Loss to follow-up of cervical smears without endocervical columnar cells is not disturbing

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Summary

Objective: To investigate the six-month recommended follow-up after mass screening of Pap smears because of the absence of endocervical columnar cells (ECC-) or ECC+ smears with atypical squamous or glandular cells of undetermined origin (ASCUS/AGUS) or low-grade squamous or glandular intraepithelial lesions (LSIL/LGIL) in a Dutch mass screening cervical cancer programme.

Methods: Data were extracted from computerised medical records of national representative Dutch general practices. We have studied the attendance at and the outcome of the subsequent Pap smears after a 6-month recommendation.

Results: The six-month follow-up was linked to 8.7% of the Pap smears (n = 1,002); 77.6% were without endocervical columnar cells (ECC-). Clear differences were found between the follow-up of ECC+ and ECC- smears; after 36 weeks of follow-up of 43.5% the women had an ECC- smear and 66.9% had other conditions. For initial ECC- Pap smears, 84.1% had no abnormalities in the subsequent Pap smear; for initial ECC+ Pap smears, in about 64% of the cases no abnormalities were found ($p < 0.0001$).

Conclusions: Repeating ECC- smears has a low follow-up rate but also lacks evidence-based necessity. However, for the other 6-month recommended Pap smears, one in five women had still not responded within one year, so improvement is necessary.

Key words: Mass screening; Cervical screening; Follow-up; ECC- smears.

Introduction

Appropriate management of precursor lesions detected by cervical screening reduces the risk of developing cervical cancer. Women with abnormal Pap smears that do not return for follow-up care can increase overall morbidity, mortality, and therefore the cost of health care [1]. Not only is high attendance important, a high follow-up rate of cytological abnormalities is also required for an effective population-based cervical cancer screening programme [2-7]. Loss to follow-up among women with abnormal or unsatisfactory Pap smears is a significant public health problem (estimates range from 30% to 50%) [1, 8-10]. The question to be addressed is how serious these figures are. Most loss-to-follow-up reports do not distinguish between the levels of severity of the Pap smear results, but concentrate on the total loss to follow-up. Mild and moderate dysplasias are, however, more likely to regress than to progress. The risk of progression from mild to severe dysplasia is only 1% per year [11].

The necessity of a repeated Pap smear after a Pap smear without endocervical columnar cells (ECC-) is being discussed. The efficacy of the recommendation for follow-up of this indication (to repeat the Pap smear after 6 months) is under review, because absence of endocervical columnar cells is no longer associated with a higher risk of cervical neoplasia [12-15]. Therefore, others suggest that there is no reason to advise women with Pap smears with no abnormal findings, but limited by the absence of endocervical columnar cells (ECC -), to undergo an additional Pap smear [12-15].

In the Netherlands, in 1996, a national cervical cancer screening programme was started [16]. The target population includes women from 30 to 60 years old, and the screening interval is five years. The population-based Pap smears (initial and follow-up) are taken in a general practice setting by general practitioners (GPs) or their practice assistants and subsequently examined by trained cytopathologists in hospitals. Results are reported to conform to the international terminology for reporting results of cervical cytology from the Bethesda System [17]. Programme Pap smears are free of charge but there are fees for the GPs taking the Pap smears. To support the organisation, computer software is available to GPs so they can search the electronic medical record system to identify the target population, invite the eligible women, and easily do the clerical work for the Pap smears.

The possible recommendations following a cervical smear taken in the context of mass screening are classified according to several categories: when no abnormal findings are found, repetition of the Pap smear test after five years is advised. Recomendations for unsatisfactory Pap smears are repetition after six weeks. For moderate or severe abnormal findings, carcinoma in situ or invasive cancer, a referral to a gynaecologist for further examination is advised.

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Patients with ECC- Pap smears are advised to have an additional Pap smear taken after six months. In the Netherlands, two other conditions have a 6-month recommendation: Pap smears with atypical squamous or glandular cells of undetermined significance (ASCUS/AGUS), or Pap smears with low-grade squamous or glandular intraepithelial lesions (LSIL/LGIL) [16].

