SECURING FOLLOW-UP IN CERVICAL CANCER SCREENING

PhD dissertation

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In 2011 when considerations for this project started more than 7,000 Danish women per year did not have timely follow-up, and it was discussed what could be done to decrease the problem. If this thesis may inspire to improve follow-up (and maybe even health) for just few women, I will be very grateful.

I am sure, that without support this thesis was never handed in!

First of all, I have to thank my dedicated supervisors. You kicked in doors and made the randomised controlled trial possible, when we in early phases met reluctance, and kept me on track, when I got absorbed in details. I am very grateful. Peter, I admire your stringent analytical competences, and still you emphasise that family comes first, and gave support in a stressed period. Thank you. Flemming, your insights and foresight in the functioning of a general practice has surprised me, and I guess you could almost have written these conclusions without results. Berit, your persistent encouraging support gave me invaluable access to both your department and your collaborators. Many of which I owe special thanks too: All employees at the Department for health programmes in Randers, especially secretary’s and Stine Heslop, for always constructive feedback of women’s reactions to wording of letters, and for the letter distribution at a daily basis. Also Ivan Christensen and Bjarne Andersen from CGI made this possible, with competent and quickly IT assistance. But not least, I am very thankful to Hans Svanholm, for checking my algorithm again and again, and for letting me use invaluable time with cyto-pathologist Rikke Holst Andersen.

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Cervical cancer screening aims to decrease the incidence, morbidity and mortality of cervical cancer. Nevertheless, approximately 400 Danish women are diagnosed with cervical cancer each year. One reason for this could be that follow-up of abnormal cervical cytology results is not carried out as intended, which could entail missed opportunities for early treatment of pre-cancer and cancer disease.

In Denmark, mainly general practitioners (GPs) obtain the cervical cytology sample and later convey the results to the investigated women. The Danish National Board of Health recommended in 2012 that all women should receive a notification of the cervical cytology results by postal letter sent directly from the pathology department and that all sample takers should receive a reminder if the women missed a recommended follow-up. Moreover, it was hypothesised that such direct notifications would decrease the number of GP contacts as women with normal cervical cytology results no longer needed to consult their GP.

To improve the cervical cancer screening programme, it is important to investigate how these recommendations have affected both the women and the GPs.
The PhD thesis is based on the following three papers:

I. **B. Kristiansen, B. Andersen, F. Bro, H. Svanholm, P. Vedsted.** Direct notification of cervical cytology results to women improves follow-up in the Danish Cervical Cancer Screening Programme - a cluster-randomised trial (Submitted).

II. **B. Kristiansen, B. Andersen, F. Bro, H. Svanholm, P. Vedsted.** Direct notification of cervical cytology results the decrease use of general practice – A Danish cluster-randomised trial (Submitted).

III. **B. Kristiansen, B. Andersen, F. Bro, H. Svanholm, P. Vedsted.** Reminders to general practitioners improve follow-up after cervical cytology: A Danish nationwide before-after natural experiment (Accepted for publication: British Journal of General Practice).
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AIS</td>
<td>Endocervical adenocarcinoma in situ</td>
</tr>
<tr>
<td>AGC</td>
<td>Atypical glandular cells</td>
</tr>
<tr>
<td>ASC-H</td>
<td>Atypical squamous cells cannot exclude HSIL</td>
</tr>
<tr>
<td>ASC-US</td>
<td>Atypical squamous cells of undetermined significance</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIN</td>
<td>Cervical intraepithelial neoplasia</td>
</tr>
<tr>
<td>DPDB</td>
<td>Danish Pathology Data Bank</td>
</tr>
<tr>
<td>FIGO</td>
<td>International Federation of Gynaecology and Obstetrics</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>HPV</td>
<td>Human papilloma virus</td>
</tr>
<tr>
<td>HSIL</td>
<td>High-grade squamous intraepithelial lesion</td>
</tr>
<tr>
<td>IRR</td>
<td>Incidence rate ratios</td>
</tr>
<tr>
<td>ICC</td>
<td>Intra cluster coefficient</td>
</tr>
<tr>
<td>LSIL</td>
<td>Low-grade squamous intraepithelial lesion</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PD</td>
<td>Prevalence difference</td>
</tr>
<tr>
<td>PR</td>
<td>Prevalence ratio</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
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</table>
CHAPTER 1: INTRODUCTION
Prevention of cervical cancer is targeted at three different levels. **Primary prevention** focuses on health education and HPV vaccination with the objective of reducing HPV infections (1). **Secondary prevention** focuses on screening, i.e. timely detection of pre-cancer and timely treatment of pre-cancer, with the objective to decrease cervical cancer incidence (1). Finally, **tertiary prevention** focuses on timely diagnosis, treatment and palliative care for women with cervical cancer with the objective to decrease the number of deaths due to cervical cancer (1). In line with the objectives in secondary prevention, the Danish Quality Database for Cervical Cancer Screening serves two main purposes in the Danish screening programme: to increase the screening participation and to improve the adherence to the recommended follow-up, to hinder missed opportunities for detection and treatment of cancer (2,3).

The main focus of this thesis is to evaluate the two new national recommendations (i.e. direct notification of cervical cytology results and GP reminder for missed follow-up), which were initiated to improve the adherence to recommended follow-up.

The following introduction chapter first outlines the epidemiology and the causes of cervical cancer and also describes the Danish cervical cancer screening programme and its effect on incidence and mortality. Next, the prevalence of women in Denmark who do not adhere to recommended follow-up are described together with the possible consequences in terms of cancer development, and new national initiatives aiming to increase the follow-up are outlined. At the end of this chapter, a health service research model is introduced; it is intended to provide guidance for the evaluation of the national initiatives. Finally, the overall aim of the thesis is presented.
Two main types of cervical cancers exist: squamous cell carcinomas (75-80%) and adenocarcinomas (20%) (4,5).

Before cervical cancer manifests, different stages of abnormal pre-cancer appears in the cervical tissue (1,4,6).

Figure 1.1 Stages in the development of cervical cancer

Infection with the sexually transmitted human papilloma virus (HPV) is the main cause for developing cervical cancer (4,7,8). Seventy percent of cervical cancers are considered to be caused by HPV number 16 or HPV number 18 (9). Other co-acting causes are low age at sexual debut, high number of sexual partners, trauma of the cervix (e.g. sexually transmitted diseases or child births), smoking and insufficient immune system (1,4,6-8). In Figure 1.1, arrows symbolise how stages of HPV infection and mild/severe pre-cancer are reversible, whereas cervical cancer is not (1).

Cervical cancer is a preventable disease (10). Still, cervical cancer is the seventh most common cancer among women in Denmark and northern Europe. Approximately 400 women in Denmark are diagnosed with cervical cancer each year, 100 women die of cervical cancer and 300 women per 100,000 live with a cervical cancer diagnose. In Denmark, cervical cancer comprises 2.2% of all cancers (except for skin cancer) (5,11).

The current age-standardised incidence rate of cervical cancer in Denmark is 11.3 per 100,000 women (world standard population all ages in 2014), with incidence peaks around 35 years of age and again around 75 years of age. Half of all Danish women are diagnosed before 45 years of age (6,11). The incidence rate is higher in Denmark than in other northern European countries with organised cervical cancer screening programmes, for instance it is twice as high as the Finish incidence rate (11,12,12).

Three out of ten women diagnosed with cervical cancer die within five years in Denmark. The 5-year age-standardised relative survival (age 0-89 years) was 69% (95% CI: 67 to 71%) in 2010-2014, whereas the highest relative survival in the northern European countries is found in Norway (72% (95% CI: 70 to 75%)). The mortality rate of
cervical cancer in Denmark was 1.8 per 100,000 women (all ages) in 2014. This figure is higher than in other northern European countries, where the mortality rates ranged from 1.0 in Finland to 1.3 in Sweden (11).

DANISH CERVICAL CANCER SCREENING

The first Danish screening programme for cervical cancer was implemented in a single county (Frederiksberg) in 1962. Cervical cancer screening programmes were implemented in more counties in the following years, and opportunistic screening became more frequent. The first Danish recommendations for a national cervical cancer screening programme were published in 1986, but 20 years passed before the programme were fully implemented in all counties (13). The recommendations were revised in 2007. From then, the programme invited women aged 23-49 years to participate in cervical cancer screening every third year and women aged 50-64 years every fifth year. The recommendations also led to the establishment of the Danish Quality Database for Cervical Cancer Screening in 2009 (13,14). The cervical cancer screening programme was most recently revised in 2012. Since then, women aged 60 years and above have had a HPV-DNA check-out test. Each of the five Danish regions is responsible for running the programme in their own area (6).

Screening-eligible women are identified through national databases. If a woman has not had a cervical cytology sample in three (or five) years, an invitation is automatically generated and sent to the woman’s home address by postal letter, unless she has declined to participate in the screening programme. In the invitation letter, the woman is encouraged to arrange an appointment with her GP to have a cervical cytology test. Reminder invitation letters are sent three and six months after the initial invitation if a cytology is not registered in the National Danish Pathology Data Bank (6,15). Roughly 65% of the women participate within one year after initial invitation, and approximately 75% of the women have had a cervical cytology performed within 42 months (women aged 23-49 years) or 66 months (women aged 50-64 years) (16).

The cytology sample is obtained in the menstruation-free period. The liquid-based sample technique is used as it allows HPV testing at the same material (6). Computer-assisted microscopic morphological investigation is used for the primary screening of women aged 23-59 years, whereas HPV testing is used as the primary screening method for women aged 60-64 years (6).

All cervical cytology samples are sent to a pathology department for diagnosing. Cytological samples of pre-cancer are classified according to the Bethesda classification
(2001)(6,17,18), using a Danish version of the Systematized Nomenclature of Medicine (SNOMED)(19,20). Classification systems are presented in chapter 2 (Material and methods: Key variables).

All laboratory test requisitions and results have been sent electronically since 2008 between pathology departments and general practices. Results are automatically stored in the electronic medical record of the individual patient (21, 22). For 95% of all cervical cytology samples obtained in general practice, test results are ready within 10 working days (16).

**Effect of cervical cancer screening**

In Denmark a remarkably decrease of both incidence and mortality were seen together with the implementation of cervical cancer screening (14).

**Figure 1.2** World age-standardised incidence and mortality rates of cervical cancer in Denmark, before and after implementation of a national screening programme.

Source: Lynge et.al 2014(14)
Similar reductions in mortality and incidence were seen in other Nordic countries after implementation of cervical cancer screening (7,11).

The effect of cervical cancer screening has never been investigated in randomised controlled trials. However, strong indications suggest that organised screening decreases both incidence and mortality (6,7,14) although the magnitude is debated (7). Decreases in incidence range from 40% to 80%, depending on setting, type of observational study design and age groups (7,23-26). Studies of modelled incidence rates for hypothetical no-screening scenarios have estimated that the Danish incidence rate of cervical cancer would have been up to five times higher without the screening programme, maybe due to increasing HPV prevalence (27).

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FOLLOW-UP

Adherence to recommended follow-up

In 2011, 3.9% of cervical cytology samples from women with the most severe pre-cancer had no follow-up within six months, and 10.1% of samples with a follow-up recommendation had no follow-up within 15 months(2). Non-adherence in follow-up may lead to missed opportunities for treatment of cervical pre-cancer or down-staging of cervical cancer. Missed opportunities have been defined as “instances in which post-hoc judgement indicates that alternative decisions or actions could have led to more timely diagnosis” (3).

More than 35,000 cervical cytology samples from women are recommended follow-up each year in Denmark. Table 1.4 presents the proportions of cytology samples obtained in general practices from women who are non-adherent to recommended follow-up. Non-adherence in follow-up was defined as the absence of a new cytology or histology sample after the initial cytological assessment and related recommended follow-up.
Table 1.1 Proportion of samples without follow-up in Denmark within different timeframes (28)

<table>
<thead>
<tr>
<th></th>
<th>2009 %</th>
<th>2010 %</th>
<th>Numbers without follow-up</th>
<th>Numbers in need of follow-up</th>
<th>2011 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervical cytologies with a recommendation for follow-up</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within recommended timeframe&lt;sup&gt;2&lt;/sup&gt;</td>
<td>20.1</td>
<td>19.2</td>
<td>7,450</td>
<td>36,536</td>
<td>20.4</td>
</tr>
<tr>
<td>Within 15 months</td>
<td>10.8</td>
<td>10.4</td>
<td>3,687</td>
<td>36,655</td>
<td>10.1</td>
</tr>
<tr>
<td><strong>Cervical cytologies with a recommendation for follow-up within 3 months</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 4 months</td>
<td>5.6</td>
<td>5.2</td>
<td>375</td>
<td>7,458</td>
<td>5.0</td>
</tr>
<tr>
<td>Within 6 months</td>
<td>3.9</td>
<td>3.6</td>
<td>292</td>
<td>7,475</td>
<td>3.9</td>
</tr>
<tr>
<td>Within 15 months</td>
<td>1.8</td>
<td>1.6</td>
<td>99</td>
<td>7,502</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Source: the Danish Quality Database for Cervical Cancer Screening (28)

<sup>1</sup> This included inadequate, mild pre cancer (LSIL, ASCUS) and severe pre cancer (HSIL, AIS, ASC-H, AGC)

<sup>2</sup> This was defined as 4 months for follow-up recommendations within 3 months (gynaecological investigation) and 6, 9 and 15 months for samples with a recommendation for follow-up in 3, 6 or 12 months, respectively

<sup>3</sup> This included severe pre-cancer with a recommended a gynaecological investigation within 3 month.

Follow-up problems have been described internationally for decades, but vary across settings, populations, and definitions: A review found that 7-49% of women with abnormal test results fail to receive adequate follow-up (29).

**Consequences of not attending follow-up**

Not all missed opportunities lead to harm of women or development of cancer. Substantial variations in cancer progression rates have been reported (7,30). A review by Oster and colleagues suggested that 12% or more of the most severe pre-cancers (CIN3) progress to cancer (31).

Table 1.2 Suggested regression/persistence/progression likelihoods of pre-cancerous lesions

<table>
<thead>
<tr>
<th>Severity of the lesion</th>
<th>Regression</th>
<th>Persistence</th>
<th>Progression to CIN3</th>
<th>Progression to invasive cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN1</td>
<td>60%</td>
<td>30%</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>CIN2</td>
<td>40%</td>
<td>&lt;5%</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>CIN3</td>
<td>33%</td>
<td>&lt;55%</td>
<td>--</td>
<td>&gt;12%</td>
</tr>
</tbody>
</table>

Source: Table adapted from Oster and colleagues (31)

Table 1.2 depicts the estimated progression and regression rates in the review. However, the findings may have been underestimated as cancer progresses on average over 10-12 years (from 5 to 50 years), and the length of cancer observation in included studies varied from less than one year to 20 years (7,31). In New Zealand, treatment was not offered women with severe pre-cancer (CIN3) in 1965-1974. It was later found
that 13% of the women had developed cancer within five years, 20% within 10 years, 26% within 20 years and 31% within 30 years, respectively (32). However, no valid method exists today to identify which pre-cancers progress and which regress (33).

Post-hoc studies among women diagnosed with cervical cancer have aimed to identify predictors for developing cancer. A meta-analysis from the USA in 2007 found that the primary reason was non-participation in cervical cancer screening. The second reason was false-negative cervical cytology samples, whereas the third most common reason was attributed to poor follow-up, defined as both delays and no follow-up at all. This latter reason accounted for 11.9% (95% CI: 9.0 to 15.6) of all cervical cancers (10). However, the estimates were based on studies of both invitation-based and opportunistic-based screening programmes. The authors argue that the percentage of cervical cancers due to false negative samples and poor follow-up care may be even higher in the invitation-based programmes since non-participation decreases (10).

Similar estimates were found in another study of seven prepaid comprehensive health plans in the USA: The most important reason for cervical cancer development was non-participation in cervical cancer screening prior to diagnosis. Thirteen percent of cancers were due to failure in the follow-up of mild or severe pre-cancer before the diagnosis. Of those with failure in the follow-up, 47% received “sporadic” follow-up with more than six months between tests (follow-up included cervical cytology, colposcopic examinations and cervical biopsies), 32% received “active” follow-up surveillance with less than six months between tests and 21% did not receive any follow-up. Twenty-one percent of women in this latter group had an explicit notation in the medical record stating that the women refused to follow the advice of the healthcare provider. The median time from an abnormal smear which was not adequately followed-up was 22 months (34).

A Danish study of 286 women diagnosed with cervical cancer in 1997-2002 showed that 5% had delayed or no follow-up of an abnormal sample 5-42 months before the cervical cytology, which later lead to a cancer diagnosis (35). However, in a recent Danish study of 112 women diagnosed with cervical cancer in 2008-2009, none of the women were expected to develop cancer due to lack of follow-up (36).

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**CHANGE OF HEALTH POLICY TO SECURE FOLLOW-UP**

Securing follow-up includes different activities and tasks for handling test results and referrals of the initial diagnostic assessment; this also depends on optimal interactions between the sample taker and the investigated woman (3). To increase the proportions of women attending a needed follow-up and to achieve more timely follow-up, the
Danish National Board of Health made two recommendations in 2012 with the purpose of increasing patient safety (6):

**All women should have the cervical cytology result conveyed directly by postal letter**
Investigated women should be notified of the cervical cytology result directly from the investigative pathology department if consent had been obtained from the women. This approach was intended to ensure that all women were systematic and timely notified of the results as the women’s awareness of follow-up recommendations was seen as a precondition for timely follow-up. Moreover, it was anticipated that 80% of women with normal cervical cytology results no longer needed to contact their GP for conveying results. As a letter costs considerably less than a GP contact, reduced costs were anticipated to be EUR 700,000 per year (2012 prices) (6).

**All cervical cytology sample takers should be reminded in case of no follow-up**
All sample takers should be reminded if a recommended follow-up had not been performed. An electronical reminder should be generated and sent to sample takers if a new test had not been registered in due time in the Danish Pathology Data Bank. This should be done as an automatic feature under the auspices of the Danish Pathology Data Bank. The objective was to increase the patient safety and support the GPs as it could help GPs recall relevant follow-up and contact the women without follow-up.

