Vloga samoodvzema brisa na HPV v presejanju za raka materničnega vratu

Role of human papillomavirus self-sampling in cervical cancer screening

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Izvleček

Pomembnost presejalnih testov za odkrivanje raka materničnega vratu (RMV) se je v mnogih državah pokazala v zmanjšanju incidence in umrljivosti zaradi te bolezni. Tudi v Sloveniji se je incidenca v obdobju 2003–2015 zmanjšala za približno 50 %. Pregledanost žensk se veča in je v zadnjem 3-letnem obdobjih okoli 72-odstotna. Glavni povzročitelj RMV je okužba s človeškim papilomavirusom (HPV), zato je od leta 2010 v državni presejalni program ZORA vključen tudi triažni test HPV. Čeprav je v Sloveniji presejanje brezplačno in dostopno, se približno 30 % žensk

Abstract

Cervical cancer screening has successfully reduced the incidence and mortality of cervical cancer in many countries. In Slovenia, the incidence of cervical cancer decreased in 2003–2015 by almost 50%. Participation in screening has reached about 72% over the last 3 years. The main cause of cervical cancer is infection with human papillomaviruses (HPVs). For this reason, in 2010, HPV testing was included in the national screening programme ZORA for triage of low-grade lesions and as a test of cure in 2010. Even though screening is free of charge and accessible in Slovenia, about

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ne odziva na vabila in ne opravi presejalnega pregleda v določenem časovnem okviru; to so predvsem ženske, stare od 50 do 64 let. Pri teh ženskah bi samoodvzem brisa na HPV lahko izboljšal odkrivanje predrakavih sprememb. Ob uporabi ustreznih testov HPV je zanesljivost testa za odkrivanje CIN 2+ na brisih nožnice in maternicnega vratu primerljiva in obenem enaka ali večja kot zanesljivost citološkega pregleda brisa maternicnega vratu. Po mnenju žensk je samoodvzem brisa za test HPV prijazen, intimen ter manj neprijeten in boleč kot odvzem brisa maternicnega vratu. Po podatkih v literaturi četrtina do tretjina žensk, ki se ne udeležujejo rednih presejalnih pregledov, opravi samoodvzem vzorca za test HPV, če imajo to možnost. V Sloveniji se je v randomizirani raziskavi odzvala dobra tretjina žensk. Odziv je bil le nekoliko večji, če so odvzemnik prejele po pošti brez naročila, kot če so ga morale naročiti. Samoodvzem brisa za test HPV bi lahko pomembno prispeval k boljšemu odkrivanju predrakavih sprememb maternicnega vratu. Evropska priporočila za zagotavljanje kakovosti v presejanju za raka maternicnega vratu svetujejo samoodvzem brisa za HPV samo za ženske, ki se ne odzovejo na redne preglede v okviru presejalnih programov.

30% of women still do not respond to invitations and are not screened regularly, especially women aged 50–64 years. HPV self-sampling could improve the detection of precancerous changes among non-attenders of the cervical cancer screening program. By using a validated PCR HPV DNA test, cervical and vaginal HPV sampling have similar accuracy for the detection of CIN 2+, resulting in the same or higher accuracy than the Pap test. Women describe HPV self-sampling as user-friendly, intimate, less embarrassing, and less painful than the Pap smear. About one-quarter to one-third of non-attenders of regular screening responded to the invitation to perform self-sampling. In a Slovenian randomised trial, the overall response rate was more than one-third and was not much higher in an opt-out compared to opt-in approach. HPV self-sampling could lead to an improvement in the detection of precancerous cervical lesions. European guidelines for quality assurance on cervical cancer screening recommend HPV self-sampling in women who do not attend regular cervical screening programmes.

INTRODUCTION

Human papillomavirus (HPV) self-sampling enables women to perform HPV testing by self-collecting a vaginal sample with a self-sampling device. Many studies have demonstrated the benefit of HPV self-sampling testing among non-attenders of cervical cancer screening programmes (1).

Although free cervical cancer screening is available in Slovenia, not all women respond to these invitations. About 30% of women invited for cervical cancer screening have not been tested within the recommended timeframe (2).

