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RESEARCH ARTICLE

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The impact of loss to follow-up in the Dutch organised HPV-based cervical cancer screening programme

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Abstract

Loss to follow-up (LTFU) within cervical screening programmes can result in missed clinically relevant lesions, potentially reducing programme effectiveness. To examine the health impact of losing women during the screening process, we determined the proportion of women LTFU per step of the Dutch hrHPV-based screening programme. We then determined the probability of being LTFU by age, screening history and sampling method (self- or clinician-sampled) using logistic regression analysis. Finally, we estimated the number of missed CIN2+/3+ lesions per LTFU moment by using the CIN-risk in women compliant with follow-up. Data from the Dutch nationwide pathology databank (Palga) was used. Women eligible for screening in 2017 and 2018 were included ($N = 840{,}428$). For clinician collected (CC) samples, the highest proportion LTFU was found following 'referral advice for colposcopy' (5.5% after indirect referral; 3.8% after direct referral). For self-sampling, the highest proportions LTFU were found following the advice for repeat cytology (13.6%) and after referral advice for colposcopy (8.2% after indirect referral; 4.3% after direct referral). Self-sampling users and women with no screening history had a higher LTFU-risk (OR: 3.87, CI: 3.55–4.23; OR: 1.39, CI: 1.20–1.61) compared to women that used CC sampling and women that have been screened before, respectively. Of all women LTFU in 2017/18, the total number of potentially missed CIN2+ was 844 (21% of women LTFU). Most lesions were missed after 'direct referral for colposcopy' ($N = 462$, 11.5% of women LTFU). So, this indicates a gap between the screening programme and clinical care which requires further attention, by improving monitoring of patients after referral.

KEYWORDS

cervical cancer screening, compliance, HPV, loss to follow-up

What's new?

Loss to follow-up within cervical cancer screening programmes can result in missed clinically relevant lesions, potentially reducing programme effectiveness. In a more sensitive HPV-based programme, the loss of effectiveness may be larger than in cytology-based programmes. This study in the Netherlands is the first to quantify loss to follow-up in an organised cervical cancer

screening programme and calculate the potentially missed cervical lesions. Along the referral pathway of the Dutch cervical cancer screening programme, most clinically relevant lesions were missed after referral for colposcopy, indicating a gap between screening and clinical care.

1 | BACKGROUND

Worldwide, the Netherlands was the first country to implement a nationwide primary high-risk human papillomavirus (hrHPV) population-based screening programme.[1] Monitoring the results of the first year of the HPV programme showed that more CIN lesions were detected than in the previous cytology-based programme,[1] demonstrating the effectiveness of implementing hrHPV-based cervical cancer screening in an organised programme. Although changing the test may have improved CIN detection, it does not necessarily improve other factors that reduce programme effectiveness, such non-attendance or loss to follow-up (LTFU).[2] LTFU is particularly interesting, because women who are LTFU were initially willing to undergo screening, as opposed to non-attenders, who do not participate in the programme at all. From an international perspective, main reasons for dropping out are among others finances, physical access to hospitals or communication of positive test results.[3–5] However, in the Netherlands these factors play less of a role as the cervical cancer screening programme is reimbursed by the government, distances to hospitals are small and the communication of test results is centralised. Therefore, especially in such a setting where factors related to the healthcare system play less of a role, it is possible to investigate other factors that play a role in the LTFU of patients, such as patient characteristics. In general, patient characteristics such as a younger age, region, low socioeconomic status, knowledge and understanding of test results and health status, as well as organisational characteristics such as a functional reminder system, have all been shown to play a role in the LTFU of patients.[6,7] For organisers of screening programmes, understanding the characteristics of women who drop out of the screening programme, and at what point, can help pinpoint what interventions might encourage women to comply with follow-up tests. Therefore, we first aimed to determine at which step most women are LTFU in the referral pathway of the Dutch cervical cancer screening programme and to investigate the participant characteristics (age, screening history and sampling method) associated with LTFU. Secondly, to understand the possible public health impact of preventing LTFU, we aimed to estimate the proportion of precancerous lesions that was potentially missed due to the LTFU using data from women compliant with follow-up as a proxy.

2 | METHODS

2.1 | Setting

This study was conducted within the context of the Dutch primary hrHVP-based cervical cancer screening programme. Women are invited once every 5 years from ages 30 until 60.[1] An exception is for women who test hrHPV-positive at the age of 60, those are invited for an exit screen at the age of 65. Moreover, only women aged 40 and 50 who tested hrHPV-negative are allowed a longer screening interval, that is, reinvited after 10 years irrespective of screening history. A reminder letter is sent to non-responders after 16 weeks. Women can either choose to have a sample taken by their general practitioner (GP) or request a self-sampling (SS) kit (see flowchart, Figure 1). Women who test hrHPV positive with SS, are referred to the GP for a reflex cytology test. For women who had a sample taken by their GP, the reflex cytology is performed on the same sample. HrHPV-negative women are referred back to the regular screening programme. Women who test hrHPV-positive but have a negative cytology test result (i.e., negative for intraepithelial lesion or malignancy [NILM]), are invited for follow-up cytology after 6 months. HrHPV-positive women who have a positive cytology test result (i.e., atypical squamous cells of undetermined significance or more severe [ASC-US+]) are referred for colposcopy. Women with an inadequate cytology test result were invited for a repeat cytology test.

