Department of Obstetrics and Gynecology

catharina hospital

Signal transduction pathway activity in normal Fallopian tube epithelium and high-grade serous carcinoma

P van der Ploeg[A,B], K Bucks[A], A van de Stolpe[C], S Bosch[D], MC Vos[E], A van der Wurff[F], J de Hullu[G], PJ van Diest[H], RLM Bekkers[A,B], JMJ Piek[A]

Affiliations: [A] Catharina Hospital, Department of Obstetrics and Gynecology, Eindhoven, The Netherlands, [B] Maastricht University, GROW School for Oncology and Developmental Biology, Maastricht, The Netherlands, [C] Molecular Diagnostics, Philips Research, Eindhoven, The Netherlands, [D] Laboratory for Pathology and Medical Microbiology (Stichting PAMM), Eindhoven, The Netherlands, [E] Elisabeth-TweeSteden Hospital, Department of Obstetrics and Gynecology, Tilburg, The Netherlands, [F] Elisabeth-TweeSteden Hospital, Department of Pathology, Tilburg, The Netherlands, [G] Radboud University Medical Center, Department of Obstetrics and Gynecology, Nijmegen, The Netherlands, [H] University Medical Centre Utrecht, Department of Pathology, Utrecht, The Netherlands

Introduction

High-grade serous carcinoma (HGSC) is the most lethal gynecological malignancy. New treatment options focus on targeted therapy based on Signal Transduction pathway Activity (STA). Tumour growth is induced by aberrant STA leading to disturbed cell proliferation and differentiation. However, knowledge about STA in healthy tissue is needed to discriminate STA in HGSC. As the Fallopian tube epithelium (FTE) is considered the tissue of origin of most HGSC[1], **the aim of our study was to determine STA in normal FTE during the menstrual cycle and compare this to STA in HGSC.**

Methods

- **17 FTE samples from premenopausal women** who underwent surgery for benign reasons. Reviewing of endometrial histologic sections by a pathologist resulted in 4 early proliferative, 2 late proliferative, 5 early secretory and 6 late secretory samples. Fimbrial ends were laser capture microdissected (*Figure 1*).
- **23 HGSC samples**, which were taken prior to start chemotherapy and macrodissected.
- Samples were analysed with the qPCR based STA-analysis which infers quantitative pathway activity scores from mRNA levels of pathway-specific target genes.[2-6]
- Among others, we investigated the **androgen receptor** (AR), **estrogen receptor** (ER) and **phosphoinositide 3-kinase** (PI3K) pathway.

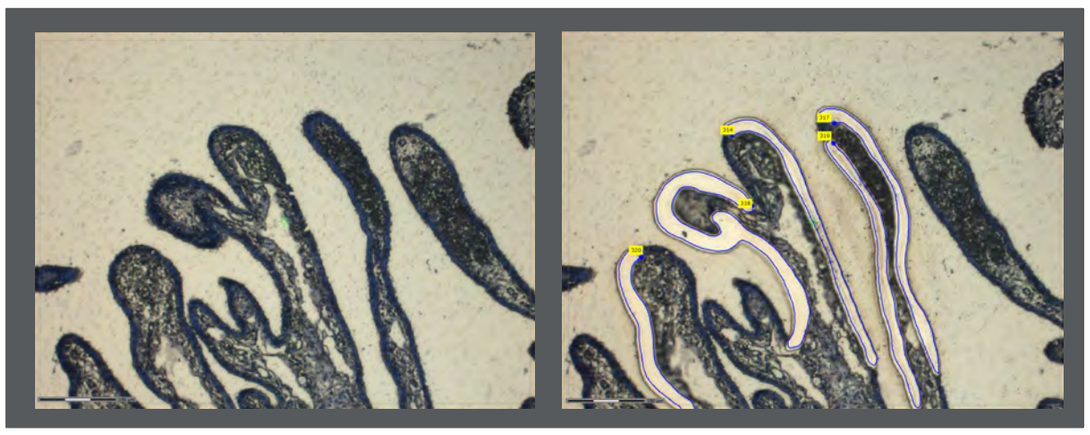

Figure 1. Microscopic images of the fimbrial ends of normal Fallopian tube epithelium before (left) and after (right) laser capture microdissection.

Results

- **AR pathway activity** increases towards the early secretory phase and significantly decreases late secretory in FTE. A broad range in AR activity was observed in HGSC, including a number of cases with very low AR pathway activity (*Figure 2*).
- Comparable changes were seen in the **ER pathway activity** with a significant decrease towards the end of the secretory phase in FTE. Remarkably, all HGSC demonstrated low ER pathway activity compared to FTE ($p < 0.001$) (*Figure 3*).
- **PI3K pathway activity** decreases early secretory and significantly increases at the end of the secretory phase in FTE. Interestingly, a subgroup of HGSC showed high PI3K activity (*Figure 4*).

