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Meeting report from the 2018 12th Biennial Ovarian Cancer Research Symposium detection and prevention of ovarian cancer

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ABSTRACT

The objective of this review is to summarize recent research advances in the detection and prevention of ovarian cancer and discuss the experts' opinions of future directions. The 12th Biennial Ovarian Cancer Research Symposium was held in Seattle, Washington, in September 2018. At this meeting, experts in ovarian cancer research gathered to present and discuss recent breakthroughs and their visions of future ovarian cancer research. Session 1 of the symposium focused on the detection and prevention of ovarian cancer. It included two invited oral presentations from Ranjit Manchanda, MD, PhD (Barts Cancer Institute) and Rosana Risques, PhD (University of Washington). Another eight oral presentations were selected from abstract submissions. Fifteen abstracts were presented in poster format. These presentations covered topics including cellular origin of high-grade serous cancer, risk factors for ovarian cancer, new methods for early detection of ovarian cancer, mechanisms underlying ovarian cancer development, and new therapeutic approaches for preventing ovarian cancer from forming or progressing. In conclusion, a clear understanding of the cellular origin and molecular mechanisms underlying the initiation of high-grade serous cancer is essential for developing effective means for early detection and prevention of this most devastating type of ovarian cancer. Recognizing the complexity of ovarian cancer and appreciating that ovarian cancer is not a single disease will help us to generate proper models, design rational experiments, and collect and analyze patient data in a meaningful way. A concerted effort in the field will help to bridge the basic science and clinical applications and lead to more precise and effective detection and treatment.

Epithelial ovarian cancer is a disease with poor prognosis. It is the fifth most common cause of death from cancer in women, and is the most lethal of all gynecological cancers. The lifetime risk of a woman developing ovarian cancer is 1 in 71, and 1 in 200 women will develop ovarian cancer between their 50th and 70th birthday. Worldwide, 224 747 new cases of ovarian cancer are diagnosed annually and there are an estimated 140 163 disease-related deaths.[1] Ninety percent of all deaths from ovarian cancer are due to high-grade serous cancer, and this cancer sub-type accounts for 75% of all cases.[2] Despite recognition of the importance of early detection and rapid progress in our understanding of the cellular origin of high-grade serous cancer, only 2% of cases can be identified at stage I.[3] As a consequence, up to 80% of women present with stages III/IV disease, and the 5-year survival rate is just 30%. This severe mortality and poor survival rates have not changed much since the 1930s.[4] Therefore, there is an urgent and unmet medical need for precise diagnosis and effective treatment for this disease at earlier stages, where the survival rate is >90%, as we have achieved in cervical cancer and breast cancer[5] after the biology/origin of these two women's cancers were unraveled.

At the 12th Ovarian Cancer Research Symposium at the Rivkin Center for Ovarian Cancer in Seattle, Washington, one session focused on the detection and prevention of ovarian cancer. Diverse topics were covered in this session, including basic biological questions such as the cellular origin of high-grade serous cancer and clinical applications such as diagnostic markers for early detection. Dr Ranjit Manchanda (Barts Cancer Institute) presented a population-based test for ovarian cancer gene mutations. He discussed the limitations associated with the current system of genetic testing, based on clinical criteria/family history, and presented data supporting the promising outcome of population-based *BRCA* testing in the Jewish population. Dr Manchanda further extended the testing for established cancer genes in non-Jewish women and suggested surgical prevention is a cost-effective approach in women at high risk identified by this test.

Dr Rosana Risques (University of Washington) also presented her recent research on using ultra-sensitive sequencing tools for detection of ovarian cancer. The presentation by Dr Risque centered on deep sequencing of genital tract fluids for *TP53* mutations using techniques to identify very small numbers of affected cells. They demonstrated the presence of *TP53* mutations in these fluids in women with ovarian cancer and also in 100% of controls. These findings underline the fact that cells containing *TP53* mutations are present in the peritoneal or other genital tract fluids of virtually all women, increasing with age and in keeping with a 'pre-malignant mutation background' discussed in their previous paper.[6] Interestingly, it complements the model proposed by Soong

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et al in a subsequent presentation, in which genetically altered but non-malignant precursor cells escape from the fallopian tubes and, in some instances, culminate in high-grade serous cancer in the peritoneal cavity.[7] The two studies superimposed on prior work attest to both the frequency of *TP53* mutations in the fallopian tube and the likelihood that such cells commonly exist in the peritoneal fluid. The mechanism(s) by which malignancy occurs and who is at risk for a rare occurrence of malignant transformation remains to be determined.

