



Research Article

Ovarian Cancer: Characteristics & Management

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Abstract

Different cells of the ovary may be involved in the development of the cancer. But epithelial cells are the main types of cells which are involved in the cancer of ovary. There are different types of the ovarian cancer depending upon the histology of the ovary. Surface epithelial-stromal tumor, Stromal tumor, Germ cell tumor and mixed tumors. Inhibition or complete suppression of ovulation and reduction of pituitary gonadotropins are the main mechanisms involved in the etiology of the ovarian cancer. Adrenomedullin acts on estrogen receptors present in the ovary and activates certain genes that are involved in developing the cancer of ovary. There are no specific symptoms of the ovarian cancer but some symptoms like abdominal distention, bloating, pain are most common. There is some correlation between the Adrenomodulin with the hormonal receptors of the ovary. Border cell migration reflects the mechanism of development of ovarian cancer. The most common neoplasm of the ovary is mature cystic teratoma of the ovary. Most recently a new subtype of epithelial carcinoma of the ovary has been recognized. This newly recognized cancer is called Primary transitional cell carcinoma (TCC) of the ovary. It occurs mostly in children. Surgery is the best way to get rid of the dangerous symptoms of the ovarian carcinoma.

Keywords: Epithelial cells of the ovary, Estrogen receptors, Transvaginal ultrasonography, Polycystic syndrome.

Introduction

Ovarian cancer can be referred as the cancerous growth that arises from different parts of the ovary. Different cells of the ovary may be involved in the development of the cancer. But epithelial cells are the main types of cells which are involved in the cancer of ovary. Other cells which may be involved in the ovarian cancer are the

germ cells and the mesenchymal cells of the ovary. There are no specific symptoms of the ovarian cancer but some symptoms like abdominal distention, bloating, pain, constipation, Diarrhea, gas, tiredness, back pain, pelvic pain, abnormal and irregular bleeding from vagina. Ovarian cancer can be diagnosed with the help of physical test, blood test, microscopic examination of the biopsy sample and surgery.

Physical examination: It includes pelvic examination.

Blood test: CA-125 is used as a marker.

Types of Ovarian Cancer

There are different types of the ovarian cancer depending upon the histology of the ovary. Surface epithelial-stromal tumor, Stromal tumor, Germ cell tumor and mixed tumors.

Infertile women and those women who have never become pregnant and are in older age are always at greater risk of the ovarian cancer. Boarder cell migration is the process, during which epithelial cells migrate towards each other and become

diffused with the surrounding epithelial cells. This process reflects the mechanism of development of epithelial ovarian cancer.

Ovarian Tumours

Ovarian tumours can be divided into three main groups:

- Functional
- Benign
- Malignant

In relative frequency, functional cysts account for about 24% of all ovarian cysts, benign cysts 70% and malignant 6%.

Table 1: Ovarian Tumors, Benign and Malignant

Benign ovarian tumors	Malignant ovarian tumors
Some are tumors are benign (not cancer) and never spread beyond the ovary. Women with these types of tumors can be treated by taking out either the ovary or the part of the ovary that has the tumor.	Malignant ovarian tumors may be solid or cystic. Malignant cystic neoplasms are usually serous or mucinous cystadenocarcinomas. They may contain solid areas, surface papillary protrusions, areas of necrosis and internal papillae. These are the most common ovarian cancer. When someone says they have ovarian cancer, they usually mean this kind. These cancers can also be divided into different types based on certain features that can be seen under a microscope.

Metastasis of Ovary

Those women who have polycystic ovarian syndrome are also at a greater risk of ovarian cancer.^[1, 2]

Usually the metastasis of ovary is associated with the non genital cancers. Surgery is the best way to get rid of the dangerous symptoms of the ovarian carcinoma. Most commonly used surgery is the cytoreductive surgery of the ovary.^[3,4]

In early days Depot-medroxy-progesterone acetate was found to have an association between ovarian cancer and the cancer of endometrium of the ovary. But later researches showed that Depot-medroxy-

progesterone acetate is only effective against endometrial cancer. It does not have any protective effect against the epithelial cancer of the ovary.^[5, 6]

Cancer of the ovary is not only confined with the menstrual disorders. There may be the involvement of the sex hormone like androgen. Androgen excess is also a risk factor for the development of cancer of ovary. Ovarian cancer is most common among the infertile women at age above forty years.^{[7, 8].}

Ovarian epithelial dysphasia is also involved in the development of ovarian cancer.^[9, 10]

Etiology of Ovarian Cancer

There are two main types of mechanisms which are involved in the etiology of the cancer of ovary.

