S, Basu P, Muwonge R, Banerjee D, Ghosh I, Sengupta MM, et al. Risk of high-grade precancerous lesions and invasive cancers in high-risk HPV-positive women with normal cervix or CIN 1 at baseline-A population-based cohort study. Int J Cancer. 2017;140(8):1850-9.

34. Preisler S, Rebolj M, Untermann A, Ejegod DM, Lynge E, Rygaard C, et al. Prevalence of human papillomavirus in 5,072 consecutive cervical SurePath samples evaluated with the Roche cobas HPV real-time PCR assay. PLoS One. 2013;8(3):e59765.

35. Spinillo A, Gardella B, Iacobone AD, Dominoni M, Cesari S, Alberizzi P. Outcome of Persistent Low-Grade Cervical Intraepithelial Neoplasia Treated With Loop Electrosurgical Excision Procedure. J Low Genit Tract Dis. 2016;20(4):307-11.

7 Tables and figures

Table 1 Selection of the exposed cohort and control cohort

Control cohort		**Exclusion criteria**	**Exposed cohort**			
Normal cytology 01.01.2006-31.12.2007			ASC-US/LSIL 01.01.2006-31.12.2011		ASC-H/HSIL 01.01.2006-31.12.2011	
N	n		n	N	n	N
31,335		**Inclusion cytology**		**3,089**		**850**
	1,914	Age ≤ 24 years	613		41	
	1,268	Age ≥ 70 years	49		76	
	591	≥ HSIL history	64		36	
	343	≥ CIN 1 history	43		13	
	1,271	≥ HSIL before/≥ CIN 1 history	101		53	
	5,387	**Excluded**	**870**		**219**	
25,948		**Eligible for study participation**		**2,219**		**631**
		Missing follow-up	107		15	
		Incomplete follow-up*	159		36	
		Back to screening	1,499		57	
		CIN2 not indicated**	9		11	
		CIN3 not indicated**	15		11	
		CIN2 indicated	128		157	
		CIN3 indicated	77		186	
		CC not indicated	0		0	
		CC indicated	0		9	
	0	**Excluded**	**1,994**		**482**	
		Normal/CIN1 histology		**225**		**149**
25,948		**Total included (index)**	**379**			

* Follow-up not according to management guidelines or case unsolved
** CIN2 and CIN3 without a preceding abnormal cytology or on symptoms and clinical judgement

Table 2 Exposed cohort and control cohort characteristics

Characteristics		Cohort		Total n (%)	Pearson chi-square
		Control n (%)	Exposed n (%)		
Inclusion cytology	2006-2008	25,948 (100)	169 (45.2)	26,117 (99.2)	14,334.5 p < 0.01
	2009-2011	0 (0)	205 (54.8)	205 (0.8)	
	Total	25,948	374	26,322	
Age	25-39	9,369 (36.1)	206 (55.1)	9,575 (36.4)	65.1 p < 0.01
	40-54	9,485 (36.6)	116 (31.0)	9,601 (36.5)	
	55-69	7,094 (27.3)	52 (13.9)	7,146 (27.1)	
	Total	25498	374	26322	
Diagnose before inclusion	No screening history	1,794 (6.9)	57 (15.2)	1,851 (7.0)	133.1 p < 0.01
	Unsatisfactory	865 (3.3)	17 (4.5)	882 (3.4)	
	Normal	22,282 (85.9)	266 (71.1)	22,548 (85.7)	
	ASC-US/LSIL	420 (1.6)	27 (7.2)	447 (1.7)	
	Normal histology	587 (2.3)	7 (1.9)	594 (2.3)	
	Total	25,948	347	26,322	

Table 3 Compliance shown as time from index to first follow-up

Control cohort compliance		Control n (%)	Exposed cohort compliance		Exposed n (%)	Total n (%)
Non-attenders		3,727 (14.4)	**Non-attenders**		20 (5.3)	3,747 (14.2)
Early	<12 mo.*	1,709 (6.6)	**Interval**	<12 mo.	260 (69.5)	1,969 (7.5)
	12-23 mo.	2,640 (10.2)	**Late**	12-23 mo.	62 (16.6)	2,702 (10.3)
Interval	24-42 mo.	10,959 (42.2)		24-42 mo.	25 (6.7)	10,984 (41.7)
Late	43-59 mo.	6,243 (24.1)		43-59 mo.	7 (1.7)	6,250 (23.7)
	80-107 mo.	670 (2.6)		80-107 mo.	0	670 (2.5)
	Total	25,498		**Total**	374	26,322 (100)

* mo. = months

Table 4 Worst histological diagnose at 42 months (first screening round) and 78 months (2nd screening round)

Worst histological diagnose	**Cohort**			
	Control n (%)		Exposed n (%)	
	42 mo.	78 mo.	42 mo.	78 mo.
CIN2	110 (0.4)	109 (0.4)	21 (5.6)	23 (6.1)
CIN3	77 (0.3)	113 (0.4)	9 (2.4)	16 (4.3)
SCC*	3 (0.0)	7 (0.0)	0	1 (0.3)
AC**	5 (0.0)	4 (0.0)	0	0
CIN2+	195 (0.8)	233 (0.9)	30 (8.0)	40 (10.7)

*SCC = Squamous cell carcinoma

** = Adenocarcinoma

Table 5 Exposed cohort HPV-status before index and screening status at 78 months

Screening status at 78 months	**Exposed cohort HPV-status before index n (%**)**		
	Missing	Negative	Positive
Not attending	9 (4.6)	1 (3.6)	10 (6.7)
Back to screening	122 (61.9)	17 (60.7)	73 (49.0)
Incomplete f-up	49 (24.9)	8 (28.6)	45 (30.2)
CIN2	9 (4.6)	2 (7.1)	12 (8.1)
CIN3	7 (3.6)	0	9 (6.0)
CC*	1 (0.5)	0	0
Total N = 379	197	28	149

* CC = 1 case of squamous cell carcinoma
** % column

Table 6 Cumulative incidence of CIN2+ and CIN3+ at 42 and 78 months of follow-up after index

Cohort	Follow-up length	Cumulative incidence of CIN2+ (%)*	95% confidence interval
Control	42 mo.	0.43	(0.34-0.52)
	78 mo.	1.4	(1.2-1.6)
Exposed normal cytology	42 mo.	7.1	(2.7-11.5)
	78 mo.	11.9	(4.1-19.7)
Exposed abnormal cytology	42 mo.	17.9	(11.6-24.2)
	78 mo.	22.0	(14.4-29.6)
Cohort	**Follow-up length**	**Cumulative incidence of CIN3+ (%)****	**95% confidence interval**
Control	42 mo.	0.24	(0.16-0.32)
	78 mo.	0.73	(0.60-0.86)
Exposed normal cytology	42 mo.	2.5	(0.0-5.2)
	78 mo.	5.2	(0.0-11.1)
Exposed abnormal cytology	42 mo.	8.5	(3.8-13.2)
	78 mo.	9.8	(4.5-15.1)

