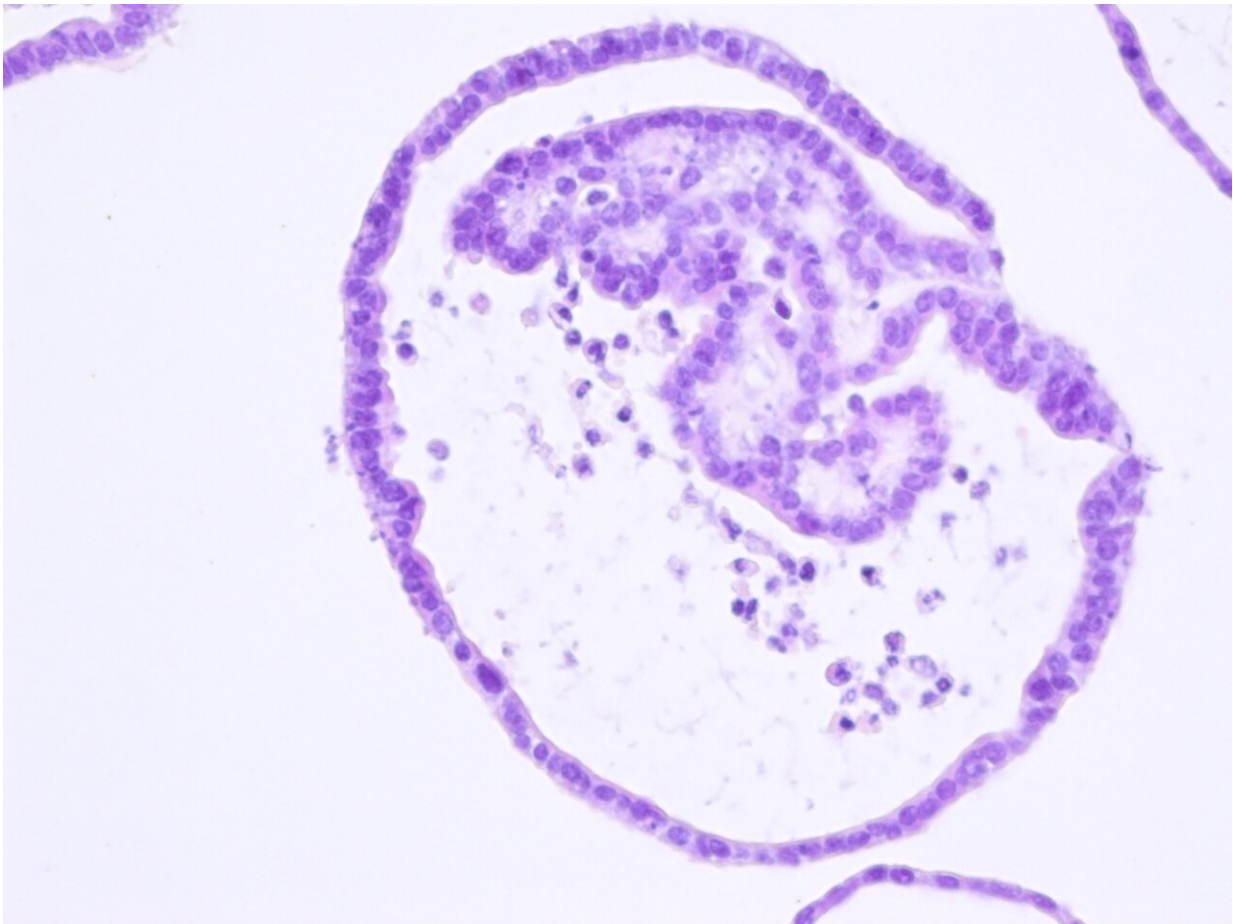


# Studying the development of ovarian cancer with organoids

May 27 2020

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Organoid of the mouse oviduct, in which three genes were disabled that are often mutated in ovarian cancer. Credit: Kadi Lõhmussaar, ©Hubrecht Institute

High-grade serous ovarian cancer is the most common type of ovarian cancer, and has the lowest rate of survival. It is often only diagnosed when it has already spread within the pelvis and abdomen, making it harder to treat. Because the early stages of ovarian cancer are not often observed, much is still unknown about the early development of the disease. Scientists do know that ovarian cancer cells often have mutations in certain genes, such as Trp53, a gene that is often mutated in many types of cancer, Brca1, a gene often mutated in breast cancer, Nf1 and Pten.

