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Ovarian Cancer Genetics and the Implications

Shyamika Mirisse Acharige and Chit Cheng Yeoh

Abstract

Ovarian cancers mostly arise sporadically, however about 20–25% of the cases arise as a part of hereditary syndromes. There are numerous mutations involved in the ovarian cancer development and more to be discovered. Knowing the pathogenic variants of the mutations present in the ovarian cancers are important in developing and practising of risk reduction strategies in asymptomatic carriers, genetic counselling, prognostication and decision on treatment. This chapter will focus on the various types of mutations found in ovarian cancers and their implications- when considering testing, treatment options and insight for the next level of Improvement in cancer care.

Keywords: ovarian cancer, somatic BRCA mutation, germline BRCA mutations, PARP inhibitors, homologous recombination

1. Introduction

BRCA1/2 somatic and germline, *PTEN* deletion, *CCNE* amplification and *RB1/NF1* loss, *RAD51C*, *RAD51D*, *BRIP 1* are some of the known mutations causing the ovarian cancers [1]; the *BRCA1/2* gene mutations are the most common and deleterious to find in this spectrum. From women who inherit a pathogenic *BRCA1* variant and *BRCA2* variant at risk of developing ovarian cancer 39–44% and 11–17% respectively by the age of 70–80 years [2, 3].

The current recommended guidelines for all high grade serous ovarian cancer patients at the diagnosis, apart from mucinous adenocarcinoma of Ovaries, are screen upfront for pathogenic *BRCA1/2* genes, regardless whether they have family history or not. The uptake of this screen is 1:10 patient, and if we extend the screening to tumour somatic testing, the uptake becomes 17% of all ovarian cancer diagnosis with germline and somatic BRCA mutations. Difference between the somatic and the germline BRCA mutations are discussed later in this chapter.

The following is a schematic representation of the various known mutation prevalence in the ovarian Cancers particularly in High grade serous ovarian carcinoma. As obvious *BRCA1* and *BRCA2* are the most common type of mutations found in the OC and signifies the importance, hence this chapter mainly focus on the BRCA mutations (**Figure 1**).

Figure 1.
Common Pathogenic mutations in high grade serous ovarian cancer.

2. Genetics of sporadic ovarian cancers

There's a multitude of genetics involved in the sporadic ovarian cancers, involving multiple cellular pathways. There are 2 types of sporadic ovarian cancers according to their behaviour, histology, genetic according to Kurman and shih's original article "The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory", type 1 and type 2 [4]. Type1 tumours are slow growing, indolent tumours and Type 2 being high grade, aggressive.

Some of the mutations associated with sporadic type1 ovarian cancers are *KRAS*, *BRAF*, *ERBB2*, *PIK3CA*, *ARID1A*, *CTNNB1* and *PTEN*. In normal cells these genes and their products will regulate the cell growth, chromatin remodelling, DNA repair, cellular proliferation and controlling of apoptosis preventing tumour development. Mutations in these genes inevitably causes increases susceptibility to development of malignancies [4].

Type 2 sporadic ovarian cancers which are high grade share the similar genetics as hereditary ovarian cancers *TP53*, *BRCA1* and *BRCA2* [4].

3. Genetics of hereditary OC

Hereditary Breast ovarian cancer syndrome, Lynch Syndrome, Li-Fraumani, Cowden and Peutz-jeghers syndrome are some of the few of Hereditary ovarian cancer syndromes, all of which inherit in autosomal dominant pattern [5, 6]. Patients who presents at young age, multiple primaries and/or a high incidence of family history of malignancy should be considered as having hereditary OC and should be investigated for the genetic mutations. Eighty percent [80%] of this type of ovarian cancers are associated with *BRCA1/2* gene mutation and minority are with *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, *BARD1*, *NBN* and *MRE11A*.

4. *BRCA1/2* gene structure and functions

BRCA1 and *BRCA2* genes were discovered in early nineties following extensive research on breast cancer patients and families, hence the name Breast cancer susceptibility gene [*BRCA*] and identified as responsible in the ovarian cancer

causation as well. *BRCA1* and *BRCA2* pathogenic mutations are found in 10–15% of sporadic ovarian cancers and about 40% of Hereditary ovarian cancers [7].