- 1) Inhibition or complete suppression of ovulation.
- 2) Reduction of pituitary gonadotropins.
[11,12]

In women at the age of fifty, the rate of occurrence of cancer of ovary becomes decreased up to some extent because of the

fact that the menstrual cycle stops and reproductive hormones get reduced in the body of the female. It shows that during the pregnancy when menstrual cycle stops and there is increase in the amount of androgen along with estrogen there are very rare chances of occurring the cancer of ovary in women and during pregnancy women usually remain protected from ovarian cancer. Other reproductive factors are the age of the woman at the birth of her first child and the age at the birth of her last child. The numbers of births at a particular age also an important reproductive factor in determining the cancer of ovary. [13,14]

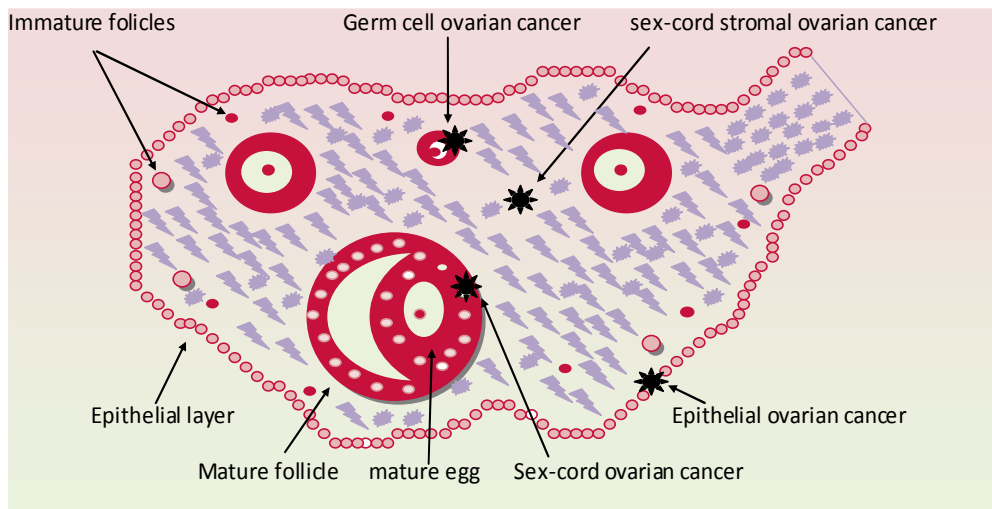


Figure 1: Stars Indicate the Different Types of Ovarian Cancers according to their Origin

Receptors of Ovary

There is some correlation between the Adrenomodulin with the hormonal receptors of the ovary. These are the receptors of the estrogen usually called as the estrogen-receptors. In order to analyze the relation of Adrenomodulin with the estrogen receptors an immunological test, polymerase chain reaction was used. When different samples of the cancerous cell linings of the ovary were analyzed by the polymerase chain reaction it was found that adrenomodulin appears on the epithelial and stromal cells of the ovary. Certain types of genes are activated or expressed in the epithelial cells of the ovary that cause an expression of adrenomodulin on the surface of cancerous tissues of the ovary. Estrogen receptors are

of two types, alpha and beta. But the occurrence of estrogen-alpha receptors is more than the estrogen-beta receptors. The numbers of estrogen receptors are much more in the cancerous cells of the ovary than the normal cells of the ovary. It indicates that there is an association of adrenomodulin with the normal cells as well as the cancerous cells of the ovary because estrogen receptors are also present in the normal cells of the ovary but in less numbers as compared to the cancerous cells. Those women which have menstrual cycle even after the age of seventy have 2-4 times increased risk of getting ovarian cancer. [15,16]

