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Population-based primary HPV mRNA cervical screening compared with cytology screening

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ABSTRACT

Primary HPV screening for cervical cancer by HPV mRNA testing (Aptima) was implemented in January 2017, for women ≥30 through 70 years, in the Region of Skåne, Sweden. HPV positive samples underwent cytology assessment, and women with any degree of abnormal cytology were referred for colposcopy. The aim was to audit the primary HPV screening program, by comparing the cytology results to those of corresponding women (aged ≥30 through 65 years) screened with conventional cytology during 2016. Overall, HPV was detected among 7.0% (4433/63,055) of the women ≥30–70 years in the primary HPV screening program. Among a co-tested (cytology and HPV) subgroup aged 40–42 years (N = 5039), HPV was detected in 100% (28/28) of high-grade squamous intraepithelial lesions (HSIL) and atypical squamous cells of undetermined significance (ASCUS) where HSIL could not be excluded (ASC−H) (9/9), and in 80% (4/5) of cases of atypical glandular cells (AGC). Among women ≥30–65 years, the proportion ASCUS or worse (ASCUS+) was similar with cytology (3.52% [2016]) and primary HPV screening (3.70% [2017]). Only the proportion of ASC-H changed by the use of primary HPV screening, from 0.13% (2016) to 0.23% (2017) (p < 0.001). The colposcopy referral rate increased by 54% (3.70 vs 2.41%), when primary HPV screening was introduced. In conclusion, the implemented primary HPV screening approach demonstrated similar prevalence of ASCUS+ cytology as conventional screening. In addition, primary HPV screening decreased cytology assessments by 86% in our screening population of women 30 through 70 years taken into account the co-tested women.

1. Introduction

Human papillomavirus (HPV) may cause cervical cancer (zur Hausen, 2000). In many industrialized countries, screening programs to find the precursors of cervical cancer were implemented decades ago (in Sweden successively from 1966), and have been successful to prevent cancer (Gustafsson and Adami, 1990). HPV testing as a means to improve screening for cervical cancer was suggested already in the 1980s (Baker et al., 1987; Jenkins et al., 1996). Primary HPV screening has been shown to be more sensitive to detect high grade cervical intraepithelial neoplasia (CIN2+) and more efficient than cytology for prevention of cervical cancer, but it has a lower specificity (Cuzick et al., 2006; Cuzick et al., 1995; Bulkmans et al., 2007; Castle et al., 2011; Arbyn et al., 2012; Ronco et al., 2014; Wright et al., 2015). However, mRNA based methods seem to have higher specificity than DNA based methods (Arbyn et al., 2015; Haedicke and Iftner, 2016). The lower specificity for HPV-testing compared to cytology to detect CIN2+, has raised the need for cytological examination of HPV-positive samples, in order to avoid excessive colposcopy. Several triage strategies have been evaluated (Wright et al., 2015; Rijkaart et al., 2012). Swedish national guidelines recommend the use of HPV testing as a primary screening test for women ≥30 years (Swedish-Regional-Cancer-Centers, 2017). HPV positive samples then undergo cytological assessment by cytotechnologists. For women under 30 years of age, primary screening with cytology is recommended, since transient HPV infections are common in young women and primary HPV testing would cause unnecessary colposcopies and anxiety (Mittal et al., 2017). Several commercial assays for the detection of nucleic acids from HPV are available and have been validated for use in primary HPV screening (Arbyn et al., 2015; Haedicke and Iftner, 2016; Reid et al., 2015). One of the approved assays is the HPV mRNA assay (Aptima, Hologic) (Arbyn et al., 2015). Furthermore, longitudinal data, have shown that the Aptima HPV mRNA assay is non-inferior to HPV-DNA testing to detect HPV up to 7 years before development of CIN3+ (Forslund et al.,

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2019). In addition, recently Iftner et al., reported a high negative predictive value (99.7%) for absence of CIN3+ for the Aptima assay among women followed over 6 years (Iftner et al., 2019).