These genes are tumour suppressor genes encode for tumour suppressor proteins, which will help in maintaining genomic stability. *BRCA1* and *BRCA2* are large genes contain about 100–70 Kilo bases respectively. *BRCA1* situated in long arm of chromosome 17 at 17q21 position and *BRCA2* gene is in chromosome 13 at 13q12. These 2 genes encode for different protein structures although still have got functional similarities [8]. *BRCA1* protein consists of nuclear localization sequence (NLS) and three functional domains; RING, coiled coil, and BRCT domains, whereas *BRCA2* protein has NLS, eight BRC repeats, and a DNA binding domain.

BRCA1 and *BRCA2* genes helps in repairing the double strand breakage in DNA by promoting the homologous recombination, which is a highly accurate process in the maintenance of genomic stability and regulating the cell cycle and apoptosis.

5. Action of *BRCA1* and *BRCA2* proteins in DNA double strand damage repair

Although the action of the *BRCA1* and *BRCA2* gene products in cancer causation is not fully discovered [9], their function in maintaining the genomic stability is well understood. This involves the DNA double strand break repair [DSB] which is the most deleterious type of DNA damage as no healthy DNA strand left for the repair mechanism [10]. The DSB will be repaired by 2 mechanisms in the healthy eukaryotic cells -The Homologous directed repair [HDR] pathway, which is a highly accurate system and Non-Homologous end joining [NHEJ] pathway which is prone to errors. *BRCA1* and *BRCA2* proteins involve in the HDR mechanism following stimulated by the cellular DNA damage response. This function is facilitated by other cellular proteins including RAD51 [11, 12], Ataxia-Telangiectasia kinase [ATM-kinase].

The following flow chart shows the mechanism of DNA DSB repair and the steps involving the *BRCA1/2* proteins (**Figure 2**).

Mutation of the *BRCA1/2* genes causing loss of the encoded protein functions causes abnormal checkpoint stimulation and genomic errors in DNA repair

Figure 2.
Action of BRCA1/2 protein in DNA double strand break repair. Source - functions of BRCA1 and BRCA2 in the biological response to DNA damage [13].

causing cancer development through uncontrolled cellular proliferation, impaired cell apoptosis in abnormal cells.

6. Somatic vs. germline *BRCA* mutations

BRCA1/2 mutations can occur in the germline causing the hereditary susceptibility to ovarian and other types of cancers. There are *BRCA* mutations can occur in the somatic cells as well - within the tumour itself which consists of 3% of whole *BRCA* mutation found in the high grade serous ovarian cancers, without mutation in the germline. Presence of germline *BRCA* mutation gives rise to specific behaviour of the ovarian cancer, response to treatment and the prognosis. Patients with germline *BRCA* mutations will develop cancers at young age, commonly have visceral disease at presentation and shows high sensitivity to platinum-based chemotherapy and PARP inhibitors.

Clear relationship between the somatic *BRCA* mutations and the features of the response to the treatment and the clinical features are yet to be identified [14].

7. Implications of *BRCA* testing in ovarian cancer

Currently there's no proven benefit of population screening for sporadic ovarian cancer as the trial results are still pending to show reduction in the mortality and survival benefit from the early screening of asymptomatic patients in this category. However screening strategies in hereditary ovarian cancers are important for the prophylactic procedures such as bilateral Salpingo-oophorectomy which can reduce the risk of development of cancer by 79% in endometrium, fallopian tube, ovaries which has been proven by meta-analysis.

8. Testing for germline *BRCA* mutations in ovarian cancer patients

Genetic testing for germline-*BRCA1/BRCA2* mutations in epithelial ovarian cancer (EOC) was commissioned by National Health Service England in 2015 [15]. In the United Kingdom, all genetic counselling take place in Cancer Centres, and all first degree family member will be given a letter to inform them of the risk in them carrying this gene and a mean to have germline *BRCA* status tested on the NHS. The NHS will also provide risk reduction surgery to prophylactic Breast and Ovarian surgery once the family planning is completed and the decision made by affected family members. For those who do not wish to embark on these prophylactic surgeries, there are guidelines for surveillance with Mammograms and blood test Ca 125 for the affected gene mutation carriers. For male gene carriers, there are now early PSA surveillance available for General physician to follow.

Germline *BRCA* testing is done via a blood test following gaining the consent of the patient, according to the NCCP [National cancer control programme] guidelines, which is then being sent to the Cancer Molecular Diagnostics Laboratory.

9. Testing for somatic *BRCA* mutations in ovarian cancer patients

Testing for somatic *BRCA* mutation was introduced in October 2020 in UK. The samples from the previous biopsy or surgery including the ovarian cancer

tissue block/slides are needed for somatic *BRCA* mutation testing. The block must be of reasonable quality, neoplastic cell content >50% included. This should be sent at room temperature with a copy of the block(s) histopathology report within 5 working days of patient registration.

