Recent Advances in Ovarian Cancer

Avid Science
Chapter 1

Ovarian Cancer and Risk Factors

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Abstract

The ovaries are the sites of ovum production and the main source of oestrogen and progesterone hormones. Ovarian cancer is the fifth most common cancer in women worldwide. It may be arise from epithelial cells and represent about 90% of all ovarian cancer. In 2012, approximately 239,000 cases were recorded and were represented about 4% of all new cases of cancer. Risk for development of ovarian cancer increases with age between 15-35 years; the rate of increasing slows after the menopause. Ovarian cancer often has no symptoms at early stages, and can be diagnostic in advanced stage. The 5-year survival rate ranges from approximately 30 to 50%. Certain factors may increase the risk of ovarian cancer such as age, microorganisms such as human papilloma virus (HPV), chlamydia trachomatis and Mycoplasma genitalium. Inherited genes mutation such as breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2) increase the risk of ovarian cancer.

Introduction

Ovarian carcinoma is a common cause of gynecologic neoplasm and about 90% of cancers arise in the ovaries are carcinomas [1,2]. With emerging evidence, so-called “ovarian” carcinomas are now believed to predominantly arise de novo by malignant transformation of the ovarian surface epithelium, and/or the serous epithelium of the fallopian tube, especially the distal portion [1,3]. Most aggressive ovarian carcinomas arise from ovarian surface...
epithelium (OSE) cells and account for about 90% of all ovarian carcinomas. Non-epithelial ovarian tumors arising from oocytes and sex cord stromal cells usually remain benign. Epithelial ovarian cancer is the fifth leading cause of cancer death in women, therefore it receive greater attention. Because the majority of patients with epithelial ovarian cancer are diagnosed at an advanced stage and because the efficacy of standard therapy is limited in such advanced cases, primary and secondary prevention strategies are critical to reduction of both cancer incidence and mortality. Even though there have been improvements in surgical techniques and treatment options, five-year survival for stage III and IV ovarian cancer still remains at approximately 45% [4].

The development of effective prevention methods depends on the identification of the anatomic origins of disease as well as specific carcinogenic mechanisms. The biological mechanism for this transformation remains elusive, although mounting evidence indicates that it likely involves a multi-step process with the accumulation of genetic lesions in at least three classes of genes, namely proto-oncogenes, tumor suppressor genes, and mutator genes.

Various microorganisms involved in the sexually transmitted diseases, including human papilloma virus (HPV), chlamydia trachomatis and Mycoplasma genitalium, have been associated with a higher risk for ovarian cancer [5,6]. Human papilloma virus family consists of small DNA viruses associated with cutaneous and mucosal squamous epithelial lesions [7]. The most important types of HPV are type 16 and type 18. The high-oncogenic risk HPV types produced two oncogenes, designed E6 and E7, which including with endogenous cell cycle regulatory proteins, including P53, retinoblastoma (Rb) and BRAC1. The interaction of virally derived and endogenous cellular proteins converges in deregulation of cell cycle progression and appears to be critical for the development of cancer. The E6 appear to alter cell growth through its effects on P53, which is an endogenous, cell-derived tumor suppressor protein. Wild-type P53 is nuclear protein that negatively regulates cell growth and division. The P53 induced G1 growth arrest allows the cell to repair the damage to its DNA. But, binding of E6 protein to P53 results in a loss of P53 activity within the cells. The expression of mutant form of P53 lead to the development of cancer. On the other hand the E7 protein binds to Rb protein. In the normal cells, the hypo-phosphorylated form of Rb protein, form complexes with transcription factors of the E2F family. These complex negatively regulated cell growth by repressing transcription of E2F-dependent genes. If the E2F-Rb complexes dissociate, free E2F becomes available. Free E2F stimulate the transcription of E2F-dependent genes and allows DNA replication.

Chlamydia is an obligatory intracellular pathogen and is able to cause chronic asymptomatic infection via evading the host immune response [8-10]. C.trachomatis is an infection of the genital tract in women worldwide[11]. The
cells infected by chlamydia may have a risk of neoplastic transformation via anti-apoptotic activity of chlamydia on infected cells [5]. The mechanisms for blocking apoptosis in the chlamydia infected cells may be via the chlamydia heat shock protein might have anti-apoptotic activity[12] or via the cytotoxic effect of chlamydia on cells promoting loss of microvilli and cell junctions that resulting in inducing pre-neoplastic cells[13,14].

*Mycoplasma genitalium* could cause chronic asymptomatic infection in the upper genital tract and might increase the risk of neoplastic transformation of tubal and ovarian tissue. The prolonged infection of benign human prostate cells in culture with Mycoplasma caused malignant transformation through an unknown mechanism[15]. Prolonged infection with *M. genitalium* could cause morphological changes in mammalian host cells may be as swelling of the tubal epithelial cilia through production of a toxin or metabolism products – hydrogen peroxide and superoxide radicals[16].

