2023 Ovarian Cancer Canada Tissue Banking Report

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**Information provided by tissue bank leads*

Ovarian cancer tissue banking: A national effort

The Ovarian Cancer Canada (OCC) Tissue Banking Network is a virtual network of tissue banks, currently in five provinces (see Table below). Tissues collected by the OCC Tissue Banking Network have contributed to large national collaborative projects, most notably the Canadian Ovarian Experimental Unified Resource (COEUR). Thanks to the generosity of the women who have donated their tissues and the philanthropic support through OCC and other partners, **the OCC Tissue Banking Network continues to provide valuable tissue resources in support of ovarian cancer research in Canada and around the world.** Those resources have been the foundation for many discoveries that continue to improve ovarian cancer care.

Name	Location	Scientific Lead	Contact
OVCARE's Gynecologic Tissue Bank	Vancouver, BC	Dr. Jessica McAlpine	jessica.mcalpine@vch.ca jkwon@bccrc.ca
Saskatchewan Tumour Testing & Ovarian Cancer Drug Prediction Program	Saskatoon and Regina, SK*	Dr. Laura Hopkins	laura.hopkins@saskcancer.ca
Ottawa Ovarian Cancer Tissue Bank	Ottawa, ON	Dr. Barbara Vanderhyden	bvanderhyden@ohri.ca
CRCHUM Ovarian Cancer Tissue Bank	Montreal, QC	Dr. Anne-Marie Mes-Masson	anne-marie.mes-masson@umontreal.ca
Canadian Ovarian Experimental Unified Resource (COEUR)	Montreal, QC		liliane.meunier.chum@ssss.gouv.qc.ca
Nova Scotia Gynecologic Oncology Tissue Bank	Halifax, NS**	Dr. Stephanie Scott	stephaniea.scott@nshealth.ca

**Opening dates Oct 2021 (Saskatoon) and Feb 2022 (Regina)*

***Opening date Feb 2021*

What is a tissue bank?

A tissue bank, also referred to as a biobank or biorepository, is a resource that collects, stores, and distributes a large number of biological samples to enable scientific research. Collection of samples from individuals with cancer requires informed patient consent; samples are then "de-identified" to protect patient confidentiality. Examples of the types of samples collected by OCC Tissue Banking Network sites include:

- ✓ Tissues/cells from benign, borderline, and malignant ovarian tumours of all types;
- ✓ Tissue/cells from normal ovaries or fallopian tubes;

- ✓ Cells and fluid from ascites;
- ✓ Blood (whole blood, serum, plasma, buffy coat);
- ✓ Saliva.

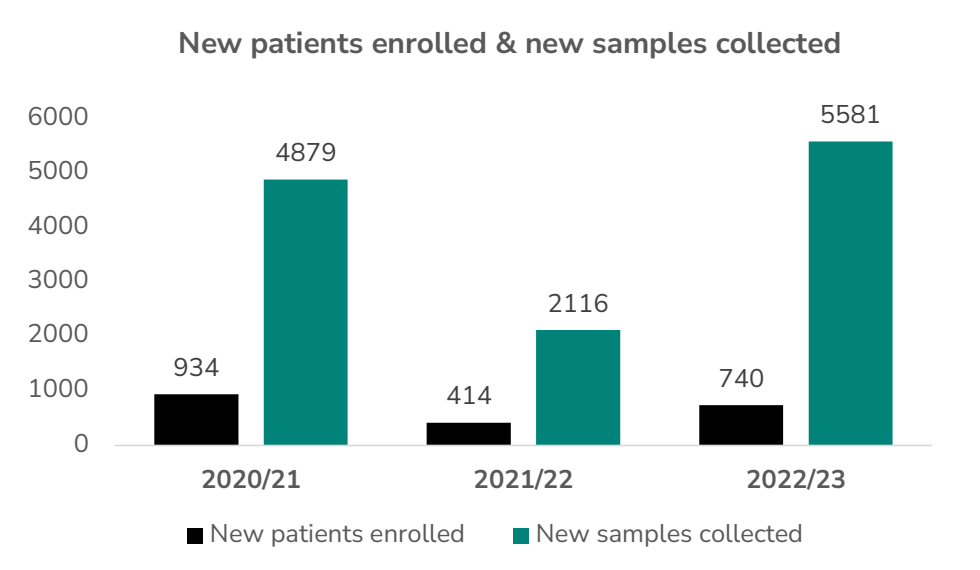
Donated samples are then used by scientists in approved research studies in many ways:

