OPINION

Rethinking ovarian cancer: recommendations for improving outcomes

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Abstract | There have been major advances in our understanding of the cellular and molecular biology of the human malignancies that are collectively referred to as ovarian cancer. At a recent Helene Harris Memorial Trust meeting, an international group of researchers considered actions that should be taken to improve the outcome for women with ovarian cancer. Nine major recommendations are outlined in this Opinion article.

Patient prognosis has considerably improved for many solid cancer types. However, the survival rate of women with epithelial ovarian cancer has changed little since platinum-based treatment was introduced more than 30 years ago[1–3] (FIG. 1). Invasive epithelial ovarian cancer is widely seen and treated as a single disease entity, with little stratification of the different histological or molecular subtypes. At a recent Helene Harris Memorial Trust (HHMT) meeting of leading ovarian cancer researchers and clinician scientists, which was sponsored and organized by Ovarian Cancer Action (see Further information) (BOX 1), we asked the question: what actions can we take to improve the outcome for women with ovarian cancer? A consensus regarding the major barriers to success and the current most pressing questions led delegates to propose nine priorities for action, which we describe in this Opinion article.

Ovarian cancer is many diseases

It is essential that researchers, pathologists, epidemiologists and clinicians understand that ovarian cancer is a general term for a series of molecularly and aetiologically distinct diseases that simply share an anatomical location. Recent pathological and genomic findings indicate that many ovarian cancers are derived from non-ovarian tissues and that the different ovarian cancer histotypes share few molecular similarities[4] (FIG. 2). For example, the distal fallopian tube has been identified as a source of high-grade serous ovarian cancers[5–7]. The relative importance of the fallopian tube compared with the ovarian surface epithelium in the genesis of high-grade serous ovarian cancers is still being debated, however, this finding has important implications for screening, prevention and understanding the molecular biology of the disease. Ovarian clear cell and endometrioid cancers have a strong epidemiological link with endometriosis. High-frequency somatic mutations of the PI3K catalytic subunit *PIK3CA* and AT-rich interactive domain-containing protein 1A (*ARID1A*) in adjacent endometriotic lesions link endometriosis, clear cell cancers and endometrioid cancers[8–10]. Most invasive mucinous ovarian cancers are actually metastases to the ovary from other solid cancer types, including gastrointestinal tumours[11–13]. Improved histotype classification using immunological markers and genomic studies has shown that many tumours that have previously been designated high-grade endometrioid cancers should be reclassified as serous cancers[14–16]. Low-grade invasive tumours are still regarded as ovarian-derived, but the initiating cells are unknown and it is possible that their site of origin will be re-evaluated in the future. Nevertheless, it is clear that serous borderline cancers are not precursor lesions for the majority of high-grade serous ovarian cancer, as they have a distinct range of mutational events[17].

Further subclassification of histotypes is based on signalling pathway activation[18], genomic events or gene expression profiling[19]. Some ovarian cancers have more in common with certain types of renal cancer or breast cancer than they have with other ovarian histologies. For example, high-grade serous ovarian cancers share genomic and transcriptional features with basal-like breast cancers[17,20]. Ovarian clear cell cancers have similar expression phenotypes to renal clear cell and uterine clear cell cancers[21], and women with ovarian clear cell cancer may benefit from the use of drugs, such as sunitinib, that are active in patients with renal cancer [22]. Taking a rigorous view, the ovarian histotypes should be regarded as distinct diseases, as their cell of origin, epidemiology and driver mutations are quite different.

The term ovarian cancer is therefore misleading. It is not a single disease, and a considerable proportion of tumours do not arise from ovarian tissue. The unifying clinical feature of all ovarian cancers is frequent loco-regional dissemination to the ovary and related pelvic organs. We considered whether the term ovarian cancer should be replaced with the terms pelvic or peritoneal cancer but we recognized the confusion that might ensue for patients and physicians, as well as in the scientific literature, especially during a transition period. Before the term ovarian cancer is abandoned, the disparate origins of this disease need to be more widely understood by patients, physicians and scientists.

