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CLASSIFICATION AND STAGING OF OVARIAN CANCER

Monaji Sanjana* and Ankit Thakur

Doctor of Pharmacy (Pharm. D), Department of Pharmacy Practice, Samskruti College of Pharmacy, Jawaharlal Nehru Technological University, Hyderabad, Telangana, India.

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***Corresponding Author: Monaji Sanjana**
Doctor of Pharmacy (Pharm. D), Department of Pharmacy Practice, Samskruti College of Pharmacy, Jawaharlal Nehru Technological University, Hyderabad, Telangana, India.

ABSTRACT

Ovarian cancer is the most common cancer which is in top fourth place with incidence of 4.9 cases per 100,000. It accounts for about 90% of all cancers that leads to death from gynecological cancers. Despite of the clinical development in this era the factors that regulate the development of ovarian cancers is still least understood. The gonadotropins are thought to be key regulators in the ovarian cell functions and the pathogenesis of the ovarian cancer. There are different types of ovarian cancer out of which ovarian epithelial cancer is the most common type of cancer. Epithelial cancers can be benign, borderline or malignant based on the ability of growth. The clinical manifestations, imaging can be used to differentiate benign and malignant ovarian cancers. Many tumors are associated with abnormal hormonal activity and abnormal sexual development. In this article we focused on the aetiology and types of ovarian cancer. There are different types of hypothesis which explain the risk of ovarian cancer which are given in brief explanation in our article.

KEYWORDS: Ovarian cancer, types of ovarian cancer, stages of ovarian cancer, hypothesis in ovarian cancer, pathology.

INTRODUCTION

According to NCI (National Cancer Institute) ovarian cancer is defined as the cancer that can be seen in the ovary. Ovaries are pair of female reproductive glands which produces the ova or eggs.[1] It is commonly known to be fifth most common cause of death in females all over the world.[2]

Epidemiology

It can be noticed that in 2020 there were around 236,511 women living with ovarian cancer in United States and estimated new cases in 2023 would be around 19,710. The deaths due to ovarian cancer estimated in 2023 is around 13,270.[3] In India incidence of ovarian cancer is around 36,170 that is 3.44% of all cancer cases is ovarian cancer. The age specific incidence rate (ASIR) increases from 35 years and the highest number of cases can be seen between 55 to 64 years.[4]

Aetiology

Factors that increase the risk of developing ovarian cancer are included below

Age

The risk of developing ovarian cancer increases from 45 years. The greatest risk can be observed between 75 to 79 years.[5]

Gene related changes

- **Inherited genetic mutations**

Mutations in some genes can be inherited that cause the increased risk of ovarian cancer. Those genes include BRCA1 and BRCA2; PTEN (PTEN tumor hamartoma syndrome); STK11 (Peutz-Jeghers syndrome); MUTYH (MUTYH- associated polyposis); MLH1, MLH3, MSH2, MSH6, TGFBR2, PMS1, PMS2 (nonpolyposis colon cancer).

- **Acquired genetic changes**

These are not inherited but instead they are developed in women body. These are result of radiation or TP53 tumor suppressor gene or HER2 oncogene mutations leads to development of ovarian cancer.[6]

- Had previous history of breast, uterine, colorectal cancer.
- Have the risk of developing endometriosis.
- Having never gave birth or have problem in getting pregnant.[7]

- Previous studies suggest other risk factors such as obesity, infertility, sedentary lifestyle, smoking, alcohol consumption, post-menopausal hormone therapy, post invitro ovarian fertilization.[4]

Who Classification of Ovarian Cancer

World health organization had classified ovarian cancer into 12 types and they are again sub divided into several types which are explained in table below. The rows indicate the type while the each column explain the further classification of those respective types.

