Genetic test for anal cancer could identify those at high risk

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A new test, based on a patient's epigenetics, could be an accurate and inexpensive way to find and treat those at highest risk of anal cancer - a disease with growing incidence in women, men who have sex with men (MSM) and people with HIV.

The early research by Queen Mary University of London (QMUL), which was funded by Cancer Research UK, finds that the test could lead to a reduction in painful procedures and minimise the over-treatment of people at low risk.

Anal cancer is mostly caused by human papillomavirus (HPV) - the same virus that causes cervical cancer. In 2014, the UK had around 1,300 new cases of anal cancer and 360 deaths. In addition to rising levels in women and MSM, anal cancer is more common in HIV-positive MSM with around 100 cases per 100,000, compared to 25 in HIV-negative MSM, and only 1.5 in men in general.

Diagnosis presents many challenges. Full biopsies are painful, and taking a small sample of cells ('cytology') is problematic because lesions can be hidden and clinicians give varying interpretations of results. High-resolution anoscopy, where the anal canal is examined with a high resolution magnifying instrument, is often used as the primary screening tool for high-risk populations but is uncomfortable for the patient, expensive, complex and generates subjective results.

Lead researcher Professor Attila Lorincz from QMUL said: "The widespread over-treatment of anal precancerous lesions is necessary today because we don't know which ones will progress to cancer. But this creates a large burden on anoscopy clinics in the UK and the procedures can be detrimental to people's quality of life. Many people are undergoing these procedures unnecessarily, so what we really need is precision medicine to identify those who do need treatment."

The research, published in the journal *Oncotarget*, involved studying anal biopsy specimens from 148 patients in London, including 116 men (mostly MSM). The specimens were analysed to look for genetic markers that may be associated with the presence of anal cancer.

The team specifically looked at the patients' epigenetics and found that all of the anal cancers showed the presence of specific epigenetic methylation markers on the patients' EPB41L3 gene (a tumour suppressor gene) and also on certain regions of their viral HPV genome.

The results suggests that epigenetic testing may be an accurate and thorough method to indicate whether a patient's lesions are destined to progress to anal cancer. This could reduce the costs, pain and anxiety from other methods of diagnosis, and minimise over-treatment of low risk people.

Professor Lorincz added: "We thought this would require a complicated genomic signature involving hundreds of genes, so we were surprised that we could get such an accurate prediction from just two biomarker genes. That's important because the expected cost of the test will be fairly low.

"Now that we can identify those at risk, and conversely, those not at risk, we hope to see a big improvement, by making sure that anoscopies and laser or chemical surgery are only given to those who need it."

Once developed, the test would involve taking a small sample of cells from the anal canal via a swab and then sending the sample off to a laboratory for epigenetic analysis.

While a test could be developed within five years, the researchers caution that the results first need to be confirmed in a much larger study across the UK, and repeated using swab samples rather than the biopsies which were used in the current study.

Dr Rachel Orritt, Cancer Research UK's health information officer, said: "This study builds on what we already know about the link between changes to cell DNA and cervical cancer, and shows that similar changes to the DNA in anal cells could suggest anal cancer.

"If other studies confirm and build upon these findings, this promising research could be used to develop a less invasive method to help doctors identify people who are at a higher risk of anal cancer and avoid unnecessary procedures for those who are at a lower risk."

The researchers say that these types of biomarker - epigenetic methylation biomarkers - are important in a large number of other diseases, and could lead to a completely new approach to diagnostics and drug therapy.

Professor Lorincz explained: "These could be the early stages of a discovery of a universal set of biomarkers for any cancer. And there may be implications on therapies, as there are new techniques where the epigenetic pathway can be targeted by drugs. This is going to be the hot new area going forward in the next 15 years, so people need to be paying attention to this space."

More information: 'Methylation of HPV and a tumor suppressor gene reveals anal cancer and precursor lesions'. Attila T Lorincz, Mayura Nathan, Caroline Reuter, Rhian Warman, Mohamed A Thaha, Michael Sheaff, Natasa Vasiljevic, Amar Ahmad, Jack Cuzick, Peter Sasieni. *Oncotarget*, 2017.

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