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Genetic factors involved in ovarian cancer

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ABSTRACT

Ovarian cancer is the most frequent type of gynecologic malignancy and is currently on the fifth place among different cancers worldwide. According to the estimations, ovarian cancer accounts for 1.3% of all new cancer cases. Ovarian cancer is considered a heterogeneous class of malignancies with a poor prognosis due to late diagnose and low treatment response. There are few types of ovarian cancer: epithelial ovarian cancer, germline cell ovarian cancer and stromal cell ovarian cancer. Epithelial ovarian cancers represent more than 90% of ovarian malignancies, and comprise high-grade serous carcinoma (HGSOC), low-grade serous carcinoma (LGSOC), endometrioid carcinoma, mucinous carcinoma, and clear cell carcinoma. Of these, HGSOC is the most frequent histological subtype. The diagnosis of most of OC cases, at an advanced disease stage is one of the reasons for high fatality rate and carries poor prognosis with current therapies.

Several aspects can increase the risk of developing ovarian cancer, including genetic factors, such as age, postmenopausal hormonal therapy use, infertility and nulliparity. Among the genetic factors, most commonly we encounter BRCA1 and BRCA2, at approximately 17% of patients. Also these mutation rise the risk for another cancers like breast cancer, pancreatic cancer, prostatic cancer and melanoma. BRCA1 and 2 are genes involved in DNA repair and maintenance. Other genes that have a similar function are RAD511C, RAD51D, BRIP1, PALB2, CHEK2, MRE11A, RAD50, ATM and TP53.

Keywords: ovarian cancer, mutations, MMR, BRCA1, BRCA2

INTRODUCTION

Ovarian cancer represents a commonly encountered malignancy affecting women worldwide which remains asymptomatic for a long period of time; therefore most cases are diagnosed in advanced stages of the disease and are associated with poor outcomes [1-3]. Meanwhile, no appropriate screening test has been identified so far [3]. Therefore, attention was focused on identifying which are the patients at risk to develop this malignancy , the most commonly investigated risk factors being represented by genetic mutations of BRCA1 and BRCA2 genes. More recently, mutations of CHEK2 gene and TP53 gene have been also cited [4,5]. The aim of the current paper is to discuss about the most important genetic factors which seem to increase the risk of ovarian cancer development.

THE BRCA1 AND BRCA2 GENES

BRCA1 (Breast Cancer Gene 1) and BRCA2 (Breast Cancer Gene 2) are tumor supressant genes that code for proteins with a wide role in DNA repair. There are over 1200 mutation of BRCA1 and over 1300 mutation of BRCA2. Although persons with HGSOC inherit a defect allele gene from one of their parents, the still have a functional allele gene.

When the second gene becomes nonfunctional the neoplastic process starts developing trough accumulation of additional mutations. It's estimated that the prevalence of BRCA mutation in general population is about 1/300 to 1/800. Women with BRCA1 or BRCA2 the risk for ovarian cancer is 39-46% and 12-20%. Ovarian cancer has a different histological phenotip at these patients, mostly serous or endometroid tumors being identified [5].

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The BRCA1 gene is situated on chromosome 11q21 and comprises 22 coding exons. The BRCA2 gene is situated on 13q12-13 and comprises 26 coding exons. Evidence showes that ovarian cancer women carrying germline BRCA mutations bear a better prognosis and overall survival when compared to sporadic cases [6]. Tumors with different modifications in either gene are sensitive to specific anticancer drugs that are damaging DNA [7]. Cells with BRCA1 and BRCA2 defects accumulate chromosomal anomalies: severe aneuploidies, centrosome amplification, chromosomal instability, all these can be the pathogenic base of tumor developing.

MISMATCH REPAIR GENES (MMR)

MMR (mismatch repair) genes are involved in a mechanism that corrects alterations that occur during DNA replication and play a vital role in keepimg genome stability. There are several genes involved in this system: MLH1, MLH3, MSH2, MSH3, MSH6, PMS1, PMS2. Inactivation of MMR in human cells is associated with genomic instability and predisposition to certain cancers [8]. In the present pathology, MMR deficiency is the most frequent cause of familial ovarian cancer (after BRCA1 and BRCA2 mutations) [9].

MMR dysfunction results from genetic and epigenetic mechanisms, and MSH6 has been described as responsible in most cases. Loss of MMR function and subsequent microsatellite instability is associated with Lynch syndrome. The prevalence of MMR deficiency or microsatellite instability is between 10% and 20% in cases of familial ovarian cancer. Loss of MMR is most common in non-serous ovarian carcinomas, especially endometrial cancer and clear cell carcinoma [10].

CHEK2 GENE

The CHEK2 gene (checkpoint kinase 2) is a tumor suppression gene located on chromosome 22.q12.2. It encodes a protein kinase that activates in response to DNA damage. It also interacts with BRCA1 promoting cell survival after DNA damage [11].

CHEK2 mutation is associated with ovarian cystadenomas, borderline ovarian tumors, and low-grade but not high-grade serous carcinoma [12].

TP53 GENE

TP53 mutations are ubiquitous in high-grade serum ovarian cancer and the presence of this mutation differntiates between high and low serum carcinoma, and is an important biomarker for clinical trials targeting p53 [13, 14].

Tumor protein p53 acts as a tumor suppressor and regulates cell division, but these functions are context-dependent and can be influenced by many factors such as cell type, microenvironment, and oncogenetic events that have been acquired during tumor evolution. p53 is one of the most studied proteins in cancer research [11].

CONCLUSIONS

During the past decades, genes other than BRCA1 and BRCA2 have been described to be involved in the hereditary susceptibility for ovarian cancer. Genome Wide Association Studies (GWAS) have led to the discovery of numerous variants in patients with this pathology.

As our knowledge on the molecular functioning of these genetic markers increases, new therapies can be developed and the management of ovarian cancer patients can become more accurate and efficient.

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