Less is known about this six-month follow-up concerning the attendance and the results of this additional Pap smear test. Insight into the necessity of this follow-up is important because inherent feelings of unease and psychological strains are associated with repeated Pap smears [18-21]. We have studied the follow-up of the 6-month recommended Pap smears and the outcome of the subsequent Pap smears. A distinction has been drawn between ECC-, ASCUS/AGUS, and LSIL/LGIL smears.

Methods

Setting and study population

Data from women eligible for population-based cervical screening in 1998, 1999 or 2000 were sampled from 1999 till 2001 from the electronic patient records of Dutch computerised general practices collaborating in a national monitoring project on cervical cancer screening within the National Information Network of General Practices (LINH). The design of LINH has been described elsewhere [22, 23]. All Pap smears with a *6-month follow-up recommendation* were included in the analysis (n = 1,002).

Practices were selected according to the availability of reliable and valid data on cervical cancer screening in the database since 1998, with a minimum of two consecutive years (n = 45). Practices which did not register the laboratory results in a uniform way in their electronic patient records registered less than 90% of the population-based Pap smears and were excluded; 35 practices proved to have complete data. The geographical distribution of these general practices was reasonably even. The total number of patients listed in the practices was 136,039 (at 1/1/1999; all practices were present). The distribution of age, sex, and type of health insurance of these patients listed correlated well with that of the general Dutch population.

The ethics committee of the Radboud University Nijmegen Medical Centre approved the study proposal.

Data collection

Information on listed patients' gender, age, and type of health insurance was derived from the regular data collection within the network. The other data were extracted from the electronic patient records using specially developed software, and included year of birth, cervical smear(s) taken (along with date), laboratory test result(s) (along with date) and accompanying follow-up advice (along with date). The three years of extracted data were compiled to one longitudinal database.

Analysis

SAS was used for the statistical analysis. Descriptive statistics (absolute numbers and percentages) were used to determine to what extent patients listed on 1/1/1999 were representative. Descriptive statistics were also used to describe the follow-up recommendations as found in the database.

Subsequently, the conditions leading to the 6-month follow-up Pap smears were examined by three different ratios: 1) "The number of 6-month recommendations for ECC- smears with respect to the total number of initial 6-month follow-up recommendations", 2) "The number of 6-month recommendations for ASCUS/AGUS smears with respect to the total number of initial 6-month follow-up recommendations" and 3) "The number of 6-month recommendations for LGIL/LSIL smears with respect to the total number of initial 6-month follow-up recommendations".

Finally, to assess the seriousness of the consequences of loss to follow-up, the percentages of abnormalities found in the subsequent Pap smears taken in the context of the 6-month recommendations were measured. A distinction was drawn between initial ECC-, ASCUS/AGUS, and LGIL/LSIL smears.

The 6-month patient follow-up was defined as correct if an additional Pap smear test or test-result as found in the electronic medical records. The period of correct follow-up-attendance was set at 36 weeks; 26 weeks (= 6 months) after the recommendation and an additional ten weeks to allow for holidays, time for making an appointment and for sufficient time for making the cytological diagnosis in the laboratory.

The date of the laboratory result as found in the electronic patient records represents the baseline measurement. The Kaplan-Meier method [24] was used for calculation of survival curves to estimate the probability of an additional Pap smear being taken. Lost cases (women that did not have an additional Pap smear or were lost to follow-up) were entered in the analysis as censored observations. The Breslow test [25] was used to test the difference between the intitial Pap smear result groups (ECC-, ASCUS/AGUS, LGIL/LSIL) on the follow-up. A probability level of $p < 0.05$ was taken to indicate statistical significance.

Results

Study population

In our database, 11,557 initial Pap smear test results were registered; these were made in the context of the nation-wide screening programme (Table 1). The advice for repetition within six months was given in 8.7% of the cases (n = 1,002).

Table 1. — *Follow-up advice as a consequence of mass screening smears, in absolute numbers, and in percentages of the total population tested (n = 11,557).*

Follow-up advice	n	%
6 weeks	181	1.6
6 months	1,002	8.7
5 years	10,307	89.2
Referral to a gynaecologist	67	0.6

Follow-up of the 6-month recommendation

Most of the cases with a 6-month recommendation for follow-up (77.6%) concerned ECC- Pap smears. The other recommendations followed ASCUS/AGUS and LSIL/LGIL Pap smears (18.4% and 4.0%, respectively) (Table 2). The overall probability of a follow-up Pap smear test performed within 36 weeks was 48.8% (confidence limits 45.5-52.1%). After one year (52 weeks), the predicted follow-up was 62.7% (CL 59.4-65.9%).