* Overall comparison, Wilcoxon (Gehan) statistic = 559.4 ($p < 0.01$)
** Overall comparison, Wilcoxon (Gehan) statistic = 199.4 ($p < 0.01$)

Table 7 Age-adjusted hazard ratio of CIN2+ and CIN3+ at 78 months of follow-up after index

Cohort	**CIN2+ Hazard ratio**	**95% confidence interval**
Control	1 (ref)	
Exposed cohort f-up		
Normal	9.0*	(4.8-17.0)
Abnormal	22.5*	(15.3-33.2)
Age		
55-69	1 (ref)	
40-54	1.8	(1.1-3.0)
25-39	6.1	(3.8-9.6)
Cohort	**CIN3+ Hazard ratio**	**95% confidence interval**
Control	1 (ref)	
Exposed cohort f-up		
Normal	6.8*	(2.5-18.3)
Abnormal	17.1*	(9.6-30.6)
Age		
55-69	1 (ref)	
40-54	1.6	(0.7-3.7)
25-39	9.0	(4.2-18.4)

* Age-adjusted

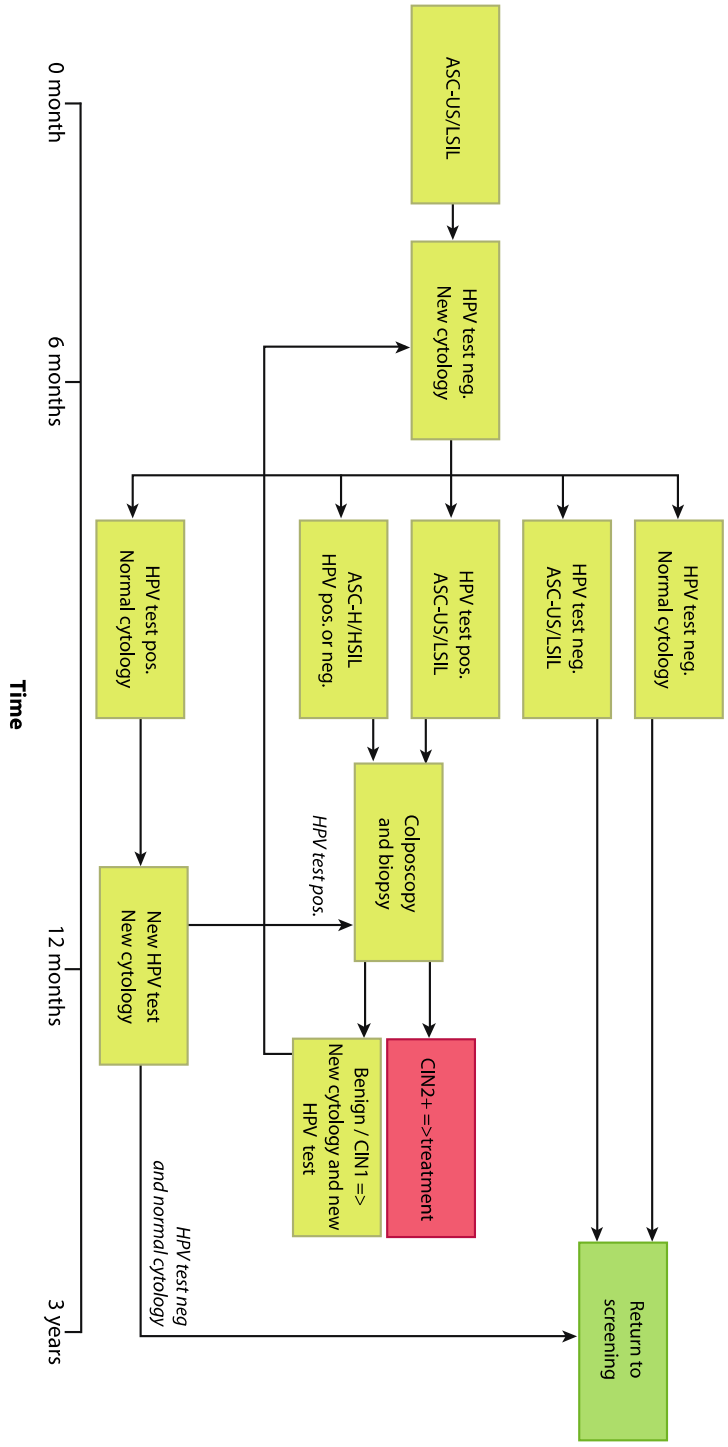


Figure 1 Flowchart showing the ASC-US/LSIL triage algorithm of 2005 (15)

