Surface Epithelial Tumors of Ovary

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INTRODUCTION

Surface epithelial tumors form two thirds of all ovarian neoplasms and 90% of all ovarian cancers are surface epithelial carcinomas. The WHO classification of ovarian tumors is based solely on the basis of the morphology of the primary tumor regardless of the associated peritoneal lesions or clinical behavior. However, for a classification to have clinical utility it should use terms in the classification which correlate with the clinical behaviour. Thus a modification of the WHO classification is more useful (Table I)

Ovarian cancer is the sixth most common cancer in women worldwide. It accounts for 4 % of cancer in women and 5 % of cancer deaths in women. The approximate distribution of the surface epithelial tumors (Table II) shows that almost 85 % of these tumors are serous or mucinous tumors and a third of these tumors are carcinomas. It is a disease of developed, industrialized countries where parity in women is low. Japanese women are an exception, who despite industrialization and low parity have low rates of ovarian cancer (lifetime risk rate of 0.45% vs 1.7% in Sweden and 1.4% in the U S A). Annual incidence rates vary from less than 5 per 100,000 in the less developed countries like Brazil, India, Thailand, Algeria etc to greater than 13 per 100,000 in the first world countries like the United States, Germany, Denmark, Norway etc. Other factors influencing the rates of ovarian cancer include age, genetic factors, reproduction factors etc.

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Table I MODIFIED WHO CLASSIFICATION FOR SURFACE EPITHELIAL TUMORS

Serous	Benign Borderline /Atypical Proliferative Carcinoma
Mucinous	Benign Borderline/Atypical Proliferative Carcinoma
Endometroid	Borderline/Atypical Proliferative Carcinoma
Clear Cell	Borderline/Atypical Proliferative Carcinoma
Transitional	Benign Borderline/Atypical Proliferative Carcinoma
Undifferentiated	Carcinoma
Mixed	Benign Borderline/Atypical Proliferative Carcinoma

Table II APPROXIMATE DISTRIBUTION OF SURFACE EPITHELIAL TUMORS

	Benign	Atypical Proliferative ("borderline")	Carcinoma	Total
Serous	30.7	5.5	16.5	52.7
Mucinous	23.7	3.8	3.6	31.1
Endometroid	—	0.4	5.7	6.1
Clear Cell	—	0.2	2.4	2.6
Transitional	3.1	0.1	0	3.2
Undifferentiated	—	—	2.1	2.1
Mixed	0.5	0.1	1.8	2.4
Total:	57.5	9.9	32.6	100

AGE

With increasing age the rates of ovarian cancer increase exponentially and the annual risk increases from less than 3 per 100,000 for women less than 30 years old to 54 per 100,000 in the 75 to 79 years old women. The mean age in the West is 60 years whereas in a study from our department the mean age was 45 years.

GENETIC FACTORS

10% of ovarian cancer are associated with the presence of BRCAI and BRCA2, tumor suppressor genes, which confer a markedly increased risk. The increased frequency of ovarian cancers seen in relatives of women with ovarian cancer is not seen in women with "borderline ovarian tumors". The rates of ovarian cancer vary in different ethnic groups. Afro-American women in the USA have two-third the rate ovarian cancers seen in Caucasian women. Whereas in Israel, Jewish women have an eighteen fold risk of developing ovarian cancers as compared to non Jewish women in Israel.

REPRODUCTIVE FACTORS

Increased parity is associated world-wide with a decreased risk of developing ovarian cancers but whether this is due to a protective effect of pregnancy, or a hazardous factor associated with infertility is not very clear. It has been seen that oral contraceptives have a protective role in the genesis of ovarian cancer. The protective role of oral contraceptives and increased parity is strongest for non-mucinous cancers of ovary and there is little or no reduction in the risk for mucinous carcinomas.Other factors associated with increased risk of ovarian cancers include use of fertility drugs, high socio-economic status, hysterectomy, tubal ligation and unilateral oopherectomy. A recent meta-analysis of hormone replacement therapy (HRT) and ovarian cancer show a slightly elevated risk with the use of HRT (odds ratio of 1.15) which is of marginal significance.