The follow-up of the 6-month recommendations as a function of time is presented in Figure 1. There was a significant difference between the follow-up uptake of the ASCUS/AGUS and ECC- Pap smears (Breslow test, Chi-square (1) = 33.0, $p < 0.0001$) and between LSIL/LGIL and ECC- smears (Breslow test, chi-square (1) = 12.0, $p < 0.0005$). No significant differences were found between the follow-up of the probability of a follow-up pap smear in the ASCUS/AGUS cases and the LSIL/LGIL cases. A follow-up Pap smear having been performed after 36 weeks was 43.5% (CL 39.7-47.2%) for the women with an ECC- smear and 66.9% (CL 60.4-73.4%) for the other conditions.

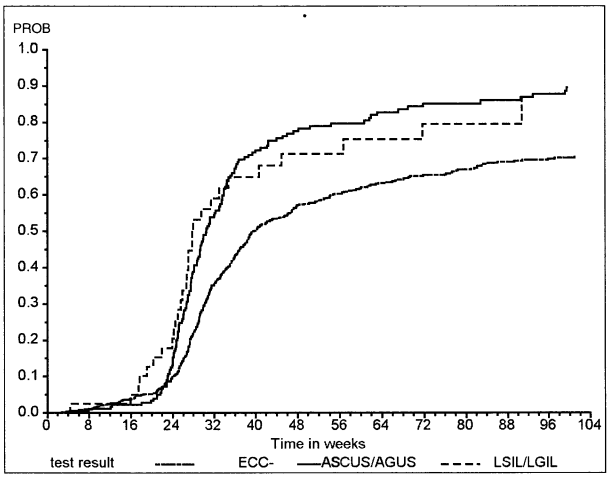

Figure 1. — Cumulative probability of follow-up of the 6-month recommendations as a function of time (in weeks), according to smear test results.

ECC- = normal smears, but limited by the absence of endocervical columnar cells; ASCUS/AGUS = smears with atypical squamous or glandular cells of undetermined significance; LSIL/LGIL = smears with low-grade squamous or glandular intraepithelial lesions.

Follow-up Pap smear outcome of ECC, ASCUS/AGUS, and LSIL/LGIL cases

After 36 weeks, there was a second Pap smear for 432 women with a former 6-month recommendation. For 66.7% of them, no abnormalities were found in the subsequent Pap smear (Table 3). For initial ECC- Pap smears, 84.1% had no abnormalities in the subsequent Pap smear. For the other Pap smear results leading to the 6-month recommendation, in about 64% of the cases no abnormalities were found in an additional Pap smear taken within 36 weeks. These differences are significant (Pearson chi square (2) = 21.9; $p < 0.0001$). For none of the women with an initial ECC- Pap smear, was the subsequent Pap smear reason to be referred to a gynecologist after 36 weeks instead it was for 18.4% of the women with the initial ASCUS/AGUS or LSIL/LGIL Pap smears.

Table 2. — *Patients classified according to the three conditions leading to a 6-month recommendation.*

	n	%
ECC-	773	77.6
ASCUS/AGUS	183	18.4
LSIL/LGIL	40	4.0

Missing = 6; ECC- = normal smears, but limited by the absence of endocervical columnar cells; ASCUS/AGUS = smears with atypical squamous or glandular cells of undetermined significance; LSIL/LGIL = smears with low-grade squamous or glandular intraepithelial lesions.

Table 3. — *Presence of abnormalities in test results of additional smears taken with respect to initial 6-month follow-up recommendations (within 36 weeks) (%).*

Initial smear	6-month recommendation ECC- (n = 296)	ASCUS/AGUS (n = 113)	LSIL/LGIL (n = 23)
Additional smear			
without abnormalities	84.1	70.8	30.4
with abnormalities	15.9	29.2	69.6

ECC- = normal smears, but limited by the absence of endocervical columnar cells; ASCUS/AGUS = smears with atypical squamous or glandular cells of undetermined significance; LSIL/LGIL = smears with low-grade squamous or glandular intraepithelial lesions.

