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Follow-up of women with unsatisfactory pap-smears - a historical prospective cohort study.

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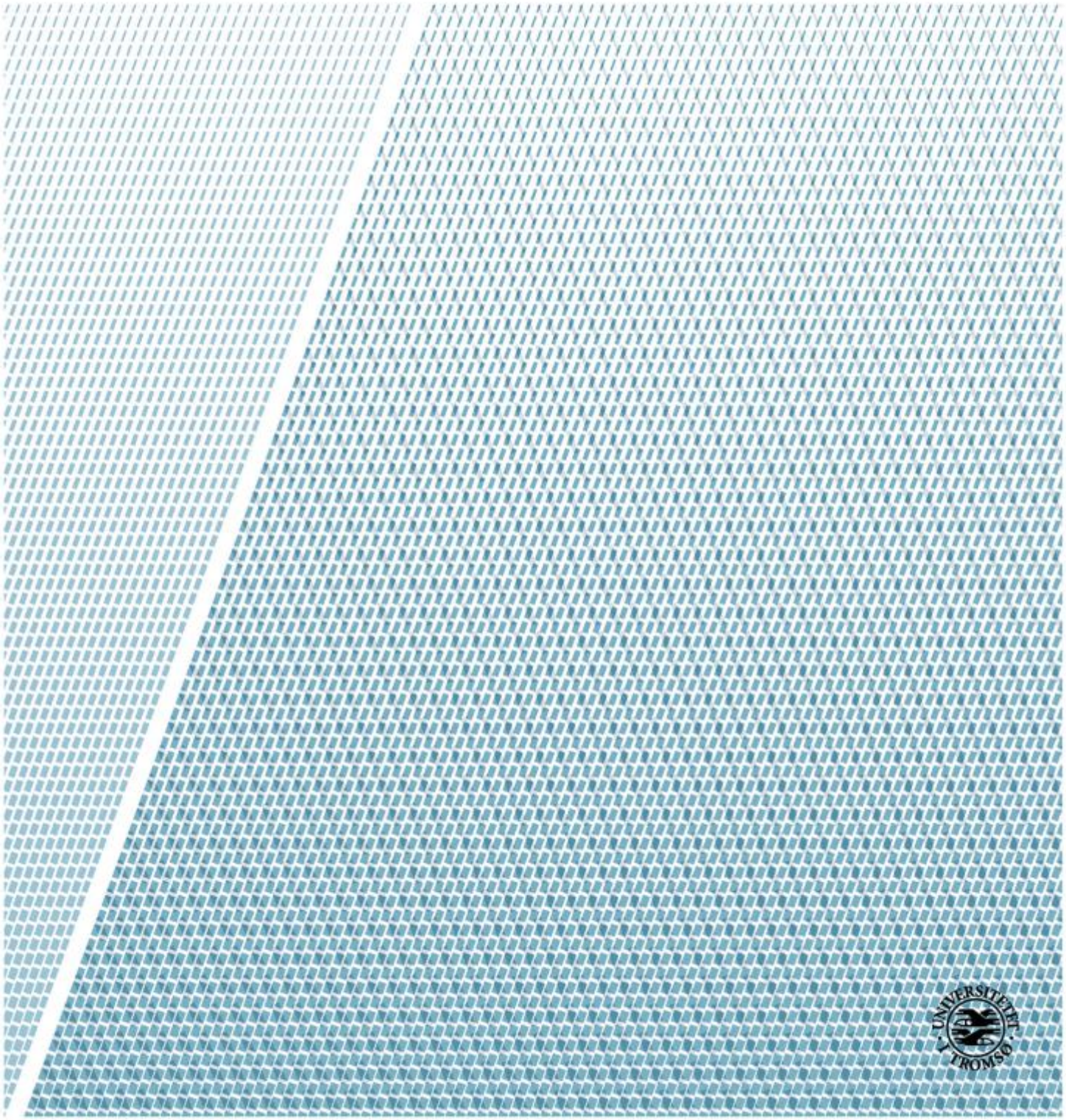
Master thesis (MED-3950)

UiT, The Arctic University of Norway

Tromsø, June 2017



1 Preface/working process

Autumn 2015, my study friend Mathilde Bjørnerem and I contacted Sveinung Wergeland Sørbye to discuss potential topics for our master thesis. We were both interested in studying topics such as gynecology and/or women's cancer, and more specifically HPV and cervical cancer. In the following 3-4 weeks, we got several articles to read, discuss and evaluate. This to get a deeper understanding in how the screening program works, the development of cancer and what topics had been studied earlier.