Improved clinical trial design

A shift in emphasis is needed from Phase III clinical trials to earlier phase trial designs that include molecular studies. Given the

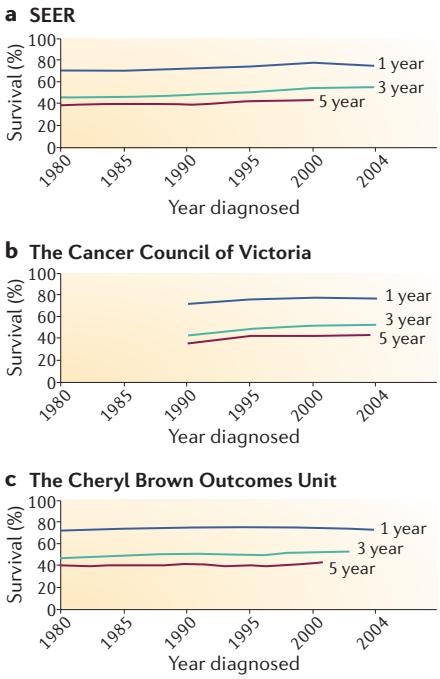

Figure 1 | **Survival in ovarian cancer.** Data from the United States (part **a**), Australia (part **b**) and Canada (part **c**) show that there has been little change in 1-year, 3-year and 5-year survival rates post-diagnosis of patients with ovarian cancer over the past 20 years. Data in part **a** are from the Surveillance, Epidemiology and End Results (SEER) database (see Further information) obtained between 1980 and 2004. Data in part **b** are from The Cancer Council of Victoria, Victoria, Australia, obtained between 1990 and 2004. Data in part **c** are from The Cheryl Brown Outcomes Unit, British Columbia, Canada, obtained between 1980 and 2004.

differences in ovarian cancer subtypes, clinical trials should no longer aggregate the various ovarian histologies. Trial design should also consider molecular parallels between ovarian cancer and other solid cancers. Clinical reporting and scientific publications should use reproducible diagnostic methods and standardized terms for these disease entities[23]. The current single approach to treatment should rapidly evolve to evidence-based stratification that is based on molecular drivers and histotype-specific treatments.

The ovarian cancer field lags behind other cancer research fields in incorporating targeted therapies into standard treatment (FIG. 3). With the possible exception of poly(ADP-ribose) polymerase (PARP) inhibitors and angiogenesis inhibitors (discussed below), single-agent, molecularly targeted therapies have only yielded small increments in progression-free survival in ovarian cancers. Therefore, a major shift in the way clinical trials are designed is urgently required. The ceiling in efficacy that has been witnessed with all-inclusive Phase III trials means that the priority should now be on subtype-specific (randomized) Phase II clinical trials that are based on sound scientific rationale. In addition, 'window trials' (REF. 24) with clear readouts of pathway inhibition that correlate with clinical outcome will expedite the clinical investigation of novel therapies.

Improved blood and imaging biomarkers that accurately measure response and residual disease are also needed: the current criteria are an impediment to the better evaluation of response. Contrast-enhanced computed tomography (CT) imaging is the standard non-surgical method for staging and assessing response; however, it is difficult to detect small peritoneal deposits. For example, when peritoneal tumour deposits are <1cm in size, the sensitivity of CT is only 7–28%, and this is further dependent on the anatomical location of the disease[25]. The measurement of circulating levels of the ovarian tumour antigen CA125 (also known as mucin 16) is routinely used to monitor disease recurrence; however, markers that are molecularly based and also sensitive for low-volume residual disease are needed. Preliminary results from the detection of the cellular by-products of ovarian cancer cells in the blood are promising but need wider evaluation[26].

