*Original Article*

# High lifetime probability of screen-detected cervical abnormalities

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## Abstract

**Objective:** Regular screening and follow-up is an important key to cervical cancer prevention; however, screening inevitably detects mild or borderline abnormalities that would never progress to a more severe stage. We analysed the cumulative probability and recurrence of cervical abnormalities in the Finnish organized screening programme during a 22-year follow-up.

**Methods:** Screening histories were collected for 364,487 women born between 1950 and 1965. Data consisted of 1 207,017 routine screens and 88,143 follow-up screens between 1991 and 2012. Probabilities of cervical abnormalities by age were estimated using logistic regression and generalized estimating equations methodology.

**Results:** The probability of experiencing any abnormality at least once at ages 30–64 was 34.0% (95% confidence interval [CI]: 33.3–34.6%). Probability was 5.4% (95% CI: 5.0–5.8%) for results warranting referral and 2.2% (95% CI: 2.0–2.4%) for results with histologically confirmed findings. Previous occurrences were associated with an increased risk of detecting new ones, specifically in older women.

**Conclusion:** A considerable proportion of women experience at least one abnormal screening result during their lifetime, and yet very few eventually develop an actual precancerous lesion. Re-evaluation of diagnostic criteria concerning mild abnormalities might improve the balance of harms and benefits of screening. Special monitoring of women with recurrent abnormalities especially at older ages may also be needed.

## Keywords

Screening, cervical cancer, borderline abnormalities, longitudinal study

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## Introduction

Only a small proportion of mild cervical abnormalities eventually lead to severe disease. There is evidence that they are likely to heal spontaneously, especially among younger women.[1–3] The lifetime cumulative probability of borderline cervical abnormalities has been studied in few population-based studies. A study by Raffle et al.[4] estimated that the lifetime risk of abnormal cytology could be as high as 40%. Detection of cervical abnormalities that would never progress to cancer may result in overtreatment, physical and psychological distress, and increased healthcare costs.[5–7] Cross-sectional detection rates, as well as the number of lifetime screening rounds, vary greatly between different programmes.[8] Thus variation in the cumulative risk of abnormal cytology may also be high. In Finland, the national recommendation is to invite all women aged 30–60 for screening every 5 years. All municipalities follow this policy, and some also invite women aged 25 and 65. Consequently, a woman may go through up to seven or, in some regions, nine routine screens during her lifetime. The purpose of this study was to determine the cumulative probability of having cervical abnormalities at ages 30–64 in organized screening. Our main interest was in the difference between borderline and more severe abnormalities. We also analysed whether previous abnormalities had an increasing effect on the risk of detecting new ones. Our study highlights the harms experienced by screened women and points out the potential need for improvement in the diagnostic criteria.

## Methods

### *Study population and data source*

The Finnish cervical cancer screening programme introduced in 1963 achieved a national coverage by the early 1970s.[9] In addition to the 5-yearly routine screen,

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a follow-up test is recommended after 1–2 years if borderline cervical abnormalities are detected, or if the woman reports signs of symptoms such as bleeding or abnormal vaginal discharge. If borderline abnormalities persist in the follow-up test, referral for colposcopy and biopsy are recommended. Referral is also recommended if a clearly positive cytology result is detected, either in primary or follow-up screening. The Mass Screening Registry of the Finnish Cancer Registry contains complete data on invitations, screening tests, and diagnostic findings in the organized programme since 1991. Screening histories between 1991 and 2012 were collected for all invited women, consisting of 3.6 million routine screens among 1.5 million women. In addition there were around 230,000 follow-up screens. To utilize the longest possible screening history of the invited women, cumulative probabilities were estimated from cohorts of subjects who had entered the follow-up between 1991 and 1995 while aged 30, 35, or 40, i.e. women born between 1951 and 1965. Each cohort had 4–5 routine screens during the follow-up, and altogether these cohorts had comprehensive data with 1.2 million routine screens and 88,000 follow-up screens among 360,000 women. Municipalities inviting women aged 25 were excluded, so that the youngest cohort aged 30 at baseline included only women being screened for the first time, as our primary interest was in the national recommended target ages for screening. Municipalities are obliged to invite all target-aged women to screening. However, some routine screening invitations might not have been sent regularly if a municipality did not invite all target groups with a 5-yearly interval, or if women had moved within or outside the country.

