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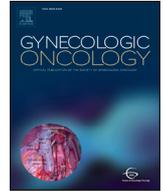
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HPV-prevalence in elderly women in Denmark

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HIGHLIGHTS

- Primary HPV-screening well received by elderly women in Denmark
- No rebound in HPV-prevalence after menopause
- High cervical cancer incidence in old age not reflected in HPV-prevalence

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ABSTRACT

Aim. In countries like Denmark, cervical cancer incidence is at present relatively high in elderly women, while routine screening stops at age 65 years. On this background, all women aged 69 and above were invited to human papillomavirus (HPV)-screening in Denmark in 2017.

Methods. Women were identified from the Central Population Register and personally invited by digital or ordinary mail to have a screening sample taken by their general practitioner. In four regions, samples were tested for high risk (HPV) with the cobas 4800® HPV-assay, and in the last region with the BD Onclarity® HPV-assay. Participation rate, prevalence of high risk HPV, and proportion of positive samples with HPV16, HPV18, and other high risk HPV-types were tabulated by 5-year age-groups.

Results. 455,612 women were invited, and 30.2% (95 confidence interval (CI) 30.0–30.3) participated. Average age of participants was 74.6 years. Overall, 4.3% (95% CI 4.1–4.4) of participants were HPV-positive, of whom 24% had HPV 16/18. HPV-prevalence decreased slightly from 4.5% in women aged 69–73 years to 3.1% in women aged 84–88 years, but was 5.2% in the very small group of participants aged 89+ years.

Conclusion. Invitation to HPV-screening was well received by elderly women. The HPV-prevalence decreased slightly with increasing age. No rebound of HPV-prevalence after menopause was found when our data were combined with previously published Danish data from younger women. The presently relatively high cervical cancer incidence in elderly women was not reflected in the HPV-prevalence.

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Abbreviations: ASCUS, Atypical squamous cells of undetermined significance; CI, Confidence interval; HPV, Human Papillomavirus.

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1. Introduction

In many high-income countries the age-specific incidence of cervical cancer at present shows a bipolar pattern with a first top on the incidence curve around the age of 35–40 years, and a second top around the age of 65–80 years. The first top on the incidence curve is well explained by the biology of cervical cancer and the onset of sexual life, as a persistent infection with high-risk human papillomavirus (HPV) is a precondition for development of this cancer; HPV-infection is sexually transmitted; and there is a long latency period from first persistent infection to cancer development. The second top on the incidence curve has been more difficult to explain. This top has been hypothesized to be associated with mid-life change of sexual partners or with reactivation of a latent HPV-infection as the immune system degenerates with age [1]. It should, however, be taken into account that after 50 years of screening, the current age-specific incidence of cervical cancer is no longer a pure reflection of the underlying risk of the disease, but it reflects also the screening history of the respective birth cohort. A study of cervical cancer patients aged 60 and above in Denmark in 2009–2013 found the average age of non-screened patients to be 76 years, in line with the current second top on the incidence curve [2].

In Denmark, cervical screening started on a county-basis between the late 1960's and the late 1990's. Since 2012, screening has been offered every third year to women aged 23–49 years, and every fifth year to women aged 50–65 years [3]. In 2015, the bipolar pattern in the age-specific incidence of cervical cancer became an issue of concern with the DaneAge Association and the Danish Cancer Society arguing for extension of the upper limit of screening age. This led to an analysis of the age-specific incidence of cervical cancer by birth cohort [4]. The analysis showed that the incidence pattern within a given birth cohort was unipolar at a gradually lower level for successively younger birth cohorts indicating that the current incidence peak in elderly women was a residual derived from previous, incomplete screening of these birth cohorts.

On this basis, the upcoming generations were expected to have a lower cervical cancer incidence in old age than seen today, and a permanent extension of the upper limit of the screening age might therefore not to be needed. There was, however, good evidence for offering screening once to the previously under-screened elderly women. Consequently, in 2017 Danish women born before 1948 were all personally invited to HPV-testing. In the present paper we report on the outcome of this screening.