2.2 | Data selection

Data from the Dutch nationwide pathology databank (Palga) was used.[8] Palga has national coverage of all pathology labs. All primary screening tests taken within the primary hrHPV cervical cancer screening programme in the Netherlands between 1 January 2017 and 31 March 2019 were selected from Palga as well as any associated follow-up testing. This comprises women invited in 2017 (and participated between 1 January 2017 until 31 March 2018) and 2018 (and participated between 1 January 2018 and 31 March 2019) based on their year of birth. Women who were born in 1957, 1962, 1967, 1972, 1977, 1982 and 1987 received an invitation in 2017. Women born in 1958, 1963, 1968, 1973, 1978, 1983 and 1988 received an invitation in 2018. The follow-up was until July 2021, which was the maximum follow-up period (ranging from 27 to 54 months after participation) at the time of receiving the data.

2.3 | Measurement of loss to follow-up

LTFU moments (Figure 1) were defined as LTFU after: (I) a hrHPV+ result with SS with the advice for having a clinician collected (CC) sample for reflex cytology, (II) advice for repeat cytology following inadequate cytology, (III) advice for repeat cytology after 6 months following negative cytology (NILM), (IV) referral advice for colposcopy following positive cytology (ASC-US+, direct referral), (V) advice for repeat cytology following inadequate cytology after 6 months, and (VI) referral advice for colposcopy following positive repeat cytology

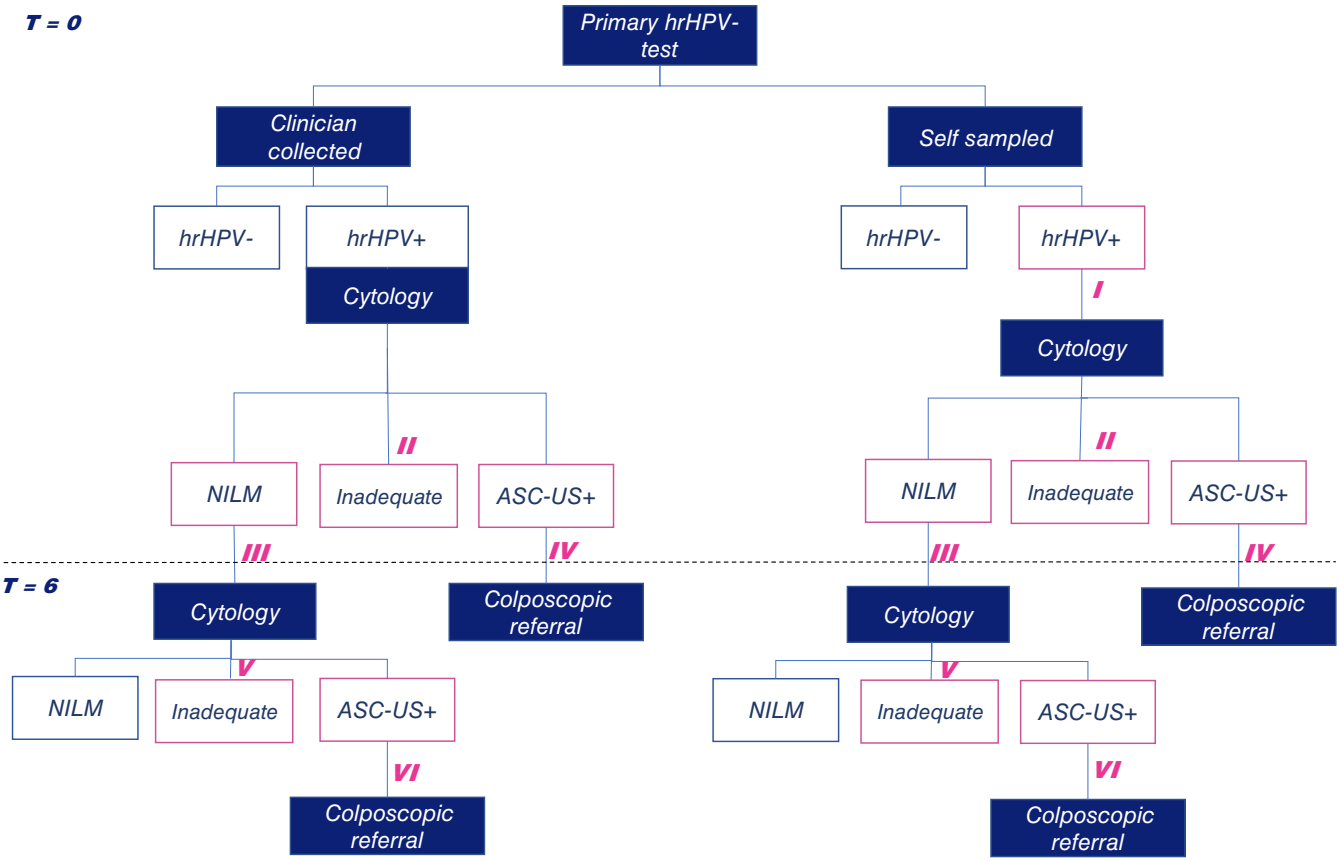

FIGURE 1 Flowchart of the Dutch cervical cancer screening programme, including loss to follow up moments (I–VI).

after 6 months (indirect referral). We did not restrict follow-up time regarding compliance with a repeat or referral advice.

