Age-specific and genotype-specific carcinogenic human papillomavirus prevalence in a country with a high cervical cancer burden: results of a cross-sectional study in Estonia

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ABSTRACT

Objectives To describe age-specific and type-specific carcinogenic human papillomavirus (HPV) prevalence prior to large-scale effect of HPV vaccines in Estonia and to analyse the risk factors associated with carcinogenic HPV.

Design Cross-sectional study using self-administered questionnaire and self-collected vaginal swabs for detection of HPV infection.

Setting Estonian Biobank database.

Participants Stratified random sample of women aged 30–33, 57–60 and 67–70 years living in one of the three largest counties in Estonia. Of 3065 women approached, 1347 (43.9%) returned questionnaires and specimens for HPV DNA detection.

Outcome measures HPV prevalence and fully adjusted ORs with 95% CIs for risk factors.

Results HPV prevalence was highest among women aged 30–33 years (18.7%; 95% CI 15.8 to 21.9) followed by those aged 67–70 years (16.7%; 95% CI 12.4 to 22.0) and 57–60 years (10.2%; 95% CI 7.8 to 13.3). HPV16 and HPV68 were the most common among women aged 30–33 years (both 4.0%; 95% CI 2.7 to 5.9), and HPV68 was the most common among women aged 57–60 years (2.8%; 95% CI 1.5 to 4.7) and 67–70 years (6.4%; 95% CI 3.6 to 10.4). Vaccination with nonavalent vaccine would have halved the carcinogenic HPV prevalence among women aged 30–33 years. The odds of infection with carcinogenic HPV were higher among women with six or more sexual partners among younger (OR 2.99; 95% CI 1.54 to 5.81) and older (OR 3.80; 95% CI 1.25 to 11.55) women and lower (OR 0.35; 95% CI 0.17 to 0.72) among younger married women.

Conclusions This study demonstrated U-shaped age-specific genotype profile of carcinogenic HPV prevalence, indicating that public health providers should focus on developing exit strategies for the cervical cancer screening programme in Estonia with a possible extension of HPV testing beyond the current screening age of 65 years. Generalisability of the findings of this study may be affected by the low response rate.

INTRODUCTION

Human papillomavirus (HPV) is estimated to be one of the most common sexually transmitted infections worldwide and persistent infection with carcinogenic types of HPV, that is, HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, is a major cause of cervical cancer (CC). Among these HPV types, HPV16 has the highest carcinogenic potential, causing half of CCs. Worldwide, approximately 70% of CCs are caused by HPV16 and HPV18 genotypes.

The incidence of CC varies among European countries, reflecting differences in the baseline prevalence, risk factors, screening and HPV vaccination policies. In countries with effective CC screening, CC incidence is decreasing. In Estonia, the national CC screening programme with Pap test and targeting women with valid
health insurance aged 30–55 every 5 years was introduced in 2006. Despite the implementation of the organised CC screening programme, the CC incidence rate in Estonia is still increasing, with one of the highest rates in Europe. According to the Global Cancer Observatory, the estimated age-standardised (world) incidence rate of CC in Estonia in 2020 was 18.5 per 100 000 inhabitants compared with that in Europe of 10.7 per 100 000 inhabitants. This is comparable with other Baltic countries (Latvia 18.4, Lithuania 18.7 per 100 000) and some other Eastern European countries (Hungary 17.2, Serbia 18.7, Slovakia 16.6 per 100 000) but is much higher than in Scandinavian countries (Finland 5.2, Denmark 10.2, Sweden 10.4, Norway 12.0 per 100 000).

Since 2021, the exit age for the screening programme was increased from 55 to 65 years and the HPV test was introduced to replace the Pap test in primary screening in Estonia.

Improving the participation of non-attenders in CC screening programmes should be a public health priority. HPV self-sampling method proved to have a good acceptability of HPV testing, and positive attitudes towards HPV diagnostic procedures by the women, and good concordance in the detection of carcinogenic HPV compared with cervical samples. Also, several studies have shown that offering self-sampling can lead to increased participation rates in CC screening and has been implemented already in many countries (eg, the Netherlands, Australia, Finland). HPV self-sampling showed significant increase in CC screening participation and high acceptance in Estonia as well and it has been offered as an option in CC screening programme in addition to clinician-obtained cervical sample collection since 2021. The efficient follow-up of screening of positives requires, however, careful planning and knowledge about the prevalence of HPV genotypes.