Table-1: Classification of ovarian cancer.[8]

Epithelial tumors	Mesenchymal tumors	Mixed tumors	Sex-cord stromal tumors	Germ cell tumors	Monodermal teratoma and somatic type
Serous tumors	Endometrial stromal sarcoma	Adenocarcinoma	Pure stromal tumors	Benign teratoma	
Mucinous tumors	Smooth muscle tumors		Pure sex cord tumors	Immature teratoma	
Endometrial tumors	Ovarian myxoma		Mixed sex cord stromal tumors	Dysgerminoma	
Clear-cell tumors				Yolk sac tumor	
Seromucinous tumors				Embryonal carcinoma	
Brenner tumors				Choriocarcinoma	
				Mixed cell tumor	
				Monodermal teratoma and somatic type	
				Germ cell sex cord stromal tumors	

Miscellaneous tumors	Mesothelial tumors	Soft tissue tumors	Tumor like lesions	Lymphoid/myeloid tumor	Secondary tumors
Rete cystadenoma/ adenoma			Follicle cyst		
Wolffian tumor			Corpus leuteum cyst		
Solid pseudopapillary tumor			Large solitary luteinized follicle cyst		
Small cell carcinoma of ovary			Hyper-reaction leuteinalis		
Wilms tumor			Pregnancy luteoma		
			Stromal hyperplasia and hyperthecosis		
			Fibromatosis and massive edema		
			Leydig cell hyperplasia		

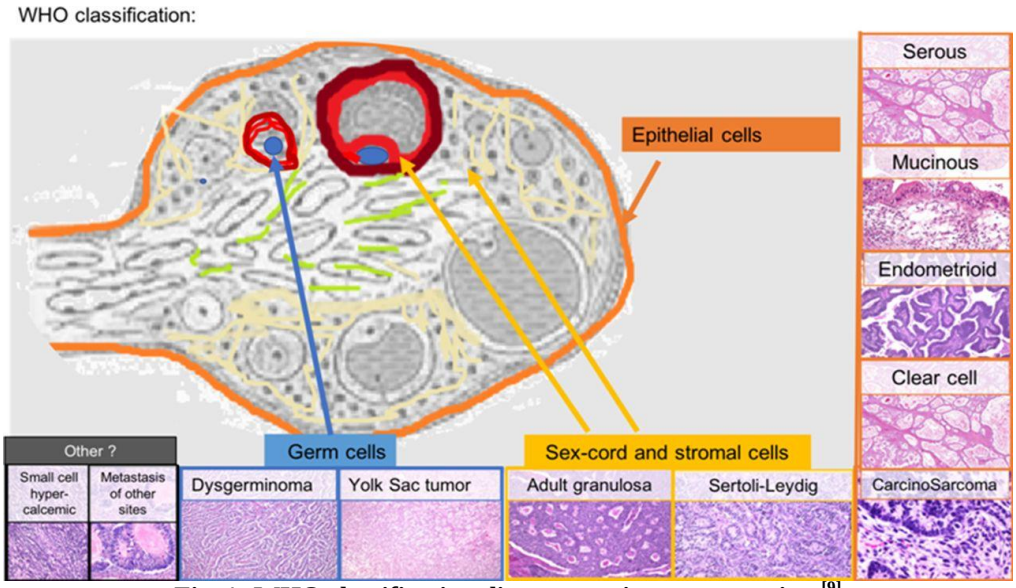

Fig. 1: WHO classification diagrammatic representation.[9]

The histopathological classification of ovarian cancer divides it into two types such as type 1 and type 2. The diagrammatic representation of this is as follows:

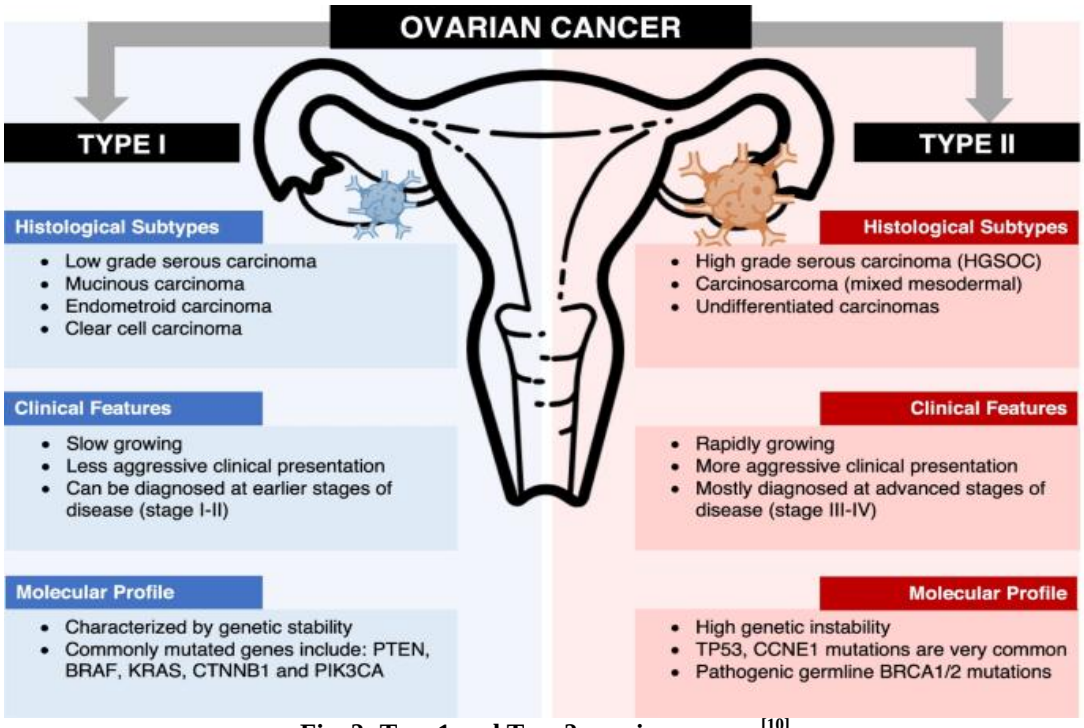

Fig. 2: Type1 and Type2 ovarian cancer.[10]

Detection and Screening of Ovarian Cancer

- Blood test
- Ultrasound scan
- Transvaginal scan
- Abdominal scan
- CT scan/Positron Emission Tomography (PET) scan.
- Needle biopsy (small sample of fluids are examined from ovaries)
- Laparoscopy (visual examination of ovaries through the small cut in abdomen)
- Laparotomy (removing the tissue or complete ovaries).(11)(12)

Signs and Symptoms

- Bloating (having increased abdominal size for long time)
- Having difficulty in eating
- Feeling stomach fullness very quickly

- Pain in pelvic or abdominal areas
- Frequent urination
- Changes in bowel habits
- Abdominal bleeding
- Post-menopausal bleeding
- Extreme tiredness/ fatigue
- Sudden drop of weight.[13]

Stages of Ovarian Cancer

It represents the extent of spread of tumor. There are four stages of ovarian cancer which include ovaries, fallopian tube and peritoneum. These stages ranges from early to advance stage.

There are two systems for giving stages, the FIGO System (International Federation of Gynecology and Obstetrics) and the AJCC TNM staging system (American Joint Committee on Cancer). Both the systems uses extent of tumor, spread to nearby lymph nodes, metastasis to distant sites which are represented with letters T, N, and M respectively.

The detailed description of stages is explained in following table-2.

Table-2: AJCC system 2018 classification of stages for ovarian, fallopian tube and primary peritoneal cancer.[14]