2.4 | Measurement of participant characteristics

Participant characteristics include age at screening (30–34, 35–39, 40–44, 45–49, 50–54, 55–59 and 60+ years) and screening region (regions 1–5). In the Netherlands, in 2017–2018 there were five regional screening organisations responsible for sending the invitations and communicating results. Therefore, screening region was defined from region 1 to 5. Furthermore sampling method (CC or SS) and screening history were analysed. Screening history was defined as the number of primary cytology screens (either from screening programme or based on medical indication) from 1 January 2007 and categorised as no previous screens ('0'), or one or more ('≥1').

2.5 | Cervical lesions

Cervical lesions were defined as Cervical Intraepithelial Neoplasia (CIN) grade 2 or worse (CIN2+) and CIN grade 3 or worse (CIN3+). CIN2+ and CIN3+ lesions were histologically confirmed and based on the highest histological diagnosis of the episode of screening. A screening episode starts with the primary screening test, includes any (cytology or histology) follow-up tests and/or treatment, and is completed once a women is advised to return to regular screening.

2.6 | Data analyses

The proportion of women LTFU was quantified at each step of the screening pathway. Descriptive analyses of age, region, screening history and primary sampling method were performed for both women LTFU and women compliant with follow-up and presented as proportion of the total participants within a category. A chi-square test was performed to compare the characteristics of those two groups. A multivariable logistic regression analysis was performed to identify risk factors for LTFU. These risk factors include age at screening (in age groups), sampling method (CC or SS) and screening history (0 vs. ≥1). 'Screening region' was excluded from the regression model as this covariate was not significant and is not relevant for the risk on being LTFU. The interaction between age at screening and screening history was taken into account using dummies. We include one model for each covariate separately (unadjusted model) and one full model including all covariates (adjusted model). The analysis was conducted in IBM SPSS Statistics for Windows Version 25.0 (Armonk, NY: IBM Corp). A *p*-value of <.05 was considered as statistically significant.