### Measures and definitions

Conventional cytology is used as the primary screening test in the Finnish programme. A screening result was considered borderline if Pap class was II indicating reactive changes or atypical squamous intraepithelial lesion with undetermined significance (ASC-US) in Bethesda 2001, or if HPV-test was positive and the reflex cytology triage did not indicate a referral.[10] Low-grade squamous intraepithelial lesion or worse (LSIL+) led to a referral to colposcopy examination, where potential cervical intraepithelial neoplasia (CIN 1+) was histologically confirmed. We conducted the analysis by looking at 5-year screening rounds. A screening round begins from an age-based routine screen and continues with possible follow-up screens during the next 4 years, or until the next routine screen. Three different outcomes were examined: (i) any abnormality (borderline or more severe), (ii) referral to colposcopy and biopsy, and (iii) any histologically confirmed finding (CIN 1 or more severe result) among the referred women. Categories were overlapping, and thus women with CIN 1 might also have a borderline finding and/or a referral to colposcopy. The most severe result of a screening round was treated as the outcome, detected either by routine or follow-up screening. By comparing the cumulative probabilities of the outcomes, we aimed to determine the risk of borderline results without more severe diagnoses and the risk of referrals without a histological confirmation in the colposcopy examinations (false positives).

### Statistical analysis

The probability of any abnormality by age was estimated using logistic regression. A longitudinal approach allowed the same individual to have multiple measurements in the data. Generalized Estimating Equation (GEE) method with an independent correlation structure was used to account for individual-level correlation.[11,12] The GEE model was chosen because it is considered appropriate for the analysis of discrete time points (here screening age categories).[13] First, analysis was conducted separately for the three cohorts (aged 30, 35, and 40 at entry). The model included attained age in 5-year age groups, number of previous abnormal results (classified as 0, 1, or 2+), and irregular invitation and attendance history (classified as 0 up to the first irregularity and 1 afterwards) as time-varying categorical covariates. By including the number of previous abnormalities as a covariate, we were able to estimate the association between previous abnormalities and the risk of subsequent ones, i.e. whether the abnormalities in the data accumulated to the same women. We adjusted for irregular invitation and attendance history to reduce bias due to different attendance patterns. A joint model was then estimated by combining all three cohorts. The joint model also included a cohort indicator as a categorical variable, and its interaction with the number of previous abnormalities, to allow previous abnormalities to have a different effect on the outcome, depending on the cohort. Similar models were also estimated for referrals and CIN 1+ results where the number of previous referrals and CIN 1+ results (classified as 0 or 1+) were controlled for, respectively. Probabilities of the first experienced event with 95% confidence intervals in 5-year age groups were derived from the model predictions. Cumulative curves were obtained by subtracting the cumulative probability of not experiencing the event at ages 30–64 from unity.[14] Program R (version 3.2.3)[15] was used with packages geepack[16] and doBy.[17]

## Results

The screening profile of the study cohort (women born between 1951 and 1965) is shown in the flowchart, with different pathways leading to follow-up screening (Figure 1). The total number of invitations and visits are shown separately for routine and follow-up screens. The screening results of routine screens are shown on the upper part of the figure (white background). Average attendance rate was 74%. Among the 1,207,017 screens, 94% were normal, 6% borderline, and 0.7% resulted in referral to colposcopy. Of the normal screening results, 3% led to a follow-up screen within the same 5-year screening round