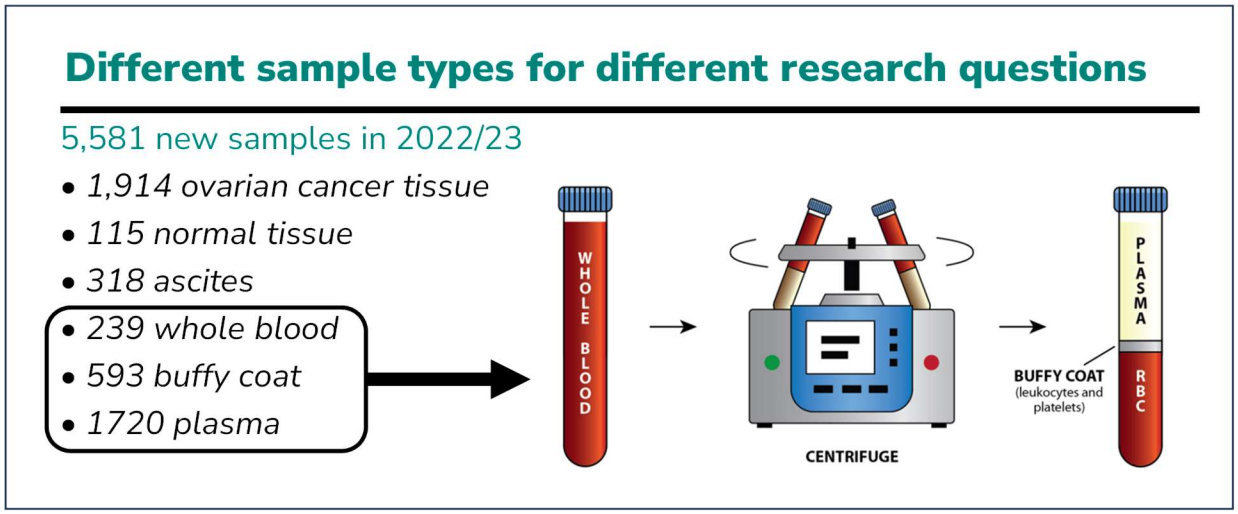
- ✓ To create 2D or 3D cell culture models to test the effect of specific treatments;
- ✓ To sequence DNA, RNA or proteins to identify biomarkers of ovarian cancer or treatment response;
- ✓ To inject into mice for establishment of patient-derived xenografts;
- ✓ To perform immunohistochemistry on tissue sections containing one or many samples to determine the expression of key cancer-associated proteins.

Many of these downstream activities are funded by OCC's OvCAN initiative, together contributing to the establishment of invaluable ovarian cancer research resources for scientists across Canada.

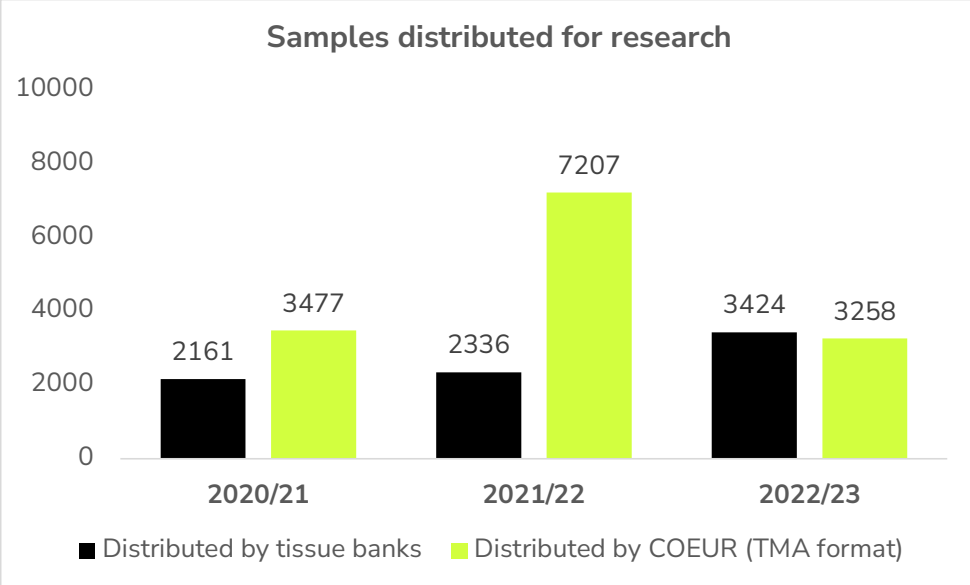
Another year of driving research progress

This year, a total of **740 individuals living with ovarian cancer** generously consented to donate their biologic materials to OCC-supported tissue banks (↑79% from 2021/22). A combined **5,581 samples** were collected from these individuals, (↑264% from 2021/22), providing an invaluable resource for translational research along the ovarian cancer continuum.