We were introduced to Finn-Egil Skjeldestad, who would later be our main supervisor. Finn Egil was a close collaborator of Sveinung, had vast experience in analyzing/programming in statistical programs such as SPSS, and had been supervising these kinds of tasks several times before. In September 2015, the four of us had our first meeting and started to discuss the further progress. Mathilde and I wanted a common overall theme, though separate objectives, to be able to discuss and help guide each other along the way. We were included in a group of 3 other students, Liv Reidun Tverrelv, Marte Slettbakk and Kristina Benedicte Dahl Olafsen. In October of our 4th year we prepared a project plan, which included the background material that would later constitute the background section of the final thesis. It was a continuous process of writing, discussion and getting feedback both by mail and through personal meetings with the supervisors.

In January 2016, we started having regular literature evaluation meetings every other week to present new articles. The articles evaluated then, were more related to our individual objectives and were going to constitute a collection of our main resources. This process was very educational in that I feel I got a more critical eye on studies done, and how to evaluate whether results are trustworthy or not. Additionally, I benefited greatly from the discussions in the group and questions considering interpretation of the results from both supervisors. In total, we had 5-6 literature evaluation meetings. A first draft of the plan for analysis was also compiled before we sat the assignment aside to focus on our last exam of the 4th year.

We continued the work for a couple of weeks in August 2016, before we headed off to fifth years clinicals. At this point we got introduced to the data file including the whole study population in SPSS. Finn Egil and I had two meetings during the fall, whereas I continuously sent him new drafts of the thesis for feedback.

From March to June 2017, most of the writing and programming was done. Tables and diagrams were made by me based on statistical analysis done by Finn Egil. The analyses were done based on my analytical plan. Results and discussion were then written with continuous feedback from my supervisor. Throughout the whole process, we had regular contact by mail and several meetings in Tromsø. I want to thank my main supervisor Finn-Egil Skjeldestad and co-supervisor Sveinung Wergeland Sørbye for a good cooperation. They have contributed with years of knowledge in the field, and have given words of encouragement when the final product seemed out of reach. The next step is to reform my master thesis into an article and to get our study published in a national-or international journal.

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2 Abstract

Objectives: To assess compliance based on screening recommendations and outcome of screening for women diagnosed with an unsatisfactory pap-smear compared to normal controls.

Setting: An eight-year prospective cohort study performed on women in Troms and Finnmark participating in the national screening program for cervical cancer from 2006-2014.

Material and methods: We assessed compliance before and after an index pap-smear. Women in the exposed cohort were defined as compliant 1 through 6 months or non-compliant >7 months. Women in the non-exposed cohort were defined as too early (<24 months), compliant (24 through 41) or too late (>42months). We identified status within 1st screening period (42 months after index smear) and calculated the detection rate. Main outcomes were CIN2, CIN3 and SCC. The women's most adverse outcome was estimated within 78 study months. Used in the study are chi-square test, t-test and survival analysis in SPSS with level of significance $p < 0.05$.

Results: 1,571 exposed women and 24,665 non-exposed women were included in the study. The exposed women were less compliant prior to index compared to the control group (41.9% vs 56.3%). Of the non-exposed women 31.7% met within the recommended interval for their first follow-up. The compliant, exposed women accounted for 51.0%. The detection rate of CIN2, CIN3 and ICC was significantly higher within the exposed women**.** A total of 1.3% CIN2+ in the exposed women and 0.2% in the non-exposed women were detected within the first screening period. Within final follow-up 2.0% and 0.8% CIN2+ were found in the exposed and non-exposed groups respectively.

Conclusion: Women with unsatisfactory tests are more compliant to recommended guidelines and have, in our low-risk population, higher incidence of CIN2+ compared to women with normal index pap-smears.

3 Background

3.1 The cervical cancer screening program

Worldwide, cervical cancer is the third and fourth most common cancer considering incidence and mortality. (1) Every year, 60 000 women in Europe die of cervical cancer, 70-80 of these in Norway. (2) Many cervical cancer cases can be prevented by routine screening with pap-smear examinations. Based on this, a national screening program was established. In 1995 “The cervical cancer screening program” was launched, recommending pap-smear screening every third year for women between 25 and 69 years of age. (3) (4) The main aim of the program is to discover premalignant lesions (cervical dysplasia), and treat them before they develop into cancer. (4)

The program’s success depends on the screening population; the women and their compliance to the recommended guidelines. Women being “lost-to-follow-up” is a problem. Although physicians and pathologists are the ones who collect, forward and analyze the samples, an optimal screening process also depends on the compliance of the women to recommended follow-up guidelines. Pap-smears that are not of satisfactory quality, called unsatisfactory tests, require closer follow-up with more frequent testing than normal smears. If the women do not follow the recommended follow-up regimen, this may result in delayed diagnosis, and the risk of losing women with “need-to-treat-dysplasia” along the way.

