Cervical pre-cancer can be detected in self-collected urine or vaginal samples

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Researchers have developed a non-invasive test to detect cervical pre-cancer by analysing urine and vaginal samples collected by the women themselves.

In a presentation at the 2019 NCRI Cancer Conference today (Monday), Dr. Belinda Nedjai said that self-sampling test had proved popular with women taking part in the study and this meant that it was likely to improve participation in cervical cancer screening programmes.

"The initial use of self-sampling is likely to be for women who do not attend clinic after a screening invitation and countries without a cervical cancer screening programme. In the longer term, self-sampling could become the standard method for all screening tests. The study indicated that women much preferred doing a test at home than attending a doctor's surgery," said Dr. Nedjai, who is Senior Research Fellow and Director of the Molecular Epidemiology Lab at Queen Mary University of London, UK.

"To the best of our knowledge, this study is the largest to test a methylation classifier, called S5, in urine and self-collected cervical samples to detect pre-cancer lesions in women who have been referred for further investigation. We expect the self-sampling test to improve acceptance rates for cervical cancer screening, as well as reducing costs to health services and improving the performance of screening programmes."

The current gold-standard pap smear test is taken in the clinic and often follows a positive test for the human papilloma virus (HPV).

Dr. Nedjai said: "HPV testing is rapidly becoming the primary screening method for cervical cancer worldwide. It is a very sensitive method, very good at detecting true positives, but lacks specificity—in other words, a second test is needed to exclude HPV positive women that are not at increased risk of developing cancer. The choice of an appropriate strategy for high-risk HPV positive women is a key issue."

The S5 test developed by Dr. Nedjai and her colleagues at Queen Mary, measures DNA methylation—a chemical change to one of the four DNA base letters that make up the human genetic code. S5 looks at DNA methylation of four HPV types most strongly associated with cancer—HPV16, HPV18, HPV31 and HPV33—and the human gene EPB41L3 to produce a score that indicates the level of risk. If the score is above a selected cut-off it indicates an increased risk of a pre-cancer lesion, and the higher the score the higher the risk of cancer. They had discovered in earlier research that when S5 was used on cervical samples, it was 100% accurate at detecting invasive cervical cancer, and 93% accurate at detecting pre-cancer in women who had an HPV positive test.

Cervical cancer is preceded by the abnormal growth of precursor cells on the surface of the cervix—so called cervical intraepithelial neoplasia (CIN) or pre-cancer—that can develop into cervical cancer. It is divided into three stages (CIN1, CIN2 and CIN3), with the likelihood of the cells developing into cancer increasing at each stage.

"We decided to assess whether S5 could identify women who had CIN3 pre-cancer lesions using urine and vaginal samples," said Dr. Nedjai.

Women attending the colposcopy clinic at the Royal London Hospital as

a consequence of an abnormal smear test or positive HPV result were asked to take part in a study led by Professor Jack Cuzick, Director of the Wolfson Institute of Preventive Medicine at Queen Mary. A total of 620 women provided vaginal samples, collected themselves using vaginal swabs, and 503 of these women also provided a urine sample. The researchers extracted and analysed the DNA in the lab and generated S5 scores.

"We found that S5 classifier with or without HPV testing worked well in both urine and vaginal samples," said Dr. Nedjai. "It distinguished between women who had no pre-cancerous lesions and those who had CIN3 or higher lesions. We evaluated two distinct ways that S5 could be used. We first tested S5 as a secondary test on HPV positive women to limit the number of patients sent to colposcopy. In urine, S5 was better at correctly identifying women who did have pre-cancer lesions than testing for the presence of HPV16 or 18; 96% of true CIN3 were identified with S5 compared to 73% with an HPV16 or 18 test. Secondly, we evaluated S5 as a standalone test, without first doing HPV testing. We adjusted the cut-offs to identify at least 85% of true positives. Urine performed as well as self-collected vaginal samples.

"We are currently working on new markers to try to improve the accuracy of the classifier even further, but these findings represent an advance in cervical cancer screening, especially for women who do not attend the clinic, such as older women, or women who find the smear test too painful or who do not have access to a screening programme in their country. We think it's promising."

In the future, Dr. Nedjai said the samples could be collected at home for both HPV and methylation analysis without the need to go to the clinic.

Dr. Manuel Rodriguez-Justo is a consultant pathologist at University College London (UK) and a member of the NCRI's sub-committee on

early detection and prevention. He was not involved with the research. He commented: "This is exciting research that shows it's possible to detect cervical pre-cancer that is at high risk of developing into invasive cancer in urine and vaginal samples collected by women in the comfort and privacy of their own homes. This has the potential to revolutionise the way a positive HPV test is followed up, as well as making it easier for women in countries with no cervical cancer screening programme to be tested.

"The cervical screening programme in the UK has been very successful but there has been also a decline in its uptake, particularly in some areas in the UK and specific ethnic groups. If the results of this study are validated by other groups, the implementation of urine-based testing and self-sampled vaginal samples will, potentially, increase uptake and reduce costs for the screening programmes whilst achieving high sensitivity to detect pre-malignant lesions

Cervical cancer is the fourth most frequently occurring cancer in women in the world. In 2018, there were an estimated 570,000 new cases of cervical cancer and 310,000 women died from the disease. Infection with HPV is almost the main cause of cervical cancer. More than 25 different types of HPV are transmitted through sexual contact and 12 of them carry a high risk of triggering the development of cancer cells by inactivating tumour suppressor proteins (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 68).

More information: Abstract no: Poster 2451, poster board number 43, area 2. "Non-invasive methylation test to detect cervical pre-cancer in self-collected vaginal and urine specimens", by Belinda Nedjai. 15.47 hrs GMT. Silent theatre 2, Exhibition Hall, Monday 4 November.