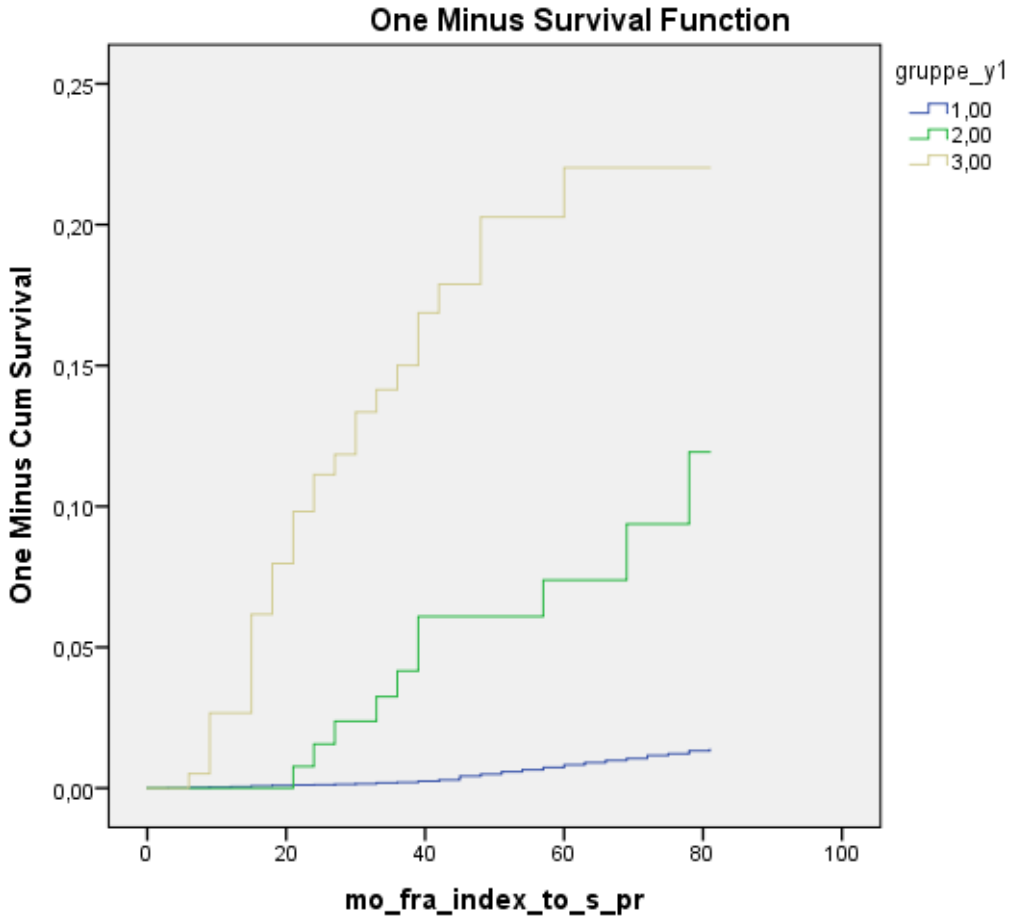


Figure 2 Cumulative incidence of CIN2+ by months of follow-up after index for the exposed cohort of women with a normal follow-up cytology (green), abnormal follow-up cytology (yellow) and the control cohort (blue).

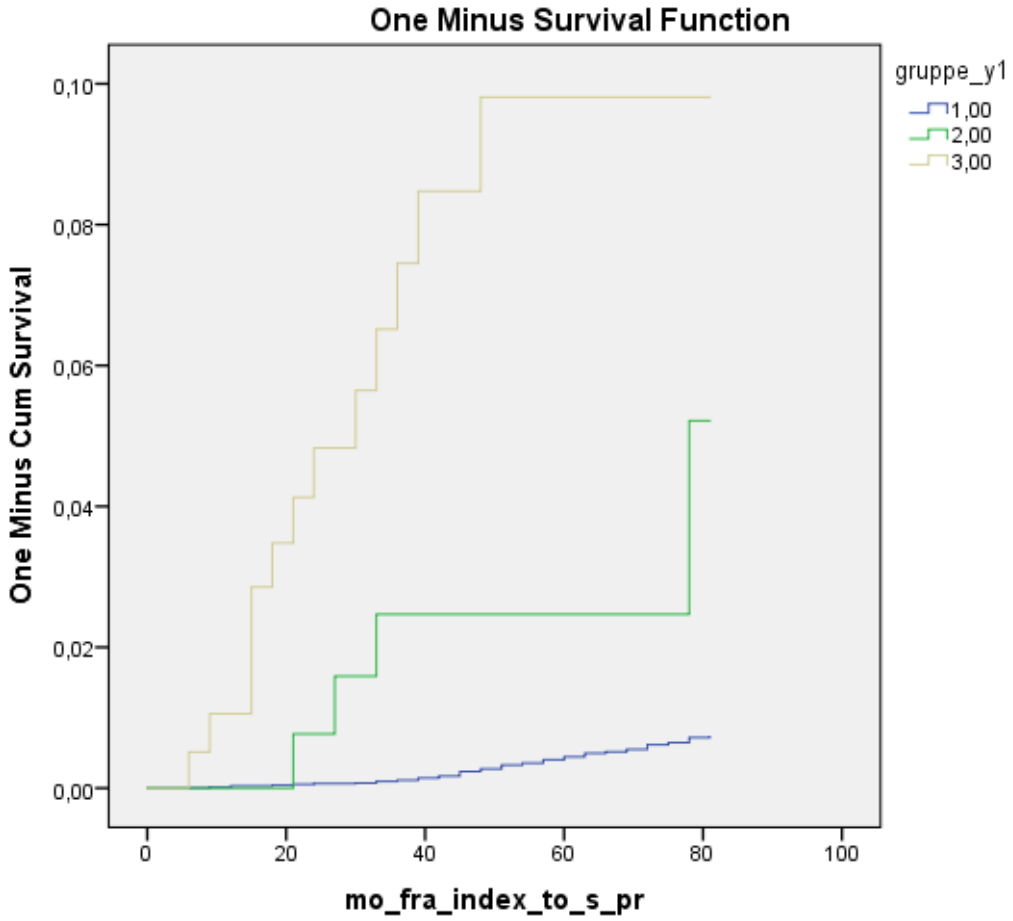


Figure 3 Cumulative incidence of CIN3+ by months of follow-up after index for the exposed cohort of women with a normal follow-up cytology (green), abnormal follow-up cytology (yellow) and the control cohort (blue).