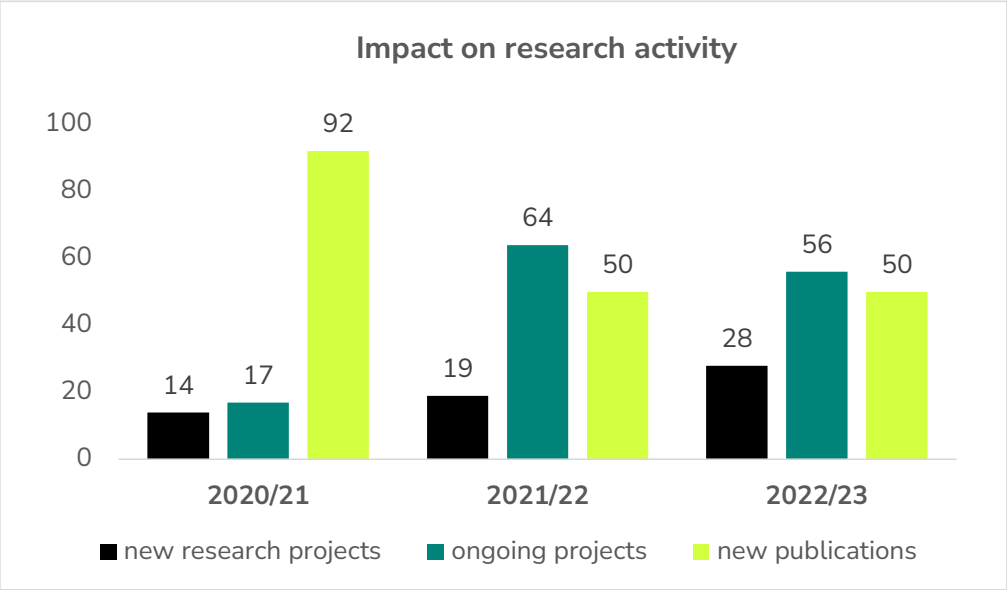


In addition to new collections, a combined **6,682 samples** were distributed to researchers; this included 3,424 samples from tissue banks and 3,258 samples from COEUR. The majority of samples distributed by COEUR were in tissue microarray (TMA) format, to facilitate biomarker studies in a large number of cases.



Tissue bank and COEUR samples were accessed by researchers for **28** new projects during the reporting period; this represents a steady increase over the past two years,

as the field recovers from the COVID-19 pandemic. There was a total of **50** new scientific publications on studies involving biobank samples and/or data.



Research highlights

Uncovering a new potential treatment option for women with small cell carcinoma of the ovary (Huntsman and Wang, BC Cancer; link to paper)

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), is a rare but aggressive type of ovarian cancer that predominantly occurs in young women in their mid-twenties.

L to R: Drs. Yemin Wang and David Huntsman

This cancer type remains difficult to treat as there are few effective treatments, and it is often resistant to conventional chemo-therapies. In previous studies, Dr. David Huntsman and his team investigated the role of two genes, SMARCA4 and SMARCA2, in development of SCCOHT. Building upon this discovery, Drs. Yemin Wang, Huntsman, and colleagues published breakthrough research reporting alanine as a potential new treatment option for SCCOHT. The study shows that, unlike most chemotherapies that kill fast-growing cancer cells and healthy cells, alanine specifically targets cancer cells with deficient

SMARCA4 and SMARCA2 and spares healthy cells (thereby leading to fewer side effects). Proper clinical testing is now needed to ensure the safety and efficacy of this potential new treatment.