2. Material and methods

2.1. Regional organisation of intervention

The special offer of screening for elderly women was part of Cancer Plan IV implemented by the Danish Government, the Danish Regions, and the Danish Municipalities in 2017. All women born before 1948 should be invited to screening in 2017, and according to the cancer plan primary HPV-testing should be used as the screening test. Women with a positive test should be followed up in the same way as test-positive women aged 60–64 years [5].

Screening in Denmark is organised by the five regions following national guidelines. Accordingly, the screening of elderly women was organised in part similarly and in part with differences across regions. A common invitation letter was developed by the National Health Authority. As in the screening programme, women were invited to make an appointment with their general practitioner to have the sample taken. Reminders were not used. All regions informed the general practitioners before the screening activity started, and the outcome of screening for the individual woman was reported back to her general practitioner, who was responsible for the follow-up in case of abnormality. Screening and eventual follow-up were free of charge for the woman.

Differences across regions were found in dates for retrieval of data for target population; in length of calendar periods used for invitation; in order of invitations by women's age; in invitation method; in length of period within which HPV-testing was used; in HPV-assay used; in use of cytology triage; and in rules applied for referral for colposcopy (Table 1). In general, the screening activity was organised fairly similarly in the North, Central, South and Zealand regions, while the Capital region followed slightly different procedures. The main differences being that the first four regions used digital invitations to the women's secured e-mail addresses, while the Capital region used ordinary mail. Furthermore, the North, Central, South and Zealand regions used the Cobas 4800® HPV-assay from Roche, while the Capital region used the BD Onclarity® HPV-assay. In the four regions, women with HPV 16 or 18, and women with other high risk types of HPV and abnormal cytology were referred for colposcopy, while women with other high risk HPV types than 16 and 18 and normal cytology were invited to repeated HPV test in a year. In the Capital region, all high risk HPV-positive women were referred for colposcopy.

Table 1
Organisation of cervical screening for elderly women in Denmark by region.

Activity	Region ^a				
	North	Central	South	Zealand	Capital
Data retrieval for population	15 March 2017	15 March 2017	15 March 2017	15 March 2017	Before invitation of given birth cohort
Invitation period	2 June – 14 Nov 2017	20 April – 27 Sept 2017	2 May – 31 Oct 2017	2 May – 31 Dec 2017	8 May 2017–22 June 2017 10 August 2017–16 October 2017
Invitation order	Youngest first	By birth day	By birth day	Youngest + oldest first	Youngest first
Invitation method	Digital ^b	Digital ^b	Digital ^b	Digital ^b	Ordinary mail
End of HPV-testing	17 May 2018	1 Jan 2018	Vejle: continued Esbjerg/Sønderborg: 31 May 2018	1 July 2018	1 Oct 2018
HPV-assay	Cobas 4800©	Cobas 4800©	Cobas 4800©	Cobas 4800©	BD Onclarity©
Result reported	16, 18, other ^c , negative	16, 18, other ^c , negative	16, 18, other ^c , negative	16, 18, other ^c , negative	16, 18, other ^c negative
Cytology triage	Other only	Other only	All positive	Other only	None
Referral for colposcopy	16, 18, other with ASCUS + ^d	16, 18, other with ASCUS + ^d	18, 18, other with ASCUS + ^d	16, 18, other with ASCUS + ^d	All HPV-positive

Notes.

- ^a Full names of regions: The North Denmark Region, The Central Denmark Region, The Region of Southern Denmark, Region Zealand, The Capital Region of Denmark.
- ^b Women exempted from digital communication were invited by ordinary mail.
- ^c Other high risk HPV-types than 16 and 18.
- ^d Atypical squamous cells of undetermined significance and worse.