CERVICAL CANCER SCREENING IN SLOVENIA

The aim of cervical cancer screening is to reduce the incidence and mortality of the disease. In Slovenia in 2003, the inefficiency of opportunistic cervical cancer screening with a high incidence of cervical cancer led to the implementation of an organised national screening programme for the early detection of cervical cancer named ZORA. Since then, the incidence of cervical cancer has almost halved. At present, the standardised incidence rate (world standard) is around 7/100.000 and one of the lowest in Europe. A strong 3-year coverage of the target population is essential and a necessary condition for a successful screening programme requires at least 70%. At the beginning of our organised screening, the 3-year coverage was 62.4%. Over the years, this coverage has increased to 71.9% (3).

HPV INFECTION

Evidence of a causal relationship between HPV infection and cervical precancerous and cancer conditions has changed the approach to primary and secondary prevention of this disease. Persistent infections with HPV are also associated with cancers of the cervix, vulva, vagina, penis, anus, rectum, and head and neck cancers. The IARC has classified 12 high risk HPV types in Group 1 in the order of risk for cervical cancer, as follows: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 (4). High risk HPV infections are common. In most cases (70–91%), the infection will clear after 12 to 24 months, but in some women, infection will persist (5,6). In a worldwide meta-analysis, the HPV prevalence in women with normal cytology was estimated to be 10.4%. The most commonly detected HPV types were HPV 16 and 18 (7). The prevalence of high risk HPV in Slovenian women aged 20–64 years is around 12%; HPV 16 and 18 are present in 34% of HPV-positive women in this age group (8). The HPV 16 and 18 high risk types are known to account for 70% of all cervical cancer cases and additional 18% are caused by HPV 31, 33, 35, 45, 52, and 58 (9). In Slovenia, HPV 16 and 18 account for around 77% of cervical cancer (10).

NON-ATTENDERS TO CERVICAL CANCER SCREENING

Cervical cancer screening in Slovenia is traditionally performed by a gynaecologist. This has many benefits in terms of communication and education.

Grunfeld has identified three groups of women targeted for cervical cancer screening. These are women who respond and are aware of the benefits and importance of the screening, women who respond to proactive approaches, such as reminder letters, and women who are "hard-to-reach with health promotion messages" (1). Low levels of screening among these hard-to-reach women have been related to such barriers as fear, embarrassment, shame, low perceived risk, absence of symptoms, lack of physician, inconvenient clinic hours, forgetting an appointment, cultural barriers (e.g. language), and indirect costs (e.g., child care, time off work) (11–16). There are multiple types of barriers preventing participation in cervical cancer screening programmes. The barriers that are most commonly endorsed are feelings of embarrassment and shame (29%), in certain sociocultural groups this may include language barriers or women who have been sexually abused. The experience of discomfort or pain at a past clinical visit can discourage women from visiting a gynaecologist. Additional barriers are intending to go but not going (21%) or fear of pain (14%) and worry about the result (12%). Lack of understanding about the importance of HPV or cervical cancer screening or underestimation of the risk of disease can also interfere with patient compliance (11–14). Certain subgroups of women are less likely to be appropriately screened, particularly women who self-identify as lesbian, women of low socio-economic status and immigrant women (17). It is not surprising that cervical cancer rates are higher in women who have not been screened according to the recommended guidelines. Cervical cancer mortality is the highest in under-screened populations (18). On average, 53.8% of invasive cervical cancer subjects had inadequate screening histories and 41.5% were never screened (19). Data from the ZORA Register and Cancer Register of the Republic of Slovenia show that 60.8% of women with cervical cancer had not been screened within the recommended interval in

2010–2011 (20). Strategies to promote the uptake of screening are multifaceted, reflecting differences in the cancers targeted, invitees, health-service contexts, and the tests themselves (21).