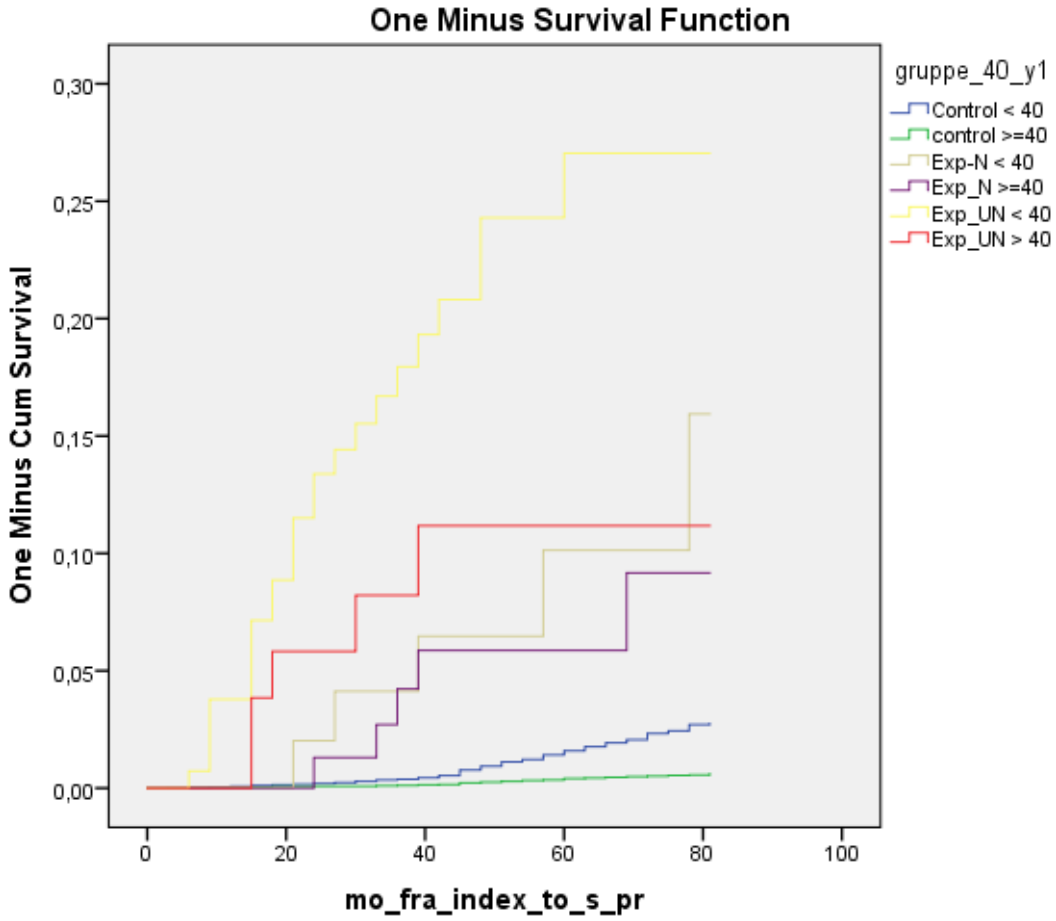


Figure 4 Age-stratified cumulative incidence of CIN2+ for the exposed cohort of women with a normal follow-up cytology (Exp_N), an abnormal follow-up cytology (Exp_UN) and the control cohort (Control).

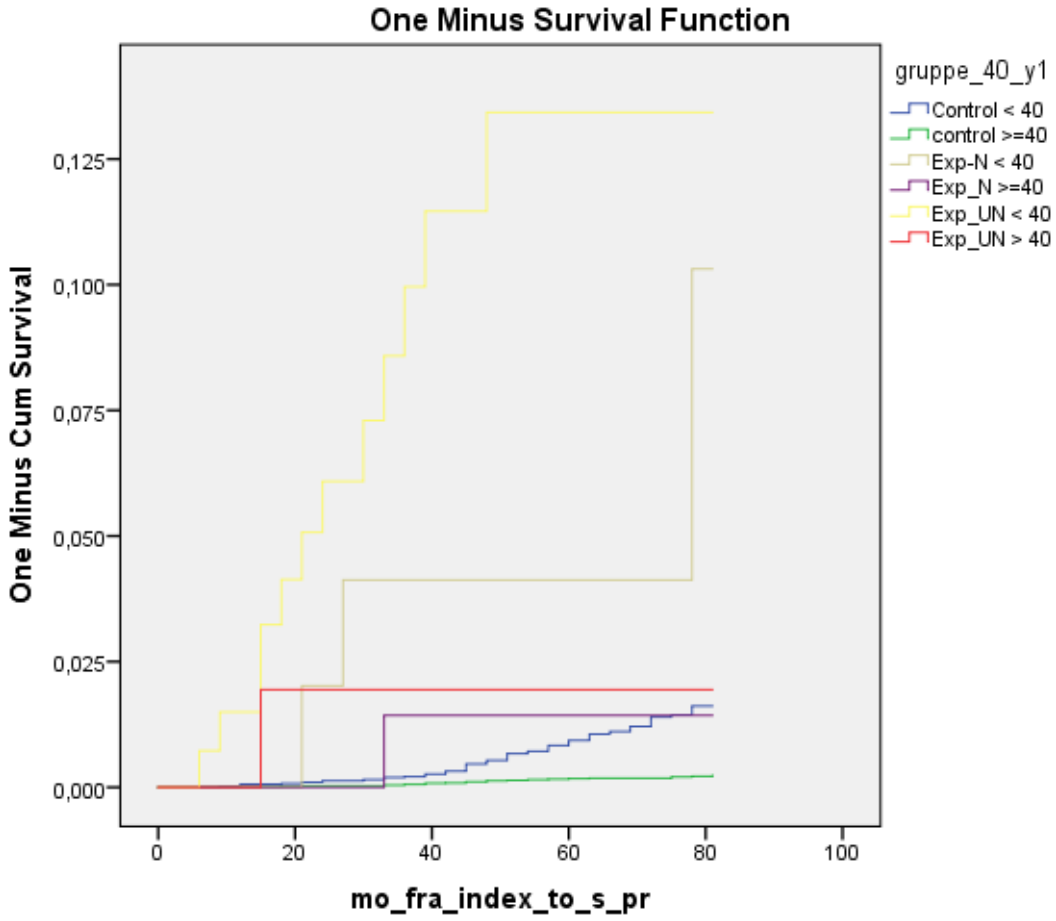


Figure 5 Age-stratified cumulative incidence of CIN3+ for the exposed cohort of women with a normal follow-up cytology (Exp_N), an abnormal follow-upcytology (Exp_UN) and the control cohort (Control).

8 Summaries and evaluations of literature (in Norwegian)

Referanse:
Katki HA, Schiffman M, Castle PE, Fetterman B, Poitras NE, Lorey T et. al. Benchmarking CIN3+ Risk as the Basis for Incorporating HPV and Pap Cotesting into Cervical Screening and Management Guidelines. Journal of Lower Genital Tract Disease. 2013;17(5):S28-S35

Design: Pasientserier	
Dokumentasjonsnivå	III
Grade:	Lav

Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer**

Formål

Å introdusere kotesting i retningslinjene for screening i henhold til prinsippet "lik håndtering av lik risiko". I praksis brukes implisitte risikogrenser for CIN3+ (ved Pap) for å bestemme oppfølging. Disse sammenlignes med CIN3+ risiko ved kotest for å bestemme hvilke resultatkombinasjoner som behøver hvilken oppfølging.

Konklusjon

Sammenligning av CIN3+ risiko ved kotest med implisitte risikoterskler basert på Pap-resultater alene kan, på bakgrunn av "lik håndtering av lik risiko", brukes til å oppnå trygg og konsekvent introdusering av kotesting i retningslinjer.

Land

USA

År data innsamling

2003-2010

Materiale og metode

Data: Kaiser Permanente Northern California (KPNC) cohort

Eksklusjon:
- Alder under 30 og over 65
- Ukjent Pap-resultat (1,1%)

Inklusjon (studiepopulasjon): Kvinner 30-64 år som kotestes ved KPNC. (N=965 360)

Oppfølging: for ASC-US/HPV+ gjøres HPV triage, nesten alltid kotest ved alder over 30.

