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Hereditary ovarian cancer

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Abstract

At least 10% of ovarian tumors are hereditary and associated with highly penetrant, autosomal, dominant genetic predisposition. Three clinical manifestations of hereditary ovarian cancer have been identified: site-specific ovarian cancer, hereditary breast and/or ovarian cancer (HBOC) and hereditary non-polyposis colorectal cancer (HNPCC) syndromes. BRCA germline mutations account for more than 90% of all hereditary epithelial ovarian tumors whereas most of the remaining 10% are caused by MLH1 and MSH2 mutations, which are susceptibility genes of HNPCC. Genetic testing is available for each of the three hereditary syndromes above mentioned. The recommendations for OC surveillance in high-risk women having a strong family history or BRCA mutation carriers include transvaginal pelvic ultrasound with color Doppler and serum CA125 every 6 months. Bilateral salpingo-oophorectomy appears to be effective to reduce the risk of ovarian cancer in BRCA mutation carriers. Hysterosalpingo-oophorectomy should be considered in HNPCC women who undergo surgery for colorectal carcinoma.
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1. Introduction

In the Western Countries, ovarian cancer (OC) is the leading cause of death from gynecological malignancy and is the fourth cancer-related cause of death among women with an estimated worldwide prevalence of 192,000 per year [1].

Due to absence of early symptoms and to the inadequacy of available screening methods, OC are often diagnosed at an advanced stage resulting in a low survival rate.

Although no particular environmental risk factors have been associated with ovarian carcinogenesis, the sex hormones exposure and patient's reproductive history are particularly important. In the general population, the birth of one live child reduces the risk of OC; after their first pregnancy women have a risk 45% lower as compared to nulliparous subjects. Every further pregnancy reduces the risk by another 15% [2]. Differently from what happens with sporadic cancer, the risk of OC in BRCA1 mutation carriers has been found to grow significantly with the number of born children; after the fifth child, subsequent pregnancies have a protective effect [3]. Moreover, the risk of OC decreases as the age at the last pregnancy increases and each 5 years interval is associated with a risk reduction of 18%. Women who have all their children after the age of 30 as well as nulliparous women, belong to the lowest risk group. A case–control study has reported that late pregnancies are protective against OC, but this has been proved only for patients with a family history of OC [4].

Among the general population, women who have breast fed at least one child present a reduced risk of developing OC but no data are available in women with an inherited predisposition.

Beside the hormonal exposure, the only relevant risk factor is a family history of OC; in fact, the risk of developing the disease rises from 1.6% in the general population to 4% in women with a first-degree relative with OC and to 7% when two relatives are affected [5,6].

In women with strong familiarity, OC is generally diagnosed at an earlier age as compared with the age of those who develop the disease without a family history.

Moreover in families with a high aggregation of cases diagnosed with OC, the risk is related to the first-degree relative's age at diagnosis. It has been established that the relative risk of OC before the age of 55 is 5.2 and it decreases to 3.4 after 55 years [7].

Anyway a first-degree relationship with an OC patient is itself the major risk factor, while the age at which a relative is diagnosed with cancer seems to have a minor effect with regard to the OC risk.

The purpose of the present review is to give the primary care clinician a useful tool to recognize and manage hereditary ovarian cancers due to mutations in either the *BRCA* or the *MMR* genes. The paper is based on current literature and on our field experience with oncogenetic counseling for hereditary breast/ovarian cancer and for Lynch II syndrome. Given the huge extension of the subject we decided to provide a state of the art review and to avoid offering our critical point of view.

2. Hereditary ovarian cancer syndromes

Up to 5–10% of all OCs are hereditary and associated with a dominant autosomic genetic predisposition at high penetrance. The detection of alterations in *susceptibility genes* is at the basis of genetic counseling, that allows to individuate germline mutation carriers among subjects at high risk of tumor [8–10].

Although serous OC is the most common histological type, other specific subtypes can be found according to the syndrome presenting the risk of an ovarian tumor [11].

OC seems to be the result of a multistep process due to the accumulation of genetic alterations, which, in women with familiarity for ovarian tumors, could be inherited. Beyond mutations in high penetrance major susceptibility genes, other low risk alleles or polymorphisms in different loci take part in the ovarian carcinogenesis and the complexity of the entire process is to date far to be completely understood [12,13].

In families with OC history, members affected by other neoplasms, like breast and colon cancer, can have a greater risk of developing OC too. A strong family history of OC and correlated tumors could suggest three main syndromes:

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