**Figure 1.3** Feature to improve follow-up adherence, current organisation and the new recommendations from the Danish National Board of Health.

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**FRAMEWORK FOR EVALUATING HEALTH POLICY**

The purpose of this thesis is to evaluate the two national recommendations from the Danish National Board of Health in 2012. We used a health service research model to guide the conceptualisation.
Ronald Andersen and Lu Ann Aday have worked intensively with a framework to explain and predict why people seek care; this is presented in Andersen “Behavioural Model of Health Service Use” together with a number of revisited models (37,38). Latest Lu Ann Aday and colleagues have presented a “Framework for Applying Health Service Research in Evaluating Health Policy”. This framework explicitly acknowledges an ecological approach in which health is produced in complex processes with multiple layers of interacting dimensions (39).

Figure 1.3 Framework for Applying Health Service Research in Evaluating Health Policy

The framework describes how “health policy” may change the structure and affect the “delivery system” (availability, organisation and financing of healthcare programmes), the “population at risk” (predisposing, enabling and needs of people served by it) and the “environment” (physical, social and economic environment people are exposed to) (39). The two Danish health policy recommendations target the delivery system by changing the structures or the organisation of the cervical cancer screening programme. The actual care is delivered through processes as transactions between patients and providers (“realized access”) and behavioural and environmental transactions which may impact “health risk”. “Health” is the outcome represented by improved follow-up adherence. Loops of arrows symbolise the ecological approach of how concepts interact. When the structures to improve the follow-up are changed,
these structures can modify and will be modified by other dimensions in the model. Finally, the framework depicts three criteria that seem relevant for evaluating the performance of a healthcare system and the two interventions studied in this thesis. These three criteria are described as effectiveness, equity and efficiency (39).

**Delimitation of evaluations in this thesis**

The criterion effectiveness explores to what extent healthcare actually improves the health of populations (39). In this thesis, two recommendations from the Danish National Board of Health are evaluated by investigating whether the proportion of women attending recommended follow-up has increased. The criterion efficiency explores the effectiveness (improved follow-up adherence) in association with the resources used to produce them (39). Efficiency is in this the thesis conceptualised as women’s use of GP contacts after implementation of direct notification of results. Finally, the criterion equity concerns fairness and health disparity of the effectiveness. The ultimate test of equity in health policies is the extent of inequalities among subgroups in the population and the use of health services producing health (39). The framework suggests that inequalities are measured. Inequality is often defined as all differences between subgroups among which some variation is inevitable. In contrast, inequity implies a moral judgement where differences can be avoided with reasonable means (40,41). In this thesis, the inequality of subgroups of women is investigated. Furthermore, it will be explored if loss to follow-up variation between general practices has been reduced after implementation of the two national recommendations.

We chose to delimit evaluations of the policy changes for women with cervical cytology samples obtained in general practice, as approximately 95% of all cervical cytology samples in Denmark are obtained in general practice (16). The cervical cytology samples obtained in general practices are a mixture of samples from screening-invited women, opportunistic samples obtained on request from women or GPs, samples due to inadequate test results or surveillance after previous dysplasia. All of these samples may need follow-up (See Appendix I for Danish follow-up algorithms, and Appendix II for the cervical cancer screening process and possible failures in follow-up). It is not recommended to use cervical cytology testing during pregnancy or on women with possible symptoms of cervical cancer in general practice. These women should instead be consulted by a specialist/gynaecologist as a normal cytology test performed by a GP does not rule out cancer (5).

The following sections first describe the structure in which the two healthcare policy recommendations were embedded, i.e. “delivery system”, “population at risk” and “environment”. Next, the current evidence of the “health policy”, i.e. direct notifications and reminders, is described in terms of effectiveness, efficiency and equity.
The delivery system

This section describes the organisation, financing and availability of the Danish delivery system in regard to follow-up, and how the delivery system may affect the follow-up.

Organisation of follow-up before changing health policy

If follow-up is needed, the pathology department must apply a SNOMED code to the cervical cytology result to define the type of follow-up recommendation (6,18). Cervical cytology results and follow-up recommendations are conveyed to the investigated woman by the GP after electronic receipt of results in general practice. All GPs use an electronical medical record to manage medication, generate problem lists, enter clinical notes, access image archives and external decision-support programs, make referrals and lab request, receive lab results and discharge summaries from hospitals (42).

The GP conveys the cervical cytology results to the woman either by phone, email or at a face-to-face consultation (6). If follow-up is needed, no further support is initiated by the programme (6,14). Therefore, follow-up used to depend on the woman’s ability to understand, remember and act upon the recommendation and the GP’s ability to monitor and act upon women who do not adhere. In 2011, a new Danish guideline from the Danish Ministry of Health, specified that the sample takers (GPs) have the responsibility to secure follow-up and encourage the women to request test results (43).

The cervical cancer screening programme holds several different complex algorithms for follow-up; these depend on the present result of the cervical cytology, human papillomavirus (HPV) tests and the woman’s anamnesis as earlier test results and possible treatment for pre-cancer must be taken into account (9) (see Appendix I for Danish follow-up algorithms). Women with mild pre-cancer are generally recommended a new cytology in 6 or 12 months. Women with an inadequate sample (either HPV or cytology test) need a new test in 3 months, whereas women with severe abnormal cytology results or a positive HPV test result must be referred to a gynaecologist within 3 months for a colposcopic examination with a histological sample (6,18). This latter examination may either be performed at a hospital or by a private gynaecologist. The purpose of the gynaecological follow-up is to clarify the stage of possible pre-cancer using the cervical intraepithelial neoplasia (CIN) classification (See Appendix III for the CIN classification) (6). The majority of women with a histologically confirmed CIN1 and often CIN2 are followed by a “watchful waiting” approach, whereas most women with CIN3 receive conisation to prevent progression to cancer.
(33,44). About 25,000-30,000 histological biopsies are obtained each year in Denmark, and the number of annual CIN treatments (e.g. conization, hysterectomy) among Danish women were more than 6,400 in 2007 (6,33). Overtreatment is a risk in Denmark. It is estimated that eight CIN treatments are currently performed to prevent one cervical cancer (33). When a carcinoma suspicion is raised in Denmark (i.e. visible tumour on cervix or a cytology/histology with suspicion of cancer cells), such woman is referred to a fast-track programme for cervical cancer, which was implemented in January 2009 (45). The stage of the disease must be clarified within 21 days using the FIGO staging system, and treatment should begin within another eight days (45).

**Financing follow-up**

The women in Denmark do not pay for attending cervical cancer screening or follow-up. Approximately 3500 GPs are paid by the tax-funded public healthcare system, and each GP has 1600 patients on average and approximately 110 cervical cytologies per year (16,46,47).

**Availability in follow-up**

Most citizens (98.7%) are listed with a specific general practice, which they must consult for medical issues (46). The GPs thus act as gatekeepers to the secondary healthcare system (e.g. practicing gynaecologists and hospitals) (47-49). The remaining 1.3% have chosen the right to consult any GP or private practicing specialist at any time against paying part of the consultation fee, but hospital admissions are still free of charge (48,49). Access constraints to gynaecologist may influence the timelines of follow-up (3,50). A maximum waiting time of one month was implemented in Denmark in September 2013 (47,51). Previously, 90% of women diagnosed with cervical cancer in 2007 had their first appointment at a private practicing gynaecologist or at a hospital within 61 days of the GP referral date (52). Therefore, it is possible to attend follow-up within three months, as recommended for women with abnormal cytology results or a positive HPV test result.

**Characteristics of the delivery system and its association with follow-up**

The proportions of women without follow-up in Danish general practice range from 0% to 100% in 2010. However, these estimates are unsure as many practices had only few samples in need of follow-up (53). Most other programmes deal with problems of non-adherence in follow-up (54,55). In addition, the systematic process in the management of follow-up in cervical cancer screening varies across countries. For instance, in some countries GPs are responsible for the referral process and in some countries the screening programme is responsible (12) (see Appendix IV for organisation of follow-up in European screening programmes). Some countries have already implemented direct notifications (e.g. England (56)).
Several aspects of the delivery system have been associated with women attending cervical cancer screening follow-up in different reviews (29,57-62). Poor communication could be a reason for women’s non-adherence in cervical cancer screening follow-up. GPs or practice staff often convey cervical cytology results, but the informational content of the communication differs markedly (63) and may surpass the individual woman’s literacy levels (64), may be delayed or results may not be conveyed at all (65,66). Furthermore, weaknesses in the GPs’ tracking systems may entail difficulties for practices, which may oblige them to use both electronic and manual paper systems to safeguard patient monitoring (67). Especially normal cervical cytology results are not always conveyed (7). This practice is inadvisable as women with abnormal test results for which GP initiatives to convey the results have failed may wrongly be reassured that no news is good news, and these women may thus fail to request the test results themselves (7,67).

Improved adherence in follow-up has been linked with patient access to the healthcare system, such as “extended opening hours” (68), “short waiting times” (50) and “on site specialist”. Other important factors are the organisation in the general practices, such as “smaller facility size” (50), “information systems” (69)) and the personal characteristics of GPs, such as, “more recent graduation” (69), “perception of severity”, “communications skills” (63) and “provider gender” (57,58,68)).

Substantial variation in follow-up management is found in countries with cervical cancer screening (70,71). In Denmark, a survey in 2006 among 152 general practices found that solo practices had higher risk of having women not adhering to cervical cancer screening follow-up compared to group practices. Six percent of all practices did not have systems to ensure follow-up, and 78% conveyed cervical cytology results when the women initiated contact (65). The GPs explained that the importance of test results sometimes was downplayed (65).

**The population at risk and the environment**

The women are the “population at risk”. According to the framework, the women are characterised in terms of predisposition (demographics and attitudes), enablement (personal and family resources) and need (perceived and evaluated health status). Additionally, the women are influenced by the environment (physical, social and economic structures) in which they live.

Several reviews have provided an overview of the characteristics influencing women’s adherence to follow-up in cervical cancer screening (29,57-62).

In Denmark, advanced cervical cancer stages are often seen among women with shorter education, older age and women living alone (77). Non-participation in screening and increased comorbidity could only explain some of this variation. Therefore, the authors suggested that the same characteristics also increased the risk of later referrals and diagnostic processes (77).

CURRENT EVIDENCE OF HEALTH POLICIES

Effectiveness of direct notifications and reminders

Effectiveness measures the improvements in health. In this thesis, this is operationalised as the women’s follow-up adherence. This section describes the current evidence of improvements due to direct notification of results and GP reminders.

Direct notification of results by letter

Postal letter invitations to women have been found to increase the participation in cervical cancer screening (78). Yet, the effect of direct notification of results by postal letters on adherence to follow-up has been explored only once in a cluster-randomised intervention study among 42 general practices in Australia conducted in 1995. The results found that none women in the intervention group with CIN missed follow-up after one year (95% CI: - to 7%), compared to 23% (95% CI: 11 to 39%) in the control group. Letters had no effect in women with atypia (79). However, almost 60% of women in intervention practices were not exposed to the letter intervention, which limits the potential impact of the intervention.

GP reminders

Reminders sent to GPs have proven to increase the participation among women who do not regularly participate in screening for cervical cancer(80,81) and for other diseases (82,83). However, it may be problematic to simply transfer this effect to the group of women who do not attend recommended follow-up after screening.
Knowledge of abnormality is expected to affect both the GPs and the women, and the type of required examinations, gender and age groups would differ markedly between populations (84). GP reminders have also been used as part of multifaceted interventions which have improved the follow-up (85,86) or not improved the follow-up (87). However, when evaluated this way, it is not possible to measure the effect of the reminder per se.

Four studies investigated whether GP-reminders as a single intervention increased adherence in follow-up for women with abnormal cervical cytologies.

Two of these were older observational studies. In Australia, 28% of women with “abnormal cells with features of HPV or significant CIN” and a recommended follow-up in three months had a GP reminder after six months (88). One year after the initial cytology, the proportion of women without follow-up had decreased to 15% (88). In total, 42% of women with “cells with features of HPV or CIN1” and a recommendation for follow-up in six months had a GP reminder after nine months. One year after, the proportion of women without follow-up was 29% (88). In Canada, 1500 reminder letters were sent to Canadian healthcare providers regarding women who did not attend follow-up after cervical screening (89). The GP reminders triggered follow-up for 10.5% of women. Yet, the follow-up had already been performed or booked for 24.0% of these women, 20.1% of the women could not be contacted, 19.5% did not give any reason for non-compliance, 15.5% did not attend booked appointments and 10.4% did deliberately not follow the management recommendations (89).

A more recent study from Boston estimated the follow-up adherence before and after implementation of reminders sent to GPs in two clinical practices (90). On the basis of unadjusted results, the proportion of women without follow-up was unchanged, but follow-up was achieved more timely. When adjusting for type of pre-cancer and practice location, significantly more women attended follow-up after the intervention (OR 15.4 (95% CI: 3.7 to 62%)). In total, 97% of women attended follow-up after the reminder (90). Even before the intervention, 93% of women were followed-up; this is far better than in the Danish setting, which limits the generalisation of results.

A Dutch study investigating 171 general practices in 2005, generated reminders to GPs of all women with abnormal or inadequate cervical cytology results 10 weeks after the recommended follow-up. A reminder was generated for 47.6% of women with milder pre-cancer and inadequate cervical cytology results. One year after, the initial cytology follow-up increased to 79.8%. The comparable estimates for women with severe pre-cancer were 12.8% and 94.9%, respectively (91). Generalisation to a Danish setting may
be limited, as follow-up adherence in this study only increased to the level women in Denmark already adhere to follow-up without GP reminders.

None of the studies investigated the timelines in follow-up to identify the time points when direct result notifications or GP reminders had effect. This may be important knowledge for optimal timing of other interventions. None of these studies were performed in a Danish setting, and they did not investigate if the women with cervical cytology results classified as normal in need of a follow-up benefitted from the interventions. This may be of special importance as these women – as part of the surveillance for earlier pre-cancer detection – may have increased risk of pre-cancer recurrence (92).

**Equity in follow-up**

The criterion equity is ultimately concerned with minimising inequalities among subgroups of women, but it also concerned with maximising fairness of distribution of services that produce better health (39).

Sociodemographic inequality is present at several levels of cervical cancer prevention (93-95), and this highlights the need to address inequality (93). If a health policy unintendedly excludes certain groups of women, this may oppose the objectives of cervical screening programmes as they aim to provide the same opportunities for all women in the target group without compromising the women’s integrity and autonomy (41,96).

In this thesis, variations among GPs are explored in terms of the proportions of women attending follow-up after reminders have been sent to GPs. The thesis also explores how direct notifications of results and GP reminders concerning follow-up affect the follow-up adherence among different subgroups of women in the target group. Hence, the following section describes the current evidence of how direct notification of results and GP reminders may affect equity.

**Direct result notifications by letter**

No studies have evaluated how direct notification of results have benefitted different groups of women (79).

**GP reminders**

One study on reminders addressed the socio-demographic characteristics of women and variations in the follow-up adherence among different providers. Reminders were generated for different types of providers, and follow-up rates were better in general practice compared to gynaecologists, hospital, pregnancy termination centres, and
sexually transmitted diseases clinics (88). Furthermore, younger women and women from the lowest social classes were found to have the highest risk of not attending follow-up; 17% were without follow-up compared to seven and eight percent for women in other social classes (88). However, the study did not investigate variations between different general practices. As this observational study lacked a control group, the results highlighted that inequality was present within a context of GP reminders but not whether GP reminders affected inequality.

**Efficiency of follow-up**

The efficiency criterion focuses on how to maximize positive health outcomes while using the least possible resources (39,96). In this thesis, we investigate whether direct notification of results by letter has decreased the use of general practice as anticipated by the Danish National Board of Health.

No previous study supported this hypothesis. On the contrary, in the intervention study of direct notifications by Del Mar and colleagues, 72% of interventions general practices reported increased use of consultation time (79). Evidence is still lacking for a potential decrease in the use of GP contacts from women due to direct notifications.

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**INTRODUCTION AT A GLANCE AND OVERALL AIM**

Cervical cancer screening involves different and complex algorithms for follow-up, and 20% of women are not returning for recommended follow-up in Denmark. Large variations in the follow-up adherence persist among subgroups of women and among general practices. A main objective in the Danish cervical cancer programme is to reduce missed opportunities for detecting and treating pre-cancer as up to 12% of cervical cancer diagnoses may originate from this problem.

The Danish National Board of Health recommended in 2012 that cervical cytology results should be sent directly to the investigated women by letter to ensure that all women were notified and to ease the work of GPs. Furthermore, the National Health of Board recommended implementation of GP reminders as an additional safety measure for women missing out on their recommended follow-up.

Evidence of the effectiveness of direct notification of results to women on follow-up adherence is lacking. Current evidence suggests that GP reminders may improve follow-up, yet it is uncertain to what extent in Denmark. Additionally, we still need to study how these two interventions improve the follow-up adherence for different types of follow-up recommendations. Moreover, it has yet to be investigated whether direct notification of results or GP reminders can improve the follow-up adherence in all
subgroups of women and if variations in follow-up adherence among general practitioners can be reduced by GP reminders. Finally, it remains to be clarified if notification of cervical cytology results directly to the women could decrease the use of general practice as anticipated.