Although the germline *BRCA* testing could be a straightforward blood test, the somatic *BRCA* mutation comes with some challenges, which are summarised below.

1. Issues with extracting high quality DNA samples from the preserved tumour samples-which needs tumour microdissection, so that a small tumour samples will not be enough for the purpose. Also poor fixation samples can cause fragmented and damaged DNA and also formalin used in fixation can cause deamination of the nucleic acids leading to sequencing errors and false mutations.
2. Analysis and interpretation of sequencing data as there is currently no standardised interpretation.
3. The stability of the somatic *BRCA* mutations can change over time due to cancer selection, resistance, treatment and within the tumour itself due to heterogeneity of the tumour cells.

For most countries the method for detecting the *BRCA* mutation still limited to one or the other due to funding issues.

10. The significance of *BRCA* mutation in HGSOC

As mentioned earlier in the chapter being positive for *BRCA* mutations when compared with the wild type, gives the ovarian cancer specific features – importantly higher response rate to platinum and other types of non-platinum chemotherapeutic agents [16] and more importantly high sensitivity to Poly(ADP-ribose) polymerase (PARP) inhibitors, which is highly important as a maintenance therapy of the patients who have responded to first line platinum based chemotherapy in improving 5 year disease free survival.

11. What are PARP inhibitors?

Poly (ADP-ribose) polymerase (*PARP*) is a protein mediated the DNA double strand break repair, which was first identified in early sixties and first PARP inhibitor was discovered in 1980 as a chemotherapy sensitizer [17].

Following figure illustrates the normal action of the PARP proteins to aid the understanding of how the PARP inhibitors work (**Figure 3**).

In 2005 and 2006, inhibiting PARP enzymes was first observed to be highly effective against cancers with homologous recombination deficiencies [19], are being utilised in the clinical setting to manage recurrent ovarian cancers. However, PARPi – Niraparib also show significant clinical benefit in patients without HR deficiencies [20]. There are currently three FDA-approved PARP inhibitors for recurrent ovarian cancer – Olaparib, Rucaparib and Niraparib.

Figure 3. Function of PARP proteins in DNA damage repair. Source: An update on PARP inhibitors—Moving to the adjuvant setting [18].

12. PARP inhibitors in the treatment of ovarian cancers

Since the discovery in 1980 s PARP inhibitors has gone through extensive scrutiny and research in the efficiency in management of the ovarian cancers. The initial monotherapy with PARP inhibitors for patients with solid tumours with a germline BRCA mutation were published in 2009. This was a study on ovarian cancer patients with known BRCA mutation [21]. Other tumours included were breast, colon, melanoma, prostate, and sarcomas. In patients with known BRCA1/2 mutations, single-agent treatment with Olaparib showed a 63% clinical benefit (including disease stabilisation). Following this study there several other trials carried out for assessing the individual efficacy of the Olaparib, Niraparib and Rucaparib and with the outcomes of these trials Olaparib has gained the FDA approval as a first line maintenance treatment in the advanced ovarian cancer [22].

Trial name	PARPi assessed vs. other treatment agent as maintenance	Population
PRIMA/ ENGOT-OV26	Niraparib vs. Placebo	Stage III with visible residual tumour after PDS, inoperable stage III, or any stage IV ovarian cancer.
SOLO-1	Olaparib vs. Placebo	BRCA1/2 mutated, CR or PR (≥30% decrease in tumour volume, or NED on imaging but CA-125 > ULN) to platinum-based chemotherapy (without bevacizumab)
] PAOLA-1/ ENGOT-OV25	Olaparib + bevacizumab vs. placebo + bevacizumab	Newly diagnosed stage III/IV high-grade ovarian cancer or other non-mucinous ovarian cancers with BRCA1/2 mutation, regardless of surgical outcome NED or CR or PR after first-line platinum + taxane + bevacizumab
VELIA/ GOG-3005	Veliparib + CP → veliparib vs. veliparib + CP → placebo a vs. placebo + CP → placebo	Newly diagnosed stage III/IV high-grade serous ovarian cancer in patients undergoing PDS or IDS

Key PDS - Primary debulking surgery, CR - complete response, PR - Partial response, IDS - interval debulking surgery, NED - no evidence of disease, C - Carboplatin, P - Paclitaxel.