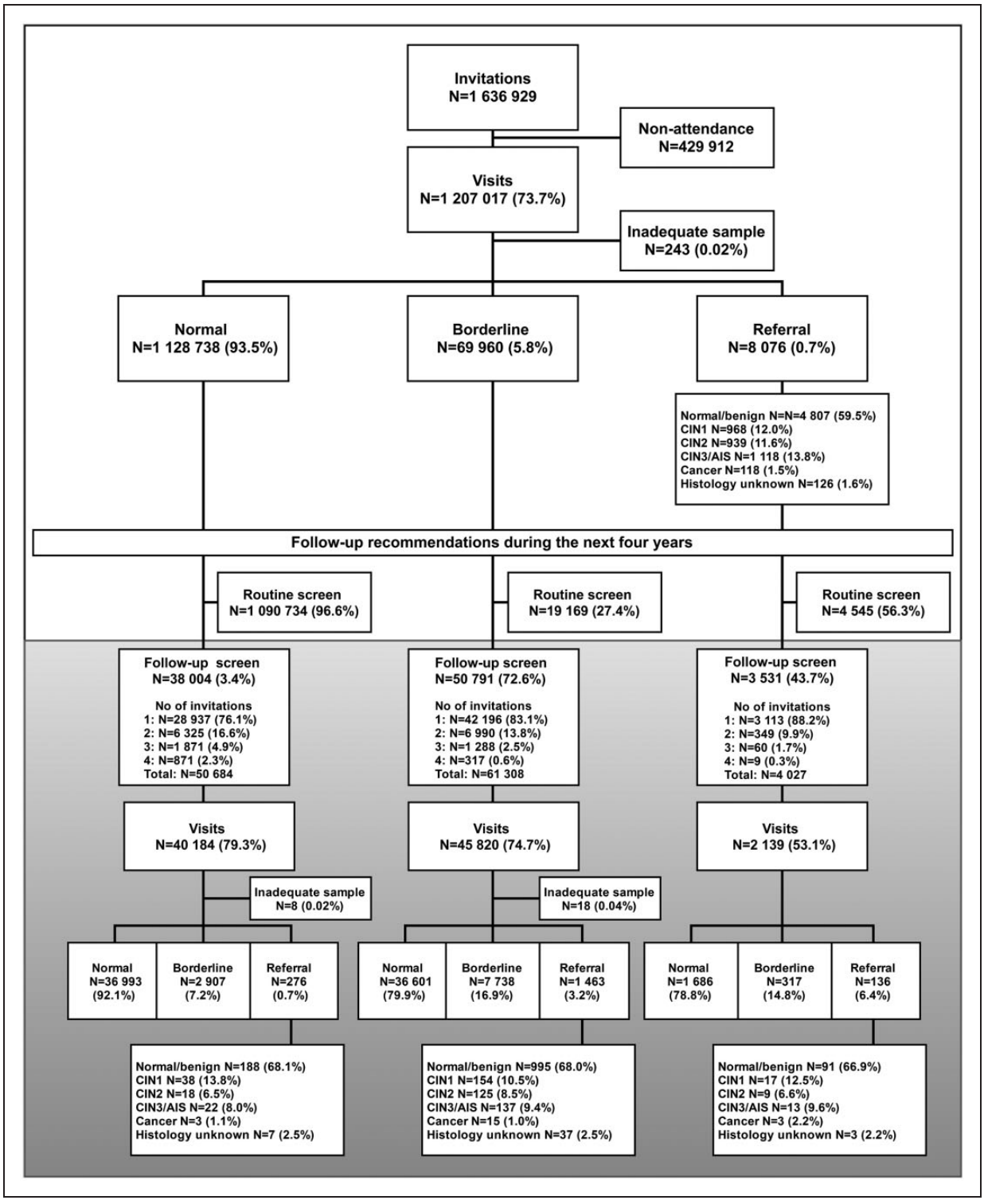


**Figure 1.** Flowchart of screening outcomes during 1991–2012 among the study cohorts: Routine screening (white background) and different pathways to follow-up screening (grey background).

during 4 years. Of these, 96% were women reporting signs of symptoms. The proportions of borderline and referral results leading to follow-up screening were 73% and 44%, respectively.

An individual might have received as many as four follow-up screens within the same 5-year screening round. Multiple follow-up screens occurred if the woman repeatedly reported symptoms, but no abnormalities warranting referral were detected by the screening test. However, the majority (>76%) of the women being followed up had only one follow-up screening before the next round, in which either a negative or a positive result was confirmed. Attendance to follow-up screening was better among women whose routine screening result was

**Table 1.** Characteristics of women in the study cohorts, % (n).

| | All cohorts (n = 393 351) | 1961–1965 cohort (n = 61 400) | 1956–1960 cohort (n = 154 743) | 1951–1955 cohort (n = 177 208) |
|---|---|---|---|---|
| Screened at least once | 92.7 (364 487) | 92.5 (56 800) | 92.8 (143 530) | 92.6 (164 157) |
| One or more[a] | | | | |
| Any abnormality | 19.1 (69 687) | 19.3 (10 949) | 19.9 (28 498) | 18.4 (30 240) |
| Referral or more severe | 2.6 (9 501) | 2.9 (1 642) | 2.9 (4 085) | 2.3 (3 774) |
| CIN1 or more severe | 1.0 (3 657) | 1.4 (766) | 1.1 (1 583) | 0.8 (1 308) |
| Borderline | 17.1 (62 239) | 17.0 (9 633) | 17.6 (25 280) | 16.7 (27 326) |
| Referral with normal histology | 1.6 (5 795) | 1.5 (866) | 1.7 (2 469) | 1.5 (2 460) |
| CIN 1 | 0.3 (1 173) | 0.4 (237) | 0.3 (481) | 0.3 (455) |
| CIN 2 | 0.3 (1 086) | 0.4 (238) | 0.3 (486) | 0.2 (362) |
| CIN 3 | 0.4 (1 282) | 0.5 (279) | 0.4 (556) | 0.3 (447) |
| Cancer | 0.0 (139) | 0.0 (17) | 0.1 (69) | 0.0 (53) |
| Two or more[a] | | | | |
| Any abnormality | 2.7 (9 922) | 2.5 (1 411) | 2.9 (4 169) | 2.7 (4 342) |
| Referral or more severe | 0.1 (253) | 0.1 (33) | 0.1 (109) | 0.1 (111) |
| CIN 1 or more severe | 0.0 (34) | 0.0 (7) | 0.0 (14) | 0.0 (13) |
| Irregularities[a] | | | | |
| Invitation | 10.6 (38 690) | 9.8 (5 581) | 8.9 (12 809) | 12.4 (20 300) |
| Attendance | 53.0 (193 316) | 62.5 (35 474) | 54.7 (78 485) | 48.3 (79 357) |

