

## CLINICAL REPORT

# High Prevalence of Oncogenic Human Papilloma Virus in Women Not Attending Organized Cytological Screening

Harriet STENVALL, Ingrid WIKSTRÖM and Erik WILANDER

Department of Genetics and Pathology and Department of Obstetrics and Gynaecology, University Hospital of Uppsala, Uppsala, Sweden

Since the introduction of organized cytological screening in Sweden, most women currently presenting with cervical cancer are those who have not attended the programme and who have no cytological screening history. The aims of this study were: (i) to measure the response rate among women not attending organized cytological screening who were offered a device for self-sampling a vaginal smear at home; (ii) to examine the prevalence of high-risk human papilloma virus (HPV) among women performing self-sampling. Women aged 35–50 years, who had not participated in organized cytological screening for more than 6 years, were offered the opportunity to collect vaginal samples at home using a self-sampling device (Qvintip®). The material collected was analysed for high-risk HPV using the Hybrid Capture 2 method. Of 369 women included in the study, 179 (49%) ordered the self-sampling device and 117 (32%) performed self-sampling at home and sent the sample to our laboratory for analysis. The mean prevalence of high-risk HPV was 26% (30/117), 31% (25/80) in women aged 35–42 years and 14% (5/37) in women aged 43–50 years. There was no significant difference in the participation rate with regard to age. The prevalence of high-risk HPV in women not covered by organized screening was considerably higher than in the general population; therefore they may represent a category at high risk of cervical cancer. The study shows that the use of a disposable self-sampling device for HPV testing is a relevant method to increase the participation rate in countries with organized cytological screening. **Key words:** vagina; HPV test; gynaecological screening; self-sampling.

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Erik Wilander, Department of Genetics and Pathology, University Hospital, SE-751 85 Uppsala, Sweden. E-mail: erik.wilander@genpat.uu.se

Gynaecological screening was launched in Sweden over 30 years ago and has decreased the prevalence of cervical cancer by about 50% (1). Currently, most women diagnosed with cervical cancer are those who have chosen not to participate in organized screening or who are not covered by the programme due to age (> 60 years) (2–4). The current major problem with cytological screening is

the non-optimal attendance rate among women who are invited for smear tests (5, 6).

As persistent infection with high-risk human papilloma virus (HPV) is known to be a prerequisite for the development of pre-malignant and malignant alterations on the cervix, HPV tests are often recommended as an adjunct in organized gynaecological screening. This recommendation is supported by the observation of a higher sensitivity of HPV tests in comparison with ordinary cytological screening (7).

For the above-mentioned reasons it is of interest to try to reach women who are not covered by organized screening, by offering them a self-sampling method for use at home, followed by testing the collected material for high-risk HPV in a laboratory. A previous study showed good agreement between HPV tests of cervical smears collected by a gynaecologist using a cytobrush (Scanmed Medical, Malmö, Sweden) and vaginal specimens collected by the women themselves using a blunt self-sampling device (SSD) (8).

The aim of this study was to examine the response rate among women who were not attending organized cytological screening, when they were offered the opportunity of collecting vaginal samples at home using a disposable SSD (Qvintip®, APROVIX AB, Uppsala, Sweden). A further aim was to examine the prevalence of high-risk HPV among non-attending women who performed self-sampling.

## MATERIALS AND METHODS

From our database (Department of Clinical Cytology, University Hospital, Uppsala, Sweden) 369 non-selected women, age range 35–50, in the County of Uppsala who had not participated in organized screening for over 6 years, were identified. They received a letter offering them the opportunity to carry out self-sampling of a vaginal specimen at home and informing them that the collected material would be sent to a laboratory for analysis of the presence of high-risk HPV. They were also informed that they had been selected because they had chosen not to participate in the organized screening service for several years, that the participation was completely voluntary, and that the collected material would not be preserved in any archive or bio-bank. Furthermore, the letter described the link between persistent infection with high-risk HPV and development of pre-malignant cell alterations on the cervix and that HPV testing can be regarded as an alternative to organized cytological screening.

All women participating in the study received a letter informing them of the HPV test results and those with a positive HPV

test were recommended to contact a gynaecologist or practice nurse for follow-up examinations.

The vaginal samples collected were analysed for high-risk HPV using the Hybrid Capture 2 method (HC2) (Digene Corp., Silver Spring, MD, USA). The test identifies 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). The HC2 technique can detect HPV DNA concentrations over 1 pg/ml, which is proportional to the light emission of the positive control and corresponds to 5000 HPV genomes per specimen in the well (9).