Prevention and early detection

The identification of patients who are at an increased genetic risk of ovarian cancer currently offers the most effective measure for prevention and early detection of this disease. High-grade serous ovarian cancer is diagnosed at an advanced stage in approximately 70% of patients, and these women have a substantially worse outcome than the outcome of those with early stage disease. It is important to recognize that the poor prognosis in advanced stage disease is a function of at least two factors — the extent of disease, and thus the ability to surgically remove the tumour, and the differences in the biology of the tumours that remain confined to the pelvic space compared with those that widely disseminate[27]. Early detection tests should focus on identifying the precursors of advanced stage high-grade serous ovarian tumours. Tests should not be evaluated on patients with low-grade stage I/II serous tumours that have activating RAS pathway mutations, as these are not typically precursors of high-grade serous tumours.

Traditional concepts of metastasis are difficult to apply to ovarian cancer. There is no anatomical barrier to seeding throughout the peritoneal cavity for a high-grade serous ovarian cancer that arises on the surface of the ovary or fallopian tube, or a clear cell ovarian cancer that arises in an endometriotic deposit. Emerging insights into disease progression of high-grade serous ovarian cancers now suggest that the early detection of low-volume advanced stage, rather than early stage, ovarian cancer may be a more realistic goal of screening studies[28], although the clinical value of this strategy remains to be determined. More data about the natural history of precursor lesions in the fallopian tube epithelium and their rate of transformation to invasive carcinoma are needed to plan future screening methods and technologies[29]. Recent data from the Prostate, Lung, Colorectal and Ovarian (PLCO) trial indicate that current serological diagnostics and imaging tests are insufficiently sensitive to alter outcome in screened populations[30], although results from the large UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial remain to be reported. On the basis of current data, widespread screening is not yet justified and its value in the management of high-risk women is unknown[31]. Screening for endometrioid and clear cell ovarian cancer will be particularly challenging, as endometriosis is a common, often subclinical, disease and risk factors for transformation have not yet been identified.

The identification of women who carry germline mutations in *BRCA1*, *BRCA2*, *RAD51C* and genes that encode other DNA repair proteins provides the most effective preventative strategy for high-grade serous ovarian cancers, as the removal of the ovaries and fallopian tubes can reduce the risk of disease in carriers by 80%[32,33]. Given the newly appreciated importance of the fallopian tube in the genesis of high-grade serous ovarian cancer, it is recommended that the complete removal of the fallopian tube should become standard of care in any woman undergoing hysterectomy and/or removal of the ovaries (oophorectomy). Oophorectomy in premenopausal women induces early menopause. As a consequence, and with the changed view of the role of the fallopian tube in ovarian cancer, some clinicians have recommended that only the fallopian tubes should be removed (salpingectomy) in women with germline *BRCA1* or *BRCA2* mutations, or in women with a strong family history of breast and/or ovarian cancer[34]. However, until comprehensive comparative data are available, the group felt it was premature to recommend that only the fallopian tubes are removed in high-risk women.

Although there is no evidence that current screening strategies reduce mortality in high-risk women, future screening approaches are likely to require the identification of those women who are at the greatest genetic risk in order to reduce the number of false-positive results in a screened population[30]. Advances in high-throughput sequencing and mutation scanning offer the potential to greatly reduce the cost of mutation testing, and to therefore extend testing to more women, especially women with high-grade serous ovarian cancers. Recent genome-wide association studies, which were enabled by large cancer cohorts assembled by research consortia (see below), have identified a number of new ovarian cancer risk loci[35,36]. The identification of novel genetic risk loci is improved by histotype stratification[35,36], and therefore genetic and epidemiological studies of tumours should embrace the appropriate classification of ovarian cancer.

