Reliable *in vitro* studies require appropriate ovarian cancer cell lines

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**Abstract**

Ovarian cancer is the fifth most common cause of cancer death in women and the leading cause of death from gynaecological malignancies. Of the 75% women diagnosed with locally advanced or disseminated disease, only 30% will survive five years following treatment. This poor prognosis is due to the following reasons: limited understanding of the tumor origin, unclear initiating events and early developmental stages of ovarian cancer, lack of reliable ovarian cancer-specific biomarkers, and drug resistance in advanced cases. In the past, *in vitro* studies using cell line models have been an invaluable tool for basic, discovery-driven cancer research. However, numerous issues including misidentification and cross-contamination of cell lines have hindered research efforts. In this study we examined all ovarian cancer cell lines available from cell banks. Hereby, we identified inconsistencies in the reporting, difficulties in the identification of cell origin or clinical data of the donor patients, restricted ethnic and histological type representation, and a lack of tubal and peritoneal cancer cell lines. We recommend that all cell lines should be distributed via official cell banks only with strict guidelines regarding the minimal available information required to improve the quality of ovarian cancer research in future.

**Keywords:** Epithelial ovarian cancer, Tubal cancer, Peritoneal cancer, Primary cultures, Immortalization

**Introduction**

Epithelial ovarian cancer (EOC) is the fifth most common cause of cancer death in women and the leading cause of death from gynaecological malignancies [1]. Survival rates have changed little since the early 1980’s despite the use of new chemotherapeutical drugs, with only 40% of all stages and 15-30% of patients with widespread metastatic disease surviving 5 years after the initial treatment [2]. This poor overall prognosis is the result of a combination of factors including a lack of distinctive symptoms and sensitive/specific tumour markers at an early stage, drug resistance for advanced disease, and a limited understanding of the early-initiating events and early stages of EOC development.

The dualistic paradigm

Among the different tumours arising from the ovary 90% are of epithelial origin [3]. The major histotypes (serous, endometrioid, mucinous, and clear cell) are partly genetically distinguishable as shown by various high-throughput studies in the past fifteen years [4]. Recent findings suggest that epithelial tumours of the ovary may be grouped on the basis of their genetic alterations into a dualistic model that subdivides the various histological types of EOC into two broad categories. The slowly developing tumours (Type I) include low grade serous, endometrioid, mucinous, and a subset of clear cell carcinomas [5-7] and are characterised by genetic alterations in *KRAS*, *BRAF*, *CTNNB1*, *PTEN*, *ARID1A*, *FBXW74*, *PIK3CA*, *PPP2R1A*, and *TGFBR2* [7-12]. The more aggressive Type II tumours harbour mutations in *TP53*, *BRCA1*, and *BRCA2* [8]. A more systematic characterization of Type II tumours, in particular high grade serous ovarian cancers, was performed by The Cancer Genome Atlas (TCGA). The Profiling of 489 samples for differential mRNA and miRNA expression, DNA copy number changes, promoter DNA methylation, and whole exome DNA sequencing revealed that almost all samples comprised *TP53* mutations and significantly recurring somatic mutations in *NF1*, *BRCA1*, *BRCA2*, *RB1*, and *CDK12* [13].

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Ovarian surface epithelium and tubal epithelium as possible tumour origins

The monolayer of epithelial cells covering the outer surface of the ovary (OSE) has traditionally been thought to be the site of origin of epithelial ovarian cancer [1]. This is supported by a recent study focusing on a stem cell niche located at the hilum region and a transitional area between OSE, mesothelium and tubal epithelium. In a comprehensive experimental mouse model the authors demonstrate that stem cell-like OSE cells have the potential to develop into EOC [14]. Another theory proposes the normal epithelium of the fallopian tube (serous), endometrium (endometrioid) and endocervix (mucinous) as the origin of the respective EOC histotypes [15,16]. According to the concept of extra-uterine Müllerian epithelium, the fallopian tube fimbria is proposed to be the primary origin of the high grade serous ovarian carcinoma, the most common EOC subtype and frequently harbouring TP53 and IL-6 mutations [17,18]. This is supported by the presence of early neoplastic serous tubal intraepithelial lesions (STIL) in prophylactically removed fallopian tubes of BRCA mutations-carrying women [19-21]. Those tubal fimbria displayed characteristic features such as TP53 mutations, DNA damage, and secretory cells, suggesting the tubal fimbria as the precursor for high grade serous ovarian cancers [20,22,23]. This was further supported by more recent studies identifying the tubal secretory cells as potential neoplastic precursors at the tubal fimbria. These cells carry TP53 mutations, show elevated γH2AX expression, a marker of DNA damage, and express Ki-67 and PAX2, two proliferation markers also expressed in serous tubal intraepithelial carcinomas and high grade serous ovarian carcinomas [24-27]. In contrast, epithelial-specific marker such as Calretinin and PAX8 do not seem suitable in the proof of EOC origin [28]. Recently, it has been demonstrated in a Brca, Tp53, Pten genetic mouse model that de novo high grade serous ovarian carcinoma are originated from the fallopian tube secretory epithelium and that these tumours are correlated with high grade serous carcinoma tumour markers and genomic alterations of the human TCGA data set [29].

