Gynecologic Cancer Initiative

TRAINEE RESEARCH DAY 2025

Abstract Booklet

June 12, 2025
8:15 am to 5:00 pm

VGH Paetzold Auditorium, 899 West 12 Ave, Vancouver

A hybrid event to showcase the exciting trainee research on gynecologic cancers happening around British Columbia.

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Survivorship & Quality of Life Posters

Evaluating a digital health tool, eSense-Cancer, for sexual difficulties after gynecologic cancer

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Objectives: To evaluate a digital health tool, eSense-Cancer, that addresses sexual difficulties among gynecologic cancer survivors and compare two different methods of treatment delivery: with or without “navigator” support.

Study methods: Eligibility criteria were: >19 years old, history of gynecologic cancer, sexual difficulties, clinically significant sexual distress, and in a relationship. Participants completed a baseline questionnaire of demographic questions, the Female Sexual Distress Scale–Revised (FSDS-R), and the PROMIS Sexual Function and Satisfaction Measure V2.0 Brief Profile (SexFs). The FSDS-R consists of 13 items, scored 0-52, with scores ≥11 indicative of clinically significant sexual distress. The SexFs includes 8 domains and enables score comparisons to the US general female population; a SexFs score in the 50th centile represents the average female population domain score. Participants then underwent a 4-week waiting time, completed a post waitlist questionnaire (FSDS-R and SexFs), and started eSense-Cancer. Those assigned to a navigator met regularly with their navigator (student trained in active listening) throughout treatment. After 16 weeks, participants completed a post-treatment questionnaire consisting of baseline measures plus measures of treatment satisfaction, global impressions, and the navigator relationship.

Results: To date we have recruited 26 of 60 participants and recruitment is ongoing. On average, participants (n=26) were aged 54 (SD=12.97) and diagnosed with cancer 10 years ago (SD=10.59). All gynecologic cancer subtypes were represented in the sample: 7 had cervical, 5 had ovarian, 1 had vulvar, 2 had vaginal, and 11 had uterine/endometrial. Most (n=23, 88.46%) underwent cancer-related surgery, and many received chemotherapy (n=9, 34.61%) and radiation (n=7, 26.92%). The average FSDS-R score at baseline was 29.92 (SD=8.66): indicating high sex related distress. SexFs scores at baseline demonstrated average sexual interest in the 11th centile and sexual satisfaction in the 19th centile. Among participants who were sexually active in the last 30 days (n=17, 65.38%), the average lubrication score was in the 11th centile, vaginal discomfort was in the 91st centile, labial discomfort was in the 78th centile, and clitoral discomfort was in the 69th centile. Average orgasm ability was in the 28th centile, and average orgasm satisfaction was in the 24th centile.

Conclusion: Participants demonstrated marked sexual distress and below-average scores on all sexual function and satisfaction domains at baseline. Future analyses will compare FSDS-R and SexFs scores pre-and post-wait period, pre- and post-treatment, and between navigator and non navigator groups. If eSense-Cancer is deemed effective, it will be scaled up for widespread use through ongoing eSense™ commercialization efforts.

Window of opportunity for cancer prevention: Metachronous BRCA-associated breast and ovarian cancers in British Columbia

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Objectives: To evaluate patients with metachronous BRCA-associated breast and ovarian cancer in British Columbia (BC), Canada, including ages and intervals between first and secondary cancer diagnoses, uptake and timing of genetic testing and risk-reducing interventions.

Study methods: This retrospective population-based cohort study used data from the High Risk Clinic (HRC) of the BC Cancer Hereditary Cancer Program from 1998-2022 and Provincial Pharmacy between 1995-2024. The Pharmacy database was first searched for those prescribed olaparib for advanced-stage high-grade serous ovarian cancer (HGSC) as a surrogate for BRCA pathogenic variant (PV) and linked to those prescribed a breast cancer treatment protocol either before or after olaparib.

Results: From HRC, there were 336 breast and 50 ovarian cancer patients, of whom 10 and 3 developed metachronous ovarian and breast cancer, respectively (crude rates 3% and 6%). From the Pharmacy database, an additional 194 patients were identified as having been prescribed olaparib for advanced HGSC. Seventeen (8.8%) received prior breast cancer treatment, and 3 (1.5%) developed subsequent breast cancer. An additional six (3%) patients were diagnosed with synchronous breast and ovarian cancer. The median age at first cancer diagnosis was 51 years (range 32-71), and the median interval to second cancer was 6 years (range 0-31). Of patients with breast cancer first, 10/15 (67%) subsequently had risk-reducing bilateral salpingo oophorectomy (RRBSO) at a median age of 58.5 years (range 42-72). There were 6 patients with triple-negative breast cancer at a median age of 45 (range 41-64), and although all were eligible for BRCA testing, only 2 (33%) were tested. Of the 6 patients diagnosed with breast cancer after ovarian cancer, the median interval was 5 years (range 2-11). None had risk-reducing mastectomy, but 5/6 had breast cancer surveillance.

Conclusions: These data demonstrate a long time interval between BRCA-associated breast and ovarian cancers, implying a sufficient window of opportunity for BRCA testing and risk-reducing surgery. Patients with triple-negative breast cancer often did not undergo BRCA testing after that diagnosis, leaving them vulnerable to metachronous ovarian cancer.

OCEAN Challenge: Advancing AI for Generalized Ovarian Cancer Diagnosis

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Objectives: Artificial Intelligence (AI) shows promise in histotyping of ovarian carcinoma, however, its validation across diverse hospitals is limited by biases affecting performance on new data. To address this, we launched Ovarian Cancer subtypE clAssification and outlier detectioN (OCEAN) competition, offering access to the largest and most diverse ovarian cancer histopathology dataset, promoting the development of more generalized models.

Study methods: The OCEAN dataset includes 2,463 samples across training, public, and private test sets, featuring Whole Slide Images (WSIs) and Tissue Microarrays (TMAs) from 24 centers across four continents. The dataset covers five main ovarian cancer histotypes and outliers (Table 1). Its diversity reflects variations in patient demographics, tissue processing, and staining protocols. Participants used the training set (n = 538) to build AI models and assessed performance on the public test set (n = 437), with winners determined by the private test results (n = 1488).

Results: The event drew global interest with 9,247 registrations and 1,772 entrants from 84 countries. Winners mainly used AI foundation models for feature extraction from patches (tiny parts of slides) and applied attention-based multiple instance learning for slide labeling. The top balanced accuracy and Cohen's Kappa for classifying the five histotypes were 65.89% and 0.5543 (TMAs at 68.91% and 0.5753, and WSIs at 67.24% and 0.5938). In outlier detection, the highest balanced accuracy was 70.15% (TMAs and WSIs at 95.45% and 26.09%). TMAs perform better due to the prevalence of normal tissue, whereas WSIs mainly contain rare histotypes. Pathology review of a random subset of misclassified samples by top models showed low tumor content, poor staining quality (i.e. old, faded slides), challenging histomorphology features (i.e. reasonable misdiagnosis as another tumor that was in the histological differential diagnosis), and occasionally normal tissue (e.g. diagnosing normal fallopian tube as LGSC) as potential reasons for misclassification.

Conclusions: The OCEAN filled a key gap by testing algorithms on multi-center datasets to build generalizable models. Many misclassified cases were not truly representative of their histotypes, indicating model performance may be better with more standardized input. Moreover, analyzing WSIs with larger fields of view instead of small patches and evaluating multiple slides per patient could enhance diagnostic accuracy. We acknowledge the contributions of the OCEAN Consortium, OTTA Consortium, Michael Smith Foundation, and Kaggle to this project.