Use of the Qvintip® SSD was approved by the ethics committee of Uppsala, Dnr 2004:M-202. The study was also approved by the board of cervical cancer screening in the County of Uppsala. Erik Wilander is a minority share holder in Aprovix AB manufacturing Qvintip®.

## RESULTS

The main results are summarized in Table I. Of the women aged 35–50 years included in the study, 49% ordered a SSD for use at home and 32% performed self-collection and sent the material to our laboratory for HPV analysis. The response rate was the same in the age groups 35–42 and 43–50 years.

Of the 117 women who returned a self-sampled specimen, 26% were positive for high-risk HPV. The HPV prevalence was considerably higher in women aged 35–42 years (31%) than in women aged 43–50 years (14%).

The time lapse for sample collection after receiving the SSD at home showed large individual variations. After 3 weeks 49% of participating women had performed a vaginal specimen collection. After 7 weeks 90%, after 10 weeks 96%, and after 5 months no further material for analysis arrived.

A 6-month follow-up showed that 73% (22/30) of the women who tested positive had been in contact with a gynaecologist or midwife (Table II). A conization was performed on one woman, with CIN 3 observed in both a cervical biopsy and a cytological smear. A biopsy was taken without a cytological smear from 2 women. Eight out of 30 women were tested for high-risk HPV infection, of whom 7 were negative and one positive. In one woman in whom a CIN 3 alteration was detected at initial cytology, several cytological follow-ups were normal and the HPV-test was negative. The

Table I. Prevalence of high-risk human papilloma virus (HPV) and response rate in women aged 35–50 years offered self-sampling of vaginal smear at home with self-sampling device (SSD)

	35–42 years	43–50 years	Total
	<i>n</i> (%) <sup>*</sup>	<i>n</i> (%) <sup>*</sup>	<i>n</i> (%) <sup>*</sup>
Participating women	264	105	369
Women ordering SSD	128 (48)	51 (49)	179 (49)
Women using SSD	80 (30)	37 (35)	117 (32)
High-risk HPV-positive	25/80 (31)	5/37 (14)	30/117 (26)
High-risk HPV-negative	55/80 (69)	32/37 (86)	87/117 (74)

\*Percentage of total participating women or percentage of all women using SSD.

Table II. Follow-up (cytology and histopathology) of 30 women showing high-risk human papilloma virus (HPV) in their vaginal smear after self-sampling

Specimen	Not done	Normal	ASCUS-CIN 1	CIN 2–3
Cytology <sup>*</sup>	10	19	1	2
Biopsy <sup>**</sup>	25	2	3	1

<sup>\*</sup>In 2 of the women 2 cytological examinations were performed.

<sup>\*\*</sup>In one of the women 2 biopsies were obtained.

ASCUS-CIN: atypical squamous cells of undetermined significance-cervical intraepithelial neoplasia; CIN: cervical intraepithelial neoplasia.

remaining (8/30) women, who had not attended any nurse or gynaecological appointment within 6 months, obtained a reminder letter containing information about the value of a follow-up examination after a high-risk HPV-positive test.

## DISCUSSION

In a previous Swedish study of healthy middle-aged women (age range 32–38 years) participating in organized cytological screening, the mean prevalence of high-risk HPV infections was 6.8% (10). Our analysis of the prevalence of high-risk HPV in vaginal specimens obtained by self-collection in women aged 35–50 years is not in accordance with that investigation, since we obtained a mean prevalence of 25%. This shows that the population of women who chose not to participate in organized cytological screening, or because of age (over 60 years) were not included in the programme, may represent a category with a high risk of developing cervical cancer. If we assume that HPV prevalence in the different female populations reflects their risk of developing cervical cancer, the risk is considerably higher in non-attending women. This observation is in agreement with the finding that more than 50% of all cases of cervical cancer are observed among the minority of women who do not respond to an invitation to attend for cervical smear collection (2–6).

Several previous studies indicate good agreement between the results for smear material collected by self-sampling and by a gynaecologist when analysed for high-risk HPV (8, 11–14). Since HPV analyses are considered to be more sensitive than regular cytological screening, it would be of value to extend the use of the self-sampling alternative, provided that women accept the procedure. Studies indicate that, among women visiting gynaecological clinics, the acceptance rate for the self-sampling method is high (11–13). Among women not attending organized screening the participation rate is thought to be lower (15). In our study 49% of the women ordered SSD and 32% performed self-sampling at home. The method of distribution of the SSD to the women seems to affect the participation rate. When an explanatory letter and SSD were distributed to non-attending women by post without them requesting

it, 58% accepted self-sampling at home (unpublished observations).