Serous carcinomas of the ovary, tube and peritoneum

Serous ovarian- (SOC), tubal- (STC), and peritoneal- (SPC) cancers are remarkably similar in term of morphology [30,31], genetics [32], and clinical behaviour and epidemiology [33]. SPC and SOC patients also have a comparable survival rate that, however, is markedly distinct from that of patients with low grade SOC metastasizing to distant locations. Cell lines have long been considered important and useful in vitro models to investigate the molecular nature and the pathological processes underlying the development of ovarian, tubal, and peritoneal tumours, and their progression to advanced diseases, and even to search for diagnostic or prognostic tumour markers as well as for therapeutic targets.

Ovarian cancer cell lines need better characterization

Falling short of the use of in vivo animal models, cancer cell lines as in vitro models have proven invaluable experimental tools for many decades in basic research. Cancer cell lines can be grown continuously in culture, allowing countless experiments to be performed without the necessary restrictions required for in vivo models. However, due to few regulations for the development and testing of these cell lines, the question arises as to the quality of long-time established ovarian cancer cell lines. Often laboratories obtain cell lines from collaborating groups and trust in their identification of cells. Conducting research on the basis of such cell lines means not only a waste of a great deal of money and time but also a risk to steer research in an undesired direction.

It is therefore of great importance to define and establish a world-wide standard applicable to all cell lines that are commercially available for research, in order to ensure that only high-quality cancer cell lines with an unequivocal molecular identity and source are distributed to the research community.

We performed a web search for currently available banks for cells and cell lines using the terms ‘cell bank’, ‘cell lines’, and ‘cell line bank’. Only web pages in English and containing normal or cancer ovarian, tubal, and peritoneal cell lines were included in the study. PubMed

Table 1 Ovarian cancer cell line banks

| ID     | Name                                                         | Homepage                          |
|--------|--------------------------------------------------------------|-----------------------------------|
| ATCC   | American Type Culture Collection                             | http://www.lgcstandards-atcc.org  |
| ECACC  | European Collection of Cell Cultures, a part of the Health Protection Agency | http://www.phe-culturecollections.org.uk/collections/ecacc.aspx |
| DSMZ   | German Collection of Microorganisms and Cell Cultures        | http://www.dsmz.de/               |
| JCRB   | Japanese Collection of Research Bioresources                 | http://cellbank.nibio.go.jp/      |
| CellBank Australia | Australian cell bank – Cell Bank Australia | http://www.cellbankaustralia.com/ |
| NCBI   | National Cell Bank of Iran                                  | http://ncbi.pasteur.ac.ir/        |
### Table 2 Human cell lines originated from ovarian cancer or human ovarian surface epithelium

