Joint IARC/NCI International Cancer Seminar Series Report: Expert consensus on future directions for ovarian carcinoma research

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ABSTRACT

Recently, ovarian cancer research has evolved considerably because of the emerging recognition that rather than a single disease, ovarian carcinomas comprise several different histotypes that vary by etiologic origin, risk factors, molecular profiles, therapeutic approaches, and clinical outcome. Despite significant progress in our understanding of the etiologic heterogeneity of ovarian cancer, as well as important clinical advances, it remains the eighth most frequently diagnosed cancer in women worldwide and the most fatal gynecologic cancer. The International Agency for Research on Cancer (IARC) and the US National Cancer Institute (NCI) jointly convened an expert panel on ovarian carcinoma to develop consensus research priorities based on evolving scientific discoveries. Expertise ranged from etiology, prevention, early detection, pathology, model systems, molecular characterization, and treatment/clinical management. This report summarizes the current state of knowledge and highlights expert consensus on future directions to continue advancing etiologic, epidemiologic, and prognostic research on ovarian carcinoma.

SUMMARY

This report highlights expert consensus on future directions to continue advancing etiologic, epidemiologic, and prognostic research on ovarian carcinoma by an panel of interdisciplinary scientists/clinicians jointly convened by the The International Agency for Research on Cancer (IARC) and the US National Cancer Institute (NCI).

INTRODUCTION

Ovarian cancer is the eighth most common malignancy in women worldwide, with almost 300,000 new diagnoses and 185,000 deaths in 2018 (1). Globally, incidence rates vary markedly from 5.0 per 100,000 person-years in Africa to 9.5 per 100,000 person-years in Europe (1) and the majority are epithelial ovarian carcinomas, the focus of this report. Non-epithelial ovarian cancers such as germ cell tumors and sex cord-stromal tumors are uncommon (10% or less). Recently, ovarian carcinoma research has evolved considerably because of the emerging recognition that rather than a single disease, but comprises several different histotypes that vary by etiologic origin, risk factors, molecular profiles, therapeutic approaches, and clinical outcome (2). The importance of the term 'histotype' is emphasized and refers to the main categories of ovarian carcinomas traditionally defined by microscopic phenotype, often confirmed by ancillary immunohistochemical tumor biomarkers (3). There are five main histotypes in descending order of frequency: high-grade serous, endometrioid, clear cell, low-grade serous, and mucinous.

The discovery of a precursor for high-grade serous carcinomas (HGSC) in *BRCA1* and *BRCA2* (*BRCA1/2*) germline mutation carriers in the fallopian tube resulted in a paradigm shift, namely, designation of the origin of the most common histotype in the fallopian tubes and not in the ovary (4-8) based on increased microscopic scrutiny of the tubal fimbriae (9) in the US, and elsewhere (10). Still, a minority of HGSC appear to arise from the ovary as a primary site, particularly in the absence of involvement of fallopian tube. Notably, shared biology has led to the emerging concept of tubo-ovarian HGSC, which includes primary peritoneal tumors. Endometriosis is associated with an increased risk of endometrioid and clear cell carcinomas (11) and shares similar oncogenic mutations (12), providing evidence of an ovarian origin for these two histotypes. Overall, the etiologic origin of ovarian carcinoma histotypes is heterogeneous.

In 2016, the Institute of Medicine published an ovarian cancer expert consensus with recommendations for research, treatment, prevention, care, and diagnosis (13); the panel prioritized HGSC, histotype-specific research, collaborative/cross-disciplinary research, dissemination of research findings, and implementation of evidence-based interventions which have led to ongoing efforts (14-17). Advances in ovarian cancer research continue to be driven in part by several large international ovarian cancer consortia including the Ovarian Cancer Association Consortium (OCAC), the Ovarian Tumor Tissue Analysis (OTTA), Ovarian Cancer Cohort Consortium (OC3), Ovarian Cancer in Women of African Ancestry (OCWAA), and the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), that collaborate widely and have available data resources (summarized (18), (19)). To accelerate research in ovarian cancer, the International Agency for Research on Cancer (IARC) and the US National Cancer Institute (NCI) jointly convened an expert panel to develop consensus on next priorities based on evolving scientific discoveries. This report summarizes the current state of knowledge and highlights expert consensus on future directions to continue advancing etiologic, epidemiologic, and prognostic research on ovarian carcinoma.