The impact of fat cells on response to oncolytic virus therapy (Ilkow lab, Ottawa Hospital Research Institute; link to paper)

Adipocytes (fat cells) in the tumour microenvironment are highly dynamic cells that have an established role in tumour progression. The impact of fat cells on response to anti-cancer therapies is becoming increasingly clear, especially in ovarian cancers which often metastasize to the omentum (a fatty tissue). Dr. Carolina Ilkow's lab investigated the role of adipose tissue and adipocytes in response to oncolytic virus therapy in adipose-rich tumours such as breast and ovarian cancer. They showed that products secreted by fat cells impaired oncolytic virus-driven tumour cell death. Notably, tumours in specific locations rich in fat cells (ovarian fat pad or intrabursal to the ovary) were significantly more resistant to oncolytic virus infection compared to tumours in other locations (subcutaneous). Further investigation of the factors secreted by fat cells revealed that lipids were driving the resistance to oncolytic virus therapy: when lipid moieties were removed, oncolytic virus could then kill the cancer cells. They further demonstrated that blocking the uptake of fatty acids by cancer cells, in combination with treatment with oncolytic virus therapy, could be an effective strategy for improving treatment response.

Enabling international research on centrosome amplification (Brenton lab, Cancer Research UK; link to paper)

L to R: Drs. James Brenton (lead author) and Anne-Marie Mes-Masson (CRCHUM Ovarian Tissue Bank)

Large scale studies require samples and cell lines from multiple biorepositories in order to provide statistical significance to translational studies. In the publication by Sauer and collaborators genomic research addressed centrosome amplification in high-grade serous ovarian cancer. Centrosome amplification was frequent in tumours and was associated with chromosome instability and genome sub-clonality. Cell-based studies were able to

highlight the association between centrosome amplification and treatment resistance, most notably taxol resistance. The authors concluded that centrosome amplification may not only be a driver of tumor evolution but may also act as a powerful biomarker for predicting response to standard of care treatment.

Expanding our understanding of endometriosis-associated ovarian cancer (Anglesio and Huntsman, BC Cancer / University of British Columbia; link to paper)

L to R: Drs. Michael Anglesio and David Huntsman

Endometriosis is a condition where endometrial-like tissue grows outside the uterus, leading to chronic pain, painful periods, and infertility. This condition affects about 10% of women of reproductive age, totaling around 175 million globally. In addition to causing pain and infertility, endometriosis is linked to a higher risk of certain types of ovarian cancer, like clear cell and endometrioid subtypes. Drs. Michael Anglesio and David Huntsman published exciting findings from their research on endometriosis. The research team used single-cell analysis to create a cellular "atlas" of the different cell types found in endometriosis specimens. From the study, they identified molecular characteristics of specific cells found in different forms of endometriosis, uncovering key features of genetic mutations in endometriosis and gene expression profiles of certain types of ovarian cancer associated with this condition.

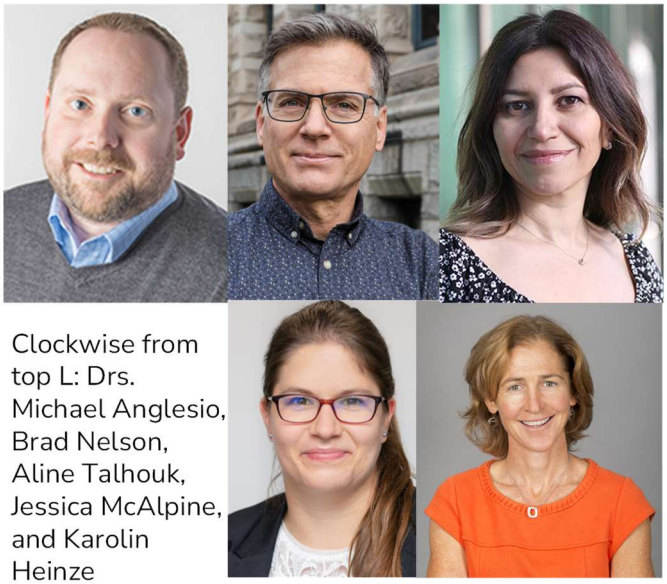
Discovering new genes associated with hereditary ovarian cancer (Tonin lab, McGill University; link to paper)

Previous work has demonstrated that not all familial ovarian cancers can be explained by the known risk genes. Here Alenezi and colleagues (Dr. Patricia Tonin lab) used a novel candidate gene approach to identify genes implicated as drivers in hereditary cases of ovarian cancer. The research was predicated on comparisons between familial and sporadic ovarian cancer patients and an ancestrally defined control group to statistically implicate specific genes related to DNA repair and hereditary ovarian cancer. The

candidate variants identified in this study can be further studied to understand their implication in other populations and analyzed in functional assays to assess the biological impact of the variants. This research was made possible by combining samples from the ovarian and breast tumour banks, as well as the Cartagene French Canadian population biobank.