Discussion

In this study we examined the current status of the follow-up examinations in general practice for initial Pap smears with a 6-month follow-up recommendation. A distinction was drawn between Pap smears which were normal, but limited by the absence of endocervical columnar cells and the other Pap smear results leading to the 6-month follow-up recommendation (ASCUS/AGUS and LSIL/LGIL).

All previous studies of follow-up have been based on pathology-laboratory data; most of them were cross-sectional. In the Netherlands, both initial and follow-up Pap smears are taken in the context of the population-based cervical screening programme in general practice, so it seemed logical to sample data in a general practice-based setting. Therefore, we followed the population-based screening Pap smears in general practice for three years and collected routinely high-quality information from the electronic medical records of the participating practices in our network. The participants were sometimes unable to fulfil their tasks due to technical computer problems or the quality of the data received was poor in some practices, so they had to be eliminated from the analyses. However, selection does not seem to have been a problem, because our data are similar to those in another Dutch study based on pathology-laboratory results [12]. In 1990 and 1991, Bos and colleagues [12] found that 87% of the Pap smears performed for screening purposes were negative and our results are comparable (89%).

A small under-registration of the unsatisfactory (inadequate) Pap smears in our database is possible, however a strong selection procedure of the participating practices on completeness of the data makes the effects of under-registration almost nil. For general practitioners it is important to adequately fill in their electronic patient records. Furthermore, we have no follow-up information on lost cases. Unfortunately we were not able to link our dataset with pathology data and thus fill up our database. However, we corrected our Kaplan-Meier and Breslow

analyses for lost cases, so the effects on our results are limited. During our study, new evidence on the clinical relevance of the lack of endocervical cells led to a guideline change in the Netherlands [26]. Since January 2002, the timing of the follow-up recommendation for the ECC- smears changed from six months to five years. In the Netherlands, where three conditions lead to a 6-month recommendation, we found clear differences in compliance between the follow-up of Pap smears with and without endocervical cells. Discontinuing the 6-month recommendation for ECC- smears would improve the follow-up rate.

The follow-up compliance within 36 weeks was about 67% for women with an ECC+ smear and a 6-month recommendation; about one in five of these women did not respond within one year. However, we do not exactly know whether the same percentage of severe abnormalities will be found in subsequent Pap smears of the non-responding women with initial ECC+ smears, our results indicate that primary care providers should persuade more women to undergo subsequent Pap smears after an abnormal ECC+ smear to prevent overall morbidity and mortality [8, 9, 27, 28].

It is to be expected that the cost of follow-up could be reduced considerably, for instance, by tailoring to low- and high-risk groups. Symptomatic patients, however, should be evaluated immediately [29]. To date, most 6-month follow-up recommendations have been related to ECC- smears (> 75%). By eliminating the recommendation for ECC- smears, general practitioners could concentrate on the loss to follow-up of the other, more severe conditions. Furthermore, the women with an ECC- smear would no longer experience anxiety through an obligatory follow-up [18-21].

The strong loss to follow-up in the case of an ECC- smear is related to the discussion in the Netherlands on the necessity of keeping track of these women [12]. In our study abnormalities were still found for 16% of the additional ECC- smears. However, the risk of invasive cervical carcinoma within eight years after normal Pap smears but without endocervical cells seems to be equal to the risk after a Pap smear with no abnormalities [12-15], and within three years after normal cytology results, high-grade squamous intraepithelial lesions (HSIL) or worse are uncommon [30]. The true prevalence of squamous lesions in women with recent ECC- smears was found significantly lower as compared with ECC+ smears [31]. It is therefore unlikely that the changed recommendation for ECC- follow-up in the Netherlands will have any serious consequences. Our study demonstrates that the effect for the women is negligible, because in most of the ECC- cases no abnormalities were found in the subsequent Pap smear taken after 36 weeks. When abnormalities were found, the abnormalities were not that severe because for none of the women with an initial ECC- Pap smear was the subsequent Pap smear reason to be referred to a gynecologist.

In conclusion, general practitioners were pragmatic in facing the challenge of evidence-based medicine, because our study has established that common practice was ahead of the new evidence in the screening setting as described in the additional guideline for general practitioners. The practices had already bridged the gap between new evidence and general practice [32].

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