CIN: cervical intraepithelial neoplasia.
[a]Proportions of screened women.

normal than among those with borderline or referral routine results (Figure 1).

Table 1 shows the number of women in the three study cohorts, separately and combined, invited to cervical screening between 1991 and 2012. Around 93% of the women participated at least once. The proportion of women who underwent 1–5 screens and had at least one borderline result during the study period was 17%. Proportions of referrals and CIN 1+ results were much lower (<2%). The overall proportion of women experiencing more than one abnormality of any kind was 2.7%, varying between 2.5% and 2.9% in the sub-cohorts. Multiple referrals and CIN 1+ results were very uncommon (0.07% and 0.01%, respectively). Invitations were sent irregularly to 11% of the women. Further, 53% of women did not attend all routine screens to which they were invited, and therefore had less than five screens during the follow-up period. Irregular attendance was more common in the younger cohorts (Table 1).

The cumulative probabilities of any abnormality in the study cohorts were approximately 25–30% after 20 years of follow-up, the proportion being larger for younger cohorts (Figure 2a–c). The probabilities for a referral and a CIN 1 or more severe result were approximately 3–5% and 1–2%, respectively, again younger cohorts having larger probabilities. Thus, the proportion of borderline results without a more severe diagnosis was more than 20% for all cohorts. Younger women were more likely to have any abnormality, with the risk starting to decrease around age 45 (Figure 2a–c). The probability of experiencing any abnormality at ages 30–64 was nearly 34.0% (95% CI: 33.3–34.7%) (Figure 2d). The proportion of borderline only, without a more severe result, was nearly 30%. Results warranting referral and results with CIN 1+ accumulated to 5.4% (95% CI: 5.0–5.8%) and 2.2% (95% CI: 2.0–2.4%), respectively. Thus, the probability of experiencing a referral without a histologically confirmed finding, by the age of 64 was approximately 3%. The risk of any abnormality began to decline after age 45 in all cohorts (Table 2). Abnormalities at least warranting referral decreased quite linearly through age. Previous occurrences were associated with an increased risk, specifically in older cohorts. The effect was stronger if there were more than one previous abnormality of any kind, with an odds ratio of 3.79 (95% CI: 3.45–4.17) in the oldest cohort. If there were irregularities in the invitation and/or attendance histories, the risk of any abnormality was slightly elevated. Irregular attendance history was also associated with an increased risk of referral and CIN 1+ results, but no effect was observed with invitational irregularities (Table 2).

## Discussion

According to our results, the cumulative probability of any abnormality detected by the Finnish organized screening programme was, on average, 34% by age 64, for women starting screening in their 30s. The difference in the magnitude between mild and more severe results was substantial, the cumulative probability of results