Identification of new targets

Novel approaches are needed to identify therapeutic targets, especially in high-grade serous ovarian cancer. Over the past decade, increasingly comprehensive genomic analyses of ovarian cancer have failed to reveal new oncogenic drivers in the more common histotypes. Large-scale gene expression[19] and DNA copy number analyses[37,38] and mutational screens[39] have not identified new high-frequency 'drugable' targets in high-grade serous ovarian cancers, perhaps with the possible exception of cyclin E1 (*CCNE1*). *CCNE1* amplification is associated with poor outcome[40] and oncogene addiction *in vitro*[41]. Further studies are needed to validate the prognostic significance of other amplified genes in high-grade serous ovarian cancers and to develop therapeutic approaches that target them. Mutations in the RAS pathway are found in more than 70% of low-grade serous ovarian cancers[18], and specific clinical trials for this unique serous neoplasm are urgently needed. Activating mutations in *PIK3CA*[8], and amplification of receptor tyrosine kinases including *MET*[22] and *ERBB2* (REF. 42), provide novel therapeutic approaches in clear cell ovarian cancers. Although high-frequency, novel somatic mutations have been found in granulosa[43] and clear cell[10] ovarian cancer, these uncommon subtypes only account for a small proportion of the overall disease mortality.

Genomic studies have reinforced the centrality of *TP53* (which encodes the tumour suppressor p53) mutations[20]; BRCA pathway disruption[44]; and homologous recombination repair (HRR) deficiency in high-grade serous ovarian cancers. The notion that many high-grade serous ovarian cancers are BRCA-like through alterations in other proteins in the HRR pathway[45] has resulted in the exploration of PARP inhibitors[46]. Preliminary findings suggest efficacy of PARP inhibitors in a number of settings, including the use of olaparib as a maintenance treatment after chemotherapy in women with platinum-sensitive recurrent high-grade serous ovarian cancers[47]. About 50% of all high-grade serous ovarian cancers show disruption of the BRCA pathway either by germline or somatic mutation, or by epigenetic silencing of pathway members[39]. Consistent with mutational studies[39], functional assays show that roughly 50% of all high-grade serous ovarian cancers have defective formation of HRR foci following DNA damage[48]. If the repair-defective tumours correspond to those patients with relatively good responses to PARP inhibitors, this may provide an important predictive test of treatment response. These data suggest that exploiting mutator phenotypes in high-grade serous ovarian cancer can offer a valuable approach to novel therapies[49,50]. Synthetic lethality as a strategy for targeting DNA repair and p53 pathways in high-grade serous ovarian cancer should be further explored with RNA interference and small-molecule screens.

One of the most challenging aspects of high-grade serous ovarian cancer is the recognition that widespread gene expression and DNA copy number changes provide extensive opportunities for adaptation and the development of resistance[17]. Ongoing genomic instability may drive intratumoural genetic heterogeneity and may increase the probability of treatment-resistant clone selection[51,52]. However, genetic alterations in tumour cells are not the only contributor to therapy resistance. Cell non-autonomous effects are mediated by the tumour microenvironment, which is recruited by the tumour cells (see below), providing a cytokine milieu on which the tumour thrives, becomes resistant to current therapies and becomes more invasive. Single-agent treatment is unlikely to be effective when cancerous cells are capable of using other non-targeted pathways. Therefore, it is crucial that we develop combination therapeutic approaches that anticipate tumour adaptive responses to individual targeted agents. The exploration of novel combinations of targeted therapeutics will only be possible if we can overcome the current reluctance of the pharmaceutical industry to be involved in clinical trials that combine drugs developed by different companies. Combination studies must be underpinned by the preclinical investigation of dosing schedules in appropriate model systems.