Development of humanized PDX mouse model for high grade serous ovarian cancer

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Introduction: High-grade serous ovarian cancer (HGSOC) is one the most lethal gynecological cancer, accounting for 70% deaths and with a 5-year survival rate below 50%. Traditionally, HGSOC are considered 'immune-cold' tumors, characterized by low immune infiltration and poor response rates to single agent immune checkpoint blockers (ICB). To improve the therapeutic potential of immunotherapies in HGSOC, combination treatments are being applied such as the Phase 2 MEDIOLA trial, which aims to identify mechanisms of response and resistance. A major challenge in this field remains the lack of suitable preclinical models for ICB-based treatments. Although patient-derived tumor xenografts (PDX) are valuable for developing new therapies, they are limited by the absence of an immunocompetent host. Here we present humanized mouse models incorporating human immune cells.

Study methods: Female NRG-W41-3GS mice (ENW) aged 7-8 weeks were used to generate the humanized PDX model. HGSOC tumors originally sourced from human patients and maintained in our laboratory's previous PDX models using NRG mice, were injected subcutaneously into ENW mice. After 3 weeks, 5x104 human hematopoietic CD34+ cells collected from umbilical cord blood of healthy donors were intravenously injected via the tail vein. To monitor human cell engraftment, bone marrow (BM) aspiration was performed at week 6 post-CD34+ cell injection, and peripheral blood (PB) samples were collected from saphenous vein starting from week 7 until the experimental endpoint. BM and PB samples were analyzed by flow cytometry using antibodies against human CD45 and mouse CD45 to determine humanization level. Tumors were harvested at the endpoint, embedded in paraffin, and remaining tumor tissues were cryopreserved for future. To confirm human immune cell infiltration into the tumors, fresh frozen paraffin embedded tumor sections were immunohistochemically stained with rabbit anti-human CD45 antibodies.

Results: We successfully generated sixteen huENW PDX mice. Robust engraftment of human CD34+ cells was confirmed in each mouse, with human CD45+ cells ranging from 35% to 90% (mean ± SD: 76.2 ± 18.5%) in BM samples and from 7% to 35% in PB samples. The huENW PDX model have revealed strong evidence of human immune infiltration with CD45+ cells on immunohistochemistry of the PDX tumors and spleen.

Conclusions: Humanized mouse models offer a valuable resource for advancing HGSOC research. Our model demonstrated significant engraftment of human immune infiltration into HGSOC tumors. We believe our model has the potential to enhance our understanding of HGSOC clonal diversity, microenvironment interactions, and contributing to the development of new therapies.

A Spoiled Egg Laid by the Uterus That Ovary Hatched: Rethinking Clear Cell Ovarian Carcinoma through the Lens of Transsulfuration

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Objectives: The ***overarching goal*** of this research is to investigate how cystathionine gamma-lyase (CTH), a key enzyme of the Transsulfuration (TSS) pathway, contributes to the emergence of clear cell ovarian carcinoma (CCOC) as a largely chemoresistant cancer and whether targeting CTH could be a useful treatment.

Study methods: Well-established CCOC cell lines, including OVISE, RMG1, and OVMANA with or without CTH KO, tumor xenografts with or without CTH KO, and patients' clinical samples from our Gynecological Tissue Bank (GTB) were utilized. CTH's contributions to the CCOC cell aggressiveness and its hypoxic signature were evaluated through a comprehensive framework incorporating an array of molecular tools as well as in vivo studies, aimed at identifying various biological functions to identify different biological functions in CCOC under ambient conditions, hypoxia, and ovarian cyst content treatment. Furthermore, the therapeutic benefits of targeting CTH in CCOC was investigated. Unless otherwise indicated, statistical analyses were conducted using Student's t-test or one-way ANOVA with post hoc Tukey test for multiple comparisons in GraphPad Prism, with p-values <0.05 considered statistically significant.

Results: We found that, in CCOC and its precursor cells, CTH expression is induced under stress, enabling tumor cells survival under harsh microenvironmental conditions and drives tumor progression via inducing HIF1α expression typical of this cancer. CTH binds HIF1A mRNA and associates with eIF4E, a central component of the eIF4F translation initiation complex, to facilitate HIF1A mRNA translation, indicating a novel non-canonical, moonlighting activity for CTH. Inactivating CTH attenuated CCOC metastatic potential in vivo and sensitized it to chemotherapy and mTOR inhibition. CTH, through both the TSS pathway and moonlighting activities, is a defining feature of CCOC and a novel therapeutic target for CCOC patients and potentially other CTH-expressing cancers.

Conclusions: CTH confers a broad level of cell plasticity to CCOC and its precursor cells. This enables such cells to survive the hypoxic, ROS-rich microenvironment of the endometrial cyst via redox regulation and enhanced HIF1α expression. The dependency of CCOC on CTH expression may present a therapeutic opportunity for this hard-to-treat cancer through targeting this transsulfuration enzyme.

G6PD-dependent metabolism as a potential targetable pathway in ARID1A mutant gynecological cancers

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Background: AT-rich interactive domain-containing protein 1A (ARID1A), a core subunit of the SWI/SNF chromatin remodeling complex, is one of the most frequently mutated genes in gynecologic malignancies, including endometrial and clear cell ovarian cancers. Our results from single-cell RNA sequencing demonstrated that S100A4 is upregulated in our ARID1A mutant organoid models, which was further validated in wild-type and ARID1A mutant CCOC and endometrial cancer cell lines. S100A4 is a calcium-binding protein that interacts with structural proteins to promote metastasis of cancer cells. However, the exact mechanism is still unknown. To understand the mechanism of S100A4 in our model, we performed immunoprecipitation of S100A4 followed by mass spectrometry analysis (IPMS) in 4 different ARID1A mutant cancer cells to analyse the interactome partners of S100A4. The results demonstrated that Glucose-6- phosphate dehydrogenase (G6PD) interacts with S100A4 in all 4 cell lines. G6PD is the rate limiting enzyme in the pentose phosphate pathway (PPP) that maintains cellular NADPH levels to support redox balance and biosynthetic processes, suggesting a potential link between ARID1A mutation and altered metabolic regulation in gynecologic cancers.

Objectives: To investigate the functional consequences of S100A4-G6PD interaction.

Study methods: To evaluate metabolic changes, mitochondrial and glycolytic function were assessed using the Seahorse XF assay in HEC1B S100A4 KO and control cells. Sensitivity to PPP disruption was assessed by treating HEC1B S100A4 KO and control cell lines with a G6PD inhibitor.

Results: Preliminary results from Seahorse XF analysis revealed that S100A4 KO cells exhibited significantly reduced maximal oxygen consumption rate (OCR), indicating impaired mitochondrial respiratory capacity. Additionally, initial experiments including G6PD inhibitor treatment led to decreased proliferation in S100A4 KO cells compared to control cells.

Conclusions: Our data suggest a potential link between the S100A4–G6PD interaction and altered metabolic regulation in ARID1A-mutant gynecologic cancers. Further investigation into the functional and biological consequences S100A4 and G6PD interaction may uncover novel metabolic vulnerabilities in ARID1A mutant gynecological cancers.

HPV integration may alter the epigenetic landscape and immunogenicity of extrachromosomal DNAs in cervical cancer

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Objectives: Cervical cancer, a human papillomavirus (HPV)-driven malignancy, remains the fourth deadliest cancer in females. Approximately 25% of primary cervical cancer samples are predicted to contain circular amplicons called extrachromosomal DNAs (ecDNAs). Often harbouring oncogenes, ecDNAs are known cancer drivers. However, neither ecDNAs containing only human DNA (i.e. human-only ecDNAs) or ecDNAs containing both HPV and human DNA (i.e. HPV-human hybrid ecDNAs) are well characterized in terms of their epigenetic regulation. Thus, we hypothesized that human-only and HPV-human hybrid ecDNAs in cervical cancer differ in their epigenetic regulation.

Study methods: We profiled ecDNAs in a Ugandan cervical cancer cohort (n = 118) using short-read whole-genome sequencing (WGS), RNA-sequencing (RNA-seq), long-read WGS (n = 72), and chromatin immunoprecipitation sequencing (ChIP-seq; n = 50).