Those women are at greater risk of the ovarian cancer which has a strong family history about the cancer of ovary. When

ovaries of such women were removed as a prophylactic measure then many histopathological changes were observed in the epithelial lining of the ovarian cells. These changes include the hyperplasia of the epithelial cells of ovary, irregular and

abnormal shape of the nucleus of epithelial cells of the ovary and dense chromatin. cisplatin, ifosfamide and mesna are the drugs that are very effective in the treatment of mixed cancer of the ovary. [17, 18]

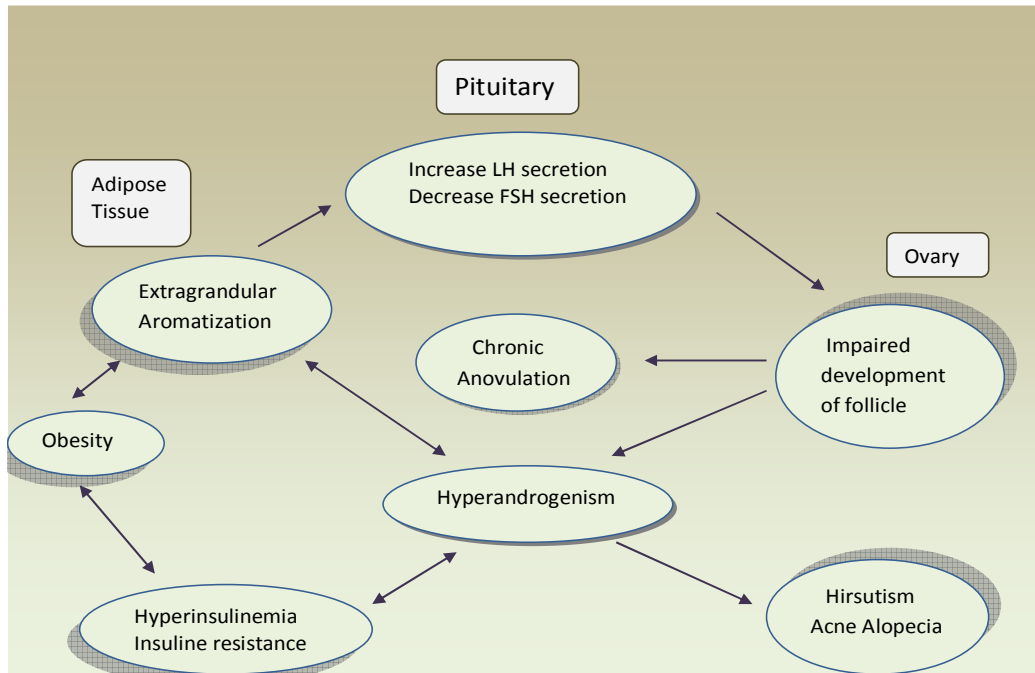


Figure 2: Pathophysiology of Polycystic Ovarian Syndrome

Boarder Cell Migration

The process through which development of ovary takes place is called as the boarder cell migration. During this process, epithelial cells migrate towards each other and become diffused with the surrounding epithelial cells. This process reflects the mechanism of development of epithelial ovarian cancer. Taiman is an analogue of steroid receptors. It is involved in the movement and migration of cancerous cells. It has been found that there is no or very little activation of these steroid receptors in the normal ovarian cells of woman. But in case of cancerous cells of ovary there is a marked increase in the activation of these steroid receptors. If we suppress the activation and expression of these steroid receptors then there will be a reduced risk of ovarian epithelial cancer and a local accumulation of kinases in the epithelial cells along with the inhibition of

migration and invasion of epithelial cells. There is no dependence of this inhibition upon the estrogen receptors. It means steroid receptors are involved in promoting the ovarian epithelial carcinoma. Effects of tamoxifen are mostly seen in the endometrium of postmenopausal women. [19, 20]