ETIOLOGIC RISK FACTORS

Genetic, hormonal, and reproductive risk factors have been well-established for ovarian carcinoma, yet the data for traditional lifestyle factors, such as physical activity and diet, is less clear (20,21). Consortial studies have revealed clear differences in risk factor profiles for distinct histotypes (20). For example, reproductive factors are more closely associated with endometrioid and clear cell carcinomas, while high-penetrance genetic factors (e.g., *BRCA1/2* mutations) are more commonly associated with HGSC. Moreover, the tumor microenvironment, particularly the immune milieu appears to be directly related to reproductive risk factors (22). However, the biologic mechanisms that underlie how known risk factors influence tumor development and the associated tumor microenvironment are still unknown. Overall ovarian cancer incidence (including primary fallopian tube and peritoneal primaries) has declined over the last two decades despite an increase in classification of fallopian tube HGSC, plausibly in response to increased use of oral contraceptives

and lower menopausal hormone therapy use (23,24). Still, future ovarian carcinoma incidence rates are expected to shift in response to changing contraception practices, such as different formulations of oral contraceptives, hormonal IUDs, as well as time-trends in other putative risk factors (e.g., changes in hormonal treatment of menopausal symptoms). Many of the important ovarian carcinoma risk factors occur during the premenopausal period. New data suggest that exposures during pubertal development could influence ovarian carcinoma risk, supporting the concept that there may be susceptible periods during a woman's reproductive years for initiating events in ovarian carcinogenesis. Recent work suggests that increases in adiposity between ages 10-18 years that continue through the premenopausal period, but not postmenopausal period, are associated with increased risk of ovarian carcinoma; similar results were observed for the protective effect of increased physical activity (25).

With the exception of oral contraceptive use, the field has not established modifiable risk factors for HGSCs, which are associated with the poorest prognosis. Consortia studies and large prospective studies suggest that systemic and local (i.e., tubal) inflammation and/or infection are important risk factors (26,27). In this regard it is notable that use of daily aspirin (anti-inflammatory medication) is associated with 10-20% reduced ovarian carcinoma risk (28,29), whereas pro-inflammatory circulating biomarkers, namely C-reactive protein (CRP), have been consistently associated with increased risk (26). There have also been studies demonstrating increased risk of ovarian carcinoma with antibodies to prior sexually transmitted infections (i.e., *Chlamydia trachomatis*) and pelvic inflammatory disease (27,30). Thus far, studies supporting inflammation/infection in the etiology of ovarian carcinoma suggest that associations are largely consistent across histotype and as such, have identified novel and potentially modifiable risk factors for ovarian carcinoma, and particularly for HGSC. The emergence of new approaches and resources have provided a remarkable opportunity to pursue new avenues of research while investigating further current questions (**Table 1**)

INHERITED RISK, PREVENTION, AND EARLY DETECTION

Recent progress in the identification and characterization of inherited alleles that confer ovarian carcinoma risk have expanded upon the linkage studies that identified rare, high-risk alleles in *BRCA1* and *BRCA2* over 25 years ago. The past decade has seen the value of genome wide association studies (GWAS) that have identified more than 40 common variants associated with modest increases in risk of ovarian carcinoma (21), generating a foundation for the underlying genetic architecture of genetic susceptibility to ovarian carcinoma and providing new insights into the underlying carcinogenesis process. Expanding on the findings from GWAS to identify target genes of risk-associated variants is also necessary and new technologies such as CRISPR can be effective in identifying the underlying variants that regulate genes that could be targets for therapy or prevention, either as new agents or repurposing of available agents. In parallel, rare, moderate effect alleles have been identified in genes including *BRIP1*, *PALB2*, *RAD51C,* and *RAD51D,* many of which are included in cancer gene panels used in clinical practice and are listed in the National Comprehensive Cancer Network (NCCN) guidelines. Still, the current estimates of disease risk for these susceptibility alleles remain imprecise. For other genes such as *ATM* and *BARD1*, there is no consensus regarding their utility in risk prediction. To optimize the identification of inherited risk, we need to better understand which genes are implicated in ovarian cancer risk, each of which could be driven by a distinct set of genes. However, the primary downside of multiplex testing is that as more genes are sequenced, the likelihood of identifying uncertain results also increases, either in the form of variants of uncertain significance (VUS), or damaging mutations in genes with unknown contributions to cancer risk. Risk estimates for inherited mutations in high-risk genes continue to be refined and their inclusion in genetic testing guidelines should be further evaluated. Large, carefully designed, family and case-control studies are needed to provide more precise penetrance estimates for use in clinical counselling (21). The known susceptibility alleles explain less than half the heritable component of disease risk and there is still much to be done to identify the remaining half, some of which could be due to rare variants in both coding and non-coding regions. Since the primary effort has focused on