Results: We report that 30% (35/118) of cervical cancer samples contained one or more predicted ecDNAs. Human-only ecDNAs (74% of ecDNAs) were larger on average (p-value = 1.5 x 10-2, Two-sided Mann-Whitney U test), whereas HPV-human hybrid ecDNAs (26% of ecDNAs) more often contained epigenetically active enhancers (particularly viral enhancers; $p < 0.01$, ANOVA), contained a higher density of structural variants (SVs; p-value = 6.0 x 10-4, Two-sided Mann-Whitney U test), and invariably bore the HPV oncogenes E6 and E7. HIV+ samples containing HPV-human hybrid ecDNAs had higher T-cell infiltration scores compared to other samples in the cohort (p-value = 0.029, ANOVA), and when HPV-human hybrid ecDNAs were present at higher copy numbers, this effect was more pronounced, suggesting that HPV-human hybrid ecDNAs may be immunogenic, possibly due to their viral DNA cargo. We also found that E6 expression was increased (adj. p-value = 0.027, Welch's two-sided t-test) and E2 expression was decreased (adj. p-value = 1.2 x 10-3, Welch's two-sided t-test) among HPV-human hybrid ecDNA-containing samples, inferring that HPV-human hybrid ecDNAs represent a form of HPV integration that promotes higher HPV oncogene expression. Although ecDNAs contained few allelic differentially methylated regions (aDMRs), we found an interesting example of two aDMRs overlapping the LINC02902/C7orf65 gene promoter within an ecDNA locus. Currently we are validating our short-read WGS results using a more direct ecDNA sequencing method, called CRISPR-CATCH, as well as investigating HPV-human hybrid transcripts from ecDNAs using long-read cDNA-sequencing.

Conclusions: Overall, our study in cervical cancer found significant differences in ecDNA structural and epigenetic features between ecDNAs containing HPV DNA compared to those without. Our study also highlights how HPV integration may form immunogenic ecDNA structures.

Multicohort development and validation of a reproducible vaginal microbiome model for endometrial cancer detection

Dollina Dodani and Aline Talhouk

Objective: To develop a robust vaginal microbiome classifier to identify individuals with endometrial cancer (EC). The vaginal microbiome has emerged as a promising source of non invasive biomarkers for gynecologic cancers, but inconsistent bioinformatics and limited reproducibility have impeded clinical translation. Endometrial cancer is the second most common gynecological cancer worldwide, yet there are no established screening programs. A vaginal microbiome signature derived from minimally invasive testing could assist in early detection.

Study methods: We conducted a retrospective multicohort analysis using publicly available 16S rRNA gene sequencing data from five studies (N=265) to assess the predictive value of vaginal microbiome profiles for endometrial cancer. After benchmarking bioinformatics pipelines to ensure the reproducibility of commonly reported microbiome metrics, such as alpha/beta diversity and differentially abundant taxonomic features, we selected a robust preprocessing approach. We then developed an ensemble classifier that integrates microbial features with individual characteristics, including age, body mass index (BMI), and ethnicity.

Results: The combined model accurately identified all individuals with EC in in an independent validation cohort, achieving an Area Under Receiving Operating Characteristic curve of 0.93 (95% CI: 0.71–0.93), negative predictive value of 1.0 (95% CI: 0.59–1.0), and sensitivity of 1.0 (95% CI: 0.74–1.0). Alpha diversity was sensitive to processing pipelines, while beta diversity patterns were driven by patient factors (age, BMI, and ethnicity) than disease status. Certain taxa, including Peptoniphilus, showed consistent enrichment in EC cases across all five studies.

Conclusions: This work demonstrates the feasibility of using vaginal microbiome data, coupled with individual characteristics, for EC screening and early detection. Our open-source pipeline and rigorous evaluation support its utility as a reproducible, non-invasive tool in precision

Toward a General-Purpose Search Engine in Pan-Cancer Computational Pathology

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Objectives: To develop the first fully unsupervised framework for building generalizable patient representations by integrating histopathology whole slide images (WSIs) with pathology reports. The goal is to enable scalable, label-free search, biomarker discovery, and survival prediction across diverse cancer types.

Study methods: Our approach combines large vision models (LVMs) for WSI analysis with large language models (LLMs), including OpenAI's and Google's models, for pathology report representation. We introduce the Boltzmann Semantic Score (BSS) to quantify the alignment between modalities and identify semantic gaps. Guided by these insights, we develop a WSI representation method using textual semantics as a guidance mechanism. Training is conducted on the TCGA datasets, covering over 12,000 patients and 30+ cancer types (30 TB of data). Evaluation is conducted on over 27 different public and private datasets (50 TB of data), including gynecological cancers.

Results: Language-guided models significantly outperform existing self-supervised and retrieval baselines in organ-specific search and subtype prediction tasks. Among LLMs, Google's Gemini produced the most clinically meaningful embeddings, resulting in better WSI alignment and higher semantic (clinical) consistency. The framework, guided by Gemini, demonstrates robust performance despite significantly smaller training sets and model sizes compared to baseline models over 10 datasets from different cancers (so far 10 datasets from a total of 27 evaluation datasets have been benchmarked and the rest are in progress).

Conclusions: This work introduces a novel, unsupervised multi-modal learning strategy that paves the way for a general-purpose search engine in computational pathology for interpretable visual and textual biomarker discovery. By aligning images and expert-written narratives, it enables interpretable, label-free profiling of patients and supports real-world use cases such as rare cancer detection and clinical decision support in precision oncology.

Complication rate of bilateral salpingectomy by indication in British Columbia

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Objectives: There is substantial evidence supporting the safety of opportunistic salpingectomy for ovarian cancer prevention. However, there is growing interest in the use of salpingectomy as a standalone procedure for ovarian cancer prevention. While there is some evidence about complication rates of bilateral salpingectomy when done for the indication of permanent contraception, the patient population who may undergo salpingectomy for cancer prevention is likely to differ in important ways from the population of patients requesting tubal sterilization. This study aims to evaluate the short-term surgical outcomes of bilateral salpingectomy performed as a standalone surgical procedure, specifically examining complication rates across different surgical indications and patient age groups.

Study methods: This retrospective population-based cohort study utilized administrative healthcare data from British Columbia, Canada, from January 1st, 2008, to December 31st, 2022. We included 7,102 people who received bilateral salpingectomies performed without concurrent surgical procedures. The primary outcome was a composite measure of complications, defined as any of the following: intensive care unit admission, return to the operating room, surgical complications, readmission, or complications diagnosed during physician visits. Postoperative outcomes were also assessed up to six weeks after discharge and included hospital readmissions, outpatient complications, frequency of diagnostic tests, and prescriptions for analgesics or antibiotics. We report both univariate and adjusted odds ratios for surgical outcomes, comparing salpingectomy performed for prophylactic versus contraceptive indications, as well as across different age groups.

Results: We found an overall complication rate of the composite complication rate of 2.8%, representing 28 complications per 1,000 surgeries. Complication rates were nonsignificant between surgical indications, with a rate of 2.7% for contraception and 4.5% for prophylaxis. We found no statistically significant differences in the odds of complications, postoperative diagnostic tests (laboratory, X-ray, or ultrasound), or prescriptions for NSAIDs or opioids between the contraceptive and prophylactic groups. However, patients who underwent salpingectomy for prophylaxis had significantly lower adjusted odds of same-day discharge compared to those in the contraceptive group (adjusted odds ratio: 0.16; 95% confidence interval: 0.06–0.43). No significant differences in surgical outcomes were observed between patients aged 35–45 and those younger than 35 or older than 45.