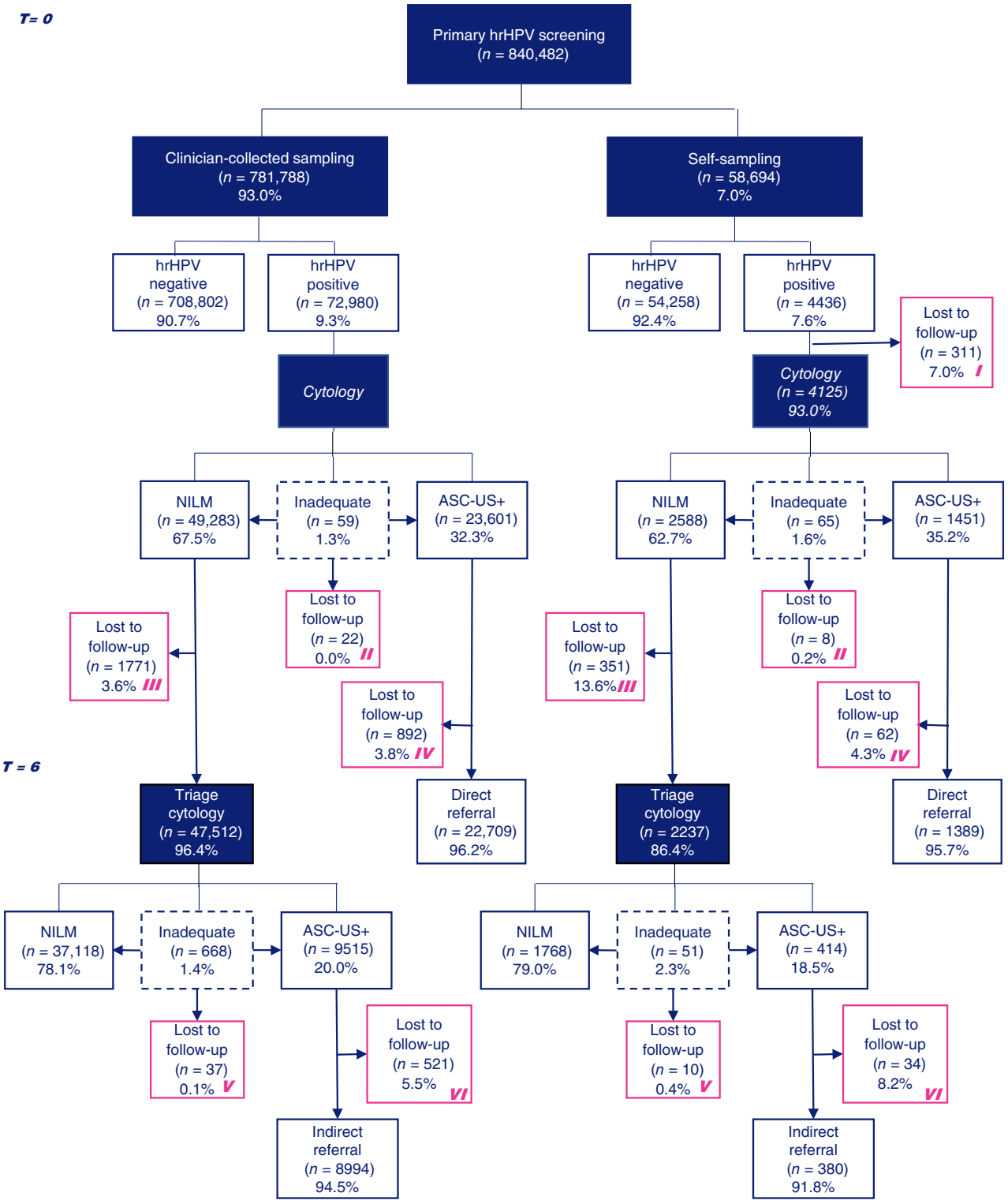

FIGURE 2 Loss to follow-up in the Dutch referral pathway of the cervical cancer screening programme, cohorts 2017 and 2018. NILM: negative for intraepithelial lesion or malignancy; AS-CUS+: atypical squamous cells of undetermined significance or higher. Not all proportions sum to 100% because a small proportion of women were given nonstandard advice following screening or follow-up tests.

The potential risk of CIN2+ and 3+ for women who were LTFU was calculated by using the number of CIN2+ and 3+ lesions found in women who were compliant with the corresponding follow-up advice as a proxy. This was necessary because there is no data available on CIN2+/3+ for women LTFU. We made the assumption that women who are LTFU are at equal risk of having CIN2+/3+ as

women compliant with follow-up. CIN2+ detection rates per LTFU moment were calculated as the proportion of women diagnosed with CIN2+ from the total number of women compliant with follow-up after a certain referral advice. The analysis was repeated to calculate the CIN3+ detection rates. In addition, the number of potential missed CIN2+ was estimated per LTFU moment (N LTFU * CIN 2+ detection rate). Similar calculations have been performed for CIN3+ detection rates. The proportion of CIN2+ cases that are missed due to LTFU was calculated as the proportion of potential missed CIN2+ from the total number of potential missed CIN2+ and detected CIN2+ in all participants screened.

3 | RESULTS

3.1 | Loss to follow-up per step in the referral pathway

A total of 840,482 women who were invited in either 2017 or 2018 were screened (781,788 [93.0%] by CC sampling and 58,694 [7.0%] by SS; Figure 2). For SS, 7% ($n = 311$) was LTFU after an advice for reflex cytology following an hrHPV positive SS test result (step I). A total of 22 (0.0%) women who used CC and 8 (0.2%) women who used SS were LTFU following an advice for repeat cytology after inadequate cytology (step II). After an advice for referral for colposcopy (step IV) the LTFU was 3.8% ($n = 892$) for CC sampling and 4.3% ($n = 62$) for SS. Regarding the triage, 3.6% ($n = 1771$) and 13.6% ($n = 351$) that used CC sampling and SS were LTFU after an advice for repeat cytology after 6 months (step III). A total of 1.4% ($n = 668$) and 2.3% ($n = 51$) of women who used CC and SS were LTFU after an inadequate repeat cytology at 6 months (step V). Lastly, a proportion of 5.5% ($n = 521$) and 8.2% ($n = 34$) women who used CC sampling and SS were LTFU after an indirect referral advice for colposcopy (step VI).

So, following CC sampling, the highest proportion of women were LTFU following either referral advice for colposcopy (5.5% of women with an indirect referral advice [$n = 521$], 3.8% of women with a direct referral advice [$n = 892$]), and after an advice for repeat cytology after 6 months (3.6%, $n = 1771$). Similar results were found for SS (8.2%, 4.3% and 13.6%, respectively), as well as after an hrHPV positive SS test with advice for CC reflex cytology (7.0%, $n = 311$) (Figure 2). Total LTFU per step in the referral pathway is shown in Appendix Figure S1.

3.2 | Participant characteristics associated with loss to follow-up

Compared with women compliant with follow-up, the proportion of women with no screening history was significantly higher in women LTFU for almost all LTFU moments (except 'after advice for repeat cytology following inadequate cytology after six months'; Table 1). In addition, the proportion of women who used SS was significantly higher among women who were LTFU across almost all LTFU moments (except 'after referral advice for colposcopy following positive cytology').

Tables 2 and 3 show the results of the logistic regression analysis of being LTFU. The unadjusted model showed higher odds of being LTFU for screening ages 29–34 and 35–39, women with no screening history and SS users (Table 2). The adjusted model showed that, in general, women with no screening history had a higher risk of being LTFU compared to women who have been screened before (OR: 1.39, 1.20–1.61). In women with no screening history, older women (who should have been screened before) had a significant higher risk on being LTFU compared to women aged 29–34 (start age for screening), with the highest risk in women aged 60+ (OR: 3.58, CI: 2.39–5.37; Table 3). No differences were observed in risk of being LTFU between age groups in women who have had one or more previous screens. Women who used SS had a higher risk (OR: 3.87, CI: 3.55–4.23) on being LTFU compared with women that used CC sampling.

3.3 | Potential missed CIN2+ and 3+ due to loss to follow-up

In 21% of all women that were LTFU, a CIN2+ lesion was calculated to have been missed, and in 11.9% of those women a CIN3+ lesion was missed (Table 4). If these women would not have been LTFU, the total number of diagnosed CIN2+ lesions would have been increased with 844 cases, and the number of CIN3+ cases with 480 cases. This means that 5.4% of the CIN2+ cases are missed due to LTFU in 2017/18. Most CIN2+ lesions are missed in women after direct ($n = 462$) and indirect ($n = 177$) referral advice for colposcopy, after a missed advice for repeat cytology ($n = 131$) and after a missed CC reflex cytology following a hrHPV positive self-sample ($n = 69$). Similar results were found for the number of potentially missed CIN3+ ($n = 278$, $n = 88$, $n = 65$, and $n = 47$).