**Overall aim**

The overall aim of this PhD thesis is to evaluate selected perspectives of the effectiveness, equity and efficiency of the two recommendations provided by the Danish National Board of Health. This thesis aims

I. To study if direct notification of cervical cytology results to women can improve follow-up proportions and if follow-up is improved for subgroups of women (Paper I)

II. To study if direct notification of cervical cytology results can decrease the number of GP contacts and how costs related to conveying results are affected (Paper II)

III. To study if GP reminders can improve follow-up proportions and if follow-up is improved for specific subgroups of women and variations in follow-up proportions are reduced between general practices (Paper III)
CHAPTER 2: MATERIAL AND METHODS

This chapter provides a brief overview of the methods and materials in the three papers. First, all used data sources and key variables are described as most of the registers have been used in all the papers. Next, the methods for Paper I and Paper II are described together, with emphasis on the direct result notification intervention, which is only briefly described in the papers (Chapter 3). Last, the method for Paper III will be presented. A more detailed description of the methods are presented in the individual papers (Chapter 3).
The three papers all include women aged 23-64 years who had a cervical cytology performed in Danish general practice. The three papers vary in terms of settings, study designs, exposure, outcome measures and unit of analysis:

**Table 2.1 Characteristics of Papers I-III**

<table>
<thead>
<tr>
<th>Study population</th>
<th>Setting</th>
<th>Study design</th>
<th>Exposure</th>
<th>Primary Outcome measure</th>
<th>Unit of analysis</th>
<th>Data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper I</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women with a cervical cytology and a recommendation of follow-up</td>
<td>Central Denmark Region, 2013-2014</td>
<td>Cluster-randomised controlled study</td>
<td>Direct result notification by postal letter</td>
<td>Follow-up proportions at different time points</td>
<td>Woman</td>
<td>DPDB¹, Statistics Denmark</td>
</tr>
<tr>
<td>Paper II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women with a cervical cytology.</td>
<td>Central Denmark Region, 2013-2014</td>
<td>Cluster-randomised controlled study</td>
<td>Direct result notification by postal letter</td>
<td>Monthly rates of GP contacts</td>
<td>Number of GP contacts</td>
<td>General practice at similar addresses</td>
</tr>
<tr>
<td>Paper III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women with a cervical cytology and a recommendation of follow-up</td>
<td>Denmark, 2009-2013</td>
<td>Before-after study</td>
<td>Electronic reminder to GPs if follow-up has not been registered in due time</td>
<td>Follow-up proportions at different time points</td>
<td>Cytologies of women</td>
<td>DPDB¹, Statistics Denmark</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

¹DPDB: Danish Pathology Data Bank  
²NHSR: Danish National Health Service Register for Primary Care
The Danish civil registration system
This register was launched in 1968. It assigns all Danish citizens with a Danish civil registration number at birth or when citizens have resided legally in Denmark for three months or more, or are required to pay tax in Denmark. This number is a unique ten-digit personal identifier. All Danish citizens are required to notify the Danish authorities if they emigrate, immigrate or change address within borders. Most importantly, the Danish civil registration number allows linkage with several other Danish registries (97).

The Danish Pathology Data Bank (DPDB)
Cervical cytology information, such as date of requisition, diagnosis and follow-up recommendations, was retrieved from the DPDB. The register contains records of all pathological material evaluated in Denmark since 1997 (20), including cervical cytology and histology samples from all hospitals, gynaecologists and GPs, regardless of the indication for the sample. All cervical cytology results are assigned codes from the Danish version of the Systematized Nomenclature of Medicine (SNOMED) (20). In 2007, a national guideline recommended to classify cervical cytology results according to the 2001 Bethesda Classification for Cervical Cytology (18). Cervical cytology diagnoses in the three studies in this thesis are based on this classification. Before this, pathology departments primarily used a Danish modification of the WHO dysplasia classification or another Danish classification system (98).

According to the Bethesda classification, the adequacy or inadequacy of the cervical cytology sample should initially be considered. Hereafter, adequate samples are classified as either “normal” (i.e. negative for intraepithelial lesion or malignancy) or “abnormal” (i.e. epithelial cell abnormality) or “other” (17). Abnormal sample results are classified depending on the presence of either abnormal squamous or glandular cells.
Table 2.2 Classification of squamous cell dysplasia according to Bethesda, CIN, modified WHO or another Danish system

<table>
<thead>
<tr>
<th>Bethesda 2001</th>
<th>Normal</th>
<th>ASCUS/ASC</th>
<th>LSIL</th>
<th>HSIL</th>
<th>Squamous cell carcinoma (SCC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN</td>
<td></td>
<td>CIN1</td>
<td>CIN2</td>
<td>CIN3</td>
<td></td>
</tr>
<tr>
<td>Modified WHO</td>
<td>Normal</td>
<td>Atypical</td>
<td>Condyloma/ M. dysplasia</td>
<td>Moderate dysplasia</td>
<td>Severe dysplasia</td>
</tr>
<tr>
<td>Another Danish system</td>
<td>Normal</td>
<td>Atypical</td>
<td></td>
<td></td>
<td>Suspected malign cells</td>
</tr>
</tbody>
</table>

Table 2.3 Classification of glandular cell dysplasia according to the Bethesda and modified WHO system

<table>
<thead>
<tr>
<th>Bethesda 2001</th>
<th>Normal</th>
<th>AGC</th>
<th>AIS</th>
<th>Adenocarcinoma (endo cervical, endometrial, extra uterine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified WHO</td>
<td>Normal</td>
<td>Atypical</td>
<td>AIS</td>
<td>Adenocarcinoma (endo cervical, endometrial, extra uterine)</td>
</tr>
</tbody>
</table>

(4,18,98,99)

For “normal” samples, the Bethesda classification recognises the possibility of findings of other benign cellular changes, e.g. candida. Furthermore, the Bethesda system operates with “another” category; this category covers cases without morphological abnormalities, but with increased risk, for, for example, benign-appearing endometrial cells in a woman above 40 years of age as this may indicate endometrial abnormalities (17).

The Danish National Board of Health further specifies that specific SNOMED codes must be applied if a follow-up is needed (6,18). Follow-up recommendations in the studies presented in this PhD thesis were categorized as seen in Table 2.4.
Table 2.4 Categorisation of follow-up recommendations

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within 3 months</strong></td>
<td></td>
</tr>
<tr>
<td>AEAA015</td>
<td>Gynaecologic examination with colposcopy is recommended</td>
</tr>
<tr>
<td>AEAX15</td>
<td>Gynaecologic examination within three months is recommended</td>
</tr>
<tr>
<td><strong>In 3 months</strong></td>
<td></td>
</tr>
<tr>
<td>AEAA001</td>
<td>Cytology control in three months is recommended</td>
</tr>
<tr>
<td>AEAA002</td>
<td>Cytology control in three months is recommended: previous conisation</td>
</tr>
<tr>
<td>AEAA003</td>
<td>Cytology control in three months is recommended: previous cryotherapy</td>
</tr>
<tr>
<td>AEAA021</td>
<td>Cytology control in two till four months is recommended</td>
</tr>
<tr>
<td>AEAX01</td>
<td>Cytology control in three months after local oestrogen treatment</td>
</tr>
<tr>
<td>AEAY01</td>
<td>Cytology control incl. HPV test in four months is recommended</td>
</tr>
<tr>
<td>AEAY02</td>
<td>Cytology control in three months is recommended: previous conisation</td>
</tr>
<tr>
<td>AEAY03</td>
<td>Cytology control in three months is recommended: previous cryotherapy</td>
</tr>
<tr>
<td>AEAX04</td>
<td>Cytology control in four months is recommended</td>
</tr>
<tr>
<td>AEAY05</td>
<td>Control, HPV test due to earlier inadequate test, in 3 months is recommended</td>
</tr>
<tr>
<td><strong>In 6 months</strong></td>
<td></td>
</tr>
<tr>
<td>AEAX01</td>
<td>If a new test is not received within six months the sample taker is reminded</td>
</tr>
<tr>
<td>AEAY02</td>
<td>Cytology control incl. HPV test in six months is recommended</td>
</tr>
<tr>
<td>AEAY04</td>
<td>Cytology control in six months is recommended</td>
</tr>
<tr>
<td>AEAY05</td>
<td>Cytology control in six months is recommended: previous abnormal result</td>
</tr>
<tr>
<td>AEAY06</td>
<td>Cytology control in six months is recommended: previous conisation</td>
</tr>
<tr>
<td>AEAY07</td>
<td>Cytology control in six months is recommended: previous cryotherapy</td>
</tr>
<tr>
<td>AEAX02</td>
<td>Cytology control with HPV test by gynaecologist in six months is recommended</td>
</tr>
<tr>
<td>AEAX03</td>
<td>Cytology control by gynaecologist in six months is recommended</td>
</tr>
<tr>
<td><strong>In 12 months</strong></td>
<td></td>
</tr>
<tr>
<td>AEAY01</td>
<td>If a new test is not received within 12 months the sample taker is reminded</td>
</tr>
<tr>
<td>AEAY08</td>
<td>Cytology control in 12 months is recommended</td>
</tr>
<tr>
<td>AEAY09</td>
<td>Cytology control in 12 months is recommended: previous abnormal result</td>
</tr>
<tr>
<td>AEAY08</td>
<td>Cytology control in 12 months is recommended: previous conisation</td>
</tr>
<tr>
<td>AEAY10</td>
<td>Cytology control in 12 months is recommended: previous cryotherapy</td>
</tr>
<tr>
<td>AEAY09</td>
<td>Cytology control in 12 months is recommended: previous hysterectomy</td>
</tr>
<tr>
<td>AEAY10</td>
<td>Cytology control in 12 months is recommended: previous radiotherapy</td>
</tr>
<tr>
<td>AEAY11</td>
<td>Cytology control in 12 months is recommended: previous abnormal histology</td>
</tr>
<tr>
<td>AEAY03</td>
<td>Cytology control incl. HPV test in 12 months is recommended</td>
</tr>
<tr>
<td><strong>Unprecise follow-up recommendation</strong></td>
<td></td>
</tr>
<tr>
<td>AEAY12</td>
<td>New cytological test recommended; the test was insufficient</td>
</tr>
<tr>
<td>AEAY13</td>
<td>New cytological test is recommended after treatment of infection</td>
</tr>
<tr>
<td>AEAY14</td>
<td>Cytological control after birth</td>
</tr>
<tr>
<td>AEAY19</td>
<td>Endo cervical sample with cytobrush is recommended</td>
</tr>
<tr>
<td>AEAY20</td>
<td>Endo cervical abrasion is recommended</td>
</tr>
<tr>
<td>AEAX00</td>
<td>New cytological test is recommended</td>
</tr>
<tr>
<td>AEAY01</td>
<td>Control is required</td>
</tr>
</tbody>
</table>

1 Few samples had more than one follow-up recommendation; if so, the “most” restrictive follow-up recommendation was valid in the study.
2 The implemented GP reminder system did not generate reminders for these recommendations; therefore, cervical cytology results with these recommendations were excluded when GP reminders were studied in Paper III.
3 These recommendations were not used by pathology departments for the cervical cytology test of women in Paper I and Paper II; therefore, for simplification, they are not applied to the letter algorithm shown in the Appendix A.3 of Paper I, or in Appendix VI in this thesis.
4 In all three papers, cervical cytology tests with these recommendations were excluded.
For a woman to be categorised as having attended recommended follow-up, at least one of the samples presented in table 2.3 had to be registered in the DBDB, after the initial cytology with a follow-up recommendation. Date of follow-up is defined as the requisition date of this new sample. If women had more than one sample, the first date is used. The definition of follow-up is in concordance with the national Danish GP reminder system (100). A GP reminder is generated if none of these samples are present in the DBDB after the initial sample recommending follow-up.

Table 2.5 Definition of follow-up samples

<table>
<thead>
<tr>
<th>Cytology</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>T8X210 Cytology, vagina</td>
<td>T81900 Vagina and uterus</td>
</tr>
<tr>
<td>T8X211 Cytology, pipette material</td>
<td>T82000 Uterus</td>
</tr>
<tr>
<td>T8X212 Cytology, vaginal abrasion</td>
<td>T82900 Corpus and cervix uteri</td>
</tr>
<tr>
<td>T8X310 Cytology, cervix</td>
<td>T82920 Uterus, both tubae and both ovaries</td>
</tr>
<tr>
<td>T8X311 Cytology, exo cervix</td>
<td>T83000 Cervix uteri</td>
</tr>
<tr>
<td>T8X312 Cytology, cervix and endo cervix</td>
<td>T83010 Cervix uteri mucosa</td>
</tr>
<tr>
<td>T8X320 Cytology, endo cervix</td>
<td>T83100 Exo cervix</td>
</tr>
<tr>
<td>T8X321 Cytology, endo cervix, special</td>
<td>T83110 Portio mucosa</td>
</tr>
<tr>
<td>T8X330 Cytology, vagina/cervix</td>
<td>T83120 Exo cervix mucosa</td>
</tr>
<tr>
<td></td>
<td>T83210 Cervix uteri, anterior lip</td>
</tr>
<tr>
<td></td>
<td>T83220 Cervix uteri, posterior lip</td>
</tr>
<tr>
<td></td>
<td>T83300 Endo cervix</td>
</tr>
<tr>
<td></td>
<td>T83320 Endo cervical mucosa</td>
</tr>
<tr>
<td></td>
<td>T83400 Cervical crypt (gland)</td>
</tr>
<tr>
<td></td>
<td>T83700 Collum stump</td>
</tr>
<tr>
<td></td>
<td>T83701 Conus</td>
</tr>
<tr>
<td></td>
<td>T83702 Top conus</td>
</tr>
</tbody>
</table>
The Danish National Health Service Register for Primary Care (NHSR)
Information on contacts to general practice were retrieved from the Danish National Health Service Register (48). The register holds information of all services in general practice, practising medical specialists, physiotherapists, dentists and psychologists. The purpose of the register is to document activities in primary care for administrative use. Since 1990, the data has been available for public health research purposes. All services must be recorded in the register for the contracted health care providers to get remuneration from the tax-funded public healthcare system. Information on both providers and citizens are collected (48). The definitions for daytime face-to-face consultations, telephone and email contacts from women used in Paper II are presented in Table 2.6:

<table>
<thead>
<tr>
<th>Table 2.6 Definition of daytime GP contacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face-to-face consultation</td>
</tr>
<tr>
<td>Telephone contacts</td>
</tr>
<tr>
<td>Email contacts</td>
</tr>
</tbody>
</table>

Statistics Denmark
Statistics Denmark has a pivotal role in Danish research as this institution administers data for researchers and publishes statistical information on the Danish population. With authorisation, researchers can upload data to the server of Statistics Denmark. Data managers at Statistics Denmark may hereafter enrich the data from several other registries on the individual level using the Danish civil registration number. All data are anonymised and only available on secure servers at Statistics Denmark with online remote access (101). Statistics Denmark also hosted the data used in this thesis and further provided the information on sociodemographic variables, such as emigration, vital status, educational attainment, cohabitation status and ethnicity (102). Educational attainment was available through the Danish Population Education Register (103). Emigration, vital status, marital status and ethnicity was available through the Danish civil registration system (97,102). Both registers are hosted at Statistics Denmark. Sociodemographic variables were defined as presented in Table 2.7.
Table 2.7 Definition of sociodemographic variables

<table>
<thead>
<tr>
<th>Sociodemographic variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educational attainment</td>
<td>The women’s highest completed education categorised into low (≤10 years of education), medium (&gt;10≤15 years) and high (&gt;15 years) as described in the International Standard Classification of Education of 2011 by UNESCO (104)</td>
</tr>
<tr>
<td>Marital status</td>
<td>Marital status was dichotomised as cohabitating or single.</td>
</tr>
<tr>
<td></td>
<td>Cohabitation included married couples, registered partnerships, couples living in consensual union (with at least one child in common) or cohabiting couples (two persons of different sex living at the same address with an age difference less than 15 years and no other adults living at the address) (102)</td>
</tr>
<tr>
<td></td>
<td>Single women comprised women which could not be categorised as above.</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Categorised as Danish, immigrant or descendant from western countries or immigrant or descendant from non-western countries.</td>
</tr>
<tr>
<td></td>
<td>Immigrants were defined as a woman born of parents with foreign citizenship.</td>
</tr>
<tr>
<td></td>
<td>Descendants were defined as born in Denmark of either parents with immigrant status or descendants with foreign citizenship.</td>
</tr>
<tr>
<td></td>
<td>Danish were, regardless of place of birth, defined as a woman with at least one parent with Danish citizenship born in Denmark.</td>
</tr>
<tr>
<td></td>
<td>Western countries included the 28 EU countries and Andorra, Iceland, Liechtenstein, Monaco, Norway, San Marino, Switzerland, Vatican State, Canada, USA, Australia and New Zealand, Non-western countries comprised the rest (102)</td>
</tr>
</tbody>
</table>

The Provider Number

The GP provider number was a key variable in all three studies. GPs who are contracted with the public healthcare system in Denmark are assigned a provider number (105). This number is also registered on all cervical cytology sample requisitions in the DPDB and enables linkage of cervical cytology results and specific general practices. GPs in partnership practices may share a provider number. In Paper I and Paper II a list of providers in the Central Denmark Region (2012) were obtained to identify GPs for the cluster-randomised study. The list also included information on addresses of general practices, number of GPs in each practice and gender of the GP.
Methods in Paper I and Paper II

Objectives
The studies aimed to investigate the consequences of direct notification of results to women by letter compared to usual care

- On the proportion of women without follow-up (Paper I)
- On the frequency of GP contacts and related direct costs (Paper II)

Design
A 1:1 parallel cluster-randomised controlled trial.

Setting
The Central Denmark Region with almost 341,000 women in screening relevant age groups (102), 844 registered GPs and 418 provider numbers at 340 different addresses.

Randomisation
A list of provider numbers of GPs in the Central Denmark Region was obtained in September 2012. Practices at similar addresses were manually grouped together and generated 340 clusters. A data manager without further knowledge of the trial performed the random allocation of clusters in STATA 11. All intervention GPs were informed of the intervention by letter.