Conclusions: These results provide evidence supporting the safety of bilateral salpingectomy as a standalone surgical procedure. Overall complication rates were low, with most post-operative complications being minor within six weeks of discharge. The findings suggest that bilateral salpingectomy can be considered a safe surgical intervention with minimal short-term risks.

Global Adoption of Opportunistic Salpingectomy for Ovarian Cancer Prevention: A Review of FIGO Member Society Guidelines

Seerit Boparai, Dr. Gillian Hanley

University of British Columbia

Objectives: This study aims to assess the global recommendations for opportunistic salpingectomy (OS) as a preventive strategy against ovarian cancer, by reviewing the policies and clinical guidelines of International Federation of Obstetrics and Gynecology (FIGO) member societies.

Study methods: The websites of all 138 FIGO member societies were reviewed to identify position statements or clinical guidelines referencing OS. If a society's website was unavailable, email or fax inquiries were sent to request information. National gynecologic oncology guidelines were also consulted where necessary. Societal stances were categorized as supportive, neutral, or opposing OS.

Results: Of the 138 FIGO member societies, 101 had publicly accessible websites. A total of 24 countries were found to formally support OS through written and published clinical guidelines, position statements, or expert letters. These countries span North America, Europe, Asia, and South America. No country formally opposed OS. Although emails and faxes were sent to 37 societies without websites, no additional data were received. The findings suggest growing international acceptance of OS as a cancer prevention strategy, as in 2018 only 9 societies had statements supporting OS.

Conclusions: This study demonstrates a significant global shift toward the endorsement of opportunistic salpingectomy to reduce ovarian cancer risk. While formal support has expanded across diverse regions, variations in uptake highlight ongoing disparities influenced by healthcare infrastructure and resource availability. Continued efforts are necessary to promote equitable access to opportunistic salpingectomy worldwide and to further investigate informal practices where formal guidelines are absent.

Long-term risk of developing cervical pre-cancers among women ≥50 years: a comparative study of negative primary HPV versus normal cytology screen results.

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Objectives: The long-term risk of cervical precancer after a negative Human Papillomavirus (HPV)-based screen in older women remains a significant knowledge gap. Clarifying this risk is critical to determine whether screening intervals can be safely extended and whether HPV screening can end at earlier ages than currently recommended. The objective of this study was to compare the risk of CIN2+ and CIN3+ (i.e., cervical intraepithelial neoplasia grade 2 or worse and grade 3 or worse) following a negative HPV-based screen versus a normal cytology-based screen in women aged ≥50 years.

Study methods: This study used 14 years of data from two robust data sources: the HPV-FOCAL trial and the British Columbia Cervical Cancer Screening Program. Two HPV-screened cohorts (HPV1: single negative screen, n=2,036; HPV2: two consecutive negative screen, n=2,263) were compared to a cytology-based screening cohort (BCS: single negative cytology screen, n=237,325). Incidence rates and hazard ratios for cervical precancer were calculated.

Results: The overall incidence rates per 1,000 person-years for CIN2+ were 2.46 (95% CI: 1.05- 5.75) for HPV1, 2.66 (95% CI: 1.22-5.79) for HPV2, and 4.40 (95% CI: 4.14-4.68) for BCS. For CIN3+, rates were 1.97 (95% CI: 0.77-5.05), 1.33 (95% CI: 0.45-3.90), and 3.20 (95% CI: 2.98- 3.44), respectively. Age-stratified analyses revealed decreasing incidence rates with increasing age across all cohorts, with no cases of CIN2+ or CIN3+ detected among women ≥60 years in the HPV-screened cohorts. The hazard ratio for CIN3+ was significantly lower in HPV1 (HR 0.08, 95% CI: 0.03-0.20) and HPV2 (HR 0.45, 95% CI: 0.20-1.02) compared to BCS.

Conclusions: After 14 years of follow-up, women ≥50 years with a negative HPV screen had a 92% lower risk of cervical precancer compared to those with a normal cytology screen. These findings support extending screening intervals and adopting more personalized, risk-based screening protocols for older women following negative HPV screens.

Temporal trends in contraceptive use in British Columbia, Canada between 2001 and 2021: a descriptive analysis

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Objectives: This study reports the changing trends in contraceptive use in BC, Canada. It is important to understand how contraceptive choices are changing to ensure that effective contraception is offered. However, contraceptive choices also have important implications for health beyond reproductive outcomes, particularly in altering an individual's risk for gynecologic cancers and breast cancer.

Design: Retrospective population-based descriptive study analyzing contraceptive use in BC, from 2001-2021.

Subjects: All individuals assigned female at birth, aged 15-55 in BC.

Exposure: We examined forms of irreversible and reversible contraception that were reliably captured in our databases. Irreversible forms of contraception captured included tubal sterilization (tubal ligation or bilateral salpingectomy), and reversible forms included combined oral contraceptives, progestin-only pills, vaginal rings, transdermal contraceptives, levonorgestrel-intrauterine systems (LNG-IUS), and inert intrauterine devices.

Main Outcome Measures: We used BC Pharmanet, data from visits with health care providers, and the hospital data to report annual rates of each form of contraceptive use. Temporal trends, stratified by age and income, were analyzed using linear regression models. Intrauterine device use is measured in incident use (new insertions) and prevalent use (assuming used for 5 years following insertion).

Results: The study found significant changes in contraceptive use in BC from 2001-2021. The incident and prevalent use of the LNG-IUS increased significantly by 0.1185 (95% CI: 0.110, 0.127) and 0.626 (95% CI: 0.587, 0.648) percent point changes per year, respectively. Combined oral contraceptives use and tubal sterilization declined by -0.2155 (95% CI: -0.270, -0.161) and -0.01 (95% CI: -0.013, -0.009) percent point changes per year, respectively. Younger age groups increasingly opted for the LNG-IUS, reflecting a preference for long-acting reversible contraceptives, as illustrated by a -0.239 (95% CI: -0.275, -0.203) change in median age per year.

Tubal sterilizations decreased significantly (-0.011%) over this period and shifted away from tubal ligations (-0.023%) and towards bilateral salpingectomies (0.015%).

Conclusions: There have been important shifts away from use of combined oral contraceptives towards the LNG-IUD over the past 20 years in BC, which was more pronounced for younger age groups. These changes may increase incidence for ovarian cancer, while decreasing incidence for endometrial cancer. The effects for breast cancer remain unclear.

Temporal trends in BRCA1 and BRCA2 testing over time in patients with ovarian cancer in British Columbia

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Background: High grade serous ovarian cancer (HGSC) is the most common and lethal histotype of ovarian cancer. Approximately twenty-five percent of patients with HGSC have a germline BRCA1 or BRCA2 pathogenic variant (PV). Given the lack of effective screening methods for ovarian cancer, prevention via genetic testing and risk-reducing interventions remains the best method for reducing the burden of ovarian cancer. An important prevention initiative for ovarian cancer is to identify more BRCA PV carriers before they are diagnosed with cancer. Changes in the treatment of HGSC, specifically the use of PARP inhibitors, mean we now have more than just prevention reasons to ensure that these cancer patients are tested for BRCA PV. To maximize prevention efforts while offering patients appropriate personalized therapies, we must ensure that high proportions of HGSC patients get genetic testing.

Study methods: To investigate, a population-based retrospective study was conducted in the province of British Columbia (BC) that included all patients diagnosed with serous ovarian cancer between 2001 and 2018. BRCA1 and BRCA2 PV genetic testing information from 2001-2019 was obtained from the Hereditary Cancer Program.

Results: During 2001-2018, 3638 patients were diagnosed with serous ovarian cancer in BC. Of these patients, 1512 were tested for BRCA1 and BRCA2 PV at the Hereditary Cancer program in BC during 200-2019. The number of serous ovarian cancer patients who got BRCA PV testing in BC increased from 12% of those diagnosed in 2001 to 68% of those diagnosed in 2018. Overall, 41% of patients with serous ovarian cancer diagnosed in BC in this period had genetic testing (1512/3638). A total of 259 (17%) had a BRCA1 or BRCA2 PV. For every one patient with serous ovarian cancer identified as a BRCA carrier, 1.61 (±2.29) carrier tests were performed in their family. The minimum number of carrier tests performed per BRCA-positive patient was 0, and the maximum was 19.