During 2017, several European countries, for example the Netherlands, the United Kingdom, and Italy, are in the process of implementing, or have implemented, primary HPV screening. In the Region of Skåne, Sweden, primary screening with the Aptima HPV mRNA assay commenced in January 2017. The aim was to audit the first year of our organized primary HPV screening, and to investigate the proportion of abnormal cytology diagnoses compared to that of traditional cervical cytology screening.

2. Materials and methods

Since 2017 all women between 23 and 70 years in the Region of Skåne regioare invited for cervical cancer screening every three to five years (five years for women over 50). Women attending screening at 64 years or older are not invited again but non-attenders from the final invitation receive yearly re-invitations until 70 years of age. Cervical cell samples are collected in Thinprep liquid based transport devices (Hologic) by midwifes. Cytology and HPV testing are performed at Clinical Pathology Lund, Sweden. Cytology diagnoses are set according to the Bethesda system by cytotechnologists who have knowledge of the HPV test results.

The present audit was register-based and utilized the local cytology registry to identify screened women.

For Aptima analysis, 1 mL of the sample was automatically transferred (Tomcat, Hologic) to an Aptima Specimen Transfer Tube (prefilled with 2.9 mL buffered solution). The Aptima HPV assay (Hologic) was performed according to the manufacturer's instructions using the Panther platform (Hologic).

2.1. Primary HPV screening

Our primary HPV screening starts at ≥30 years. For HPV positive samples, reflex cytology is performed, and if the cytology is normal the woman is invited for a new screening test three years later, whereas if abnormal cells of atypical squamous cells of unknown significance or worse (ASCUS+) are found, she will be referred for colposcopy. If the HPV test is negative, no cytology is performed, and the woman returns to the screening program.

During 2017 (12 months, from January 23, 2017 through January 21, 2018) 63,055 women 30–70 years were analysed for presence of HPV within the primary HPV screening (Fig. 1a).

2.2. Co-testing

In order to assess the frequency of cases displaying cellular changes in the absence of an active HPV infection, women aged 40–42 years constituted a control group where both cytology and HPV testing was performed. During 2017 (from February 1st 2017 through February 28, 2018) 5039 women were co-tested (Fig. 1a).

2.3. Primary HPV screening versus cytology screening

On January 23, 2017, our region changed from cytology screening to primary HPV screening. Thus, it was possible to compare proportions of abnormal cytology diagnoses between the two strategies over two successive 12 month periods. For both periods we included women 30–65 years of age who attended the screening program. Data from cytology screened samples (N = 45,906) were collected from 2016 (from January 21, 2016 through January 22, 2017) (Fig. 1b). Data from these samples were separated from the samples not belonging to the screening program by special registration numbers in the pathology data base. Data were obtained from primary HPV screened samples during 2017 (from January 23, 2017 through January 21, 2018) (N = 49,842) (Fig. 1b). The cytology screened and the primary HPV screened women had a similar age distribution (Supplementary materials, Table 1).

A comparison of proportion of women referred for colposcopy during cytology screening 2016 and primary HPV screening 2017 was performed. We estimated the total number of referral for colposcopy during 2016 to be 1105. During 2016 a triage was used where women with ASCUS or low-grade squamous intraepithelial lesion (LSIL) were HPV-mRNA tested. Women with ASCUS or LSIL were referred for colposcopy only if they were also HPV positive, otherwise they were instead re-invited for new cytology and HPV testing after 1 year. Therefore, when calculating the number of colposcopies during 2016, HPV negative ASCUS (N = 448, 56.7% of 790) and LSIL (N = 65, 13.5% of 481) cases were subtracted from the total number of ASCUS+ cases (N = 1618) (Supplementary materials Tables 2 and 3).

