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Ovarian Carcinogenesis - An Enigma

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Review Article

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Abstract

The time honoured concept that ovarian cancer originates from the ovarian surface epithelium (mesothelium) which then invaginates into the underlying stroma resulting in inclusion cysts that eventually undergo malignant transformation and ovarian cancer spreads from the ovary to the pelvis, abdomen and distant sites has been challenged by the recent studies. Attempts to improve detection of ovarian cancer when it is still confined to ovary and thereby improve survival have miserably failed over the years. The overall survival of women with ovarian cancer is unchanged over the last fifty years. Utilizing the available imaging techniques and the better understanding of ovarian carcinogenesis we will be able to develop newer preventive strategies and screening methods for ovarian cancer. Lot of clinical studies are required to achieve this goal and to reduce the mortality from ovarian cancer.

Keywords: Salpingo-Oopherectomy; Ovarian Carcinogenesis; Mucinous carcinomas; Malignant Brenner tumors

Introduction

Ovarian carcinoma is the most lethal gynecological malignancy. It is estimated that there will be >140000 deaths per year worldwide. Although many surgical techniques and chemotherapies have been developed for ovarian carcinoma, the prognosis remains poor, with a five-year survival rate of 45%. Although the prognosis is more favorable in patients with stage I/II tumors, the majority of patients present with advanced stage disease (III/IV). There are no effective preventive strategies and screening methods for ovarian cancer. Basically the reasons for this sad situation are (1) Deep intrapelvic situation of ovaries and (2) Lack of clear knowledge about the pathogenesis of ovarian tumors.

Epidemiology and New Information about Carcinogenesis

In India, according to 2008 statistics, ovarian cancer is the fourth most common cancer among women and third most common cause of mortality among cancers in women. Incidence of ovarian cancer in India is 5.2% and mortality is 5.7% [1]. This says that mortality rate is very high in ovarian cancer. Worldwide ovarian cancer is the seventh most common malignancy diagnosed in women, the fifth leading cause of death from cancer in women and the leading cause of death among gynecologic cancers.

Approximately 75% of all ovarian cancer cases are in an advanced stage at the time of diagnosis, thereby increasing the mortality and morbidity associated with the condition. The median overall survival period for advanced ovarian cancer is 15-23 months, with a 5-year survival rate of only 20%.Unforrunately, there are no effective prevention or screening programs currently in place that have been shown to improve patient survival for this disease.

For most women, the lifetime risk of developing ovarian cancer is ~1-1.5% & that of dying from ovarian cancer is 0.5%. However, for women carrying BRCA1 or BRCA2 gene mutations that risk increases to 54% and 23%) respectively [2]. Therefore the need for prevention and screening programs is even more significant for this population of women.

Studies have shown that epithelial ovarian cancer can be classified according to morphologic and molecular genetics features. One group of tumours, designated type I, is composed of low-grade serous, low-grade endometrioid, clear cell, mucinous and transitional (Brenner) carcinomas.

These tumours generally behave in an indolent fashion, are confined to the ovary at presentation and, as a group, are relatively genetically stable. They lack mutations of *TP53* but each histologic type exhibits a distinctive molecular genetics profile. KRAS, BRAF& ERBB2 mutations are seen in low grade serous carcinomas. Moreover, the carcinomas exhibit a shared lineage with the corresponding benign cystic neoplasm often through an intermediate (borderline tumor) step, supporting the morphologic continuum of tumor progression.

In contrast, another group of tumors, designated type II, are highly aggressive, evolve rapidly and at presentation itself is in an advanced stage and hence early detection is almost always impossible. This category constitutes about 75% of advanced ovarian cancers. Type II tumors include conventional high-grade serous carcinoma, undifferentiated carcinoma and malignant mixed mesodermal tumors (carcinosarcoma). They display *TP53* mutations in over 80% of cases and rarely harbour the mutations that are found in the type I tumors [3]. Early detection is not possible because, to begin with itself they are at an advanced stage. The only ray of hope lies in novel strategies to prevent it.

Recent studies have also provided evidence that many of the ovarian tumors traditionally thought to be of ovarian origin, primarily originate in other pelvic organs and ovarian involvement is actually secondary [3]. Thus, it has been proposed that serous tumors arise from the implantation of epithelium (benign or malignant) from the fallopian tube. Endometrioid and clear cell tumors have been associated with endometriosis, which is regarded as the precursor of these tumors. Since it is generally accepted that endometriosis develops from endometrial tissue by retrograde menstruation it is reasonable to assume that the endometrium is the source of endometrioid and clear cell carcinomas. Finally, preliminary data suggest that mucinous and transitional (Brenner) tumors arise from transitional-type epithelial nests at the tubal-mesothelial junction by a process of metaplasia.

The time honoured concept that ovarian cancer originates from the ovarian surface epithelium (mesothelium) which then invaginates into the underlying stroma resulting in inclusion cysts that eventually undergo malignant transformation and ovarian cancer spreads from the ovary to the pelvis, abdomen and distant sites has been challenged by the recent studies.

Attempts to improve detection of ovarian cancer when it is still confined to ovary and thereby improve survival have miserably failed over the years. This is evidenced by the fact that the overall survival for women with ovarian cancer has not changed over the last 50 years. The reasons for this are that the concepts of histogenesis on which these approaches are based, are flawed.