In addition, Ms Heydrich and colleagues (Color Genomics) presented their studies in Texas supporting the benefit of providing broad access to genetic testing in the obstetrics and gynecology care setting. Using a next-generation, sequencing-based assessment of 30 genes associated with hereditary cancer risk, they identified 90 patients with increased risk for cancer among 1113 people included in this study. Significantly, 70 of the 90 identified as at increased risk had no significant family history of ovarian cancer and would not have been obvious candidates for screening. This finding suggests that broader genetic testing would be beneficial in identifying a larger set of patients at risk.

Developing rational and effective screening and cancer preventive strategies for ovarian cancer, particularly high-grade serous cancer, requires a better understanding of the origin of this disease. During the past decade, clinical and molecular evidence has increasingly suggested that many, if not all, cases of high-grade serous cancer arise from the fallopian tube.[8] In the original serous carcinogenesis model, high-grade serous cancer was thought to arise through dissemination of tumor cells from serous tubal intra-epithelial carcinomas.[9] However, many cases are found not to be associated with serous tubal intra-epithelial carcinomas. Drs Thing Rinda Soong and Christopher Crum (University of Washington and Harvard Medical School, respectively) presented data to support a new alternative model termed 'precursor escape'. In this model, a pre-cancerous lesion termed 'early serous proliferation' bearing p53 mutations is found in the distal fallopian tube of patients with high-grade serous cancer.[10] Their study indicates for the first time a lineage continuity between early serous proliferation in the distal tube and some metastatic high-grade serous cancer via shared, site-specific TP53 mutations, explaining the apparent sudden onset of cancers without co-existing serous tubal intra-epithelial carcinomas. This new pre-cancer–cancer paradigm for high-grade serous cancer suggests that precursor initiation and progression to malignancy are separated spatially and temporally.

The study presented by Dr Burdette (University of Illinois, Chicago) explained why the ovary is the primary metastasis site for tumors derived from the fallopian tube. Using imaging mass spectrometry, Dr Burdette and colleagues found that norepinephrine and a series of new molecules may facilitate the colonization of fallopian tube-derived tumor cells on the ovarian surface. Therapeutic intervention blocking ovarian metastasis can be developed targeting pathways activated by these molecules.

Using genetic mouse models, Drs Shuang Zhang and Benjamin Neel (New York University-Langone Medical Center) showed that PAX8 + fallopian tube cells can be transformed in the presence of combined retinoblastoma inactivation and *TP53* mutations and give rise to serous cancer. Dr Zhang and colleagues also claimed that under the same conditions, ovarian epithelial cells can be transformed to form serous-like tumors. It is important to notice that the serous-like tumors generated from transformed ovarian surface epithelial cells do not express PAX8, a hallmark of high-grade serous cancer, whereas the tumors generated from transformed fallopian tube epithelial cells express all the hallmarks of this cancer as shown in publications from various laboratories.[11 12] A presentation given by Dr Sophia George (University of Miami) further investigated the fallopian tube as the site of origin of high-grade serous cancer by performing RNAseq analysis of fallopian tube from patients with and without *BRCA* mutations. The women carrying a deleterious mutation in the *BRCA1/2* genes have an increased risk of this cancer of up to 40%. Dr George and colleagues found that the fallopian tube epithelium of a *BRAC1/2* carrier shows distinct unique pre-neoplastic processes, such as increased metabolic activity and aberrant regulation of DNA repair pathways. Their study using a *BRCA* model may provide new insights into the early development of ovarian cancer.