The tumour microenvironment

Targeting the tumour microenvironment provides an important adjunct to molecular therapeutics and chemotherapy that are directed towards the tumour cell. The inherent instability of the genome of high-grade serous ovarian cancer has shifted attention to targeting the tumour microenvironment, which comprises a large proportion of the cell mass of many ovarian cancers. To date, encouraging results have been obtained with trials in ovarian cancer that target the angiogenic factor vascular endothelial growth factor (VEGF) using the therapeutic antibody bevacizumab. The addition of bevacizumab to conventional chemotherapy improves progression-free survival in relapsed, platinum-resistant ovarian cancer[53]. In addition, large randomized Phase III trials that investigated the role of bevacizumab maintenance therapy in the first-line setting (Gynecologic Oncology Group (GOG-0218) (ClinicalTrials.gov identifier: NCT00262847) and ICON7 (NCT00483782)) and in platinum-sensitive relapsed disease (OCEANS) (NCT00434642) have been completed. The results of all three

Box 1 | **The meeting**

For 25 years the Helene Harris Memorial Trust (HHMT) has recognized the importance of communication between scientists and clinicians for improving the early detection of ovarian cancers and the treatment of patients with advanced disease, bringing together international experts on a biannual basis (see the Helene Harris Memorial Trust International Forum on Ovarian Cancer website; see Further information). In January 2011 researchers met in Florida, USA, over 4 days at the HHMT 12th International Forum on Ovarian Cancer (sponsered by Ovarian Cancer Action) to consider the latest findings in basic, translational and clinical research in ovarian cancer. With both a sense of optimism that was associated with recent advances and a sense of frustration with the limited improvements in outcomes in the past, we considered new ways forwards on the basis of recent findings. The delegates attending the meeting are listed in Supplementary information S2 (table) (see Further information). The resulting Opinion article reflects the consensus of the meeting and the listed authors have all contributed to this manuscript.