Prophylactic HPV vaccines have been introduced in many countries with the objective of eliminating viral infection and reducing the risk of CC. A bivalent vaccine targets HPV16 and HPV18, a quadrivalent vaccine additionally targets HPV6 and HPV11, and a nonavalent vaccine further targets HPV31, HPV33, HPV45, HPV52, HPV58. In Estonia, the national HPV vaccination programme for 12 to 14-year-old girls started in 2018, which highlights the importance of monitoring both the HPV-type-specific prevalence and associated factors among women. Risk factors associated with HPV infection, and progression to malignant lesions, are well known, including sociodemographic and behavioural factors such as marital status, ethnicity, smoking, early age of sexual debut, multiple lifetime sexual partners and long-term hormonal contraceptive usage.

To inform CC prevention strategies in Baltic countries and Eastern Europe, there is an urgent need to increase the body of knowledge about the HPV genotype distribution to improve the understanding of the expected effect of HPV vaccination on the HPV genotype distribution and to develop follow-up algorithms for women with positive HPV tests in newly introduced HPV screening programmes.

The objective of the study was to describe the age-specific and genotype-specific carcinogenic HPV prevalence among women in Estonia and to analyse the risk factors associated with carcinogenic HPV.

**METHODS**

**Study design**

A cross-sectional study using a self-administered survey and self-collected vaginal swabs for high-risk HPV detection was carried out among 30 to 33, 57 to 60 and 67 to 70-year-old women in Estonia from October 2020 to May 2021 as a part of the project ‘Towards elimination of cervical cancer: intelligent and personalized solutions for cancer screening’.

**Setting**

The sample basis for this survey was the Estonian Biobank (EstBB), which is a population-based biobank with a current cohort size of more than 207 000 individuals closely reflecting the age, gender and geographic distribution of the adult Estonian population. Considering that approximately 20% of the adult population in Estonia has joined the EstBB, this database is representative of both the absolute and relative number of participants as a proportion of the total population.

**Sampling and participants**

Stratified random sampling from the list of EstBB female participants was carried out. The sample frame consisted of 30 to 33, 57 to 60 and 67 to 70-year-old women living in one of the three largest counties (Harjumaa, Tartumaa, Ida-Virumaa) in Estonia (n = 17 351). Women who had undergone a hysterectomy (n = 87) were excluded from the sample.

Sample size calculations assumed a high-risk HPV prevalence of 20% among women aged 30–33 years, 10% among women aged 57–60 years and 5% among women aged 67–70 years, a margin of error of 3%, and a non-response rate of 55%, requiring a total of 1715 women aged 30–33 years, 850 women aged 57–60 years and 500 women in the oldest age group.

Of the women (n = 3065) invited to participate in the study, 1347 returned a completed questionnaire and vaginal sample. The overall response rate was 43.9% (37.5%, 55.3% and 46.8% among women aged 30–33, 57–60 and 67–70 years, respectively). In this study, non-attenders were those women who returned only a completed questionnaire or vaginal sample, those who refused to participate in the study, and those who did not answer the invitation letters or were not available. A flow-chart of the data collection is shown in figure 1.

**Data collection**

The data used in this study was based on a cross-sectional postal and web-based survey that collected individual-based data on risk factors for carcinogenic HPV.

All eligible women were approached using the following study materials: all women received the first invitation letter; and potential participants received the informed...