Biopsi- og kreftinformasjon samlet t.o.m. 31. desember 2010. Matchet med Bay Area Cancer Registry for å idendifisere alle caser, inkludert kvinner ikke lenger med i KPNC.

Deretter beregnet implisitt risikogrense for Pap-test alene og overført dem til ny håndteringsveiledning for kotesting.

5-års risiko for CIN3+, anbefalinger:
- > 5.2 % → kolposkopi
- Ca. 2.6 % → ny test innen 6-12 mnd.
- Rundt 0.26% → Ny test om tre år

Resultater

CIN3+ risiko ved kotestrestultater sammenlignet med risikogrenser (basert på Pap-tester i screening) som er implisitt brukt for å bestemme oppfølgingsstrategi i screening.

Anbefalt oppfølgings-strategi basert på Pap	**Implisitt risikoterskel: 5-års CIN3+ risiko ved baseline Pap (uavh. HPV)**			**5 år CIN3+ risiko ved baseline kotest**		
	Resultat som bestemmer oppfølging	Frekv. kvinner 30-64 år %	CIN3+ risiko %	HPV/Pap resultat	Frekv. kvinner 30-64 år %	CIN3+ risiko %
Kolposkopi	SCC	< 0.01	84	HPV+/HSIL	0.20	49
	HSIL	0.21	47			
	ASC-H	0.17	18	HPV+/AGC	0.05	33
	AGC	0.21	8.5	HPV-/HSIL	0.01	30
	LSIL	0.97	5.2	HPV+/ASC-H	0.12	25
				HPV-/ASC-H	0.05	3.5
				HPV-/AGC	0.16	0.9
				HPV+/ASC-US	1.1	6.8
				HPV+/LSIL	0.81	6.1
Ny test innen 6-12 mnd.	ASC-US	2.8	2.6	HPV+/Pap-	3.6	4.5
				HPV-/LSIL	0.19	2.0
3 år screen	Pap-	95.6	0.26	HPV-/ASC-US	1.8	0.43
5 år screen				HPV-/Pap-	92.0	0.08

Beregning av CIN2+ risiko finnes også i artikkelen.

Diskusjon/kommentarer

Sjekkliste:
- Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? Nei
- Var det sikret at utvalget ikke var selektert? Usikkert
- Var inklusjonskriteriene for utvalget klart definert? Ja
- Er svarprosenten høy nok? Ikke spesifisert.
- Var alle pasientene i utvalget i samme stadium av sykdom? Ja
- Var oppfølgningen tilstrekkelig (type/omfang/tid) for å synliggjøre endepunktene? Ikke spesifisert
- Ble objektive kriterier benyttet for å vurdere/validere endepunktene? Ja
- Ved sammenlikninger av pasientserier, er seriene tilstrekkelig beskrevet og prognostiske faktorers fordeling beskrevet? Ja
- Var registreringen av data prospektiv? Historisk prospektiv

Styrke
Kan også brukes for res. etter kolposkopi (risikostratifisering).
Stort utvalg
Populasjonsbasert

Svakhet
Basert på amerikanske anbefalinger og retningslinjer.
Oppfølgingstid?

Referanse:
Katki HA, Gage JC, Schiffman M, et al. Follow-up Testing After Colposcopy: Five-Year Risk of CIN2+ After a Colposcopic Diagnosis of CIN1 or Less. J Low Gen Tr Dis 2013;75(5):S69-S77

Design: Pasientserier

Dokumentasjonsnivå:	III
Grade:	Lav

Formål

Beregne CIN2+ risiko blant kvinner med normal/CIN1 biopsi. Identifisere hvilke oppfølgingsstrategier med negative tester (HPV/cyt/kotest) som gir lav nok CIN2+ risiko forenlig med å utføre neste oppfølging innenfor et lengre intervall.

Konklusjon

Flere negative oppfølgingsprøver (i ulike kombinasjoner) ga ikke lave nok CIN2+ risikoer forenlig med oppfølging etter fem år.

For kvinner med HPV+ og ASC-US/LSIL før biopsien, gav én negativ kotest en CIN2+ risiko forenlig med oppfølging etter tre år.

Land

USA

År datainnsamling

2003-2010

Materiale og metode

Data: Kaiser Permanente Northern California (KPNC) cohort

KPNC retningslinjer:
- HPV+/ASC-US or LSIL+ → kolposkopi og biopsi
- Normal/CIN1 oppfølging → kotesting, intervaller ikke spesifisert

Inklusjon: Kvinner >25 år ved baseline med cytologi eller kotest som indikerer kolposkopi. Screenet mellom 2003-2010. (N=36801)

Eksklusjon:
- Ingen flere oppfølgingsdata (n=11759)
- CIN2+ biopsi (n=4177)
- Behandlet for <CIN2 (n=335)
- Tvetydige utfall (n=103)
- Mangler oppfølging, HPV- og cytologidata (n=108)

Studiepopulasjon: Normal/CIN1 biopsi eller antatt normal kolposkopi uten biopsi. (N=20319)

Follow-up: KPNC retningslinjer. Histologisk utfall registrert t.o.m. 31. desember 2010.

Beregninger:
Kotestingen ble delt opp og analysert i tre kategorier:
1) Cytologi
2) HPV
3) Kotest

… hvorav 5-års CIN2+ risiko ble beregnet blant kvinner med **negative oppfølgingsprøver i alle kategoriene.**

Resultater

Tabell 3 5-års CIN2+ risiko hvis HPV+/ASC-US eller LSIL før biopsi, fremstilt mot klinisk risikoterskel som brukes for å bestemme oppfølging

		Oppfølging cyt		Oppfølging HPV		Oppfølging kotest	
Nåværende anbefalt oppfølging basert på screening med kun cyt	Implisitt risikoterskel: 5-års CIN2+ risiko (%) ved baseline cyt-resultat	Cyt-resultat(er)	5-års CIN2+ risiko etter siste test (%)	HPV-resultat(er)	5-års CIN2+ risiko etter siste test (%)	Kotest resultat(er)	5-y CIN2+ risiko etter siste test (%)
Kolposkopi	LSIL: 16						
6-12 mnd ny prøve	ASC-US: 6.9	1 negativ 2 negative	5.4 4.0				
Intermediær				1 negativ 2 negative	2.0 1.8		
3 år ny prøve	Cyt-: 0.68					1 negativ 2 negative	1.1 1.0