Conclusions: This work illustrated that a significantly higher proportion of patients with serous ovarian cancer diagnosed in 2018 received genetic testing than at the start of the study period, but that over 30% of these patients did not get tested. This implies that while BRCA testing rates are improving, there remain missed opportunities to identify BRCA carriers in this patient population. Carrier testing uptake also remains low, further limiting prevention opportunities. Additional efforts may be needed to ensure patients are supported in communicating positive results to relatives.

Risk Evaluation and Screening to Tailor Prevention and Reduce the Incidence of Endometrial Cancer

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Background: Endometrial cancer (EC) incidence is increasing worldwide and is projected to rise by 50% in the next decade. As EC prevalence increases, it is necessary to identify those at high risk and implement risk reduction protocols. Risk modeling can identify high-risk individuals by predicting absolute risk using known risk factors. The Risk Evaluation and Screening to Tailor prevention and Reduce the incidence of Endometrial cancer (RESToRE) study uses a risk model to identify high-risk individuals for further intervention. This project aimed to further understand the associations between various EC risk factors through an exploratory data analysis using the RESToRE study data.

Study methods: The RESToRE study data (n = 619) was collected on a REDCap database through a REDCap-generated survey. The survey inquires about reproductive history, hormone treatments, medical history, lifestyle, and demographics. The RESToRE data was visualized using a variety of graphing methods. Codes were developed to calculate absolute risk for three EC risk models: the Pfeiffer et al. model, the Husing et al. model, and the Shi et al. model. The data was run through each model, and an absolute risk criterion of 2 was utilized to identify high-risk participants. The data was also analyzed to determine which participants were identified as high-risk by all versus some models to assess whether the models coincide with their risk score assessments.

Relevance: Cancer screening and corresponding risk-reduction programs are essential for prevention, early diagnosis, and timely treatment. The findings of this project contribute to current knowledge of EC risk factors and risk models. These results can assist clinicians in fine-tuning EC risk models to detect high-risk individuals early and administer preventive programming. Further studies can build on the risk models investigated within this project and potentially result in a provincial EC screening program to reduce the incidence of EC in British Columbia.

Non-Invasive Strategies for Early Detection of Uterine Cancer in Patients with Abnormal Uterine Bleeding

Jennifer Ellis-White, Karman Johal, Dr. Andrea Neilson, Dr. Aline Talhouk

Background: In 2024, an estimated 8,600 Canadian women were diagnosed with uterine (endometrial) cancer, with an estimated mortality of 1,600 people. Abnormal uterine bleeding (AUB) typically presents as the first noticeable symptom of endometrial cancer (EC) and its precursors. Although AUB prompts the detection of EC via endometrial biopsy, it is a non specific symptom that is purported to afflict up to 30% of women, most commonly during perimenopause period. Given the low specificity of AUB in predicting cancer, better indicators prior to endometrial biopsy are needed to effectively risk-stratify patients who are at higher risk of EC and limit unnecessary biopsies for those at lower risk. Study objectives are to integrate population-based epidemiological risk scores, calculated from health questionnaires of participants referred for endometrial biopsy due to AUB, with biological biomarkers to improve EC risk prediction and identify opportunities for earlier intervention.

Study methods: Individuals aged 35 years or older scheduled to undergo diagnostic evaluation for AUB via endometrial biopsy are invited to participate in Part A of the study at the time of their endometrial biopsy appointment by their gynecologist. In Part A, participants will provide vaginal samples via swabs (DNA, microbiome) and a pH kit during their biopsy visit as well as self-reported health history via a questionnaire. A smaller cohort of participants from Part A will be invited to Part B of the study, which involves a 6-month longitudinal data monitoring period via weekly health questionnaires and a wearable health monitor (Fitbit) to track health data including exercise, sleep, and heart rate over time. At the conclusion of Part B, eligible participants will be invited to perform a vaginal self-collection via swabs (DNA, microbiome) and a pH kit to assess for persistent or resolved somatic mutations associated with EC or its precursors.

Relevance: Health questionnaire and biological data can be integrated to train a model that predicts pathology which can be utilized to predict the onset of EC or its precursors. Considering the prevalence of asymptomatic patients diagnosed with EC and the low specificity of AUB as a noticeable symptom of EC or its precursors, a non-invasive approach to EC cancer screening can improve patient outcomes through the reduction of unnecessary biopsies, enhanced accessibility, and earlier detection.

The role of minimally invasive screening for endometrial cancer surveillance in patients with Lynch syndrome

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Background: Lynch syndrome (LS) is a hereditary cancer syndrome caused by germline mutations in DNA mismatch repair genes, which increase the lifetime risk for various cancers, including endometrial (49%) and ovarian (17%). Despite the substantial risk for developing these cancers, LS gynecologic screening recommendations remain unclear, and the survival benefit has not been determined. In British Columbia (BC), patients with LS are recommended to self monitor and undergo risk-reducing surgery at age 35-40 or once childbearing is complete, which can lead to premature surgical menopause and other complications. For patients without surgery, recommendations are to consider annual endometrial biopsy with transvaginal ultrasound, which is an invasive approach to regular screening. However, there is a potential screening role for detecting endometrial cancer (EC)-associated biomarkers from minimally invasive vaginal sampling. This study aims to investigate healthcare services utilization and screening in the female LS population and evaluate LS patient attitudes and acceptability of a vaginal self-swab method for EC screening.

Study methods: Population Data BC and the BC Cancer Hereditary Cancer Program (HCP) administrative data will be used to evaluate a female LS cohort. Healthcare services utilization, screening trends and prevention strategies will be compared between and within individuals with and without cancer to investigate differences in health outcomes. Data from the Lynch-SCAN trial will be used to evaluate LS patient perceptions of novel EC screening approaches. The trial will enroll ~30 LS patients aged ≥ 30 years who have an intact uterus and have not been diagnosed with EC. Participants will complete a questionnaire to collect demographics and analyze reproductive and medical histories and LS experiences. They will conduct an at-home vaginal sample collection kit including two vaginal swabs to analyze somatic DNA mutations and the microbiome, and a pH test kit. Participants will then complete an acceptability questionnaire developed using the Theoretical Framework of Acceptability to assess participant attitudes toward the EC screening approach.

Relevance: Despite their strong genetic cancer predisposition, research has shown that LS gynecologic cancer surveillance is low. By evaluating current patterns in healthcare, we can identify gaps in care that affect high-risk populations. Understanding current surveillance adherence and attitudes towards self-screening as a tool for surveillance can help inform future screening recommendations and areas for research. A minimally invasive, accessible approach for regular EC screening in individuals living with LS could promote earlier cancer detection and improved survivorship in these patients.

Evaluating public knowledge of HPV self-screening tests and reasons for patient preferences of provider- versus self-collected cervical cancer/HPV screening tests

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Background: Cervical cancer is one of the top three most prevalent cancers in women younger than 45. The implementation of organized population based screening using the pap test has significantly decreased the incidence of cervical cancer. In January of 2024, BC transitioned to HPV primary screening with an option for self-sampling. HPV testing is more accurate than the pap test with higher sensitivity and higher negative predictive value. Additionally, HPV self-sampling addresses traditional barriers to cervix screening participation including cultural or religious sensitivities, history of trauma and access. Self-sampling improves equity by increasing accessibility to cervical cancer screening in marginalized populations, those who do not have a primary care provider, and individuals who have never been screened or do not screen frequently. Given the recent rollout of HPV self-swabs in BC, the present study aims to evaluate the public's perceived knowledge of HPV self-screening tests and the reasons why patients may prefer provider- vs self-collected samples.