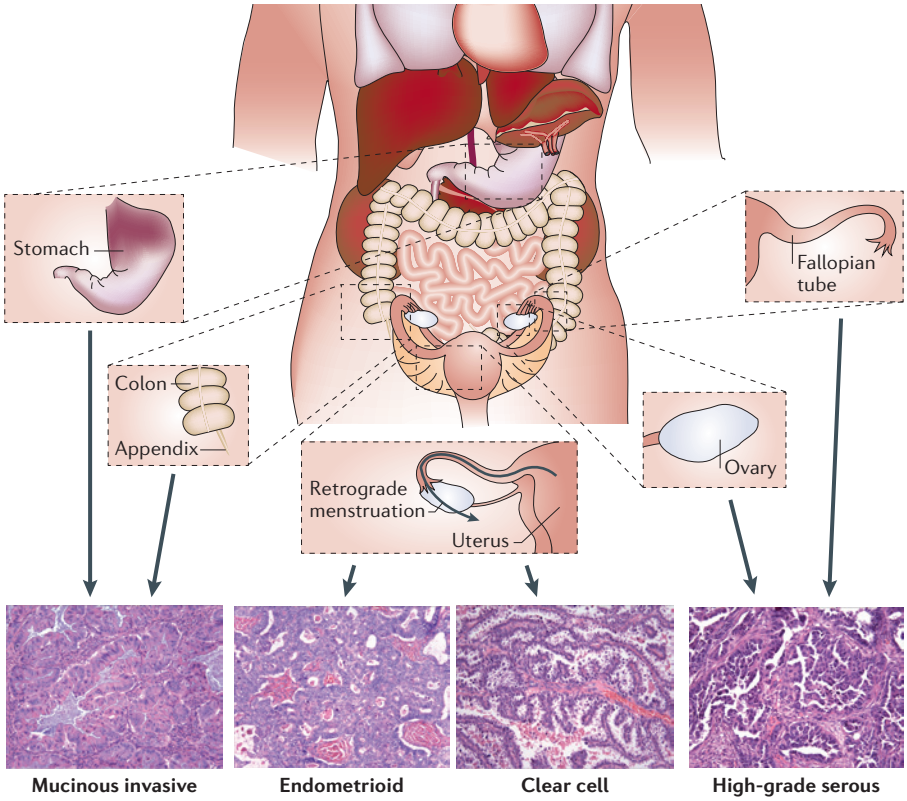

Figure 2 | **The origins of ovarian cancer.** Ovarian cancer is a collective term for invasive cancers that are derived from different tissues. Most invasive mucinous ovarian cancers are metastases to the ovary, often from the gastrointestinal tract, including the colon, appendix or stomach. Endometrioid and clear cell ovarian cancers are derived from endometriosis, which in turn is associated with retrograde menstruation from the endometrium. High-grade serous ovarian cancers are derived from the surface of the ovary and/or the distal fallopian tube; the relative contribution that the two sites make to these tumours remains unclear. Benign and low-malignant potential (borderline) tumours are not shown. Such tumours are thought to be of ovarian origin, however, the originating cells are not defined and their derivation may be revised in the future. Histological images courtesy of R. Drapkin, Dana-Farber Cancer Institute, USA, and C. Crum, Brigham and Women's Hospital, USA.

trials, presented in abstract form only, suggest improvements in progression-free survival when bevacizumab is given as concurrent or maintenance therapy. However, despite the presumed stability of the tumour endothelium, resistance to anti-VEGF agents has rapidly emerged. Understanding resistance pathways and developing predictors of patient response are crucial for better exploiting anti-angiogenic therapies[54,55].

A spontaneous antitumour immune response in the form of tumour-reactive T cells and/or antibodies has been demonstrated in some patients with ovarian cancer[56,57]. The increased infiltration of lymphocytes in tumour islets predicts significantly longer survival in ovarian cancer[58]. Conversely, the detection of high numbers of T regulatory cells, which mediate immune suppression, predicts poor patient survival[59,60]. The presence of additional immunosuppressive cell subtypes, such as B7-H4-expressing tumour macrophages[61], has also been correlated with poor outcome.

Complex networks of inflammatory cytokines and chemokines[62] regulate communication between malignant cells and supporting stroma in ovarian cancer. These cytokines and their intracellular signalling pathways can make malignant cells resistant to apoptosis, can facilitate the evasion of tumour immunity and can promote angiogenesis. Tumour cells typically trigger inflammatory cytokine networks as a means of escaping immune recognition in spite of surrounding inflammation[63,64]. In experimental animal models, targeting these key inflammatory cytokines and chemokines has been shown to abrogate these processes that are key to the progression of ovarian cancer[62,65].

The association of intratumoural T cells with increased survival, and T regulatory cells with worse survival, indicates that ovarian cancers could respond to immune therapy. Pilot studies indicate that therapies that capitalize on pre-existing antitumour immune responses can be successful in ovarian cancer. For example, objective responses and/or prolonged survival have been seen with immune checkpoint blockade using an antibody against cytotoxic T lymphocyte protein 4 (CTLA4)[66,67], and Phase II studies are currently underway. The understanding that some conventional chemotherapy drugs also have immunomodulatory activity offers new opportunities for designing combinatorial approaches for women with ovarian cancer whose tumours exhibit pre-existing antitumour immunity in terms of high levels of intraepithelial tumour-infiltrating lymphocytes. In addition, trials targeting inflammatory cytokines[68,69] are currently in early stages, but they can offer important biological lessons for clinicians.

There needs to be rapid development of further Phase II/III studies that focus on agents targeting key pathways in the tumour microenvironment that not only assess their efficacy alongside established cytotoxic regimes, but that also aim to establish the optimal use of these agents for maintenance therapy.

Tumour adaptation and resistance

Improved understanding of clonal diversity in tumours prior to treatment and mechanisms of tumour adaptation and the acquisition of resistance following treatment are essential if more durable responses to therapy are to be achieved. Many women respond well to first-line treatment, but frequently relapse with chemotherapy-resistant disease. Evolutionary models of clonal selection may explain drug resistance in cancer. In acute lymphocytic leukaemia and chronic myeloid leukaemia, point mutations that confer resistance to imatinib exist at low prevalence before treatment and can become highly enriched during relapse[70,71]. Autopsy studies on advanced pancreatic cancer have shown profound genetic heterogeneity, with 52% of mutations being present in subclonal populations[72,73]. Whether this paradigm can explain resistance in ovarian cancer, and in particular whether heterogeneity is associated with primary platinum resistance, needs further investigation. With advances in next-generation sequencing we now have the tools to investigate clonal diversity[84,85] and to start inferring the evolutionary changes that may contribute to resistance.