populations of European ancestries, similar studies in African and Asian populations are needed to identify variants that are trans-ethnic or population-specific.

The most effective strategy for preventing HGSC is appropriately timed risk-reduction surgery with removal of the fallopian tubes and ovaries, once childbearing has been completed (31). The downside of this intervention in premenopausal women is surgically induced menopause, which can have serious health consequences, especially if hormone therapy is not administered. Concerns about surgical menopause, coupled with the awareness that many if not most HGSCs arise within the fallopian tube, has led to increased interest in the alternative strategy of interval salpingectomy with delayed oophorectomy. This approach may substantially reduce the risk of malignancy while delaying the onset of surgical menopause, however the safety, efficacy of cancer prevention, and benefits of this approach are unknown. There is still a lack of consensus on the risk threshold and the optimal age for risk-reducing surgery given the concept of precursor escape, which suggests that fallopian tube epithelium may shed onto other surfaces and undergo malignant transformation later.

Risk prediction models have been generated, some based on epidemiologic risk factors (e.g., parity, oral contraceptive use, menopausal hormone use, and family history), others addressing a polygenic risk score (PRS), and those that combine the two. Risk models based on epidemiologic risk factors alone have shown modest areas under the curve (AUCs), which are not yet clinically actionable. So far, models using a PRS have achieved similar AUCs and provided little improvement when the two approaches have been combined. In contrast, among *BRCA1/2* carriers who have a substantially increased risk compared to the general population, a PRS predicted a range of lifetime risks of ovarian cancer from 6% in the lowest decile to 19% in the highest decile (32). Associations of risk factors, biomarkers, and genetic variation vary substantially between ovarian carcinoma histotypes and most risk factors show the weakest association for the most common and most aggressive histotype, HGSC (20,33). Identifying biomarkers of HGSC and including their measurements in risk models could improve risk prediction.

Despite many clinical screening trials with biomarkers, none have demonstrated reduction in mortality. A promising approach could be a combination of change in circulating levels of cancer antigen 125 (CA125) and imaging with transvaginal ultrasound, although this approach is not sufficient for population screening (34). A key advancement has been the significant improvement in performance characteristics with longitudinal algorithms rather than a single threshold (35). Data from prospective cohort studies suggest using a CA125 single threshold can detect ovarian cancer only in the relative near-term to diagnosis and only in individuals subsequently diagnosed with later-stage disease. The second-best available marker, human epididymis secretory protein E4 (HE4) performs similarly. Circulating CA125 and HE4 had limited specificity as initially evaluated, however this has been addressed by using a combination of longitudinal biomarker algorithms and second-line imaging (36). Currently, population screening for ovarian cancer is not recommended and the unique characteristics of HGSC arising in the distal fallopian tube with access to the peritoneal cavity and high proliferation rates pose particular challenges for sampling and/or visualization.