Table 2.2 Distribution of general practices and randomisation

<table>
<thead>
<tr>
<th>Clusters of GPs at similar addresses</th>
<th>Control, n (%)</th>
<th>Intervention, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- clusters with 1 GP</td>
<td>170 (50)</td>
<td>170 (50)</td>
<td>340 (100)</td>
</tr>
<tr>
<td>- clusters with 2 GPs</td>
<td>47 (28)</td>
<td>58 (34)</td>
<td>105 (31)</td>
</tr>
<tr>
<td>- clusters with 3 GPs</td>
<td>58 (34)</td>
<td>48 (28)</td>
<td>106 (31)</td>
</tr>
<tr>
<td>- clusters with 4 GPs</td>
<td>30 (18)</td>
<td>26 (15)</td>
<td>56 (16)</td>
</tr>
<tr>
<td>- clusters with 5 GPs</td>
<td>20 (12)</td>
<td>21 (12)</td>
<td>41 (12)</td>
</tr>
<tr>
<td>- clusters with 6 or more GPs</td>
<td>7 (4)</td>
<td>12 (7)</td>
<td>19 (6)</td>
</tr>
<tr>
<td>Number of GPs</td>
<td>434 (51)</td>
<td>410 (49)</td>
<td>844 (100)</td>
</tr>
<tr>
<td>- women</td>
<td>195 (45)</td>
<td>184 (45)</td>
<td>379 (45)</td>
</tr>
<tr>
<td>- men</td>
<td>239 (55)</td>
<td>226 (55)</td>
<td>465 (55)</td>
</tr>
<tr>
<td>Provider numbers</td>
<td>222 (53)</td>
<td>196 (47)</td>
<td>418 (100)</td>
</tr>
</tbody>
</table>

The intervention: direct notification of results
In intervention practices, direct notification of cervical cytology results were sent to the home address of the investigated woman by letter. In order to send the direct notification, it was necessary to develop an algorithm to translate complex cervical cytology SNOMED codes from the DPDB into letters without delay and to develop
letters in lay language. After a development process, the algorithm was pilot tested in the period (from 10 October 2012 until 6 January 2013). The final algorithm was implemented on 7 January 2013. (Appendix V describes the development process.)

**Figure 2.1 Translation of SNOMED codes into letters**

All letters commenced in the same way: “Dear XXXXX. On DD.MM.YYYY, we received a cervical cytology from your general practitioner” and continued in three different ways: “your test result is normal”, “your test result is inadequate” or “your test results is not normal”. Furthermore, the letters included a recommendation for follow-up if a SNOMED code for follow-up had been applied by the pathology department. This was phrased as: “we would recommend you to contact your general practitioner for follow-up” if follow-up to gynaecologist was recommended within 3 months or “we would recommend you to contact your general practitioner and have a new test in X months” if follow-up was recommended in 3, 6 or 12 months. If the cervical cytology results were normal without a recommendation for follow-up, the women were informed on regular screenings intervals and encouraged to contact their GP if they had new or persisting gynaecological symptoms (6,64,106-109).

Few cervical cytology results exempted from the algorithm rules described above. In these letters, the women were instead encouraged to “contact their GP to have the results conveyed”. Exemptions included: 1) normal cervical cytology results with incidental findings (see Appendix VII for types of incidental findings), 2) unknown diagnoses, 3) uncommon topography codes as these women may demand a clinical assessment together with the sample results and 4) women with no follow-up recommendation but a LSIL or ASCUS diagnosis.
All letters were signed “Yours sincerely/The Pathology Department and Department of Public Health Programs, Randers Regional Hospital”. The final SNOMED code algorithm and examples of different types of notification letters are presented in Appendix VIII.

Women who did not have a postal address could not receive a letter. In these cases, the GPs were informed by a separate postal letter that they should convey the sample results to the women. In more rare cases, diagnosis codes or follow-up recommendations were changed after dispatch of the letters. In these situations, the women did not receive a second letter, but the GPs were informed by postal letter and asked to convey the changed cervical cytology result to the women.

All intervention practices continued to receive cervical cytology results electronically from pathology departments as always. The intervention practices had no restrictions; they could carry on the usual practice or stop to convey sample results themselves to women, and their responsibility for securing follow-up was unchanged. Intervention practices also received a GP reminder if the women did not attend recommended follow-up in due time (see organisation of GP reminders in the method section of Paper III).

**Usual care**
In control practices, all women had their cervical cytology results conveyed as usual by a face-to-face consultation or telephone/email contact. The GPs received the results electronically from pathology departments as always, and the GPs also received a GP reminder if the women did not attend recommended follow-up in due time.

**Study populations**
All cervical cytologies obtained in general practices were eligible for inclusion. However, in Paper I (adherence to follow-up after direct notification), only women with a follow-up recommendation were included, whereas Paper II (use of GP contacts after direct notification) comprised both women with and without follow-up recommendations.

**Outcome measures**
In Paper I “no follow-up” was defined as the absence of a new cervical cytological or histological sample within specific time frames after requisition of the initial cervical cytology. In Paper II, the monthly rates of the women’s daytime GP contacts were measured in a two-month period before and a five-month period after the date of the electronic notification of the cervical cytology results to GPs (index date).
**Statistical methods**

In both papers, the unit of analysis for primary outcomes were the individual women. All women had the same length of observation time, and intention-to-treat analysis was applied. All statistical analyses were conducted using STATA, version 14.

In Paper I, the prevalence of women who did not return for recommended follow-up was estimated at four different time points. Estimation of prevalence ratios and prevalence differences was accommodated using a generalised linear model from the binomial family, and robust standard errors were used to correct for clusters of women within general practices at the same address (110). To determine if the effect on the women’s follow-up adherence was modified by the sociodemographic factors, proportions of women without follow-up were studied on both relative and absolute scales (111).

In Paper II, monthly incidence rates of GP contacts were measured in each randomisation group and compared with incidence rate ratios. A multi-level mixed-effect negative binomial regression model was applied due to overdispersion to allow for repeated measurement of the women. Stratified analyses were performed for women with and without a follow-up recommendation.

To explore variations in the women’s use of GP services among practice clusters, we calculated the mean number of GP contacts during the first month after the index date per women per practice cluster.

In Paper II, a cost analysis with a societal perspective was used to estimate direct costs accumulated from one month before until two months after the index date in each randomisation group (112). The cost difference between randomisation groups were extrapolated to national Danish settings per year. Similarly, calculation of used GP time was done for each randomisation group and extrapolated to a national Danish setting.

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**METHOD PAPER III**

**Objective**

The study aimed to investigate the effects of GP reminders on the proportion of women without follow-up, on sociodemographic variations in follow-up and on follow-up variations among general practices.

**Design**

Before-after study, as electronic GP reminders were implemented in 2012 (6,14)
Chapter 2: Material and methods

Setting
In 2011 the Danish population consisted of approximately 1,480,000 women in screening relevant ages (102), and roughly 3500 GPs (46,47,105).

GP reminders
Cervical cytologies with a recommendation of follow-up within three months generated a GP reminder if no new cervical cytology or histology was registered in the DPDB four months after the first cervical cytology requisition. Cytology results with a recommendation of follow-up in 3, 6 or 12 months generated a reminder after 6, 9 or 15 months, respectively. The GP reminder system was launched nationwide in Denmark on 18 January 2011, but was not fully operational before 2 February 2012. No management protocol or additional resources were given to the GPs.

Study population
All cervical cytology samples obtained in a general practice of women from 2009 to 2013 were identified. Cytologies of women were eligible for inclusion if they had a recommendation for follow-up. As follow-up data were retrieved on 30 May 2014, only cytologies with a reminder dated before 1 December 2013 were included to secure six months of observation of women’s follow-up adherence. The study population was divided into a before group (with a simulated reminder date before activation of the reminder system) and an after group (with a reminder date after activation).

Statistical analysis
Not attending recommended follow-up was defined as in Paper I. The unit of analysis was the individual cervical cytology. Proportions of women (cervical cytologies) without attending recommended follow-up in the before and the after group were compared with odds ratios (ORs) using multilevel mixed-effects logistic regression with random effects to correct for clustering of women within general practices and for clustering of measurements within women (110). To determine whether the effect of GP reminders on follow-up was modified by socio-demographic factors the proportions of women without follow-up were studied on a relative scale.

GP-practice variation in follow-up proportions was explored by calculating the proportion of no follow-up for each practice. The interquartile ranges were estimated and Pitman’s test for comparing variances of no follow-up proportions of paired practices was additionally used.
The Danish Data Protection Agency permitted use of registry data in the three studies (ID: 2009-41-3471, ID: 2010-41-5646). The Danish National Board of Health permitted use of patient journal data from the DPDB (ID: 3-3013-1371/1) for Paper I and Paper II, but this was not necessary at the time we applied for data from the DPDB for Paper III. An inquiry regarding the intervention in Paper I and Paper II was made to the Committee on Health Research Ethics in the Central Denmark Region (ID: 211/2011). The cluster-randomised controlled study (Paper I and Paper II) is registered at ClinicalTrials.gov (TRN: NCT02002468).
CHAPTER 3: RESULTS

This chapter consist of the three papers. An additional explorative analysis relating to Paper I is presented as well.
CHAPTER 4: DISCUSSION OF METHODOLOGICAL PROBLEMS

This chapter discusses strengths and weaknesses of study designs and the accuracy of study results in terms of internal validity (selection, information, and confounding bias) and statistical precision. Finally, external validity is discussed.
STUDY DESIGNS

Randomisation of the direct result notification intervention (Papers I and II) was used to avoid confounding. Randomisation at the level of GP clusters instead of the individual level of women was performed to avoid contamination bias (110). If individual randomisation was performed, it was a concern that general practices may forget to convey cervical cytology results to women in the control group and thus increase these women’s risk of having no follow-up, which could have compromised the study results in Paper I. On the other hand, it was also a concern that general practices for ease and security continued to convey cervical cytology results to all women, regardless of intervention status, which could have compromised the study results of GP contacts in Paper II. The cluster randomisation ensured that the intervention practices could adjust daily routines for conveying cervical cytology results in a uniform way and that the women, at the time of the sample requisition, could be informed of how the cytology results would be conveyed.

To investigate the effect of GP reminders (Paper III), the before-after design was pragmatically chosen as the GP reminder system was already implemented nationwide. The primary weakness of the design was the possibility that other temporal changes may have occurred simultaneously with the implementation of GP reminders, which could have created the found effects. Cervical cytologies before 2009 were not included. This ensured that all pathology departments followed the recommendations made by the Danish National Board of Health in 2007 on SNOMED coding practice for diagnosis and follow-up recommendations (18). Before 2007, pathology departments did not always state follow-up recommendations and used different diagnosis classification systems (113). The study period was limited by the date when the follow-up data were retrieved from the DPDB.

SELECTION BIAS

Selection of women and cytologies in all three papers were register-based. Therefore, self-selection bias from women who did not wish to participate was not present (114-116). For all three papers, identification of the study population required data on cervical cytologies in the DPDB. In general, the completeness of the DPDB is considered high (20,117). In 2005, it became mandatory to report all investigated pathological material to the DPDB (118).
When follow-up adherence was studied (Paper I and Paper III) women were excluded if a follow-up recommendation was not applied. Yet, only few women were excluded for this reason. In Paper I, the majority of all cervical cytology samples obtained in general practice in the study period did not have a follow-up recommendation (i.e. 89.1%). Of these, 0.8% had an abnormal or inadequate cervical cytology result, and a follow-up recommendation SNOMED code may have been forgotten by pathology departments. Corresponding figures for Paper III were 88.9% and 0.2%. Only few cervical cytology results were excluded for this reason. Exclusions did not seem to be related to exposure status (direct notification of results or GP reminders); therefore, it is considered not to cause bias of associations.

We excluded women due to death, missing civil registration number or emigration in all three papers. As this was not considered to depend on exposure status, it would not cause bias of associations although prevalence estimates may have been underestimated, for instance if emigrated women have poorer follow-up adherence.

In the GP reminder study (Paper III), it is worth mentioning that all women in the intervention arm of the cluster-randomised study of direct notifications of results were identified and excluded. Otherwise, the after group may have performed falsely better. Moreover, in this paper, we considered to include only the women’s first cervical cytology with a follow-up recommendation to ensure statistical independency between women. However, this would entail that women with a second abnormal cytology would be excluded from the after group, whereas women regardless of abnormality anamnesis could be included in the before group. As it is likely that the women’s anamnesis could affect the follow-up, we chose to include all cervical cytologies of women, and the unit of analysis was changed from women to cervical cytologies.

In all three papers, we used complete-subject analysis when studying effects in different sociodemographic groups. Missing data bias due to a reduced study population was not a major concern as less than 1% of the sociodemographic variables were missing (see baseline characteristics for Paper III on GP reminders), and missing variables did not vary depending on exposure status (direct result notification or GP reminders) (116).

INFORMATION BIAS

All information in the papers was based on prospectively collected data in registries. Therefore, misclassification due to recall bias was eliminated (114,119).
Misclassification of women who attended recommended follow-up (outcomes in Paper I and Paper III) was not likely as registry data from the DPDB is updated daily. In addition, the DPDB has included information on all pathological material investigated in all of Denmark since 2005(20). Further, women are unlikely to have sought care out of Denmark making follow-up data unavailable (61).

Misclassification of GP contacts (outcome in Paper II) is not considered disturbing either even though the validity of the NHSR is unknown (48). The GP contacts were assessed regardless of the reason for contact. The NHSR does not contain information on whether GP services were used with the purpose of conveying cervical cytology results (48). This is considered a strength as the women’s individual anxiety levels caused by the intervention may have made the women contact their GP more or less for other reasons as well. Under-reporting of GP contacts are probably minimal as the register is used for reimbursement purposes. The risk of possible economic incentives causing over-reporting is minimal because the regional health administration monitors the use in all general practices (48). Computerised general practices further minimise possible misclassification of GP contacts between citizens (48).

Misclassification of exposure status (direct notification of results or GP reminders) is not likely in any of the three papers as the study designs ensured that exposures were precisely defined.

The information on the characteristics of the women was obtained from Statistics Denmark on the 1 January preceding the initial cervical cytology sample (101,102). Even though Statistics Denmark is updated annually, even daily for some variables, the information on especially educational level and cohabitation status may have changed in the period between the update and the date of the cytology requisition (102). However, if misclassification is present, it is not considered to be associated with exposure status (direct result notifications or GP reminders), and it is, therefore, considered to be non-differential. Misclassification of age and ethnicity is not plausible.

CONFOUNDING

Confounding bias is traditionally said to occur when the association in exposure outcomes is affected by other factors. These may differ between exposure groups and influence the outcome although they are not part of the causal chain leading from exposure to outcome (115,120).
Paper I (direct notification of results and adherence to follow-up)

Even in randomised study designs, imbalanced baseline characteristics may occur (116). In cluster-randomised trials, this risk may be even higher (110). In Paper I, the number of GPs per cluster and the educational levels of the women differed. More women with high educational attainment and larger general practices were represented more often in the control group. Both educational level and size of general practice (group practices compared to solo practices) have been associated with follow-up (65,95). Therefore, we tried to adjust for these variables in the analysis of Paper I, but this changed the estimates only slightly. However, educational status of the women and GP cluster size may be associated with other factors, which may affect follow-up, e.g. health beliefs and organisational factors in general practices.

Paper II (direct notification of results and use of GP contacts)

In Paper II, we adjusted for the same factors as in Paper I, but this did not change the estimates markedly. However, pathology department differed a bit between randomisation groups in this paper. Therefore, a more complex model was tried as well as we also adjusted for pathology department, women’s age and prior use of GP contacts, but this did not change the estimates markedly either.

Still, both for Paper I and Paper II, confounding and residual confounding cannot be ruled out completely.

Paper III (GP reminders)

In Paper III, the “before” follow-up proportions was an attempt to measure the women’s counterfactual adherence in the recommended follow-up without reminders. However, diagnosis in each type of follow-up recommendation in were different between the before and after groups (see Appendix B, Paper III). This may partly be explained by the temporal implementation of the HPV test triage of women with ASCUS and the change to liquid-based screening techniques in pathology departments (6,14). In several studies, more severe cervical cytology results have been associated with better follow-up than milder cervical cytology results (57). Therefore, we adjusted for type of diagnosis in a sensitivity analysis. This changed the estimates only slightly, but residual confounding may persist.

Other temporal changes may also have confounded the study results. For instance, follow-up adherence may have improved due to press publicity in the mass media (121,122). Moreover, a new Danish guideline on handling paraclinical tests from the Ministry of Health was adopted in 2011 which specified that the sample taker was always responsible for securing follow-up (43). Additionally, a maximum waiting guarantee of one month for diagnosis was implemented in 2013 (47,51). We did not
adjust for the potential influence of these changes. Nevertheless, it could be argued that these temporal changes would have improved the follow-up before the GP reminder was generated, which was not particularly the case. Still, these temporal changes may have motivated the GPs to react more intensively to a reminder. Therefore, the effect of reminders may increase or decrease over time, depending on other circumstances. This highlights the importance of the ecological viewpoint presented in the Framework for Applying Health Service Research in Evaluating Health Policy.

STATISTICAL METHODS AND PRECISION

**Paper I and Paper II (direct notification of results)**

In Paper I and Paper II, we used intention to treat analysis to ensure that randomisation was kept even though one intervention GP cluster did not wish to participate and followed usual care.

Randomisation was based on clusters of general practices with similar addresses. When the unit of analysis was the individual woman, the women within a cluster may have shared some similarities. This clustering entailed loss of power. To account for the design effect of clustering, the calculated sample size was inflated by prolonging the study period (110,123,124).

In Paper I, generalised linear models from the binomial family with robust standard errors were used to correct for clusters. The chosen cluster correction method did not change the estimates, but it did decrease the precision of estimates (123). Outcomes were estimated as prevalence ratios and prevalence differences instead of odds ratios as outcome of interest was frequent (125). Degree of similarity of women’s adherence in recommended follow-up within clusters was measured using the intra-cluster correlation coefficient (ICC)(124). In this study, the ICC was estimated to be 0.01. This may be interpreted as 1% of variation in the women’s follow-up between clusters and 99% within clusters (therefore, it depended on the women) (123). The estimated ICC of 0.01 and the average cluster size of 21 corresponded to a required design effect of 1.2. Sample size calculations before study start estimated that 1,394 women with carcinoma, HSIL, AIS, ASCH and AGC needed to be included. However, the length of the study was also timed to meet the sample size calculations in Paper II; hence, more than 5,000 women with these diagnoses were included. The study in Paper I achieved relatively high statistical precision for most investigated types of follow-up recommendations, except for women with a recommendation for follow-up in six
months, but the precision was lower when the study population was stratified into sociodemographic subgroups of women.

