New approaches in ovarian cancer based on genetics and carcinogenesis hypotheses (Review)

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Received November 12, 2021; Accepted December 13, 2021

DOI: 10.3892/etm.2022.11351

Abstract. Ovarian cancer is the leading cause of death among gynecological malignancies and its incidence is rising in the last decades especially in developed countries. High-grade serous ovarian cancer (HGSOC) represents 70% of ovarian cancers. Oral contraceptive use and salpingo-oophorectomy or salpingectomy are well known protective factors against development of ovarian cancer. Identification of specific mutations associated with a high risk of developing ovarian cancer, especially BRCA1/2 mutation and TP53 mutations, has paved the way for implementation of new strategies for early diagnosis and therapy. Hereditary forms of ovarian cancer account for 5-10% and have BRCA1/2 gene mutations or TP53 mutations. BRCA1/2 gene mutations appear in 22% of HGSOC and are associated with the defective homologous repair (HR)/DNA repair pathway. Genetic testing in ovarian cancer is important for risk assessment and therapeutic options. Although 'universal genetic testing' is not recommended yet, the procedure remains highly recommended in women with high risk. Genes involved in the development of ovarian cancer as TP53 may be targeted by gene therapy. Poly (ADP-ribose) polymerase (PARP) inhibitors may enhance the cytotoxic effect of DNA-damaging chemotherapy, and induce synthetic lethality in cases with BRCA1/2 mutations. Other strategies are designed to target pathways driven by various gene mutations, including the use of tyrosine kinase inhibitors in low-grade serous ovarian cancer (LGSOC), or the use of drugs, which target growth factors, or epigenetic events including methylation, and acetylation of genes. The tubal involvement in ovarian carcinogenesis provides an important tool for the clinician to implement risk-reducing strategies including salpingo-oophorectomy or salpingectomy in high-risk cases at appropriate ages.

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Key words: ovarian cancer, genes, targeted therapy, carcinogenesis, risk-reducing strategies

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1. Introduction

The aim of this review was to provide to clinicians data on ovarian cancer carcinogenesis that may be applied in disease prophylaxis and management. Articles were searched in PubMed, Scopus and Google Scholar databases using the key words 'ovarian cancer' combined with 'epidemiology', 'genes', 'carcinogenesis', 'targeted therapy', 'risk-reducing strategies'. The search covered years 2010-2020 and two eloquent articles published earlier were added. The main inclusion criteria consisted in new theories concerning the genetics and carcinogenesis of ovarian cancer. After analyzing and refining the search, the total number of studies cited in this review is 38.

Ovarian cancer, the leading cause of cancer-related deaths among gynecological malignancies worldwide (1), has a high incidence exceeding 8/100,000/year in Northern, Central and Eastern Europe as well as the USA with a lower incidence in Asia and Africa (less than 3/100,000/year) (2) The peak incidence is in women aged 55-64 years old. The five-year survival rate is 90% in the early stages of the disease, 75% in case of regional diffusion and 29% in cases with distant metastases (3). Ovarian cancer accounts for 5% of cancer-related deaths in women (4). In the last three decades, the incidence of ovarian cancer has increased by 153.7% and deaths from the disease by 122.6% (5). The aim of the present review was to introduce the impact of new scientific developments regarding the genetics and carcinogenesis of ovarian cancer, with a

special focus on high-grade ovarian cancer and its prophylaxis and management.

2. Histology of ovarian cancers

In developed countries, the histological profile of ovarian cancer according to the cell of origin is the following: Epithelial origin, 90%; sex cord stromal (granulose tumours, tecoma, theratoma), 5-6%; and germ cell tumours, 2-3%. Cancers of epithelial origin include high grade serous ovarian carcinomas (HGSOC), 70%; endometrioid carcinomas, 10%; clear cell carcinomas, 10%; and low grade serous ovarian carcinoma (LGSOC), <5% (2).

3. Risk factors for ovarian cancer

General risk factors for ovarian cancer include age, a first degree relative with ovarian cancer, premature menarche and late menopause (>52 years), increased number of ovulatory cycles, nulliparity, endometriosis, postmenopausal hormone replacement therapy (HRT), obesity, diabetes, smoking and perineal talc exposure. Protective factors against development of ovarian cancer are parity, oral contraceptive use for more than 5 years, early menopause, salpingo-oophorectomy or salpingectomy, and daily aspirin use (2,6-9). Oral contraceptives or HRT in well-selected cases, may mitigate the general risk of developing ovarian cancer.