Researchers from the group of Hans Clevers at the Hubrecht Institute have modeled the development and progression of high-grade serous ovarian [cancer](#) in tissue from the female reproductive organs of mice. They report that the cells of the oviduct, the equivalent of fallopian tubes in humans, are more prone to develop into tumors than those of the ovarian surface epithelium, the outer layer of the ovaries. In the future, such organoids, mini-versions of human tissue, may be used to better understand how this disease, often diagnosed very late, develops. The researchers published their results in the scientific journal *Nature Communications* on 27 May.

## Organoids

Researchers in the group of Hans Clevers at the Hubrecht Institute used mini-versions of two parts of female reproductive tract of mice to study the early development of ovarian cancer. In the lab, they grew organoids of the oviducts (in humans called the fallopian tubes) that transport the egg from the ovary to the uterus, and of the ovarian surface epithelium, the outer layer of the ovaries, from small pieces of tissue from mice. In these organoids, they recreated the mutations found in ovarian cancer. Using the state-of-the-art CRISPR-Cas9 genome editing approach, they mutated the genes Trp53, Brca1, Nf1 and Pten to study how these genes contribute to the development of a [tumor](#).



Healthy organoids of the mouse oviduct, all the cells are colored in bright green.  
Credit: Kadi Lõhmussaar, ©Hubrecht Institute