AJCC STAGE and FIGO STAGE	STAGE GROUPING	STAGE DESCRIPTION
I	T1 N0 M0	The cancer is defined to only ovary or fallopian tube (T1). It is not spread to nearby lymph nodes (N0) or to different sites (M0)
IA	T1a N0 M0	The cancer is confined to only one ovary or fallopian tube and is inside the ovary or fallopian tube respectively. No cancer cells can be seen in the fluid or washings of abdomen or pelvis (T1a) There is no spread to lymph nodes (N0) and to different sites (M0)
IB	T1b N0 M0	The cancer is in both the ovaries and fallopian tubes only inside but not outer surface. No cancer cells can be seen in the fluid or washings of abdomen or pelvis (T1b) There is no spread to lymph nodes (N0) and to different sites (M0)
IC	T1c N0 M0	The cancer is seen in both the ovaries or fallopian tube along with surgical spill (the tissue surrounding the tumor broke while surgery and leak into abdomen and pelvis called IC1 stage, cancer can be observed on outer surface of at least one ovary or fallopian tube or the tissue broke before the surgery called IC2 stage, cancer cells are found in fluid or washings of abdomen and pelvis called IC3 stage. There is no spread to lymph nodes (N0) and to different sites (M0)
II	T2 N0 M0	The cancer is seen in one or both ovaries or fallopian tube and spread to uterus, bladder, and sigmoid colon, rectum within the pelvis or primary peritoneal cancer (T2). There is no spread to lymph nodes (N0) and to different sites (M0)
IIA	T2a N0 M0	The cancer spread to uterus or fallopian tube or ovaries (T2a). There is no spread to lymph nodes (N0) and to different sites (M0)
IIB	T2b N0 M0	The cancer can be seen on outer surface of pelvic organs or grown into bladder, sigmoid colon, rectum (T2b). There is no spread to lymph nodes (N0) and to different sites (M0)
IIIA1	T1 or T2 N1 M0	The cancer is seen in one or both the ovaries or there is primary peritoneal cancer (T1) and may spread into nearby pelvis organs (T2). It is spread to retroperitoneal lymph nodes (N1) and not spread to distant sites(M0)
IIIA2	T3a N0 or N1 M0	The cancer is seen in one or both the ovaries or there is primary peritoneal cancer and may spread into nearby pelvis organs. While surgery the cancer cells cannot be seen with naked eye but the tiny deposits of cancer can be found in lining of abdomen in the laboratory test (T3a). There may or may not be any spread to retroperitoneal

		lymph nodes (N1, N0 respectively). There is no spread to distant sites (M0)
IIIB	T3b N0 or N1 M0	The cancer is seen in one or both the ovaries or there is primary peritoneal cancer and may spread into nearby pelvis organs. The cancer deposits can be seen with naked eye with size of 2 cm (T3b). There may or may not be any spread to retroperitoneal lymph nodes (N1, N0 respectively). There is no spread to distant sites (M0)
IIIC	T3c N0 or N1 M0	The cancer is seen in one or both the ovaries or there is primary peritoneal cancer and may spread into nearby pelvis organs. The cancer deposits are larger than 2 cm found on outside of the liver or spleen (T3c) there may or may not be any spread to retroperitoneal lymph nodes (N1, N0 respectively). There is no spread to distant sites (M0)
IVA	Any T Any N M1a	Cancer cells are found in fluids around lungs. There is no other spread of cancer outside the abdomen (M1a)
IVB	Any T Any N M1b	Cancer has spread to inside the spleen or liver to lymph nodes other than retroperitoneal lymph nodes and to other organs outside peritoneal cavity such as lungs and bones (M1b)

Pathogenesis Due To Hormonal Induced Ovarian Cancer

There are few hypothesis that explain the pathology of ovarian cancer. Such as

- The incessant ovulation hypothesis: the origin of cancer occur due to repeating of the trauma to epithelial cells in the process of ovulation and then healing the trauma. As a result the factors that supress ovulation are protective. According to this theory women around 20's are in increased risk to develop ovarian cancer.
- The pituitary gonadotropin hypothesis: this states that high levels of gonadotropins that act via the stimulation of oestrogens cause ovarian epithelial cells cancer by getting trapped in cysts and undergoing different changes that forms the cancer.
- The androgenic/progesterone hypothesis: this hypothesis say that androgens stimulate cancer while progesterone is protective.
- The inflammation hypothesis: the inflammatory risk factors like pelvic inflammatory disease increases the risk of development of cancer.
- The ovarian stromal hypothesis: this states that after the ovulation process during menstrual cycle, the granulosa cells and some theca fail to apoptose and retain the ability to produce steroids and then induce the stimulating effects on cancer.
- The incessant menstruation hypothesis: this states that the iron-induced oxidative stress due to retrograde menstruation causes the exposure of fimbriae cells of fallopian tubes which are floating in bloody peritoneal fluid causes the cancer.(15,16)

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Conflicts of Interest

None.

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