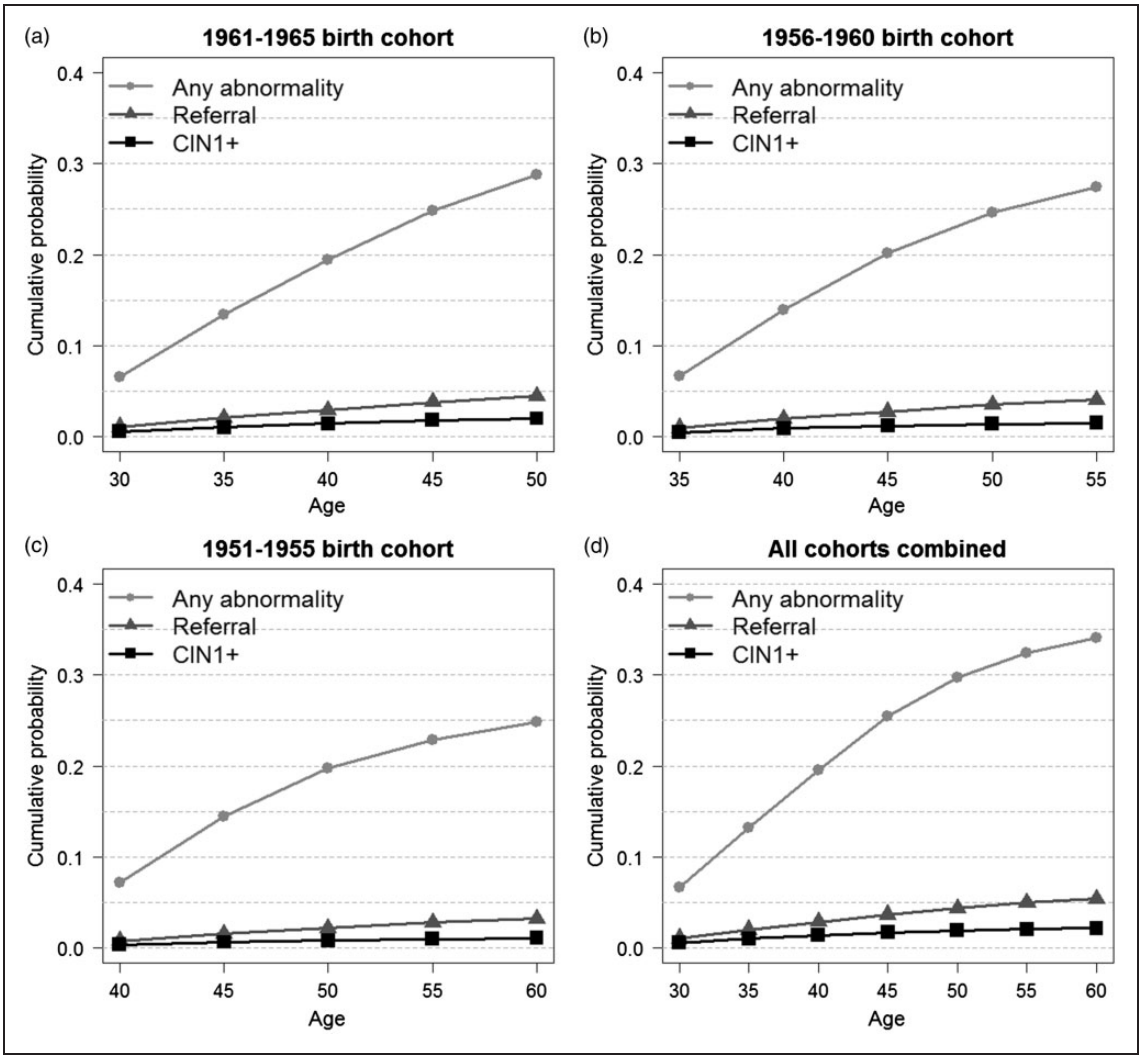


**Figure 2.** Cumulative probabilities of the first occurrence of any abnormality (borderline+), referral and CIN 1+ results by age in the three birth cohorts (a–c) and in all cohorts combined (d). Adjusted with irregular invitation / attendance history.

warranting referral being 5%, and results of CIN 1+ 2% in the programme. The incidence of borderline results in Finland is higher than in many other countries, whereas referrals to colposcopy and histologically confirmed CIN 1+ results are comparatively less frequent.[8] When cumulated over the long study period, these differences are emphasized. There seems to be an imbalance in the diagnostic practice with an overemphasis on borderline abnormalities.

The Finnish programme screens women using a 5-year interval. Although this seems to detect a large amount of mild abnormalities, the cumulative burden of abnormal test results is also likely to be high in other countries, especially if the screening interval is shorter than 5 years and the number of lifetime screening rounds is high.[5,18,19] The risk of developing high-grade CIN is elevated for women with mild cervical abnormalities.[2,20] Nevertheless, excessive detection of low-grade abnormalities may result in unnecessary follow-up testing, which in turn has a negative effect on the cost-effectiveness of screening. From an individual woman's perspective, receiving information on an abnormal screening result that requires follow-up testing causes adverse psychological effects of distress and anxiety.[5,7]

The use of secondary HPV testing in addition to conventional cytology or primary HPV testing with cytology triage in women with borderline results could improve the specificity of referral to colposcopy and recommendations for follow-up screens.[21,22] However, HPV testing appears to perform best among women aged 35 or older, and has a poorer specificity than conventional cytology among younger women.[23,24] Secondary HPV testing has not been used extensively in Finland. During the study period, primary HPV testing with cytology triage has been used in a large randomized implementation study since 2003[10,25] and, according to information at the Mass Screening Registry, in a large municipality starting primary HPV screening in 2012.