2.4. Statistical analysis

Chi-square with Yates correction was used for analysis of differences between distribution of cytology diagnoses among primary HPV

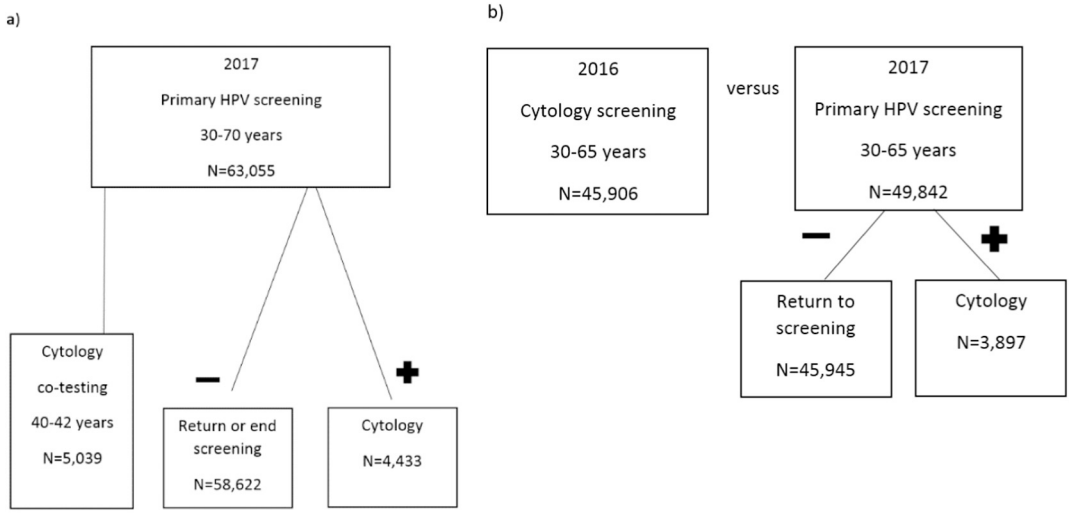

Fig. 1. Overview of included samples in the audit. a) Primary HPV screening. b) Comparison of cytology screening year 2016 and primary HPV mRNA screening 2017. + and − indicate HPV mRNA positive and negative results, respectively.

Table 1
HPV prevalence by primary HPV screening stratified by age groups.

Age group	HPV positive samples, #	HPV-tested samples, #	HPV positivity, %
30–39	1937	17,322	11.18
40–49	1121	16,079	6.97
50–65	853	16,441	5.19
66–70	522	13,213	3.95
Total 30–65	3911	49,842	7.85
Total 30–70	4433	63,055	7.03

screening and by cytology screening using GraphPad Software (https://www.graphpad.com/quickcalcs/contingency2/).

Pearson's Chi-square test was used for analysis of trends for distribution of cytology diagnoses between age groups by EpiTools epidemiological calculators (http://epitools.ausvet.com.au/content.php?page=trend). p-Values < 0.05 were considered significant.

2.5. Ethical approval

The audit was approved by the Ethical Review Board in Lund (Dnr 2013/390).

3. Results

3.1. HPV prevalence and cytology abnormalities

During 2017, the overall HPV mRNA prevalence was 7.0% (4433/63,055) among the population based screened women aged 30 to 70 years. The HPV prevalence decreased with increasing age, from 11.2% to 3.95% among women aged 30–39 and 66–70 years, respectively (Table 1) (Fig. 2). Among the screened women, 3.13% (1976/63,055) had abnormal cytology of ASCUS+.

For the HPV positive women a significant increased trend of normal cytology by age was observed, with proportions of 49% for women aged 30–49 years, 66% of 50–65 year old, and 74% of women aged 66–70 ($P < 0.0001$) (Supplementary materials, Table 4).

