Early Diagnosis of Ovarian Cancer. Is It Possible?

Liane Deligdisch*
Department of Obstetrics-Gynecology and Reproductive Science, The Mount Sinai School of Medicine, USA

INTRODUCTION

General considerations

Ovarian Cancer (OC) is the most lethal gynecologic tumor, notorious for being diagnosed in late stages. Approximately 15000 women in the USA and over 160000 women worldwide die every year of OC. In the USA about 22000 new cases were diagnosed in 2012. Morbidity and mortality due to OC have changed very little over the past 5 decades, despite extensive research efforts, identification of risk factors, chemotherapy and cytoreductive surgery. This is in contrast with other gynecologic malignant tumors which underwent spectacular decline in their mortality rates, such as cervical cancer due to the successful identification of precursor lesions and etiopathogenic infectious (HPV) mechanisms. OC results in more deaths than all the other gynecologic cancers combined.

The reason for this dismal outcome is the fact that the vast majority of OC cases (about 80%) are diagnosed in advanced stages of the disease, when the tumor is spread beyond the ovary. This is due to the lack of early specific symptoms (a notion recently challenged) and the absence of reliably sensitive and specific tumor markers. Anatomic characteristics of the ovaries such as their “hidden” location and paucity of sensorial nerves (early tumors are painless and clinically mute) preclude early diagnosis in most cases despite the current sophisticated technologies of pelvic visualization. The risk for developing OC is still poorly understood: a small percentage (about 10%) of women with inherited mutated genes BRCA1 and 2 are known to be at risk, while most cases of OC are considered to be sporadic.

Recent classification of OC

Based on the identification of tumor markers correlated with phenotypical structural characteristics OC are divided into low-grade and high-grade tumors, the latter unfortunately representing the majority. Low grade OC are growing slowly and are amenable to an earlier diagnosis, while high-grade OC, characteristically fast and aggressively growing, are diagnosed in late stages, when spread beyond the ovaries, and are highly lethal. The most common histopathologic entity is the serous (papillary) adenocarcinoma, a predominantly high-grade tumor originating in the ovarian surface epithelium, an extension of the peritoneal mesothelium, and much more often than previously thought, in the secretory cells lining the Fallopian tube fimbriae.

Less common high-grade OC are some endometrioid carcinomas and Malignant Mixed Mullerian Tumors. These tumors are frequently associated with perturbations in the P53 pathway resulting in P53 nuclear overexpression in the cell nuclei. The common simultaneous involvement by high-grade serous carcinoma of ovaries, Fallopian tubes and pelvic peritoneum justifies the term “high-grade serous pelvic carcinoma” potentially of multicentric origin, which is presently in use when the primary site of the tumor is not identifiable.

Low-grade OC are less common and include rare (and controversial) low-grade serous papillary carcinomas, probably derived from borderline serous papillary tumors, mucinous, endometrioid and clear cell carcinomas also presumed to develop from the respective borderline tumors. They have a slower and more indolent growth pattern, are more often unilateral and less often associated with extraordinarv spread.

The immunophenotype of the two categories of OC is different as well: low-grade OC are associated with mutations of K-ras, B-raf, beta-catenin, PTEN, while high-grade serous carcinomas and some endometrioid carcinomas are frequently associated with P53 nuclear overexpression. The genetic alterations are also quite different in the two groups, with microsatellite instability being more common in the high-grade OC.

Precursors of OC

The successful decline in morbidity and mortality due to numerous cancers can be attributed to the identification of precancerous lesions the removal of which intercepts their progression to invasive lesions. This is the case with uterine cervical, breast, colonic, skin and many other precancerous lesions, known as dysplasia or carcinoma-in-situ of epithelial tissues. In the case of the ovaries, their detection is a complex and much controversial issue because of the difficult access to the organ and the difficult interpretation of subtle changes at cellular and molecular levels. Precursors of the low-grade ovarian carcinomas are presumed to be the borderline serous tumors, especially the micropapillary variants, the borderline mucinous tumors and atypical endometriosis. Endometriosis is a very common ovarian lesion and fortunately benign in most cases. It seems however that endometriotic cysts lined by atypical epithelium may progress to endometrioid carcinoma and in rare cases, to clear cell carcinoma. Ovarian cystadenofibromas with endometrioid and clear cell atypia also represent potential, though uncommon cancer precursors.