| ID number | Cell line | Origin | Source |
|-----------|-----------|--------|--------|
| Homo sapiens – human | | | |
| 1 | 222 | | |
| 2 | 2008 | Ovary | |
| 3 | 2008/C13.R | Ovarian adenocarcinoma | NCBI |
| 4 | 41M7/OAW28 | Ovarian cancer ascites | ECACC |
| 5 | 41 M cisR | Ovarian cancer ascites | |
| 6 | 59 M | Ovarian cancer ascites | ECACC |
| 7 | A2780 | Ovarian adenocarcinoma | ECACC |
| 8 | A2780ADR | Ovarian adenocarcinoma; A2780 | ECACC |
| 9 | A2780cis | Ovarian adenocarcinoma; A2780 | ECACC |
| 10 | A2780 CP | Ovarian adenocarcinoma | NCBI |
| 11 | A2780 S | Ovarian adenocarcinoma | NCBI |
| 12 | Caov-3 | Ovarian adenocarcinoma | ATCC |
| 13 | Caov-4 | Metastatic fallopian tube mass from ovarian tumour | ATCC/NCBI |
| 14 | CH1 | Ovarian adenocarcinoma | |
| 15 | CH1cisR | Ovarian adenocarcinoma | |
| 16 | COLO-704 | Metastatic colonic ascites from ovarian tumour | DSMZ |
| 17 | COV318 | Ovarian cancer ascites | ECACC |
| 18 | COV362 | Ovarian cancer pleural effusion | ECACC |
| 19 | COV362.4 | Ovarian cancer pleural effusion; COV362 | ECACC |
| 20 | COV413A | Metastatic sigmoid mass from ovarian tumour | ECACC |
| 21 | COV413B | Metastatic bladder dome mass from ovarian tumour | ECACC |
| 22 | COV434 | Ovarian granulosa tumour from a solid primary tumour | ECACC |
| 23 | COV504 | Ovarian pleural effusion | ECACC |
| 24 | COV644 | Ovarian cancer (primary tumor) | ECACC |
| 25 | EFO-21 | Ovarian cancer ascites | DSMZ |
| 26 | EFO27 | Metastatic omental mass from ovarian tumour | DSMZ |
| 27 | ES-2 | Ovarian adenocarcinoma | ATCC |
| 28 | FU-OV-1 | Malignant ovarian mass | DSMZ |
| 29 | HAC-2 | Ovarian cancer cell derived from mesonephros | JCRB |
| 30 | Hey-A8 | Ovary | CCLE |
| 31 | HOSE 6-3 | Ovarian surface epithelium | |
| 32 | HOSE 17-1 | Ovarian surface epithelium | |
| 33 | HOSE 105 | Ovarian surface epithelium | |
| 34 | HOSE 111 | Ovarian surface epithelium | |
| 35 | HOSE 129 | Ovarian surface epithelium | |
| 36 | HOSE 130 | Ovarian surface epithelium | |
| 37 | Hs 38.T | Ovarian teratoma | ATCC |
| 38 | Hs 571.T | Ovarian adenocarcinoma | ATCC |
| 39 | Hs904.T | Ovarian adenocarcinoma | |
| 40 | IGROV1 | Ovarian adenocarcinoma | |
| 41 | JHOC-5 | Ovarian adenocarcinoma | CCLE |
| 42 | JHOM-1 | Ovarian adenocarcinoma | CCLE |
Table 2 Human cell lines originated from ovarian cancer or human ovarian surface epithelium (Continued)