Study methods: Papapalooza education workshops are being held at UBC Vancouver, UBCO, UVic, UNBC. These education workshops are single-day, community-based events organized by UBC medical students often in collaboration with other community organizations, to offer more information about cervical cancer and/or cervical cancer screening topics. All participants who attend a Papapalooza education workshop will be invited and eligible to participate in our survey study. The survey is designed to address the study objectives, focusing on perceived knowledge and preferences regarding cervical cancer screening. Specific variables studied include confidence, knowledge, and acceptability of HPV self-screening. The surveys include multiple-choice, short-answer, and Likert scale questions.

Relevance: This project aims to understand general public perception of their own knowledge of cervical cancer screening, and reasons why people may prefer self-sampling vs provider-collected samples. This will add to the evidence base of cervical cancer screening and provide practical information on the preferences of the BC patient population.

Feasibility and Acceptability of Endometrial Cancer Screening and Risk-Reduction Interventions in High-Risk Populations

Nimmy Sebastian, Arabella Helgason, Rachel Woima, Dr. Jessica McAlpine, Dr. Anna Tinker, Dr. Michael Anglesio, Dr. Andrea Neilson, Dr. Aline Talhouk

Uterine cancer is a major health concern, particularly for postmenopausal women at elevated risk due to factors like obesity. Early detection can improve outcomes and reduce the need for invasive procedures, such as endometrial biopsies. This study evaluates the feasibility and acceptability of screening and risk-reduction interventions while exploring the potential of vaginal fluid DNA and microbiome testing to predict biopsy results. Recruitment ended in November 2024, with 575 participants enrolled. High-risk postmenopausal women, identified via a risk assessment questionnaire, undergo a progesterone challenge test (PCT) to assess estrogen-driven endometrial proliferation. Participants also self-collect vaginal fluid samples using tampons and vaginal swabs. Swabs are stored in the OVCARE gynecological tumor bank, while tampons are processed for genetic material extraction. DNA analysis, including extractions and targeted sequencing of endometrial cancer-associated genes. Microbiome samples are processed at Microbiome Insights using next-generation sequencing. Feasibility is assessed based on enrollment (≥80%), retention (≥50%), and adherence (≥75%). We anticipate that molecular testing will predict biopsy outcomes, potentially reducing the need for invasive procedures. This study has the potential to refine endometrial cancer screening, offering a less invasive, personalized approach to prevention. Findings will inform future research on early detection, risk stratification, and intervention strategies.

Balancing Cancer Risk with Progestogen Therapy: A Research Proposal

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Background: Endometrial cancer (EC) arises when there is unopposed estrogen without sufficient counteracting progesterone. In individuals with this imbalance, progestogen hormone therapy (HT) can counteract the effects of estrogen. However, current literature presents conflicting evidence regarding the association between progestogen HT and breast cancer (BC) incidence. Despite strong evidence supporting the protective effects of progestogens on the endometrium, large-scale, population-based studies evaluating the balance of benefits and risks across different HTs in Canadian populations are lacking. The objectives of this research are to; 1) characterize how females in British Columbia and Alberta use HTs, 2) examine the incidence rates of EC and BC in women based on HT use, timing of exposure, duration and administration and 3), using an epidemiological risk model, identify how EC and BC incidence varies with different risk factors.

Study methods: This study is a retrospective, population-based cohort analysis using British Columbia and Alberta administrative data. Eligible individuals are those assigned female at birth, residing in either province between January 1, 1999, and December 31, 2023, and must be 35 years or older by January 1, 2018. Exposure groups will be defined based on HT type, administration method, duration of use, and HT initiation. HT exposures will be identified through British Columbia's PharmaNet and Alberta's Pharmacy Information Network. The CANPATH database will be used to assess individual risk factors with the epidemiological risk model. Cancer outcomes will be captured via linkage with British Columbia and Alberta Cancer Registries. The primary outcomes are incident cases of EC and BC diagnosed at least three years post-exposure. Cancer incidence rates will be calculated per 100,000 person-years. Associations between hormone therapy exposure and cancer risk will be estimated using Poisson regression and Cox proportional hazards models, adjusting for age, calendar year and potential confounders. The Pfieffer model will assess independent risk factors and their impact on EC and BC incidence by comparing the expected-to-observed cases ratio.

Relevance: Clarifying how different HTs influence cancer risk will provide essential insights for preventive care and clinical decision-making. By analyzing population-level data, this study will help identify subgroups who may benefit most from HT while minimizing potential risks. Ultimately, this research aims to bridge critical knowledge gaps and guide evidence-based recommendations for hormone therapy use in Canadian populations.

Investigating STING Pathway in Low Grade Serous Ovarian Cancer

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Background: Low grade serous ovarian carcinoma (LGSOC) is one of five major histotypes of ovarian carcinomas. It is a rare histotype with a relatively stable genome and is slow growing, resulting in it often going undetected until late stage. In comparison, the more common high grade serous histotype (HGSOC) has a more unstable genome, making it a more aggressive cancer. The stimulator of interferon genes (STING) pathway is an innate immune signalling system that activates interferon-beta type I production through phosphorylation when cytosolic double-stranded DNA (dsDNA) is detected. Stromal interaction molecule 1 (STIM1) is a protein involved in regulating cellular calcium levels and interacts with the STING protein. STIM1 prevents STING from translocating out of the endoplasmic reticulum (ER) and phosphorylating the STING pathway when not in the presence of cytosolic dsDNA, preventing autoimmune reactions. Abnormally high expression of STING protein has been observed in LGSOC compared to HGSOC, however, there is low STING signalling. STIM1 is also observed to be abundant in LGSOC, and we believe it may play a role in the defective STING pathway in LGSOC.

Study methods: Multiple LGSOC cell lines and two HGSOC cell lines as controls were treated with dsDNA through lipofection for 1/3/5 hours to activate the STING pathway. Poly I:C, an RNA equivalent was used as a control, as it does not trigger the STING phosphorylation but instead the retinoic acid-inducible gene I (RIG-I) pathway, which converges downstream with the STING pathway. The cell lines are then prepared for immunofluorescence to investigate STING translocation from the ER to Golgi apparatus and western blot to investigate the phosphorylation of proteins in the STING pathway. The same western blots were also performed on LGSOC cell lines that had their STIM1 gene knocked out using CRSIPR-Cas9 to observe the constitutive activation of STING pathway in STIM1 KO cell lines. Additionally, qPCR was performed on the cell lines to quantify the STING:STIM1 ratio.

Relevance: The research on this innate immune response may lead to potential immunotherapeutic approaches for LGSOC by reactivating the STING pathway when inhibiting STIM1, providing a stronger immune response by the STING pathway. By repeating the experiments with viruses instead of dsDNA, there is an opportunity to observe virus-activated immune response against cancerous cells. Alternatively, oncolytic virus therapy may be able to take advantage of the compromised STING pathway in LGSOC.

Dual targeting of cystathionine gamma-lyase and mTOR pathway in clear cell ovarian cancer

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Background: Clear cell carcinoma of the ovary (CCC) is the 2nd most common ovarian cancer and is histologically and clinically distinct from other subtypes. Deep endometriosis of the ovary, known as endometrioma or endometriotic cyst, is the most common precursor for CCC. Recently, we identified cystathionine gamma-lyase (CTH), a key enzyme in the transsulfuration pathway, as a marker of Mullerian tract derived ciliated cells and CCC of both the ovary and uterus regardless of which mutations are present. Our recent studies showed that inhibiting CTH expression has led to remarkable attenuation of CCC metastatic capacity in vivo, , alongside an increase in both proliferative potential and apoptosis. Facing a scarcity of clinically viable CTH inhibitors, our team conducted a computer-aided screening using the ZINC22 database, which houses over 40 billion commercial compounds, ultimately identifying 22 compounds with the potential to inhibit CTH by binding to its active site. Further, we found that CTH confers CCC with metastatic fitness via post-transcriptional regulation of hypoxia-inducible factor 1 alpha (HIF1α). In CCC, HIF1α expression is driven mainly by the highly active PI3K/AKT/mTOR pathway, which enhances HIF1α translation. While mTOR inhibitors such as Everolimus successfully inhibit HIF1α in CCC, it has no impact on CTH expression. So, we hypothesized that dual targeting CCC with CTH and mTOR inhibitors might represent a novel treatment strategy for patients with CCC.