Malignant transformation of normal ovarian epithelial cells is caused by genetic changes that disrupt proliferation, programmed cell death and senescence [17]. Leptin, the product of obesity gene is suggested to be associated with cancer development and progression in many epithelial cancers including ovarian cancer [18]. More recently, it has been reported that Cyclooxygenase-2 (COX-2) overexpression may contributes to tumor growth and invasion in epithelial ovarian cancer and that COX-2 inhibition may have therapeutic potential in ovarian cancer [19]. S-phase kinase protein 2 (SKP2), an F-box protein, target cell-cycle regulators including cyclin-dependent kinase inhibitor p27Kip1 through ubiquitin-mediated degradation. SKP2 is frequently overexpressed in ovarian cancer [20]. P13K/AKT signaling pathway plays an important role in cell growth, proliferation and tumorgenesis of various malignancies including ovarian cancer [21].

Genes that commonly associated with hereditary ovarian cancer are the proto-oncogenes. c-erbB-1/epidermal growth factor receptor (EGFR) is a member of the type I tyrosine kinase receptor family, play a primary role in the control of epithelial cell proliferation and that is expressed in normal ovarian surface epithelium and overexpressed in 35–70% of ovarian cancers. However, the gene is rarely amplified or mutated in ovarian cancer. Human epidermal growth factor receptor 2 (HER-2) expression in ovarian cancer varies widely; overexpression is found in 20–30% of cases. It has been reported that approximately 40% of hereditary breast ovarian cancer (HBOC) cases overexpress HER2 [22].

c-Myc is a transcription factor that regulates expression of many genes. The c-Myc gene is amplified in both hematopoietic and solid neoplasms, including more than 30% and 40% of endometrioid and clear cell carcinomas, respectively. Overexpression of c-Myc has been reported in 30% of all ovarian tumors, but most frequently in serous adenocarcinomas.
K-RAS is a G-protein that promotes growth through MAP kinase pathway. Mutations in the K-RAS gene have been reported in approximately 60% of borderline tumors, in nearly 70% of low-grade tumors, and in 50% of mucinous adenocarcinomas.

Tumor suppressor genes, TP53 is an example of a prototype tumor suppressor gene that promotes cell cycle arrest/apoptosis in cells with DNA damage. Mutation of this gene is seen in many human malignancies including 50–60% of ovarian serous carcinomas. TP53 mutations have also been detected in ovarian inclusion cysts adjacent to cyst adenocarcinomas, in microscopic ovarian cancer, and in tubular intraepithelial carcinomas removed prophylactically from patients with BRCA1 mutations, suggesting that the p53 inactivation may be a relatively early event in ovarian cancer pathogenesis.

BRCA1 (breast cancer susceptibility gene 1) is one of the most intensively studied susceptibility genes and has a profound role in breast and ovarian cancer etiology owing to its involvement in several important cellular processes. Deleterious mutations in BRCA1 are found in 5–6% of ovarian cancers, but up to 80–90% in HBOC cancer cases. Among its many biological functions, the BRCA1 protein is involved in DNA repair.

BRCA2 (breast cancer susceptibility gene 2) is a tumor suppressor that shows similar but less common associations with HBOC as compared with BRCA1. Extensive genetic and biochemical characterization has shown that BRCA2 is involved in the maintenance of chromosomal stability and that it has an important role in recombination-mediated double-strand DNA break repair. Epigenetic changes (hyper-methylations): Up to seven mismatch repair (MMR) gene mutations and epigenetic hyper-methylations are seen in ovarian cancers associated with the Lynch syndrome, most of which are non-serous epithelial carcinomas [23]. Microsatellite instability (MSI) is detected in 50% of low-grade endometrioid tumors.

Mutations in the BRCA1 and BRCA2 account for approximately 90% of the ovarian cancers in the hereditary breast–ovarian cancer syndrome [24-27] and some 65–85% of all hereditary ovarian cancers [28,29]; mutations in at least four mismatch repair (MMR) genes (MLH1, MSH2, MSH6 and PMS2) (National Center for Biotechnology Information [NCBI], 2008) in the Lynch syndrome account for another 10–15% of hereditary ovarian carcinomas [28,30]. El-Harith et al, in 2002 found that BRCA1 and BRCA2 mutation are likely to contribute to the pathogenesis of familial breast cancer in female patients [31]. Other study was conducted on Palestinian Arab (AP) to study the mutation in BRCA1 and they found that a novel BRCA1 mutation in a family of AP origin with history highly compatible with BRCA1 phenotype. This mutation was not found in additional PA women affected with breast cancer or ovarian cancer [32].

Hereditary ovarian cancer syndromes appear to be
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genotypically and phenotypically heterogeneous diseases, characterized by variable clinical courses. Comprehensive family histories are currently fundamental for hereditary cancer syndromes diagnosis, thereby enabling the prevention of ovarian-like carcinomas in genetically susceptible individuals. Today’s epidemiological, clinical, and pathological investigations and the current search for molecular pathways in sporadic and hereditary ovarian carcinogenesis are basic for the prophylaxis, early detection, treatment, and final elimination of these cancers in the future.