We chose CIN 1 or a more severe histologically confirmed lesion as an outcome, indicating at least

**Table 2.** Odds ratios (95% confidence intervals) for the probability of an occurrence of any abnormality (borderline+), referral, and CIN 1+ in the three birth cohorts.

| | Any abnormality | Referral | CIN 1+ |
|---|---|---|---|
| 1961–1965 cohort | | | |
| Age | | | |
| 35 | 1.14 (1.07–1.20) | 0.88 (0.76–1.02) | 0.88 (0.72–1.08) |
| 40 | 1.07 (1.00–1.13) | 0.76 (0.65–0.89) | 0.69 (0.55–0.86) |
| 45 | 1.03 (0.97–1.09) | 0.83 (0.71–0.97) | 0.64 (0.51–0.81) |
| 50 | 0.79 (0.73–0.87) | 0.61 (0.48–0.77) | 0.32 (0.21–0.48) |
| Previous occurrence | | | |
| 1 | 1.75 (1.64–1.86) | | |
| 1 or more | | 2.03 (1.43–2.88) | 2.03 (0.96–4.29) |
| 2 or more | 2.61 (2.17–3.15) | | |
| Irregular history | | | |
| Invitation | 1.31 (1.21–1.42) | 1.02 (0.80–1.30) | 0.71 (0.46–1.08) |
| Attendance | 1.13 (1.08–1.17) | 1.31 (1.17–1.47) | 1.40 (1.18–1.67) |
| 1956–1960 cohort | | | |
| Age | | | |
| 40 | 1.17 (1.14–1.21) | 0.99 (0.91–1.08) | 0.94 (0.82–1.07) |
| 45 | 1.07 (1.03–1.11) | 0.78 (0.71–0.85) | 0.60 (0.51–0.70) |
| 50 | 0.83 (0.80–0.86) | 0.83 (0.76–0.92) | 0.45 (0.38–0.53) |
| 55 | 0.54 (0.51–0.57) | 0.54 (0.46–0.62) | 0.24 (0.18–0.32) |
| Previous occurrence | | | |
| 1 | 1.93 (1.86–2.00) | | |
| 1 or more | | 2.79 (2.28–3.40) | 2.64 (1.53–4.56) |
| 2 or more | 3.10 (2.80–3.43) | | |
| Irregular history | | | |
| Invitation | 1.19 (1.12–1.26) | 1.07 (0.91–1.27) | 1.06 (0.78–1.44) |
| Attendance | 1.12 (1.09–1.15) | 1.27 (1.18–1.36) | 1.61 (1.43–1.82) |
| 1951–1955 cohort | | | |
| Age | | | |
| 45 | 1.09 (1.06–1.12) | 0.94 (0.85–1.03) | 0.80 (0.69–0.92) |
| 50 | 0.85 (0.82–0.87) | 0.79 (0.71–0.86) | 0.49 (0.41–0.57) |
| 55 | 0.53 (0.51–0.55) | 0.79 (0.72–0.87) | 0.39 (0.33–0.47) |
| 60 | 0.34 (0.32–0.36) | 0.51 (0.44–0.59) | 0.30 (0.23–0.39) |
| Previous occurrence | | | |
| 1 | 2.09 (2.02–2.17) | | |
| 1 or more | | 3.7 (3.05–4.49) | 3.84 (2.22–6.64) |
| 2 or more | 3.79 (3.45–4.17) | | |
| Irregular history | | | |
| Invitation | 1.15 (1.09–1.22) | 1.02 (0.88–1.18) | 0.79 (0.58–1.09) |
| Attendance | 1.14 (1.11–1.17) | 1.36 (1.26–1.48) | 1.69 (1.47–1.95) |

CIN: cervical intraepithelial neoplasia.

mild dysplasia. Since 2010 the Finnish guidelines recommended that, in general, CIN 1 should be managed with surveillance. Thus, a clinically more meaningful outcome currently would be CIN 2+. During earlier years of the follow-up, however, all cervical lesions (CIN 1+) were treated in Finland. In addition, by choosing CIN 1 as the cut-off, we were able to quantify the so-called false positive screens, i.e. colposcopy referrals where histologically confirmed lesions were not detected.