Drugs for Epithelial Cancer of Ovary

Drugs that are prescribed for the epithelial ovarian cancer are the vinblastine and bleomycin cisplatin. These three drugs are very effective in controlling the epithelial ovarian cancer as well as the mixed type of ovarian tumors. Cisplatin is administered intravenously at a dosage regimen of 20mg for 5 days. Vinblastine is also administered at a dose of 0.17mg/kg for two days. Bleomycin is given at a dose of 30mg/kg for 4 days then dose is decreased at 15mg/kg for 30 days. Among these three

drugs cisplatin is the most toxic drug. It causes neurotoxicity in the brain.^[19, 20]

Those women which have menstrual cycle even after the age of seventy have 2-4 times increased risk of getting ovarian cancer.^[21, 22]

Polycystic Syndrome of Ovary

Polycystic syndrome of the ovary is a major disorder of the ovary among the women of age twenty that usually leads to infertility among young women at teen age, infertility and hirsutism.^[23, 24]

To save the life of women during the cancer of cervix the position of both ovaries in young women is changed slightly. But there should be a balance between the metastasis of the ovary and ovarian cancer.^[25, 26]

Estrogen that is produced after the postmenopausal interval comes from the conversion of androgen into estrogen. In the peripheral tissues of ovary androgen is converted into estrogen. Androgen is produced from adrenal glands present in the ovary. The major contribution of estrogen is in the development of neoplasia of the endometrium. When the number of stromal cells increase in the ovary there is an increased production of androgen in the ovary. This is the cause of pathology in the endometrium. Due to this increased production of androgen there will be an increased production of estrogen. Because androgen acts as a pro-hormone or precursor of estrogen in the ovary. Androgens are converted into estrogens in the peripheral tissues of the ovary by an enzyme called as the cytochrome P450 aromatase. This estrogen leads to the formation of epithelial and ovarian cancer in the ovary. It shows that aromatase inhibitors can be a very useful therapy for the malignancies of the ovary.^[27, 28]

Expression of the Selenium Binding Protein in Ovary

There is an expression of the selenium binding protein in the epithelial cells of the ovary. In order to know that is there any expression of selenium binding protein in

the normal epithelial cells of the ovary different experiments were done by the gynecologists. It was found that expression of selenium is more in the normal epithelial cells of the ovary as compared to the cancerous epithelial cells of the ovary. Further in ovaries having tumors the expression of selenium binding proteins was also less in normal epithelial cells of the ovary that were laying close to these tumor cells.^[29, 30]

Metabolism of Nitrosodimethylamine occurs in the ovaries and its metabolism produces reactive metabolites in the ovary. These reactive metabolites of ovary bind and react with the proteins present in the ovary and along with the nucleic acid. Nitrosodimethylamine is metabolized in the ovary by mitochondria and the microsomal enzyme system. Microsomes and mitochondria cause the degradation of Nitrosodimethylamine in the ovary. Upon degradation nitrosodimethylamine is converted into reactive toxic metabolites and formaldehyde. Both these metabolites bind with a covalent bond to the proteins of the ovary. Major part of this degradation is done by microsomes. When DNA of normal ovarian epithelial cells was separated and was analyzed by immunological tests it showed altered sequence of bases of deoxyribonucleic acid. This change in the bases of DNA was due to the toxic effect of the reactive metabolites of Nitrosodimethylamine on the DNA of the normal epithelial cells of the ovary. So women should avoid any environmental source having NDMA (N-Nitrosodimethylamine) e.g. tobacco beverages etc.^[31, 32]

To determine the amount of conjugated and un-conjugated oxosteroids among the women having the cancer of ovary gas chromatography and liquid chromatography were used. Basically these techniques were used for breast, ovary and uterine cancer. Aetiocholanolone, androsterone and dehydroepiandrosterone were detected in the blood serum by the gas liquid chromatography. These were un-conjugated oxosteroids. The amount of these steroids was too low to detect in the blood. The amount was about $.23 \mu\text{g}/10 \text{ ml}$

of blood. There was excess of conjugated oxosteroids in the blood serum. [33, 34]

Effect of Temperature on Ovary

Increase in temperature has a significant effect on the normal epithelial cells of the ovary and may lead to infertility among young women. When temperature of ovarian epithelial cells was increased to about 40- 44°C there was a decrease in the concentration of the potassium ions in the epithelial cells of the ovary. It was found that this decrease in concentration of potassium ions was associated with the loss of sexual and reproductive functions of the ovary.