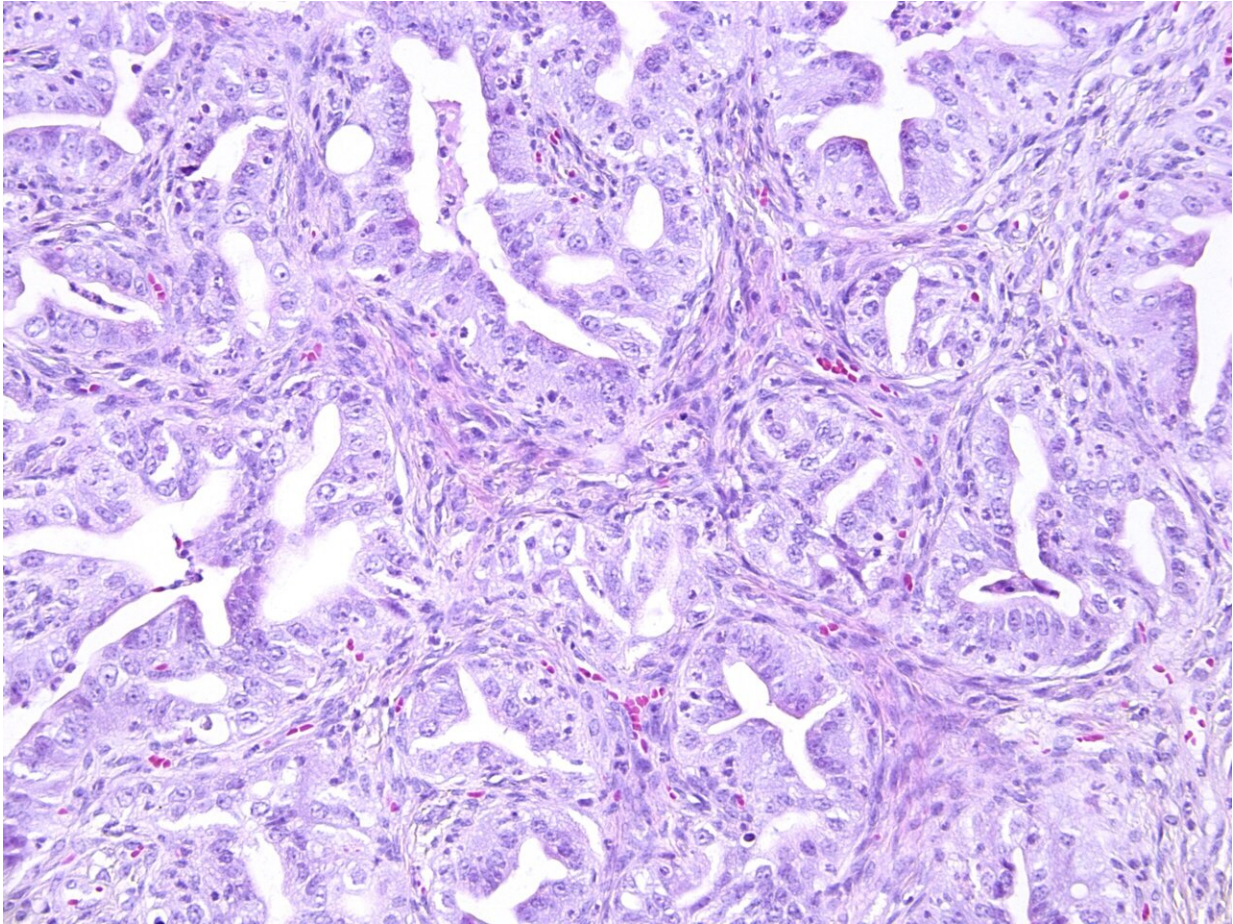
## **Mutations**

When mutations were introduced in three of the four genes, namely Trp53, Brca1 and either Nf1 or Pten, the organoids acquired characteristics of tumors, such as more densely packed cells and changes in chromosome number. In addition, when these organoids were transplanted back into mice, they developed into tumors that are similar to ovarian cancer tumors in humans.

The researchers found that organoids from the oviduct were more likely to develop into tumors, grew faster and grew into larger tumors than the organoids from the ovarian surface epithelium. This suggests that ovarian cancer is more likely to originate in the oviduct, or the fallopian tube in humans, compared to the ovarian surface epithelium.

## **Earlier diagnosis and preventive care**

Studying the development and progress of ovarian cancer in such [organoid](#) models may shed light on how ovarian cancer develops. Researchers in the group of Hans Clevers have previously shown that organoids can also be made from the human fallopian tube and the human ovarian surface epithelium. In the future, the researchers may also introduce the specific mutations found in ovarian cancer in these human organoids to further study the development of this disease.



A tumor derived from organoids of the mouse oviduct, in which three genes were disabled that are often mutated in ovarian cancer. These organoids grew into large, high-grade serous ovarian cancer-like tumors quickly. Credit: Kadi Löhmußaar, ©Hubrecht Institute

Patients with a mutation in one of the Brca [genes](#) are at a high risk of ovarian cancer and can receive preventive treatment. This includes radical surgery in which both ovaries as well as the fallopian tubes are removed, leading to premature menopause in women. The results in this study support the emerging view that the [fallopian tube](#), not the ovarian surface epithelium around the ovaries, are the main origin for ovarian cancer, which may direct future changes in preventive treatment. For

example, the Dutch Gynecological Oncology Group recently launched a clinical trial to study whether early removal of only the fallopian tubes and later removal of the ovaries can improve the quality of life for these patients, while also reducing the risk of ovarian cancer.

Knowing more about the development and progression of ovarian cancer may help doctors to better recognize ovarian cancer in the future, enabling earlier treatment and a higher chance of survival.

**More information:** Assessing the origin of high-grade serous ovarian cancer using CRISPR-modification of mouse organoids. Kadi Löhmußaar, Oded Kopper, Jeroen Korving, Harry Begthel, Celien P. H. Vreuls, Johan H. van Es, Hans Clevers. *Nature Communications* 2020., [DOI: 10.1038/s41467-020-16432-0](https://doi.org/10.1038/s41467-020-16432-0)

Provided by Hubrecht Institute

Citation: Studying the development of ovarian cancer with organoids (2020, May 27) retrieved 1 February 2024 from <https://medicalxpress.com/news/2020-05-ovarian-cancer-organoids.html>

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