Review

Genetic Cancer Ovary

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Abstract

About 10% to 15% of ovarian cancers are linked to genetic abnormalities, including breast cancer susceptibility gene (*BRCA*) mutations, and Lynch syndrome. The aim of this work was to provide comprehensive and updated review of this distinct type of ovarian cancer that carries genetic alterations in relation to its pathology, prevention, prognosis, and management. Genetic ovarian cancer has a distinct pathologic and molecular biology features. *BRCA1* and *BRCA2* mutation ovarian cancers are most likely to be high-grade serous adenocarcinomas. Many *BRCA1*-mutated tumors harbor a mutant *p53* gene, c-myc overexpression, and epidermal growth factor receptor overexpression. Clinically, genetic ovarian cancer presents at a younger age than sporadic ovarian cancer. For prevention, risk-reduction salpingo-oophorectomy is an effective tool. Chemoprevention by oral contraceptives may represent an option. A recent study demonstrates improved progression-free survival and overall survival in patients whose ovarian cancer displays *BRCA1* and *BRCA2* mutation, relative to those who have normal *BRCA1* and *BRCA2* function. Recent management advances include PARP (poly[adenosine diphosphate {ADP}–ribose] polymerases) inhibitors. Significant progress has been recently made in elucidating the role of *BRCA1* and *BRCA2* mutation and Lynch syndrome on ovarian cancer prognosis and management.

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Introduction

Ovarian cancer represents the sixth most common cancer among women worldwide. It accounts for 4% of all new cancer cases. Despite recent advances in diagnosis and management, more than 60% of patients present with stage III or stage IV. The 5-year overall survival (OS) remains around 47%, and nearly 50% of patients die from this cancer.[1-3]

About 10% to 15% of ovarian cancers are linked to genetic abnormalities. Breast cancer susceptibility gene (*BRCA*) germline mutations account for 85% of all hereditary ovarian cancer.[4,5]

Genetic ovarian cancer appears to be heterogeneous diseases in comparison with sporadic cancer ovary. It is characterized by variable clinical courses, associate with other cancers, and includes different molecular pathways.[6]

The aim of this work was to provide comprehensive and updated review of this distinct type of ovarian cancer that carries genetic alterations in relation to its pathology, prevention, prognosis, and management.

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Genetic Abnormalities

Genetic ovarian cancer is part of several cancer syndromes. The most commonly associated syndromes are *BRCA1* and *BRCA2* mutation syndromes. *BRCA1* and *BRCA2* germline mutations account for approximately 65% to 85% of the genetic alterations associated with genetic ovarian cancer.[7]

Both *BRCA1* and *BRCA2* are transmitted as autosomal dominant trait. Certain ethnic groups, eg, Ashkenazi Jews, have the highest rates of mutation of these genes.

BRCA1 gene is a tumor-suppressor gene, located on 17q21, from base pair 43,044,294 to base pair 43,125,482. *BRCA1* gene mutation is associated with increased risk for breast cancer and ovarian cancer by 65% to 80% and 45% to 60%, respectively.

BRCA2 gene is another tumor-suppressor gene, located on 13q12.3, from base pair 32,315,479 to base pair 32,399,671. *BRCA2* gene mutation is associated with increased risk for breast cancer and ovarian cancer by 45% to 60% and 20% to 30%, respectively (Figure 1).[8-10]

BRCA1 and *BRCA2* gene mutations are associated with other cancers including contralateral breast cancer (40%), cancer pancreas (7%), cancer prostate (20%-39%), melanoma (4%), colon cancer (5%), fallopian tube, peritoneal cancer, male breast cancer (2%-6.8%), and acute myeloid leukemia.[11-13]

Genetic ovarian cancer has also been associated with Lynch syndrome which in the general population occurs in about 1 in 2000 individuals. Lynch syndrome–associated disease accounts