Recent morphologic and molecular genetic studies have illuminated our understanding of ovarian carcinogenesis in ways that have been quite unexpected and have challenged the conventional wisdom regarding their origin and development. Indeed, they have resulted in a paradigm shift that has important implications for research and for radically changing our approaches to early detection, prevention and treatment.

One interesting feature of ovarian cancer is that 75% of them presents with extensive peritoneal involvement. The occurrence of primary peritoneal cancer without involvement of ovaries and primary peritoneal cancer in patients who underwent total abdominal hysterectomy and bilateral salpingo-oopherectomy prompted investigators to look into non ovarian origin of carcinoma ovary [4].

It is a well known fact that prophylactic salpingo-oopherectomy reduces the risk of carcinoma ovary and carcinoma breast. The specimens of these prophylactic surgeries revealed p53 signatures and STIC. So majority

of type 2 tumors appear to arise from serous tubal intra epithelial carcinoma.

One of the significant aspects of ovarian carcinogenesis that remains unclear is the precursor lesion responsible for this disease. For almost all epithelial gynecological cancers, whether they arise from the vulva, vagina, cervix or endometrium, they arise via a sequence of events that begins in normal epithelium, then passes through non-obligatory precursor lesions to become invasive neoplasias. Since the ovarian cancer is usually diagnosed at an advanced stage, ovarian precursor lesions have not been identified. However, in the last few years, increasing evidence has indicated that tubal fimbrial lesions are candidates to be precursor lesions of ovarian high-grade serous carcinomas. Additional studies have further pinpointed the distal fimbrial portion of the fallopian tube as the most common site of origin.

Putative precursor lesions have been identified in the fallopian tube that morphologically and molecularly resembles high-grade ovarian serous carcinoma and that has been designated “serous intraepithelial tubal carcinoma (STIC)”. Thus, rather than developing *de novo* from the ovary, as previously proposed, the majority of type II tumors appear to arise from a STIC in the fabricated end of the fallopian tube that spreads to the ovary.

Pathological detailed evaluation of fallopian tube has given clear evidence to the early tubal origin of ovarian cancer. This is accomplished by a new protocol, which entails Sectioning and Extensively Examining the Fimbrial end (SEE-FIM), exposes approximately 60% more surface area of the fimbria for examination.

It is also suggested that Type I ovarian tumours also originate from the fallopian tube. The dislodgement of normal tubal epithelium from the fimbria, which implants on the site of rupture where ovulation occurred results in the formation of an inclusion cyst that may then undergo malignant transformation. Thus, serous tumors may develop from inclusion cysts, as has been thought, but by a process of implantation of tubal (mullerian-type) tissue rather than by a process of metaplasia from ovarian surface epithelium (mesothelial). Thus, there is mounting evidence that type I and type II ovarian tumors develop independently along different molecular pathways and that both types develop outside the ovary and involve it secondarily. This explains why current screening strategies designed to detect ovarian cancer, when it is confined to the ovary, are ineffective in accomplishing this goal.

Given the obstacles in early detection (screening) and the significant, but relatively limited success in treatment, attention should be directed to primary prevention. The relevance of studying fallopian tubal involvement in ovarian carcinoma comes here because identifying a precursor lesion in the fallopian tube can bring revolutionary changes in the management of ovarian carcinoma.

Identifying a precursor lesion in carcinoma cervix and effective screening methods has brought down its incidence and mortality drastically. Extrapolating the same to carcinoma ovary will be beneficial, especially in a developing country like India where the financial burden and morbidity associated with carcinoma ovary is high.

If it is confirmed that carcinoma ovary arises from a precursor lesion in fallopian tube, Salpingectomy alone may be sufficient to reduce the risk of ovarian cancer while preserving ovarian function. Ovarian conservation appears to be particularly important for a woman's health, as it has been shown that oophorectomy is associated with increased overall mortality and a higher frequency of nonfatal coronary heart disease. In any case, new diagnostic, prevention and therapeutic approaches must be developed based on our evolving understanding of ovarian carcinogenesis [5].

There is a latest model for the ovarian carcinogenesis. The new model divides type I tumors into three groups: i) endometriosis-related tumors that include endometrioid, clear cell, and seromucinous carcinomas; ii) low-grade serous carcinomas; and iii) mucinous carcinomas and malignant Brenner tumors. As in the previous model, type II tumors are composed, for the most part, of high-grade serous carcinomas that can be further subdivided into morphologic and molecular subtypes. Type I tumors develop from benign extraovarian lesions that implant on the ovary and which can subsequently undergo malignant transformation, whereas many type II carcinomas develop from intraepithelial carcinomas in the fallopian tube and, as a result, disseminate as carcinomas that involve the ovary and extraovarian sites, which probably accounts for their clinically aggressive behavior. The new molecular genetic data, especially those derived from next-generation sequencing, further underline the heterogeneity of ovarian cancer and identify actionable mutations. The dualistic model highlights these differences between type I and type II tumors which, it can be argued, describe entirely different groups of diseases [6].

Newer Opportunities

Utilizing the available imaging techniques and the better understanding of ovarian carcinogenesis we will be able to develop newer preventive strategies and screening methods for ovarian cancer. Lot of clinical studies is required to achieve this goal.

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