4 | DISCUSSION

4.1 | Main findings

Within the Dutch cervical cancer screening programme, most women are LTFU after a referral advice for colposcopy, after being advised to have repeat cytology and after a hrHPV positive SS test. In those groups also the most CIN2+ and 3+ were potentially missed. In total, 5.4% of the CIN2+ lesions were potentially missed due to LTFU. Women with no screening history had a higher risk of being LTFU compared to women who have been screened before. The use of SS was associated with a 4-times higher risk of LTFU compared to women who were screened by their GP.

The relatively high proportion of LTFU after a referral advice for colposcopy might indicate a gap in the screening process between the screening programme and clinical care.[9,10] The screening organisation is responsible for communicating the results of screening with the participants and GPs. After a referral advice for colposcopy, the cervical cancer screening programme is no longer involved (the gynaecologist's examination is not part of the screening programme) and the

TABLE 1 Participant characteristics of women lost to follow-up compared to women compliant with follow-up (see Figure 1).

(A)	Loss to follow-up moments								
	I			II			III		
	LTFU ($n = 311$)	Compliant ($n = 4125$)	*p*-value	LTFU ($n = 30$)	Compliant ($n = 994$)	*p*-value	LTFU ($n = 2122$)	Compliant ($n = 49{,}749$)	*p*-value
Sampling method			N/A			**<.001**			**<.001**
SS	311 (100.0)	4125 (100.0)		8 (26.7)	57 (5.7)		351 (16.5)	2237 (4.5)	
CC	N/A	N/A		22 (73.3)	937 (94.3)		1771 (83.5)	47,512 (95.5)	
Age			**.015**			**.026**			**<.001**
30–34	90 (28.9)	1412 (34.2)		6 (20.0)	198 (19.9)		650 (30.6)	12,155 (24.4)	
35–39	57 (18.3)	747 (18.1)		2 (6.7)	124 (12.5)		382 (18.0)	7643 (15.4)	
40–44	32 (10.3)	502 (12.2)		1 (3.3)	98 (9.9)		275 (13.0)	6411 (12.9)	
45–49	28 (9.0)	456 (11.1)		2 (6.7)	108 (10.9)		272 (12.8)	6676 (13.4)	
50–54	47 (15.1)	406 (9.8)		8 (26.7)	107 (10.8)		243 (11.5)	6611 (13.3)	
55–59	28 (9.0)	329 (8.0)		9 (30.0)	169 (17.0)		166 (7.8)	5809 (11.7)	
60+	29 (9.3)	273 (6.6)		2 (6.7)	190 (19.1)		134 (6.3)	4444 (8.9)	
Screening region			**<.001**			.50			**.014**
Region 1	28 (9.0)	377 (9.1)		0 (0.0)	5 (0.5)		198 (9.3)	4568 (9.2)	
Region 2	43 (13.8)	674 (16.3)		7 (23.3)	316 (31.8)		333 (15.7)	8315 (16.7)	
Region 3	65 (20.9)	806 (19.5)		8 (26.7)	138 (13.9)		386 (18.2)	9740 (19.6)	
Region 4	84 (27.0)	971 (23.5)		6 (20.0)	194 (19.5)		477 (22.5)	10,740 (21.6)	
Region 5	89 (28.6)	1297 (31.4)		9 (30.0)	340 (34.2)		723 (34.1)	16,356 (32.9)	
Unknown	2 (0.6)	0 (0.0)		0 (0.0)	1 (0.1)		5 (0.2)	30 (0.1)	
Screening history			**<.001**			**.011**			**<.001**
0	185 (59.5)	1688 (40.9)		11 (36.7)	181 (18.2)		829 (39.1)	10,791 (21.7)	
≥1	126 (40.5)	2437 (59.1)		19 (63.3)	813 (81.8)		1293 (60.9)	38,958 (78.3)	

(B)	Loss to follow-up moments								
	IV			V			VI		
	LTFU ($n = 954$)	Compliant ($n = 24{,}098$)	*p*-value	LTFU ($n = 47$)	Compliant ($n = 675$)	*p*-value	LTFU ($n = 555$)	Compliant ($n = 9374$)	*p*-value
Sampling method			.34			**<.001**			**.018**
SS	62 (6.5)	1389 (5.8)		10 (21.3)	41 (6.1)		34 (6.1)	380 (4.1)	
CC	892 (93.5)	22,709 (94.2)		37 (78.7)	634 (93.9)		521 (93.9)	8994 (95.9)	
Age			**<.001**			.47			.33
30–34	249 (26.1)	7311 (30.3)		12 (25.5)	113 (16.7)		173 (31.2)	2617 (27.9)	
35–39	171 (17.9)	4455 (18.5)		5 (10.6)	62 (9.2)		84 (15.1)	1627 (17.4)	
40–44	136 (14.3)	3505 (14.5)		3 (6.4)	87 (12.9)		69 (12.4)	1331 (14.2)	
45–49	120 (12.6)	3260 (13.5)		4 (8.5)	74 (11.0)		70 (12.6)	1311 (14.0)	
50–54	133 (13.9)	2820 (11.7)		7 (14.9)	86 (12.7)		72 (13.0)	1205 (12.9)	
55–59	86 (9.0)	1775 (7.4)		6 (12.8)	137 (20.3)		55 (9.9)	799 (8.5)	
60+	59 (6.2)	972 (4.0)		10 (21.3)	116 (17.2)		32 (5.8)	484 (5.2)	
Screening region			**<.001**			.37			.14
Region 1	74 (7.8)	2328 (9.7)		1 (2.1)	15 (2.2)		48 (8.6)	947 (10.1)	
Region 2	135 (14.2)	3953 (16.4)		14 (29.8)	188 (27.9)		85 (15.3)	1617 (17.2)	
Region 3	301 (31.6)	5368 (22.3)		8 (17.0)	104 (15.4)		154 (27.7)	2144 (22.9)	