Study methods: We used well-established CCC cell lines, including OVISE, OVMANA, and RMG1. Cells were treated with CTH inhibitor, mTOR inhibitor, or combined treatment, and effects on cell proliferation and mTOR pathway activity were assessed using IncuCyte, western blotting, and MTT assay. Growth rate differences will be measured using the Hill slope coefficient in GraphPad Prism, with significance assessed by a Student's t-test against the Hill slope of Aviglycine hydrochloride, a commercial CTH inhibitor.

Result: Our in vitro data demonstrate that targeting CTH alone using Aviglycine increases cell proliferation, which, surprisingly, confers a therapeutic advantage when combined with an mTOR inhibitor. Intriguingly, the combination of Aviglycine and 10nM Everolimus was more potent than treatment with 20nM Everolimus alone. Among the 22 identified CTH inhibitors, 4 exhibited superior synergy with mTOR inhibitors compared to Aviglycine, the control CTH inhibitor from prior research. This suggests a novel therapeutic strategy for CCC through CTH and mTOR inhibitor combination.

Conclusions: Targeting CTH in CCC and potentially other cancers might represent a novel and impactful therapeutic approach. Particularly, the combined treatment of CTH and mTOR inhibitors may present novel therapeutic strategies for individuals with CCC. The current research underway is optimizing better dose usage and CTH inhibitors (among the 22) for applying combined treatment in both in vitro and in vivo studies.

Relevance: Targeting cystathionine gamma-lyase (CTH) in clear cell carcinoma of the ovary (CCC) is a significant advancement in gynecologic cancer treatment. Given CCC's aggressive nature and limited treatment options, identifying CTH as a key marker offers a promising intervention. Dual targeting of CTH and mTOR pathways highlights an innovative approach to enhance treatment efficacy and address the need for novel therapies. Ongoing optimization of dose usage and CTH inhibitors in both in vitro and in vivo studies underscores this research's potential impact, aligning with the Gynecologic Cancer Initiative's mission to reduce incidence, death, and suffering.

Integrated multi-omics approach for the characterization of molecular outliers in endometrial carcinoma

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Background: The ProMisE molecular classification system groups patients into: POLEmut, MMRd, p53abn, and no specific molecular profile (NSMP). It is increasingly used to guide treatment decision-making in endometrial carcinoma (EC). NSMP patients make up the largest group, and while most of these patients have good outcomes, there exists a subset of patients with unexpectedly poor outcomes. Additionally, there are some NSMP EC patients with uncommon histological classifications, where the molecular profiles are not well understood. This study aims to use a multi-omics approach to better understand the underlying molecular drivers of these outlier ECs and to identify potential targets that can be used in clinically applicable assays for the identification of these EC types.

Study methods: We have identified 42 mesonephric NSMP patients, 102 DDEC NSMP patients, 37 poor outcome endometrioid NSMP patients, 14 ER-negative endometrioid NSMP patients, 15 p53abn-like NSMP patients, and 65 good outcome NSMP control patients. For each of these patients, we have obtained several types of data, including tissue microarray, immunohistochemistry (IHC), multiplex IHC, shallow whole genome sequencing, proteomics, whole genome sequencing, and histological images.

Unsupervised clustering methods built for multi-omics datasets (MOFA2, DIABLO, iClusterBayes, SNF Fusion) will cluster these patients into diUerent groupings, testing each approach on its ability to diUerentiate the patients based on prediction of outcome and risk stratification. DiUerential expression will then be performed for each modality according to the clusters, followed by gene ontology, revealing the underlying biological pathways diUerentiating the clusters. Potential assay targets will also be identified using the diUerential expression results.

Relevance: Currently, all patients in the NSMP group are assumed to have good survival and will not receive any aggressive treatments. Splitting this group into multiple classifications that can diUerentiate their survival will allow physicians to better care for these patients and provide more aggressive treatment to those with worse survival odds. This will, in eUect, improve their prognosis, as they can start on the proper treatment plan at an earlier time.

AI-Powered Pathology Image Analysis for Classifying Aggressive and Non-Aggressive Endometrial Cancer Subtypes

Supervisor: Dr. Ali Bashashati
Presenter: Maedeh Mirzazadeh

Endometrial cancer (EC) is one of the most prevalent gynecological malignancies, with early detection and accurate classification playing a pivotal role in improving patient outcomes. The ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) system, developed from the Cancer Genome Atlas (TCGA) in 2013, stratifies EC into four prognostic subtypes: (i) POLE mutant (POLEmut), (ii) mismatch repair deficient (MMRd), (iii) p53 abnormal (p53abn), and (iv) No Specific Molecular Profile (NSMP). Recent advances in artificial intelligence (AI)-based histopathology image analysis have enabled differentiation between the p53abn and NSMP subtypes, revealing a subset of NSMP patients, termed ‘p53abn-like NSMP,’ who exhibit significantly worse survival outcomes.

This project explores the potential of leveraging AI and deep learning to analyze pathology images, specifically Tissue Microarray (TMA) and Whole Slide Imaging (WSI), for classifying EC into aggressive and non-aggressive subtypes. By applying advanced image-based techniques, we aim to enhance the precision of classifying endometrial cancer subtypes based on visual data, complementing molecular profiling.

The integration of AI-driven image-based tools into clinical workflows can significantly refine prognostic assessment within ProMisE subtypes, potentially guiding treatment decisions. Specifically, AI can aid in determining the appropriate surgical approach and direct which patients require comprehensive molecular testing. Furthermore, the use of AI at first triage may facilitate early identification of patients requiring tailored treatment plans, thus improving patient outcomes and advancing personalized medicine in endometrial cancer care.

Developing models to study HER2 intratumoural heterogeneity in p53abn endometrial cancers

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Background: Endometrial cancer (EC) is the most common gynecologic cancer in North America, with the p53 abnormal (p53abn) subtype being the most aggressive and lethal, accounting for approximately 15% of all EC cases, but responsible for 50-70% of EC mortality. We have previously found that 21% of p53abn EC are human epidermal growth factor 2 (HER2) positive on immunohistochemistry, with a wide range of HER2+ tumour cells (intratumoral heterogeneity). Clinical cutoffs for HER2 expression have not been assessed and are critical for future clinical trial design. The objective of this study is to develop models of HER2 heterogeneity to be used to study treatment response.

Study methods: Cell line models will be created from fresh or viably frozen surgical tissue or tissue from previously made patient derived xenografts (PDXs). The tissue is digested with collagenase, followed by a red blood cell lysis, further digestion with dispase, and trypsin-EDTA. To optimize digestion, single cells were plated at three stages; before digestion, post-collagenase digestion, and at the end of the protocol. The attachment and morphology of the plated epithelial cells were assessed.

Fluorescence-activated cell sorting (FACS) for HER2+/EPCAM+ and HER2-/EPCAM+ populations was optimized on breast cancer cell lines, testing HER2 antibody concentrations of 0.25x, 0.5x, 1x, and 2x to find the optimal concentration. Using the optimized protocol, sorting of HER2+/EPCAM+ and HER2-/EPCAM+ populations derived from a viably frozen tumour was performed.