To estimate the monthly rates of GP contacts in Paper II, we intended to use a multi-level mixed-effects negative binomial regression model with two random effects to allow for clustering of women in general practices at similar addresses and for repeated measurements of women. Accounting for random effects may change both estimates and precision slightly (123). However, due to convergence problems, the intended model with two random effects was not possible, and we only allowed for one random effect due to repeated measurements of women. ICC was estimated to be 0.06 for all GP contacts in the first month after index date; this required a design effect of 12 with an average cluster size of 200, which was not achieved. Especially the precision of estimates for women with a follow-up recommendation was low.

**Paper III (GP reminders)**

In Paper III, the unit of analysis was the individual cervical cytology. Therefore, the analysis accounted for clustering of women within general practices and for clustering of measurements within a woman. We included all cervical cytologies in Denmark, and limitations in sample size were based on available data. We used a multi-level mixed-effects logistic regression model with two levels of clusters. This model only allowed for estimation of odds ratios in contrast to prevalence ratios or prevalence differences. Since outcome of interest was not always rare, odds ratios may have overestimated the prevalence proportion (125). The large sample size secured high precision of estimates.

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**EXTERNAL VALIDITY**

To generalize findings in the studies to other settings, a high internal validity is a precondition (115).

**Paper I and Paper II (direct notification of results)**

These studies were carried out in the Central Denmark Region, which has organised the cervical cancer screening programme similarly to the rest of Denmark (6). The study results on how direct notification of test results, increased adherence in follow-up and decreased number of GP contacts may be generalised from regional to national level for the target group for cervical cytology samples obtained in Danish general practices. It is unsure if the study results could be generalised to cytology samples obtained in the hospital setting or at a private gynaecologist. These cytology samples are more often obtained from women with a gynaecological anamnestic, and therefore may demand a clinical assessment before conveyed to women. For the same reason, relevant follow-
up may differ from follow-up recommendations applied by pathologist departments. Consequently, we doubt the appropriateness of a similar intervention in this setting.

Generalising the results of the study to other cancer screening programmes in Denmark gives other considerations: In Denmark, the screening programmes for breast and colorectal cancer have already implemented direct notification of results to women (and men). However, in both programmes, results are only sent for screening samples, whereas results of follow-up are not provided as part of the programme, but by clinicians. Furthermore, the direct notification holds only two possible results (either a follow-up is necessary or it is not), and the timeframe for recommended follow-up is within few weeks. This simplicity stands in contrast to the intervention investigated in this thesis, where different samples obtained in general practice (i.e. screening, opportunistic and surveillance) generated multiple different results letters to women and recommendations for follow-up up to one year after initial cytology. A Danish study found that approximately 90% of all cytologies in Denmark were performed as opportunistic or invited screening, 8% was performed as surveillance and 0.7% due to inadequate cervical cytology results (15). We hypothesise that the effect of direct notification of results on follow-up may be generalised to other screening programmes although the effect size on follow-up adherence is unsure.

To generalise study results of follow-up adherence to other countries, it is important to acknowledge the Danish setting in which the direct notification intervention was incorporated. For instance, the free-of-charge follow-up service to all women should be considered. We excluded women with unknown address, women with unknown diagnosis and women with incidental findings. These women were few in the Central Denmark Region, but the frequency may vary significantly between screening settings in different countries. Results of the studies may, therefore, be generalised to other countries with similar healthcare screening organisation, where eligible women can be contacted by letter.

The study results could possibly be generalised to other types of sample results, but effect sizes may vary. A precondition for using direct notification of results is the possibility for developing valid algorithms that can translate diagnosis to simple patient letters. This may be a challenge for other diagnoses/diseases, where much different clinical information must be considered together (82).

**Paper III (GP reminders)**

It is considered a strength that the effect of GP reminders was assessed as a singular intervention because the effect of multifaceted interventions with GP reminders seldom gives prioritisation to which part of the intervention that was the most
important (126). Hence, it may be easier for other healthcare settings to assess if GP reminders could be a favourable approach to secure cervical cytology follow-up. The impact of GP reminders on follow-up also has been studied in other cervical cancer screening settings (90,91) and for other diseases (83,127,128). This suggest that GP reminders may serve as a robust intervention that works across different settings with different workflows, user behaviour, health information technologies and patient groups. A precondition for effect of GP reminders is the possibility for developing an algorithm which can identify and monitor patients who postpone follow-up.
CHAPTER 5: DISCUSSION OF RESULTS

This chapter first presents the study results in general. The remaining sections discuss limitations of the model, study results and criteria applied, specifically concerning effectiveness, equity and efficiency.
Implementing GP reminders in the Danish cervical cancer screening programme in 2012 at national level almost halved the proportion of women not attending follow-up six months after a reminder (Paper III), regardless type of follow-up recommendation. Pre-existent variation between general practices and follow-up proportions were minimised, and GP reminders benefitted all investigated sociodemographic groups of women (age, ethnicity, educational level and cohabitation status). Effect of GP reminders differed depending on the sociodemographic characteristics of the women. The youngest age groups of women benefitted relatively less from the intervention compared to women above age 34 years. The same applied to women living alone compared to cohabitating women. Effect of GP reminders was most pronounced in the first three months after the reminder.

Direct notification of results by letter to women decreased the proportions of women who did not attend timely follow-up; this was found for all types of follow-up recommendations (Paper I). Direct notification of results benefitted all investigated sociodemographic groups of women (age, ethnicity, educational level and cohabitation status). Cohabitating women benefitted relatively less from direct notification of results than women living alone. Effect of letters was most pronounced until the GPs had received a reminder.

Direct notification of results decreased the use of general practice in the first two months after dispatch of the letter (Paper II). Extrapolated to a national Danish setting with 400,000 cervical cytologies per year, the decrease in GP contacts corresponded to 3.9 full-time equivalent GPs per year and a cost of approximately EUR 736,119 per year.

The framework provided guidance on how to evaluate policy changes in healthcare and how to achieve relevant knowledge of effects. The ecological perspective highlights the importance of considering the context when study results are interpreted (39). The framework visualises that only limited associations of structures and outcomes were assessed in this thesis, whereas the processes surrounding the interventions and transactions between GPs and women were not investigated (39).
An important consideration when interpreting the thesis results is the choice of outcome measure:
Firstly, the framework depicts the importance of measuring improved health of women (39). In line with this, reviewers of follow-up studies have recommended that “diagnostic resolution” or “cancer incidence” are studied instead of follow-up adherence (58). We acknowledge that improved follow-up will not necessarily lead to improved health of the women, but we consider it an objective in itself to avoid any preventable missed opportunity in the diagnostic process and to limit delays in pre-cancer and cancer treatment (3). In our opinion, the outcome of adherence in recommended follow-up thereby better captures whether the interventions achieve their main goal; changing the behaviour of GPs or women that leads to improved follow-up.

Secondly, the definition of adherence in follow-up must also allow for possible waiting time related to access constraints among private gynaecologists or in secondary healthcare, which may affect the women referred from general practice. It would be inappropriate to attribute all follow-up delays to factors in the women or GPs if follow-up delay is due to factors in the delivery system. However, we do not consider access constraints to be common in Denmark. In 2007, 90% of women with cervical cancer identified by screening did not experience specialist appointment delays above 55 days (52). A one-month guarantee implemented in 2013 for diagnosis further minimised this possibility (47,51). Finally, a review have recommended that adherence in follow-up be stratified on type of abnormality and not only measured as adherence at one specific time point (58). We chose to stratify on type of follow-up recommendation instead of type of abnormality. This approach was taken with the primary objective to study if women and GPs complied with the recommendations rather than to study if adherence differed depending on diagnosis. Yet, as different types of follow-up recommendations roughly correspond to specific diagnoses, adherence related to diagnosis was indirectly studied (7,129).

**EFFECTIVENESS**

We investigated effectiveness by measuring to what extent women attended recommended follow-up (Paper I and Paper III).

**Direct notification of results by letter (Paper I)**
Implementation of direct notification of results improved the follow-up at “date of recommended” by four percent points and worked across different types of follow-up recommendations. Letters have the advantage of being systematically delivered to all
women with only few days of delay, in contrast to some of the described safety weaknesses for results conveyed in general practices (65,67), such as misunderstandings of cervical cytology test results (66,130-132), delayed conveyance of results (65) or no conveyance at all, which could entail that women may interpret no news as good news (133). An Australian survey published in 1994 showed that 7% of women with abnormal cervical cytology results did not recall being notified (66).

Another important result of the letter intervention is the timing of effect. For some women, follow-up occurred even before the recommended date and may not have left time enough for pre-cancer to regress. In a Danish setting, positive effects of the letter intervention on follow-up seemed to decline when a reminder was generated to GPs. We found that 31.4% of women receiving direct notification of results had not returned for follow-up one month after the recommended date. Others have found that 14% of the women who recalled to be notified of abnormal cervical cytology results still did not have follow-up six months after the recommendations (66). Persisting follow-up problems must be expected as women seem to have multiple barriers for attending follow-up (29,57,61,62,134).

We phrased the letters using the words “normal”, “not normal” or “inadequate” as recommended by the Danish National Board of Health (6). Letters may be compromised by communication problems, just as when the GP conveys cervical cytology results (107). The letters, which were written in Danish lay language, encouraged the women in need of follow-up to contact their GP to discuss the test results and to schedule an appointment. Furthermore, the letters provided an internet address with further information and a recommended time frame for follow-up. Preparing patients ahead of medical consultations has been found to increase patient inquisitiveness and satisfaction (135). The letters may have influenced the women’s perceived and evaluated need for follow-up, empowered them to adopt an active role and legitimised them to express possible concerns when communicating with GPs (3,136).

In our study, the largest absolute improvement in follow-up adherence was seen in women with a follow-up recommendation in three months. In this group, 99.5% of the cervical cytologies were classified as inadequate. Women with a recommendation for follow-up in 12 months had the smallest absolute improvement. In this group, 63% of the cervical cytologies were classified as normal and 37% as abnormal. An explorative analysis stratified on whether the cervical cytology letters included “normal” or “not normal” wording revealed that only the not normal group had better follow-up (see the extra study results for Paper I in chapter 4). Therefore, it seems likely that both the timing of the recommended follow-up and the phrasing in the notification letters affect the intervention in terms of ability to secure follow-up.
Women needing to see a gynaecologist within three months also benefitted from the letter intervention. In this group, 98.1% of the cervical cytology results were classified as abnormal. An explorative analysis, which stratified women on the basis of milder or more severe abnormalities, showed that women with severe abnormalities benefitted relatively more from the intervention than women with milder abnormalities (see the extra study results for Paper I in chapter 4) even though these women received the same type of letter stating that the cervical cytology results were “not normal”. Varying effects of letters depending on diagnosis have also been found in international research on direct notification of results. For example, follow-up for women with CIN pre-cancer seemed to be improved due to the intervention in contrast to women with atypia even though these women received the same type of letter (79). This is somehow surprising as women have been found to fear cancer to the same degree, regardless of stage of pre-cancer, and not understand technical jargons of different stages (137). We hypothesise that the women’s perception of the cervical cytology results and the recommendations provided in the letters is modified by further information seeking (e.g. from GPs, family, friends or the internet (138)). This is underpinned by the fact that GPs have been found to downplay the seriousness of cervical cytology results and recommended follow-up to decrease the women’s anxiety (65). Furthermore, it has been found that women rely more on cervical cancer information provided by GPs than on information provided by friends and family or the cervical cancer screening programme (139).

It is possible that refined phrasings in letters may improve the effectiveness of direct notification of results. Additional initiatives that may help the women getting more information could be providing the women with an informational leaflet or a motivational brochure, state examples of questions in the letter that the women could ask their GP or use the precise medical term of the identified abnormality (instead of simply stating “not normal” as we did) (64,108,109,140,141). Some women also find it difficult to understand the justification behind the recommended time interval between the initial cytology and the follow-up (108,137,142,143). Therefore, it may be relevant to include an explanation of the rationale behind the watchful waiting approach in letters (108). This could be especially relevant for cervical cytology results classified and phrased as normal.

**GP reminders (Paper III)**
A health information technology generating reminders to GPs may assist the GPs to recall information and provide the knowledge at relevant time (83). Follow-up monitoring is generally challenged by a grey area of mixed computerised and time-demanding manual processes in general practice for safeguarding diagnostic follow-up
We found that the women’s adherence in follow-up was markedly improved six months after a GP reminder; this was seen for all types of follow-up recommendations. Improvements seemed to occur in the first three months after the GP reminder. Still, the proportions of women who did not return for recommended follow-up six months after a reminder varied from 2.5% to 11.7% depending on type of follow-up recommendation.

The women who benefitted the most (relatively and absolutely) from the GP reminder intervention in our study were the women with a recommendation for follow-up in 12 months; this group was also the group which benefitted the least from the intervention with direct notification of results. However, 11.7% of women in the after group had not attended follow-up six months after a GP reminder (i.e. nine months after recommended follow-up). In this group, 78% of the cervical cytology results were classified as normal. We hypothesise that lack of follow-up for these women could be related to difficulties for the women to understand the watchful waiting approach and for GPs to explain it.

The women who benefitted the least (relatively and absolutely) from the GP reminder were the women who were recommended to consult a gynaecologist within three months: 2.5% in this group had not attended follow-up ten months after the initial cytology (i.e. six months after a GP reminder or seven months after date of recommended follow-up). This is slightly better than for outcomes 12 months after the initial cervical cytology, identified in international studies, where 3% and 5.5% of women did not attend follow-up (90,91). This group of women is especially important to target as they have the most severe abnormalities. Therefore, even small improvements may have large impact.

Almost 11% of women with a recommendation for follow-up in three months still missed follow-up 12 months after the initial cytology (i.e. six months after a reminder or nine months after date of recommended follow-up). In this group, 99% of cytology results were classified as inadequate. This estimate is comparable to that reported for inadequate results in a cluster-randomised trial, where 10% still missed follow-up after 12 months (91).

The last percentages of women who do not attend follow-up may be mostly reluctant, and these groups may need multiple and different interventions to motivate them to attend follow-up (145,146). On the other hand, as the GPs already know the women, GPs are in a position that gives them a unique opportunity to obtain insight on how to approach and address the women to overcome their individual barriers, which may not be possible with other generic systematic interventions initiated by the programme.
Equity as a criterion for evaluating health policies is concerned with minimising inequalities among subgroups of women, and maximising fairness of the distribution of service that produces health. In this thesis we investigated equity as variation in follow-up among general practices and subgroups of women.

**Sociodemographic inequality in follow-up among women (Paper I and III)**

In the study of GP reminders (Paper III), we found that women of younger age (23-34 years), women from non-western countries and women with the lowest level of educational attainment had increased risk of not returning for recommended follow-up. This is in line with the findings in other studies (10,57,62,95).

Furthermore, we explored whether GP reminders and direct notification of results by letter affected the adherence in follow-up differently among subgroups of women. We found that both interventions improved the women’s adherence in follow-up across all the investigated subgroups (age, ethnicity, educational level and cohabitation status), although insignificantly for some subgroups as reported in Paper I (direct notification of results).

Effect of GP reminders on follow-up adherence differed depending on the women’s age: Women in the youngest age groups (23-34 years of age) benefitted relatively less from the GP reminder compared to women above 34 years of age. Explanations for this effect modification may be related to different lifestyles of age. For instance, 23% of younger women change GP provider in one year, whereas only four percent of women aged 50 or more do (147). This knowledge is important as the GP reminders per default are generated to the general practice that performed the cytology. Thus, GP reminders may address the social inequality of age if they are sent to the women’s current GP as well. In contrast, communication of alerts to two recipients have (for other tests than cervical cytology results) been found to almost double the risk of not receiving timely follow-up, possibly because it is less clear who has the responsibility (148).

Effect of GP reminders on follow-up adherence also differed depending on the women’s cohabitation status: Women living alone benefitted relatively less from reminders than cohabitating women. One explanation may be that 18.3% (95% CI: 17.8 to 18.9) of adults in Denmark describe it as difficult or very difficult to “discuss things with healthcare providers until you understand all you need to” (149). These difficulties appear to be worse for women living alone than for cohabitating women, but this is not associated to age (149).
Effect of direct notification of results on follow-up adherence also differed depending on cohabitation status: Women living alone had a relatively better effect than cohabiting women. It has been found that 12.8% (95% CI: 12.4 to 13.3) of adults in Denmark report it difficult or very difficult to “understand written health information”. Women living alone more often reported difficulties than women cohabiting (149). This does, therefore, not explain the effect modification in our study.

Both citizens with low education and foreign ethnicity find it more difficult to “discuss things with healthcare providers until you understand all you need to” and to “understand written health information” than higher educated Danish citizens (149). Effect modification depending on educational attainment or ethnicity was not present for either of the two interventions.

To decrease the persisting inequality in follow-up adherence, it is possible that direct notification of results by letter can be refined and adjusted to address specific subgroups of women, for instance translated into other languages (64). Above, we presented possible reasons for subgroups of women to not attend recommended follow-up. However, sociodemographic characteristics are linked with complexity. For instance, women from lower social classes have more stressful events at work and at home, negative beliefs about screening, lack of confidence in dealing with the medical system and in own chance of success, other illness experiences, and they more often focus on short-term consequences (e.g. unpleasant colposcopic examination) than on long-term consequences (e.g. cancer) (93,150). Women from different social classes may, therefore, prioritise challenges (e.g. follow-up) very differently. Some groups may thus deliberately decline treatments that other groups would tend to prioritise.

**Variation in follow-up between general practices (Paper III)**

The reminders were directed to GPs with the objective to support the GPs in their clinical work in coordination of the diagnostic follow-up. This helped counterbalance potential administrative weaknesses that could lead to variation in the women’s follow-up adherence between general practices. In Paper III, we found that GP reminders decreased follow-up variation between general practices. Still, despite introducing this fail-safe system in Denmark, variation persisted. Primarily two reasons for variation may be considered. Firstly, the sociodemographic profiles of women in general practice may vary considerably (49). This entails that the effort a GP must invest in securing follow-up may vary considerably. For instance, a Canadian study of GPs acting on the information of a reminder found that 20.1% of women could not be contacted and 15.5% did not keep booked appointments (89). These problems may be worse in some general practice populations. Secondly, differences at process level between general practices regarding workflow, organisational policies and general rules may persist.
(151). For instance, information overload in general practices has been associated with GPs missing test results (3,152), also described as alert fatigue (3). In the Netherlands, research has shown that 77% of general practices indicated that the results of cervical cytologies needed follow-up, but only 42% used this information to systematically monitor follow-up (153). In the USA, 18% of test result alerts, for example for X-rays and CT scans, in an outpatient setting were not acknowledged (i.e. clicked on and opened) (148).

