

Victoria Zotter
Public Relations and Event Management

Medical University of Graz
Neue Stiftingtalstraße 6
8010 Graz
victoria.zotter@medunigraz.at

Press release
For immediate release

New precursors of both HPV-associated and HPV-independent cervical cancer described for the first time

Graz, July 1st 2025: Cervical cancer is the fourth most common type of cancer in women worldwide. Two studies by Medical University of Graz researchers Olaf Reich, Sigrid Regauer and Karl Kashofer are significantly changing our understanding of this cancer. The new findings have shown that precursors of HPV-associated cancer frequently develop on the cervix as so-called thin high-grade squamous intraepithelial lesions (thin HSILs) and thus in another location on the cervix that is susceptible to cancer than previously assumed. Besides the HPV-associated pathway, there is also a second HPV-independent pathway whose tumors have other unusual biological features.

From HPV infection to cervical cancer

Worldwide around 600,000 women develop cervical cancer annually, and roughly half of these women die—above all in countries with insufficient prevention. Cervical cancer is the fourth most common malignant disease in women. In Austria around 400 cases are newly diagnosed each year. The main cause of this type of cancer is a persistent infection with certain types of the human papillomavirus (HPV), which is mainly spread through sexual contact. HPV is widespread and normally kept in check by the immune system of those infected. In individual cases and often under the influence of cofactors (e. g., smoking), HPV can cause damage to the cervical mucosa, which develops from minor changes to severe changes to cancer. Particularly dangerous are the so-called high risks types such as HPV -16 und HPV-18, which increase the risk of disease by a factor of 400 as compared to in the uninfected population and are responsible for 70% of all cervical cancer cases. Thanks to vaccination and HPV tests and pap smears for prevention, the disease is on the decline in many developed countries—provided that it is discovered early.

HPV-associated cancer: "thin HSIL" a previously unknown precursor of cancer

It used to be unclear whether thin high-grade squamous intraepithelial lesions (thin HSILs) could actually be considered true precursors of cancer. The study published in the journal Laboratory Investigation has provided the first genetic evidence: Thin HSILs exhibit changes in their DNA and gene activity that are similar to those in malignant and advanced cancers. This proves that thin HSILs are early forms of HPV-associated cervical cancer. These thin HSILs have been difficult to detect; rarely appearing conspicuous under the microscope or in clinical tests with a colposcope, they often require the use of biomarkers in diagnostics. "We were also able to show that this common precursor of HPV-associated cancer does not develop in the flat squamous epithelium of

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Medizinische Universität Graz, Neue Stiftingtalstraße 6, 8010 Graz, www.medunigraz.at

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the outer layer of the cervical mucosa as previously assumed but in the columnar epithelium (inner layer of the cervical mucosa) without any minor changes as precursors," explains Olaf Reich, head of the dysplasia and research unit of the Division of Gynaecology at the Medical University of Graz. "These findings have important consequences for future prevention, diagnostics and therapy," says the researcher.

HPV-independent cancer: rare precursors described for the first time

In a second study published in the American Journal of Surgical Pathology, the researchers describe HPV-negative changes to the cervical mucosa that can develop into cancer without the presence of HPV. These rare differentiated cervical intraepithelial neoplasia (d-CIN) resemble precursors of vulvar cancer. Karl Kashofer, head of the Diagnostic Genome Analysis lab at the Diagnostic and Research Institute of Pathology at Med Uni Graz, explains: "Instead of HPV-associated changes, HPV-independent precursors of cancer exhibit typical defects in genes such as TP53, PIK3CA or SMARCB1, which promote malignant tumor growth and reduce the effectiveness of chemotherapy to treat tumors." These highly differentiated changes to the cervix can be easily overlooked because they first appear to be harmless and are also difficult to distinguish from benign changes in cervical smears. "Our work shows that there are true HPV-negative precursors to cervical cancer. Thus we have refuted the so-called "hit-and-run" theory according to which HPV originally played a role in tumor development then disappears during tumor growth," explains WHO author Sigrid Regauer of the Diagnostic and Research Institute of Pathology at Med Uni Graz. "For the first time, we have verified that there are actually HPV-independent types of cervical cancer," says Regauer.

Consequences for prophylaxis and therapy

These new findings have important consequences for prophylaxis and treatment of cervical cancer and its precursors, especially for women whose immune system cannot effectively control the early stages of the disease. "We used to protect against HPV-associated cancer with the HPV vaccine by preventing HPV infection. In the future, the earliest precursors of cancer in the thin HSIL might be induced to regress by therapeutic HPV-specific cervical carcinoma vaccines. Because of their specific gene defects, HPV-independent carcinomas are candidates for the new molecular therapies, which are also referred to as targeted therapies. They are associated with the hope of being able to effectively stop HPV-independent cancer cells that have developed in the cervix and also of having fewer side effects," says Reich.

Further information and contact:

Olaf Reich
Division of Gynaecology
Medical University of Graz
Tel.: +43-316 38581616
olaf.reich@medunigraz.at

Sigrid Regauer
Diagnostic and Research Institute of Pathology
Medical University of Graz
Tel.: +43 316 385 71728
sigrid.regauer@medunigraz.at

Karl Kashofer
Diagnostic and Research Institute of Pathology
Medical University of Graz
Tel.: +43 316 385 71752
karl.kashofer@medunigraz.at

Research field cancer research

Links to the studies

Copy Number Profiling Implicates Thin High-Grade Squamous Intraepithelial Lesions as a True Precursor of Cervical Human Papillomavirus-Induced Squamous Cell Cancer:

<https://www.sciencedirect.com/science/article/pii/S0023683724017860?via%3Dihub>

The Histologic and Molecular Spectrum of Highly Differentiated HPV-independent Cervical Intraepithelial Neoplasia:

https://journals.lww.com/ajsp/fulltext/2023/08000/the_histologic_and_molecular_spectrum_of_highly.11.aspx