TABLE 1 (Continued)

(B)	Loss to follow-up moments								
	IV			V			VI		
	LTFU	Compliant		LTFU	Compliant		LTFU	Compliant	
	(*n* = 954)	(*n* = 24,098)	*p*-value	(*n* = 47)	(*n* = 675)	*p*-value	(*n* = 555)	(*n* = 9374)	*p*-value
Region 4	189 (19.8)	5767 (23.9)		14 (29.8)	128 (19.0)		114 (20.5)	2014 (21.5)	
Region 5	255 (26.7)	6669 (27.7)		10 (21.3)	239 (35.4)		154 (27.7)	2646 (28.2)	
Unknown	0 (0.0)	13 (0.1)		0 (0.0)	1 (0.1)		0 (0.0)	6 (0.1)	
Screening history			**<.001**			.30			**<.001**
0	326 (34.2)	6801 (28.2)		12 (25.5)	117 (17.3)		178 (32.1)	2291 (24.4)	
≥1	628 (65.8)	17,297 (71.8)		35 (74.5)	558 (82.7)		377 (67.9)	7083 (75.6)	

Note: Loss to follow-up moments: (I) a hrHPV+ result with self-sampling with the advice for having a clinician collected (CC) sample for reflex cytology; (II) advice for repeat cytology following inadequate cytology; (III) advice for repeat cytology after 6 months following negative cytology (NILM); (IV) referral advice for colposcopy following positive cytology (ASC-US+, direct referral); (V) advice for repeat cytology following inadequate cytology after 6 months; and (VI) referral advice for colposcopy following positive repeat cytology after 6 months (indirect referral). Bold values denote statistical significance at the $p < 0.05$ level.
Abbreviations: CC, clinician collected; LTFU, lost to follow-up; SS, self-sampled.

TABLE 2 The unadjusted risk of loss to follow-up by age, screening history and sampling method.

Unadjusted model		
Covariates	**OR (95% CI)**	***p*-value**
Age		
29–34	1.24 (1.08–1.42)	**.002**
35–39	1.18 (1.02–1.37)	**.022**
40–44	1.06 (0.91–1.24)	.43
45–49	1.02 (0.88–1.19)	.80
50–54	1.11 (0.95–1.29)	.20
55–59	0.94 (0.80–1.11)	.47
60+	1.00	
Screening history		
0	2.00 (1.87–2.13)	**<.001**
≥1	1.00	
Sampling method		
CC	1.00	
SS	4.56 (4.19–4.96)	**<.001**

Note: Bold values denote statistical significance at the $p < 0.05$ level.
Abbreviations: CC, clinician collected; CI, confidence interval; OR, odds ratio; SS, self-sampled.

actual referral of patients is the responsibility of the GP. In addition, it is possible that patients first have to make an appointment with their GP in order to be referred to the colposcopy clinic, which might form a barrier. Costs may also play a role for patients. Participation in the screening programme is free for invitees, as it is funded by the government but after referral, the costs of follow-up are dependent on a woman's health insurance. In the Dutch health insurance system, there is a mandatory deductible (€385/USD 493) for healthcare costs.[11] In addition, people may pay a voluntary deductible up to €500 (USD 641) on top of the mandatory deductible, in exchange for a lower monthly premium. Patients have to cover the costs up to the deductible themselves before the insurance covers the healthcare costs of follow-up care, which may induce lower compliance with a follow-up advice after a positive test result. Furthermore, it is possible that some women experienced psychological consequences (i.e., distress and anxiety) as a result of positive screening results, leading to LTFU.[12]

We found that a high proportion of potentially missed lesions was due to LTFU after an hrHPV positive SS test. This result is particularly important for organisers of the Dutch screening programme as the use of SS has risen since 2020. Especially during the COVID-19 pandemic, the proportion of women who used SS has doubled.[13] Due to this increase, the implications of our findings will have even more public health impact and this group should be closely monitored.

In our study, most clinically relevant lesions were potentially missed due to LTFU after a referral advice for colposcopy (4% and 6% women were LTFU after a direct and indirect referral advice; Appendix Figure S1). Compared to other studies, this LTFU rate is relatively low, which may be explained by the fact that we did not restrict follow-up time and barriers such as finances and physical access to hospitals play less of a role. Annual monitoring of the Australian Cervical Cancer Screening Programme showed that 60.8% of the women who were referred for colposcopy had a colposcopy within 3 months.[14] The mean compliance rate for colposcopy in Europe was 76.6% based on data from Finland (98.8%), Hungary (100.0%), Italy (87.7%), the Netherlands (76.1%), Poland (39.0%), Portugal Azores (39.5%), Slovenia (80.7%), Sweden (66.0%) and Wales UK (97.2%) between 2009 and 2014.[15] The lower compliance rate in the Netherlands in 2009 (76%) as compared to the compliance rate in the current study might be explained

TABLE 3 The risk of loss to follow-up, adjusted for age, screening history and sampling method.