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Eligible women in Estonian Biobank (EstBB)

30–33-years-olds
n=7145

57–60-years-olds
n=5998

67–70-years-olds
n=4208

Randomly selected initial sample size

30–33-years-olds
n=1715

57–60-years-olds
n=850

67–70-years-olds
n=500

Electronic or paper invitation were sent to all potential participants

Refused
n=47

Refused
n=74

Refused
n=104

n=1668

n=776

n=396

Study materials were sent to those consented to participate and to all non-responders

Final study population n=1347
(sent back questionnaire and swab sample)

n=643
n=470
n=234

Figure 1 Flowchart for data collection.

consent form, questionnaire and self-sampling kit for HPV DNA detection with instructions for collecting the specimen. Self-sampling compares favourably with cervical sampling provided by clinicians11 and has shown feasibility and good acceptance among long-term non-attenders in CC screening in Estonia.15

An invitation letter was sent by mail or email to disclose the study information, explain the voluntary nature of participation, and to specify the language (Estonian or Russian) and the preferred way (paper or electronically) to receive further materials.

Women who agreed or did not refuse (did not respond to the invitation letter) to participate in the study were sent two copies of the informed consent form, the study package with a 51-item structured self-administered questionnaire (paper or web-based as per the participant’s preference) based on standardised study items and questions from established survey instruments,28 and a self-sampling dry vaginal swab kit (FLOQSwab, Copan) with instructions for collecting the specimen. The questionnaires and vaginal swabs were mailed back to the researchers in separate prepaid and preaddressed envelopes. All non-responders were sent additional study materials as a reminder 1 month later. Those who still did not respond were contacted by phone 1 month later.

HPV testing procedure

Vaginal swabs were HPV genotyped in the accredited laboratory certified for the national cancer screening programme. The vaginal swabs were held for up to 3 days at 4°C prior to DNA extraction and HPV was genotyped within 5 days from receiving at the lab. The material from swab specimens was suspended in 1 mL 1x PBS. The laboratory personnel were not informed about the age of the respondents.

DNA was extracted using the Roche MagNAPure96 system with the Roche Small Volume Kit according to the manufacturer’s instructions (200 µL as input volume
and 100 µL of NA extraction volume). Amplification of the human β-globin gene was performed to confirm the integrity of the DNA in the samples.

HPV genotyping
Samples were analysed using a clinically validated ISO 15189:2012 certified high-risk HPV DNA targeting assay based on multiplex-PCR and Luminex hybridisation (Luminex, Austin, Texas, USA) that detects 16 individual HPV types: HPV16, HPV18, HPV31, HPV33, HPV35, HPV51, HPV52, HPV53, HPV56, HPV58, HPV59, HPV66, HPV68, HPV82. No inadequate results were detected.

Study variables
Questionnaire-based data
Information on sociodemographic (ethnicity, marital status, education) and behavioural factors (current sexual activity, number of sexual partners during lifetime, last visit to gynaecologist, use of hormonal contraception) was used.

HPV genotyping
Sixteen individual HPV types were determined: HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV53, HPV56, HPV58, HPV59, HPV66, HPV68, HPV82.

Vaccine-targeted carcinogenic HPV
Carcinogenic HPV types included in the bivalent vaccine were HPV16, HPV18 and carcinogenic HPV types included in the nonavalent vaccine were HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, HPV58.

Statistical analysis
The genotype-specific, carcinogenic HPV, possibly carcinogenic HPV and vaccine-targeted carcinogenic HPV prevalence were estimated irrespective of potential coinfections. The HPV prevalence with corresponding 95% CIs were estimated separately for women aged 30–33, 57–60 and 67–70 years by dividing the number of carcinogenic HPV types in each age group by the number of tested specimens in the age group, that is, \( n = 643 \), \( n = 470 \) and \( n = 234 \), respectively.

HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV53, HPV56, HPV58, HPV59, HPV66, HPV68 and HPV82 were grouped together as possibly carcinogenic. To assess carcinogenic HPV prevalence in a hypothetical setting, it was assumed that vaccine-targeted HPV types were either married (41.9%) or cohabiting (27.9%).

RESULTS
Description of participants
Among the 1347 participating women, 47.7% (\( n = 643 \)) were 30–33 years old, 34.9% (\( n = 470 \)) were 57–60 years old and 17.4% (\( n = 234 \)) were 67–70 years old. Of the sample, 82.1% were Estonians and 17.9% non-Estonians (mainly Russians). A total of 58.7% had higher, 39.5% had secondary and 1.8% basic education and two out of three participants were either married (41.9%) or cohabiting (27.9%).