There is some variation between the municipalities in practices concerning the implementation of national guidelines for follow-up criteria. It has been reported that large variation existed between cytopathology laboratories in the rates of follow-up recommendations and referrals, although this was not shown to have an impact on the effectiveness of screening.[26] According to national guidelines, borderline results should always be followed up with an intensified frequency. We reported that only 73% of the borderline results led to recommendation for follow-up screening, suggesting that not all municipalities followed the guidelines. This means that the costs of the intensified follow-up practice could potentially be higher than currently. Of the normal routine screening results, 3% resulted in a follow-up recommendation due to symptoms reported by the woman. In this group it was more common to receive multiple follow-up invitations during the same 5-year screening round. Since 2009 the symptom-based follow-up recommendations have changed, and are now more conservative: only vaginal bleeding after sexual intercourse is considered for follow-up. Symptom-based follow-up testing within the programme is therefore expected to decrease in the future.

Recurrent abnormalities, diagnosed during several rounds for the same woman, were quite rare, even though women experiencing abnormalities once were at greater risk of experiencing subsequent ones. The effect seemed to be more pronounced in older than in younger women, and a similar trend was seen in all outcomes studied. Persistent HPV infections have been shown to be more prominent among older women.[27,28] Our results indicate that although fewer abnormalities are detected among older women, the risk of recurrent abnormalities increases with age. Previous research has supported the screening of women above the currently recommended target ages.[29] It may also be worthwhile to monitor abnormal recurrences, especially at older ages, as a persistent HPV infection is a strong risk factor of progression to a higher grade lesion.

Our results are based on extensive nationwide data with a 22-year follow-up, with valid information on follow-up procedures and diagnostic findings following the routine screen. However, the numbers reported here are based on the Mass Screening Registry, which contains only data on the organized screening programme. Abnormalities detected outside the programme are not included in the analysis, as opportunistic Pap testing was not registered centrally during the study period. In addition, a large proportion of CIN 1+ cases are detected in women under the screening ages, solely by opportunistic testing.[30] Opportunistic activity also affects age groups targeted by the organized programme, as additional tests are performed even between the organized screens. Therefore, the true cumulative proportion of referrals and CIN 1+ cases for the target screening ages is likely to be higher than reported here.[31] Also, it is possible that variation exists in the diagnostic criteria between organized and opportunistic screening. To elaborate the results in future studies we have started to incorporate opportunistic data in the analysis. In this study, however, we were specifically interested in the differences between the

cumulative probabilities of the three outcomes. We do not expect the overall patterns in these differences to change meaningfully, even after taking into account CIN diagnoses between the organized screens. It is also noteworthy that women who receive a referral after an opportunistic Pap test are entitled to have their colposcopy and treatment within the same public healthcare system as women who are referred within the organized programme.

An individual woman's lifetime risk of having screen-detected mild abnormalities is strikingly high in our data. The presented estimates are, in fact, conservative, as the 5-year screening interval is comparatively long, and no opportunistic screening is taken into account. An abnormal screening result in itself cannot be considered as a harm, but the handling of these abnormalities can potentially be harmful if follow-up tests and treatment are assigned where they are not needed.

Re-evaluation and improvement of diagnostic criteria concerning borderline abnormalities may reduce the overdiagnosis. Moreover, women with recurrent abnormalities, especially at older ages, should be monitored well, as they are at a greater risk of disease progression. Our analysis can serve as a benchmark for assessing harms of cervical cancer screening from an individual woman's perspective.

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#### Declaration of conflicting interests