Discussion and conclusion

During the menstrual cycle, AR, ER and PI3K pathway activity in FTE seem to be activated in a controlled manner. Estradiol levels increase **towards the ovulation** which is supported by the observed **increasing ER** pathway activity. Although little is known about AR and PI3K pathway activity in normal FTE, we report a **mid-cycle peak in AR** activity which significantly decreases late secretory. **PI3K** pathway activity is the **highest during the proliferative phase** and decreases after ovulation.

The relatively low ER pathway activity in **HGSC** might explain the **minimal effects of anti-hormonal therapy** in these patients. Whereas high **AR or PI3K** activity in HGSC could indicate aberrant activation and may therefore be an **attractive target for therapy in individual patients**.

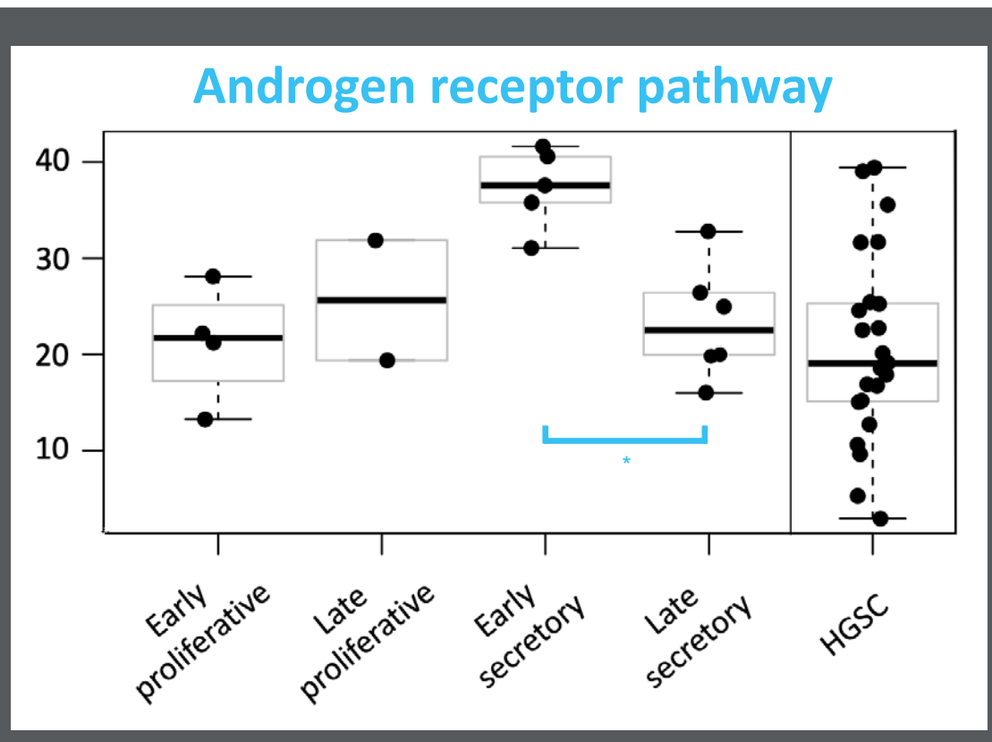

Figure 2. Androgen receptor pathway activity in normal Fallopian tube epithelium during the menstrual cycle and high-grade serous carcinoma. * $p < 0.05$