Unraveling the molecular subtypes of endometrioid ovarian cancer (OVCARE team, BC Cancer / University of British Columbia; link to paper)

Endometrioid ovarian carcinoma is the second most common type of ovarian cancer; however, our understanding of the immune system in this cancer type is limited. OVCARE researchers and colleagues conducted a study exploring the different molecular subtypes of endometrioid ovarian cancer and the immune response across these subtypes. They found that certain subtypes with a high number of mutations had more immune cell activity. They also reported that molecular subtypes were more critical for predicting patient outcomes than immune response alone. The researchers concluded that understanding the different molecular subtypes of endometrioid ovarian cancer is crucial for understanding how the immune system responds to the cancer and should be investigated in future studies.



Clockwise from top L: Drs. Michael Anglesio, Brad Nelson, Aline Talhouk, Jessica McAlpine, and Karolin Heinze

Overcoming resistance to PARP inhibitors (Montreal-Toronto collaboration; link)

A major advance in the treatment of ovarian cancer is the introduction of PARP inhibitors like Olaparib. A major impediment to cure in this context is the development of treatment resistance. Sauriol and collaborators have identified a novel therapeutic option to counter both innate and acquired PARP inhibitor resistance by controlling the production of NAD+ via an essential regulator of the pathway known as nicotinamide phosphoribosyltransferase (NAMPT). Importantly, combinations of Olaparib and a NAMPT inhibitor were effective in overcoming resistance both in mouse pre-clinical

models and in clinically relevant patient-derived organoids. This research was possible thanks to an important collaboration between Canadian researchers and points to a promising new strategy to treat ovarian cancer patients.

Clockwise from top left: Drs. Diane Provencher, Anne-Marie Mes-Masson, Stephanie Lheureux, Amit Oza, Rob Rottapel, Nikolina Radulovich

Annex. New publications made possible by OCC-funded tissue banks and COEUR.

Risk factors & genetic testing

Alenezi WM et al. Case Review: Whole-Exome Sequencing Analyses Identify Carriers of a Known Likely Pathogenic Intronic BRCA1 Variant in Ovarian Cancer Cases Clinically Negative for Pathogenic BRCA1 and BRCA2 Variants. Genes (Basel). 2022 Apr 15;13(4):697. PMID: 35456503

Alenezi W. M. et al. Genetic analyses of DNA repair pathway associated genes implicate new candidate cancer predisposing genes in ancestrally defined ovarian cancer cases. Front Oncol. 2023 Mar 8;13:1111191. PMID: 36969007

Alenezi WM et al. The Genetic and Molecular Analyses of RAD51C and RAD51D Identifies Rare Variants Implicated in Hereditary Ovarian Cancer from a Genetically Unique Population. Cancers (Basel). 2022 Apr 30;14(9):2251. PMID: 35565380

DeVries AA et al. Copy Number Variants Are Ovarian Cancer Risk Alleles at Known and Novel Risk Loci. J Natl Cancer Inst. 2022 Nov 14;114(11):1533-1544. PMID: 36210504

do Valle HA et al. Bone health after RRBSO among BRCA1/2 mutation carriers: a population-based study. J Gynecol Oncol. 2022 Jul;33(4):e51. PMID: 35557034

Fierheller C.T. et al. Molecular Genetic Characteristics of FANCI, a Proposed New Ovarian Cancer Predisposing Gene. Genes (Basel). 2023 Jan 20;14(2):277. PMID: 36833203

Kwon JS et al. Germline Testing and Somatic Tumor Testing for BRCA1/2 Pathogenic Variants in Ovarian Cancer: What Is the Optimal Sequence of Testing? JCO Precis Oncol. 2022 Oct; 6:e2200033. PMID: 36265114

Nitschke AS et al. Long-Term Non-Cancer Risks in People with BRCA Mutations following Risk-Reducing Bilateral Salpingo-Oophorectomy and the Role of Hormone Replacement Therapy: A Review. 2023 Jan 24;15(3):711. PMID: 36765666

Diagnosis

Farahani H et al. Deep learning-based histotype diagnosis of ovarian carcinoma whole-slide pathology images. Mod Pathol. 2022 Dec;35(12):1983-1990. PMID: 36065012