A major methodologic limitation of discovery studies for early detection markers is that they have been conducted predominantly in hospital-based case-control studies. Since ovarian carcinoma is often diagnosed at advanced stage, this has predominantly led to the identification of biomarkers with limited sensitivity for early stage disease. Currently, there is an expanded effort toward implementing the PRoBE (Prospective specimen collection, Retrospective Blinded Evaluation) principle for discovery and validation of early detection markers (37). In light of the low incidence of ovarian carcinoma and its heterogeneity, these efforts have historically been hampered by a limited number of cases with prospectively collected biospecimens collected shortly prior to diagnosis (or, in the case of pre-operatively collected samples, a limited number of earlier stage cases). While use of prospectively collected samples limits methodologic biases related to study design and sample selection, a major assumption is that biomarkers with diagnostic discrimination prior to clinical diagnosis will correspond

to clinically meaningful detection with diagnosis at an earlier, more treatable stage **(Table 2.).** Studies applying PRoBE criteria with novel analytic platforms are underway for discovery and validation of circulating early detection markers and marker signatures, toward the goal of improving diagnostic discrimination of blood-based markers for earlier stage disease. Further, studies in samples collected more proximate to the site of a potential malignancy are of mounting interest, with the promise of higher specificity. Early studies using uterine lavage, Papanicolaou (Pap) tests, and Tao brush samples have yielded promising preliminary results toward earlier detection but require further characterization (38). The exploration for early detection biomarkers has recently expanded to include the concept of liquid biopsies, i.e., measuring circulating tumor DNA, circulating tumor cells, cell free microRNA, and/or autoantibodies (e.g., TP53 autoantibodies) that may prove useful in screening high risk populations (39-42).

PATHOLOGY, PRECURSOR LESIONS, MODEL SYSTEMS

Histopathological classification is the primary means for discriminating ovarian carcinoma histotypes; it can be augmented by immunohistochemical (IHC) staining to improve classification with four markers (3,8). It has emerged that many, if not most "ovarian" HGSCs arise from precursor lesions in the fallopian tube (i.e., serous tubal intraepithelial carcinoma [STICs]). STICs are morphologically similar to invasive HGSCs and are found in ~3-5% of prophylactically removed fallopian tubes of women with hereditary predisposition to HGSC (43,44). In the general population where estimates vary widely, STIC has been identified in 18-71% of surgical specimens removed for HGSC (45,46) and only rarely (<0.01%) in fallopian tube specimens removed for benign indications (47). STICs found in the context of concurrent HGSC share clonal *TP53* mutations and other mutational signatures of genomic instability (8). Tubal lesions that fail to meet diagnostic criteria for STIC (so-called early serous proliferations– ESPs) have also been shown to share *TP53* mutations with concurrent HGSC, indicating shared lineage between ESP and HGSC within the same patient (48). ESPs can be multifocal and shared *TP53* mutations can be found in more than one lesion, which suggest that *TP53*-mutant cells can exfoliate and "escape" from their site of origin, and subsequently, undergo malignant transformation elsewhere (48). Precursor escape likely also applies to the pathogenesis of other ovarian carcinoma histotypes, such as endometrioid and clear cell carcinomas that develop from endometriosis. Additionally, benign-appearing fallopian tube epithelium is commonly found outside the tube (endosalpingiosis) and can also undergo malignant transformation. Moreover, the concept of "motile precursors" and its potential impact on strategies to improve prevention, early detection, and treatment of HGSC remain incompletely explored.

Robust pre-clinical models (including cell lines, organoids, patient-derived xenografts, and animal models) of each histotype should continue to be investigated now that a better understanding of the heterogeneity and distinct molecular features of histotypes indicate that no single model can be generally applicable (**Table 3.).** A sizable number of cell lines representing the most common histotypes have been developed (49-51), and selection of appropriate cell lines representing the histotype of interest is essential. So-called "organoid" or 3-dimensional cell culture systems are becoming more widely utilized because they recapitulate many histologic, molecular, and phenotypic features of the tumors from which they were derived, which can be combined with other cellular components to reconstruct the tumor microenvironment *in vitro* (52,53). Patient-derived xenografts (PDXs) from primary ovarian carcinomas or ascites specimens have been generated and are useful, particularly for preclinical testing of novel therapeutics (54). PDXs may not be well suited for studies evaluating interactions of tumor cells with the immune systemif they are generated and/or propagated in immunocompromised mice. Genetically engineered mouse models (GEMMs) provide an important complement to other pre-clinical model systems such as cell lines, organoids, and PDXs. Several ovarian cancer GEMMs have been developed, with most attempting to model HGSC (55-59). GEMMs that recapitulate the likely cell of origin, i.e., fallopian tube epithelium, underlying genetic defects, histology, and biologic behavior of human HGSCs, have been reported. More recently, tumors arising in select GEMMs can acquire somatic changes (i.e., mutations and widespread copy number