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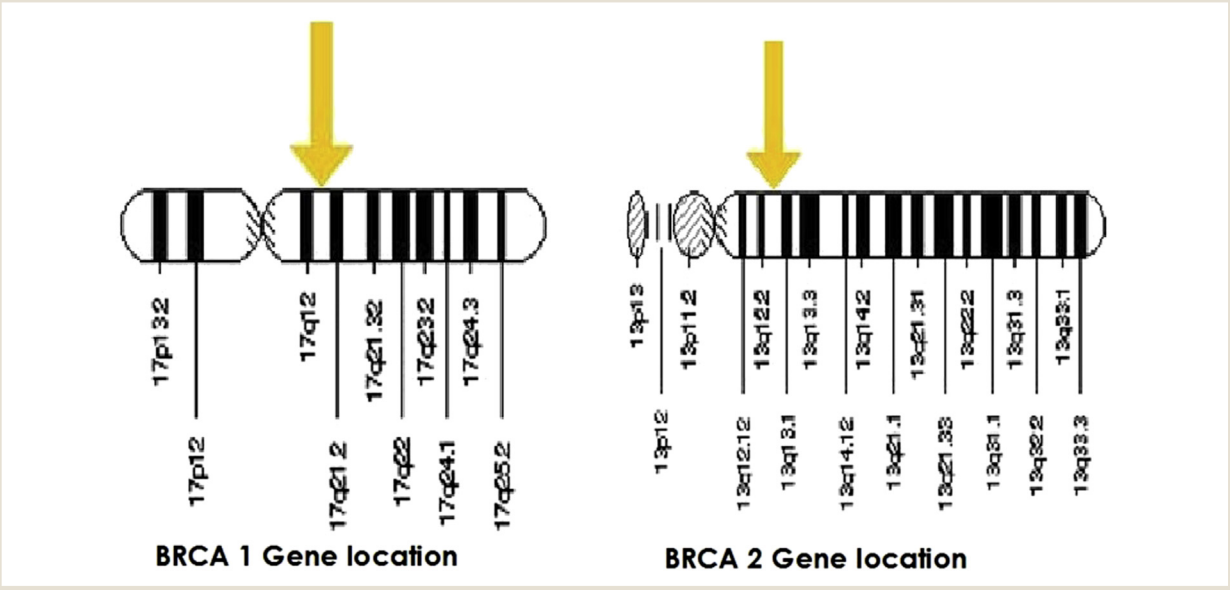
Figure 1 *BRCA1* and *BRCA2* Gene Location



for another 10% to 15% risk for developing genetic ovarian cancer.[14]

Lynch syndrome is an autosomal dominant syndrome that includes mutation in 1 of the 4 genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*, with subsequent impairment in mismatch repair.

Lynch syndrome is associated with other cancers apart from including cancer colon (80%), stomach cancer (11%-19%), hepatobiliary cancer (2%-7%), urinary tract cancer (4%-5%), small bowel cancer (1%-4%), brain tumor (1%-3%), and endometrial cancer (20%-60%).[15,16]

Studies showed that ovarian cancer is associated with mutation of *MLH1*, *MSH2*, and *MSH6* in 20%, 24%, and 1% of patients, respectively. Other recent reports noted that *MSH2* gene mutation had nearly twice the incidence rate observed in *MLH1* gene mutation.[16,17]

Other genetic abnormalities that were associated with ovarian cancer include Li-Fraumeni syndrome due to *p53* mutations, Cowden syndrome due to *PTEN* mutations, basal cell nevus (Gorlin) syndrome, and multiple endocrine neoplasia type 1. They account for 4% to 5% of genetic ovarian cancer.[18]

Pathology

Several studies have confirmed the distinct entity of genetic ovarian cancer from sporadic ovarian cancer.

BRCA1 and *BRCA2* mutation ovarian cancers are most likely to be high-grade serous adenocarcinomas. In a study by Lu et al., more than 90% of their 48 patients with *BRCA1*-mutated ovarian cancer were high-grade serous adenocarcinoma, compared to 50% in patients without *BRCA* mutation. The second common pathology is endometroid carcinoma (10%-14%).[6,19,20]

Further, a recent study failed to identify the exact site of origin in *BRCA*-mutated ovarian cancer. They observed that, in risk-reducing salpingo-oophorectomy (RRSO) specimens from *BRCA* mutation carriers, the premalignant lesion was found in the distal, fimbriated end of the fallopian tube, rather than the ovary.[21]

For Lynch syndrome—associated ovarian cancer, the commonest pathology has been yet determined. Although high-grade serous carcinoma was the commonest pathology in 2 studies (50% in both), it was detected only in 25% of the third trial, with endometroid, or mixed serous—mucinous pathology, being more common.[6,22]

Molecular Biology

Data support for distinct molecular pathways of carcinogenesis for *BRCA1*- and *BRCA2*-mutated ovarian cancer when compared to sporadic ovarian cancer. However, for Lynch syndrome—associated ovarian cancer, the molecular pathways are not yet understood.[23]

BRCA1 *is Implicated in Multiple Cellular Functions Based on Its Protein Interactions*

Many *BRCA1*-mutated tumors harbor a mutant *p53* gene. Studies suggest that loss of *p53* is a programmed hit in the pathway of *BRCA1*-mutated tumor development.[23]

Also, *BRCA1* is phosphorylated (activated) mainly by the DNA damage sensors; the protein kinases mutated in the ataxia telangiectasia syndrome, and checkpoint-2, implicating it in the DNA damage response. However, to date, there are limited data as to how extent each phosphorylation event affects function of *BRCA1*.[24]

Furthermore, it is believed that *BRCA1* modulates transcriptional control mainly via its interactions with many transcription factors, including c-Myc. Overexpression of c-Myc has been reported in 30% of *BRCA*-mutated high-grade ovarian serous adenocarcinomas. Interestingly, *BRCA* mutations also disrupt the binding of *BRCA1* to the histone deacetylase (HDAC) complex. *BRCA1* has 2 opposing roles in chromatin activation; it may recruit HDAC