Variation in follow-up proportions between GPs may not relate to either GPs or the women, but it may interact with complexity as depicted at the process level in the framework. An Australian survey from 2013 underpinned the importance of the GP-women encounter as they found that 39% of the women preferred to share the decision for cervical cytology follow-up of milder pre-cancer with their GP, 49% preferred to make the final decision themselves, and 11% of women preferred to leave the final decision to the GP (139). Communication among patients and GPs also vary depending on the patient’s sociodemographic status as GPs are affected by how patients express themselves. Compared to women with higher sociodemographic levels, the communication with women from lower levels entails less positive socio-emotional utterances, significantly less information and less direction (136). However, women with lower levels of education more often prefer not to be actively involved in the decision-making process of cervical cytology follow-up than women with a university degree (139).

**EFFICIENCY**

Direct notification of cytology results to women may entail new procedures for managing cervical cytology results in general practice. It was hypothesised that women with cervical cytology results classified as normal and without a recommendation for follow-up did not to the same extent need to consult their GP.

The *efficiency* of direct notification of results was measured in terms of use of GP contacts (Paper II). We found that direct notification decreased the number of total GP contacts (face-to-face consultations, emails and telephone contacts) in the first two months after dispatch of letters among the women with a normal cervical cytology result without a recommendation for follow-up. For women with a recommendation for follow-up, the intervention did not change the number of total GP contacts in the same period. However, the decrease in GP contacts did not cover the direct societal expenses of the letters. Extrapolated to the national Danish setting with 400,000 cervical cytologies per year, the decreased GP contact equalled 3.9 full-time equivalent
GPs per year to an added cost of approximately EUR 740,000. On average, a Danish GP had a gross earning corresponding to approximately EUR 278,303 in 2014 (46). Yet, the long-term cost effectiveness from a societal viewpoint is uncertain as it is unknown to what extent improved follow-up proportions may lead to cancer prevention (or overtreatment), lower cancer treatment costs, improved quality of life for the women and opportunity for staying active in the workforce. In Denmark, the treatment costs of conisation are much lower than the treatment costs of cervical cancer; in 2007 these costs were estimated to be EUR 3,000 and EUR 25,500, respectively (154,155). Finally, the cost analysis did not account for the gained health value of the 3.9 full-time equivalent GPs per year that could be of benefit to other patients in the practices.

We hypothesise that the direct notifications of results from a long-term perspective can decrease the use of GP contacts even more and become more efficient for two reasons.

Firstly, in the explorative analysis, we found that only half of intervention GP clusters had decreased the number of contacts for women with a normal cervical cytology result without a recommendation for follow-up (Figure 3A, Paper II). This implied that some intervention general practices may have been reluctant to adapt new procedures and continued to convey cervical cytology results to the women as usual. When introducing the letter intervention, we informed intervention practices to decide themselves how to adjust routines for sample result management. Some GPs articulated concern about the intelligibility and precision of the letters, which may have been a barrier for changing routines. The reluctance may diminish as GPs get more confident with direct notification of results or if another implementation strategy were used. However, differences in the number of GP contacts among the two subgroups of intervention practices may also be explained by case mix of the listed women.

Secondly, it is currently discussed in Denmark whether to deliver cervical cytology results as emails instead of postal letters (16). Almost every adult in Denmark has a personal electronic mail box (E-boks) linked to their unique civil registration number; this mail box is used for most communication from public authorities (156). With emails, the extra societal cost would be reduced to approximately EUR 300,000. However, these calculations presuppose that the number of GP contacts did not change. A study of colorectal cancer screening compared different mailing approaches and found that more people attended colonoscopy if the mailings included a yellow sticky note with a short message (157). This may underpin the importance of a postal letter, which the women can read several times and bring along, compared to email (106). Furthermore, all citizens in Denmark have since 2013 had access to their own medical pathology reports on www.sundhed.dk (or E-record) (158). This online platform stores all personal healthcare data (e.g. hospital reports), but it was only used
by one third of the Danish population in 2016 (159). Email notifications were seldom favoured by patients in the USA in 2012 (160). Today, women in Denmark receive other cancer screening results by email, just as email contacts with GPs increase rapidly (138). Regarding direct notification of results in cervical cancer screening, we consider it inconclusive whether emails will affect the proportions of follow-up. Still, the women’s preference for either email or letter may change rapidly (160).

On the other hand, direct notification of results may also be less efficient if, as currently discussed, a feature is applied to the cervical cytology requisition, where women and/or GPs can decline a direct notification of a result (6). In 1999, only 42% of Australian women preferred to receive a cervical cytology result by mail, whereas the rest of women preferred telephone contact or a consultation with the GP (161). In our study, women or their GPs declined the letter by contacting the distributing department. However, this may have been inconvenient as less than five women or GPs did. In the study by Del Mar, less than half of women in the intervention group received a letter, but GPs reported on average that only six % of the women declined to have the letter sent. Consequently, it could be considered if GPs declined letters on behalf of women and why (79).
CHAPTER 6: MAIN CONCLUSIONS
In 2011, one in five women in Denmark did not attend recommended follow-up after a cervical cytology test. This non-adherence in follow-up entails missed opportunities for decreasing the incidence and down-staging cervical cancer. Moreover, socioeconomic inequalities in follow-up adherence and variations in follow-up adherence between general practices were evident.

Two recommendations from the Danish National Board of Health were launched in 2012 to enhance patient safety and improve cervical cytology follow-up of women. These two health policy recommendations were evaluated in this thesis.

The Danish National Board of Health recommended that all women with a cervical cytology systematically should have their results revealed directly from the pathology department by letter instead of by their GP as usual. Our aim was to study if direct notification of cervical cytology results to the women improved the follow-up proportions and if the follow-up improved for specific subgroups of women (Paper I). In a cluster-randomised trial, we demonstrated that direct notification of results had improved the follow-up adherence by four percent one month after the date of follow-up recommendation. Moreover, we showed that follow-up adherence improved in all investigated sociodemographic subgroups of women (age, cohabitation status, educational attainment and ethnicity); this was seen although the letters were written in Danish and although health information is generally considered difficult to understand. We found that the effect of letters was relatively higher for single women than for cohabiting women. For some women, follow-up attendance occurred even before the recommended date of follow-up, and the effect of letters did not weaken until approximately three months after the date of recommended follow-up. Moreover, we anticipated that direct notification of results to women with a normal cervical cytology result and without a recommendation for follow-up would imply that they did not need to consult their GP to receive the results. Our aim was to study if direct notification of results decreased GP contacts and how the direct costs related to conveying results were affected (Paper II). We showed that the letters decreased the number of general practice contacts by 21% for this group of women in the first month after dispatch of the letter. However, only half of the intervention general practices had less GP contacts, whereas the other half had the same number of GP contacts as the control group. We hypothesise that either the case mix of listed women or non-adaption to new optional procedures for management of cervical cytology results could be possible explanations for the identified differences between subgroups of general practices. Moreover, we demonstrated that direct notification of results did not entail that women with a recommendation for follow-up had less contact with general practice. This is an important finding as these women need to consult a GP to get further information on the cervical cytology result and follow-up recommendations.
The decrease in GP contacts was not enough to cover the expenses of the intervention with direct notification of results by letter. The direct additional costs of implementing the direct notification of results by letter on a nationwide scale would amount to approximately EUR 740,000.

The Danish National Board of Health also recommended that GPs should be reminded if the women did not return for recommended follow-up in due time. Our aim was to study if GP reminders improved the follow-up proportions, improved the follow-up for specific subgroups of women, and reduced variations in follow-up between general practices (Paper III). We demonstrated that this intervention almost halved the proportion of non-adherent women in follow-up six months after a GP reminder; this effect was found for all types of follow-up recommendations. However, due to the before-after design of the study, other temporal changes may have confounded the study results. The effect of systematic GP reminders was most pronounced in the first three months after receipt of reminder. Furthermore, we found that women in all investigated sociodemographic groups (age, cohabitation status, educational attainment and ethnicity) benefitted from the intervention, although younger and cohabitating women did not benefit to the same extent as older and single women. Finally, we demonstrated that GP reminders decreased the variation in follow-up proportions between general practices.
CHAPTER 7: PERSPECTIVES AND FUTURE RESEARCH

This chapter presents implications of the thesis and future research that may optimise the effect of direct notification of results and GP reminders on women with a cervical cytology obtained in general practices.
The evidence from this thesis may contribute to development of international guidelines: In 2001, more than forty professional cancer and pathology societies from more than 20 countries recommended not to use direct notification of results because of worries that it would interfere with the patient-clinician relationship (17). The European guidelines for cervical cancer screening (2008) currently recommend using systematic reminders to GPs. Recommendations on how to convey cervical cytology results to women are vaguer (7). The European guidelines state, “Depending on regional or national legal practice, informing the woman of the result of the smear is the responsibility of the sample taker or of the laboratory ...” and “…Each woman must be informed (verbally or written) about the screening test result” (7).

Future research

The Framework for Evaluating Health Policy highlighted the importance of gaining more insights into the process level. We still need more knowledge about how women interpret the phrasings in direct notification of result. Firstly: Why do women with a recommendation for follow-up in 12 months only benefit from letters if the cervical cytology result is phrased as “not normal” in the letter (in contrast to women with letters phrased as “normal”)? Secondly: How do women receiving letters with the phrase “normal” results without a follow-up recommendation interpret the letter? For instance, 33.5% of English women did not relate a “normal” cervical cytology result to a specific medical condition, but interpreted the result as “overall health is all clear” (162). If women interpret the result as a broader guarantee of health, this may affect these women’s future help-seeking behaviour in an undesirable way. On the other hand, this may also apply to results conveyed by GPs. Finally: Why did only half of the GPs have reduced contact with women receiving a direct notification revealing a normal cervical cytology result and without a recommendation for follow-up?

Regarding GP reminders, the processes surrounding the intervention are preconditions for effect. From a sociotechnical perspective, it may be possible to gain more insight into these processes (151). This may include exploring workflow, communication and coordination when a GP reminder is received, both within general practices and between women, staff and GPs. For example, if the clinical content of the GP reminder is adequate, timely and relevant, if the software is configured without errors, if the human-computer interface fits the need of GPs and staff in the practice, if GPs use all available features for securing follow-up in the electronic medical report (22,42), and if external rules and legislation impact the effectiveness (151). For instance: What consequences would be seen if the reminder is sent to the current GP instead of the sample taker?
Considerations for organisation of follow-up in cervical cancer screening

To improve the adherence in follow-up, cervical cancer screening programmes may choose to implement the patient-directed intervention (direct notification of results) and the system-directed intervention (reminders to GPs). A precondition for implementation is development of valid algorithms for both direct notification of results and GP reminders. Both health information technologies are relatively simple, but requires a robust pathology register, a stringent SNOMED coding practice at the involved pathology departments (for both diagnosing and follow-up recommendation) and – for direct notification of results – also an updated valid register with the addresses of the women.

If a cervical cancer screening programme aims to address problems with adherence in follow-up, by either implement GP reminders or direct notification of results, we suggest to begin with GP reminders for several reasons: 1) In our studies, GP reminders seemed to have a larger absolute effect on follow-up adherence compared to direct notification of results, and the effect of direct notification almost diminished when GP reminders were generated. However, this entails that fewer women receive timely follow-up, but this delay concerns only few months, 2) It could be considered to generate GP reminders earlier as this may help reduce the length of the delay for the women, 3) A GP reminder algorithm does not require a valid register with the addresses of the women, 4) The coding practice at pathology departments for diagnosing may be less restrictive, but still it is very important to apply follow-up recommendations. Therefore, a GP reminder algorithm is expected to be more easily operationalised and require less maintenance.

It is also important to emphasise that the two interventions supplement each other. For instance, GP reminders did not increase the follow-up in single women to the same extent as in cohabitating women, whereas direct result notifications functioned had most impact among single women. Other important arguments for implementing direct notification of results were cost efficiency and releasing GP time to do other tasks. In our study, the costs increased by the implementation of direct notification of results, hence it must be considered if these costs were better allocated to target the women who were still non-adherent to follow-up after a GP reminder. Yet, it is possible that the direct notification of results would be increasingly efficient over time. For instance, if GPs were encouraged to stop conveying results to women with a cervical cytology result classified as normal without a follow-up recommendation or if emails could be used instead of postal letters. Finally, the degree of satisfaction among women or the general aim for increased digitalisation in Denmark – topics that have not been studied in this thesis – may talk in favour of implementing direct notification of results.
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ENGLISH SUMMARY
Background and aims

The Danish screening programme for cervical cancer is challenged. Up to one in five Danish women did not receive timely follow-up in 2011; this corresponds to approximately 7,500 women. Similar problems with follow-up are also seen in other countries, and studies have shown that up to 12% of all cancer cases could have been avoided if there had been no failure in the follow-up. In Denmark, approximately 400,000 samples are taken each year for cervical cancer. More than 90% of these are taken in general practice, corresponding to approximately 110 samples per GP per year. Each sample is analysed at a pathological department, and test results are forwarded electronically to the general practitioner (GP) with a recommendation of follow-up. The GP is then responsible for conveying the test results to the woman and for ensuring follow-up.

With the test result, the woman also receives information on recommended follow-up: to follow the general screening programme, to be referred to a gynaecologist within 3 months, or to have a new examination in 3, 6 or 12 months. Studies have shown that it is difficult for many women to understand a test result and the need for follow-up. Lack of follow-up occurs more frequently among women in lower social classes and is also more frequent in some general practices than in others. For example, there may be problems with how and when the GP convey the result, or there may be failures in the administrative procedures in practices that are intended to help ensure timely follow-up.

The National Board of Health, therefore, recommended two new initiatives in 2012 to form part of the screening programme. First, investigated women were to receive their cervical cytology test result directly from the pathology department by letter (direct notification), while their GP still received the result electronically as usual. This was intended to remedy communication problems, as the letter to the woman were sent systematically to all women without delay and described the sample in lay language as normal, not normal or inadequate for analysis. As an added bonus, it was expected that the number of GP contacts could be reduced, as women with normal cervical cytology test results who could follow the usual screening programme did not need to contact their GP. Second, the GP was to receive an electronic reminder if the woman did not get timely follow-up. This was intended to remedy administrative challenges in general practice relating to monitoring the women without follow-up.
This thesis aims:

I. To study if direct notification of cervical cytology results to women can improve follow-up proportions and if follow-up is improved for subgroups of women (Paper I)

II. To study if direct notification of cervical cytology results can decrease the number of GP contacts and how costs related to conveying results are affected (Paper II)

III. To study if GP reminders can improve follow-up proportions and if follow-up is improved for specific subgroups of women and variations in follow-up proportions are reduced between general practices (Paper III)

Method

The women’s follow-up adherence after direct notification and use of GP contacts was evaluated in a cluster-randomised trial in the Central Denmark Region in 2012-2014 (Paper I and Paper II). Women listed with half of the general practices in the region received their cervical cytology test result directly from pathology departments by letter (intervention group), whereas women listed at the other half general practices received their test results from the GP as usual (control group). Reminders to GPs were introduced in 2012. The women’s adherence to recommended follow-up was assessed by comparing a period before and after the implementation (Paper III). All data in the studies are based on prospectively collected register data from the Danish National Pathology Data Bank, The Danish National Health Service Register for Primary Care, and Statistics Denmark.

Results

Paper I showed that four percent point more of the women who received a direct notification had been followed up at the recommended date compared with women who received the cervical cytology results from their own GP as usual. The follow-up was improved for all groups of women (i.e. age, cohabitation status, ethnicity and educational level), although women who lived alone had greater benefit from the direct letter intervention than cohabiting women. However, part of the follow-up took place earlier than recommended for women in the intervention group. The effect from direct notifications diminished when the GPs in Denmark received a reminder for the women who lacked follow-up.

Paper II showed that the number of GP contacts from women, who received a direct notification with cervical cytology results classified as normal and without a recommendation for follow-up, fell by 21% in the first month after dispatch of the letter, compared with women who did not receive a direct notification. Women who
were recommended follow-up did not have fewer GP contacts in the same period of time. An analysis of the direct societal costs showed that the reduction in GP contacts did not cover the extra costs of sending direct notifications by letters. For the entire Denmark, this would result in additional costs of approximately EUR 740,000 per year. However, subanalyses showed that only about half of the intervention practices had fewer GP contacts than the control practices. If the GPs can cease to communicate normal test results to women who do not need follow-up, and if test results can be revealed by e-mail instead of letter, the expenses are expected to be further reduced.

Paper III showed that the number of women without follow-up six months after a GP reminder was almost halved in the period after the implementation of GP reminders compared to the period before. GP reminders had a positive effect on all groups of investigated women (i.e. age, cohabitation status, ethnicity and educational level). Yet, the positive effect was lower among young women and women who lived alone. In addition, the study showed that variation between general practices in terms of ensuring follow-up were minimised. Approximately three months after a GP reminder, no additional effect of the reminder was seen.

Finally, Paper I and Paper III also showed that many women were still not followed up, despite the new initiatives. Additionally, follow-up was found to be best among the women who should be referred to a gynaecologist within 3 months and worst among the women who were recommended follow-up in 12 months. A large proportion of this latter group was women with a normal test result.

Conclusions and implications
This PhD dissertation sheds light on some of the consequences of introducing direct notification of test results by letter and GP reminders in the Danish screening programme for cervical cancer. The new knowledge can contribute to international guidelines that may specify how follow-up is best ensured.

The studies show that both direct letters and GP reminders provide faster follow-up for all types of follow-up recommendations and for all groups of women (ethnicity, age, cohabitation status and educational level). GP reminders appear to provide good support as they seem to reduce the variations seen among different general practices in terms of success rates for completing follow-up. Compared with direct letters, GP reminders also provide the largest absolute reduction in the number of women without follow-up. The costs of direct letters are not sufficiently counterbalanced by fewer GP contacts, at least not in a Danish context. GP reminders are expected to be easier to operationalise. Therefore, in other screening programmes, GP reminders could be a good first method to ensure follow-up. However, it should also be pointed out that
direct letters and GP reminders also complement each other. For example, direct letters worked best for single women, whereas GP reminders worked best for cohabiting women.