Results: The cells plated after collagenase digestion yielded the best results, as cells plated before digestion, and cells plated at the end of digestion had poor attachment and morphology.
Optimization of the FACS protocol determined that the antibody concentrations recommended by the manufacturer provided the most optimal results. Additional optimizations to the labelling protocol, including the method of cell dissociation and filtering prior to analysis, further improved FACS results. Applying the optimized protocol to a viably frozen patient sample yielded 37.6% HER2+/EPCAM+ and 56.3% HER2-/EPCAM+ cell populations.

Future Directions: With optimized cell culture and FACS protocols, viably frozen patient tumours will be sorted into HER2+/EPCAM+ and HER2-/EPCAM+ populations and expanded in cell culture for experiments using anti-HER2 therapies.

Relevance: Patients with p53abn EC represent a major therapeutic challenge, and treatment options remain limited with significant improvements in survival lacking. The results of this study will help determine the significance of intratumor HER2 heterogeneity and the therapeutic implications for anti-HER2 therapy in this aggressive subtype.

Identifying tumor heterogeneity and phenotypic plasticity in response to drugs in high-grade serous ovarian cancer at the single-cell level

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Background: Half of high-grade serous ovarian cancers (HGSOC) are homologous recombination deficient (HRD), meaning they cannot accurately repair double-stranded DNA breaks and must rely on error-prone pathways. This vulnerability is exploited by poly (ADP-ribose) polymerase inhibitors (PARPi), which selectively target HRD tumors, offering significant progression-free survival benefits in first-line maintenance settings. Current guidelines recommend platinum-based chemotherapy followed by PARPi maintenance. However, the genomic instability and intratumor heterogeneity characteristic of HGSOC contribute to frequent relapse and resistance. Since most clinical trials follow the platinum-first sequence, it remains unclear if this strategy offers the best outcomes or if starting with PARPi might improve survival. Clarifying this requires deeper insight into tumor composition and drug-induced changes. In this study, we aim to explore how tumor composition changes following exposure to PARPi and platinum alone, as well as in reverse sequence. Recent advances in single-cell technologies now enable simultaneous co-measurement of genome, chromatin accessibility, and transcriptomes using single-cell DNA and multiome ATAC-sequencing to study tumor clones at unprecedented resolution.

Study methods: Treatment-naïve, HRD tumor samples have been collected from patients and Case 1 has completed sequential drug exposure. We will select three HRD tumors to treat with sequential therapy: platinum followed by PARPi or PARPi followed by platinum, along with untreated PDX lines. The fitness of clones after sequential drug treatment will be assessed through competitive growth experiments. Clonal composition will be analyzed at each passage using single-cell sequencing. We will use established computational tools to assess clone-specific copy number (CN) profiles and trajectory based differential expression analysis. Tumor microarrays will also be prepared for biomarker analysis.

Results: From scWGS data of case 1 PDX, we observed initial clonal heterogeneity leading to emergent clones in later passages. CN changes were found on chromosomes 19, 8, and 3, along with TP53 loss of heterozygosity on Chr17p. Despite normal ploidy, focal CN alterations were visible in all plasma samples. In patient 1, gains and amplifications appeared on chromosomes 3 and 8, with losses on 4, 15, and 16. Bulk tumor CN profiles of patient 1 and corresponding PDXs closely matched those from the same patient's plasma.

Relevance: This study will deepen our understanding of how HGSOC tumors evolve under different treatments. By tracking clonal dynamics and selective pressures from specific treatment sequences, we aim to identify biomarkers, predictive signatures, and tumor cell mechanisms of response.

Relevance: This study will deepen our understanding of how HGSOC tumors evolve under different treatments. By tracking clonal dynamics and selective pressures from specific treatment sequences, we aim to identify biomarkers, predictive signatures, and tumor cell mechanisms of response.

Unraveling the Cellular and Molecular Characteristics of Mesonephric-Like Adenocarcinoma: A Multi-Omics Approach

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Background: Endometrial cancer (EC) is the most common gynecologic cancer, with incidence and mortality rising and expected to continue increasing. The biggest challenge in this disease is identifying high-risk patients to accurately inform prognosis, guide surgery, and provide optimal adjuvant therapy to improve outcomes.

Mesonephric-like adenocarcinoma (MLA) is a rare and understudied EC histotype. MLA often resemble low-risk EC under the microscope and is frequently misdiagnosed, however it is clinically aggressive, with increased risk of early lungs metastasize. Misclassification of MLA can lead to undertreatment. The goals of these studies are to perform in depth characterization of MLAs and to create models to study these tumors.

Study methods: Shallow whole genome sequencing (sWGS) was performed on 42 of MLAs and 73 controls (endometrioid EC) at a depth of 0.1-3X. A multiplex immunohistochemistry (IHC) panel was used to identify immune cell infiltration in MLA tumors compared to other EC histotypes. Fresh, viably frozen surgical tumor samples were implanted subcutaneously into immunocompromised mice to develop patient derived xenografts (PDXs). Tumor tissue was processed and plated into cell culture to develop cell lines for further analysis.

Results: Copy number analysis from sWGS revealed recurrent gains of chromosomes 1q, 10, and 12, and losses of chromosomes 1p, 9p, 18, and X. MLAs tend to have an “immune cold” phenotype, with few immune infiltrates observed in the tumors. Two PDX models have been developed to date which resemble the primary tumor by histology and protein marker expression. Cells are being maintained in culture to make cell line.

Conclusions and Future Directions: MLAs display a pattern of chromosomal instability that may drive mesonephric tumorigenesis and an immune cold phenotype. Further characterization, including targeted panel sequencing to detect recurrent mutations, proteomics, spatial transcriptomics and artificial intelligence histopathology will be performed. PDX and cell culture models of MLAs being developed will be used for future studies.

Digital Storytelling as a Therapeutic and Resiliency Tool: Insights from Endometriosis Management and Applications in Cancer Research

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Background: Endometriosis is a debilitating gynecological condition affecting approximately 10% of women worldwide and an unmeasured number of transgender and gender-diverse individuals. Characterized by the presence of endometrial-like tissue outside the uterus, endometriosis is marked by chronic pelvic pain, significant menstrual irregularities, potential fertility issues, and an increased risk of developing clear cell and endometrioid ovarian cancers. Despite various therapeutic options such as hormonal therapies and surgical interventions, endometriosis remains incurable, and symptoms often persist. The persistent and recurrent nature of the condition parallels the long-term management challenges seen in chronic diseases such as gynecological cancers. Digital Storytelling (DST) has emerged as a valuable arts-based methodology in the context of those living with endometriosis, facilitating personal and emotional processing, enhancing social support, and contributing to the resiliency narrative in chronic disease management. Previously used in oncology as a legacy-making intervention, DST has been shown to benefit individuals by promoting acceptance of their experiences and condition, supporting symptom management, and improving quality of life.

Study methods: This study engaged 36 individuals with endometriosis in 7-week virtual DST workshops. In these workshops, participants co-created 3–5-minute personal stories about their endometriosis journey. Data collection was multifaceted, incorporating participant reflective journals to capture in-depth personal narratives, and researcher observations to assess immediate reactions to and engagement in the workshops. Data analysis was guided by a qualitative, Interpretive Description approach, with findings highlighting participants' use of chronic pain management, and their cultivation of emotional resilience and community ties. The program will culminate in a public film festival, where participants' digital stories will be showcased, thereby supporting other people with endometriosis, strengthening community awareness, and attuning healthcare providers to the multifaceted challenges caused by endometriosis.

Relevance: This study not only underscores the efficacy of DST in enhancing emotional processing in people with endometriosis but also highlights its potential applicability as a therapeutic tool in other chronic conditions such as cancer. The findings suggest relevance of DST in chronic disease management, through the bolstering of resilience and quality of life across diverse patient populations. The insights gained may guide future therapeutic interventions, fostering improved coping strategies, and better health outcomes for those affected by chronic illnesses.