This decrease in K⁺ ions in the epithelial cells was not due to the changes in the cell volume, hyperplasia of epithelial cells and inhibition of sodium and potassium pumps. [35, 36]

Ovarian Carcinoma

The most common neoplasm of the ovary is mature cystic teratoma of the ovary. It is the most common neoplasm of the ovary. Usually this type of neoplasm occurs in early childhood and is diagnosed at the age of puberty. Transformation of malignancy is not very much common it is very rare. Transformation of malignancy occurs through the germ layers of the embryo during pregnancy. The most common malignancy of the ovary is of squamous cells and is called as squamous cell carcinoma of the ovary. An undifferentiated adenocarcinoma of the ovary was observed when the transformation of malignancy occurred through the epithelium of the gastrointestinal tract. The layers of the embryo called as germinal layers are responsible for the transfer of malignancy of the ovary during pregnancy. [37, 38]

Table 2: Percentage of Occurrence of Cancer in Women of Age >20 Years

HISTOLOGY	%AGE OCCURRENCE
Carcinoma	5.5%
Surface epithelial stromal tumor	89.7%
Papillary serous cystadenocarcinoma	26.4%
Endometrial tumor	9.8%
serous cystadenocarcinoma	5.7%
Papillary	5%
Mucinous cystadenocarcinoma	4%
Clear cell ovarian tumor	4.3%

Epithelial Carcinoma of the Ovary

Most recently a new subtype of epithelial carcinoma of the ovary has been recognized. This newly recognized epithelium of the cancer of the ovary is called as the Primary transitional cell carcinoma (TCC) of the ovary. It is the cancer of epithelium. It has been found that if we have the ability to recognize these types of tumors and epithelial cancer then we can have a very useful clinical background while using chemotherapy for epithelial cancer of the ovary. In this way survival conditions of the patient are improved.

Size of the epithelial tumor varies between 4-22cm. [39, 40]

Treatment of Epithelial Ovarian Cancer

Treatment of epithelial ovarian cancer was described by the New York institution of cancer in America a few years ago. It was demonstrated that all the women patients having cancer of epithelial cells must be treated with the surgery. However epithelial cancer of ovary may also be treated with the radiation therapy and chemotherapy but the best platform to treat ovarian cancer is the surgery. This is because of the fact that all types of carcinomas of the ovary are very much sensitive to the exposed radiations for killing and degradation of epithelial cancerous cells. But the best combination therapy for treatment of epithelial cancer of ovary is radiations along with surgery.

Now a day the most recent technique has been introduced in America for the treatment of cancer of ovary. This technique is palliative x-ray therapy. In this therapy x-rays are put on the cancerous cells. This technique is very much useful for those patients who have lost all their hopes even after the failure of surgery. [41, 42]

Diagnosis of Ovarian Cancer

Polycystic syndrome of the ovary can be diagnosed very easily from the clinical symptoms of the patient. Menstrual disorders, bleeding from the uterus and vagina miscarriage of the fetus increased amount of androgen in the ovary loss of hairs from the scalp infertility and hirsutism are some of the clinical symptoms of the polycystic syndrome of the ovary. Polycystic ovarian syndrome also involves changes in the hormonal level of the blood plasma serum. Concentration of following hormones is changed in the blood plasma. FSH (follicle stimulating hormone), Prolactin and LH (leutiinzing hormone). [43, 44]

Effect of Tamoxifen on the Ovary

Tamoxifen is a drug that was used once for the prevention and delay of the breast cancer among healthy women having

family history of breast cancer. In order to study the effect of tamoxifen on the ovary and uterus of women different trails were done among women. For this purpose postmeupausal women having age between 50-70 years were selected in a hospital. The effect of tamoxifen on the ovary and uterus was examined through following techniques; transvaginal ultrasonography microscopic examination of endometrial biopsies and color Doppler imaging

Different effects of tamoxifen were observed among women taking tamoxifen at regular intervals. Increase in the size of uterus, abnormality in the endometrial cells, decrease in the flow of blood in uterine arteries, typical hyperplasia, thickening of endometrium.