Prevalence of carcinogenic HPV and possibly carcinogenic HPV
The prevalence of carcinogenic HPV was the highest at 18.7% (95% CI 15.8 to 21.9) in women aged 30–33 years, 16.7% (95% CI 12.4 to 22.0) in women aged 67–70 years and 10.2% (95% CI 7.8 to 13.3) in women aged 57–60 years.

The prevalence of possibly carcinogenic HPV was higher among women aged 57–60 years (6.4%; 95% CI 4.5 to 9.0) and 67–70 years (6.4%; 95% CI 3.9 to 10.4) and lower among women aged 30–33 years (5.4%; 95% CI 3.9 to 7.5).

Prevalence of genotype-specific carcinogenic HPV and possibly carcinogenic HPV
Among women aged 30–33 years, HPV16 and HPV56 were the most common HPV types (4.0%; 95% CI 2.7 to 5.9), followed by HPV52 (2.2%; 95% CI 1.2 to 3.6); among women aged 57–60 years, HPV68 was the most common (2.8%; 95% CI 1.5 to 4.7), followed by HPV56 (1.9%; 95% CI 0.9 to 3.6), and HPV31 (1.5%; 95% CI 0.6 to 3.0). HPV68 was also the most common type among women aged 67–70 years (6.4%; 95% CI 3.6 to 10.4), followed by HPV31 (3.0%; 95% CI 1.2 to 6.1), and HPV51 (2.1%; 95% CI 0.7 to 4.9) (figure 2).

Of the remaining three possibly carcinogenic HPV types, HPV53 was the most prevalent in all age groups among women aged 30–33 years (3.0%; 95% CI 1.8 to 4.6), among women aged 57–60 years (4.9%; 95% CI 3.1 to 7.3) and among women aged 67–70 years (5.6%; 95% CI 3.0 to 9.3) (figure 2).

Carcinogenic HPV types targeted by HPV vaccines
The combined prevalence of HPV types targeted by bivalent HPV vaccines among women with carcinogenic HPVs...
was 4.7% in the age group of 30–33 years, 1.9% in the age group of 57–60 years and 1.3% in the age group of 67–70 years (Table 1). The combined prevalence of HPV types targeted by nonavalent HPV vaccines among women with carcinogenic HPVs was 11.7% in the age group of 30–33 years, 4.5% in the age group of 57–60 years, and

Table 1  Prevalence of carcinogenic HPV*, carcinogenic HPV types targeted by HPV vaccines, and hypothetical prevalence of carcinogenic HPV types after removing those targeted by HPV vaccines among women in Estonia, by age group, in 2020

<table>
<thead>
<tr>
<th>Characteristics</th>
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<td>Carcinogenic HPV types targeted by HPV vaccines</td>
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<td>Bivalent 16, 18</td>
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<td>9.4 to 14.4</td>
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<td>Prevalence of carcinogenic HPV types after removing those targeted by HPV vaccines</td>
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<tr>
<td>Bivalent 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68</td>
<td>14.9</td>
<td>12.4 to 17.9</td>
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<td>Nonavalent 35, 39, 51, 56, 59, 68</td>
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*The prevalence of carcinogenic HPV women aged 30–33, 57–60 and 67–70 years was calculated from the number of carcinogenic HPV types in each age group divided by the number of tested specimens in those age groups.
HPV, human papillomavirus.
5.6% in the age group of 67–70 years. In a hypothetical scenario after successful immunisation, in the age group of 30–33 years, the overall prevalence of carcinogenic HPV was reduced from 18.7% to 14.9% when no positivity to HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, HPV58 was assumed; in the age group of 57–60 years, the prevalence was reduced from 10.2% to 9.6% and 7.0%, respectively; and in the age group of 67–70 years, the prevalence was reduced from 16.7% to 16.2% and 15.0%, respectively.