For cytological abnormalities among the HPV positive women, significant downward trends by corresponding age groups were present for ASCUS ($P = 0.0152$) and LSIL ($P < 0.0001$) (Supplementary materials, Tables 5 and 6). For atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H) a significant downward trend was observed from 30 to 39 years of age up to 66–70 years ($P = 0.0174$) (Supplementary materials, Table 7). For HSIL, its proportion was lower for HPV positive women aged 50–70 years compared to those at 30–49 years ($P < 0.0001$) (Supplementary materials, Table 8).

Table 2
HPV prevalence among co-tested women 40–42 years old, stratified by cytology.

Cytology diagnosis	Cytology, #	HPV negative, #	HPV positive, #	HPV positive, %
Normal	4787	4599	188	3.9
ASCUS	136	57	79	58.1
LSIL	62	6	56	90.3
ASC-H	8	0	8	100
HSIL	29	0	29	100
AGC	5	1	4	80
Unsatisfactory	12[a]	12	0	0
Total	5039	4675	364	7.22

[a] 0.24% (12/5039) had unsatisfactory cytology. ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesions; HSIL: high-grade squamous intraepithelial lesions; ASC-H: atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; AGC: atypical glandular cells.

3.2. Co-testing

The HPV prevalence in the age group of 40–42 years was 7.2% (364/5039). All women with ASC-H ($N = 8$) and high-grade squamous intraepithelial lesion (HSIL) ($N = 29$) were HPV-positive. For women with atypical glandular cells (AGC), 4 out of 5 were positive in the HPV test. In contrast, HPV was detected in 3.9% (188/4787) of women with normal cytology, whereas it was detected in 58.1% (79/136) and 90.3% (56/62) of women with ASCUS and LSIL, respectively (Table 2). The sensitivity was 97.6% (41/42) for the HPV test to find severe dysplasia, here defined as ASC-H, HSIL or atypical glandular cells (AGC). The specificity was 93.5% (4662/4985) (i.e. the proportion of HPV negative results defined as normal-, ASCUS- or LSIL-cytology) (Table 2).

Overall, within the primary HPV screening 4433 cytology evaluations were performed, and in addition 4675 samples ($N = 5039$ minus those with HPV mRNA positive tests $N = 364$) were assessed in the co-testing group of women with HPV mRNA negative tests. Thus, 9108 cytology assessments (14%) were performed among the 63,055 women while for 86% of the samples no cytology was done.

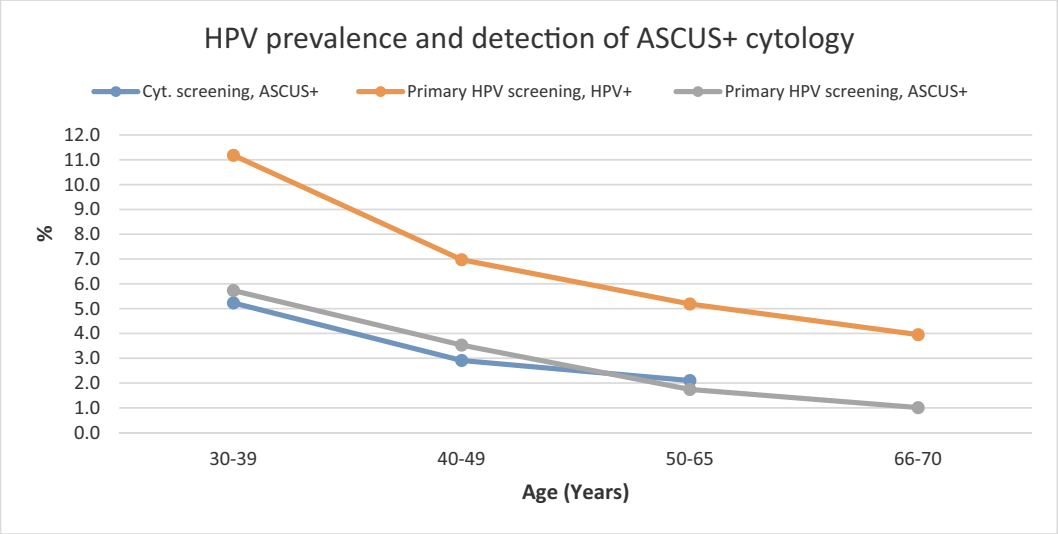

Fig. 2. Prevalence of HPV-mRNA stratified by age groups (orange), and prevalence of ASCUS+ cytology by the use of cytology screening year 2016 (blue) and by primary HPV screening 2017 (grey). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Cytology results with cytology screening 2016 and with primary HPV-screening 2017 of women 30–65 years.