In future, it could be relevant to shed light on the women's response to and understanding of the letters. The studies suggest that women with certain types of test results do not benefit from letters. The wording in the letters could possibly be improved and thereby help increase the impact of direct letters. It would be interesting to explore different work processes around test results and reminders in general practice. This may uncover initiatives that can provide better follow-up and reduce the use of general practice among women who do not need follow-up. The studies also indicate that many general practices still have contact with women, with normal test results and no need of follow-up, although these women have received a direct notification by letter.

The groups of women who do not get follow-up – despite both direct notifications and GP reminder – might benefit from other targeted initiatives. An appropriate time to implement other interventions could be after approximately three months, where the effect of GP reminders has shown to weaken. Additionally, it could be considered whether GP reminders could be generated at an earlier point in time and thus help reduce delays in the women's follow-up.
Baggrund og formål

Det danske screeningsprogram for livmoderhalskræft er udfordret. Op mod hver femte danske kvinde udeblev fra rettidig opfølgning i 2011, svarende til ca. 7.500 kvinder. Lignende problemer med opfølgning ses i udlandet, hvor studier har vist, at op mod 12 % af alle kræfttilfælde kunne være undgået, hvis der ikke var forsinkelse i opfølgning. I Danmark tages der årligt ca. 400.000 prøver for livmoderhalskræft. Mere end 90 % af dem tages i almen praksis, svarende til ca. 110 prøver per læge pr år. En patologisk afdeling analyserer prøven og sender svaret (inklusive en anbefaling om opfølgning) elektronisk tilbage til den praktiserende læge, der herefter har ansvaret for at videreformidle svaret til kvinden og sikre opfølgning.

Kvinden får sammen med prøvesvaret at vide, at hun enten bør følge det almindelige screeningsprogram, bør henvises til gynækolog inden 3 måneder, eller bør have en ny prøve om 3, 6 eller 12 måneder. Studier viser, at det er svært for mange kvinder at forstå et prøvesvar og behovet for opfølgning. Manglende opfølgning forekommer hyppigere for kvinder i lavere sociale lag og er også hyppigere i nogle praksis. Eksempelvis kan der være problemer med, hvordan og hvornår den praktiserende læge formidler svaret, eller der kan være svigt i de administrative procedurer, der skal være med til at sikre opfølgning.

Sundhedsstyrelsen anbefalede derfor i 2012 at implementere to nye tiltag i screeningsprogrammet. For det første skulle de undersøgte kvinder have tilsendt det cervix cytologiske prøvesvar per brev (brevsvaret) direkte fra patologisk afdeling, samtidig med at deres læge fik svaret elektronisk som vanligt. Det skulle afhjælpe kommunikationsproblemer, da brevet skulle afsendes systematisk til alle kvinder uden forsinkelse, og i lægmandssprog beskrive prøven som enten normal, ikke normal eller uegnet til analyse. Som en sidegevinst blev det forventet, at antallet af lægekontakter kunne reduceres, eftersom kvinder med normale svar, der kunne følge vanlig screening, ikke behøvede at kontakte sin læge. For det andet blev det anbefalet, at lægen skulle have en elektronisk påmindelse (påmindelser), hvis kvinden udeblev fra opfølgning. Dette skulle afhjælpe administrative udfordringer i praksis med at monitorere de kvinder, der manglede opfølgning.
Dette ph.d.-projekt undersøger:

I. om brevsvar til kvinderne kan forbedre opfølgningen, og om opfølgning forbedres for forskellige grupper af kvinder (Artikel I).

II. om brevsvar kan reducere antallet af kontakter til den praktiserende læge og undersøger hvordan omkostninger til svarafgivelse påvirkes (Artikel II)

III. om påmindelser til den praktiserende læge kan forbedre opfølgningen, om opfølgning forbedres for forskellige grupper af kvinder, og om variation i opfølgning mellem praksis mindskes (Artikel III).

Metode


Resultater

Artikel I viste, at fire procent flere af de kvinder, der fik et brevsvar, var blevet fulgt op til den anbefalede dato, sammenlignet med de kvinder, der fik svaret overleveret af egen læge som vanligt. Opfølgningen blev forbedret for alle undersøgte grupper af kvinder (dvs. alder, samleverstatus, etnicitet og uddannelsesniveau). Sub-analyser viste dog, at kvinder, der boede alene, havde større gavn af brevsvar end samlevende kvinder. En mindre del af opfølgningen skete dog også tidligere end anbefalet for kvinder i interventionspraksis. I en dansk kontekst, hvor påmindelser til praktiserende læger var til stede, svandt effekten af brevsvar, når lægen modtog påmindelser om kvinders udeblivelse.

Artikel II viste, at antallet af lægekontakte for kvinder der modtog et brevsvar, hvor den cervix cytologiske prøve var beskrevet som normal uden behov for yderligere opfølgning, faldt med 21 % i den første måned efter svaret sammenlignet med kvinder, der ikke fik brevsvar. Kvinder der havde behov for opfølgning, havde ikke færre lægekontakte i samme periode. En analyse af de direkte samfundsøkonomiske omkostninger viste, at reduktionen af udgifter til lægekontakte ikke i sig selv kunne dække de ekstra omkostninger, der var forbundet med at udsende brevsvar. Omsat til tal for Danmark som helhed ville det give en merudgift på ca. 5,5 millioner kr. per år.
Sub-analyser viste dog, at kun cirka halvdelen af interventionspraksis havde færre lægekontakter end kontrolpraksis. Hvis lægerne på længere sigt kan ophøre med at formidle normale svar til kvinder, der ikke har brug for opfølgning, og hvis svar pr. brev kan erstattem udgifterne at falde yderligere.


Endelig viste Artikel I og Artikel III også, at – selv med de nye tiltag – var der mange kvinder, der ikke blev fulgt op. Ligeledes sås det, at opfølgningen var bedst for kvinder, der skulle henvises til gynækolog inden 3 måneder, og dårligst for kvinder, der skulle følges op om 12 måneder. En stor andel af sidstnævnte gruppe var kvinder med et normalt svar.

**Konklusioner og implikationer**

Denne ph.d.-afhandling belyser udvalgte konsekvenser ved at indføre brevsvær og påmindelser i det danske screeningsprogram for livmoderhalskræft. Den nye viden kan bidrage til internationale guidelines, der anviser, hvorledes opfølgning kan sikres bedst.


Det vil fremover være relevant at belyse kvinders reaktion på og forståelse af brevene. Studierne tyder på, at kvinder der får bestemte typer af prøvesvar ikke har gavn af breve. Ordlyden i disse brevsvær kan måske forbedres og dermed øge effekten af brevsvær. Det vil være interessant at undersøge forskellige arbejdssupper processer omkring
prøvesvar og påmindelser i almen praksis. Herved kan der muligvis afdækkes initiativer, der kan give bedre opfølgning og reducere brugen af almen praksis for de kvinder, der ikke skal følges op. Studierne tyder også på, at flere almene praksis stadig har kontakt til kvinder med normale svar uden behov for opfølgning, selvom kvinden får et brev.

De grupper af kvinder, der stadig ikke får opfølgning efter både brevsvar og lægepåmindelser kunne måske have gavn af andre særligt målrettede initiativer. Et relevant tidspunkt for at iværksætte andre tiltag kunne være efter ca. tre måneder, hvor effekten af lægepåmindelser stagnerer. Yderligere kunne det overvejes, om påmindelser kunne sendes på et tidligere tidspunkt og derved mindske forsinkelser i kvindernes opfølgning.
APPENDIX I: DANISH NATIONAL FOLLOW-UP RECOMMENDATIONS

Flow chart for follow-up of morphological cytological investigations for women aged 25 to 59 years

Source: The National Health of Board (6)
Flow chart for follow-up of HPV-DNA cytological investigations for women aged 60 to 64 years

Follow-up of HPV-DNA test

- HPV not present
  - HPV type unknown
    - Cytology
      - Normal
      - ASCUS +
  - New HPV test in 12 months
    - HPV not present
    - HPV present

- HPV present
  - HPV type not 16 or 18
    - Inadequate
      - HPV test in 3 months
      - Inadequate HPV test
        - HPV present
        - Inadequate cytology
        - HPV not present
        - HPV present and adequate cytology
          - Follow flow chart from beginning
          - Referral to gynaecological specialist

- Inadequate HPV test
  - HPV test in 3 months

Stop regular screening
Flow chart for follow-up after cystectomy.

Source: The National Health of Board (6)
Primary, secondary and tertiary prevention is shown in the figure below. Problems of follow-up occur several places in the process. General practice is involved in all both follow-up of initial screening samples or surveillance samples after earlier abnormalities.

**Figure:** The cervical cancer screening process
APPENDIX III: CLASSIFICATION OF HISTOLOGICAL SAMPLES

Histological samples are obtained during a colposcopy examination by a gynaecologist and samples are classified according to the CIN classification.

Classification of histological squamous samples according to the dysplasia classification and the CIN-classification systems

<table>
<thead>
<tr>
<th>WHO dysplasia</th>
<th>CIN</th>
<th>Normal</th>
<th>Mild dysplasia/Condyloma</th>
<th>Moderate dysplasia</th>
<th>Severe dysplasia</th>
<th>Carcinoma in situ</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>CIN I</td>
<td>Normal</td>
<td>CIN II</td>
<td>CIN III</td>
<td>Carcinoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: National Health of Board, 2012(6)

For glandular cell changes, only three classification groups are used; “benign glandular changes” “adenocarcinoma in situ” or “adenocarcinoma”. Other precancerous changes are not identified.
### APPENDIX IV: EUROPEAN CERVICAL CANCER SCREENING PROGRAMMES

#### Characteristics of cervical cancer screening programmes among European countries

<table>
<thead>
<tr>
<th>Country</th>
<th>IR²</th>
<th>Exam interval (age-range)</th>
<th>Pay-ment</th>
<th>Sample taker</th>
<th>Coverage⁴</th>
<th>Test outside⁵</th>
<th>Responsible for referral process</th>
<th>QA²</th>
<th>Regi-stry³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>4.3</td>
<td>5 years (30-60)</td>
<td>No</td>
<td>Primary care nurse Midwife</td>
<td>70%</td>
<td>60%</td>
<td>Programme</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Netherlands</td>
<td>5.9</td>
<td>5 years (30-60)</td>
<td>No</td>
<td>GP Primary care nurse</td>
<td>73%</td>
<td>9%</td>
<td>Smear taker</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Italy</td>
<td>6.7</td>
<td>3 years cytology, 5 years HPV (25-64)</td>
<td>No</td>
<td>Primary care nurse Midwife</td>
<td>75%</td>
<td>50%</td>
<td>Programme</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>Sweden</td>
<td>7.4</td>
<td>3 years (23-50)</td>
<td>Yes</td>
<td>Midwife</td>
<td>78%</td>
<td>84%</td>
<td>Programme</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Iceland</td>
<td>7.9</td>
<td>2 years (20-39)</td>
<td>Yes</td>
<td>GP Gynaecologist</td>
<td>72%</td>
<td>75%</td>
<td>Programme</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>England</td>
<td>8.5</td>
<td>3 years (25-49)</td>
<td>No</td>
<td>GP Primary care nurse</td>
<td>74%</td>
<td>82%</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>France</td>
<td>8.8</td>
<td>3 years (25-65)</td>
<td>?</td>
<td>GP Midwife</td>
<td>13%</td>
<td>?</td>
<td>Smear taker</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Scotland</td>
<td>8.9</td>
<td>3 years (20-60)</td>
<td>No</td>
<td>GP Primary care nurse</td>
<td>73%</td>
<td>79%</td>
<td>Few</td>
<td>Programme</td>
<td>Yes</td>
</tr>
<tr>
<td>Norway</td>
<td>9.8</td>
<td>3 years (25-69)</td>
<td>Yes</td>
<td>GP Gynaecologist</td>
<td>67%</td>
<td>84%</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>Slovenia</td>
<td>10.5</td>
<td>3 years (20-64)</td>
<td>No</td>
<td>Gynaecologist</td>
<td>72%</td>
<td>0</td>
<td>Smear taker</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Denmark</td>
<td>10.6</td>
<td>3 years (25-49)</td>
<td>No</td>
<td>GP Gynaecologist</td>
<td>75%</td>
<td>10%</td>
<td>Smear taker</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Poland</td>
<td>12.2</td>
<td>3 years (25-59)</td>
<td>No</td>
<td>Midwife Gynaecologist</td>
<td>25%</td>
<td>?</td>
<td>Programme</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Iceland</td>
<td>13.6</td>
<td>3 years (25-44)</td>
<td>No</td>
<td>Mix of healthcare providers</td>
<td>70%</td>
<td>?</td>
<td>Programme</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Latvia</td>
<td>17.3</td>
<td>3 years (25-70)</td>
<td>Yes</td>
<td>GP Gynaecologist</td>
<td>59%</td>
<td>41%</td>
<td>Smear taker</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hungary</td>
<td>18.0</td>
<td>3 years (25-65)</td>
<td>No</td>
<td>Primary care nurse Gynaecologist</td>
<td>&lt;10%</td>
<td>?</td>
<td>Smear taker</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Estonia</td>
<td>19.9</td>
<td>5 years (30-59)</td>
<td>No</td>
<td>Midwife</td>
<td>35%</td>
<td>80%</td>
<td>Smear taker</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lithuania</td>
<td>26.1</td>
<td>3 years (25-60)</td>
<td>No</td>
<td>GP Midwife</td>
<td>40%</td>
<td>?</td>
<td>Smear taker</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Romania</td>
<td>28.6</td>
<td>5 years (25-64)</td>
<td>No</td>
<td>GP Gynaecologist</td>
<td>?</td>
<td>?</td>
<td>Smear taker</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Source: Table adapted modified from Elfstrom et.al 2015 (12)

1 Data from an international survey (2012-2014) with responses from countries with a publicly organised screening programme. ²IR: incidence rates per 100,000. ³Countries do not calculate this proportion in a uniform way. ⁴Proportion of test outside programme. ⁵QA quality assurance programmes. ⁶Proportion of test outside programme. ⁷Mass screening registry.
### Organisation of cervical cancer screening within the Europe

<table>
<thead>
<tr>
<th>Country (screening programme)</th>
<th>Smear taker (who?)</th>
<th>Screening interval following negative result</th>
<th>Communication of results (Normal)</th>
<th>Communication of results (Suspicious)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Gynaecologists</td>
<td>1 year</td>
<td>Mail or phone to the smear taker</td>
<td>Mail or phone to the smear taker</td>
</tr>
<tr>
<td>Belgium</td>
<td>Gynaecologists/GPs</td>
<td>3 years</td>
<td>Report to the smear taker</td>
<td>Report to the smear taker</td>
</tr>
<tr>
<td>Denmark</td>
<td>GPs</td>
<td>3 years</td>
<td>Directly to the woman to contact GP</td>
<td>Report to GP</td>
</tr>
<tr>
<td>England</td>
<td>GPs or general practice nurses</td>
<td>3-5 years</td>
<td>Report to the smear taker</td>
<td>Report to the smear taker</td>
</tr>
<tr>
<td>Finland</td>
<td>Trained nurses (midwives)</td>
<td>5 years</td>
<td>Letter directly to the woman</td>
<td>By phone if possible, always by mail</td>
</tr>
<tr>
<td>France</td>
<td>Gynaecologists/GPs</td>
<td>3 years (following 2 negative smears)</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Germany</td>
<td>Office-based gynaecologists and GPs</td>
<td>1 year</td>
<td>By the smear taker</td>
<td>Mail or phone by the smear taker</td>
</tr>
<tr>
<td>Greece</td>
<td>Gynaecologists (Ovaryia)</td>
<td>1 year following the first smear, then every 3 years (Ovaryia) 2 years (Masturnia and Ilia)</td>
<td>Letter directly to the woman (both programmes)</td>
<td>Phone and personal meeting with screening physician (Ovaryia) Phone or home call (Masturnia and Ilia)</td>
</tr>
<tr>
<td>Ireland</td>
<td>GPs, family planning and community clinics, hospitals</td>
<td>5 years (pilot)</td>
<td>Letter directly to the woman</td>
<td>Advised to contact smear taker</td>
</tr>
<tr>
<td>Italy</td>
<td>Midwives (mainly) and gynaecologists</td>
<td>3 years</td>
<td>Varies, Most frequently letter directly to the woman</td>
<td>Varies</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>GPs and/or gynaecologists</td>
<td>1 year</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>GPs and their practice assistants</td>
<td>5 years</td>
<td>Via the GP</td>
<td>Via the GP</td>
</tr>
<tr>
<td>Portugal</td>
<td>GPs</td>
<td>1 year following the first normal smear, then every 3 years</td>
<td>Letter via the GP</td>
<td>Letter via the GP</td>
</tr>
<tr>
<td>Spain</td>
<td>Family doctors</td>
<td>3 years</td>
<td>Letter via the primary care physician</td>
<td>By the primary care physician</td>
</tr>
<tr>
<td>Sweden</td>
<td>Trained midwives</td>
<td>3 years</td>
<td>Letter directly to the woman (6 counties do not inform women in cases where results are negative)</td>
<td>Via the local gynaecology clinic</td>
</tr>
</tbody>
</table>

Source: table adapted from: Linos, Riza 2000 (163)

1 Data from an international survey, published in 2000,
This appendix presents the development process of the SNOMED code algorithm and the final SNOMED code algorithm translating complex SNOMED codes into simple letters in lay language to women that secured GP contact when necessary.