Tabell 4 Samme som over, men gjelder for ASC-H/HSIL og AGC før biopsi

		ASC-H/HSIL+ cyt resultat forutgående for kolposkopi		AGC cyt resultat forutgående for kolposkopi	
Nåværende anbefalt oppfølging basert på screening med kun cyt	Implisitt risikoterskel: 5-års CIN2+ risiko (%) ved baseline cyt-resultat	Oppfølgings-resultat etter kolposkopi	5-års CIN2+ risiko etter oppflg-test (%)	Oppfølgings-resultat etter kolposkopi	5-års CIN2+ risiko etter oppflg-test (%)
Kolposkopi	LSIL: 16				
6-12 mnd return	ASC-US: 6.9	1 negativ cyt 1 negativ HPV	7.0 4.4		
Intermediær		1 negativ kotest	2.2	1 negativ cyt	1.7
3-y return	Cyt-: 0.68			1 negativ HPV	0.58

Diskusjon/kommentarer

Sjekkliste:
- Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? Nei
- Var det sikret at utvalget ikke er for selektert? Usikkert
- Var inklusjonskriteriene for utvalget klart definert? Ja
- Er svarprosenten høy nok? Ikke beskrevet
- Var alle pasientene i utvalget i samme stadium av sykdom? Ja
- Var oppfølgningen tilstrekkelig (type/omfang/tid) for å synliggjøre endepunktene? Ja
- Ble objektive kriterier benyttet for å vurdere/validere endepunktene? Ja
- Ved sammenlikninger av pasientserier. Ikke relevant
- Var registreringen av data prospektiv? Historisk prospektiv

Styrke
Populasjonsbasert
Stor studiepopulasjon.
Tatt hensyn til screeningresultat før biopsi.

Svakhet
Ikke tatt hensyn til scr. historie.
Ikke kontrollgruppe.
Beskriver ikke frafall.
15-40% uten biopsi mellom index og oppfølging.
Muligens ikke overførbart til noen andre populasjoner utenom KPNC

Referanse:
Guido R, Schiffman M, Solomon D, Burke L. Postcolposcopy management strategies for women referred with low-grade squamous intraepithelial lesions or human papillomavirus DNA-positive atypical squamous cells of undetermined significance: a two-year prospective study. American journal of obstetrics and gynecology. 2003;188(6):1401-5.

Design: Pasientserier

Dokumentasjonsnivå	III
Grade:	Lav

Formål

Å sammenligne oppfølginger av kvinner henvist til kolposkopi/biopsi pga. LSIL eller HPV+/ASC-US, der resultatet var CIN1 eller mindre.

Konklusjon

Den mest effektive testen for å identifisere CIN2-3 etter kolposkopi, kan være HPV-test alene etter 12 mnd.

Land

USA

År datainnsamling

1997-2001

Materiale og metode

Bakgrunnspopulasjon: ASC-US LSIL triage study (ALTS)

Inklusjon:
Immediate colposcopy (IC)-arm:
- HPV+/ASC-US (n=1132)
- LSIL (n=852)

Eksklusjon:
- Conservative management (CM)-arm av LSIL
- Unormal kolposkopi, mangl. biopsi (n=42)
- CIN2+ (n=355)
- CIN2+ mellom initial og oppf. biopsi eller LEEP før dette (n=48)

Studiepopulasjon:
- CIN1 (HPV+/ASC-US) (n=881)
- CIN1 (LSIL) (n=658)
- N=1539

Oppfølging:
6, 12 og 18 mnd med cyt, HPV, cervigram.
HSIL henv. til kolposkopi.
Exit undersøkelse ved 24 mnd.

Endepunkt:
Histologisk verifisert CIN2+.

Resultater

Table 1 Distribution of enrollment colposcopy and directed biopsy results by referral cytology group for study population and risk for subsequently diagnosed CIN2 or 3.

Enrollment colposcopy and directed biopsy result	ASC-US	LSIL	All	Risk of subsequently diagnosed CIN grade 2 or 3 N (%)*
Normal colposcopic impression, no biopsy	192	96	288	30 (10.4)
Negative biopsy	338	203	541	53 (9.8)
CIN1	351	359	710	80 (11.3)
All	881	658	1539	163 (10.6)

P=0.70 comparing percentage diagnosed with CIN grade 2 or 3 in three groups. *Risk for CIN2-3 detected either during 2-year follow-up or at exit colposcopy.

Table 4 Performance of repeat cytology in post colposcopy management of women with CIN1 or less.

Management strategy	Sensitivity of detection of subsequent CIN grade 2 or 3 (% [95%CI])	Women who would be positive (% [95 % CI])
Repeat cytology at HSIL threshold		
1	23.9 (17.4-30.5)	4.7 (3.6-5.8)
2	37.5 (29.9-45.1)	7.2 (5.8-8.5)
3	44.9 (36.8-52.8)	8.3 (6.8-9.8)
Repeat cytology at LSIL threshold		
1	49.1 (41.4-56.8)	25.2 (22.9-27.4)
2	70.5 (63.3-77.7)	34.6 (32.1-37.1)
3	77.2 (70.4-83.9)	38.3 (25.7-40.9)
Repeat cytology at ASC-US threshold		
1	76.7 (70.2-83.2)	51.7 (49.1-54.3)
2	88.0 (82.9-93.1)	63.6 (61.1-66.1)
3	95.1 (91.6-98.6)	70.0 (67.5-72.5)

Diskusjon/kommentarer

Sjekkliste:
- Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? Ja
- Var det sikret at utvalget ikke var selektert? Usikkert
- Var inklusjonskriteriene for utvalget klart definert? Ja
- Er svarprosenten høy nok? Ikke beskrevet frafall
- Var alle pasientene i utvalget i samme stadium av sykdom? Ja
- Var oppfølgningen tilstrekkelig (type/omfang/tid) for å synliggjøre endepunktene? Ja
- Ble objektive kriterier benyttet for å vurdere/validere endepunktene? Ja
- Ved sammenlikninger av pasientserier, er seriene tilstrekkelig beskrevet og prognostiske faktorers fordeling beskrevet? Ikke relevant
- Var registreringen av data prospektiv? Historisk prospektiv

Styrke
Stor studiepopulasjon.
Bakgrunnspopulasjonen er randomisert til ulike oppfølginger (konservativ, kolposkopi/biopsi, triage).

Svakhet
ALTS ikke designet for å se på oppfølging etter kolposkopi. Tatt ut noen kvinner med CIN2-3 på kvalitetskontroll, dermed friskgjøres studiepopulasjonen mtp. klinisk realitet.
Risiko for detection bias pga direkte kolposkopi, ved exit visste klinikeren tidligere resultater.