	Cytology screening, 2016		Primary HPV screening, 2017			
	Cytology, #	Cytology, %	HPV+, #	HPV-, #	Proportion of total number of HPV-tested samples,%	*P*-value
HPV	–	–	3897	45,945		
Cytology diagnosis						
Normal	44,147	96.17	2055	–	96.30[a]	n. s
Atypia in cells of uncertain origin	22	0.05	4	–	0.01	n. s
ASCUS	790	1.72	887	–	1.78	n. s
LSIL	481	1.05	572	–	1.15	n. s
ASC-H	60	0.13	115	–	0.23	< 0.0001
HSIL	236	0.51	235	–	0.47	n. s
AGC	22	0.05	19	–	0.04	n. s
Cancer	7	0.02	10	–	0.02	n. s
Unsatisfactory	141	0.31	14	–	0.03[b]	–
Total cytology	45,906	100	3897	–	–	–

[a] Cytology was not performed for HPV mRNA negative samples. Percent was calculated as follows: (Count of HPV mRNA negative samples N = 44,945 + count normal cytology of HPV positive samples *N* = 2055)/count of all HPV mRNA tested samples N = 49,842.

[b] Percent of cytology samples that were classified unsatisfactory (*N* = 14) among all HPV tested samples. Please note that cytology was only performed for HPV mRNA positive samples (*N* = 3897). ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesions; HSIL: high-grade squamous intraepithelial lesions; ASC-H: atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; AGC: atypical glandular cells.

3.3. Primary HPV screening versus cytology screening

The proportion ASCUS+ was 3.52% and 3.70% with cytology and primary HPV screening, respectively. Concerning cytology grade, only the proportion of ASC-H cytology changed by the use of primary HPV screening, from 0.13% to 0.23% ($p < 0.0001$) (Table 3). The proportion of ASCUS+ cytology decreased with increasing age, from 5.23% to 2.10% among cytology screening, and from 5.73% to 1.74% by primary HPV screening (Table 4; Fig. 2).

Among women 30–65 years, the referral rate for colposcopy increased by 54%, from 2.41% (1105/45,906) to 3.70% (1842/49,842) when primary HPV screening replaced primary cytology screening ($P < 0.0001$) (Table 4).

4. Discussion

To the best of our knowledge we report the first results of an implemented population based primary HPV screening that used an automated platform for detection of HPV mRNA. The HPV prevalence was 7.0% among women aged 30 to 70 years. In comparison to screening by the use of cytology only, we observed a similar proportion of women with ASCUS+ (3.70% vs 3.52%) aged 30 to 65 years after introduction of the primary HPV screening. Among a sub-set of co-tested screening women aged 40–42 years, the sensitivity was 97.6% and the specificity 93.5% for the HPV mRNA test to detect severe dysplasia. Furthermore, the overall cytology assessment decreased by 86% within our primary HPV screening.

The observed HPV mRNA prevalence (7.0%) was similar to other screening studies that used Aptima, such a Dutch study (7.6%) of women aged 29–63 years (Huijsmans et al., 2016), an USA study (9.1%) of women aged 30+ (Chorny et al., 2018), among Italian women (7.0%) aged 25–64 years (Maggino et al., 2016), and in a German study (4.9%) of women aged 30–60 years (Iftner et al., 2015).