ETIOLOGY AND PATHOGENESIS

Since SEC of the ovary have wide variety of histologic types, to understand their pathogenesis they should be considered individually by their cell type. It appears that the serous carcinomas develop denovo where as others (mucinous, endometriod and clear cell carcinomas) arise from benign and atypical proliferative precursor lesions. It must be noted that this difference between serous and non-serous lesions of the ovary may be due to a rapid adenoma carcinoma sequence in the serous lesions rather than a qualitative difference in pathogenesis. It may be that the serous carcinomas rather than developing denovo may have obliterated the precursor lesion because of rapid growth, as 75 percent of the serous carcinomas are high grade and disseminated throughout the peritoneum at the time of diagnosis. There is some evidence to indicate that most serous carcinomas are derived from surface epithelium or inclusions which display subtle abnormalities or marked cytological atypia. It is seen that the rare low grade micropapillary serous carcinomas (MPSC) are often associated with atypical proliferative (borderline) serous tumors (APST). A transition from APST to MPSC is frequently seen in these lesions. Molecular studies have consistently shown different molecular alterations in serous cystadenomas, APST and frankly invasive serous carcinomas, indicating that they probably develop de novo and not from precursor lesions. Mutations of p53 and loss of heterozygosity (LOH) are seen commonly in invasive serous carcinomas but are extremely uncommon in cystadenomas and APSTs. The available evidence would indicate that invasive serous carcinomas of the ovary arise de novo from the surface of epithelium or inclusion cysts in the ovary and that MPSC arise from APST and not de novo.

In contrast to the serous carcinomas, mucinous, endometriod and clear cell carcinomas frequently display precursor benign lesions, of hyperplasia, atypical hyperplasia and borderline lesions. This suggests a pathway of development of the carcinoma similar to the adenoma-carcinoma sequence of colon cancers. Supporting this pathogenetic pathway is data on intra tumoral heterogeneity, high number of Stage I lesions, K ras mutational analysis (frequency of K ras mutations in APMTs and carcinomas are similar) and the finding of intraepithelial carcinoma merging with foci of atypical proliferative mucinous tumors (APMT) in over 65 percent of the mucinous carcinomas. Evidence for this pathway is most convincing for mucinous carcinomas. For endometriod and clear cell carcinomas it is not so convincing especially the poorly differentiated (high grade) lesions

which seem to be more like serous carcinomas in their biological behavior.

Precursor lesions of ovarian carcinomas are for the most part uncertain. They include dysplasia of surface epithelium, germinal inclusions, endometriosis, benign neoplasms (cystadenoma and cystadeno fibromas). These studies on precursor lesions are hindered by the fact that ovaries are not readily accessible for screening, and ovarian carcinomas are often large and stage III and IV lesions at presentation. These will obliterate or render non recognizable any precursor lesion that may have been present.

Endometriosis, seen in 7 to 20% of women, is the best documented precursor lesion in ovarian cancers. Though the risk of malignant transformation of endometriosis in a given woman is negligible, it is considered as a precursor lesion in almost 21% of ovarian cancers especially the endometroid and clear cell type. Atypia in the glands of endometriosis, is associated with DNA aneuploidy, LOH (chromosomes 9 p, 11q and/or 22q) and monoclonal methylation patterns of the androgen receptor gene locus. Six percent of ovarian carcinomas are associated with ovarian endometriosis and 9% of the ovarian carcinomas have extra ovarian endometriosis. When specifically looked for, the percentage climbs upto 12 to 21 percent and this may be an underestimation as the advanced ovarian carcinomas may have obliterated these lesions. The most common hypothesis for genesis of ovarian carcinomas is the **"Incessant Ovulation Hypothesis"**. It is postulated that the repeated traumatization of the surface epithelium during ovulation, with reparative proliferation of the surface epithelium creates a milieu which predisposes to malignant transformation. Thus the longer the reproduction period in a woman the more the number of ovulation traumas and the greater the predisposition for ovarian carcinoma to develop. Epidemiological studies support this. High levels of circulating gonadotrophins leding to altered-estrogen levels directly or via primary ovarian failure forms the basis of the **Gonadotrophin** Hypothesis for formation of ovarian carcinomas. This is less favoured than the Incessant Ovulation Hypothesis.

Angiogenesis and microvessal density (MVD) in ovarian carcinomas has been correlated with stage and grade of the tumor and inversely with survival. Over- expression of vascular endothelial growth factor (VEGF) has been reported in ovarian carcinomas when compared with benign ovarian neoplasms (cystadenomas, cysadeno-fibromas) and normal ovaries.