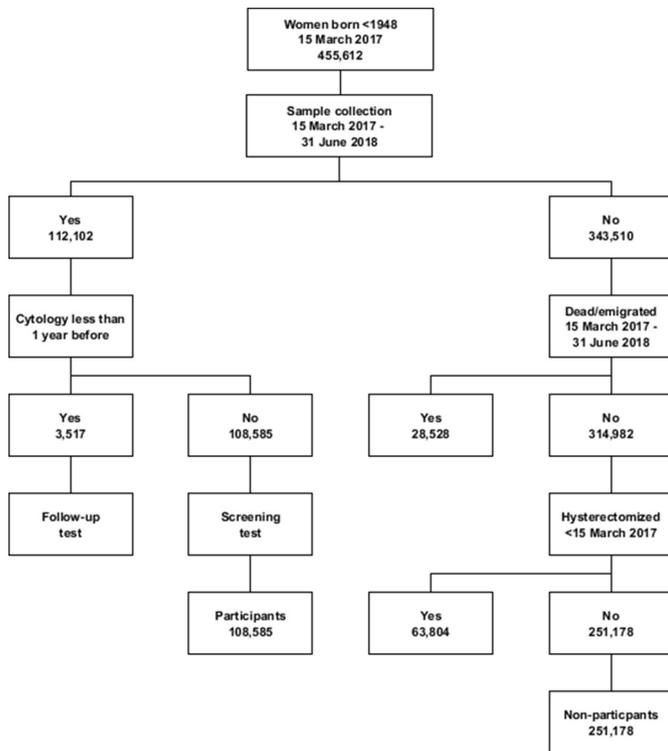


Fig. 1. Flow diagram for analysis of cervical screening for women born before 1948 in Denmark in 2017.

2.2. Data

For the analysis, data were retrieved from the Central Population Register on women born in 1947 or earlier and living in Denmark on 15 March 2017, and on dates of death and emigration in these women during the period 15 March 2017 to 31 June 2018. Data on cytology samples taken in the invited women between 15 March 2017 and 31 June 2018 were retrieved from the National Pathology Register. In addition, in women with a sample, data were retrieved on previous samples within the last year. Data on hysterectomies in women without a cytology sample were retrieved from the National Patient Register from 1977 to 2017.

The HPV-tests were coded for adequacy and outcome of HPV-test into four categories HPV-16; HPV18; other HPV-types; and HPV-negative. The outcomes of cytology triage and follow-up testing are not included in the present report. Definitions and codes are listed in Supplementary Table 1.

2.3. Analysis

As individual dates of invitation were not known, all women without a sample who died or emigrated between 15 March 2017 and 31 June

2018 were considered ineligible for screening. Participation rate was calculated as [women with a sample/(invited women – (women in follow-up + dead/emigrated women + hysterectomised women))]. Percent HPV-positive women was calculated as (women HPV-positive/women with sample adequate for HPV-testing). 95% confidence intervals (CI) were calculated with the Clopper-Pearson method.

For the present analysis data were retrieved centrally by the Danish Clinical Registries. Data were analysed using SAS version 9.4. The study was part of the routine quality assurance of cervical screening in Denmark. The Central Denmark Region guaranteed that data were used in accordance with the data protection legislation.

3. Results

In total, 455,612 women were invited, ranging from 36,133 women born in 1947 to 9 women born in 1909 or earlier. Out of these women 112,102 had at least one sample taken between 15 March 2017 and 31 June 2018. For 3517 women, their sample seemed to be a follow-up of earlier findings, as they had a previous sample taken less than one year before. As a result, 108,585 women participated in the screening. The mean age of participants was 74.6 years.

Of those without a sample, 28,528 died or emigrated between 15 March 2017 and 31 June 2018. Furthermore, 63,804 women without a sample were hysterectomized before 15 March 2017. Women in follow-up, dead/emigrated, or hysterectomized were considered ineligible for screening. As a result, 251,178 eligible women did not participate in the screening (Fig. 1). In total, 30.2% of eligible women participated in the screening, ranging from 44.0% in women aged 69–73 years to 1.9% among women aged 89+ years (Table 2).

Overall, 4.1% of participating women were HPV-positive. Among women in follow-up this percentage was 10.4% (Table 3). Together, 4.3% (95% CI 4.1–4.4) of all screened women were HPV-positive; slightly decreasing from 4.5% (95% CI 4.4–4.7) in women aged 69–73 years, to 3.1% (95% CI 2.5–3.7) in women aged 84–88 years; and being 5.2% (95% CI 3.4–7.5) in women aged 89+ years based on the very small numbers. Among HPV-positive women, HPV16 was found in 20%; HPV18 in 5%; other HPV-types in 81%; and HPV16/18 in 24% (Table 4). These numbers add up to more than 100%, as a given woman can have more than one infection type. Among HPV-positive women, there was a slight increase in proportion of HPV16/18 positive from 24% in women aged 69–73 years, to 33% in women aged 84–88 years.