Galan A et al. (2023). GD2 and GD3 gangliosides as diagnostic biomarkers for all stages and subtypes of epithelial ovarian cancer. Front Oncol. 13:1134763. PMID: 37124505

Early events

Alwosaibai K et al. PAX2 induces vascular-like structures in normal ovarian cells and ovarian cancer. Exp. Ther. Med. 2022 Jun;23(6):412. PMID: 35601066

Rare ovarian cancers

Bolton K.L. et al. Molecular Subclasses of Clear Cell Ovarian Carcinoma and Their Impact on Disease Behavior and Outcomes. Clin Cancer Res (2022) 28 (22): 4947–4956. PMID: 35816189

Cheasley D et al. Molecular characterization of low-grade serous ovarian carcinoma identifies genomic aberrations according to hormone receptor expression. 2022 Jun 29;6(1):47. PMID: 35768582.

Fonseca MAS et al. Single-cell transcriptomic analysis of endometriosis. Nat Genet. 2023 Feb;55(2):255-267. PMID: 36624343

Guo N et al. CD8 + T cell infiltration is associated with improved survival and negatively correlates with hypoxia in clear cell ovarian cancer. Sci Rep. 2023 Apr 21;13(1):6530. PMID: 37085560

Heinze K et al. Validated biomarker assays confirm ARID1A loss is confounded with MMR deficiency, CD8 TIL infiltration, and provides no independent prognostic value in endometriosis-associated ovarian carcinomas. J Pathol. 2022 Apr; 256(4): 388–401. PMID: 34897700

Ji JX et al. The proteome of clear cell ovarian carcinoma. J Pathol. 2022 Dec;258(4):325-338. PMID: 36031730

McCluggage WG et al. Well-differentiated Sertoli-Leydig Cell Tumors (SLCTs) Are Not Associated With DICER1 Pathogenic Variants and Represent a Different Tumor Type to Moderately and Poorly Differentiated SLCTs. Am J Surg Pathol. 2023 Apr 1;47(4):490-496. PMID: 36583307.

McCluggage WG et al. An Unusual Enteric Yolk Sac Tumor: First Report of an Ovarian Germ Cell Tumor Associated With a Germline Pathogenic Variant in DICER1. Int J Gynecol Pathol. 2022 Jul 1;41(4):349-355. PMID: 34380971.

Meagher NS et al. Profiling the immune landscape in mucinous ovarian carcinoma. Gynecol Oncol. 2023 Jan;168:23-31. PMID: 36368129.

Meagher NS et al. Gene-Expression Profiling of Mucinous Ovarian Tumors and Comparison with Upper and Lower Gastrointestinal Tumors Identifies Markers Associated with Adverse Outcomes. Clin Cancer Res. 2022 Dec 15;28(24):5383-5395. PMID: 36222710

Praetorius TH et al. Molecular analysis suggests oligoclonality and metastasis of endometriosis lesions across anatomically defined subtypes. Fertil Steril. 2022 Sep;118(3):524-534. PMID: 35715244.

Surgery

Kumar A et al. Into the future: A pilot study combining imaging with molecular profiling to predict resectability in ovarian cancer. Gynecol Oncol. 2022 Sep;166(3):508-514. PMID: 35931468

Long AJ et al. Reoperation and pain-related outcomes after hysterectomy for endometriosis by oophorectomy status. Am J Obstet Gynecol. 2023 Jan;228(1):57.e1-57.e18. PMID: 36029832.

Phung MT et al. Lifestyle and personal factors associated with having macroscopic residual disease after ovarian cancer primary cytoreductive surgery. Gynecol Oncol. 2023 Jan;168:68-75. PMID: 36401943.

Pathology

Gilks CB et al. Data Set for the Reporting of Ovarian, Fallopian Tube and Primary Peritoneal Carcinoma: Recommendations From the International Collaboration on Cancer Reporting (ICCR). Int J Gynecol Pathol. 2022 Nov 1;41(Suppl 1):S119-S142. PMID: 36305537.

'Omics

Funnell T et al. Single-cell genomic variation induced by mutational processes in cancer. Nature. 2022 Dec;612(7938):106-115. PMID: 36289342

Kommoss FKF et al. Genomic characterization of DICER1-associated neoplasms uncovers molecular classes. Nat Commun. 2023 Mar 25;14(1):1677. PMID: 36966138.