3.2 Cervical dysplasia

Approximately 400,000 pap smears are taken every year in Norway. 25,000 of these are classified as unsatisfactory or abnormal (with cervical dysplasia). (4) Cervical dysplasia, which is seen within the cells, is the morphological sign that there is an ongoing inflammatory low grade squamous intraepithelial lesion (LSIL) or a transforming process, a high grade squamous intraepithelial lesion (HSIL). Cervical dysplasia is almost exclusively a result of infection or transformation by human papillomavirus (HPV). (5) (6) More than 80% of sexually active women and men will once or several times during their lifetime become infected by the HPV virus. (7) Approximately 90% of infections will heal on their own over

the course of 6-24 months. The remaining 10 % of HPV-infections could persist and pose risk of high-grade lesions and development of cancer. (8, 9) Considering that HPV is the underlying factor in most cases of cervical cancer (10-14); detection and treatment of early cervical dysplasia, caused by HPV, may prevent further development toward cancer. (15) Dysplastic lesions are classified according to morphological changes (Bethesda 2001). (16) The classification is based partly on the relationship between cytoplasm and nucleus, as well as the cell's ability to absorb color. Lesions are classified as following:

Normal

ASC-US: Atypical squamous cells of undetermined significance

LSIL: Low grade squamous intraepithelial lesion

ASC-H: Atypical squamous cells, whereas HSIL cannot be excluded

HSIL: High grade squamous intraepithelial lesion.

In 2011 approximately 3% (>12,000) of pap-smears were classified as unsatisfactory. (4) According to the Bethesda criteria a minimal squamous cellularity is required for the test to qualify as satisfactory. If a conventional smear contains less than 8000 well-visualized squamous cells, and a liquid-based preparation less than 5000, the specimen adequacy is considered poor. (16) These samples are not suitable for diagnostics and the woman is asked to return for a new smear.

3.3 Follow-up

Of the 13,000 annual abnormal (ASC-US+) pap-smears, the largest share contains low-grade lesions. (4) Women with abnormal pap-smears are followed until the smear is normal or they are diagnosed with treatment-requiring dysplasia (CIN2+). What ought to be done with the distinctive results is determined by risk estimation. Due to this, the recommended guidelines for follow-up of cervical-cytological screening tests (17) are based on a principle of equal management of equal risk for high grade lesions/cervical cancer. (18-20)

If the woman's test is normal, she continues in the screening program at 3 years' interval. The cancer registry sends out a reminding letter if the woman has not attended after 42 months. A woman whose test is unsatisfactory is recommended to have a new pap-smear within 1-3 months. If the cervical dysplasia is classified as high grade (ASC-H or HSIL), the woman should be referred directly to colposcopy and biopsy. Between these two extremes

is follow-up of low-grade dysplasia. If the pap-smear shows ASC-US or LSIL, the woman is recommended a delayed triage, with a new pap- and HPV test after 6-12 months.
The remaining material of the liquid based pap-test is HPV tested because of the virus' close relation to development of CIN2+. (21) Studies have shown a 3-fold increase in CIN2+ risk in women with LSIL and positive HPV compared to women with LSIL and a negative HPV test. (19) Women with repeated ASC-US/LSIL and positive HPV test are referred to colposcopy and biopsy. Women with ASC-H/HSIL at delayed triage are also referred to colposcopy and biopsy, independent of HPV test outcome. Women with a normal pap-smear and negative HPV test, as well as women with repeated ASC-US/LSIL and negative HPV-test, are all recommended further follow-up at a 3-year interval.

When the doctor performs a colposcopy, the cervical mucosa is examined in order to evaluate the severity of the dysplasia. Simultaneously, the doctor takes biopsies which are sent to a pathologist who performs a histological examination in a microscope. The histological samples are studied considering the different tissues and to what degree the dysplasia extends from the basement membrane towards the surface. Biopsies taken of cervical dysplasia are categorized as CIN1, CIN2 and CIN3 in increasing severity according to the extent to which the epithelium is replaced by dysplastic cells. The preinvasive lesions are categorized as CIN1 (low grade lesions - await treatment), where the cells involve the first third of the epithelium. CIN2 involve two thirds of the cervical epithelium and CIN3 (high grade lesions) involve the full thickness of the epithelium. The basement membrane is intact in all three pre-cancerous classifications. Both CIN2 and CIN3 are further managed identically and are therefore categorized as CIN2+. If the biopsy shows CIN2+, the woman is recommended surgical treatment; conization, in which the area with dysplasia is removed. If the basement membrane is infiltrated or destroyed by malignant epithelial cells, the dysplasia has evolved into invasive cancer.

3.4 Participation in the screening program

Despite efficient ways of screening, an 80% national coverage is reached after two reminders over five years. (4) In Norway, 50 % of cervical cancers occur among women in the non-participating group. Of women with unsatisfactory pap-smears, 62% show up for a recommended follow-up smear within 12 months. (4) A woman with consecutive

unsatisfactory results is advised to return for new pap-smear testing shortly after. Several follow-ups within a short period of time, without any precise answers on whether she has cervical dysplasia or not, could make the woman tired and increase the risk of further non-participation ("lost to follow-up").