alterations, gene expression profiles, and immune microenvironment) that characterize human HGSCs (60) but it takes several months for tumors to develop and progress in selected models, rendering them particularly well suited for studying the early phases of HGSC pathogenesis and for testing prevention and early detection strategies. GEMMs also provide researchers with an opportunity to test immunotherapies in immune-competent animals. However, several issues have prevented ovarian cancer GEMMs from being more widely utilized by the research community. For example, most GEMMs are in a mixed genetic background, which precludes studies of tumor cell biology in syngeneic animals but overall GEMMs are likely to play an important role in ovarian carcinoma research.

MOLECULAR CHARACTERIZATION

Each ovarian carcinoma histotype has specific molecular features (8). For example, endometriosis-associated endometrioid and clear cell carcinomas harbor frequent somatic *ARID1A* mutations and infrequent *TP53* mutations while 13% of endometrioid carcinomas display mismatch repair deficiency (61). Endometrioid carcinomas show the same molecular subtypes as their endometrial counterparts (62). Low-grade serous carcinomas have common MAPK pathway mutations and prognostically adverse loss of CDKN2A protein (63). Mucinous carcinomas show copy number loss of *CDKN2A*, have common *KRAS* and *TP53* mutations (often co-occurring), and *ERBB2* amplifications (64). HGSCs have uniform *TP53* mutations with complex copy number signatures that seem to split into homologous recombination repair pathway deficiency (HRD) or non-HRD, although optimal methods to measure this have not yet been defined (65). HGSC have been subclassified based on mRNA expression profiling (66-68), prognostic mRNA signatures (69), or based on methylation signatures (70). The emerging molecular subtype will further refine effective histotype-specific treatments; to date only a few validated prognostic markers exist for HGSC **(Table 4).**

With the discovery that BRCA-associated breast and ovarian cancers are uniquely sensitive to polyADP ribose polymerase inhibitors (PARPi) through a mechanism termed ‘synthetic lethality’, numerous clinical trials have led to regulatory approvals for several PARPi. Molecular testing for *BRCA1* and *BRCA2* mutations in tubo-ovarian carcinomas is now a standard of care. Germline genetic testing is important for risk-reducing approaches in family members and now carries the added benefit of directing therapeutic decisions. Somatic mutations in *BRCA1* and *BRCA2* are present in an additional 5-10% and appear to be equivalent to germline mutations in predicting response to PARPi (71,72). Other mutations and non-mutational events can lead to HRD which, in general, has been associated with response to PARPi. Nevertheless, widespread adoption of HRD testing outside of clinical trials remains limited as the sequencing of germline and somatic testing for newly diagnosed women with tubo-ovarian carcinomas remains controversial and lacks validation. Despite known benefits and national guidelines, there are many barriers in place to genetic testing, and most women with ovarian carcinoma are still not tested. US estimates indicate genetic testing rates in women with ovarian carcinoma are between 11–44%, well below national guidelines (73,74). The need for germline and somatic genetic testing currently exceeds the availability of genetic counselors and creative solutions need to be explored, perhaps using virtual resources. Most germline events could be screened through somatic testing.