4. Discussion

4.1. Main result

The offer of cervical screening to elderly women was well received with 44% of women in their early 70s participating; 35% of women in their late 70s; and close to 20% of women in their early 80s. This was less than the overall 67% of women responding to invitation within

Table 2

Number of invited women, women with follow-up test, participating women, ineligible women due to death/emigration, ineligible women due to hysterectomy.

Age in years ^a	Birth cohort ^a	Invited women	Sample taken		Sample not taken		Eligible women ^b	Percent participants/eligible	95% confidence interval
			In follow-up	Participants	Dead/emigrated	Hysterect-omised			
69–73	1943–47	170,073	2257	60,921	3451	25,865	138,500	44.0%	43.7–44.3
74–78	1938–42	116,067	926	31,990	4088	18,225	92,828	34.5%	34.2–34.8
79–83	1933–37	80,524	262	12,057	5342	11,383	63,537	19.0%	18.7–19.3
84–88	1928–32	50,955	60	3122	6206	5697	38,992	8.0%	7.7–8.3
89+	1909–27	37,993	12	495	9441	2634	25,906	1.9%	1.7–2.1
Total		455,612	3517	108,585	28,582	63,804	359,763	30.2%	30.0–30.3

Notes.

^a 69–73 years defined as women born 1943–1947. Approximate age, as almost one fourth of women born in 1947 will have turned 70 years on 15 March 2017. Same principle applied for the other age-groups.

^b Invited women – (in follow-up + dead/emigrated + hysterectomized).

Table 3
Number of participants with adequate HPV-test, with positive HPV-test, and by HPV-type.

Age in years ^a	Participants					Women in follow-up				Total percent positive HPV-test	95% confidence interval
	All	Adequate HPV-test	Positive HPV-test	Percent positive	95% confidence interval	All	Adequate HPV-test	Positive HPV-test	Percent positive		
69–73	60,921	60,861	2621	4.3%	4.1–4.5	2257	2112	234	11.1%	4.5%	4.4–4.7
74–78	31,990	31,963	1322	4.1%	3.9–4.4	926	864	78	9.0%	4.3%	4.0–4.5
79–83	12,057	12,038	420	3.5%	3.2–3.8	262	239	21	8.8%	3.6%	3.3–3.9
84–88	3122	3116	91	2.9%	2.4–3.6	60	54	6	11.1%	3.1%	2.5–3.7
89+	495	492	25	5.1%	3.3–7.4	12	10	1	10.0%	5.2%	3.4–7.5
Total	108,585	108,470	4479	4.1%	4.0–4.2	3517	3279	340	10.4%	4.3%	4.1–4.4

Notes.

^a See definition Table 2.

the regular screening programme [6]. But it should be taken into account that almost half of women responding in the regular screening programme come after at least one of the two reminders, while no reminder was used in this special offer to elderly women.

In total, 4% of elderly women were HPV-positive, a proportion slightly decreasing across age-groups, and among the HPV-positive women 24% had HPV16/18.

4.2. Other studies

In the Central region, a number of women previously, erroneously exempted from invitation to screening were invited in 2013. At time of invitation, the group included 5976 women aged 70 years and above, of whom 8.1% were HPV-tested, and 4.9% (95% CI 3.2–7.2) of the tested women were HPV-positive [7]. This was well in line with the 4.3% (95% CI 4.1–4.4) found in this study of elderly women. The 2013-group was tested with the Cobas 4800 assay, which was also the predominant assay used in this study of elderly women. As only 8.1% of the target group were HPV-tested in the 2013-group as compared with 24.5% in the present study, the concordance between the HPV-positivity rates indicated that these rates seem to be robust to a potential selection bias.

Consecutive liquid-based cytology samples from 40,382 women collected in 2002–2005 from the pathology department in the Capital region were analysed with the Hybrid Capture 2® HPV-assay [8]. The HPV-positivity rates varied from 46% for women aged 20–23 years, decreased rapidly after the age of 35, and reached 5.7% (95% CI 4.4–7.3) for women aged 65+ years. Although this was an open age-group, the HPV-positivity rate here was well in accordance with an HPV-positivity rate of 6.0% (95% CI 4.2–8.2) found for 65–69 years old women in the 2013-study [7]. While the HPV-positivity rate thus declined rapidly after 35 years of age, a slowly declining rate was seen throughout the rest of the women's lives (Fig. 2).