3.5 Previous studies

By now, there are only a few studies done based specifically on the unsatisfactory pap-smear. The main focus of these studies has been causes of unsatisfactory tests, typically which factors are most likely to contribute (22, 23). Results have shown that scant cellularity is the most common cause (95.7%) of an unsatisfactory pap-smear. (22) Other reasons are obscuring inflammation, blood, foreign material, endometrial cells, poorly fixed material or low squamous component. In addition, the authors have focused on whether patients with unsatisfactory tests have any factors in common. Unsatisfactory tests were according to Alsharif et al more likely to appear in older patients and were more frequent in menopausal women, post hysterectomy, and post hysterectomy with radiation and/or chemotherapy for malignancy. (22) Aspects considering other characteristics than age will not be further discussed in the present study.

Some earlier studies are based on follow-up and development of CIN2+, specifically among women with unsatisfactory tests compared to women with normal tests. (3, 22-24) Alsharif et al found that the group with unsatisfactory tests had a higher proportion of abnormal follow-up pap-smears, as well as higher incidence of CIN1+. However, the study population is of small (278-cases and 284 controls) sample size with little statistical power. Furthermore, these patients are only followed up for 24 months, and not the full recommended 3-year screening period. This may have given a lower rate of follow-up pap testing and biopsies in the control group, thereby probably influencing the final results to show a higher proportion of abnormalities in the unsatisfactory group.

A historical prospective cohort of women in the USA studied clinical factors associated with compliance after an unsatisfactory pap-smear. (23) Though to my knowledge, neither this, nor other previous studies have assessed compliance in different aspects such as both before and after the index smear. Furthermore, there are few studies that have discussed

the context of compliance and outcome; regarding both in single follow-up testing and in total risk estimation of development of CIN2+ during the whole study period.

4 Objectives

In a cohort design I aim to compare compliance with screening recommendations and outcome of screening for women diagnosed with an unsatisfactory smear compared to women who have normal smears.

5 Material and methods

5.1 Study population

The Department of Clinical Pathology, University Hospital of North-Norway, Tromsø, receives pap-smears from women in Troms and Finnmark county. Each year approximately 22-25,000 cervical smears and histological samples are analyzed and added to a clinical database (SymPathy). Within this database, we created a cohort study and identified women with an unsatisfactory smear during 01.01.2006 through 31.12.2011 as exposed women, while women with a normal smear during 01.01.2006 through 31.12.2007 where defined as non-exposed women. Follow-up ended 31.12.2014.

From 1991 through 2011, 481,857 women were registered with 523,620 pap-smears. We utilized the screening history of eligible study participants to define our final study population. Among 31,770 eligible non- exposed women and 2,203 exposed women, we excluded women with a previous history of CIN1 or higher, women with a history HSIL or higher, and women whose last smear prior to index were abnormal (Figure 1). After these exclusions, the final study population comprised 1,571 exposed women and 24,665 non-exposed women.

5.2 Outcomes

In our analysis, we had two main outcomes- compliance to recommended guidelines and detection of CIN2, CIN3 and cervical cancer (CC).

Compliance was assessed in two aspects from most recent to index smear (background compliance) and from index to 1st follow-u smear (study compliance). Background compliance was categorized as too short (less than 24 months), within interval (24 through 41 months), and too late (> 42 months) or no previous specimen collection (index smear was 1st smear). Participants that did not have any follow-up after index smear were defined as the "non-attender" category in study compliance. For the control cohort, study compliance was defined as too short if the specimen was collected less than 24 months after index smear, within interval at 24 through 41 months' range, and too late when collection took place 42 months or later after index smear. For exposed women, compliance was too early (less than 1 month), within interval 1-6 months and too late if the smear was taken 7 months or later after an index smear. Age was categorized in three groups (25-39, 40-54-55-69 years).

We identified "status within 1st screening period" (< 42 months) and calculated the detection rates of CIN2, CIN3 and cervical cancer (CC). Finally, we estimated the women's most adverse outcome within 78 study months (two screening rounds).

5.3 Statistical methods

Used in the study are chi-square test, t-test and survival analysis in SPSS with level of significance $p < 0.05$.

5.4 Formal approvals

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 (2015/1795/REK Nord). Norwegian regulations exempt quality assurance studies from written informed consent from the patients. The Patient Ombudsman, University Hospital of Northern Norway, Tromsø, approved study start.

6 Results

A higher proportion of the women with unsatisfactory index test were recruited from the first versus the second time period (61.8 % vs 38.2%). Furthermore, exposed women were significantly younger than non-exposed women in the control cohort. Study population characteristics are displayed in table 1.

Compared to the control cohort, a larger proportion of the exposed women had no previous smear collected (15.4% vs 7.3%). In addition, a higher proportion of the women in the exposed group had too long or too short interval from most recent to index smear, meaning they were less compliant compared to the control cohort (Table 1).