| #  | Line Name       | Primary Site          | Tissue Type          | Source     |
|----|-----------------|-----------------------|----------------------|------------|
| 43 | JHOM-2B         | Ovarian adenocarcinoma| CCLE                 |
| 44 | JHOS-2          | Ovarian adenocarcinoma| CCLE                 |
| 45 | JHOS-4          | Ovarian adenocarcinoma| CCLE                 |
| 46 | KURAMOCHI       | Ovarian cancer ascites | JCRB                 |
| 47 | MCAS            | Ovarian adenocarcinoma| JCRB                 |
| 48 | NCC-OvC-K119    | Ovarian adenocarcinoma| JCRB                 |
| 49 | OAW28/41 M      | Ovarian cancer ascites | ECACC               |
| 50 | OAW42           | Ovarian cancer ascites | ECACC               |
| 51 | OC 314          | Ovarian cancer ascites | CCLE                 |
| 52 | OC 315          | Ovarian adenocarcinoma| CCLE                 |
| 53 | OC 316          | Ovarian cancer ascites | CCLE                 |
| 54 | ONCO-DG-1a      | Ovarian adenocarcinoma| DSMZ                 |
| 55 | OV-7            | Ovarian adenocarcinoma derived from solid tumour | ECACC               |
| 56 | OVI7R           | Ovarian cancer ascites | ECACC               |
| 57 | OV56            | Ovarian cancer ascites | ECACC               |
| 58 | OV-58           | Ovarian cancer ascites | ECACC               |
| 59 | OV-90           | Ovarian cancer ascites | ATCC                 |
| 60 | OV-1063a        | Ovary                    | NCBi                 |
| 61 | OVC1-Pt 32      | Ovarian cancer ascites | ATCC/NCBi            |
| 62 | OVCAR-3         | Ovarian cancer ascites | CCLE                 |
| 63 | OVCAR-4         | Ovarian adenocarcinoma| CCLE                 |
| 64 | OVCAR-8         | Ovarian adenocarcinoma| CCLE                 |
| 65 | OMSE            | Metastatic ovarian adenocarcinoma | JCRB/CCLE |
| 66 | OVK18           | Ovarian adenocarcinoma| JCRB                 |
| 67 | OVKATE          | Ovarian adenocarcinoma| JCRB                 |
| 68 | OVMANA          | Ovarian adenocarcinoma| JCRB                 |
| 69 | OVMILa          | Ovarian adenocarcinoma| JCRB                 |
| 70 | OVMIL-IIa       | Ovarian adenocarcinoma| JCRB                 |
| 71 | OVS AHO         | Ovarian adenocarcinoma| JCRB                 |
| 72 | OVSAYOa         | Ovarian adenocarcinoma| JCRB                 |
| 73 | OVTOKO          | Ovarian adenocarcinoma| JCRB                 |
| 74 | PA-1            | Ovarian cancer ascites | ATCC/JCRB/ECACC     |
| 75 | PA-1/6TG-r      | Ovarian cancer ascites | JCRB                 |
| 76 | PEA1            | Ovarian cancer pleural effusion | ECACC |
| 77 | PEA2            | Ovarian cancer ascites | ECACC               |
| 78 | PEO1            | Ovarian cancer ascites | ECACC               |
| 79 | PEO4            | Ovarian cancer pleural effusion | ECACC |
| 80 | PEO6            | Ovarian cancer ascites | ECACC               |
| 81 | PEO14b          | Ovarian cancer ascites | ECACC               |
| 82 | PEO16           | Ovarian cancer ascites | ECACC               |
| 83 | PEO23b          | Ovarian cancer ascites | ECACC               |
| 84 | RKN             | Ovarian adenocarcinoma| JCRB                 |
| 85 | RMG-a           | Ovarian adenocarcinoma| JCRB                 |
| 86 | RMG-II          | Ovarian adenocarcinoma| JCRB                 |
Our search algorithm retrieved 153 cell lines. ECAAC distributes almost 40% of all publicly available cell lines, followed by JCRB (19%). A number of cell lines (7.2%) are distributed by two or more cell banks. A listing of the ID number, cell line designation (name), origin, and source of the retrieved normal and malignant ovarian, tubal, and peritoneal cell lines is presented in Tables 2 and 3. About two thirds (68.0%) of the normal and ovarian cancer cell lines used in research is of human and about one fourth (23.5%) of Chinese hamster (Cricetulus griseus) origin. About 3% originate from mice (Mus musculus) and 4.5% from various species such as Spodoptera frugiperda (Fall armyworm), Esox lucius (Northern pike fish), Ictalurus punctatus (Channel catfish), and Sus domesticus (Domestic pig). Strikingly, one third of the 104 described human ovarian cancer-derived cell lines were in reality not from ovarian tissue but from peritoneal ascites (21.2%), pleural fluid (3.8%), or metastatic masses (6.7%).

It is noteworthy that cell line banks do not stock human cell lines described originating from primary tubal or peritoneal origin. However, only recently the isolation and culturing of normal ovarian and fallopian tube epithelial cells from the same healthy female has been described [35]. This finding may fill the current gap of knowledge and may help clarifying the apparent ambiguity of the origin of ‘ovarian cancer’ and enabling a clear distinction among ovarian, tubal, and peritoneal cancer at their later stages. However, peritoneal cell lines are still not available as are a subset of histologically distinct ovarian cancer cell lines such as borderline cancers, cystadenomas and carcinosarcomas.