Studies on tumor infiltrating lymphocytes show that ovarian carcinomas have more activated T lymphocytes and more CD 4+ lymphocytes as compared to atypical proliferations but the proportion of natural killer (NK) cells was similar in both carcinomas and atypical proliferations. Correlation of these with survival and outcome has been attempted. Amplification of the c-erbB-2 or HER2/neu is seen in 42 percent of ovarian carcinomas but no consistent prognostic correlation of this has been reported. Many other genes and receptors like EGFR, K-ras, c-myc, TGFA etc have been studied in ovarian carcinomas with mixed results. Among the tumor suppressor genes p53, BRCA1 and BRCA2 have been extensively studied in ovarian carcinomas. The retinoblastoma gene has found to be normal in almost all the ovarian carcinomas. P53 gene mutations are seen in 50 60% of ovarian carcinomas and immunoperoxidase staining for its protein correlates with the mis-sense mutation but not the nonsense or splicing mutations or deletions. These correlate with increasing stage and grade of the tumor. These mutations are almost never seen in benign and atypical serous and mucinous types of lesions.

Studies on apoptosis and bcl-2 family of genes, DNA methylation, telomerases and cytogenetic studies have been done on ovarian carcinomas with varying results. ER-PR expression is seen in almost 50 percent of ovarian carcinomas and their cell lines, but data on the relationship of steroid receptor status and prognosis is conflicting.

PROGNOSTIC FACTORS IN OVARIAN CANCERS

The only accepted prognostic factors for ovarian carcinomas are the FIGO stage and in advanced-stage patient the volume of residual disease. Other factors like patient age, histopathologic grade and DNA ploidy are debatable. Histologic subtype is not an independent prognostic factor

when stage is taken into account. However, because of the distinctly different stage distribution of various histologic types there are differences in overall prognosis for each type.

A three grade system exists for grading ovarian carcinomas based on their architecture, nuclear grade and mitosis. Numerous studies using this have concluded that grading is important only for stage I patients because, chemotherapy is with held for the low grade, Stage I tumors as the survival figures are outstanding even when these patients are not given chemotherapy.. In over 51 percent of ovarian cancers which present as stage III disease, grading has no role to play in prognostication.

Volume of residual disease offer cytoreductive surgery, both pumary and secondary, is an important prognostic parameter both in prolonging survival and progression free interval. Serum CA 125 levels correlate well with volume of tumor and therefore is very useful though it is not an independent factor in multivariate analysis. Data regarding tumor rupture and capsular penetration is conflicting. DNA flowcytometry and image cytometry still remain as investigational tools and are not used for routine prognostication.

ROLE OF CYTOLOGY IN OVARIAN CARCINOMA

Two types of specimens are examined cytologically in ovarian tumors, fine needly aspiration (FNA) of the ovarian cysts and peritoneal fluids (peritoneal washes or ascitic fluid). Ninety percent of ovarian cysts can be diagnosed by FNA, however a high false positive rate of 73 percent and a false negative rate of 12 percent in this is a matter of concern. Unsatisfactory specimens seen in 18-70 percent of the cases further cloud their role.

Peritoneal fluid cytology is a must for accurate FIGO staging of ovarian carcinomas . Cytology is more sensitive in detecting cancers in ascitic fluids when compared with peritoneal washes, as well as detecting peritoneal metastasis less than 0.5 cm in diameter. Peritoneal cytology and histology are concordant in 87 % of patients with ovarian carcinomas. The most important pitfall for cytology is in women with begnin epithelial proliferations (endometriosis, endosalpingosis etc). It is important to be aware of cytological abnormalities caused by intraperitoneal chemotherapy as it may mimic malignancy. existence with uterine carcinoma.

Carcinomas, when they occur simultaneously in the ovary and uterus is an uncommon but well recognized event. If they have different histological appearances there is no problem. However, when they are of similar histologic subtypes (usually endometrioid and occasionally papillary) it could be the result of[1] metastasis of an endometrial carcinoma to the ovary[2] two independent primaries or[3] metastasis from an ovarian carcinoma to the endometrium which is the least commonly occurring event. Ovarian metastasis from an endometrial carcinoma is likely in the presence of multiplicity, bilaterality and/or a very small ovarian tumor, involvement of the lumen of the fallopian tubes and presence of deep myometrial invasion and/or vascular invasion in the uterine tumor. Immunohistochemistry and DNA flow studies may sometimes help in this distinction.

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