As part of the National Social Life Health and Aging Project in the United States in 2005–2006, self-administered vaginal swab specimens were collected from 1010 women and tested with Hybrid Capture 2®. Mean age was 68 years, and 6% (95% CI 4.5–7.9) were HPV-positive

[9]. In a gynecology outpatient clinic in Sweden in 2013–2015, clinician-collected samples from 1051 women were tested with a multiplex real-time PCR-assay. Mean age was 68 years, and 4.1% (95% CI 3.0–5.5) were HPV-positive [10]. These results are in line with the Danish data.

4.3. Strengths and limitations

The number of invited women was 455,612, which was well in accordance with the number of 462,765 women aged 69 years and above in Denmark on 1 April 2017 [11], as almost one fourth of the women born in 1947 had turned 70 years before 15 March 2017. The Danish Patient Register became nationwide in 1978. As hysterectomy is a rare event before the age of 40 [12], we can assume to know the hysterectomy history for women born in 1938 or later, while the true hysterectomy rate for women born before 1938 is likely to be higher than recorded here.

We cannot rule out selection in participation. It was, however, noteworthy that the HPV-positivity rates for women aged 70 years and above corresponded well between our study where 25% of women participated and the 2013-study where only 8% participated. When we compare with other studies, we cannot rule out differences in results deriving from differences between HPV-assays. In the present study the majority of samples were tested by Cobas 4800 and a minority with BD Onclarity. In the Capital region data for women below age 70 (Fig. 2), Hybrid Capture 2® was used for the testing. However, in a split-sample study of 5072 consecutive liquid-based cytology samples from the Capital region collected in 2011, overall 20.4% tested positive on Hybrid Capture 2®, while 26.8% tested positive on Cobas 4800 [13], so if anything, the rates for elderly women are overestimated in this comparison.

4.4. Interpretation

To our knowledge this is the first population-based HPV-screening study offered to all women above the age of 69 years. We compared the HPV-prevalence in these elderly women with those available from

Table 4
Number of women with positive HPV-test by subtype.

Age in years ^a	Positive HPV	HPV-positive typed	HPV 16		HPV 18		HPV other		HPV 16/18
			Number ^b	% of positive with type	Number ^b	% of positive with type	Number ^b	% of positive with type	% of positive with type
69–73	2621	2611	499	19%	123	5%	2140	82%	24%
74–78	1322	1319	256	19%	56	4%	1075	82%	23%
79–83	420	420	86	20%	19	5%	331	79%	25%
84–88	91	91	25	27%	5	5%	66	73%	33%
89+	25	25	8	32%	1	4%	19	76%	36%
Total	4479	4466	874	20%	204	5%	3631	81%	24%

Notes.

^a See definition Table 2.

^b Numbers not mutually exclusive.