All these above effects were independent of the concentration of tamoxifen in the blood and age of the women. Now it is clearly evident from these effects that tamoxifen can cause some potentially unwanted pathological changes in the uterus, ovary and endometrium of women. These effects of tamoxifen are mostly seen in the endometrium of postmenopausal women. Transvaginal ultrasonography of the uterus is very important technique to study the effect of tamoxifen and other drugs acting on uterus and ovary of women. [45, 46]

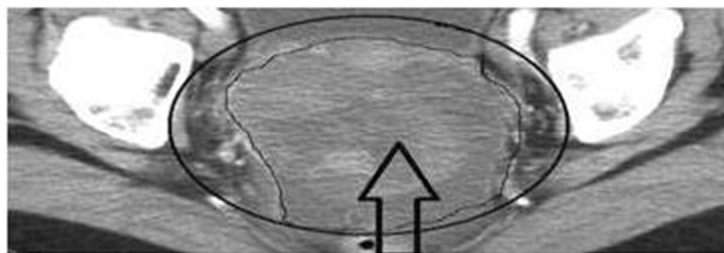


Figure 3: Ovarian Carcinoma

Biochemistry of Ovarian Cancer

Polycystic ovary syndrome (PCOS) is a genetic disorder. It is heterogeneous type of disorder. It involves abnormality in endocrinology and metabolism. Polycystic syndrome of ovary mostly occurs in the women of reproductive age. Biochemically polycystic ovary syndrome can be characterized by an increase in the amount

of androgen. this specific syndrome has a very marked negative effect on the metabolism and normal functioning of the body. Polycystic syndrome of the ovary may change into the metabolic syndrome of the whole body. It can be manipulated as, Increase in the blood insulin, Obesity of the abdomen, Increase in blood pressure, dyslipidemia, insulin resistance, Type 2 diabetes mellitus Hyperplasia of

endometrium Cardiovascular diseases. There are also present some abnormalities in the endocrinology in case of polycystic ovarian syndrome. In polycystic ovarian syndrome there are some pathological changes in the regulation of gonadotropic releasing hormone (GRH). It causes the feed back inhibition of steroids of the ovary. As a result the secretion of leutinizing hormone (LH) increases in the body of women. Secretion of follicle stimulating hormone increases. there is hyperactivity of stromal and thecal cells of the ovary. Due to hyperactivity of stromal cells there is an increased production and secretion of androgen. All these factors lead to the abnormality in the biochemistry and metabolism of the body of women after menopause. [47, 48]

Polycystic syndrome of the ovary is seen among the women of reproductive age. Different types of pharmacological therapies are available to treat the symptoms of polycystic syndrome of the ovary. For example changes in the life style e.g. in diet and exercise may help us while treating the ovarian syndrome. Metabolism of Nitrosodimethylamine occurs in the ovaries and its metabolism produces reactive metabolites in the ovary. These reactive metabolites of ovary bind and react with the proteins present in the ovary and along with the nucleic acid. Nitrosodimethylamine is metabolized in the ovary by mitochondria and the microsomal enzyme system. Microsome and mitochondria cause the degradation of Nitrosodimethylamine in the ovary. Upon degradation nitrosodimethylamine is converted into reactive toxic metabolites and formaldehyde. Both these metabolites bind with a covlant bond to the proteins of the ovary. Major part of this degradation is done by microsomes. When DNA of normal ovarian epithelial cells was separated and was analyzed by immunological tests it showed altered sequence of bases of deoxyribo nucleic acid. This change in the bases of DNA was due to the toxic effect of the reactive metabolites of Nitrosodimethylamine on the DNA of the normal epithelial cells of the ovary. So women should avoid any environmental

source having NDMA (N-Nitrosodimethylamine) e.g. tobacco beverages etc. [49, 50]

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