The precursors of high-grade carcinomas are tubo-ovarian epithelial dysplasias that were defined by histologic, morphometric, immunohistochemical and lately, molecular analysis. Dysplastic cells are characterized by irregular stratification, loss of polarity, nuclear atypia consisting of increased profiles, abnormal texture, thickened irregular nuclear membrane. Positive immunohistologic stain for P53 in phenotypically unremarkable cells is also described as “P53 signature” in cells that may (or may not) precede the dysplastic changes. The finding of similar dysplastic changes in specimens removed preventively from women at high risk for OC (Prophylactic salpingo-oophorectomies) to those seen in the vicinity of invasive overt OC validates their potential carcinogenic transformation. Unfortunately no follow-up of these lesions, as for the cervical or other dysplastic lesions, is possible for the tubo-ovarian dysplasia unless the ovarian surface could be examined directly and repeatedly, as tentatively proposed with confocal microscopy, as it is practiced on the precancerous changes of the gastrointestinal tract.

**Early stage OC**

Ovarian Serous Papillary Carcinomas (OSPC) represent about 80-87% of all ovarian cancers of epithelial origin (carcinomas). Their vast majority, as mentioned before, are diagnosed in advanced stages (Stage III-IV) when spread to the pelvic and abdominal cavity. In a recent study of 99 cases of Stage I Ovarian carcinoma only a minority of less than one third were OSCP, while the majority was Non-Serous Ovarian Carcinomas (NSOC). The rare Stage I OSCP were mostly diagnosed fortuitously when confined only to the ovaries in patients under close surveillance for personal or family high risk for breast cancer and/or BRCA positivity, or due to associated unrelated pathologic changes in the pelvic or abdominal cavity, leading to investigative surgery or laparoscopy. Five of these patients had hysterectomies for uterine pathologies (one after Tamoxifen-therapy for breast cancer) coexisting with asymptomatic, clinically “mute” Stage I ovarian carcinomas. Ascites and Ca125 positivity usually occur in the presence of widespread tumors.

The NSOC represented the majority of the tumors diagnosed in Stage I, although overall (in all stages) they are by far less common. They were diagnosed at an early stage because of their association with symptomatic pathologic lesions In other words, while the ovarian tumor itself is mute, asymptomatic, associated symptomatic pathologic changes such as endometriosis, endometrial polyps, endometrial hyperplasia and/or neoplasia is symptomatic bringing the patient to medical attention. Pelvic and ovarian endometriosis, often cystic, adherent to neighboring organs, are manifested by painful masses; at surgery the occasionally detected endometrioid and clear cell carcinomas present in the endometriotic cyst are usually Stage I carcinomas and therefore their prognosis is far better than that of ovarian carcinomas not associated with symptomatic lesions. Uterine pathologic lesions, benign (leiomyomas, adenomyosis, endometrial polyps) or malignant (endometrial carcinoma) manifested as vaginal bleeding and diagnosed clinically as “pelvic masses” also bring the patient to medical attention and during the hysterectomy performed to remove the uterus an early asymptomatic OC is occasionally discovered in Stage I. In the study the patients with NSOC were younger and had a clinical background of hyperestrogenic syndromes (infertility, endometriosis, irregular menses). None of the patients with NSOC was BRCA positive, while 5 of the OSCP patients were BRCA 1 and one patient was BRCA2 positive (out of 17 tested)

**Challenges and conclusions**

The mystery of ovarian carcinogenesis is far from being solved and early detection is still elusive. The classification into low and high-grade OC is not an absolute one since some endometrioid and clear cell carcinoma can behave as highly aggressive tumors.

OC is presently rarely diagnosed in early stages because of paucity of symptoms and a still elusive tumor marker. However efforts should be directed to identify associated symptomatic gynecologic lesions, of which the most common is endometriosis, now considered as a potential precancerous condition that is often detected along with a work-up for infertility. Low-grade OC are more amenable to early diagnosis as well because of their slower growth and frequent origin in associated symptomatic lesions.

As for the precursors of OC it is now assumed that they evolve through a multistep and multifactorial progression from tubal-ovarian dysplastic changes the study of which is now much facilitated by the availability of prophylastic salpingo-oophorectomies from women at risk for OC [4]. The recent reports supporting a Fallopian Tube involvement in ovarian and pelvic serous carcinogenesis indicate the need for careful studies of early potentially carcinogenic changes in both ovarian and fallopian tube epithelium.

The surgical accessibility by new laparoscopy techniques for early lesion detection [5,6], the discovery of efficient biomarkers, and the implementation of algorithmic systems of prevention may open possibilities for intercepting the tumor growth before it reaches its lethal course.

**REFERENCES**