Referanse:
Mittal S, Basu P, Muwonge R, Banerjee D, Ghosh I, Sengupta MM, et al. Risk of high-grade precancerous lesions and invasive cancers in high-risk HPV-positive women with normal cervix or CIN 1 at baseline-A population-based cohort study. International journal of cancer. 2017;140(8):1850-9.

Design: Pasientserie	
Dokumentasjonsnivå	III
Grade:	Lav

Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer**
CIN2+ risiko i oppfølging av HR-HPV-positive kvinner med normal/CIN1 histologi, og se på faktorene som påvirker risikoen. **Konklusjon** ***Ca. ¾ av HR-HPV+ og lavgradig histologi klarerer infeksjonen ila kort tid, derav lav CIN3+ risiko.*** ***Eldre kvinner og høy/økende viral load har høyere risiko for HPV-persistens og en risikobasert oppfølgingsstrategi kan vurderes.*** **Land** **India** **År datainnsamling** April 2010 – mars 2015	**Inklusjon:** HR-HPV positive (HCII test) kvinner (n=2045) 30-60 år offentlig screeningsdemonstrasjonsprosjekt av CNCI, Kolkata, India. CIN1/normal biopsi eller normal kolposkopi. Ingen tidligere cervical neoplasi. N=1608 **Eksklusjon:** CIN2+ baseline, N= 220 **Oppfølging:** HR-HPV, kolposkopi og biopsi årlig. Aktiv påminnelse og oppsøking av pas. dersom ikke møtt. **Endepunkt:** CIN2+ **Analyser, risiko for CIN2+ påvirket av:** - Baseline karakteristika - HPV viral load, HPV persistens - HPV-status på evt. CIN2+ resultat	46,8 % minst én oppfølging. Median oppfølgingstid 2,1 personår. Tabell 3. Karakteristika som påvirker progresjon til CIN2+. Ikke tatt med utdanning, sivilstatus, gift ved alder, paritet, menopause. Progresjon av CIN 1 hos 27/177 (15,3 %), eneste signifikant faktor var HPV persistens. 25,6 % hadde persistent HPV-infeksjon.	**Sjekkliste:** - Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? **Rural area selektert ut fra gjennomførbarhet på prosjektet og lokale behov.** - Var det sikret at utvalget ikke var selektert? **Usikkert** - Var inklusjonskriteriene for utvalget klart definert? **Ja** - Er svarprosenten høy nok? **Nei** - Var alle pasientene i utvalget i samme stadium av sykdom? **Ja** - Var oppfølgningen tilstrekkelig (type/omfang/tid) for å synliggjøre endepunktene? **Ja** - Ble objektive kriterier benyttet for å vurdere/validere endepunktene? **Ja** - Ved sammenlikninger av pasientserier, er seriene tilstrekkelig beskrevet og prognostiske faktorers fordeling beskrevet? **Ikke relevant** - Var registreringen av data prospektiv? **Ja** **Styrke** - Relevant for utfordringer i lavressurspopulasjon - Ekskludert historie med cervical intraepitelial neoplasi **Svakhet** Selektert populasjon. Høyt frafall - Ift. egen oppgave: ikke-etablert screeningprogram i lavressurspopulasjon og inklusjon kun basert på HPV

Baseline character-istics	Women with no disease or CIN1 at baseline (N)	Women who progr-essed to CIN2+ N (%)	PYO of obser-vation	Incid-ence rate of CIN2+/ 100 PYO	Crude hazard ratio (95 % CI)	Adjus-ted hazard ratio (95% CI)
Participants	650	41 (6,3)	1357	3,0		
Age 30-39 40-49 50-60	 357 179 114	 13 (3,6) 7 (3,9) 21 (18,4)	 784 355 217	 1,7 2,0 9,7	 1,00 1,25 (0,5-3,15) 6,35 (3,6-12,75)	 1,00 1,19 (0,43-3,35) 4,32 (1,05-17,74)
HPV status Cleared Persistent	 466 160	 10 (2,1) 31 (19,4)	 1000 313	 1,0 9,9	 1,00 10,78 (5,78-22,01)	 1,00 6,28 (2,87-13,73)
HPV viral load 1-10 10-100 100+	 300 138 212	 12 (4,0) 9 (6,5) 20 (9,4)	 644 266 446	 1,9 3,4 4,5	 1,00 1,93 (0,81-4,58) 2,43 (1,19-4,98)	 1,00 1,33 (0,53-3,34) 1,23 (0,56-2,67)
Final diagnosis at baseline Normal CIN1	 311 339	 14 (4,5) 27 (8,0)	 644 712	 2,2 3,8	 1,00 1,71 (0,90-3,26)	 1,00 1,22 (0,60-2,46)

Referanse:
Sørbye SW, Arbyn M, Fismen S, Gutteberg TJ, Mortensen ES. HPV E6/E7 mRNA Testing Is More Specific than Cytology in Post-Colposcopy Follow-Up of Women with Negative Cervical Biopsy. PLoS ONE. 2011;6(10):1-8.

Design: Historisk Kasusserie

Dokumentasjonsnivå	III
Grade:	Middels

Formål

Undersøke om HPV E6/E7 mRNA-testing er mer spesifikk enn oppfølgingscytologi uten tap av sensitivitet postdiagnostisk av kvinner med negativ biopsi

Konklusjon

Post-kolposkopi HPV mRNA-testing er like sensitiv, men mer spesifikk, enn post-kolposkopi cytologi. mRNA-testen hadde høyere PPV.

Land

Norge – Troms og Finnmark

År data innsamling

2005-2009

Materiale og metode

Celleprøver fra screening, populasjon Troms og Finnmark. 2005-2009 63740 celleprøver og 6027 biopsier fra kvinner 25-69 år. 1484 med ASC-H, HSIL eller ASC-US/LSIL og positiv HPV mRNA.

Eksklusjonskriterier:
- kvinner uten biopsi
- CIN2+ på første biopsi
- flere unormale cyt. og/eller HPV+ på post-kolposkopioppfølging, men uten rebiopsi

520 kvinner med negativ/lavgradig biopsi inkludert. 192 tok en væskebasert cytologi for HPV mRNA-testing. 328 ble det mottatt vanlig Pap-smear der HPV-testing ikke er mulig (cytologigruppe).