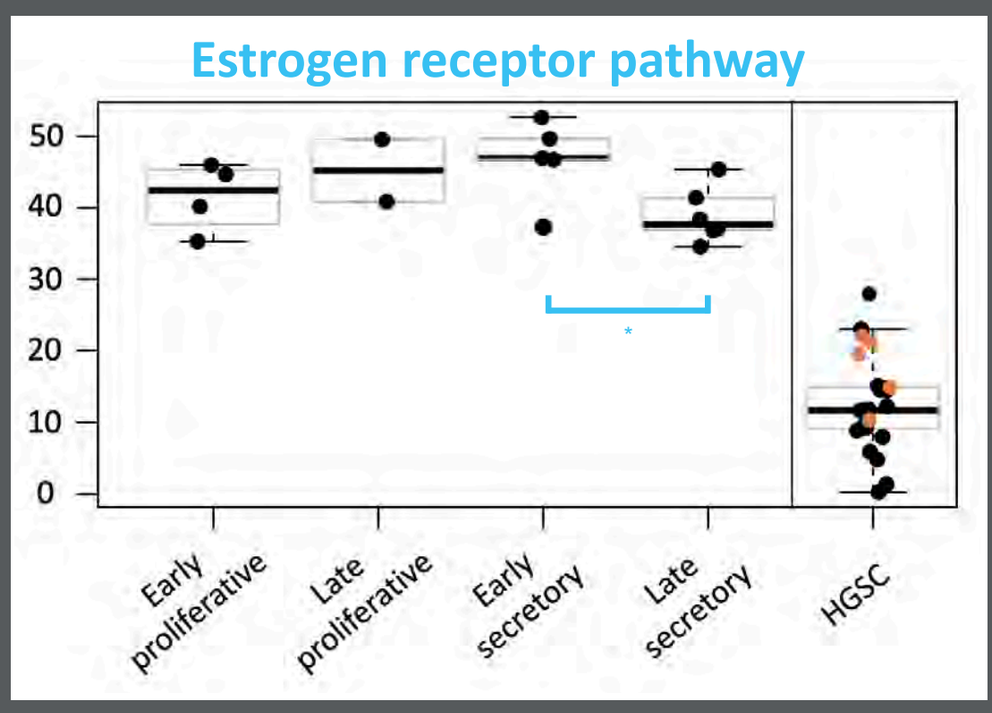

Figure 3. Estrogen receptor pathway activity in normal Fallopian tube epithelium during the menstrual cycle and high-grade serous carcinoma. Orange dots indicate women with high-grade serous carcinoma aged < 50 years at time of diagnosis. * $p < 0.05$

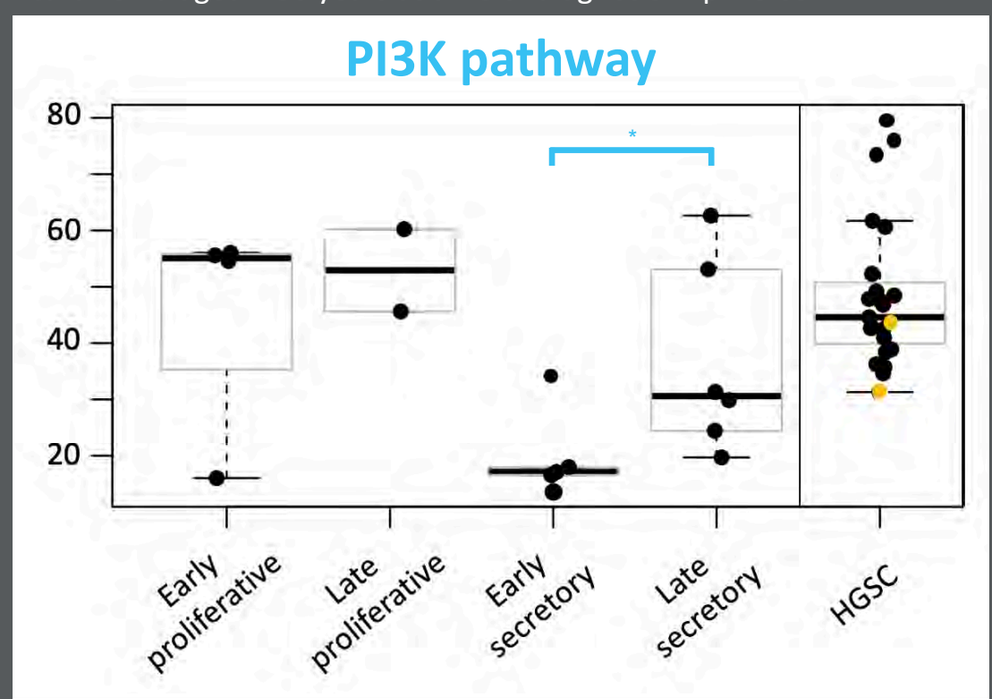

Figure 4. Phosphoinositide 3-kinase (PI3K) pathway activity in normal Fallopian tube epithelium during the menstrual cycle and high-grade serous carcinoma. Yellow dots indicate samples with relative high superoxide dismutase (SOD) activity, indicating high oxidative stress which may lead to lower measured PI3K activity. * $p < 0.05$

References: **1** Piek JM, Verheijen RH, Kenemans P, Massuger LF, Bulten H, van Diest PJ. BRCA1/2-related ovarian cancers are of tubal origin: a hypothesis. Gynecol Oncol. 2003;90(2):491. **2** Verhaegh W, van Ooijen H, Inda MA, Hatzis P, Versteeg R, Smid M, et al. Selection of personalized patient therapy through the use of knowledge-based computational models that identify tumor-driving signal transduction pathways. Cancer Res. 2014;74:2936–45. **3** Verhaegh W, Van de Stolpe A. Knowledge-based computational models. Oncotarget. 2014;5:5196–7. **4** Van Ooijen H, Hornsveld M, Dam-de Veen C, Velter R, Dou M, Verhaegh W, et al. Assessment of Functional Phosphatidylinositol 3-Kinase Pathway Activity in Cancer Tissue Using Forkhead Box-O Target Gene Expression in a Knowledge-Based Computational Model. Am J Pathol. 2018;188:1956–72. **5** Stolpe A van de, Holtzer L, van Ooijen H, de Inda MA, Verhaegh W. Enabling precision medicine by unravelling disease pathophysiology: quantifying signal transduction pathway activity across cell and tissue types. Sci Rep. 2019;9:1603. **6** Van de Stolpe A. Quantitative Measurement of Functional Activity of the PI3K Signaling Pathway in Cancer. Cancers. 2019;11:293.

een santeon ziekenhuis