HPV SELF-SAMPLING ACCURACY

The value of HPV self-sampling relies on its ability to detect high grade cervical intraepithelial neoplasia (CIN) and early stage cancer, its acceptability to the target population, and the willingness of women to follow-up on positive test results. Studies from a range of countries have shown that offering self-sampling can lead to increased participation rates in cervical cancer screening (22). In a meta-analysis by Arbyn et al., using data from 36 studies with 154,556 women enrolled, HPV testing on self-samples was less sensitive and specific than atypical squamous cells of undetermined significance (ASCUS) or worse as a cut-off with clinician-taken samples in the detection of CIN2 or worse (CIN2+). For the detection of CIN3 or worse (CIN3+), HPV testing on self-samples was as sensitive as ASC-US or worse cytology in clinician specimens. Self-sampled HPV tests based on polymerase chain reaction (PCR) for the detection of CIN2+, which did not have statistically different sensitivity or specificity compared with clinician-sampled tests. However, self-sampled HPV tests based on signal amplification were not as accurate for the detection of CIN2+ (1). In Slovenia, we have organised a randomised pilot study of HPV self-sampling among non-attenders. The study included female non-attenders aged 30–64 years with 26,556 women enrolled by random selection from the ZORA registry. The follow-up of women with a positive HPV test result in a self-taken sample lasted one year. The study showed a positive predictive value (PPV) of 12.0% for CIN2+ and 9.6% for CIN3+. The highest PPV (with 40.8% for CIN2+ and 38.3% for CIN3+) was obtained by women who were non-attenders of screening programmes for more than 10 years. The overall HPV positivity rate in the total study population was 8.3% (23). Among Swedish women aged 30–49 years the HPV positivity rate was slightly lower than among Slovenian women (6.3%), probably because of the different age group. The PPV for CIN2+ was higher in the screening of non-attenders than in those who routinely attended HPV and cytology screening (36.5% vs. 25.6%) (24). A randomised trial in Australia of non-attenders aged 30–69 years, found the overall detection of CIN2+ was 0.67%. The HPV positivity rate of 8.5% was similar in Slovenia (25). The effect of providing vaginal self-sampling HPV testing to non-attenders in a Dutch cervical cancer screening, with a follow-up of 18 months and concordance of HPV test results between physician-taken cervical scrapes and vaginal self-sampling was evaluated (26). In a meta-analysis, Snijders et al. combined HPV self-sampling with a follow-up clinic visit and Pap smear by positive HPV results and concluded that HPV testing on self-samples appeared at least as sensitive for CIN2+ as cytology or HPV detection in clinician-obtained cervical samples, though often less specific (27). The sensitivity for CIN2+ in the HPV self-test (66.1%) was equivalent to cytology at the ASCUS threshold (67.9%), but higher when compared to cytology with LSIL as a threshold (60.7%). The specificity of the HPV self-test (81.4%) was lower than the cytology at both the ASCUS (86.4%) and LSIL (95.9%) thresholds (28). Although HPV detection using self-sampling is less specific than clinically collected samples exhibiting CIN2+ (HPV-positive specimens often show less severe cytology), the increased sensitivity of HPV self-sampling could potentially decrease the morbidity and mortality associated with cervical cancer (27).

BENEFIT OF HPV SELF-SAMPLING TESTING

By offering women the option to self-collect vaginal samples at home, we aim to increase their participation in cervical cancer screening programmes. Women taking part in self-sampling trials reported a positive experience. The existing literature suggests that using HPV self-sampling methods increases the uptake of cervical cancer screening programmes.

The applicability and accuracy of vaginal self-sampling in detecting HPV among Dutch women was investigated in the VERA study from April 2013 to May 2015. This study had evaluated self-sampling as convenient (97.1%), user-friendly (98.5%), and