The following is a summary of the trials on PARP inhibitors and the SOLO-1 trial being of the pivotal trials in the history of the use of PARP inhibitors [23].

13. Current UK standards for testing ovarian cancer genetics

According to current British Gynaecological Cancer Society guidelines for testing ovarian cancer genetics,

Women with High grade serous ovarian cancer or G3 endometrioid ovarian adenocarcinoma have >10% risk of an underlying BRCA mutation should be offered clinical genetics counselling and testing. (GRADE C) Recently it has been shown that ~18% (much higher in certain groups such as Ashkenazi Jews) of the population of women presenting with high grade serous or G3 endometrioid ovarian adenocarcinoma carry a germline BRCA mutation, 44% of whom have no positive family history. Every patient with a current or past histological diagnosis of HGSC or G3 endometrioid ovarian carcinoma therefore qualifies for BRCA counselling and testing, as advised by National institute for Health and Care Excellence, which should be discussed and offered.

The above guidelines and standards are supported by the evidence from the GTEOC (Genetic Testing in Epithelial Ovarian Cancer) [24] study in which the primary objective of the study was to determine the feasibility, acceptability and cost-effectiveness of screening all newly diagnosed women with EOC for *BRCA1/BRCA2* mutations by determining the mutation prevalence, calculating the cost for each gene mutation detected and assessing the psychological impact based on questionnaire responses and qualitative interviews.

This study has shown the mutation yield in unselected women diagnosed with EOC from a heterogeneous population with no founder mutations was 8% in all ages and 12% in women under 70 [25]. Unselected genetic testing in women with EOC was acceptable to patients and is potentially less resource intensive.

14. Challenges in development of universal process on screening genetic mutations in ovarian cancers

In Our Opinion, all the patients diagnosed with invasive, epithelial ovarian cancer should be offered germline genetic testing, regardless of histologic subtype, because Ovarian cancers with a *BRCA1/BRCA2* mutation are most likely to be of high-grade serous histology, although these mutations have been found in endometrioid and clear cell histologic subtypes as well. Endometrioid and clear cell ovarian cancers are also frequently associated with Lynch syndrome (germline mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*). Additionally, nonepithelial ovarian cancers - Sertoli-Leydig cell tumours can be associated with other genetic disorders such as Peutz-Jeghers syndrome and DICER1-associated disorders and small cell carcinoma of the ovary, hypercalcaemic type has been linked to germline mutations in *SMARCA4*.

All these mutations have got clinical relevance in the management of these patients and yet to discover the treatment options and preventing the development of the other cancer types associated with the above syndromes in the future generations with genetic predisposition.

There are several identified limitations in screening these mutations including cost of testing, lack of patient and provider education regarding the importance of genetic information, and limited availability of genetic counsellors and access to genetic testing [26].

In the era of unforeseen issues with Covid-19 there are other issues with genetic testing including social distancing making the genetic counselling, consenting difficult necessitating these steps to be delivered audio-visually.

15. In summary

There are numerous types of genetic mutations causing sporadic and hereditary ovarian cancers and more to be discovered yet. These mutations cause genomic instability in turn leading to cancer causation. Having a certain type of mutation will give rise to clinically specific type of ovarian cancer, with different response to treatment, prognosis and predictability in behaviour.

Early identification of these mutations, genetic counselling will optimise the patient outcome, prevention of the ovarian and other genetically predisposed cancers in next generations.

Developing a universal testing pathway which is cost effective, is still challenging due to various factors.

The arrival of personalising treatment with Molecular typing of Ovarian Cancer has revolutionised maintenance therapy in Ovarian Cancer that has never seen before. Not only we are routinely screening for germline and somatic BRCA mutation upfront in all newly diagnosed Ovarian Cancer, we increasingly modify our treatment paradigm by providing PARPi in DNA mismatch repair deficiency detected patients. This extends from just BRCA mutation to the other Homologous recombination deficiency genes as delineated in **Figure 1**. In 2020, FDA approved of MEK-inhibitor, Trametinib for Low grade Ovarian Cancer. And soon to be NICE guidelines for routine screening for Microsatellite instability genes, MMR MSI in all Endometrial Cancer, in search for 40% incidence of MSI MMR deficiency.

In 2021 November, with the sentinel FDA approval for liquid biopsy testing in solid cancers, which was predominantly based on detection of BRCA genes and most HRD genes, this has solid foundation in one test for defective molecular markers in blood, hopefully well before development of Cancer, for our exciting future to come.

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