**Translation of SNOMED codes into letters**

The algorithm development consisted of five steps:

1 **Evaluation of the algorithm proposed by the National Health of Board**

The first draft algorithm was based on the 2012 recommendations from the Danish National Board Health (6). This entailed a proposed algorithm based on the newest recommended SNOMED codes, without giving women recommendations for “time point of relevant follow-up”, and with a result stated as *normal*, *inadequate* or *not normal*. The normal letter was, moreover, divided into two groups: if women had received a screening invitation within one year of the result, they were encouraged to participate in screening at next invitation, but if this was more than one year after screening invitation, they were encouraged to contact their GP to ask if follow-up was necessary. We evaluated this algorithm using a retrospective pathology databank dataset from 2011 and chose to differ from the national recommendations in three ways: 1) In order to highlight the time point of when follow-up was appropriate for the women, we chose to provide this information in the letter, contrary to the proposed algorithm, 2) The proposed algorithm divided all normal results in two groups. However, this entailed that some women would not be notified of the follow-up recommendations provided by the pathology departments. Moreover, as 30% of opportunistic or screening samples in Denmark are performed more than 9 months after invitation (15), many women would unnecessarily have to contact their GP even
though results is normal; this may cause unnecessary anxiety in the women, which was another reason for including SNOMED follow-up codes in “our” algorithm and 3) The proposed algorithm did not address possible incidental findings (e.g. herpes), and we were concerned that these women were “only” notified that the result was normal. Therefore, we chose to include SNOMED codes for incidental findings and, as a precaution, in all normal result letters women were encouraged to contact their GP if they had any gynaecological symptoms.

2 Testing a draft algorithm on retrospective dataset
Hereafter, a first draft of the algorithm was developed. This was evaluated using a larger retrospective dataset, which found other challenges that we needed to address: 1) Few times the pathology departments used other diagnostic SNOMED codes than recommended. Therefore, we added extra SNOMED codes from former classifications systems to the algorithm, 2) Some women did not have an address, and therefore we chose to inform GPs in these cases so that they could convey results, 3) Some results had ambiguous SNOMED coding (e.g. a normal and an abnormal code at the same time). In these situations we chose not to inform women of the result in the letter. Instead the letter to these women encouraged her to contact her GP to have the result, 4) Few results had an uncommon topography SNOMED code. As these women could have had special gynaecological anamneses, they were also encouraged in the letter to contact the GP to have the result conveyed. 5) Incidental findings, which we for ethical reasons thought that the women were entitled to know of; therefore, the letter to women with normal results but with incidental findings initially was worded: “the result is normal, but you are encouraged to contact your general practitioner to ask if other follow-up was recommended”( Just as the letter proposed by the Danish National Board of Health to women with normal results, but with a sample obtained more than one year after invitation.), 6) Few cervical results had the diagnosis or the follow-up recommendation changed after dispatch of the result letter. For ethical reasons, we chose to contact the GPs in these cases to let him/her convey the new result to the woman, instead of sending the woman a new letter, 7) Few times the pathology departments forgot to apply a SNOMED code follow-up recommendation, and therefore the algorithm secured that all women receiving an abnormal result by letter always, as a minimum, had to contact the GP.

3 Adjusting wording in letters
The wording of letters was based on the recommendations made by the Danish National Board of Health (6) and was thoroughly discussed with selected women (employed at the Pathology Department and the Department of Public Health Programs in Randers) and with GPs. Furthermore, the literature on the women’s perception and understanding of cervical cytology results was consulted (64,106-108).
4 Testing the algorithm in “real life” without sending letters
The algorithm was hereafter implemented in the DPDB. This secured that all letters were stored together with the women’s sample results and were available for all pathology employees at all times. The implementation was performed in cooperation with the IT company which is responsible for running the database (CGI). In a period of 14 days, letters were generated in real settings, but they were not sent. We tested if the algorithm performed as expected by extracting data in excel files each day and compared the results of each woman with the generated letter in a manual manner. Few technical changes were made in this period.

5 Piloting the algorithm and collecting feedback
From 10 Oct. 2012 and three months ahead, the algorithm was pilot tested, and all women from intervention general practices received letters. Feedback from GPs and women was collected by a one person in the pathology department and few persons at the Department of Public Health Programs in Randers, which distributed the letters. Based on this feedback, three changes were made: 1) the wording of the letter for incidental findings was changed, and instead women were encouraged to contact their GP for the result (see point 5, in the second step of development). We did so as both GPs and women reported to fear that something was missed as they perceived the letter as ambiguous. Was follow-up necessary or not? 2) Further limitations were made for which types of incidental findings that would entail this letter: Some results with incidental findings may be more important than others (e.g. if incidental findings such as candida was present, the women still received a letter stating that the result was normal (see Appendix VII for definition of incidental findings), 3) Triage with HPV testing was expected to be implemented in the study period. This meant that ASCUS/LSIL and negative HPV could possibly follow regular screening intervals, and we had to adjust the algorithm to this. Regretfully, it was not possible for the pragmatically chosen and simplified algorithm to distinguish between a forgotten a SNOMED code follow-up recommendation and a missing code because women could follow regular screening. Therefore, we chose to let this small group of women receive a letter encouraging her to contact the GP to get the result.

A final algorithm was implemented on 7 January 2013 (see Appendix A.3, Paper I or Appendix VI). All letters were dispatched after the electronical result was sent to the GPs to ensure that the GPs could be prepared when talking with the women. Furthermore, letters were not dispatched up to any holidays or weekends, where the women could not get in contact with their GP.
<table>
<thead>
<tr>
<th>Letter sequence number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6.7.12</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>1.6.7.12</td>
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<td>1.6.7.12</td>
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</tr>
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</table>

**APPENDIX VI: LETTER ALGORITHM**

<table>
<thead>
<tr>
<th>Algorithm codes to determine diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE10A1 OR WES10A1</td>
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</tbody>
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**SNOMED Codes to determine diagnosis**

<table>
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<tr>
<th>SNOMED Code</th>
<th>Diagnosis</th>
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</thead>
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<tr>
<td>PDE10A1</td>
<td></td>
</tr>
<tr>
<td>WES10A1</td>
<td></td>
</tr>
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</table>

**Diagnosis**

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
</tr>
</tbody>
</table>

**Additional notes**

SNOMED-Code algorithm used to generate reimbursement codes for medical conditions.
APPENDIX VII: INCIDENTAL FINDINGS IN CERVICAL CYTOLOGY

This appendix elaborates the Bethesda classification (described in Chapter 2 Method: Key variables) and the letter algorithm (Appendix V).

Adequate cervical cytology results may be classified as “normal” (i.e. negative for intraepithelial lesion or malignancy) or “abnormal” (i.e. epithelial cell abnormality) or “other”:

In some cervical cytologies without pre-cancer (i.e. normal), numerous different benign findings may still be reported; some may be without consequences, whereas others might entail further examinations or treatment. In this thesis, we named these findings *incidental*. The Bethesda classification describes that reporting of these findings is optional (7). Incidental findings for normal cervical cytology results may, for instance, include hormonal patterns (post-partum or atrophic), repair changes, hyperplasia, metaplasia, irradiation changes, cell alterations changes due inflammation or intrauterine contraceptive device (IUD), which are most often benign changes and usually do not entail any consequences if they match the women’s age, hormone status and date of last menstruation (4,7). Findings with candida, actinomyces, gardnerella vaginalis or leptothrix may be reported as well, but generally only women with symptoms of vaginitis require treatment (4). In contrast, findings such as chlamydia trachomatis, gonorrhoea, trichomonas vaginalis or herpes more often may prompt GPs to initiate examinations or treatment (7).

The “other category” comprised women without pre-cancer but with benign endometrial cells and above 40 years of age as this indicates an increased risk for endometrial cancer and requires more investigations (7). These findings were also categorised as incidental in this thesis.

In the final algorithm, incidental findings entailed that women did not have a “result” in the direct notification by letter, but instead she was encouraged to contact the GP to have the cervical cytology result conveyed.
The following pathology reportings were defined as incidental:

- Trichomonas
- Negative cervix cytology does not exclude endometrial neoplasia
- Abnormal cytological hormonal changes
- Abnormal presence of normal cells
- Abnormal presence of endometrial cells
- Presence of Low risk HPV
- Inadequate HPV testing
- Herpes
- Enterobius vermicularis

The following pathology reportings were not defined as incidental:

- Candida
- Fungus
- Actinomyces
- Gardnerella
- Degenerative cell changes
- Cell changes due to inflammation
- Inflammation
- Atrophy
- Unspecific reactive changes
- Severe bacteria flora
SNOMED codes generating letter example number 1 is shown in Appendix VI

Letter example number 1

“NAME”
“ADDRESS”

Dear “NAME”

“The DATE” we received a cervical sample from your general practitioner.

The test showed cell changes and was therefore not normal.

Cervical cells may be changed for several reasons, and it is possible to have different stages of cell changes. Some cell changes demand treatment, whereas other disappear spontaneously and is therefore kept under surveillance for a period. You therefore need further examinations by your general practitioner or a gynaecologist.

We would recommend you to discuss the result with your general practitioner.

Your general practitioner has also been told that your sample was not normal. If you already have spoken with your general practitioner you may ignore this letter.

Yours sincerely

Department for public health programmes
The Central Denmark Region

The Pathology Department
Regional Hospital of Randers

Read more about screening on www.kraftscreening.rm.dk
SNOMED codes generating letter example number 2 is shown in Appendix VI

Letter example number 2

“NAME”
“ADDRESS”

Dear “NAME”

The “DATE” we received a cervical sample from your general practitioner.

The test showed cell changes and was therefore not normal, and you may need a new sample in X months.

Cervical cells may be changed for several reasons, and it is possible to have different stages of cell changes. Some cell changes demand treatment, whereas others disappear spontaneously and is therefore kept under surveillance for a period. You therefore need further examinations by your general practitioner or a gynaecologist.

We would recommend you to discuss the result with your general practitioner.

Your general practitioner has also been told that your sample was not normal. If you already have spoken with your general practitioner you may ignore this letter.

Yours sincerely

Department for public health programmes
The Central Denmark Region

The Pathology Department
Regional Hospital of Randers

Read more about screening on www.kraftscreening.rm.dk
SNOMED codes generating letter example number 3 is shown in Appendix VI

**Letter example number 3**

Dear “NAME”

The “DATE” we received a cervical sample from your general practitioner.

Your general practitioner has had the result of your sample. You may contact your general practitioner to have the result conveyed.

If you already have spoken with your general practitioner you may ignore this letter.

Yours sincerely

Department for public health programmes
The Central Denmark Region

The Pathology Department
Regional Hospital of Randers

Read more on screening on [www.kraftscreening.rm.dk](http://www.kraftscreening.rm.dk)
SNOMED codes generating letter example number 4 is shown in Appendix VI

Letter example number 4

"NAME"
"ADDRESS"

Dear "NAME"

The "DATE" we received a cervical sample from your general practitioner.

The sample showed HPV (Human Papilloma Virus) and is therefore not normal.

HPV may cause cell changes on the cervix. It is possible to have different stages of cell changes. Some cell changes demand treatment, whereas other disappear spontaneously and is therefore kept under surveillance for a period.

We would recommend you to discuss the result with your general practitioner, which may refer you to a gynaecologist if needed.

Your general practitioner has also been told that your sample was not normal. If you already have spoken with your general practitioner you may ignore this letter.

Yours sincerely

Department for public health programmes
The Central Denmark Region

The Pathology Department
Regional Hospital of Randers

Read more about screening on www.kraftscreening.rm.dk
SNOMED codes generating letter example number 5 is shown in Appendix VI

**Letter example number 5**

```
“NAME”
“ADDRESS”

Dear “NAME”

The “DATE” we received a cervical sample from your general practitioner.

The test was inadequate for assessment.
It happens once in a while that the sample is insufficient. It can for instance be if too few cells were obtained in the sample.

We would recommend you to discuss the result with your general practitioner, and schedule to have a sample obtained.

Your general practitioner has also been told that your sample was inadequate.

If you already have spoken with your general practitioner you may ignore this letter.

Yours sincerely

Department for public health programmes
The Central Denmark Region

The Pathology Department
Regional Hospital of Randers

Read more about screening on www.kraftscreening.rmA.dk
```
SNOMED codes generating letter example number 6 is shown in Appendix VI

Letter example number 6

“NAME”
“ADDRESS”

Dear “NAME”

The “DATE” we received a cervical sample from your general practitioner.

The sample is normal, but you may need to have a new sample obtained. We recommend that you discuss the result with your general practitioner.

Your general practitioner has also been told your sample was normal. If you already have spoken with your general practitioner you may ignore this letter.

Yours sincerely

Department for public health programmes
The Central Denmark Region

The Pathology Department
Regional Hospital of Randers

Read more about screening on www.kraftscreening.rm.dk
SNOMED codes generating letter example number 7 is shown in Appendix VI

**Letter example number 7**

```
“NAME”
“ADDRESS”

Dear “NAME”

The “DATE” we received a cervical sample from your general practitioner.

The sample is normal, but you may need a new sample in X months.
We recommend that you discuss the result with your general practitioner.

Your general practitioner has also been told your sample was normal.
If you already have spoken with your general practitioner you may ignore this letter.

Yours sincerely

Department for public health programmes
The Central Denmark Region

The Pathology Department
Regional Hospital of Randers

Read more about screening on www.kraftscreening.rm.dk
```
SNOMED codes generating letter example number 8 is shown in Appendix VI

Letter example number 8

“NAME”
“ADDRESS”

Dear “NAME”

The “DATE” we received a cervical sample from your general practitioner.
The sample is normal.

Depending on your age you will be invited to screening again. Women between 23 and 49 years of age is invited every third year and women above 50 every fifth year. If you are above 60 years the screening programmes ends with this test and you will not be invited anymore.

If you are used to be investigated more often for cervical cancer, you are encouraged to talk with your general practitioner to clarify if you still need this.

If you experience any other symptoms from your lower body, you should always contact your general practitioner, even if you just have had a cervical sample.

Your general practitioner has also been told your sample was normal.

If you already have spoken with your general practitioner you may ignore this letter.

Yours sincerely

Department for public health programmes
The Central Denmark Region

The Pathology Department
Regional Hospital of Randers

Read more about screening on www.kraftscreening.rm.dk
SNOMED codes generating letter example number 9 is shown in Appendix VI

**Letter example number 9**

Dear “NAME”

“DATE”

The “DATE” we received a gynaecological sample from your general practitioner.

Your general practitioner has had the result of your sample. You may contact your general practitioner to have the result conveyed.

If you already have spoken with your general practitioner you may ignore this letter.

Yours sincerely

Department for public health programmes
The Central Denmark Region

The Pathology Department
Regional Hospital of Randers

Read more on screening on [www.kraftscreening.rm.dk](http://www.kraftscreening.rm.dk)
### GLOSSARY

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E-boks</strong></td>
<td>97% of all Danish adults have a personal electronic mail box (E-boks). This mail box is linked to the unique Danish Civil Registration Number and access is granted using NemID at log-in. NemID consists of a personal user name, password, and a card containing unique onetime tokens to increase security. Authorities in Denmark aim for Danish digitization, and most contacts to public authorities and many private companies therefore occur using E-boks and/or NemID, e.g. hospital notices, online banking, change of address, or applying for social support (156).</td>
</tr>
<tr>
<td><strong>Human Papilloma Virus</strong></td>
<td>A sexual transmitted disease with a lifetime risk of infection of 80% (7) to 90% (5). The infection most often clears within a year or may become more persistent. More than 100 different human papilloma virus' is known. 15 of these are so called high risk virus'. HPV-16 and HPV-18 causes 70% all cervical cancers, and another 13 causes almost 25%. These oncogenic HPV-types may also be related to vulva cancer, cancer in vagina, anal, perianal, penis, oral cavity, larynx, and skin cancers. When infected the infection are most often without symptoms. Prevalence of HPV has been increasing (7)</td>
</tr>
<tr>
<td><strong>HPV vaccination</strong></td>
<td>In Denmark HPV vaccination was introduced in 2009 to all girls at the age of 12 (129). Not before 2059, all Danish women in actual screenings relevant ages have been offered vaccination (14,129). Not all may choose to be vaccinated. For instance, only 40% of Danish girls born in 2003 received one vaccination free of charge (129). Currently all vaccinated women are recommended to participate in screening (164)</td>
</tr>
<tr>
<td><strong>Design effect</strong></td>
<td>Design effect = 1 + (“average cluster size”-1) x ICC The design effect may also be expressed as variance inflation factor (IF) (110,123)</td>
</tr>
<tr>
<td><strong>Inequality</strong></td>
<td>Health inequality generically refers to differences in the health of individuals or groups(40)</td>
</tr>
<tr>
<td><strong>Inequity</strong></td>
<td>Health inequity, or health disparity, is a specific type of health inequality that denotes an unjust difference in health. By one common definition, when health differences are preventable and unnecessary, allowing them to persist is unjust(40)</td>
</tr>
<tr>
<td><strong>Inadequate</strong></td>
<td>Another term for the Bethesda classification term “unsatisfactory for evaluation”</td>
</tr>
</tbody>
</table>
**Missed opportunity**
Missed opportunities are instances where it post hoc is possible that alternative decisions or actions could have led to more timely diagnosis. However not all missed opportunities lead to harm of patients (3).

**Opportunistic screening**
In Denmark opportunistic screening is defined as a cervical cytology sample obtained without a screening invitation (i.e. more than one year after the last invitation and more than three months before a scheduled screening invitation) (16).

**Organised screening programme**
“Provide for a national or regional team responsible for implementation and require providers to follow guidelines, rules, or standard operating procedures. They also define a quality assurance structure and mandate supervision and monitoring of the screening process. To evaluate impact organised programmes also require ascertainment of the population disease burden” (12).

**Population based screening programme**
“Programmes identify and personally invite each eligible person in the target population to attend a given round of screening” (12).

**Pre-cancer**
In this thesis dysplasia, precancerous lesions, mild or severe changes are considered as pre-cancer.

**Publicly mandated screening programme**
“Have a law, official regulation, decision, directive or recommendation that provides the public mandate to implement the programme with an authorised screening test, examination interval, target group and funding and co-payment determined” (12).

**Sundhed.dk**
Also termed Health.dk. A platform, were all personal healthcare data is stored together (e.g. hospital reports and services provided by GPs). In 2016 sundhed.dk had 1.6 million unique users. Access is granted using NemID as with E-Boks (159).