While most HGSC are responsive to initial treatment, primary treatment resistance occurs in 15-20% of women. The mechanisms underlying treatment resistance are slowly being identified. For example, *CCNE1* amplification, which appears to be a biomarker of more aggressive tumors, associated with primary platinum resistance (75,76). A dearth of high-resolution characterization of the molecular changes that occur during disease recurrence has further limited options. Investigating the mechanisms behind chemoresistance has led to discovery of reversion mutations in HRD-associated genes. These reversion mutations were first described in *BRCA1* and *BRCA2*, but have now been identified in other HRD-associated genes such as *PALB2*, *RAD51C*, *RAD51D*, and *BRIP1* (77). Secondary mutations in these genes can restore the function of proteins and are seen in recurrent

tumors after treatment with chemotherapy or PARPi. Gene fusions involving the drug transporter gene *ABCB1,* encoding P-glycoprotein (P-gp), can occur in the tumors of patients treated with paclitaxel or other substrates of P-gp. There are currently no reliable approaches toward overcoming acquired resistance through reversion mutations or gene fusions. Multiple mechanisms of resistance to PARPi have been reported, suggesting that the approach to overcome resistance will be challenging and require a multi-pronged approach. Research is also needed across patients with varied patterns of recurrence and treatment response (e.g., exceptional responders, multiple recurrences, etc.) to understand the biology behind these events. For example, tumors with both *BRCA1/2* and *RB1* loss appear to be associated with long-term survival (78). Studies focused on understanding mechanisms of drug resistance can better inform on the best approach to delaying or preventing resistance.

TREATMENT/CLINICAL MANAGEMENT

Most patients with ovarian carcinoma are diagnosed with advanced stage disease and the great majority of these patients eventually succumb to disease (79,80) (**Table 5**). Clinical experience and epidemiologic evidence clearly indicate that a small fraction can experience long-term survival. Despite the recent advent of targeted therapy, such as PARPi, aggressive cytoreductive surgery is central to standard of care for women who can tolerate a major surgical procedure and have disease that appears resectable to no gross residual disease, initially or after neoadjuvant chemotherapy. Residual tumor size after cytoreductive surgery is the strongest prognostic factor (81,82) which is why gynecologic oncologists place great effort on achieving complete gross resection (83). Adjuvant chemotherapy with a platinum and taxane-based regimen is highly effective, and most patients will enter clinical remission after initial treatment. Neoadjuvant chemotherapy has been shown to be non-inferior to primary cytoreductive surgery in randomized trials of highly selected women, however the outcomes reported to date are uniformly poor. Current trials (84,85) with strict surgical competence requirements are underway to compare progression free and overall survival between primary surgical cytoreduction and neoadjuvant chemotherapy. Recent data suggest that tumors treated with primary cytoreductive surgery have distinct molecular abnormalities, cellular changes, and immune cell repertoire alterations compared to those treated with neoadjuvant chemotherapy (86). Clinical approaches for triaging upfront surgery versus neoadjuvant chemotherapy have been reported (87,88), but reliable predictive algorithms are not widely implemented.

Clinical application of initial triage approaches has been hampered by the lack of widely inclusive criteria in clinical trials that are important for assessing treatment response. Vulnerable populations are often excluded from surgical trials as frailty is a liability and likely contributes to observed biases in treatment response. Accordingly, a consistent definition for frailty should be employed across studies and exclusion criteria should better reflect real-world scenarios. In addition to common molecular characteristics and clinical features, other clinical considerations such as body mass index and age can inform prognosis.

Ovarian cancer patients have better outcomes when care is provided at a high-volume center (89-94) that follows current standard guidelines issued by professional organizations and governmental bodies. Aggressive interventions should be prioritized for those patients with the greatest likelihood for cure when treated under optimal circumstances. It should be further acknowledged that some patients will benefit most from a focus on quality of life and minimal use of high-risk treatments that may result in unnecessary complications and hasten death. Currently, three PARPi are FDA approved in settings such as primary maintenance or switch maintenance, as well as for treatment of patients with *BRCA* mutation or HRD. Despite presence of a prognostic and predictive biomarker, PARPi have not demonstrated universal activity in patients with HRD and clinical activity can be of limited duration. As more patients are treated with PARPi, the presence and/or development of resistance is becoming more common.