Adjusted model		
Covariates	**OR (95% CI)**	***p*-value**
Age of women with no screening history		
29–34	1.00	
35–39	2.14 (1.84–2.49)	**<.001**
40–44	2.56 (2.07–3.18)	**<.001**
45–49	2.56 (1.99–3.30)	**<.001**
50–54	3.10 (2.40–4.00)	**<.001**
55–59	3.27 (2.38–4.51)	**<.001**
60+	3.58 (2.39–5.37)	**<.001**
Age of women with screening history		
29–34	1.12 (0.93–1.34)	.24
35–39	0.98 (0.84–1.16)	.83
40–44	1.00 (0.84–1.18)	.96
45–49	1.01 (0.86–1.20)	.87
50–54	1.10 (0.93–1.29)	.27
55–59	0.94 (0.79–1.12)	.47
60+	1.00	
Screening history		
0	1.39 (1.20–1.61)	**<.001**
≥1	1.00	
Sampling method		
CC	1.00	
SS	3.87 (3.55–4.23)	**<.001**

Note: $n = 4265$ loss to follow-up; $n = 73{,}393$ compliant to follow-up. Bold values denote statistical significance at the $p < 0.05$ level.
Abbreviations: CC, clinician collected; CI, confidence interval; OR, odds ratio; SS, self-sampled.

by the different screening protocols and the restricted follow-up time in that study (i.e., 12 months). Differences in screening protocols include the change of a cytology based programme to an hrHPV-based programme and the introduction of the SS test. In concordance to our high adherence results, a pilot study in England including 442,174 women with primary hrHPV screening showed an attendance rate of 98% after immediate (direct) referral for colposcopy and of 96% after indirect referral for colposcopy after 12 months.[16] This study did also not restrict follow-up time. Another retrospective observational study in the UK showed high attendance rates of 94% to colposcopy within 4 months.[17] A recent study in Denmark found 91% attendance rates to colposcopy within 4 months.[7] However, cross-country comparisons are difficult due to colposcopies outside the programme (Italy, Poland and Portugal Azores) or delay in reporting (Portugal Azores). Moreover, in Hungary, colposcopy is part of the screening visit resulting in a compliance rate of 100%. In Australia, due to a two-tier healthcare system of private and public hospitals, finances may play a role in its lower compliance rate compared to our study, as waiting times to public hospitals can be extremely long. Also, physical access is an important factor in this country as distances are longer for people living in remote areas as compared to the Netherlands.[14] Whereas other studies used the term 'referral for colposcopy', in our study we use 'referral advice for colposcopy' which is not exactly the same. A referral advice is given by the screening organisation to the GP, to refer a patient. The actual referral is done by the GP. In our study we only have information about the screening organisation and do not know whether the patient actually was referred. However, as referral advices are both communicated to the patient and GP by the screening organisation, it is likely that most patients will be referred.

A review found that younger age is correlated with LTFU.[6] In the unadjusted regression model of our study we found the same association. However, when we took the interaction with screening history into account, older age (reflecting women that have an increased number of missed screening rounds) was found to be correlated with a higher risk on being LTFU in women with no screening history. Older women who are inadequately screened have been found to have a lower risk perception of cervical cancer.[18] In addition, age-related attendance might depend on the referral advice. Green et al. found that younger women (<30 years) were less likely to attend repeat cytology at 12 months in England compared to older women aged 30+ but did not found any significant differences by age for attendance to colposcopy.[19] Besides participant characteristics, organisational characteristics may also have influenced the adherence to follow-up of women in our study. For example, a reminder system has frequently been demonstrated to be beneficial for the adherence to follow-up.[6,20] Moreover, understanding of test results may have played a role. A study that examined follow-up in patients with a positive test result after colorectal cancer screening has showed that a higher comprehension of test results was associated with better adherence to follow-up.[21]

4.2 | Strengths and limitations

This is the first study that quantifies LTFU for each step within an organised HPV-based cervical cancer screening programme, including SS, and that investigates the potential public health impact in terms of missed CIN2+/3+ lesions for those women LTFU. This information can be used to improve the effectiveness of organised population-based screening programmes and emphasises the importance of compliance with follow-up after a referral advice. For example, interventions can be developed to increase compliance to follow-up after a referral advice, targeted to those groups at highest risk such as sequential reminders. Furthermore, we used high quality national data which allows us to link screening records of women and be able to follow those women over time. Our study also has some limitations. First, we used data of women compliant with follow-up as a proxy for women LTFU to calculate the risk of CIN2+/3+. The key assumption here is that the risk of CIN2+/3+ is the same for women who were LTFU and those who complied with their referral advice. This assumption may result in an underestimation of the number of missed lesions because previous research has shown that the risk of invasive cervical cancer is higher in women that have inadequate screening history or poor follow-up.[22] Second, as colposcopies are not registered in Palga, compliance with referral for