Kendall Greening from Dr David Huntsman's laboratory (University of British Columbia) presented preliminary data suggesting that 42% of post-menopausal women had p53 lesions in the fallopian tube. They plan to study the effect of the use of oral contraceptive pills and its association with >40% reduction in the risk of high-grade serous cancer by studying p53 lesions in the fallopian tubes. Their study may disclose the impact of oral contraceptive pills on the earliest known precursors of serous cancer. Dr Angela Russo and colleagues (University of Illinois at Chicago) presented their work on the effect of loss of PAX2 and PTEN in the fallopian tube epithelium.[13] Their data suggested that loss of PTEN or PAX2 mediated a cancer stem cell phenotype that initiates formation of high-grade serous cancer. These findings may help to define early events of carcinogenesis and help to refine the strategies of targeted therapeutics or marker discovery for early detection of serous cancer. Dr Kara Bernstein and colleagues (University of Pittsburg) presented their work on characterization of cancer-associated mutations in the RAD51 paralogs on homologous recombination proficiency. This may help us to develop more effective predictive models of targeted therapies, such as poly-ADP-ribose polymerase inhibitors. Using yeast 2/3-hybrid assays, they found that mutations in RAD51 disrupted the interaction between RAD51 and XRCC2, a protein required for the early response of RAD51 to DNA damage,[14] and subsequently affect homologous recombination proficiency.

Several presentations mentioned recent progress with tools to deal with the unmet clinical need for early detection of ovarian cancer. The recent discovery of fallopian tube as the site of origin of high-grade serous cancer has re-shaped strategies of early detection.[15] For instance, Dr Jennifer Barton (University of Arizona) presented her work on a second-generation falloposcope for minimally invasive imaging of the fallopian tube. They propose to use this imaging test as an adjunct confirmatory test after an initial positive or suspicious blood test with known or recently uncovered markers for serous tubal intra-epithelial carcinoma lesions in their laboratory. Their continuous work on identifying sensitive and specific serum protein markers and optimizing the falloposcope may create a reliable and efficient detection method for general screening of the general population for early epithelial ovarian cancer.

Dr Amy Skubitz (University of Minnesota) and colleagues presented their work using Proseek Multiplex Oncology II plates to simultaneously measure the expression of 92 cancer-related

proteins in serum in order to bypass the inability of CA125 and HE4 screening of the general population to identify early-stage disease. Their analysis of women with advanced serous cancer compared with age-matched healthy women showed that CA125 alone achieved a sensitivity of 93.4%, but by adding five proteins to CA125, they increased sensitivity to 98.4%. They hope that this Proseek technology will help to identify biomarkers to improve the sensitivity and specificity of detection methods for early stages of high-grade serous cancer.

Dr Karen Belkic (Karolinska Institution) summarized the key achievement of the fast Pade transform in magnetic resonance spectroscopy for diagnosis of early ovarian cancer. Their meta-analysis showed that cancerous and benign ovarian lesions are inadequately distinguished via fast Fourier transform-based magnetic resonance spectroscopy. In contrast, the high-order, non-parametric fast Pade transform has clear display with identification and exact quantification of key metabolic transformation, including the ovarian cancer biomarker phosphocholine. Their next step is pursuing this strategy in vivo for diagnosis of ovarian cancer. Dr Kristin Boylan and colleagues from the University of Minnesota, also used mass spectrometry-based proteomics methods for early detection. They hypothesized that ovarian cancer cells can be detected during a routine Pap test performed for cervical cancer prevention. Given the convincing data supporting the fallopian tube as the site of origin of ovarian cancer, they think it is likely that ovarian cancer protein can be found in the lower genital tract, perhaps even in the early stages. Using the extract from patient's tumor tissue run on 2D-liquid chromatography tandem mass spectrometry, followed by bioinformatics integration, they identified thousands of protein markers shared by several patients, including well-known markers of ovarian cancer such as CA125. Their further analysis using patient-matched normal tissues will help to uncover cancer-specific markers that could be used for the quantification of proteins from Pap test fixatives and cervical swabs for ovarian cancer protection.

