



The impact of smears without endocervical cells on the cervical cancer screening program

L. Corbeij¹, J. Berkhof¹, A.M. Uyterlinde², J.A. Bogaards¹

¹Amsterdam UMC, Department of Epidemiology and Data Science, ²Amsterdam UMC, Department of Pathology

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Introduction

The human papillomavirus (HPV) causes almost all cases of cervical cancer. Therefore, the Dutch cervical cancer screening program has used primary HPV-screening since 2017. When high risk-HPV (hrHPV) is found, cytological triage is performed where cells are checked for abnormalities. Since the introduction of primary HPV-screening, the cytological evaluation has seen an increase in smears without endocervical cells (EC). So called EC minus smears are missing columnar cells from the endocervix, the mucous membrane that covers the inside of the cervix. Previous analyses reported less cases of histological abnormalities (CIN2+) and cervical cancer among EC minus smears compared to smears with EC. This summary of the research report, as assigned by the RIVM-CvB, focusses on the question of what the impact is of the noticeable increase in EC minus smears on the results of the cervical cancer screening program.

Methods

For this analyses, PALGA data from 2017 to mid-2024 were used including test results under the old hrHPV-referral scheme (2017 – mid-2022) and under the current hrHPV-referral scheme (mid-2022 – mid-2024) (for more information see: [Referral schedule for the cervical cancer screening programme | RIVM](#)). The data contains the whole first round of primary HPV-screening as well as up to two and a half years of the second round of primary HPV-screening. Data from two rounds can provide insight into the remaining risk, or the potential increased risk of high-grade abnormalities over two rounds for participants who were not referred during the first round, in relation to cytological EC status.

Most important results

Chance of EC minus smear

The proportion of smears with an EC minus result in primary cytological testing has increased from 21% in 2017 to 35% in 2024. An increase is observed across all laboratories, although considerable differences exist between laboratories. Participants with an EC minus result in a primary smear are more likely to have another EC minus result in subsequent testing than participants without an EC minus result. This applies both to a follow-up smear within the same screening round (2,1x higher probability) and to a primary smear in a subsequent round (1,6x higher probability).

Research question

What is the impact of the noticeable increase in EC minus smears on the results of the cervical cancer screening program?

Types of histological diagnoses:

No cervical intraepithelial neoplasia	CIN0
Mild cervical intraepithelial neoplasia	CIN1
Moderate cervical intraepithelial neoplasia	CIN2
Severe cervical intraepithelial neoplasia	CIN3
Adenocarcinoma in situ	AIS, starts in columnar cells
Adenocarcinoma	Cancer, starts in columnar cells
Squamous cell carcinoma	Other cancers



Impact on screening results within one round

Participants with an EC minus smear have a statistically significantly lower probability (3,2% less) of receiving a Pap 3a2+ score (moderate to severe cytological abnormalities) compared to participants with a smear containing EC. Accordingly, a lower referral rate is also observed among EC minus smears compared to smears with EC (relative risk EC minus vs. EC = 0,59)¹. Fewer CIN2+ cases are also diagnosed among participants with a primary EC minus smear (10,2% among smears without EC vs. 20,8% with EC). When looking only at the group of participants referred to a gynecologist, the difference in risk of a high-grade histological abnormality becomes smaller. This happens because the difference in referral probability between smears with and without EC is then eliminated. After this selection, the difference in CIN2+ diagnosis decreases, but it remains present. It can be concluded that the difference in histological diagnosis is not solely due to the higher referral rate among smears with EC, but also to an actual difference in the risk of abnormalities detected through histological examination. Among referred participants under the old referral scheme, 45,1% (EC minus) and 56,3% (smear with EC) were actually diagnosed with a high-grade abnormality (CIN2+). With the new referral scheme, this increased to 52,8% and 62,3%, respectively. Although squamous cells are present in an EC minus smear, both squamous and columnar abnormalities are found less frequently among EC minus smears: 25,2% vs. 30,6% and 1,5% vs. 2,7%, respectively.

The risk that remains after the first screening round

No differences are found in the risk of interval cancers² between smears with EC and those without EC. Likewise, the residual risk over two screening rounds shows no difference between EC minus smears and smears with EC in the first round, regardless of the presence of EC in primary and/or follow-up smears in round 1. Table 1 presents the comparison between having EC minus results twice (on both the primary and the follow-up smear) versus not having two EC minus results in round 1. For this analysis, only smears with EC in round 2 were included, ensuring that any abnormalities potentially missed due to repeated EC minus results in round 1 (on both the primary and the follow-up smear) would be detected in round 2. The analysis shows that the group with two consecutive EC minus results in round 1 does not have an increased risk of CIN3+, cancer, or AIS/adenocarcinoma in round 2, indicating that no high-grade abnormalities or cervical cancers were missed in round 1.

Table 1: Residual risk of CIN3+, cancer and AIS/adenocarcinoma over 2 rounds, stratified by 2x EC minus or not 2x EC minus round 1.

	Total participants	CIN3+	CIN3+ risk	Cancer	Cancer risk	AIS/adenocarcinoma	AIS/adenocarcinoma risk
2x EC minus round 1, with EC round 2	923	75	8,1%	4	0,43%	6	0,65%
Not 2x EC minus round 1, with EC round 2	9193	812	8,8%	47	0,51%	121	1,3%
Odds ratio (95% CI)			0,91 (0,71–1,2)		0,84 (0,30–2,4)		0,50 (0,22–1,1)

Conclusion

Looking at a single screening round, the conclusion is clear: EC minus smears lead to fewer referrals and also to a lower probability of detecting histological abnormalities after referral. The results confirm that since 2017, the proportion of EC minus smears has further increased. These findings suggest that, within a single screening round, among HPV-positive participants in the cervical cancer screening program, high-grade abnormalities and cancer are detected less frequently in smears without EC than in smears with EC. This could potentially undermine the effectiveness of the screening program.

¹ For old and new referral scheme respectively: 24,4% and 12,7% after EC minus, and 40,3% and 22,2% after smear with EC..

² An interval cancer is a diagnosis of cervical cancer within the same screening round as primary test participation, without referral to a gynecologist following the screening.



However, across two rounds, no evidence has been found of under-detection due to EC minus smears. No higher rate of interval cancers is observed after an EC minus smear. In addition, a risk analysis over two rounds shows that EC minus smears in round 1 do not result in an increased probability of high-grade abnormalities in round 2. Even columnar abnormalities, the type of lesions where the greatest effect might be expected since an EC minus smear is not assessed for columnar cells, were not found more often among participants with an EC minus smear in round 1 who had a smear with EC in round 2.

The cause of the increase in EC minus smears and the difference in probability of detecting high-grade abnormalities within a single round between smears with and without EC remain unclear. Based on this analysis, it is recommended to conduct further research into potential causes of diagnosis differences related to EC status, including differences in registration, quality of sampling technique, and registration bias. It cannot be ruled out that effects will become visible in the longer term. Therefore, it is advised to repeat the analysis when more data are available, for example after two or three screening rounds with complete follow-up. At present, adjustments to the cervical cancer screening program based on EC status are not recommended.