CIN2+ brukt som endepunkt og CIN0-1 som fravær av sykdom. ++

Sens, spes, PPV, NPV beregnet fra 2x2-tabell for cytologi, HPV mRNA og begge. Cutoff ASC-US+ og ASC-H+.

Diagnosene hentet fra SymPathy. Biopsier evaluert av erfarne patologer.

Statistikk:
- Pearson chi square for å undersøke assosiasjon mellom testresultat og endelig sykdomsstatus

Resultater

Cytologi (n=328):

Utfall i cytologigruppe med cutoff ASC-US+

Cytologi	Utfall				%	95% CI
	CIN2+	<CIN2	Total	Sensitivitet	84.6	76.6, 92.6
ASC-US+	66	59	125	Spesifisitet	76.4	71.1, 81.7
NILM	12	191	203	PPV	52.8	44.0, 61.6
Total	78	250	328	NPV	94.1	90.8, 97.4

Cutoff ASC-H+

Cytologi	Utfall				%	95% CI
	CIN2+	<CIN2	Total	Sensitivitet	53.8	42.8, 64.9
ASC-US+	42	9	51	Spesifisitet	96.4	94.1, 98.7
NILM	36	241	277	PPV	82.4	71.9, 92.8
Total	78	250	328	NPV	87.0	83.0, 91.0

HPV mRNA (n=192):

Utfall ved kun postkolkoskopi HPV mRNA

HPV mRNA resultat	Utfall				%	95% CI
	CIN2+	<CIN2	Total	Sensitivitet	89.1	80.1, 98.1
Positiv	41	11	52	Spesifisitet	92.5	88.2, 96.7
Negativ	5	135	140	PPV	78.8	67.7, 89.9
Total	46	146	192	NPV	96.4	93.3, 99.5

Ratio for sens, spes og PPV for HPV mRNA sammenlignet med cytologi hhv 1.05, 1.21 og 1.49.

Utfall for HPV mRNA-gruppe hvis triage med HPV mRNA kombinert med cytologi:
- Cutoff ASC-US+ sens 97.8, spes 63.0, PPV 45.5, NPV 98.9.
- Cutoff ASC-H+ sens 93.5, spes 89.0, PPV 72.9, NPV 97.7.

Diskusjon/kommentarer

Sjekkliste:
- Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? Nei
- Var det sikret at utvalget ikke var selektert? Usikkert
- Var inklusjonskriteriene for utvalget klart definert? Ja
- Er svarprosenten høy nok? Usikkert
- Var alle pasientene i utvalget i samme stadium av sykdom? Ja
- Var oppfølgningen tilstrekkelig (type/omfang/tid) for å synliggjøre endepunktene? Ja
- Ble objektive kriterier benyttet for å vurdere/validere endepunktene? Ja
- Ved sammenlikninger av pasientserier, er seriene tilstrekkelig beskrevet og prognostiske faktorers fordeling beskrevet? Ikke relevant
- Var registreringen av data prospektiv? Historisk prospektiv

Styrke
Populasjonsbasert
Stor studiepopulasjon

Svakhet
Tar ikke høyde for høygradige forandringer i screeninghistorie

Referanse: Spinillo A, Gardella B, Iacobone AD, Dominoni M, Cesari S, Alberizzi P. Outcome of Persistent Low-Grade Cervical Intraepithelial Neoplasia Treated With Loop Electrosurgical Excision Procedure. Journal of lower genital tract disease. 2016;20(4):307-11.			Design: Pasientserier Dokumentasjonsnivå: III Grade: Middels
Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer**
Å evaluere utfall av persistent (> 2 år) CIN1 behandlet med loop electrosurgical excision procedure (LEEP). **Konklusjon** ***Det var lav CIN2+ insidens i oppfølgingen av LEEP-behandlede persistente histologisk bekreftede CIN1 etter ASC-US/LSIL cytologi. Andelen kvinner med lavgradige celleforandringer var fortsatt høy, med 10 caser per 100 personår ved 25 mnd median oppfølging.*** **Land** **Italia** **År datainnsamling** 2007-2014	**Bakgrunnspopulasjon:** kvinner som var til kolposkopi i perioden 2007-2014 ved University of Pavia, IRCCS Fondazione Policlinico San Matteo, Pavia, Italia. **Inklusjonskriterier (N=324):** • CIN1 etter ASC-US/LSIL • Persistens av lavgradig cervixlesjon enten ved ASC-US/LSIL eller CIN1 ved minst 2 tilfeller under 2 år oppfølging. • Vellykket kolposkopi • Klinisk vurdert til LEEP for lavgradig cervixlesjon **Eksklusjon:** • Ikke utført LEEP (n=20) • Høygradig LEEP (n=22) • LEEP negativ for CIN (n=10) • Utilstrekkelig oppfølging (<1 år) (n=20) **Studiepopulasjon:** Persistent eller intermitterende CIN1 med minst 24 mnd varighet behandlet med LEEP (N=252) Persistens dokumentert ved: • 64.7 % ASC-US/LSIL x 2 • 35.3 % cyt + biopsi **Oppfølging:** Cytologi, kolposkopi, molekylærdiagnostikk 6 mnd, 1 år og deretter hvert år post-LEEP.	Alle hadde minst ett år oppfølging. Median oppf. tid 25 mnd. 69.8 % hadde minst 2 år oppfølging og 50.8 % hadde minst tre år. Alle tilfeller av CIN2+ hadde celleforandringer i oppfølgingen. Kumulativ insidens av CIN2+ • Ved 2 år: 2.3 % (4/276) • Ved 3 år: 5.5 % (7/128) Lavgradige cervixlesjoner post-LEEP diagnostisert hos 70 kvinner (27.8 %) Persisterende og høyrisiko HPV-infeksjon i oppfølging var assosiert med høyere rate av CIN persistens/progresjon.	**Sjekkliste:** • Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? Nei • Var det sikret at utvalget ikke var selektert? Usikkert • Var inklusjonskriteriene for utvalget klart definert? Ja • Er svarprosenten høy nok? Ja • Var alle pasientene i utvalget i samme stadium av sykdom? Ja • Var oppfølgningen tilstrekkelig (type/omfang/tid) for å synliggjøre endepunktene? Ja • Ble objektive kriterier benyttet for å vurdere/validere endepunktene? Ja • Ved sammenlikninger av pasientserier, er seriene tilstrekkelig beskrevet og prognostiske faktorers fordeling beskrevet? Ikke relevant. • Var registreringen av data prospektiv? Ja **Styrke** Populasjonsbasert Lite frafall **Svakhet** Ikke tatt hensyn til screeninghistorie Intensiv oppfølging øker risiko for deteksjonsbias.