The re-naming of cell lines causes constant confusion as respective annotations are often not found in cell banks. For example, 41 M cells are the same as OAW28 cells. Some cell lines have similar names and require caution in the selection of the cell line of choice: a majority of the animal cell lines and several human cell lines are derived from a parental line (e.g. A2780, CHO) and have been modified in vitro to display chemo resistance (e.g. cisplatin-resistant A2780CP) or different cellular factors. In addition, the verification of information given by the cell bank is difficult,
Table 3 Non-human cell line originated from the ovary

| Cricetulus griseus – Chinese hamster | | |
|---|---|---|
| 105 | A2 | Ovary | ECACC |
| 106 | A2H | Ovary; A2 | ECACC |
| 107 | AR-EcoScreen | Ovary | JCRB |
| 108 | CHO | Ovary | ECACC/NCBI |
| 109 | CHO 1–15 500 | Ovary | NCBI |
| 110 | CHO CD28 | Ovary | NCBI |
| 111 | CHO-CHRM1 | Ovary; CHO-K1 | ECACC |
| 112 | CHO-CHRM2 | Ovary; CHO-K1 | ECACC |
| 113 | CHO-CHRM5 | Ovary; CHO-K1 | ECACC |
| 114 | CHO DG-44 | Ovary | NCBI |
| 115 | CHO/dFr-Ovary | Ovary | ECACC/DSMZ/NCBI |
| 116 | CHO/dFr-Ac-free | Ovary; CHO/dFr- | ECACC |
| 117 | CHO-FFAR2 | Ovary; CHO-K1 | ECACC |
| 118 | CHO-GPR120 | Ovary; CHO-K1 | ECACC |
| 119 | CHO/HGPR | Ovary | JCRB |
| 120 | CHO (His9) | Ovary | JCRB |
| 121 | CHO-K1 | Ovary; CHO | ECACC/JCRB/DSMZ |
| 122 | CHO-K1/SF | Ovary; CHO-K1 | ECACC |
| 123 | CHO-OPRL1 | Ovary; CHO-K1 | ECACC |
| 124 | CHO (pMAM-HS{\text{Luc}}) | Ovary | JCRB |
| 125 | CHO (pMAM-luc) | Ovary | JCRB |
| 126 | CHO Protein-Free | Ovary; CHO | ECACC |
| 127 | CHO-SSTR1 | Ovary; CHO-K1 | ECACC |
| 128 | GRL101 (KC7) | Ovary | ECACC |
| 129 | GRL101 (MIX) | Ovary | ECACC |
| 130 | M1WT3 | Ovary; CHO-K1 | ECACC |
| 131 | NCTC 4206 | Peritoneum; B14F2AF8-G3 | ECACC |
| 132 | P22 | Ovary | ECACC |
| 133 | RRI-CHOKI | Ovary; CHO-K1 | ECACC |
| 134 | T02J-7/10 (CHO-M3 (CHRM3)) | Ovary; CHO-K1 | ECACC |
| 135 | T02J-9/10 (CHO-H2 (HRH2)) | Ovary; CHO-K1 | ECACC |
| 136 | T02J-10/10 (CHO-GGGR (GGGR)) | Ovary; CHO-K1 | ECACC |
| 137 | T26J-1/09 (CHO-Beta-2 (ADRB2)) | Ovary; CHO-K1 | ECACC |
| 138 | T35J-S/09 (CHO-FFAR3 (FFAR3)) | Ovary; CHO-K1 | ECACC |
| 139 | UT-1 | Ovary; CHO-K1 | ECACC |
| 140 | Xr56 | Ovary; CHO-K1 | ECACC |
| 141 | Xrs6-hamKu80 | Ovary; CHO-K1 | ECACC |

| Mus musculus – mouse | | |
|---|---|---|
| 142 | OV3121 | Ovary | JCRB |
| 143 | OV3121-ras4 | Ovary | JCRB |
| 144 | OV3121-ras7 | Ovary | JCRB |
| 145 | p53-def-MOSE | Ovary | JCRB |
| 146 | T-Ag-MOSE | Ovary | JCRB |
because not all cell lines are linked to their original publications and their depositors are rarely mentioned.

One apparent shortcoming is that the ethnicity of the ovarian cancer patient from whom the tumour is derived is indicated in only 30.5%. Apart from the JCRB cell bank where all the deposited cell lines were derived from Japanese females (48.3%), the majority of samples where ethnical details are provided were from Caucasian females. Since we know that different ethnic groups can have a propensity for specific genetic mutations, for example in the BRCA and APC genes of Ashkenazi Jews [36,37], it is extremely important to have cell lines that represent the spectrum of ethnic groups around the world. This will reduce the risk of an ethnic bias and ensure that research into different ethnic groups will allow the most benefit for these patients.