4. Ovarian cancer genetics

As in other cancers, in ovarian cancer extensive genetic studies have allowed researchers and clinicians to develop new strategies for earlier diagnosis, prevention and treatment, starting from gene mutations and their driven pathways. According to the dualistic model of carcinogenesis (10) ovarian cancers may be divided into type I and type II tumours, which express different genetic disorders, carcinogenesis patterns, evolution, response to treatment and prognosis (11). Type I tumours include LGSOC, endometrioid, mucinous, clear cell carcinomas and malignant Brenner tumours (10,12). Type I tumours develop in a stepwise manner from benign to malignant tumours, are usually low grade, chemoresistant, but have a favorable prognosis (10,12). The subtypes of type I tumours express different gene mutations such as KRAS, BRAF, HRAS, PTEN, PIK3CA, ARID1A inactivation, TERT, and ERRB2 (6,10,13-16). Type II tumours are highly aggressive and usually in advanced stages at the time of diagnosis. Type II tumours are chemosensitive at the beginning of treatment, but relapse is frequent and have a poor prognosis (6,7,10,17). Among type II tumours, HGSOC is the most frequent and exhibits the TP53 mutation in 50 to 96% of cases (10,13,18). Mutant p53 protein loses its tumour suppressive function, or may acquire a gain in oncogenic properties resulting in increased aggressiveness and chemoresistance (6,19). Germline and somatic mutations of BRCA1/2 genes appear in 22% of HGSOC, and are associated with the defective homologous repair (HR)/DNA pathway. Loss of function of BRCA1/2 genes and mutations of mismatch repair genes (MLH1, MSH1 and MSH6 which are associated with Lynch syndrome) are associated with high genomic instability (6,10,16,19). Other genes as RAD51C, RAD51D, BRIP1, BARD1, PALB2, and CHEK2, are described as having 'BRCA-ness phenotype', since they are also associated with HR/DNA repair defects and genomic instability (15,20). Hereditary forms of ovarian cancers represent 5-10% (21,22) to 12-24% of cases (19). Up to 90% of hereditary cancers have BRCA1/2 mutations, 10% are part of the Lynch syndrome with mutated mismatch repair genes (MLH1, MLH2, MLH6) (15,17) and others, as Li-Fraumeni syndrome, have a TP53 mutation (cr.17p.13) (15). Gene expression may be influenced by modification of promoter or enhancer activity, epigenetic DNA methylation, expression of coding or noncoding RNAs, post-translational glycosylation, phosphorylation, or ubiquitination (23).

Genetic testing in ovarian cancer is important for risk assessment and therapeutic options. The risk of a woman developing ovarian cancer during her lifetime is ~1.37% (4). The overall risk increases after the age of 40, and BCRA1 and BCRA2 carriers have a lifetime risk of 66 and 27%, respectively (17,24). Women with Lynch syndrome have an 8-12% lifetime risk (9). In selected cases, genetic testing may be used to determine the risk for ovarian cancer. Universal genetic screening is not recommended, with the exception of certain ethnic groups in which prophylactic strategies are well implemented (9). Genetic testing for already diagnosed cases of high-grade serous ovarian cancer (HGSOC), or for those with family history of ovarian cancer must be performed before the age of 35 (9). For other genes such as RAD51C, RAD51D, BRIP1, BARD1, PALB2 and CHEK2, the tests may be performed before the age of 45 (9).

Genes involved in ovarian cancer and their pathways can be targeted by therapeutic agents. Targeting pathways driven by BRCA1/2 mutations with PARP inhibitors may enhance the cytotoxic effect of DNA-damaging chemotherapy, and induce synthetic lethality (19,20). Olaparib and recently rucaparib were approved as second line therapy in HGSOC with a 60% response in BRCA-mutation positive cases (6,12,25).

p53 is a tumour suppressor gene, which is important in regulating cell proliferation and apoptosis (22) and may be also targeted. Nultlin 3a which inhibits MDM-2, a negative regulator of p53, restores p53 activity (19) and p53-synthetic long peptide vaccine with cyclophosphamide is currently in a clinical trial (22). Gene therapy may be used to restore tumour suppressor gene p53 by an adenovirus-mediated p53 gene transfer system (22). Removal of BRCA1/2 germline alleles is a gene therapy attempting to avoid chemoresistance (26). The pathways which mediate cancer development may be also targeted. KRAS, BRAF and ERBB2 mutations expressed in LGSOC activate the MAPK pathway and MAPK inhibitors (tyrosine kinase inhibitors) may improve survival in advanced cases (11). Inhibitors of the RAS/RAF/MEK/ERK pathway (selumetinib, binimetinib and trametinib) were used in LGSOC (12,27). Tumour angiogenesis mediated by vascular endothelial growth factor receptor (VEGFR) may be targeted by cediranib, pazopanib and nindetanib, which are antiangiogenetic multikinase inhibitors of VEGFR 1-3 and antiangiopoietin inhibitor trebananib (25). Antiangiogenetic gene therapy used for silencing VEGFRs or endostatin had favorable results in the inhibition of ascites development (7). VEGF-A may be targeted by specific humanized monoclonal antibody (bevacizumab), or by receptor tyrosine kinase