Dr Naoko Sasamoto (Brigham and Women's Hospital) and colleagues presented their efforts on improving the efficiency and accuracy of using CA125 as a prediction method. They hypothesized that the distinct personal characteristics among individuals contributed to the low specificity of CA125 as an ovarian cancer screening biomarker. Thus they proposed to identify personal characteristics that influence CA125 levels in order to create personalized thresholds for CA125, thereby improving its performance as an ovarian cancer screening biomarker. They conducted internal and external validation of two prediction models (linear and dichotomous) of circulating CA125 among post-menopausal women using 28 842 controls without ovarian cancer in four large population-based studies. Although both models appeared to provide some improvement to the CA125 method, a further fine-tuning of these models is required to increase the predictive ability of these models.

Estrogen-induced DNA damage may contribute to the early development of ovarian cancer.[16] To overcome the technical challenges in detecting and analyzing the variety of different DNA lesions that are formed by estrogen compounds, Dr Kaushlendra Tripathi (University of Alabama) and colleagues have developed a new method. They used biotinylated estrogens to allow immunodetection of estrogen-induced DNA adducts by slot-blot and single-cell molecular cloning and proximity ligation assays. Using this method, they quantitatively detected these adducts on DNA and showed that estrogen activates replication-associated DNA damage response and induces chromosomal instability. Thus, the biotin-labeled estrogens could be used as a tool to detect the early stage of ovarian carcinogenesis.

Several research groups presented their work on identifying risk factors for the development of ovarian cancer that might reduce its burden. Dr Kara Michels (National Cancer Institute) presented a study examining the association between metabolic dysregulation and development of ovarian cancer by a case–control study within the Surveillance, Epidemiology and End Results Medicare linked database. Their results suggest that individual components of metabolic syndrome, rather than the syndrome itself, are associated with ovarian cancer. Thus high levels of triglycerides are associated with an increased risk of high-grade serous cancer, whereas a high level of fasting glucose is linked with a reduced risks for this cancer.

Dr Holly Harris (Fred Hutchinson Cancer Research Center) and colleagues presented their work on the use of Mendelian randomization to examine the association between polycystic ovary syndrome and ovarian cancer. They evaluated the single nucleotide polymorphisms associated with polycystic ovary syndrome using publicly available data from genome-wide association studies. Based on seven associated single nucleotide polymorphisms, they found an inverse association between genetically predicted polycystic ovary syndrome and high-grade serous cancer and endometrioid tumors.

As full-term births have been known to be protective for ovarian cancer,[17] Dr Alice Lee (California State University) and colleagues presented their work on incomplete pregnancies and risk of ovarian cancer based on the pooled epidemiologic data from 16 population-based, case–control studies from the Ovarian Cancer Association Consortium. They found that both incomplete and complete pregnancies are protective against ovarian carcinogenesis, although full births are more protective. The protective association is strongest for clear cell ovarian cancer and less apparent for high-grade serous cancer and mucinous ovarian cancers. Randomized trials and recent meta-analysis have shown better survival for women who took hormone therapy after their diagnosis in comparison with women who did not.[18] Dr Celeste Pearce from the same research group (California State University) presented their study on the relationship between use of hormone therapy before ovarian cancer diagnosis. They analyzed 4700 patients with ovarian cancer recorded in the Ovarian Cancer Association Consortium and found that women who used hormone therapy before diagnosis had an 11% decreased risk of death compared with those who did not. It appears that the longer duration confers better survival in both serous and mucinous ovarian cancer.

Other factors linked with reduced ovarian cancer risks are higher parity and oral contraceptive use.[19] In order to understand the association between the lifetime number of ovulatory cycles and ovarian cancer risk, Dr Britton Trabert and colleagues (National Cancer Institute) analyzed 3866 cases of ovarian cancer collected by the Ovarian Cancer Cohort Consortium. In this large prospective analysis of pooled cohort study data, they observed a positive association between increased risk of ovarian cancer of several histotypes, including serous, endometrioid, and clear cell tumors, but not mucinous tumors. Their data suggest that a DNA damage-rich

environment created by ovulation at the ovary surface and within the fallopian tube increases the risk of ovarian carcinogenesis.