Sociodemographic and behavioural factors associated with carcinogenic HPV

In the bivariate analysis, carcinogenic HPV was significantly (p<0.2) associated with marital status, education, current sexual activity and the number of lifetime sexual partners among women in the age group of 30–33 years; with marital status and the number of lifetime sexual partners in the age group of 57–60 years, and with ethnicity and number of lifetime sexual partners in the age group of 67–70 years. No differences were found in the prevalence of carcinogenic HPV by the date of the last visit to a gynaecologist or use of hormonal contraceptives in any age group (online supplemental table 1).

The final fully adjusted multivariate model among 30 to 33-year-old women showed that the odds of having carcinogenic HPV was significantly (p<0.05) lower (OR 0.35; 95% CI 0.17 to 0.72) among those who were married (vs not having a partner) and significantly higher (OR 2.99; 95% CI 1.54 to 5.81) among those with six or more sexual partners during their lifetime (vs 1–2 sexual partners) (online supplemental table 1).

No significant associations were found between carcinogenic HPV and sociodemographic and behavioural factors among women aged 57–60 years (online supplemental table 1).

The model among 67 to 70-year-old women showed that compared with women with 1–2 sexual partners during their lifetime, those with six or more sexual partners had significantly higher odds (OR 3.80; 95% CI 1.25 to 11.55) of having carcinogenic HPV (online supplemental table 1).

DISCUSSION

The prevalence of carcinogenic HPVs was high in all age groups (30–33, 57–60, 67–70 years old) of women in Estonia in 2020, demonstrating that the prevalence of carcinogenic HPV is common in women across a large age span, as well as among those outside the current CC screening target population. HPV16 was the most common genotype among 30 to 33-year-old women while HPV68 was the most prevalent genotype among women aged 57 years and older, confirming that the HPV genotype profile in Estonia is strongly age-dependent and should be considered carefully when developing strategies for CC prevention. A high number of lifetime sexual partners was a predictor of HPV infection among younger and older women; living without a partner was a predictor among younger women only. It should be considered that the generalisability of the findings of this study may be affected by the low response rate (43.9%).

Carcinogenic HPV prevalence in comparison to other countries

The prevalence of carcinogenic HPV was the highest among women aged 30–33 years (18.7%) followed by women aged 67–70 years (16.7%) and 57–60 years (10.2%). Compared with the study in 2006 in Estonia, the prevalence of carcinogenic HPV was 21% in women aged from 18 to 35 years, no increase in the prevalence of carcinogenic HPV was observed in the youngest age group of women. At the same time, the prevalence of carcinogenic HPV in Estonia is still very high as in Europe this ranges from less than 5% (Spain, Netherlands) to more than 15% (Denmark, UK).

In Estonia, a U-shaped prevalence curve of carcinogenic HPV was observed with higher values among 30 to 33 and 67 to 70-year-old women. A U-shaped HPV prevalence curve has also been described by other studies, with the highest estimates in women younger than 34 years, especially after sexual intercourse debut, followed by a decrease and an increase again in older age groups. New infections at 50 years of age can lead to invasive CC in women far beyond the screening target groups; new exposures to HPV through new male sex partners or their partners becoming infected through new partners can lead to an increased ability to detect HPV in the cervical epithelium of ageing postmenopausal women, and age-related immune senescence leading to increased reactivation of latent infections. In contrast, some countries, typically with a well-functioning screening programme, do not show in women increased HPV prevalence in older women.

The results of this study showed that carcinogenic HPV is common across a large age span in Estonia, including among those outside the current CC screening target population that ends at the age of 65 years. Moreover, in 2020, the estimated age-standardised incidence rate of CC among women aged 65 years and older was 33.8 per 100 000 in Estonia and CC in this age group is usually discovered at advanced stages and has a poor prognosis.

On the other hand, the average life expectancy has increased during the last three decades in Estonia, and women older than 65 years are healthy, continue to work and have an active sexual life. Thus, the results of this study suggest urgent change in the CC prevention strategy by expanding the screening exit beyond 65 years of age in Estonia.