14.4% in the control group and 10.4% in the exposed group had no smear collected after their index smear. The women in the non-exposed cohort were significantly less compliant to the recommended guidelines compared to the exposed women, respectively 31.7% vs 51.0% (Table 2). Regardless of age, the exposed women were more compliant than the non-exposed women.

By first screening period, a higher proportion of the exposed women returned to screening, while a higher proportion in the non-exposed group had incomplete follow-up (Table 3, Column A). A total of 54 CIN2+ (0.2 %) among the non-exposed women and 20 CIN2+ (1.3 %) in the exposed women were diagnosed within first 42 months. In both groups, most cases were diagnosed on indication, as follow-up after an abnormal smear. A higher percentage of CIN2 was found in the exposed group (0.6%) compared to the non-exposed group (0.1%). 24 (0.1 %) and 8 (0.5 %) cases of CIN3 were diagnosed among non-exposed and exposed women, respectively. Within first screening period, three cervical cancers were diagnosed, 2 (0.2%) in the exposed women and 1 (0.0%) in the non-exposed women. The difference in proportion of diagnostic cases of CIN2, CIN3 and CC in the two groups was highly significant ($p<0.01$).

Within 2nd screening round, a higher proportion of the exposed women returned to regular screening compared to the non-exposed women (Table 3, column B). At this point, 42.3% of

women in the control group still had incomplete follow-up compared to 23.9% of the exposed group.

At 78 months, a total of 101 CIN2 (0.4 %), 100 CIN3 (0.4%) and 10 CC (0.0%) were diagnosed in the non-exposed women. In the exposed women 11 CIN2 (0.7 %), 17 CIN3 (1.1 %) and 3 CC (0.2 %), were diagnosed. This accounted for an overall higher percentage of diagnosed cases in the exposed group compared to the non-exposed group. Our results show an increasing cumulative incidence of CIN2+. The difference in cumulative incidence between the two cohorts increases over time. (Figure 2, survival analysis) The cumulative incidence among exposed women were significantly higher at 24, 42 and 78 months compared to the control cohort. (Table 4)

The women diagnosed with cervical cancer were young, all below 60 years of age. Most of the cancers were diagnosed in incomplete follow-up after a previous smear. (Table 5)

7 Discussion

In our study, women with unsatisfactory pap-smear, regardless of age, were significantly more compliant to recommended guidelines compared to women with normal index smear. We observed an increasing compliance with increasing age in both groups. Of the non-compliant women, most met too late. A total of 54 CIN2+ (0.2 %) in the non-exposed women and 20 CIN2+ (1.3 %) in the exposed women were diagnosed within first screening period. Of these, the cumulative incidence of both CIN2, CIN3 and CC was higher among exposed women, compared to the non-exposed women. Within 78 month, a total of 211 CIN2+ cases (0.8 %) were diagnosed in the non-exposed women, compared to 21 CIN2+ cases (2.0 %) in the exposed women. ($p<0.001$).

While a previous Norwegian study (24) did not assess compliance with follow-up after an unsatisfactory smear, two studies from the US (22, 23) estimated compliance with different windows for compliant follow-up. Owen's et al evaluated follow-up within 120 days in agreement with the recommendations from the American Cancer Association and within 24 months. They found that 53.4% of women with unsatisfactory pap-smears had a follow-up within recommended window, and a total of 80% within a two years' period. Additionally, their results show that women aged 50+ were more likely to meet within 120 days for a follow-up smear, compared to women below 50 years of age (57.2% vs 48.8%). These results are equivalent to ours with a satisfactory compliance of 51.0 % as well as our increased compliance with increasing age.

Alsharif et al reported compliance within a 24- months window and found a much lower compliance in the control group compared to the unsatisfactory study group, respectively 22.5% vs 65.1% (22). Similar findings are reported from a previous Norwegian study estimating follow-up rates to 83.7% and 40.7 % in the exposed and non-exposed women, respectively (24).

To my knowledge, our study is first to differentiate between too early/too late show-up when assessing compliance to recommended screening interval. While Owen's et al do not distinguish between "no follow-up" and "non-compliant" women when estimating overall rates of CIN2+, Alsharif et al estimate CIN2+ rates only among women who have a follow-up.

Nygård et al have, similar to our study, included women with “no follow-up” in their analysis of CIN2+.

Both Alsharif, Owens and Nygård have assessed CIN2+ within a two-year period. CIN2/3 and ICC develops over time, and one would question whether 24 months is sufficient to make an estimate of CIN2+ occurrence. Nevertheless, Alsharif's results at 24 months show a CIN2+ risk of 1.8% in the exposed group and 0.35% in the control group.

Owens et al utilizes two control groups for women with unsatisfactory smears. (23) One control group comprised women with all satisfactory smears after excluding those with a history of HSIL, endocervical adenocarcinoma in-situ, squamous cell carcinoma and other cervical malignancy, while the other control group consisted of all women with a valid cytological diagnosis. Within a two-year’s follow-up a total of 10 CIN2+ were diagnosed, of these 8 within 120 days. Their results implicate no increase in CIN2+ development in women with unsatisfactory smear, compared to either control groups. However, the short follow-up time and the low number of outcomes makes this study invalid for any comparison to other studies.