It has been well known for nearly two decades that patients whose tumors show the presence of an active tumor immune microenvironment, including those with brisk tumor infiltrating lymphocytes or an immunoreactive gene expression signature, have improved survival (95,96). Immunotherapy

appears to be a promising avenue for treatment; however, current response rates are only modest (97). Thus, a deeper understanding of barriers to success of immune therapy are needed. Anti-angiogenic agents are a great example of successful targeted therapy in ovarian cancer despite lack of a predictive biomarker. Bevacizumab, in combination with chemotherapy, yields improved overall and progression free survival as well as objective response (98,99). Bevacizumab is FDA approved in the upfront setting in combination with chemotherapy, as well as in the platinum-sensitive and -resistant recurrent ovarian cancer settings. Similar to PARP inhibition, activity is not universal and presence of resistance, whether innate or adaptive, limits the role of this therapy. A number of cellular (e.g., macrophages, platelets) and molecular changes in various components of the microenvironment have been shown to contribute to adaptive resistance and represent novel targets for clinical development (100). Liquid biopsies or circulating tumor markers may also be applicable to understanding prognosis, developing targeted treatments and/or in evaluating treatment response (39-42). Further progress may be realized by investigating rational combination therapy with adaptive clinical trial designs, improving immune therapies, and overcoming adaptive resistance to anti-angiogenics and PARPi.

SUMMARY

The emergence of multiple high-throughput omics technologies allows for deep molecular and biomarker studies in ovarian cancer research. High dimensional molecular data, including the genome, RNA expression, methylation patterns, and proteomes of tumors from patients contribute to development of novel research areas. Potential risk-related biomarkers can now be systematically assessed with these technologies, utilizing strategic samples such as prospectively collected specimens. Integration of multiple high-throughput -omic technologies with spatial information across all research areas offers a new dimension with which to move the field forward.

While each research area discussed above could command formidable resources, there is an important, but often overlooked, research need: inclusion of diverse populations in all areas of ovarian cancer research. Aside from the obvious advantage of research findings becoming applicable to understudied populations and improving cultural competency in cancer prevention, diagnosis, and care, diverse study populations will facilitate the identification of critical differences that may not otherwise be apparent in homogeneous populations. For example, epidemiologic comparisons across populations can identify how variation in the distribution of known ovarian carcinoma risk factors influence future patterns of incidence. Expanding genetic studies to include diverse populations would contribute to a more comprehensive understanding of how differences across ancestral populations and their environment may predispose development of specific histotypes. Finally, ovarian carcinoma disparities arise not only from biological factors, but social and societal constructs that affect prevention, diagnosis, and treatment. Evaluation of the role of social factors across the cancer care continuum would improve quality of life and mortality from ovarian carcinoma.

Despite advances made in the understanding of ovarian carcinoma, a main challenge continues to be the limited variation in number of specimens and types of cases available. Existing consortia highlight the utility of collaborative approaches for ovarian carcinoma research. The need to continue to build consortia for advances across all areas of research remains and should be maintained as a priority. Consortia are especially powerful in investigating etiologic heterogeneity for rare subgroups. Additionally, there is a strong need for prospective collection of biospecimens to facilitate important research aims related to etiology, prevention, early detection, and screening, particularly with the evolving understanding of epidemiologic risk factors, cell of origin, and treatment approaches for all disease subtypes. Large collections of serial samples leading up to the diagnosis of cancer across diverse populations will serve to be the most valuable resource to ensure that novel hypotheses can be tested rapidly in well curated sample collections.

In conclusion, crucial gaps in ovarian cancer research remain and acceleration of an understanding of the molecular bases of heterogeneous types of ovarian carcinoma should inform both preventive and

therapeutic approaches. It is imperative that collaborations between basic scientists, epidemiologists, and clinicians are cultivated to identify and utilize ovarian cancer research across the cancer continuum.

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Disclaimer

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Conflict of Interest Statement

J-EK serves on advisory boards for AstraZeneca, Clovis, and GlaxoSmithKlein and reports travel expenses from Roche and AstraZeneca; KF reports receiving research grants and personal fees from MSD, Astra Zeneca, and Chugai Roche UM has shares awarded to her by UCL in Abcodia which has an interest in early detection of cancer; AKS reports consulting for Merck and Kiyatec, a shareholder in BioPath, and research support from M-Trap; All other authors report no conflicts of interest.