Genotype-specific carcinogenic HPV and possibly carcinogenic HPV prevalence

Consistent with the worldwide literature, in this study it was found that carcinogenic HPV types HPV16 (4.0%) and HPV56 (4.0%) were the most prevalent among women aged 30–33 years. Among women aged 57–60
years and 67–70 years, the most prevalent carcinogenic HPV type was HPV68 (2.8% and 6.4%, respectively). It is fair to note, that the composition of carcinogenic HPV genotypes among older age groups was driven by other carcinogenic HPV types among women aged from 30 to 33 years. In addition, the HPV18 prevalence was low in all three age groups in Estonia. The results of this study were in line with those of the previous study conducted in 2006 in Estonia where HPV16 was the most prevalent genotype and the prevalence of HPV18 was relatively low among 18 to 35-year-old women and with those of studies from other post-Soviet countries such as Latvia, Belarus and Russia. This supports the notion of regional differences in the HPV genotype distribution, and ultimately, the need for regionally adapted CC prevention strategies.

**Vaccine-preventable carcinogenic HPV types**

The prevalence of vaccine-targeted carcinogenic HPV types was highest among younger women in Estonia. Moreover, the results of this study demonstrated that when all nonavalent vaccine-targeted HPV types are eliminated, the carcinogenic HPV prevalence will be two times lower among women aged 30–33 years who enter the screening programme in Estonia, one-third lower among women aged 57–60 years who exit the screening programme and slightly lower among women aged 67–70 years who are outside the target screening age. This potential effect of prophylactic vaccines will be seen in Estonia in the distant future as the national HPV vaccination programme for 12 to 14-year-old girls only started in 2018; thus, surrogate markers such as prevalent infection allow for an early assessment of vaccine effectiveness on a population level. Although prophylactic vaccines are effective in protecting against 90% of HPV infections, they offer limited benefits in eliminating pre-existing infections. Therefore, new advances have been made in the development of therapeutic vaccines, which aim to stimulate cell-mediated immunity and kill the infected cells rather than neutralise antibodies.

**Risk factors associated with HPV infection**

In this study, independent risk factors for carcinogenic HPV infection included higher number of lifetime sexual partners in the youngest and oldest age groups and living without a partner in the youngest age group, which is consistent with risk factors for HPV infection found in other studies.

**Strengths and limitations**

This study represents the largest and most comprehensive epidemiological assessment analysis of carcinogenic HPV prevalence in Estonia. Knowledge about HPV types, especially in women older than 60 years, is extremely limited but relevant to understand the importance of HPV-based screening. The main strength of EstBB data used in this study was that it is a population-based biobank including a considerable proportion of the population with wide range of recruited individuals with different ages and phenotypes. Another strength was related to the use of validated tests for HPV testing in Estonia.

As participation in the EstBB is entirely voluntary, the Estonian Genome Centre of the University of Tartu was not allowed to send invitation letters to the home addresses of potential participants. Therefore, the EstBB does not represent a classical random sample and could be subject to selection bias. Although recruitment was open to everyone, it might be that more health-conscious people with higher education levels and better health indicators joined the EstBB, which might be associated with an underestimation of the HPV prevalence in this study. Among EstBB participants, the proportion of women with higher education was higher than the average in Estonia. However, a considerable proportion of the population recruited for the EstBB could compensate for this bias. Hence, although not classically random, the cohort can still be considered representative of the population. At the same time, the representativeness of this study sample may be affected by the low response rate (43.9%) as non-responders may be systematically different from responders. Additionally, self-reported data on sociodemographic and behavioural factors can result in bias as participants are less likely to be honest about measures relating to risk behaviours. Moreover, problems with a recall can influence the frequency of specific behaviours as longer recall intervals result in either the under-reporting or inaccurate recall of sexual practices and partners.

**CONCLUSION**

This study demonstrated that the HPV genotype profile in Estonia was strongly age dependent with a U-shaped age-specific prevalence of carcinogenic HPV where the highest values were observed among women aged 30–33 years and among women aged 67–70 years, that is, the age group outside the target population of the screening programme. Public health providers should focus on developing exit strategies for the screening programme in Estonia with the possible extension of HPV testing beyond the current screening age of 65 years.

The results of this study indicate the importance of understanding the burden of HPV infection among females outside the target populations of CC screening programmes in countries with a high burden of CC to develop targeted CC prevention strategies.

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Patient consent for publication Not applicable.

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