Despite the plethora of research that has been dedicated to the mechanisms of platinum resistance, this is yet to translate to clinical practice. Undoubtedly, deficiencies in our knowledge of the fundamental changes that occur within the tumour — both the epithelial fraction and the microenvironment — throughout treatment have impeded progress in this area. More recently, studies with paired tumour samples that were collected before treatment and following disease relapse have provided some of the first insights into clonal variation and mechanisms of resistance *in vivo*[52,74], including reversion of germline mutations in *BRCA1* or *BRCA2* (REF. 86). Serially obtained biopsy samples of disease sites should be a central component in clinical trial design.

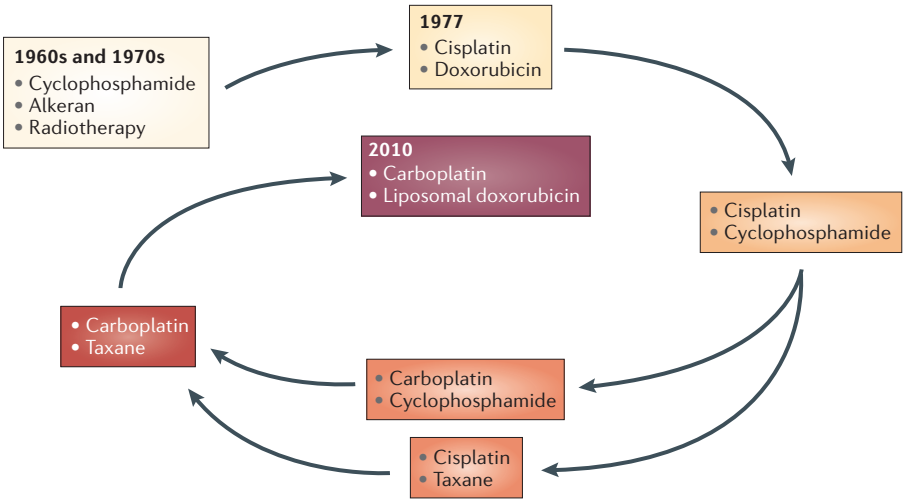

Figure 3 | **Evolution of chemotherapy for ovarian cancer over the past 50 years.** It has proved difficult to progress beyond platinum-based therapy, which was introduced in the late 1970s and which remains the standard of care. Cisplatin, and subsequently carboplatin, which has a lower toxicity profile, have been combined with other agents, including taxanes. Most recently, liposomal doxorubicin has become commonly used with carboplatin, especially in a relapse setting. It is notable that the combination of carboplatin and liposomal doxorubicin involves similar drugs to those that were used in the mid-1970s, albeit with reduced side effects. It is likely that ovarian cancer treatment will considerably evolve in the coming years with the introduction of molecularly targeted agents, such as poly(ADP-ribose) polymerase (PARP) inhibitors, histotype-specific treatments and dose-dense regimes, including the use of weekly taxane administration.

