CLINICAL APPROACH TO DIAGNOSIS AND MANAGEMENT OF OVARIAN, FALLOPIAN TUBE, AND PERITONEAL CARCINOMA

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KEYWORDS

• Ovarian cancer • Fallopian tube cancer • Primary peritoneal cancer • Genetic screening • Epidemiology • Staging procedures • Cytoreductive surgery • Chemotherapy

ABSTRACT

Ovarian, fallopian tube and peritoneal carcinomas make up the deadliest group of malignancies of the female genital tract. Ovarian carcinoma is the second most common malignancy of the female reproductive tract in developed countries and the sixth most common cancer diagnosed in women in the United States. While signs and symptoms of ovarian carcinoma related to the mass-effect of advanced disease are used for diagnosis, no reliable signs or symptoms are seen in patients with early ovarian carcinoma. The diagnosis can only be made by surgical removal and pathologic evaluation of a suspicious mass. This review details staging procedures and surgical and chemotherapeutic techniques for management of various stages of ovarian cancer. The authors present an overview of the disease, discussion of genetic predisposition, screening and prevention and diagnosis of ovarian cancer, cancer of fallopian tube, and peritoneal carcinoma.

OVERVIEW

Ovarian, fallopian tube and peritoneal carcinomas make up the deadliest group of malignancies of the female genital tract. While peritoneal and fallopian tube cancers are rare, ovarian carcinoma, as currently defined, is the second most common malignancy of the female reproductive tract in developed countries and the sixth most common cancer diagnosed in women in the United States affecting 1 in 70 women in their lifetime.[1] The highest incidence is found in Northern European countries, the United Kingdom, and the United States. Native Japanese have the lowest incidence.[2] Although the primary anatomic sites of fallopian tube and peritoneal carcinomas appear to differ, their histologic characteristics resemble those of ovarian carcinoma. Similarly, issues surrounding detection, treatment and outcomes reflect a commonality within this group of diseases. Therefore, ovarian carcinoma is used as the model for the following discussion on their detection and treatment.

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It is increasingly recognized that ovarian carcinoma is heterogenous, not only from a clinical standpoint, but also morphologically, biologically and genetically. An appreciation of these specific features has led to the recognition that each type is distinctive and constitutes a unique disease entity. These include: low grade serous carcinoma, high grade serous carcinoma, low grade endometrioid carcinoma, high grade endometrioid carcinoma, clear cell carcinoma and mucinous carcinoma.

High-grade (grades 2 and 3) serous carcinoma, the prototypic "ovarian cancer," represents between 80 and 85% of ovarian carcinomas in North America. Almost all diagnostic and therapeutic efforts in the clinical realm have been developed with the mistaken assumption that lessons learned from studying this prototype can be generalized to less common ovarian cancer types. This will undoubtedly change in the coming years. All of the details concerning diagnosis and treatment in this review address high-grade serous carcinomas specifically, unless otherwise noted. One should remain hesitant to assume that these generalities are applicable across the ovarian carcinoma spectrum. Details regarding diagnosis and treatment of the less common entities will be covered in the relevant articles.

EPIDEMIOLOGY

Ovarian carcinoma is typically a postmenopausal disease identified in women with a median age of 63. Although the etiology of ovarian carcinoma is still unclear, several theories have been hypothesized. The previously, the most popular causation theory was associated with ovulation. It was postulated that ovulation resulted in epithelial damage and subsequent repair. With repeated cyclical injuries to the ovarian epithelium there may be an increased rate of chromosomal aberration leading to an increased likelihood of oncogenic mutation and carcinogenesis. This theory was supported by the known protective effects of multiple pregnancies, oral contraceptives, and lactation. Conversely, early menarche, late menopause and nulliparity are risk factors and the use of ovulation induction agents has been associated with an increased incidence of ovarian cancer.[3–5]

There are accumulating data that suggest that some, if not most, high grade ovarian serous carcinomas derive from intraepithelial neoplasms of the fimbriated end of the fallopian tube. If these neoplastic cells become incorporated into the ovarian cortex through disruptions in the ovarian surface that occur during ovulation, this hypothesis would account for both the protective effects of multiple pregnancies, oral contraceptives, lactation, tubal ligation, and also the presence of fimbrial intraepithelial serous carcinoma in an appreciable number of risk-reducing salpingectomy specimens and in the fimbria of patients with established ovarian cancer. This is discussed in detail in this publication by Shaw, in Hereditary Carcinomas of the Ovary, Fallopian Tube, and Peritoneum.

There are conflicting reports that implicate dietary, environmental and carcinogen exposures (such as talc, asbestos, and radiation) as risk factors of ovarian cancer. It is theorized that their direct exposure to the peritoneal cavity through the endometrial canal and fallopian tubes may result in a carcinogenic effect to the surface of the ovary. The theory that ovarian carcinogenesis is a result of exogenous toxins is supported by studies that have demonstrated a decreased incidence of ovarian cancer in women who have undergone prior tubal ligation.[6]

A known genetic predisposition is associated with 8 to 13% of ovarian carcinomas, specifically high-grade serous carcinoma.[7–9] *BRCA1* and *BRCA2* (chromosomes 17q and 13q) genes code for DNA repair proteins. While *BRCA* mutations are strongly associated with breast cancer, *BRCA1* gene mutations also result in a 35% to 60% lifetime risk of ovarian cancer. Mutations in *BRCA2* result in a lifetime risk of 10% to 20%.[10–13] Hereditary Nonpolyposis Colon Cancer (HNPCC) or Lynch Syndrome is a result of inherited defects in the mismatch repair genes *MLH1*, *MLH2*, and *MSH6*. Women with Lynch syndrome have a 12% lifetime risk of developing ovarian cancer in addition to being at increased lifetime risk for colon, endometrial, and gastric cancers among others.[14] Even without genetic information available, a family history of early onset breast or ovarian cancers increases the relative risk of developing ovarian cancer by 3- to 5-fold.[15]

SCREENING AND PREVENTION

The single most important change that must occur in the discipline of curing ovarian carcinoma is the development of an accurate and reproducible method to screen or detect the disease at its earliest stages. Difficulties in identifying a reliable screening tool are multifactorial. The adnexa and peritoneal surfaces are internal structures, not easily accessible to an examining physician; and the heterogeneity of the disease makes it difficult to pinpoint a single marker. High-grade serous carcinoma, the most common

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