Nygård’s study is most comparable to ours. As Nygård et al, we excluded women with previous HSIL+, CIN1+ and abnormal test on the most recent before index. These exclusions make both populations low-risk populations for assessment of CIN2+.

Because the recommended follow-up of unsatisfactory- and normal smears differs greatly in compliance interval, assessment done prior to 40 months will be invalid based on the high percentage incomplete follow-up in the non-exposed women. An ideal comparison of exposed and non-exposed women should therefore be follow-up through two screening rounds, which equals 78 months. To my knowledge, no other study than the study from the Norwegian Cancer registry (24) have this long-term follow-up. Women with no histologically verified CIN2/3 or ICC within 2 years’ follow-up, were in Nygård’s study followed an additional 5 years, compared to our 42 months and additional 3 years (36 months). Their results implicate a hazard rate of being diagnosed with CIN2/3 after an unsatisfactory test during the long-term follow-up as 1.2 (95% CI: 1.04-1.45) compared to the control group.

They do not display numbers of cumulative incidence in long term-follow up. Their results are slightly lower than ours, but highly comparable. Within our 78 months of follow-up, a total 2% had CIN2+ as most adverse outcome compared to a 0.8% in the control group of women with normal smears.

Today's guidelines are based upon risk estimation and the principle of "equal management of equal risk". Katki et al (11, 20) based their thresholds on cumulative incidence of CIN3+ within 5 years after a negative co-test (negative pap-smear combined with a negative HPV test). They calculated risk of CIN3+ for all possible combinations of the co-test, and benchmarked it to the already established risk thresholds for pap-alone to further suggest adequate management. E.g. all women with results that equals a five year CIN3+ risk of 2.6% are recommended to have a follow-up smear within 6-12 months and women with results equaling a 5-year CIN3+ risk of 0,26% are sent back to regular screening with 3-years interval.

The CIN3+ risk at 78 months in our study was 1.3% in the exposed women, a lower risk than what, according to the risk-thresholds (20), would implicate a new pap-smear within few months. In our study, a negative smear prior to index was a requirement. However, it has not been performed systematically HPV testing, and we thereby do not have data to consider HPV results in our analysis. Thus, we could further not calculate risk of CIN3+ development based on the unsatisfactory pap-smear in combination with the HPV test.

In clinical practice the recommended guidelines are not as strictly practiced as in a clinical register-based study. Intervals are shortened and extended both by the woman herself, but also by the practitioner who's performing the testing. Our study show that 51% of exposed women are compliant to recommended guidelines, a percentage of coverage that is not satisfying.

Starting March 2015, 4 counties introduced HPV testing in primary screening. It is further discussed use of the HPV test in residual material from the unsatisfactory smear, to decide if the woman can be returned to regular screening (HPV negative) or if she needs a follow-up smear (HPV positive). This would make it possible to estimate a more accurate risk at first

unsatisfactory smear, instead of having the woman returning for several smears before she gets a diagnose. Fewer unnecessary follow-up consultations might increase the compliance among the women with unsatisfactory pap-smears. In addition, using HPV test in primary screening will also reduce the number of unsatisfactory smears because only HPV positive samples are triaged by cytology. Future studies should include consistent HPV-testing at each visit during assessment of unsatisfactory smear, in order to settle management regimens for follow-up.

Our study adds to the literature in several ways. Few previous studies done have as large study population of women with unsatisfactory tests who are followed up long-term basis. Because of our population-based study design, the results reflect clinical practice within the Norwegian cervical screening program. An ideal study would be performed as a randomized two-arm study with HPV test in one arm, and pap-smears as the other. All testing should additionally be done by a selected group of practitioners who were all trained in the same standards of analyzing and further management.

In our study, we present numbers of a low risk population. As expected the overall incidence of cancer is low, but significantly higher in the exposed women compared to the non-exposed. In the exposed women, three cancers were diagnosed. One diagnosed within three months as follow-up of an unsatisfactory index. Two of the cervical cancers were diagnosed in follow-up of symptoms, with normal smears as most recent. Thus, the three occurring cancers in our exposed cohort cannot be acquired to the unsatisfactory pap smear itself. The cancers are rather cases of coincidental occurrence, which no screening program can one hundred percent prevent.

8 Conclusion

We observed a significantly higher compliance among exposed women compared to a non-exposed cohort. Additionally, our study shows a significantly higher cumulative incidence of CIN2+ at all months measured in the group of women with unsatisfactory smears. Nevertheless, the incidence is low in both groups. Based on the overall low cancer risk in the population, we question the necessity of such short intervals in today's recommendations for women with unsatisfactory pap-smears. However, our study population is too small to make a statement on cancer risk in women with unsatisfactory pap-smears. Further recommendations for follow-up should be calculated based on studies with adequate long-term observations done in large populations with HPV testing and cytological smears in combination.