inhibitors, with most promising results for cediranib (6). Epidermal growth factor receptor (EGFR) may be targeted by transtuzumab and cetuximab, humanized monoclonal antibodies, directed against the extracellular domain of EGFR (28). Most important epigenetic modifications, DNA methylation and histone modification may be targeted by DNA methyltransferase (DNMT) inhibitor 5-azacytidine, which restores platinium sensitivity (19) and DNMT inhibitor, decitabine, which restores carboplatin sensitivity. Histone deacetylase (HDAC) inhibitors promote acetylation of p53 and restore its apoptotic and tumour suppressive function (19).

5. Carcinogenesis of ovarian cancer

In 1971, Fathalla (6,11) developed the hypothesis of 'incessant ovulation' in ovarian cancer. According to this hypothesis, numerous cycles of repair and regeneration of ovarian surface epithelium (OSE) following ovulation create a pro-inflammatory and pro-oxidative microenvironment, rich in reactive oxygen species (ROS), cytokines, interleukins, which may produce DNA damage (29). Inability of OSE to repair DNA damage may result in carcinogenesis. Epithelial breaks during ovulation may favor the invagination of fragments of OSE, which become trapped under the ovarian surface and develop as cortical inclusion cysts (CICs). High gonadotropin levels during ovulation may stimulate tumour cell growth in CICs (16,21). This hypothesis may also be considered as a 'chronic inflammation model of carcinogenesis' (29) and offers support for advocacy in favor of oral contraceptive use as a prophylactic strategy in ovarian cancer.

In 2001, Piek *et al* (30) revealed the presence of small dysplastic lesions in the fallopian tubes, histologically resembling HGSOC, in women bearing BRCA1/2 mutations. These lesions later became known as serous tubal intraepithelial carcinomas (STICs). STICs harbor a TP53 mutation in 90% of cases (11). The association between STICs and HGSOC was detected using the sectioning and extensively examining the fimbriated end (SEE-FIM) protocol, by Callahan in 100% of cases, by Hirst in 80% and by Reitsma in 75% of cases (20). Immediately following STICs, 'p53 signatures' were identified (31) as short stretches of 12 or more secretory cells that appear as benign, bearing p53 mutations and γ-H2AX marker for DNA double-strand breaks (16,20,22,32). p53 signatures are more frequently identified in tubal epithelium which exhibits STICs (33). According to Nakamura *et al* (22) and Mehra *et al* (24), HGSOC evolves following this pattern: tubal epithelial secretory cells-PAX2 mutation (loss of expression)-secretory cell outgrowth (SCOUT)-p53 mutation-p53 signature-serous tubal intraepithelial lesion (STIL)-STIC-HGSOC. Once the hypothesis of tubal origin of HGSOC was accepted, risk reducing salpingo-ooforectomy (RRSO) became a prophylactic procedure indicated for at risk women. RRSO is indicated at different ages according to the lifetime risk associated with certain mutations. RRSO is indicated in BRCA1 carriers (risk: 39-46%) between the age of 35-40 years, following childbearing completion, and in BRCA2 carriers (risk: 10-27%) between the age of 40-45 years (32,34,35). In RAD51C and RAD51D and BRIP1 carriers (risk: 10-15%) RRSO is indicated between the age of 45-50 years, and in MSH2 and MLH1 carriers (risk: 1-24%) RRSO may be also considered (35,36). According to the actual knowledge regarding the common pathway of carcinogenesis in the fallopian tube, ovary and peritoneum, tubal ligation is also presumed to have a protective role against the development of HGSOC (32). Ovarian cancer risk is reduced due to RRSO by 42-78%, and due to tubal ligation by 13-41% (35). Genetic counseling regarding risk-reducing procedures, including 'opportunistic salpingectomy' during other surgical procedures, may be offered to all women at risk (9). However, RRSO may not be enough in certain BRCA1/2 carriers who may develop primary peritoneal carcinoma following this procedure (37) (up to 3% of cases during a 5-year follow-up) (38).

6. Conclusions

Encouragement of oral contraceptive use and tubal ligation may mitigate the general risk for ovarian cancer development. Genetic screening, at least for women with a family history of ovarian cancer, followed by 'cascade testing' of other relatives and genetic counseling are highly recommended. Genes and pathways involved in ovarian cancer may be targeted with specific drugs in cases resistant to classic treatment. Women at high risk to develop ovarian cancer should be informed about the prophylactic benefits of risk-reducing procedures and the optimum age to perform these procedures.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

RAMM, RP and AC had substantial contributions to the conception, design and interpretations of data. AET, TC and PP contributed by drafting the work and MG revised the article. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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