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#### References

1. Furber SE, Weisberg E and Simpson JM. Progression and regression of low-grade epithelial abnormalities of the cervix. *Aust N Z J Obstet Gynaecol* 1997; 37: 107–112.
2. Schlecht NF, Platt RW, Duarte-Franco E, et al. Human papillomavirus infection and time to progression and regression of cervical intraepithelial neoplasia. *J Natl Cancer Inst* 2003; 95: 1336–1343.
3. Wright JD, Rader JS, Davila R, et al. Human papillomavirus triage for young women with atypical squamous cells of undetermined significance. *Obstet Gynecol* 2006; 107: 822–829.
4. Raffle AE, Alden B, Quinn M, et al. Outcomes of screening to prevent cancer: analysis of cumulative incidence of cervical abnormality and modelling of cases and deaths prevented. *BMJ* 2003; 326: 901.
5. IARC. *IARC handbooks of cancer prevention volume 10: cervix cancer screening*. Lyon, France: IARC Press, 2005.
6. Kyrgiou M, Mitra A, Arbyn M, et al. Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis. *BMJ* 2014; 349: g6192.
7. Rogstad KE. The psychological impact of abnormal cytology and colposcopy. *BJOG Int J Obstet Gynaecol* 2002; 109: 364–368.
8. Ronco G, van Ballegooijen M, Becker N, et al. Process performance of cervical screening programmes in Europe. *Eur J Cancer* 2009; 45: 2659–2670.
9. Anttila A, Pukkala E, Söderman B, et al. Effect of organised screening on cervical cancer incidence and mortality in Finland, 1963–1995: recent increase in cervical cancer incidence. *Int J Cancer* 1999; 83: 59–65.
10. Anttila A, Hakama M, Kotaniemi-Talonen L, et al. Alternative technologies in cervical cancer screening: a randomised evaluation trial. *BMC Public Health* 2006; 6: 1–8.
11. Liang K-Y and Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986; 73: 13–22.
12. Xue X, Gange SJ, Zhong Y, et al. Marginal and mixed-effects models in the analysis of human papillomavirus natural history data. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 159–169.
13. Twisk JWR, Smidt N and de Vente W. Applied analysis of recurrent events: a practical overview. *J Epidemiol Community Health* 2005; 59: 706–710.
14. Gelfand AE and Wang F. Modelling the cumulative risk for a false-positive under repeated screening events. *Stat Med* 2000; 19: 1865–1879.
15. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computinghttps://www.R-project.org/ (2015, accessed 2 March 2016).
16. Højsgaard S, Halekoh U and Yan J. The R package geepack for generalized estimating equations. *J Stat Softw* 2006; 15: 1–11.
17. Højsgaard S and Halekoh U. *doBy: Groupwise Statistics, LSmeans, Linear Contrasts, Utilities*. https://CRAN.R-project.org/package=doBy (2015, accessed 2 March 2016).
18. Anttila A, von Karsa L, Aasmaa A, et al. Cervical cancer screening policies and coverage in Europe. *Cerv Cancer Screen Eur Union* 2009; 45: 2649–2658.
19. Stout NK, Goldhaber-Fiebert JD, Ortendahl JD, et al. Trade-offs in cervical cancer prevention: Balancing benefits and risks. *Arch Intern Med* 2008; 168: 1881–1889.
20. Holowaty P, Miller AB, Rohan T, et al. Natural history of dysplasia of the uterine cervix. *J Natl Cancer Inst* 1999; 91: 252–258.
21. Denise Zielinski G, Snijders PJF, Rozendaal L, et al. High-risk HPV testing in women with borderline and mild dyskaryosis: long-term follow-up data and clinical relevance. *J Pathol* 2001; 195: 300–306.
22. Rebolj M, Bais AG, van Ballegooijen M, et al. Human papillomavirus triage of women with persistent borderline or mildly dyskaryotic smears: comparison of costs and side effects of three alternative strategies. *Int J Cancer* 2007; 121: 1529–1535.
23. Cuzick J, Sasieni P, Davies P, et al. A systematic review of the role of human papilloma virus (HPV) testing within a cervical screening programme: summary and conclusions. *Br J Cancer* 2000; 83: 561–565.
24. Leinonen M, Nieminen P, Kotaniemi-Talonen L, et al. Age-specific evaluation of primary human papillomavirus screening vs conventional cytology in a randomized setting. *J Natl Cancer Inst* 2009; 101: 1612–1623.
25. Leinonen MK, Nieminen P, Lönnberg S, et al. Detection rates of precancerous and cancerous cervical lesions within one screening round of primary human papillomavirus DNA testing: prospective randomised trial in Finland. *BMJ* 2012; 345: e7789.
26. Lönnberg S, Nieminen P, Kotaniemi-Talonen L, et al. Large performance variation does not affect outcome in the Finnish cervical cancer screening programme. *Cytopathology* 2012; 23: 172–180.
27. Castle PE, Schiffman M, Herrero R, et al. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. *J Infect Dis* 2005; 191: 1808–1816.
28. Maucort-Boulch D, Plummer M, Castle PE, et al. Predictors of human papillomavirus persistence among women with equivocal or mildly abnormal cytology. *Int J Cancer* 2010; 126: 684–691.
29. Lönnberg S, Anttila A, Luostarinen T, et al. Age-Specific Effectiveness of the Finnish Cervical Cancer Screening Programme. *Cancer Epidemiol Biomarkers Prev* 2012; 21: 1354–1361.
30. Salo H, Nieminen P, Kilpi T, et al. Divergent coverage, frequency and costs of organised and opportunistic Pap testing in Finland. *Int J Cancer* 2014; 135: 204–213.
31. Salo H, Leino T, Kilpi T, et al. The burden and costs of prevention and management of genital disease caused by HPV in women: a population-based registry study in Finland. *Int J Cancer* 2013; 133: 1459–1469.