62.8% of participants preferred self-sampling over a physician-taken sampling for the next screening round. This shows that the implementation of vaginal HPV-self-sampling as a screening tool may be considered (29). The acceptability of HPV self-sample testing among Dutch non-attenders compared to the regular cervical screening programme was up to 30% (native Dutch showed better results than immigrants) (26). In the latest meta-analysis by Yeh and Kennedy, 33 studies and 34 articles were analysed and showed that a likelihood of attendance in the self-sampling arm was twice as high as the control (30). In the Slovenian study of HPV self-sampling, there were 26,556 women enrolled, 8.972 (33.8%) responded with a self-sample for HPV testing and/or traditional cytology within 1 year of enrolment. The response rates were 37.7%, 34.0%, and 18.4% ($p < 0.050$) for opt-out (HPV self-sampling kit mailed directly to the home), opt-in (HPV self-sampling kit mailed or ordered with an option of undergoing a gynaecological examination) and control groups (23). In the PROHTECT study, 53,937 non-attenders were allocated to the self-sampling group and 545 to the recall control group. In the self-sampling group, the response rate to HPV self-sampling was 29% (26). A systematic review and meta-analysis from Verdoodt evaluated the participation among under-screened women after receiving an invitation to self-sample with a sampling device (self-sampling arm) versus an invitation to have a sample taken by a health professional (control arm). The pooled participation in the self-sampling arm was 23.6% when self-sampling kits were sent by mail to all women, versus 10.3% in the control arm (participation difference: 12.6%) (31). In a study of over 3,000 Norwegian women, offering self-sampling materials instead of an invitation for physician-sampling increased the attendance from 23.2% to 33.4% (32). Similarly, in a study performed among Swedish women who have not been screened for at least 6 years, 39% accepted an invitation for HPV self-sampling testing (33). In the Slovenian randomised pilot study, the level of protection was categorised in two groups: medium protection (last cytology was done 4–9 years before the enrolment) and no/low protection (last cytology was done 10 years or more before the enrolment). Women with medium protection had a 2.8-times higher response rate than women with no/low protection (23). A large study among Italian women showed that 11.9% responded to an invitation to Pap smear compared with 21.6% who sent a sample from an HPV self-sampling kit (34). In a recently published review, HPV self-sampling was found to be highly acceptable among these hard-to-reach women across most studies. Mailing of self-sampling kits has been shown to increase the participation among hard-to-reach women. Some concerns remain about further follow-ups if the HPV test is positive (16).

HPV SELF-SAMPLING AND THE GUIDELINES

The 2015 European guidelines provide recommendations for HPV self-sampling in screening programmes using HPV primary testing for non-attenders. They recommend that routine HPV screening can begin at the age of 35 years; however, not before the age of 30 years. The screening interval for women with a negative HPV primary test may be at least 5 years and can be extended up to 10 years depending on age and screening history (35). The Netherlands was the first country to provide female non-attenders with the possibility to self-collect samples for HPV testing instead of going to a clinic for a Pap smear within a screening programme (36,37). In 2017, the National Cervical Screening Programme in Australia switched to a recommended primary HPV cervical screening (taken by physicians) every 5 years for women aged 25–74-years-old, with HPV self-sampling for women over 30 years of age who are under-screened (the last screening test min. of two years ago) or never-screened (38). In other countries, trials with self-sampling to evaluate the incorporation of this methodology in official national cervical cancer programmes (UK, Norway, Denmark, Switzerland) have been initiated. Slovenia has also conducted studies aimed to reach a potential upgrade of the Slovenian cervical cancer screening programme ZORA with HPV self-sampling.

CONCLUSION

With recent technological advancements in cervical

cancer screening methods, the incidence of cervical cancer can be significantly reduced through high sensitivity screening methods that are self-administered and cost-effective. The most important advantage of newer screening tools is the potential of self-sampling, which may be particularly useful for non-attenders to screening programmes. The use of self-collection vaginal specimens for HPV screening has the potential to improve patient access to care and lead to higher patient compliance than current cervical cancer screening programmes. High risk HPV testing with PCR DNA HPV tests of self-collected vaginal specimens, followed-up by visiting a physician, with cytology on positive cases, has shown to be more sensitive in detecting CIN2+ pathology compared to Pap smears taken by a physician. However, women will need clear instructions. Education is important to ensure proper patient engagement. Additional infrastructure and guidelines will be needed to support the use of HPV self-sampling. The Netherlands is already offering HPV self-sample testing in an organised screening for female non-attenders of conventional Pap smear visits. Due to the positive experience in increased screening rates and cervical cancer prevention, self-sampling may become an even more viable option for many women. With appropriate patient education and access to follow-up, HPV self-sampling has the potential to increase the participation in screening programmes, reduce socio-economic barriers, improve the subjective patient experience and further reduce the continued morbidity and mortality related to HPV infection and cervical cancer. In Slovenia, the most cost-effective HPV self-sampling approach in the local setting remains to be identified and the role of potential PPV predictors after a positive result of HPV testing on self-collected samples needs to be clarified. At present, according to European guidelines for quality assurance in cervical cancer screening, HPV self-sampling should not be the primary option for women participating in cervical cancer screening, but it might be appropriate for women who have not attended screening despite a personal invitation and a reminder.

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