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Table 1. High Priority Directions for Research on Etiologic Risk Factors of Ovarian Cancer

- Disease surveillance efforts should include monitoring trends in primary ovarian carcinoma, primary fallopian tube, and primary peritoneal carcinomas to characterize the changing epidemiology of ovarian cancer and its underlying biology. Inclusion of this expansive disease definition (ovarian, fallopian tube, and primary peritoneal carcinoma) should be applied to new population-based research endeavors.
- Research focused on risk factors should evaluate etiologic heterogeneity in the context of histotype, molecular subtype, cell of origin, and tumor aggressiveness.
- Since most established risk factors are related to premenopausal exposures, investigations should concentrate on known and putative risk factors assessed at different periods during the lifecourse. Experimental research should identify the aspects of ovulation that drive carcinogenesis and how different exposures may influence these factors.
- Case-control studies of recent birth cohorts should be initiated to examine associations with newer contraceptive methods and other novel risk factors.
- Enhanced collaborations between basic and population scientists should be cultivated to understand the biologic mechanisms of putative and novel risk factors on both tumor development and the associated microenvironment by leveraging novel experimental models of ovulation, the menstrual cycle, and menarche, as well as animal model systems that spontaneously develop ovarian carcinoma.
- Emphasis should be afforded to both discovery of novel risk factors and unresolved risk factors (e.g., common over the counter medications, fertility treatment and *in vitro* fertilization, psychosocial stress). Identifying circulating markers to characterize exposures that are challenging to measure via traditional epidemiologic methods may accelerate progress.

Table 2. High Priority Directions for Biomarkers and Genetic Susceptibility of Ovarian Cancer

- Ovarian carcinoma risk prediction efforts should combine histotype-specific risk prediction based on epidemiologic risk factors and polygenic risk scores and biomarkers with independent validation.
- Prospective collection of cases should be prioritized to facilitate future discovery and validation studies with a focus on multi-omic technologies.
- Optimal modes of proximate sampling and biomarker discovery should be evaluated to investigate a role in early detection (e.g., biospecimens collected from tubal, uterine or vaginal sites, etc.).
- The long-term impact and effectiveness of risk-reducing bilateral salpingectomy should be evaluated to inform patients of risk/benefits and inform decision-making process.

Table 3. High Priority Directions in Ovarian Carcinoma Molecular Pathology

- In light of the heterogenous origins of ovarian carcinomas, accurate, cost-effective, and clinically feasible strategies to identify/refine relevant molecular subtypes within histotypes are needed to associate with known and/or putative etiologic factors, clinical outcomes, and/or treatment response.
- Strategies should identify the most informative precursor lesions and determine how they progress to invasive carcinoma.
- The development and implementation of robust and diverse pre-clinical models (cell lines, organoids, patient-derived xenografts, GEMMs) of each histologic type/molecular subtype are needed to investigate tumour initiation, development, and progression, as well as novel strategies to improve clinical outcomes.

Table 4. High Priority Directions in Molecular Characterization for Therapeutic Decision Making in Ovarian Cancer

- Barriers to implementing standardized and widespread germline genetic testing should be identified and resolved.
- The frequency and consequence of defined, acquired resistance mechanisms to targeted therapies should be characterized through clinical trials.
- New mechanisms of sensitivity and resistance to platinum agents and lethality of other mechanisms of response to alterations in DNA repair and cell cycle regulation should be identified.

Table 5. High Priority Directions for Therapeutic Outcomes

- Efficient adaptive clinical trials should be conducted that incorporate high quality predictive biomarkers to evaluate histotype specific treatment modalities.
- With extended patient survival following initial therapy, ways to clinically manage long-term sequalae of ovarian cancer treatment are needed, including modalities to improve quality of life among ovarian cancer survivors that can be widely disseminated.
- Improve clinical-genomic stratification by identifying prognostic markers that can improve treatment outcomes.
- Collection of germline DNA in clinical trials should be encouraged to enable discovery of possible germline factors that could influence outcomes.
- Improve the characterization of the immune microenvironment to better inform the development of novel immunotherapies or chemotherapeutic agents for ovarian cancer.