TABLE 4 The number of potentially missed CIN2+ and 3+ in women lost to follow-up per step of the referral pathway in 2017/18.[a]

	Compliant with follow-up					Lost to follow-up				
	A	*B*	*B/A*	*C*	*C/A*	*D*	*D* * (*B/A*)	*D* * (*C/A*)	(*D* * (*B/A*))/∑*D*	(*D* * (*C/A*))/∑*D*
LTFU moment[b]	Compliant (*n*)	CIN2+ (*n*)	CIN2+ RISK (%)	CIN3+ (*n*)	CIN3+ RISK (%)	LTFU (*n*)	Missed CIN2+ (*n*)	Missed CIN3+ (*n*)	Missed CIN2+ out of total LTFU (%)	Missed CIN3+ out of total LTFU (%)
I	4125	916	22.2	617	15.0	311	69	47	1.7	1.2
II	994	118	11.9	59	5.9	30	4	2	0.1	0.0
III	49,749	3072	6.2	1524	3.1	2122	131	65	3.3	1.6
IV	24,098	11,663	48.4	7016	29.1	954	462	278	11.5	6.9
V	675	25	3.7	12	1.8	47	2	1	0.0	0.0
VI	9374	2995	32.0	1484	15.8	555	177	88	4.4	2.2
Total		14,805[c]		8569[c]		4019 (∑*D*)	844	480	21.0	11.9

Abbreviation: LTFU, loss to follow-up.

[a]The numbers of loss to follow-up moment 2–6 are totals of both CC and SS users.

[b]Loss to follow-up moments: (I) a hrHPV+ result with SS with the advice for having a clinician collected (CC) sample for reflex cytology, (II) advice for repeat cytology following inadequate cytology, (III) advice for repeat cytology after 6 months following negative cytology (NILM), (IV) referral advice for colposcopy following positive cytology (ASC-US+, direct referral), (V) advice for repeat cytology following inadequate cytology after 6 months, and (VI) referral advice for colposcopy following positive repeat cytology after 6 months (indirect referral).

[c]This is the total CIN prevalence in all compliant participants counting each lesion once per individual.

colposcopy was based on the combination of an advice for colposcopy and subsequently reported cytology taken by the gynaecologist or histology results. Women who attended colposcopy and had no cytology or histology taken might therefore be considered as LTFU, which might have resulted in a potential overestimation of the number of women LTFU after referral for colposcopy. However, this number is expected to be small as those women should be retested by protocol by the gynaecologist in 12 months and we did include sufficient follow-up to capture these women. Nevertheless, a colposcopy registration system is warranted in order to improve the monitoring of women after a referral advice for colposcopy. Third, in our study we did not include steps after referral for colposcopy because it is outside the scope of the screening programme. The European guidelines of quality assurance in cervical cancer screening recommend screening programmes to carefully monitor the management of HPV-positive women, including compliance with follow-up of positive test results and results of triage, colposcopies, biopsies and treatment of precancers.[23,24] Additionally, it might be necessary to examine the LTFU rate after colposcopy and CIN diagnose because of an increased cervical cancer risk. We previously showed that in the Dutch cytology based screening programme, in 3%–10% (depending on age) of the women referred to colposcopy, no diagnose was recorded (which indicated LTFU). After diagnose, 85.1% of the CIN3 lesions and 67.8% of the CIN2 lesions were treated with excision. Furthermore, in 14.6% of the CIN3 and 29.7% of the CIN2 diagnoses, only a biopsy was performed during follow-up (which indicates a wait-and-see policy).[25]

5 | CONCLUSION

In conclusion, although the proportion of LTFU is relatively low in the Dutch HPV-based screening programme, still 5.4% of CIN2+ lesions are potentially missed due to LTFU. Most CIN 2+/3+ lesions were missed due to LTFU after receiving an advice for referral for colposcopy. The transfer of responsibility of follow-up of patients might be suboptimal. Monitoring patients after their referral for colposcopy as recommended by the European guidelines could be improved, for example by implementing a colposcopy registration system. The existing gap in the Dutch screening process between the screening programme and clinical care requires further attention, in order to enhance the transition between screening and diagnosis and to assure better follow-up. With the increased use of SS, extra attention should be paid to monitor the follow-up of these women.

AUTHOR CONTRIBUTIONS

E. M. G. Olthof: conceptualisation, data curation, formal analysis, software, methodology, project administration, visualisation, writing—original draft, writing—review & editing. **C. A. Aitken**: conceptualisation, supervision, writing—review & editing. **A. G. Siebers**: resources, writing—review & editing. **F. J. van Kemenade**: writing—review & editing. **I. M. C. M. de Kok**: conceptualisation, project administration, supervision, validation, writing—review & editing. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sources and handling of the dataset used in this study are described in the Methods. Further details and other data that support the findings of this study are available from the corresponding authors upon request.

ETHICS STATEMENT

This study was conducted as part of the national evaluation of the Dutch Cervical Cancer Screening Programme, which is legislated under the *Population Screening Act* (*Wet Bevolkingsonderzoeken*) in the Netherlands using pseudonymised data, which is exempt from internal review boards or requirements for informed consent by screenees aside for a formal approval by the screen authorities and the requirement for data anonymity. Data owners and data-custodians gave approval for the use of their data for this project. Ethical approval by a medical ethical committee was not required under Dutch law as no patients were involved in the development of the research and only non-identifiable data were used for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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