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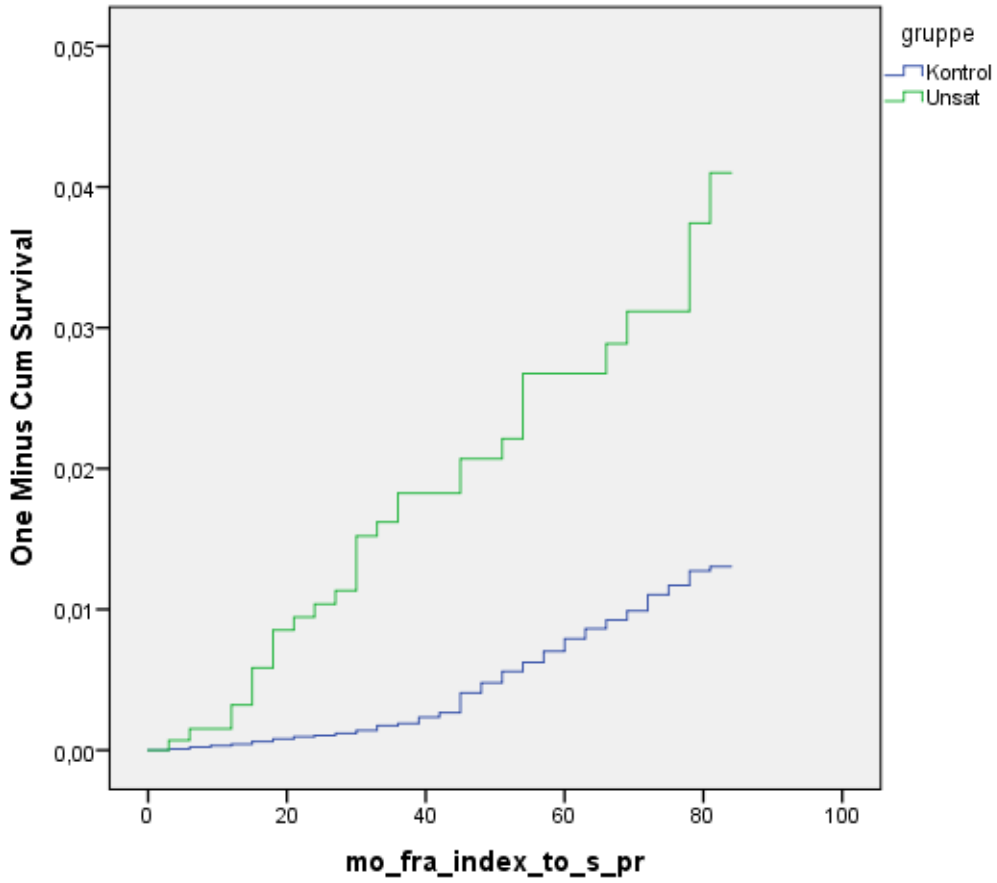
10 Attachments

10.1 Figure 1- Selection of study population

Control cohort		**Criteria of exclusion**	**Exposed cohort**	
N	n		n	N
31,770				2,203
	1,991	Age ≤ 24 år	256	
	1,277	Age ≥ 70 år	67	
28,502				1,880
	653	≥ CIN1 before index	47	
	359	≥ HSIL before index	31	
	1,417	≥ HSIL før/≥ CIN1 before index	95	
26,073				1,707
	475	Unsatisfactory as last smear before index.	46	
	782	ASCUS as last smear before index.	67	
	151	LSIL as last smear before index.	23	
24,665		**Study population**		**1,571**

10.2 Figure 2 – Cumulative incidence of CIN2+ by cohort



10.3 Table 1- Study population characteristics

	Control cohort	Exposed cohort	P-value
	N = 24,665	N = 1,571	(Chi-square)
	%	%	
Age (yrs.)			P < 0.001
25-39	35.5	52.1	
40-54	36.6	33.8	
55-69	27.9	14.1	
Background compliance			P < 0.001
No previous smear	7.3	15.4	
Too short interval	11.6	12.3	
Within interval	56.3	41.9	
Too long interval	24.8	30.3	

10.4 Table 2 – Compliance from index test to first follow-up by cohort

	Control cohort	Exposed cohort	
	N = 24,665	**N = 1,571**	**P-value**
	%	**%**	(Chi-square)
No follow-up	14.4	10.4	
No compliance			
- **Too early**	16.4	8.3	P < 0.001
- **Too late**	37.6	30.4	
Compliance	31.7	51.0	