Dr Faina Linkov (University of Pittsburgh) presented their study of 1840 patients with ovarian cancer at the University of Pittsburgh Medical Center facilities and concluded that intra-peritoneal chemotherapy showed enhanced long-term survival of patients. Since intra-peritoneal chemotherapy has not been widely used outside specialty hospitals, increasing its use in clinical practice for the treatment of patients with ovarian cancer may improve outcomes.

Christina Clarke (Kaiser Permanente Colorado) and colleagues presented a retrospective observational study of high-grade serous cancer to explore predictors of long-term survival, using data from five participating health plans in the Cancer Research Network. They confirmed that younger age, lower stage, and receipt of chemotherapy were statistically significantly associated with long-term survival.

In this session, a few researchers also presented their findings for the development of new approaches for early treatment. Tiffany Lam and colleagues (University of Minnesota) hypothesized that some tumor cells can evade initial chemotherapy treatment by entering a dormant state. They used a silica gel encapsulation platform to capture the subset of cells capable of dormancy. They observed a connection between cells' ability to enter dormancy and chemoresistance in ovarian cancer. Therefore they suggest that silica gel technology might be used as a predictive clinical tool to identify patients at risk of early recurrence or serve as a research tool to study the mechanisms underlying dormancy, chemoresistance, and recurrence.

Dr Chang Li (University of Washington) and colleagues presented their attempts to develop preventive approaches for patients with ovarian cancer at high-risk of disease recurrence or patients with cancer-predisposing inherited mutations. Their approach is based on in vivo genetic modification of hematopoietic stem cells.[20] By microRNAseq and microRNA arrays, these researchers identified microRNAs that were absent in tumor-associated leukocytes, allowing for tumor-restricted therapeutic transgene expressions by inserting these microRNAs in the 3' untranslated region of the transgenes. They hypothesized that these genetically engineered tumor-associated neutrophils and macrophages can overcome the immunosuppressive tumor environment allowing effector T-lymphocyte cells to stop tumor growth at an early stage. They are using oncogene-transgenic mice that develop spontaneous tumors to test this hypothesis.

CONCLUSION

The American Cancer Society describes the 'signs' of ovarian cancer as 'bloating, abdominal pain, a feeling of fullness'—clearly all indications of late-stage disease. Indeed markers such as CA125 and imaging by transvaginal ultrasound also report frank cancer which, if not cured by surgery, represents a largely protracted medical struggle with limited odds of success.[21] It would seem that the future should include early detection afforded by the large period of time presented by most pre-cancerous lesions and non-invasive cancer form of other organs. A molecular analysis of an early lesion that could be tied to high-grade serous cancer would provide an array of targets that are either secreted by these cells or presented on the cell surface, with potential screening and therapeutic value, respectively. Monoclonal antibodies to secreted proteins have the potential to form the basis of population-wide screening methods from blood or cervical fluid for those at risk who might benefit from salpingectomy. Monoclonal antibodies to surface proteins of the cells in these lesions might assist in alternative detection via imaging technologies through the fallopian tube isthmus, similar to the confocal endoscopy performed today with Barrett's esophagus. They might also provide potentially non-invasive means of eradicating these early lesions though cytotoxic effects. While it seems that imaging technologies akin to the endoscopy and colonoscopy employed are not yet available for monitoring the fallopian tube, it would seem with the rapid pace of development that the fallopian tube will soon be within range of these modalities.

One goal of all cancer therapy is to provide early screening and pre-emptive intervention to avoid the challenges presented by highly metastatic cancers. Thus, the stages of cancer have a huge influence on the outcome. Early diagnosis of cancer will fundamentally affect the management of these tumors. The Ovarian Cancer Research Society has started to explore the current hypothesis that the fallopian tube is the origin of high-grade serous cancer and aims to develop new, sophisticated and yet simple strategies to detect the cancer in its earliest stage: the pre-cancerous lesion. If successful, we would have filled an important unmet medical need that has been troubling the medical profession for decades. Continuously developing new knowledge in this field is essential for us to develop medical diagnostic technologies that might save lives and improve the quality of global healthcare.

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