The role of genetic changes in the characterization of ovarian cancer cell lines

The (molecular) characterization of EOC in the clinics significantly depends on the presence and type of genetic alterations in the cancer and may define the treatment options and the patients’ outcome. The tumor origin where the cell lines derived from was not precisely provided in 51.2% (Table 4). Considering the clinico-pathological (histotype, FIGO stage, grade) as essential criteria to categorize EOC in type I and II tumours, the respective information provided by cell banks is not sufficient. The data review on available human ovarian cancer cell lines (n = 95) reflects that cell banks provide the histological subtype in 76.8% with discrepancies to original publications (Table 5), stage in 34.7%, and the initial grade in only 20%. In contrast, the information on chemotherapy resistance is provided adequately. Epithelial (−)like cells are characterized with epithelial or stromal markers in more than half (57.9%) of all cell lines, and out of these 85.4% had at least epithelial-like features. Another essential criterion is the doubling time that is provided in only 29.5%.

We also collected and evaluated data provided by cell banks in regards to molecular markers. This information was very limited and only few cell lines were evaluated for expression of progesterone (7.4%) and oestrogen (6.3%) receptors, vimentin (5.3%), TP53 mutations (4.2%), Her2/neu (3.2%), EpCAM (3.2%), and cytokines 7, 8, 17, 18, and 19 (ranging from 5.3% to 8.4%).

Potential risks of the use of cell lines for in vitro research

The misidentification and cross-contamination of cell lines is problematic in research and may increase the risk for false results and misinterpretations. The extent of misidentification is documented in a recent study wherein a panel of ovarian and endometrial cell lines was analysed by DNA profiling [38]. The authors found that 8 out of the 51 ovarian cancer cell lines were in fact breast cancer, teratocarcinoma, or cervical cancer cell lines and that normal endometrial cancer cells were in fact HeLa cervical cancer or MCF-7 breast cancer cells. Likewise, cross-contamination of cell lines, i.e. the accidental generation of mixed cell cultures, is not a lesser problem. Jäger et al. 2013 reported that the popular and frequently used KU7 urothelial carcinoma cell line was cross-contaminated years ago with HeLa cervical cancer or MCF-7 breast cancer cells. Likewise, cross-contaminations may occur when multiple cell lines are cultured simultaneously (a practice that should be avoided) and becomes only apparent if multiple morphologies are suddenly observed but fatally remains unnoticed if cells have indistinguishable morphology.

Bacterial/fungal/yeast/mycoplasma contamination presents another problem adversely affecting research results. Of these, mycoplasma species are most likely to be detrimental to cell functioning. Unlike most bacterial, fungal or yeast infections, mycoplasma are macroscopically and microscopically undetectable; it may remain in culture for extended periods of time affecting cell growth, gene expression and overall cell functioning [40]. This may be one reason for why different research groups report contradictory findings. For this reason, Cell Bank Australia has
collated a database of known cross-contaminated or mis-
identified cell lines based on the literature. Other cell
banks such as the JCRB have also made an effort to screen
the database and identified which of their own cell lines
were originally misidentified (Table 1).

The unavailability of a considerable number of in vitro
cell line models to the research community is also an issue.
The problem is two-fold: firstly, there is no quality control
of cells generated in individual laboratories when they are
not deposited in a professional cell bank. Even when these
cells are meticulously generated and cultured, independent
quality checks and verifications are not possible. This flaw
is overcome by directly contacting the laboratory where
the cell lines were generated. This, however, can lead to
the second problem; the passing on of cell lines from la-
boratory to the other, thereby bypassing the critical quality
control cell banks. In the past it has been common practice
to obtain cells from collaborating groups, and with the re-
quired permission, to again distribute these to other la-
boratories. Whilst this practice is in the spirit of research
collaborations, it increases the risk of receiving contami-
nated or misidentified cell lines that, in turn, can be detri-
mental to research.

Conclusions
To ensure a unique quality of cancer research around the
world we recommend that all cell lines used for research
should be deposited in a cell bank and be readily acces-
sible for all researchers. Ovarian cancer cell bank operators
should provide development protocols and comprehensive
clinical data for all commercially available cell lines.