Although a limited amount of cervical samples were co-tested (*N* = 5039) we found as expected high sensitivity (97.6%) and specificity (93.5%) of the HPV mRNA test to detect severe dysplasia, supporting the reliability of the HPV mRNA assay for primary HPV screening. This is in agreement with Aptima assays performed on other screening populations, where the mean corresponding sensitivity and specificity for four studies were 97.4% and 90.4%, respectively (Haedicke and Iftner, 2016).

The current approach of primary HPV screening demonstrated comparable proportions of ASCUS+ between cytology (3.52%) and primary HPV screening (3.70%). Similar to another study, the proportion of our ASCUS+ cytology of HPV mRNA positive cases (47%) was comparable to an Italian study of primary HPV mRNA screening (53%) which also included women aged 25–29 years (Maggino et al., 2016).

Concerning abnormal cytology such as ASCUS and LSIL, women with these lesions will only be identified with the current screening strategy if they are HPV mRNA positive. Since we observed that about 57% of ASCUS and 14% of LSIL were HPV mRNA negative among our screening women aged ≥30 in year 2016 one could expect that the proportion of ASCUS in 2017 to be about half of that in 2016, and the LSIL diagnosis to decrease by about 14%. But instead, there was no significant difference in these diagnoses between 2016 and 2017. It is obvious that an increased proportion of HPV mRNA positive women

Table 4
Comparison of ASCUS+ cytology by cytology screening year 2016 and by primary HPV screening 2017 stratified by age groups.

	Cytology screening, 2016			Primary HPV screening, 2017			
Age group	ASCUS+, #	Total cytology, #	ASCUS+, %	ASCUS+, #	Total cytology, #	ASCUS+, %	*P*-value
30–39	874	16,710	5.23	993	17,322	5.73	0.0444
40–49	471	16,171	2.91	563	16,079	3.50	0.0030
50–65	273	13,025	2.10	286	16,441	1.74	0.0289
66–70	–	–	–	134	13,213	1.01	–
Total 30–65	1618	45,906	3.52	1842	49,842	3.70	0.1616
Total 30–70	–	–	–	1976	63,055	3.13	–
Referral to colposcopy 30–65 years	1105[a]	45,906	2.41[a]	1842	49,842	3.70	< 0.0001

[a] Due to negative results of HPV-triage (HPV-mRNA) of women with ASCUS and LSIL aged 30–65 years, we estimated that 513 subjects of the 1618 women were withheld colposcopy at base line (1618–513 = 1105, ASCUS + LSIL) during cytology screening period 2016.

were diagnosed with ASCUS, but also with LSIL, in 2017 compared to that of 2016. The absence of an expected difference in the proportions of these diagnoses between 2016 and 2017 could be due to the fact that our cytotechnologists knew that only HPV-positive screening women were subjected to cytology (except the co-testing subgroup of 40–42 year old women). Such knowledge of HPV status has been demonstrated to result in a higher rate of upgrading to ASCUS or worse but did not improve sensitivity for detection of disease (Doxtader et al., 2017). However, we have previously demonstrated that the used HPV mRNA assay has high sensitivity for future CIN2+ among women with these minor cytological abnormalities (Johansson et al., 2015). In addition, among women with ASCUS and LSIL, the assay showed high negative predictive value for future CIN3, indicating that HPV-mRNA-negative women are at low risk of progression to high grade CIN (Johansson et al., 2015). Notably, even for the majority (91%) of HPV positive women with ASCUS or LSIL, the HPV infection will be cleared within 6–24 months (Plummer et al., 2007), and about 70% of ASCUS and low grade lesions regress spontaneously (Alanen et al., 1998).