The 2 main weaknesses of the current organized cytological screening programme are the non-optimal participation rate and the relatively low sensitivity of cytological screening (2, 5–6, 16). Approximately 75% of all cases of cervical cancer are related to a lack of coverage and occurrence of “false” negative cytology (2–4).

Since the prevalence of high-risk HPV in women not covered by organized screening is considerably higher than in the general population, non-responding women represent a category at high risk of developing cervical cancer. This study shows that the use of SSD for HPV testing is a relevant method to increase the participation rate in countries with an organized cytological screening programme.

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*Conflict of interest:* Erik Wilander is a minority share holder in Aprox AB manufacturing Qvintip®.

#### REFERENCES

- Bergström R, Sparen P, Adami HO. Trends in cancer of the cervix uteri in Sweden following cytological screening. *Br J Cancer* 1999; 81: 159–166.
- Sasieni PD, Cuzick J, Lynch-Farmery E. Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer. The National Co-ordinating Network for Cervical Screening Working Group. *Br J Cancer*. 1996; 73: 1001–1005.
- Stenkvist B, Söderstrom J. Reasons for cervical cancer despite extensive screening. *J Med Screen*. 1996; 3: 204–207.
- Jansson Å, Gustafsson M, Wilander E. Efficiency of cytological screening for detection of cervical squamous carcinoma. *Ups J Med Sci* 1998; 103: 147–154.
- Eaker S, Adami HO, Sparen P. Reasons women do not attend screening for cervical cancer: a population-based study in Sweden. *Prev Med* 2001; 32: 482–491.
- Eaker S, Adami HO, Granath F, Wilander E, Sparen P. A large population-based randomized controlled trial to increase attendance at screening for cervical cancer. *Cancer Epidemiol Biomarkers Prev* 2004; 13: 346–354.
- Brink A, Snijders P, Meijer C, Berkhof J, Verheijen R. HPV testing in cervical screening. *Best Practice & Research Clinical Obstetrics & Gynaecology* 2006; 20: 253–266. Available from: <http://www.sciencedirect.com>
- Stenvall H, Wikström I, Wilander E. HPV testing of vaginal smear obtained with a novel self-sampling device. *Acta Derm Venereol* 2006; 86: 465.
- Digene Corporation: Hybrid Capture Technology HC2. Available from: <http://www.digene.com>.
- Forslund O, Antonsson A, Edlund K, van den Brule AJ, Hansson BG, Meijer CJ, et al. Population-based type-specific prevalence of high-risk human papilloma virus infection in middle-aged Swedish women. *J Med Virol* 2002; 66: 535–541.
- Harper DM, Hildesheim A, Cobb JL, Greenberg M, Vaught J, Lorincz AT. Collection devices for human papillomavirus. *J Fam Pract* 1999; 48: 531–535.
- Sellors JW, Lorincz AT, Mahony JB, Mielzynska I, Lytwyn A, Roth P, et al. Comparison of self-collected vaginal, vulvar and urine samples with physician-collected cervical samples for human papillomavirus testing to detect high-grade squamous intraepithelial lesions. *CMAJ* 2000; 163: 513–518.
- Gravitt PE, Lacey JV Jr, Brinton LA, Barnes WA, Kornegay JR, Greenberg M, et al. Evaluation of self-collected cervicovaginal cell samples for human papillomavirus testing by polymerase chain reaction. *Cancer Epidemiol Biomarkers Prev* 2001; 10: 95–100.
- Nobbenhuis MA, Helmerhorst TJ, van den Brule AJ, Rozendaal L, Jaspars LH, Voorhorst FJ, et al. Primary screening for high risk HPV by home obtained cervicovaginal lavage is an alternative screening tool for unscreened women. *J Clin Pathol* 2002; 55: 435–439.
- Wright TC Jr, Denny L, Kuhn L, Pollack A, Lorincz A. HPV DNA testing of self-collected vaginal samples compared with cytologic screening to detect cervical cancer. *JAMA* 2000; 283: 81–86.
- Bais AG, Rebolj M, Snijders PJ, de Schipper FA, van der Meulen DA, Verheijen RH, et al. Triage using HPV-testing in persistent borderline and mildly dyskaryotic smears: proposal for new guidelines. *Int J Cancer* 2005; 116: 122–129.