Sauer CM et al. (2023), Molecular landscape and functional characterization of centrosome amplification in ovarian cancer. Nat Commun. 14(1):6505. PMID: 37845213

Tessier-Cloutier B et al. The impact of whole genome and transcriptome analysis (WGTA) on predictive biomarker discovery and diagnostic accuracy of advanced malignancies. J Pathol Clin Res. 2022 Jul;8(4):395-407. PMID: 35257510.

Wang C et al. Methylation Signature Implicated in Immuno-Suppressive Activities in Tubo-Ovarian High-Grade Serous Carcinoma. Cancer Epidemiol Biomarkers Prev. 2023 Apr 3;32(4):542-549. PMID: 36790339.

Mechanisms of treatment resistance

Asare-Werehene M et al. Plasma Gelsolin Confers Chemoresistance in Ovarian Cancer by Resetting the Relative Abundance and Function of Macrophage Subtypes. Cancers (Basel). 2022 Feb 18;14(4):1039. PMID: 35205790

Gerber E et al. (2023). Predicting chemoresponsiveness in epithelial ovarian cancer patients using circulating small extracellular vesicle-derived plasma gelsolin. J Ovarian Res 16(1): 14. PMID: 36642715

Kong B et al. (2022) Prohibitin 1 interacts with p53 in the regulation of mitochondrial dynamics and chemoresistance in gynecologic cancers. J Ovarian Res. 15(1):70. PMID: 35668443

Sauriol A et al. (2023). Inhibition of nicotinamide dinucleotide salvage pathway counters acquired and intrinsic poly(ADP-ribose) polymerase inhibitor resistance in high-grade serous ovarian cancer. Scientific reports, 13(1), 3334. PMID: 36849518

Surendran A et al. Fatty acid transport protein inhibition sensitizes breast and ovarian cancers to oncolytic virus therapy via lipid modulation of the tumor microenvironment. Front. Immunol. 2023 Mar 10;14:1099459. PMID: 36969187

Veneziani AC et al. Fighting resistance: post-PARP inhibitor treatment strategies in ovarian cancer. Ther Adv Med Oncol. 2023 Mar 1;15:17588359231157644. PMID: 36872947.

Wong B et al. Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, sensitizes cancer cells to VSVΔ51 oncolytic virotherapy. Mol. Ther. 2023 Nov 1;31(11):3176-3192. PMID: 37766429

Ovarian cancer research models

Dorrigiv D et al. Pixelated Microfluidics for Drug Screening on Tumour Spheroids and Ex Vivo Microdissected Tumour Explants. Cancers (Basel). 2023 Feb 7;15(4):1060. PMID: 36831403

Discovering novel treatment strategies

Bauer TM et al. A Phase Ib Study Assessing the Safety, Tolerability, and Efficacy of the First-in-Class Wee1 Inhibitor Adavosertib (AZD1775) as Monotherapy in Patients with Advanced Solid Tumors. Target Oncol. 2023 Jul;18(4):517-530. PMID: 37278879.

Canals Hernaez D et al. Targeting a Tumor-Specific Epitope on Podocalyxin Increases Survival in Human Tumor Preclinical Models. Front Oncol. 2022 May 4;12:856424. PMID: 35600398

Cremona M et al. BRCA mutations lead to XIAP overexpression and sensitise ovarian cancer to inhibitor of apoptosis (IAP) family inhibitors. Br J Cancer. 2022 Aug;127(3):488-499. PMID: 35501389.

Zhu X et al. Alanine supplementation exploits glutamine dependency induced by SMARCA4/2-loss. Nat Commun. 2023 May 20;14(1):2894. PMID: 37210563

Prognostic factors

Kang EY et al. CCNE1 and survival of patients with tubo-ovarian high-grade serous carcinoma: An Ovarian Tumor Tissue Analysis consortium study. Cancer. 2023 Mar 1;129(5):697-713. PMID: 36572991.

Köbel M et al. p53 and ovarian carcinoma survival: an Ovarian Tumor Tissue Analysis consortium study. J Pathol Clin Res. 2023 May;9(3):208-222. PMID: 36948887.

Orr NL et al. KRAS mutations and endometriosis burden of disease. J Pathol Clin Res. 2023 Jul;9(4):302-312. PMID: 36977195.

Weir A et al. Increased FOXJ1 protein expression is associated with improved overall survival in high-grade serous ovarian carcinoma: an Ovarian Tumor Tissue Analysis Consortium Study. Br J Cancer. 2023 Jan;128(1):137-147. PMID: 36323878.