Interestingly, among our HPV mRNA positive women, we observed increased proportions of normal cytology with older age. An explanation for this could be, that for a substantial proportion of HPV-positive older women identified by the primary HPV screening, HPV-positivity may originate from a few shredded cells of a retracted transformation zone which may be difficult to reach and obtained cytology samples are diagnosed as normal cytology. However, HPV testing will most likely improve the chances to find women above 50 years that are in risk of developing severe cervical dysplasia. Interestingly, Hermansson et al., recently showed that persistently HPV-infected older women can have a normal cytology, despite histological diagnoses of HSIL in subsequent cones or biopsies (Hermansson et al., 2018). Furthermore, the Swedish guidelines for prevention of cervical cancer (Regional Cancer Centers in collaboration) recently recommended that HPV16/18 positive screening women with normal cytology should be invited for re-testing after 18 months, and if persistently HPV-infected the women should be referred for colposcopy, regardless of the cytology. Re-tested women with HPV negative results and with normal cytology will be returned to normal screening.

Notably, among our women aged 50–65 years we observed a slightly lower proportion of ASCUS+ by primary HPV screening (1.75%) compared to cytology screening (2.10%). In this age group, it was particularly equivocal cytology (ASCUS) that demonstrated a tendency to be less frequently detected by the primary HPV screening strategy (0.93%) compared to cytology screening (1.17%). An explanation could be the same as above: for older women, cytology is less reliable, whereas HPV testing is more sensitive and only requires a few infected cells to be positive. For this age group, as well as for the entire screening population, the number of HPV positive ASCUS cases did not decrease between 2016 (30–65 years: ~340 cases) and 2017 (30–65 years: 887 cases), since a substantial proportion of women with ASCUS cytology in 2016 tested HPV triage negative. However, the proportion of mild atypia such as ASCUS (18%) among our HPV mRNA positive screening cases aged 50–65 years was similar to that of a Finish study of primary HPV DNA screening, where 19% of ASCUS was seen among HPV positive women 50–64 years (Leinonen et al., 2013), indicating comparable proportions of mild cytological abnormalities among the HPV positive women in the older ages of the screening population.

Concerning colposcopy and primary HPV screening, we observed a 54% higher proportion of referrals of 30–65 year old women during the primary HPV screening period (3.70 vs 2.41%). However, for this age group we estimated that the average cost for screening and colposcopy per women was only slightly increased from €49.6 to €54.2 during 2016 and 2017, respectively (Supplementary materials, Tables 9 and 10). Furthermore, the screening cost in our county is expected to decrease when the length of the routine screening interval will be extended to 7 years among women negative for HPV. In conjunction with implementation of the primary HPV screening in our region, the program was also extended to 70 years, instead of 65 years in the previous cytology screening period. The number of 30–65 year old women participating in the screening program has also increased from 2016 to 2017. Thus, as an example, in our setting with about 63,000 women aged 30–70 years, there will be about 2000 colposcopy referrals yearly, since 3.13% of the women are HPV positive and have ASCUS+ cytology (Table 4). This is an increase of colposcopies by about 80% compared to 2016, when an estimated number of 1105 colposcopies were performed (Table 4), meaning that about 900 additional colposcopies have to be performed in our region every year, as a consequence of the joint effects of introduction of HPV-based primary screening and an extended age span of the tested population. Our increase of the colposcopy referral rate of 54% among 30–65 year old women, compared to conventional screening, was substantially less than that of HPV-mRNA testing in the Venice area where the corresponding referral rate doubled (Maggino et al., 2016). A significant difference is that the Venice study commenced primary HPV screening at the age of 25, where the proportion of positive HPV-mRNA test was 16% among 25–29 year old women (Maggino et al., 2016).

5. Conclusions

We performed an audit of the implemented primary HPV mRNA screening program in one county (Skåne) of Sweden. In comparison to our previous cytology screening, we observed that the proportion of ASCUS+ was similar, and that the colposcopy referral rate increased by 54% among women aged 30–65 years. In addition, our primary HPV screening strategy has greatly reduced the need for cytology assessment, with 86% reduction among screening women aged 30 to 70 years taken into account the co-tested women. Furthermore, the used Aptima Panther system is highly automated, which decreases the work load.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2019.04.021.

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