Hereditary transmission of an autosomal dominant trait predisposing women to both breast and ovarian cancers was first published in the early 1970s by Lynch’s group at Creighton University [33-35]. Narod et al.[25] demonstrated that genetic locus was linked to cancers in the HBOC syndrome described twenty years earlier by Lynch et al. This gene is BRCA1 and a second gene was linked to breast cancers is designated as BRCA2.

The risk for ovarian cancer in BRCA2 mutation carriers from HBOC syndrome families has been estimated between 10% and 20% [36,37]. Antoniou et al. [38] estimated average cumulative lifetime risks for ovarian cancer in BRCA1 carriers to be 39% and 11% in BRCA2 carriers. Certain relatively closed and geographically confined populations carry well-defined mutations. Some populations are known to be particularly susceptible to ovarian cancer because of founder mutations in BRCA1 and/or BRCA2.

The Ovarian cancer cluster region (OCCR) of the BRCA2 gene appears to predispose to an excess of ovarian cancer. Gayther et al.[39, 40] identified truncating mutations clustered in a BRCA2 region of approximately 3.3 kb in exon 11 in families with the highest risk of ovarian cancer in relation to breast cancer. The extra-ovarian peritoneal serous carcinomas identified in families with BRCA1 and BRCA2 mutations appear morphologically similar to the high-grade ovarian serous cancers but often show no significant lesions in the ovaries. Approximately 50% of peritoneal serous carcinomas cases with unknown BRCA mutation status showed these microscopic changes [41,42].

For several years improved prognosis and response to standard antineoplastic chemotherapy of epithelial ovarian cancers diagnosed in carriers of BRCA1 and BRCA2 mutations from HBOC syndrome families has been noted by the majority of investigators [43-50]. The mean or median ages of ovarian carcinoma diagnosis among BRCA1 mutation carriers were significantly younger than the ages at which ovarian carcinomas were diagnosed in those who carried BRCA2 mutations [45,51,52]. These observations and data raise the hope of proving more favorable prognosis and higher expectations from platinum based chemotherapy for ovarian carcinoma arising in BRCA1 and BRCA2 mutation carriers.
Replication errors in somatic DNA without chromosomal allelic loss of heterozygosity (LOH), demonstrated by microsatellite instability. Such patterns are known to represent the possibility of significant nucleotide deletions and other nucleotide rearrangements [53]. Rapidly thereafter, other MMR homologues were analyzed, and the next most frequent human MMR gene linked to Hereditary nonpolyposis colorectal cancer (HNPCC) and designated MLH1. Subsequently, mutations in these genes (MSH2 and MLH1), as well as two other human mismatch repair genes, MSH6 and PMS2 (NCBI, 2008), were linked to other cancers that have been found to be integral to Lynch syndrome [54–58].

Several in vitro experiments have addressed problems of defining the mechanism of defective MMR that accompanies inheritance of mutated MLH1 in Lynch syndrome. European and multi-institutional studies have shown that some 90% of American and European Lynch syndrome families tested with DNA- or RNA-based techniques carried mutations in MSH2 or MLH1 [53, 59–61] and absence of MSH2 and MLH1 functional expression appears to be the fundamental defect in the majority of typical Lynch syndrome families, such as those families that feature both CRC and endometrial carcinomas [59, 62].

Hereditary transmission of MSH6 mutations is less common in Lynch syndrome families, accounting for only 7% in the International Society of Gastrointestinal Hereditary Tumors database [59] and although germline mutations in MSH6 have been associated with an attenuated form of Lynch syndrome with later onset of tumors, the 71% cumulative lifetime risk for endometrial carcinomas seems to be greater in these kindreds than in those which are associated with germline mutations in MLH1 and MSH2 [59, 63, 64]. MSI-H and associated loss of MMR gene expression are found more frequently in ovarian carcinomas of non-serous ovarian histologies, particularly endometrioid and related clear cell types, than in serous carcinomas, which are more common in general populations. BRCA1 and BRCA2 mutations are nucleotide substitution, MSH2*190G → C, which results in a substitution of proline for alanine in the MSH2 protein. Up to 20% of all deleterious mutations within this MMR gene, including the AFM, are large germline deletions which would not have been detectable prior to the methodology developed by Wagner et al. [65] and used to identify the AFM. Now, because of the prevalence of this mutation, a specific assay can be utilized in routine DNA analysis to screen American Lynch syndrome families without already determined cancer-associated mutations [60, 66–68].

Conclusion

Ovarian carcinoma is a common cause of gynecologic neoplasm and epithelial ovarian cancer. There are multistep process with the accumulation of genetic lesions including three classes of genes, namely proto-oncogenes,
tumor suppressor genes, and mutant genes are responsible for the development of ovarian cancer. Also different sexually transmitted microorganisms, such as human papilloma virus, *chlamydia trachomatis* and *Mycoplasma genitalium* have been associated with a higher risk for ovarian cancer. Mutations in the breast cancer-associated genes 1 & 2 (BRCA1) and (BRCA2) represent about 90% of the ovarian cancers in the hereditary breast–ovarian cancer syndrome.

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