Importance of international consortia

International consortia involving large biological and clinical data sets must be encouraged; however, these require high fidelity and transparency in analytical approaches. Ovarian cancer is a relatively uncommon disease and, together with its histological diversity, it is thus difficult to collect substantial numbers of samples of specific subtypes. With the increased recognition of the importance of stratification by subtype, global collaborations and consortia such as the Ovarian Cancer Association Consortium (OCAC), The Cancer Genome Atlas (TCGA), The Australian Ovarian Cancer Study (AOCS), Ovarian Cancer Therapy – Innovative Models Prolong Survival (OCTIPS) and Ovarian Tumour Tissue Analysis Consortium (OTTA) are crucial to furthering our understanding of the molecular biology of ovarian tumours and genetic risk factors. Such collaborative endeavours require highly ordered, standardized and quality-controlled strategies for the collection and management of biological specimens. The combination of high-throughput technologies with large sample sets allows detailed biological and translational studies. However, the challenges of managing large molecular data sets, each identifying a multitude of putative abnormalities — many of which may prove to be artefacts — are substantial. Moreover, the opportunity to introduce human operator error remains unacceptably high. Methodologies used in the analysis of such data sets should be wholly transparent, reproducible and biologically validated in the laboratory before any such findings can be put into practice. Errors made in the development of the OvaCheck early detection test underscore the importance of rigorous biostatistical support, especially when dealing with complex molecular data sets[75].

Better experimental models

Improved experimental models of ovarian cancer are required that more closely resemble the human disease. New model systems are needed that reflect the various originating cells, as well as the underlying genomic events driving each disease. Although mouse models of ovarian cancer have been developed[76–79], these have not for the most part recapitulated human disease. In particular, a model that recapitulates the most important single histotype, high-grade serous ovarian cancer, has remained elusive. Mouse transgenic and knockout studies are likely to substantially benefit from an improved understanding of the key driver mutations, such as the loss of *ARID1A* in clear cell ovarian cancer and the importance of secretory cells of the fallopian tube in high-grade serous ovarian cancer. Recent reports of fallopian tube-based model systems will help to define the physiology and susceptibility of this epithelium to transformation[7,80].

Now that it is appreciated that clear cell, mucinous, low-grade endometrioid and high-grade serous ovarian cancers are as molecularly distinct as, for example, breast and renal cancers, researchers must pay strict attention to the human cell line models that they use to explore different aspects of the disease. Comparative molecular studies that fail to recognize the histopathological origins of the ovarian cancer cell lines used are no longer appropriate. Currently, the origins of many of the ovarian cancer cell lines are poorly defined — the field would benefit enormously from the creation of new cell lines that reflect the different histotypes and molecular subtypes of ovarian cancer.

It is also timely to consider *in vitro* models that are more appropriate than the two-dimensional growth of cells on plastic. Three-dimensional cell culture systems that mimic the peritoneal microenvironment have provided important insights into ovarian cancer biology[81,82].

Quality of life and symptom benefit

It is essential that measures of quality of life and symptom benefit are included with response and survival rates as primary end points in clinical trials that investigate palliative treatments. The primary end point of most clinical trials has traditionally been objective response and survival. Most patients relapse after first-line treatment; response rates and time to progression typically diminish with each recurrence. Although there are numerous studies of palliative chemotherapy regimes in platinum-resistant ovarian cancer, there is scant evidence to confirm that these

treatments are truly palliative and improve symptom control[83]. Attempts to address this important question with the currently available quality-of-life questionnaires have not been successful, and toxicity data completed by physicians may give a false impression of the patient's experience. Robust instruments are needed that measure the effect of palliative chemotherapy on symptom control given that this should be the major aim of treatment. Treatment should be stratified in accordance to prognosis, with more emphasis placed on minimizing side effects and avoiding inappropriate therapy in patients with a low likelihood of benefit. Prognostic indices are required to better categorize patients with recurrent ovarian cancer into poor, intermediate and good subsets rather than the current approach of grouping patients together.

Conclusion

The past 5 years have seen an explosion in our understanding of the heterogeneity of ovarian cancer. This comes with an emphatic commitment to changing the way that clinical trials in ovarian cancer should be designed. Treatment of ovarian cancer will benefit from the careful alignment of target, drug, patient and trial design. The greatest challenge will be to craft combinations of therapy that result in years of improved survival. There is an outstanding level of cooperation and willingness to share ideas among those in the ovarian cancer research field, as exemplified by the HHMT meeting. A high level of cooperation bodes well for the women whose lives we hope to improve.

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Competing interests statement

The authors declare competing financial interests. See Web version for details.

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