10.5 Table 3 – Status of follow-up at 42 and 78 months by cohort

	Control cohort		Exposed cohort	
	N = 24,665		N = 1,571	
	Column A	Column B	Column A	Column B
	42 months %	78 months %	42 months %	78 months %
No follow-up	14.4	14.4	10.4	10.4
Back to screening	7.2	42.5	29.0	63.7
CIN2	0.1	0.4	0.6	0.7
CIN3	0.1	0.4	0.5	1.1
CC	0.0 (n=1)	0.0 (n=10)	0.2 (n=2)	0.2 (n=3)
Incomplete f-up	78.2	42.3	59.4	23.9

10.6 Table 4 – Cumulative incidence of CIN2+ at 24, 41 and 78 months by cohort

	Control cohort Cumulative incidence (95% CI)	**Exposed cohort** Cumulative incidence (95% CI)
24 months	0.12 (0.07-0.17)	1.1 (0.5-1.7)
42 months	0.4 (0.3-0.5)	2.1 (1.2-3.0)
78 months	1.3 (1.1-1.5)	4.1 (2.5-5.7)

10.7 Table 5 - Women diagnosed with cervical cancer within 78 months

Group	**Age** (years)	**Time from index to diagnose** (months)	**Most recent smear prior cancer diagnosis**
Non-exposed cohort	53	3	After symptoms/normal smear
Non-exposed cohort	33	38	Follow-up of abnormal smears
Non-exposed cohort	56	38	Follow-up of abnormal smears
Non-exposed cohort	37	44	Incomplete follow-up of previous smear
Non-exposed cohort	34	45	Incomplete follow-up of previous smear
Non-exposed cohort	38	50	Incomplete follow-up of previous smear
Non-exposed cohort	29	57	Incomplete follow-up of previous smear
Non-exposed cohort	35	67	Incomplete follow-up of previous smear
Non-exposed cohort	37	70	Incomplete follow-up of previous smear
Non-exposed cohort	48	74	Incomplete follow-up of previous smear
Exposed-cohort	49	4	Follow-up of an unsatisfactory smear
Exposed cohort	31	33	After symptoms/normal smear
Exposed cohort	39	78	After symptoms/normal smear

11 Summary of outcomes in own study compared to main articles

	Eksklusjonskriterier	Studiepopulasjon	Compliance	CIN2+
Kaasa, Norge 2006-2014	Alder < 25 og > 69 år Abnormal test som siste prøve før index Tidligere HSIL+ og/eller CIN1+	**N =** 26236 **Kasus:** 1571 **Kontroll:** 24665	**Ihh til retningslinjene** **Eksponert** 51,0% **Ikke eksponert:** 31,7%	**<u>Innen første screening</u>** **Eksponert:** 1,3 % **Ikke eksponert**: 0,2% **<u>Innen siste oppfølging.</u>** **Eksponert** 2,0 % **Ikke eksponert**: 0,8%
Owens, USA 2004-2010	Kvinner med tidligere cervikal cancer eller total hysterektomi. Resultater fra konvensjonelle celleprøver. Alder < 21 og >65	N = 351877 **Kasus:** 1442 **Kontroll:** - A: 250366 - B: 249718	**Oppfølging innen 120d** 53,4% (varierte mellom 41,1-65,6%) **Innen 2 år:** 80% **Assosiasjoner til oppfølging** Kvinner < 50 vs >50: 57,2 % vs 48,8% + HPV vs ingen HPV: 84,6% vs 53,9 % - HPV vs ingen HPV: 42,1% vs 53,9 %	**CIN 2+ etter uegnet prøve:** Totalt 10 (8 innen 120 d,2 med tidl CIN2+) HR 0,91 (0,50-1,7) – kontrollgruppe A HR 1,2 (0,63-2,1) – kontrollgruppe B (referent normal index)
Alsharif, USA 2003-2008	Uegnede prøver som ikke ble prosessert. Gjentatte uegnede prøver fra kvinner som allerede var med i studien. Unormale prøver som ASC-US, LSIL, HSIL+ 4 uegna for evaluering CPS og Thinprep prøver.	N= 548 **Kasus:** 278 **Kontroll:** 284	**Ny test innen 24 mnd:** **Kasus:** 65,1% **Kontroll:** 22,5%	**<u>Forekomst CIN 2+:</u>** **Kasus:** 1,80 % **Kontroll:** 0,35 %
Nygård, Norge 1995-2001	CIN2/3 eller ICC mellom 1.jan 1990 og indexprøven. Indexprøve ASCUS, LSIL, HSIL, ICC. Abnormal prøve som siste før index. Celleprøve ila de 6 mnd før indexprøven. Alder < 25 og >69 år	N= 613632 **Kasus:** 21405 **Kontroll:** 536661	**2 års oppfølging** **Kasus:** 83,6% **Kontroll:** 40,7 %	**<u>2 års oppfølging, CIN2+</u>** **Kasus:** 0,6% **Kontroll:** 0,21% **<u>Langtidsoppfølging, CIN2+</u>** **Kasus**: 191 kvinner HR 1,2 (ref norm prøve)