Depositors of cell lines should ensure that they have care-
fully collected all relevant clinical information from the
donor individuals. This information includes: the exact
origin of the cells, the stage during disease progression the
cells were taken, the type of therapy the patient underwent
prior to sample collection, the data on the patient’s sur-
vival, the ethnicity and family history (including known
genetic alterations), and the preoperative plasma CA125
levels currently provided by only 5.3% of all human ovar-
ian cancer cell lines. Additionally, we recommend that all
cell bank operators conform to the same style of reporting
the cell line information and only bank cells where all ne-
necessary information is available. This will ensure that the
highest standard of research is maintained worldwide.

Short tandem repeat (STR) profiling, a highly-sensitive
method to detect cellular cross-contamination, should be
performed by researchers for all newly generated cell lines
and should be confirmed by the cell bank once deposited
and prior to the sale of the cells. The service for STR pro-
file is provided by various laboratories, e.g. American
Type Cell culture Collection (ATCC-USA, http://www.atcc.
org), China Center for Type Culture Collection (CCTCC,
http://www.cctcc.org), Australian Cell Bank (http://www.
cellbankaustralia.com), European Culture Collection of
Cell Cultures (ECACC, http://www.hpcultures.org.uk), or
German Cell Culture Collection (DSMZ, http://www.dsmz.
de). From a recent study that histotyped standard ovarian
cancer cell lines by short tandem repeats, immunohisto-
chemistry, and mutation analysis it was concluded that the
knowledge of the mutation status of cancer genes such as
ARID1A and TP53 and of the general immunoprofile

| Table 4 Origin of human ovarian cancer cell lines |
|-----------------------------------------------|
| **Origin specified (cell line banks)**        |
| Ascites | Metastasis | Ovary | Pleural effusion |
|---------|------------|-------|-----------------|
| Ascites | 9          | 0     | 5               |
| Metastasis | 0         | 2     | 6               |

| Origin specified (original references)  |
|----------------------------------------|
| Not specified | 0 | 0 | 11 |
| Ovary | 0 | 0 | 9 |
| Pleural effusion | 0 | 0 | 1 |

| Table 5 Histotypes of human ovarian cancer cell lines |
|-----------------------------------------------|
| **Origin specified (cell line banks)**        |
| Clear cell | Endometrioid | Mixed | Mucinous | Other | Serous | Unknown |
|-----------|--------------|-------|----------|-------|--------|---------|
| Clear cell | 6            | 0     | 0        | 0     | 0      | 0       |
| Endometrioid | 0          | 2     | 0        | 0     | 0      | 0       |
| Mixed | 0             | 0     | 1        | 0     | 0      | 1       |
| Mucinous | 0             | 0     | 3        | 2     | 0      | 0       |
| Other | 0             | 0     | 0        | 3     | 0      | 0       |
| Serous | 0             | 0     | 0        | 1     | 6      | 7       |
| Unknown | 0             | 0     | 0        | 7     | 0      | 1       |
would be beneficial for the determination of the histotype of ovarian cancer cells [41]. Following the model of the Cancer Cell Line Encyclopedia (CCLE), we suggest the establishment of a centralized cell line database that would harbour all the relevant details of new cell lines and would be updated with new details in real time as experimental results are reported in the literature. This is believed to reduce the overlap of research performed and to continually improve the quality and appropriateness of future cell line studies. A cell bank professional with expertise in cancer research would be beneficial for researchers who need advice in correctly choosing the cell line appropriate for a specific research question. The expansion of the current offer of cell lines deposited in the cell banks by additional types of cells is desirable. These include primary, recurrent and metastatic ovarian-, tubal- and peritoneal cancers, a set of cell lines representing all known EOC histotypes, age-matched normal control OSE and tubal cells, and cell lines derived from primary, recurrent and metastatic tumours from the same patients at different progression time points. It is clear that worldwide collaborative efforts are to be taken to reach these recommendations, but we believe that this will be of benefit for the research results in the future.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
FJ carried out literature research, data analysis and drafted the manuscript. SN carried out literature research drafted the manuscript. NFH drafted the manuscript. VAS conceived the review and drafted the manuscript. All authors read and approved the final manuscript.

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