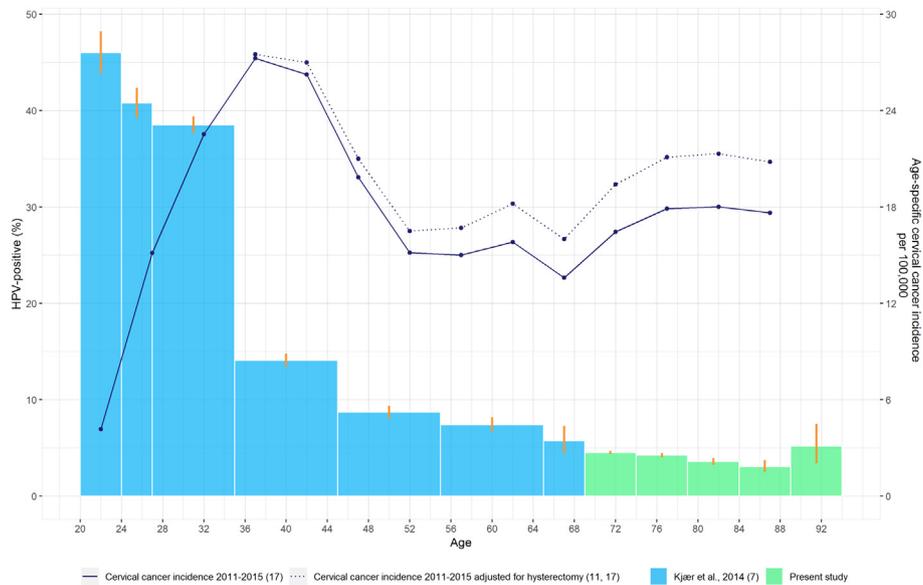


Fig. 2. Prevalence of high risk HPV-positivity in Danish women, aged 20–65 from 2002 to 2005 and aged 69+ from 2017, observed and adjusted¹ cervical cancer incidence 2011–2015.

younger age-groups of Danish women. After the age of 35 years, the HPV-prevalence decreased gradually with increasing age.

HPV-prevalence data from Northern Europe covering ages up to 65 + years have indicated a moderate rebound after menopause in women with normal cytology [14,15], a pattern not indicated in our data, although it should be noted that our data included results from all HPV-tested women as cytology was not part of the screening.

It has been hypothesized that HPV-prevalence and cervical cancer incidence would increase due to the effect of increasing exposure to HPV in the post-1945 cohorts [16]. In a United States survey from 2008 to 2011, 65% of women aged 35–39 reported to have had 5 or more sexual partners in their lifetime, while this percentage was 55% in women aged 55–60 [17]. Modelling of data from the United States National Health and Nutrition Examination Survey indicated a substantial increase in HPV prevalence in more recent birth cohorts [18]. When our samples were collected in 2017, women born in 1945 were 72 years old, and the HPV-prevalence in women aged 69–73 did not differ from the gradual decline with increasing age. Future data will show whether this pattern will change with the aging of upcoming generations.

One exception from the decreasing pattern in our data was the HPV-prevalence of 5.2% in women aged 89 and older, though based on very small numbers. It might be noted, however, that these women were born in the late 1920s and were young at the end of World War II, where Denmark had a record high number of sexually transmitted diseases [19].

Denmark is among the countries with a bipolar pattern in the age-specific incidence of cervical cancer (Fig. 2); both in the observed rates from NORDCAN from 2011 to 2015 [20], and in the rates corrected for number of hysterectomised women [12]. Our data did not support the hypothesis that the second peak in the bipolar pattern of cervical cancer incidence was related to an increase in active HPV-infection in older age. An alternative pathway for cervical cancer in old age might be reactivation of an existing HPV-infection, e.g. initiated by use of steroids suggested to increase the risk of HPV-persistence [21].

It is an attractive idea that another screen at 75 or 80 years in those who have not had 3 normal prior to 65 years might detect the interval cancers from persistent HPV. It should be noted, however, that an HPV infection may become undetectable at a late stage of the oncogenic process [22]; an observation supported by our data where the old age peak in cervical cancer incidence was not reflected in the HPV-prevalence pattern. At present, Danish women exit the regular screening program at age 60–64 with an HPV-test. The fact that 4% of women aged 69–73

were HPV-positive in the present study indicates a need for monitoring outcome of the exit-tests.

The further follow-up of the HPV-positive, elderly women will show whether the second peak is reflected in the detection of pre-cancerous lesions.

5. Conclusion

Invitation to HPV-screening was well received by elderly women with in total 30% of women 69 year and above participating. The overall HPV-prevalence was 4.3%. In combination with data from previous Danish studies, our data indicated a high HPV-prevalence up until the age of 35, where after a gradual decline of the HPV-prevalence was observed with increasing age.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ygyno.2019.04.680>.

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Roles and responsibilities

Elsebeth Lynge designed the study and drafted the manuscript. Petra Hall Viborg undertook the data analysis. Remaining authors organised the screening of elderly women in Denmark and were responsible for the data collection. All authors commented on the draft of the manuscript and approved the final version. All authors affirm that the manuscript is an honest, accurate and transparent account of the study being reported. No important aspects of the study have been omitted.

Conflict of interest

Berit Andersen received HPV-test kits from Roche and self-sampling kits from Axlab for a study. Tonje Johansen received HPV-test kits from Roche for a study. Elsebeth Lynge receives HPV-test kits from Roche for a screening trial. Remaining authors had no conflict of interest.

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